The Development of Intraoperative Electronic Perfusion Data Processing to Improve the Practice of Cardiopulmonary Bypass

By

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Past-President, Australian & New Zealand College of Perfusionists (ANZCP)

Chair, Australian & New Zealand Collaborative Perfusion Registry (ANZCPR)

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Many individuals have contributed to this undertaking over the last 20 years or more. My career as a Perfusionist started at the Royal Adelaide Hospital in 1993, and after 4 years' experience I was motivated to move to Flinders Medical Centre to undertake both clinical and research work with Dr Rob Baker. Very early on, Rob encouraged me to play a role in developing the role of information technology to support research data management, which soon became the focus for my interest in the development of data management techniques to understand and improve clinical practice. I am extremely grateful for this opportunity, and the autonomy, and mentorship and collaborative support that Rob has provided during the undertaking of the research over many years and for his supervision and support in the preparation of this thesis. Rob's meticulous approach to data collection, dedication to ensuring data quality, and most importantly his advocacy for the best interests of the patient have provided me with sturdy footsteps to follow throughout this journey.

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In the most recent database report (2007-2021) they have provided the opportunity collectively to report data from over 43,000 patients undergoing cardiopulmonary bypass over 9 different hospitals.

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Thank you to Professor Alan Merry and Professor Prof Paul Myles for their support of the collaborative registry, sharing of their wisdom through caring guidance, but mostly for their friendship, personal encouragement and recognition.

Over the last 18 years my involvement in the Perfusion Downunder Meeting has provided me with tremendous opportunity to engage with many inspirational individuals from the perfusion and cardiac surgical community, including faculty, colleagues, organisers and corporate partners. This engagement has been a significant source of inspiration for this work and in my personal and professional growth.

I would like to extend my heartfelt gratitude to Al Stammers and Dr. Stephen Horton for their unwavering personal support and friendship throughout my career. Their continual professional inspiration and mentorship have been invaluable, providing guidance and encouragement that have profoundly shaped my academic and professional development.

I also wish to make special mention of my co-authors who have embraced my vision for this research and for promoting the ethos for the application of electronic data collection to understand and provide the basis for the improvement of clinical practice. Their feedback and contributions to manuscript revisions has been greatly appreciated. In particular, I would like to thank Tim Willcox for his considerable input into the research process, the collaborative registry, recognition of the importance of contributing to the understanding and improvement of our profession, and inspiration as a mentor.

Most of all I would like to thank my wife Catherine, and my daughters Lina, Maddison and Sienna for their love and support through this journey, that has opened a window through which the practice of cardiopulmonary bypass can be seen.

Declaration

I certify that this thesis:

1. does not incorporate without acknowledgment any material previously submitted for a degree or diploma in any university

2. and the research within will not be submitted for any other future degree or diploma without the permission of Flinders University; and

3. to the best of my knowledge and belief, does not contain any material previously published or written by another person except where due reference is made in the text.

Terms of Use

List of Abbreviations

Abbreviations used in this thesis.

ABC	Achievable Benchmark of Care
ACT	Activated clotting time
AKI	Acute kidney injury
AKIN	Acute Kidney Injury Network
AmSECT	American Society of ExtraCorporeal Technology
ANZCPR	Australian and New Zealand Collaborative Perfusion Registry
ANZSCTS	Australian and New Zealand Society of Cardiothoracic Surgeons
APF	Adjusted performance fraction
ASCTS	Australasian Society of Cardiac and Thoracic Surgeons
AUC	Area under the curve
AUROC	Area under the receiver operating characteristic curve
BIC	Bayesian Information Criteria
BMI	Body mass index
CABG	Coronary artery bypass graft
CI	Confidence intervals
CI	Cardiac index
COPD	Chronic obstructive airway disease
CPB	Cardiopulmonary bypass
CQI	Continuous quality improvement
CSD	Cardiac surgery database
CSR	Cardiac surgery research
DMAIC	Define, measure, analyse, improve, control

DMS	Data Management System
DPMO	Defects per million opportunities
DO_2	Oxygen delivery
DO_2i	Indexed oxygen delivery
EACTS	European Association of Cardiothoracic Anaesthesiology
EACTS	European Association of Cardiothoracic Surgery
EMR	Electronic medical record
EPD	Electronic perfusion data
GEPA	Gastroepiploic artery
GIFT	Goal-directed perfusion trial
Hb	Haemoglobin
Hct	Hematocrit
HLM	Heart lung machine
H-L	Hosmer-Lemeshow
ICU	Intensive care unit
IQR	Interquartile range
KDIGO	Kidney Disease: Improving Global Outcomes
LCL	Lower control limit
LIMA	Left internal mammary artery
MAP	Mean arterial pressure
MI	Myocardial infarction
MSE	Mean square error
Naso	Nasopharyngeal
NYHA	New York Heart Association
ODBC	Open database connectivity
OR	Odds ratio

PDUC	Perfusion Downunder Collaboration
PDUCD	Perfusion Downunder Collaborative Database
QC	Quality control
QI	Quality indicator(s)
RADG	Radial artery
RAP	Retrograde autologous prime
RBC	Red blood cells
RIMA	Right internal mammary artery
RIFLE	Risk, Injury, Failure, Loss of renal function and End-stage renal disease
ROC	Receiver operating characteristic
RCT	Randomised clinical trial
SCA	Society of Cardiovascular Anesthesiologists
SQL	Structured query language
SPC	Statistical process control
STS	Society of Thoracic Surgeons
UCL	Upper control limit
VCO_2	Carbon dioxide elimination

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Abstract

The intraoperative electronic perfusion data (EPD) collected provide an enormous resource for undertaking studies to provide better understanding and improvement of the practice of cardiopulmonary bypass (CPB), however the application of data for this purpose has been limited. Potentially the most important influence that EPD may have on clinical practice is the identification of modifiable predictors of patient outcome, and with integration of EPD into perfusion registries facilitation of quality improvement through benchmarking. To date, the Australian and New Zealand Collaborative Perfusion Registry (ANZCPR) is the only multicentre CPB registry to have reported the integration of EPD. Aiming to improve the understanding and practice of CPB a series of ten publications included in this thesis addressed the application of intraoperative EPD processing from 2006 to 2023.

This thesis demonstrates a considerable undertaking of the development of intraoperative EPD processing to improve the understanding and practice of CPB. This was achieved through the development of:

- Automated generation of CPB quality indicators (QI) from electronic perfusion data to provide a process for continuous QI monitoring.
- A multicentre CPB registry to facilitate reporting and quality improvement through benchmarking (ANZCPR)
- Determining the impact of CPB practice on patient outcome (acute kidney injury) at Flinders Medical Centre
- Identification of modifiable CPB practice predictors of patient outcome (acute kidney injury and 30-day mortality) using ANZCPR multicentre registry data.

This combined body of work has contributed to international guidelines for CPB best practice, recognizing the role of EPD for quality improvement in CPB, and the importance of EPD integration into registries to improve understanding and practice through identification of modifiable factors associated with patient outcome, facilitation of continuous quality monitoring and benchmarking. This work provides the foundation for future development of an international CPB registry to further understanding and improvement of CPB practice by facilitating large international observational studies and registry-based randomized trials, leveraging the registry as a platform for data collection, randomization, and follow-up.

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Publications Included in This Thesis

Electronic data processing: the pathway to automated quality control of cardiopulmonary bypass.

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J Extra Corpor Technol. 2006 Jun;38(2):139-43. PMID: 16921687; PMCID: PMC4680750.

Continuous quality improvement of perfusion practice: the role of electronic data collection and statistical control charts.

Baker RA, **Newland RF**.

Perfusion. 2008 Jan;23(1):7-16. doi: 10.1177/0267659108093853. PMID: 18788212.

The Perfusion Downunder collaborative database project.

Newland R, Baker RA, Stanley R, Place K, Willcox TW; Perfusion Downunder Collaboration.

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Integration of Electronic Perfusion Data for Perfusion Registries.

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Developing a benchmarking process in perfusion: a report of the Perfusion Downunder Collaboration.

Baker RA, **Newland RF**, Fenton C, McDonald M, Willcox TW, Merry AF; Perfusion Downunder Collaboration.

J Extra Corpor Technol. 2012 Mar;44(1):26-33. PMID: 22730861; PMCID: PMC4557436.

Hyperthermic perfusion during cardiopulmonary bypass and postoperative temperature are independent predictors of acute kidney injury following cardiac surgery.

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Rewarming Temperature During Cardiopulmonary Bypass and Acute Kidney Injury: A Multicenter Analysis.

Newland RF, Baker RA, Mazzone AL, Quinn SS, Chew DP; Perfusion Downunder Collaboration.

Ann Thorac Surg. 2016 May;101(5):1655-62. doi: 10.1016/j.athoracsur.2016.01.086. Epub 2016 Mar 31. PMID: 27041450.

Predictive Capacity of Oxygen Delivery During Cardiopulmonary Bypass on Acute Kidney Injury.

Newland RF, Baker RA, Woodman RJ, Barnes MB, Willcox TW; Australian and New Zealand Collaborative Perfusion Registry.

Ann Thorac Surg. 2019 Dec;108(6):1807-1814. doi: 10.1016/j.athoracsur.2019.04.115. Epub 2019 Jun 22. PMID: 31238029.

The role of cardiopulmonary bypass parameters in risk prediction for 30-day mortality following cardiac surgery.

Newland RF, Baker RA.

Perfusion. 2022 Dec 22:2676591221146505. doi: 10.1177/02676591221146505. Epub ahead of print. PMID: 36547056.

Contributions To Conjoint Work Undertaken And Included In The Published Papers In This Thesis

Electronic data processing: the pathway to automated quality control of cardiopulmonary bypass.

Newland RF, Baker RA, Stanley R.

J Extra Corpor Technol. 2006 Jun;38(2):139-43. PMID: 16921687; PMCID: PMC4680750.

I led the development of the process of integration of EPD into our unit's clinical patient registry, and jointly developed with Ms R Stanley the database application and visual basic programming module used to interface between the patient data collection software and the registry to perform the integration process. Professor Rob baker and I jointly developed the conception and refinement of the CPB quality indicator definitions and the process of monitoring, and automated feedback of quality indicators to clinicians. I contributed to the development of the automated software used to collect the EPD (Data Management System (DMS) (Stockert, Munich, Germany) with Mr C Hofstetter (Program Developer, Stockert). I wrote the initial draft of the manuscript and generated all figures and jointly contributed to revised versions of the manuscript with Professor Rob Baker. I presented the paper at the CREF Cardiothoracic Surgery Symposium in San Diego, USA in 2006.

Continuous quality improvement of perfusion practice: the role of electronic data collection and statistical control charts.

Baker RA, **Newland RF**.

Perfusion. 2008 Jan;23(1):7-16. doi: 10.1177/0267659108093853. PMID: 18788212.

Professor Rob Baker is the senior author on this paper, and the manuscript was included in this thesis given that I led the development of the process of clinical quality improvement using statistical control charts as a method of data feedback to clinicians, and the organization of clinical improvement meetings. We jointly developed the conception and refinement of the CPB quality indicator definitions and the process of monitoring, and automated feedback of quality indicators to clinicians. I prepared the initial draft of the manuscript and Professor Rob Baker performed the statistics and we jointly co-authored subsequent drafts. I presented

the paper at the Australian and New Zealand College of Perfusionists Annual Scientific Meeting in Adelaide in 2008. Although I did not contribute >75% to the data analysis in the final manuscript I played a significant role in its conceptualisation, clinical application, and preparation.

The Perfusion Downunder collaborative database project.

Newland R, Baker RA, Stanley R, Place K, Willcox TW; Perfusion Downunder Collaboration. J J Extra Corpor Technol. 2008 Sep;40(3):159-65. PMID: 18853827; PMCID: PMC4680641.

I led the development of the collaborative registry application based on the dataset proposed at the initial Perfusion Downunder Meeting in 2005, which was expanded to include CPB quality metrics and calculated variables from electronic intraoperative data. I developed the initial draft for the manuscript. Professor Rob Baker provided input into the methodological approach and reviewed the manuscript. Rebecca Stanley aided in the development of visual basic programming within the database. Kathryn Place and Tim Willcox were the first Perfusionists to implement the registry in a hospital outside of Flinders Medical Centre and played a key role in providing feedback on database implementation, development and site data management, and Tim Willcox reviewed the final draft of the manuscript.

Integration of Electronic Perfusion Data for Perfusion Registries.

Newland RF, Baker RA, Barratt CA.

J Extra Corpor Technol. 2018 Jun;50(2):102-112. PMID: 29921989; PMCID: PMC6002640.

I proposed the concept of the development of a 'white paper' during a discussion with Dr Donald Likosky (custodian of the Perform perfusion registry, USA) at the Perfusion Downunder Data Managers meeting in 2016 in which he identified the need for publication for other perfusion registries to follow that allows for reproducing the process of integration of electronic perfusion data. Chris Barratt revised the existing visual basic programming module to significantly reduce the processing time requirement at the point of care. From this I developed a standalone database and programming module from which the structure and programming code could be described in the manuscript for generalisation to other

hospitals using the Connect perfusion software (LivaNova, UK). I conceptualised and developed the initial draft for the manuscript. Professor Rob Baker reviewed the subsequent drafts of the manuscript.

Developing a benchmarking process in perfusion: a report of the Perfusion Downunder Collaboration.

Baker RA, **Newland RF**, Fenton C, McDonald M, Willcox TW, Merry AF; Perfusion Downunder Collaboration.

J Extra Corpor Technol. 2012 Mar;44(1):26-33. PMID: 22730861; PMCID: PMC4557436.

Prof Rob baker is the senior author on this paper, and it is included in the thesis at his request as I was a major contributor to the development of the benchmarking methodology for the collaborative registry participants. Success was achieved and participation in the process by contributing hospitals through presentation, database modifications and reporting processes. I developed the initial draft for the manuscript. Professor Rob Baker provided input into the methodological approach and reviewed all versions of the manuscript. I presented the results of the study at the Perfusion Downunder Meeting in 2011. Carmel Fenton, Michael McDonald, Tim Willcox and Professor Alan Merry provided feedback on the final draft of the manuscript and lead the integration into clinical practice as senior clinicians from participating hospitals.

Hyperthermic perfusion during cardiopulmonary bypass and postoperative temperature are independent predictors of acute kidney injury following cardiac surgery.

Newland RF, Tully PJ, Baker RA.

Perfusion. 2013 May;28(3):223-31. doi: 10.1177/0267659112472385. Epub 2013 Jan 11. PMID: 23314194.

I conceptualised and developed the initial draft for the manuscript. Phil Tully was undertaking a PhD under the supervision of Professor Rob Baker at the time that this study was undertaken and provided consultation on the statistical approach for the analysis and reviewed the final draft of the manuscript. Professor Rob Baker provided input into the methodological approach and reviewed all drafts of the manuscript. I presented the results of the study at the Perfusion Downunder Meeting in 2012.

Low Oxygen Delivery as a Predictor of Acute Kidney Injury during Cardiopulmonary Bypass.

Newland RF, Baker RA.

J Extra Corpor Technol. 2017 Dec;49(4):224-230. PMID: 29302112; PMCID: PMC5737422.

I developed the initial draft for the manuscript. Professor Rob Baker provided input into the methodological approach and reviewed all drafts of the manuscript. I presented the results of the study at the Perfusion Downunder Meeting in 2012.

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Ann Thorac Surg. 2016 May;101(5):1655-62. doi: 10.1016/j.athoracsur.2016.01.086. Epub 2016 Mar 31. PMID: 27041450.

Professor Derek Chew provided expert advice on the statistical methodology undertaken in this study to allow for both fixed and random affects associated with integration of data from different clinical practice across multiple hospitals. I co-jointly undertook the statistical analysis with Steven Quinn from Flinders University. I developed the initial draft for the manuscript. Professor Rob Baker provided input into the methodological approach and reviewed all drafts of the manuscript. Annette Mazzone who was undertaking her PhD on the topic of acute kidney injury under the supervision of Professor Rob Baker and the other authors provided feedback on the final draft of the manuscript. I presented the results of the study at the Perfusion Downunder Meeting in 2015.

Predictive Capacity of Oxygen Delivery During Cardiopulmonary Bypass on Acute Kidney Injury.

Newland RF, Baker RA, Woodman RJ, Barnes MB, Willcox TW; Australian and New Zealand Collaborative Perfusion Registry.

Ann Thorac Surg. 2019 Dec;108(6):1807-1814. doi: 10.1016/j.athoracsur.2019.04.115. Epub 2019 Jun 22. PMID: 31238029.

Richard Woodman and Mary Barnes from Flinders University provided expert advice on the statistical methodology undertaken in this study. I conceptualised and developed the initial draft for the manuscript. Professor Rob Baker provided input into the methodological approach and reviewed the initial and subsequent drafts of the manuscript. All authors reviewed the final draft of the manuscript. I presented the results of the study at the Perfusion Downunder Meeting in 2017.

The role of cardiopulmonary bypass parameters in risk prediction for 30-day mortality following cardiac surgery.

Newland RF, Baker RA.

Perfusion. 2022 Dec 22:2676591221146505. doi: 10.1177/02676591221146505. Online ahead of print. PMID: 36547056.

I conceptualised and developed the initial draft for the manuscript. Feruza Kholmurodova from Flinders University provided expert advice on the statistical methodology undertaken in this study. Professor Rob Baker provided input into the methodological approach and reviewed the final draft of the manuscript.

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Rewarming Temperature During Cardiopulmonary Bypass and Acute Kidney Injury: A Multicenter Analysis.

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Contextual Statement

A1. Introduction

A perfusionist is a highly specialized healthcare professional who plays a crucial role in cardiac surgery and other medical procedures that involve the use of cardiopulmonary bypass (CPB) or extracorporeal circulation. The primary responsibility of a perfusionist is to operate the heart-lung machine, which temporarily takes over the functions of the heart and lungs during surgery, allowing the surgeon to perform procedures on a still and bloodless field. They also manage the administration of drugs and blood products that may be necessary to support the patient's cardiovascular, hematological and anaesthetic requirements, as well as providing myocardial and cerebral protection during periods of ischemia. Perfusionists are responsible for regulating the patient's body temperature during CPB to alter metabolic rate and minimise ischemic injury. The perfusionist is an integral member of the multidisciplinary cardiac surgical intraoperative team, which requires close collaboration with anaesthetists, nurses and operating room technicians to optimize safety and patient outcomes.

One of the unique opportunities for perfusionists is their involvement in collecting intraoperative data. Since they closely monitor and maintain various physiological parameters throughout the procedure, they have the opportunity to gather valuable data related to the process and management of CPB. This intraoperative data includes information on blood gases, hemodynamic parameters, temperature, oxygen delivery and other relevant metrics including CPB interventions. The value of this data is in its potential to improve both the understanding and improvement of CPB and outcomes for patients. This relies on not only the data collection process, but importantly the data accuracy and the process of feedback to clinicians and other stakeholders.

The use of electronic perfusion data (EPD) collection systems as an integral component in the modern clinical practice of CPB during cardiac surgery has evolved slowly over the last 2 decades, and the potential value of these systems has been underrecognized. Prior to work undertaken in this thesis, the accuracy of recording intraoperative data had been examined in anaesthetic records, where computer-generated records were compared with handwritten

data, demonstrating normalisation toward expected rather than accurate values (Cook, et al., 1989; Hollenberg, et al., 1997; Thrush, 1992). These early studies found that handwritten intraoperative records should not be used as a source of data for research purposes.

The intraoperative EPD collected provide an enormous resource for undertaking observational studies to provide better understanding of the practice of CPB, however the application of data for this purpose has been limited. Potentially the most important influence that electronic intraoperative data collection may have on clinical practice is the identification of modifiable predictors of patient outcome, and with the integration of EPD into perfusion registries facilitation of quality improvement through benchmarking. To date, the Australian and New Zealand Collaborative Perfusion Registry (ANZCPR) is the only multicentre perfusion registry to have reported the integration of EPD.

A1.1. Electronic Perfusion Data Collection.

EPD software was introduced into clinical practice at Flinders Medical Centre in the year 2000. At that time, the objective of EPD software was to automate recording of intraoperative patient physiological data (blood pressures, body temperature, heart rate, etc) together with heart lung machine data (blood flows, CPB circuit pressures and temperatures, gas flows, etc) and data from monitoring devices (blood gas machine, activated clotting time, cerebral saturation monitor, etc). Prior to the introduction of this software required the perfusionist to manually record these data on a paper chart, EPD software provided the opportunity to reduce the burden of manual recording and allow focus on more important clinical tasks. The benefits of implementation of EPD software reported in the literature were limited, however our group were able to demonstrate that the EPD software produced more accurate records in comparison to the traditional handwritten report (Ottens, et al., 2005). Prior to the introduction of EPD our unit had a clinical registry, which captured a record of each patients perioperative journey, including preoperative risk factors, some intraoperative variables relevant to cardiac surgery (such as CPB time, aortic cross clamp time, blood gas and cardioplegia values, etc), details of the type of surgery, and postoperative outcomes, and we recognised the value in developing a method of data transfer from the EPD software into the unit clinical registry. The appeal of automation of data transfer at the time was focused on

improving accuracy of information through reducing transcription error, reducing the burden of manual data entry for clerical staff within the unit, and as a data source for future research.

A1.2. Outcomes, understanding and improvement of cardiopulmonary bypass.

For over 50 years, CPB has been a widely utilised method in cardiac surgery, with thousands of successful procedures performed daily worldwide. While most patients tolerate CPB well, both subtle and clinically apparent adverse effects may arise postoperatively, such as excessive bleeding, systemic inflammation, stroke, neuropsychological dysfunction, and other organ injury. The techniques for CPB evolved from physiologic principles, utilizing available materials, animal testing, and subsequent clinical trials. Over the last five decades, advancements in equipment and techniques have improved morbidity and mortality (Murphy, et al., 2009). Although these changes have been influenced by logical principles, lab investigations, and clinical studies, they are sometimes driven by personal biases, clinical impressions and experiences, and industry pressures, leading to significant variations in CPB practices among different teams (Bartels C, et al., 2002). Over the period of undertaking the studies included in this thesis, the ability to make strong recommendations regarding the optimal conduct of CPB have been limited by the available evidence. In 2002, Bartels et al aimed to evaluate the amount and quality of evidence supporting principles that were being applied for CPB performance and concluded; '*The scientific data concerning the effectiveness and safety of key principles of cardiopulmonary bypass are insufficient in both amount and quality of scientific evidence to serve as a basis for practical, evidence-based guidelines'* (Bartels C, et al., 2002). More recently, professional societies have convened expert panels to write clinical practice guidelines based on evidence using a more rigorous and structured methodology. In 2007, guidelines related to blood management and transfusion for cardiac surgery were written with collaboration from the Society of Thoracic Surgeons (STS) and The Society of Cardiovascular Anesthesiologists (SCA) (Ferraris, et al., 2007), and an update to these guidelines was written in 2011, which included collaboration with the American Society of Extracorporeal Technology's (AmSECT's) International Consortium for Evidence Based Perfusion Committee (Ferraris, et al., 2011), and again in 2021 (Tibi, et al., 2021). The STS, SCA, and AmSECT also have collaborated on guidelines for temperature and anticoagulation

management during CPB (Engelman, et al., 2015; Shore-Lesserson, et al., 2018;) and for the prevention of AKI (Brown, et al., 2022). The 2019 European Association for Cardio-Thoracic Surgery (ECTS)/European Association for Cardiothoracic Anaesthesiology (EACTA)/European Board for Cardiovascular Perfusion guideline on CPB in adult cardiac surgery, includes a broad structured review of the available literature, and where evidence is lacking, expert consensus from all 3 disciplines is provided (Wahba, et al., 2020). The European guideline provides 113 recommendations. Forty-three (38%) are class I, 32% class IIa, 19% class IIb, and 10% class III. Only about 6% are supported by class A evidence, whereas 50% are supported by class B evidence and 44% by class C evidence. Of the 43 class I indications, , only 4 are supported by class A evidence and 4 by class B evidence (Hessel & Groom, 2021). These findings demonstrate that a need for high quality clinical studies in CPB still remains. Specifically, 2 key messages can be derived that are relevant to the work undertaken in this thesis;

- Observational data and the infrastructure to support observational studies such as registries have a significant role in the development of contemporary CPB practice recommendations.
- Infrastructure to support the conduct of multicentre RCT's could have a significant impact on providing high quality evidence to improve the strength of CPB practice recommendations.

Outcomes of CPB can be classified as either process (care based) or clinical (patient based). Comprehensive quality indicators that quantify specific processes of care are an important component of the assessment of quality of care (Shahian, et al., 2007). Essentially, CPB management factors can be classified broadly as blood pressure, flow, temperature, and composition. Blood composition factors incorporate cellular composition as well as electrolyte, glucose, lactate, and blood gas values, gaseous and particulate emboli and inflammatory factors. To date, CPB quality indicators that encompass modifiable CPB management factors that have an association with clinical outcome have not been well defined. Furthermore, much of the existing literature that has focused on the relationship between CPB practice and outcomes have been based on intraoperative data that has been collected using handwritten recording, since studies utilizing EPD are limited. Two single centre studies have evaluated the relationship between CPB and AKI which have incorporated EPD. Haase et al aimed to identify whether intraoperative hypotension, anaemia, or their

combination, red blood cell transfusion or vasopressor use are independent risk factors for postoperative AKI from 920 consecutive cardiac surgery patients undergoing CPB. Independent risk factors for AKI were haemoglobin concentration and red blood cell transfusion. Mean arterial pressure during CPB alone was not independently associated with AKI, however, In patients with severe anaemia (<25th percentile of lowest haemoglobin), the independent effect of hypotension (>75th percentile of area under the curve MAP <50 mmHg) on AKI was more pronounced [OR 3.36 (95% CI 1.34–8.41); P ¼ 0.010] (Haase, et al., 2012). In a study using data from ANZCPR, Turner et al evaluated the influence of length of time the perfusion flow was <1.6 L/min/m^2 and perfusion pressure was < 50mmHg on postoperative AKI as the primary outcome, and on the incidence of stroke or mortality as secondary outcomes. Using a multivariate regression model adjusting for patient preoperative risk factors and intraoperative CPB duration, neither of the pressure or flow metrics were found to be independent predictors of AKI (Turner, et al., 2021).

Documentation of care processes is said to result in healthcare quality improvement as it helps those involved in patient care to develop a shared understanding of care to be provided. It serves as a reference point, aiding in the identification of areas that warrant improvement in the delivery of care. The primary objective is to guarantee that patient services align with current clinical knowledge, thereby ensuring the achievement of desired health outcomes. The impetus for adapting and changing any given care process specification arises from deviations observed in the provision of care (referred to as variation), which prompts the need for adjustments to maintain alignment with established quality standards. (McLachlan, et al., 2020). Considered broadly, data detailing the role played by CPB techniques and equipment in the treatment and outcomes of patients undergoing heart surgery are often limited, lacking detailed information about what is defined as "current" CPB practice; however, authors frequently refer to the patient's treatment during CPB as "conventional bypass" (Likosky, et al., 2018). One approach to determine the impact of CPB on patient outcome has been to compare CPB with ‘off pump’ surgery for coronary artery bypass graft procedures (Lamy, et al., 2017). Frequently these comparative studies offer scant or no information about the CPB equipment and techniques utilised; for example, roller vs. centrifugal pump, cardioplegia techniques, volume control, blood control, and glucose control (Likosky & Baker, 2017). As a result, there are less possibilities to: 1) assess the research

behind the published literature; and 2) enhance CPB practice. The conduct of CPB to assure reproducibility of findings is not subject to minimum reporting requirements specified by peer-reviewed journals, either within or outside the perfusion specialty. The benefits of gathering data through a multicentre CPB registry for reporting purposes has been demonstrated in a paper which analysed prospectively collected data among isolated CABG procedures submitted to either the Australian and New Zealand Collaborative Perfusion Registry (ANZCPR) or Perfusion Measures and outcomes (PERForm) Registry across 47 centres (ANZCPR: 9; PERForm: 38) in 2015 (Likosky, et al., 2018). The report found significant centres variation in nearly all aspects of the equipment and conduct of CPB in both registries. Whilst this study was able to demonstrate that the concept of 'standard CPB practice' as commonly referred to is a misnomer, it also highlights the potential to focus on standardization of practice through benchmarking as a process of practice improvement. A limitation of this paper was that EPD is not collected in the PERForm registry, therefore EPD variables were reported for ANZCPR data only. The authors reported that '*Development of greater integration of electronic perfusion data into perfusion registries would facilitate clearer understanding of the variation of physiological variables such as arterial pressure and flow rates*'. Furthermore, the study did not evaluate the impact of the equipment and practice of CPB on clinical outcomes. The authors concluded that *'There is a need to develop and implement minimal criteria for reporting on the equipment and practice of CPB to strengthen the existing evidence base.'* Participation in multicentre registries offers a solution to bridge this gap, particularly with integration of EPD.

In the realm of clinical practice, clinicians are dedicated to refining their methods and interventions with the goal of optimizing outcomes while minimizing adverse effects. This pursuit inevitably entails introducing changes to established practices. To substantiate the effectiveness of such clinical changes, a systematic and scientific approach is essential (Newland & Baker, 2009). The decision to implement change often arises when new products or techniques emerge, which show potential for enhancing outcomes. As clinicians, our challenge lies in assessing whether a proposed change is advantageous for our patients by assimilating and evaluating existing evidence. However, the evaluation of evidence for practice change may encounter limitations in both quality and quantity. In cases where evidence is inconclusive, there exists an opportunity to contribute to the body of evidence

through research, aiding in the definition of best practices. Establishing a benchmark for our current processes is crucial for defining improvement in practice, a task accomplished through the implementation of clinical audits. The cyclical process of data collection and analysis inherent in audits lays the groundwork for continuous quality improvement. Once clinical improvement is attained, the knowledge gained can be disseminated through publication, extending the impact of the achieved advancements. These processes are applicable to various aspects of clinical practice, encompassing changes in products or management techniques. Routine data collection at the point of care presents the opportunity to audit existing practices, ensuring adherence to established best practice guidelines. Analyzing audit data allows for the identification, enhancement, and standardization of compliance with care process guidelines. Despite the current limitation of evidence-based guidelines for optimal CPB, there exists the opportunity to implement quality assurance and improvement processes based on institutional process of care guidelines. The inability to demonstrate cause and effect relationships in observational studies, together with the low frequency of adverse clinical outcomes following cardiac surgery, limit the usefulness of clinical endpoints as metrics for quality improvement studies. The numbers required to achieve adequate statistical power in such studies may result in the introduction of bias associated with changes in practice over time (Newland & Baker, 2009).

Perfusionists are well placed within the cardiac surgical community to engage in, and report change in a scientific manner, for the dissemination of the results of improvement initiatives, to strengthen the CPB knowledge base, and to highlight the importance of our care. This opportunity is underpinned by our potential to harness the data that we have available to us and participate in registries. As a perfusionist I have endeavored to embrace this ethos in the development of novel methods of data collection, processing and application. Aiming to improve the understanding and practice of CPB a series of ten publications is included in this thesis, which address the application of intraoperative EPD processing from 2006 to 2023.

A2. Contextual statement for Chapter 1.

The first section of this thesis focusses on the development of a novel method to facilitate automated generation of CPB quality indicators (QI) from electronic perfusion data and to provide a process for continuous monitoring of QI parameters.

Since the EPD software was not designed to facilitate integration with other databases, we needed to develop two methods to integrate the EPD data into our clinical registry. Firstly, we needed access to the recorded data from each CPB procedure, and secondly a method to automate the import of the data. With both requirements in mind, we developed a method of manually importing the collected data from data files stored in text format, that were routinely transferred from the heart lung machine computer to the server computer following an individual procedure into a Microsoft Access (MS Access) database. Furthermore, we were able to develop a series of data queries that would create calculated variables of interest and store the data in our clinical registry. A significant achievement in the automation of the data import and processing of the data using the queries created in MS Access was through the development of a visual basic programming module. The module was able to be activated through the click of a button in our clinical registry, making the process accessible at the point of care.

The first paper in this thesis reports the achievement of these two objectives, which provided the foundation for the following studies. The intraoperative electronic data collected provided a new resource for undertaking observational studies to provide better understanding of the practice of CPB. Additionally, we were able to create a dataset of perfusion variables and quality indicators for CPB procedures. This provided both immediate automated performance feedback to the perfusionist following CPB procedures, and direction of performance improvement initiatives via retrospective or prospective data analysis as part of a continuous quality improvement process. The idea for providing automated quality indicators built upon the work of Dickinson et al, in which they describe the collection and benchmarking of seven CPB process indicators from manual records; 1)

lowest sustained mean arterial pressure, 2) lowest sustained cardiac index, 3) lowest sustained mixed venous oxygen saturation, 4) lowest sustained hematocrit, 5) lowest activated clotting time, 6) highest sustained arterial blood temperature and 7) average sodium bicarbonate administered (Dickinson, et al., 2004). The authors reported that analysis of hospitals designated by Blue Cross of California as 'Centers of Expertise' revealed statistically significantly greater compliance ($p < 0.05$) in all but one CPB indicator. We sought to improve this concept through an automated approach to providing CPB quality feedback. To date, a dedicated method of continuous collection and utilization of EPD has not been reproduced in the literature. In 2006 I received the Utley Award at the San Diego CREF Cardiothoracic Surgery Symposium for this paper, which recognizes excellence in scientific research and presentation and is awarded for the best oral abstract presented. This paper has been cited in papers focusing on improving CPB safety and quality of care (Kurusz, 2011; Stammers, et al., 2009) and the 2019 EACTS/EACTA/EBCP guidelines on cardiopulmonary bypass in adult cardiac surgery recognizing that electronic charting should lead to participation in QI initiatives and that response feedback systems can lead to improved care (Wahba, et al., 2020).

The second paper provided the first evidence that the process of automated generation of QI and feedback of the data to perfusionists resulted in significant clinical improvement, as defined by adherence to practice protocols and reduction in practice variation. We defined several CPB QI based on the cumulative time during CPB (cardiac index < 1.6 l/min/m^2, mean arterial pressure < 40 mmHg, venous saturation < 60%, arterial blood temperature of > 37.5^{0}C) or incidence (minimum pCO_2, maximum pCO_2, and minimum pO_2 and minimum haemoglobin). Patients undergoing CPB were divided into three consecutive groups: The first group consisted of 363 patients who had CPB procedures immediately prior to the introduction of automated QI feedback (Group 1). The second group underwent surgery in the period between the introduction of automated QI feedback and the introduction of our CQI program (Group 2 = 253 patients), and Group 3 (n=363 patients) were operated on after the introduction of the CQI program. The CQI program involved the establishment of a feedback mechanism to promote group discussion. Quality performance review meetings

were introduced to discuss variation in practice and possible practice changes that were identified from the QI data. The paper was able to demonstrates that the implementation of a CQI process for CPB based on integration of EPD can improve adherence to institutional processes of care. This paper highlighted the importance of providing QI data to the perfusionist team in a manner which facilitated continuous quality improvement processes, such as statistical control charts as a tool for the team to visualize the data and develop clinical improvement initiatives. Subsequently, Stammers et al were able to demonstrate that the process of software-based generation of CPB QI using the Stockert Data Management System could be used to reduce variability amongst perfusionists and assure compliance with policies and standards of care (Stammers, et al., 2009). The authors created a CPB data source using a spreadsheet format to serve multiple administrative functions including patient and procedure sequencing, predictive algorithms for yearly caseload, summary statistics, and inter-perfusionist comparison. This data source was then linked to EPD to determine individual perfusionists compliance with policies and standards of care.

Our papers most significant citing was the 2019 EACTS/EACTA/EBCP guidelines on cardiopulmonary bypass in adult cardiac surgery recognizing that electronic charting should lead to participation in QI initiatives and that response feedback systems can lead to improved care (Wahba, et al., 2020). This work also prompted the vendors of the EPD software system (Stockert, Munich, Germany) to incorporate the ability for clinicians to define CPB quality indicators within the software and utilize these parameters for quality improvement.

A3. Contextual statement for Chapter 2.

The second part of this thesis describes the development of a multicentre CPB registry uniquely integrating EPD to facilitate reporting and quality improvement through benchmarking.

Clinical registries assume a crucial role in monitoring disease prevalence and patterns in healthcare delivery, serving as a source of real-world evidence regarding the impact of treatment modalities and service delivery models on health outcomes (Hoque, et al., 2016). There is a growing trend in utilising clinical registries for quality improvement initiatives, aiming to enhance healthcare processes, ensure adherence to clinical practice guidelines and

standards, and mitigate the overall cost of care provision. These registries typically function by providing participating hospitals and clinicians with detailed information on clinical care, compliance with evidence-based guidelines, and patient-reported outcomes. Beyond their role in healthcare improvement, clinical registries also play a pivotal part in medical research. The data housed within these registries offer an advantageous platform for conducting randomized clinical trials, substantially reducing the time and costs associated with prospective data collection. Real-world data collected through registries contributes significantly to research endeavors by generating hypotheses, facilitating descriptive studies, and supporting health service research. The integration of biomarker, and imaging information with registry data further enhances research opportunities (Hoque, et al., 2016). Clinical registries not only address research questions impractical or unethical for randomized clinical trials but also provide a foundation for the execution of registry-based randomized clinical trials.

Our recognition of the potential for the application of EPD gave rise to an initiative to create a multicentre registry, with participation leveraged through our involvement in the leadership of the Perfusion Downunder Meeting, held annually in either Australia or New Zealand. In 2006 an initial dataset was defined comprising of patient preoperative factors, procedural data and outcomes, with definitions based on the Australian & New Zealand Society of Cardiac & Thoracic Surgeons (ANZSCTS) Database (Dinh, et al., 2009-2010). Through our successful integration of EPD at Flinders Medical Centre, we were able to gain support for the viability of creating a dedicated multicentre CPB focused registry. The Perfusion Downunder Collaboration was formed by interested participants and a registry developed at Flinders Medical Centre to support the objectives of the collaboration; to promote the reporting and understanding of the effect of CPB on patient outcomes through encouraging evidence-based practices, quality assurance, quality improvement and research. The development of the registry is reported in the third paper in this thesis, named at the time as the Perfusion Downunder Collaborative Database. At the time of publication, this work represented a significant achievement; the development of the first multicentre CPB focused registry, and furthermore, that it included EPD recorded automatically at the point of care highlighting the benefits of electronic CPB data collection as a research and clinical improvement tool within a collaborative network. In a comparison of initial data collected with data collected

regionally in the ANZSCTS database we were able to demonstrate concurrent validity (Tuble, 2011). This paper was cited in a publication validating the methodological approach and initial findings of the PERForm Registry, to highlight the benefit of collaborative registries to drive CPB quality assurance and improvement targets (Paugh, et al., 2012).

Through our engagement with managers of other CPB registries internationally, we recognized the need to publish in detail our method of EPD data integration for other registries to be able to reproduce. This work is presented in the fourth paper, with the visual basic libraries and code required listed in the appendices 1-5 of this thesis. Although this work provides an original contribution to the knowledge base by providing the opportunity for integration of EPD into other perfusion registries, to date, the method has not been reproduced to our knowledge. This highlights the need for further development of solutions that can be provided to CPB clinicians and other stakeholders that can be more easily operationalised without the need for specific knowledge and/or abilities. An example of a registry which could benefit from EPD integration is PERForm, which is embedded in the Michigan Society of Thoracic & Cardiovascular Surgeons Quality Collaborative and is endorsed by the American Society of Extracorporeal Technology. The PERForm registry is the largest outside Australia and New Zealand and provides participants with quarterly benchmark reports reflecting CPB practices. Participating PERForm centres can compare discrete perfusion practices to other institutions and identify the relationship between these practices and clinical outcomes. Additionally, centres may use these data to support quality assurance and improvement (Likosky, et al., 2024). The ANZCPR participants have similarly benefited from the process of registry data collection and reporting, with the integration of electronic perfusion data providing unique insights into CPB practice and opportunities for improvement. The manuscript, Integration of Electronic Perfusion Data for Perfusion Registries, was selected for the Journal of Extracorporeal Technology Technique Article Award in 2019. The Technique Award is presented to the Perfusionist who has published an exceptional technique article in the Journal. This papers most significant citing was the 2019 EACTS/EACTA/EBCP guidelines on CPB in adult cardiac surgery recognizing that electronic charting should lead to participation in QI initiatives and national and/or international registries and that response feedback systems can lead to improved care (Wahba, et al., 2020).

Benchmarking of clinical practice is an important objective for registries, and the ability for our registry to integrate EPD provided a unique opportunity for the collaboration to define and report the incidence of CPB quality indicators. The fifth paper in this thesis reports data collected using the collaborative database from 5465 procedures performed in 8 Australian and New Zealand cardiac centres between March 2007 and February 2011. At the Perfusion Downunder Meeting in 2010, it was agreed by consensus, to report QIs for glucose level, oxygenator arterial outlet temperature and pCO_2 management during cardiopulmonary bypass. The values chosen for each QI were: blood glucose ≥ 4 mmol/l and ≤ 10mmol/l; arterial outlet temperature ≤ 37^{o}C; and arterial blood gas pCO_2 ≥ 35 and ≤45 mmHg. The QI data were used to derive benchmarks to identify the incidence of QIs at the best performing centres. This was the first multicentre report of these CPB QI in the literature, indicating significant variation in practice. The incidence of the blood glucose QI ranged from 37% to 96% of procedures, arterial outlet temperature 16% to 98% of procedures, while the arterial pCO_2 QI occurred in 21 to 91%. This work was seminal in demonstrating that EPD integration could provide a platform for improving the quality of several key aspects of CPB by providing a baseline for the implementation of multicentre continuous quality improvement processes for perfusion practice and cited in the 2019 EACTS/EACTA/EBCP guidelines on cardiopulmonary bypass in adult cardiac surgery (Wahba, et al., 2020).

The introduction of this process has had a significant impact on practice for sites contributing to the ANZCPR. As the Data Administrator for the ANZCPR, I generate in collaboration with Prof Rob Baker an annual report for participating sites which provides Perfusionists the opportunity to reflect on their sites detailed practice and performance data. The 2022 annual report is contained in this thesis as appendix 6. Additionally, sites are provided with an executive summary report for dissemination to key institutional clinical and administrative stakeholders. Figures 1-3 illustrate the overall improvement in CPB practice following the introduction of benchmarking in 2012. Importantly what is evident from these figures is that improvement has been maintained following the introduction of ongoing performance data feedback, demonstrating improvement and standardization in practice. Other than survey data (Searles, et al., 2020), provision of multicentre clinical variability feedback data based on registry integration of EPD is unique to the ANZCPR.

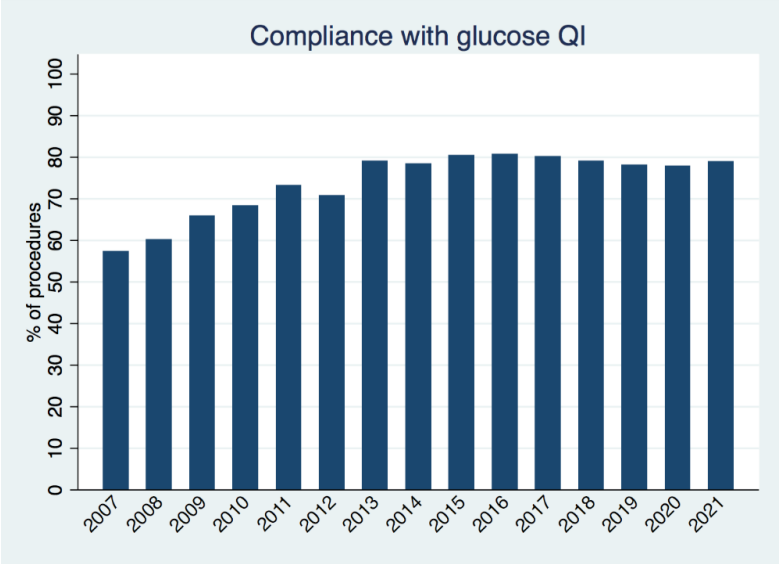

Figure 1. Compliance with CPB blood glucose ≥ 4 mmol/l and ≤ 10mmol/l at sites participating in the ANZCPR each year. Improvement and standardization of practice can be seen after the introduction of benchmarking in 2012. CPB blood glucose may be influenced by patient factors such as diabetes, surgical stress response, or management factors such as addition of glucose in IV solutions. Improvement after benchmarking was seen due to removal of glucose from the cardioplegia solution at one site, followed by a period of stability which likely reflects the challenges associated with CPB management of blood glucose related to patient factors.

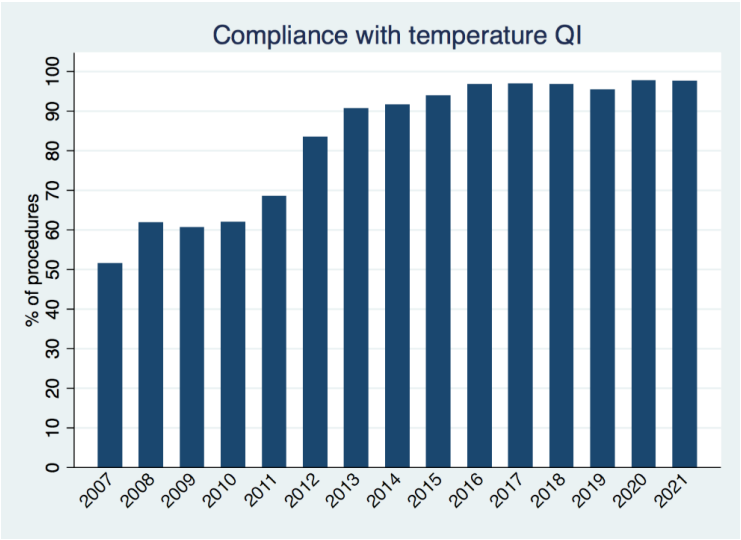

Figure 2. Compliance with arterial outlet temperature ≤ 37°C at sites participating in the ANZCPR each year. Improvement and standardization of practice can be seen after the introduction of benchmarking in 2012. Since this QI is under direct control of the perfusionist through regulation of the arterial outlet temperature, relatively greater compliance can be seen with this QI as compared with other QI's that are also influenced by patient factors.

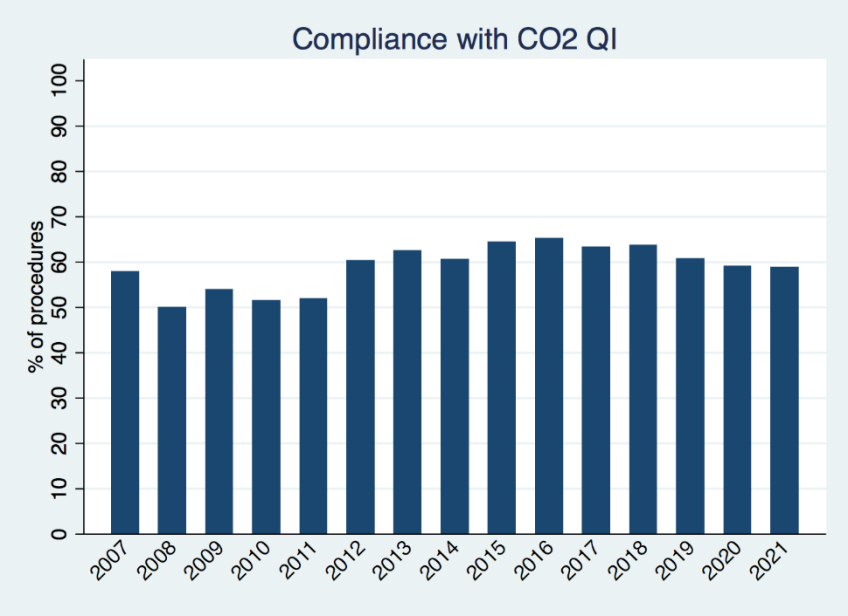

Figure 3. Compliance with arterial blood gas pCO_2 ≥ 35 and ≤45 mmHg at sites participating in the ANZCPR each year. Improvement and standardization of practice can be seen after the introduction of benchmarking in 2012. This QI shows improvement following benchmarking, however compliance is lower compared with other QI's. This is likely to reflect that compliance requires all arterial blood gas pCO_2 sample results to be within the range ≥ 35 and ≤45 mmHg, which is a challenging management objective considering that the arterial blood gas pCO_2 may be influenced by patient factors such as metabolic derangements, temperature, and metabolic demand.

Aside from benchmarking of CPB QI's specifically, more broadly the sharing of the ANZCPR data to participants through the annual reports has had a significant impact on the understanding of CPB within the ANZCPR community and the data has also been presented at international scientific meetings. In the most recent annual report, we have now successfully collected data from over 46,000 patients undergoing CPB over 9 different hospitals, since the inception of the registry in 2007. The information outlined in the yearly multicentre report affords individual units the opportunity to assess their performance across various dimensions within the collaborative dataset for the most recent data collection period. This enables a contemporaneous evaluation of their practices in comparison to other collaborative partners. Data is presented for each site for the collection period (calendar year). Sites are de-identified, with each site having access to their specific site code which is randomly allocated each year. Periodically we provide each participating site a report of their

own registry data for the last 10 years of their participation. This allows sites to reflect on changes in their practice over time and contrast this data to the multicentre report. The benefits of measuring clinical practice and reviewing performance have recently been highlighted by the Australian Commission on Safety and Quality in Health Care demonstrating the need for clinical registries such as the ANZCPR. Australia faces constraints in its ability to gauge and oversee the extent to which healthcare contributes to patient well-being and aligns with evidence-based practices. Presently, only a limited set of data collections capture and report data on processes and outcomes for particular clinical conditions or interventions. This creates substantial voids in Australia's existing health information, leaving questions about the suitability and efficacy of specific healthcare interventions unanswered (ACSQHC, 2014). The establishment of national clinical quality registries provide a cost-effective strategy to bridge these gaps (Larsson, , et al., 2012). As an outcome of the work undertaken as part of this thesis, the effectiveness of the ANZCPR registry can be measured through the interest arising from our endeavors, and the engagement from multidisciplinary colleagues including perfusion, surgery, anesthesia, nursing, intensive care, and administration. This collective interest serves to deepen our understanding and enhance clinical practices, ultimately leading to improved outcomes for the patients who have placed their trust in our care.

Whilst these data provided a platform for the improvement of both CPB process and patient outcomes, the potential for increasing the understanding of the impact of CPB practice specifically on patient outcomes was the next objective and forms the third section in this thesis; Use of EPD to demonstrate impact of CPB practice on patient outcome (acute kidney injury) at Flinders Medical Centre (FMC).

A4. Contextual statement for Chapter 3.

Initially, we focused on acute kidney injury (AKI) following CPB as an endpoint of interest given its association with increased mortality, requirement for dialysis, and longer intensive care unit (ICU) and hospital length of stay (Pickering, et al., 2015), and due to its relatively greater frequency in comparison to other endpoints such as stroke or mortality following cardiac surgery (Turner, et al., 2021). The first study of patient outcomes was undertaken with data from FMC focusing on the role of hyperthermic perfusion during CPB, defined as the duration

of oxygenator arterial outlet temperature > 37°C on AKI following cardiac surgery using the RIFLE (renal Risk, Injury, Failure, Loss of renal function and End-stage renal disease) criteria. This study was undertaken with data from FMC following change in our protocol for maximum arterial outlet temperature during rewarming which was reduced from 37.5°C to 37°C in October 2009. This protocol change was based on evidence that rewarming was an independent risk factor for renal injury, however evidence to identify hyperthermic perfusion as a risk factor had not been reported. We had also previously shown that the arterial CPB blood temperature was 0.5°C higher than the heart lung machine measured temperature at 37°C (7). Using a multivariate logistic regression model, data from 1393 consecutive adult patients undergoing isolated on pump coronary artery bypass graft (CABG), valve repair and/or replacement and valve/CABG procedures identified the following predictors of AKI; CPB hyperthermia (Odds ratio [OR] 1.03 per minute increase [95% confidence interval (CI) 1.01-1.05]; P = 0.01), ICU admission temperature ([OR] 1.44 per degree increase [(CI) 1.13-1.85]; P < 0.001), minimum CPB haemoglobin ([OR] 0.83 per g/dl increase [(CI) 0.71-0.97]; P = 0.02) use of intra-aortic balloon pump ([OR] 2.69 [(CI) 1.24-5.82]; P = 0.01) and ICU readmission ([OR] 3.13 [(CI) 1.73-5.64]; P < 0.001). To contextualize these results, we would expect to see variables such as minimum CPB haemoglobin (Habib, et al., 2005) and use of intra-aortic balloon pump as predictors of AKI, however this is the first study to provide evidence to identify duration of arterial outlet hyperthermia as an independent predictor of AKI following cardiac surgery using CPB. The result translated to a 34% increase in odds for AKI with every ten minutes spent >37^{o}C and provides a modifiable CPB practice variable to guide improvement of CPB. In 2017 I received the Utley Award at the San Diego CREF Cardiothoracic Surgery Symposium for this work, which recognizes excellence in scientific research and presentation. In August 2015 the Society of Thoracic Surgeons (STS), The Society of Cardiovascular Anesthesiologists (SCA), and The American Society of ExtraCorporeal Technology (AmSECT) published Clinical Practice Guidelines for CPB focusing on temperature management during CPB, and made a class 1, level C recommendation that arterial outlet temperature should be limited to below 37°C to avoid cerebral hyperthermia (Engelman, et al., 2015). More recently in 2022 the paper was cited in 'The Society of Thoracic Surgeons/Society of Cardiovascular Anesthesiologists/American Society of Extracorporeal

Technology Clinical Practice Guidelines for the Prevention of Adult Cardiac Surgery-Associated Acute Kidney Injury' (Brown, et al., 2022).

The second study in this section focused on the role of low oxygen delivery indexed by body surface area (DO_2i) during CPB and its association with an increase in the likelihood of AKI, with critical thresholds for oxygen delivery previously reported to be 262-272 ml/min/m^2. In 2005, Ranucci et al identified that nadir DO_2i was associated with the development of AKI postoperatively in 1048 patients undergoing coronary revascularization with CPB, however the finding in this sentinel paper that had significant impact on the understanding and conduct of CPB was the identification of a threshold of DO_2i, below which the likelihood of AKI increased significantly (Ranucci, et al., 2005). The value of this initially reported threshold was 272 ml/min/m^2 for the development of acute renal failure requiring renal replacement therapy and peak postoperative serum creatinine levels. In 2011, this finding was supported by De Somer et al who reported that a nadir DO_2i level < 262 ml/min/m^2 was independently associated with AKI (De Somer, et al., 2011). Since evidence of a threshold of oxygen delivery during CPB below which the risk of AKI was increased was limited, we aimed to explore whether a relationship existed for oxygen delivery during CPB, in which the integral of amount and time below a critical threshold, is associated with increased incidence of AKI. At the time that the study was undertaken, we harnessed oxygen delivery data collected from a point of care monitor (M4 monitor (Spectrum Medical, Gloucester, UK)) utilized routinely for CPB procedures at FMC. The area under the curve (AUC) with DO_{2i} during CPB above or below 270 ml/min/m^2 was calculated in 210 patients as a metric of oxygen delivery. To determine the influence of low oxygen delivery on AKI, a multivariate logistic regression model was developed including AUC<0, Euroscore II to provide preoperative risk factor adjustment, and incidence of red blood cell transfusion to adjust for the influence of transfusion. Having an AUC<0 for an oxygen delivery threshold of 270 ml/min/m^2 during CPB was an independent predictor of AKI, after adjustment for Euroscore II and transfusion (OR 2.74, CI (1.01-7.41), p=0.047). This means that on average, patients having an AUC<0 for an oxygen delivery threshold of 270 ml/min/m^2 during CPB were 2.74 times more likely to develop AKI, after accounting for the impact of patient risk factors and blood transfusion. These results increased the existing evidence that a relationship exists for oxygen delivery during CPB, in

which exposure below a critical threshold is associated with the incidence of postoperative AKI. Furthermore, this was the first study to utilize electronic intraoperative CPB data on oxygen delivery to demonstrate a relationship with AKI. The manuscript, 'Low Oxygen Delivery as a Predictor of Acute Kidney Injury During Cardiopulmonary Bypass, was selected for the 2018 Journal of Extracorporeal Technology Research Article Award. The paper was also cited in The Society of Thoracic Surgeons/Society of Cardiovascular Anesthesiologists/American Society of Extracorporeal Technology Clinical Practice Guidelines for the Prevention of Adult Cardiac Surgery-Associated Acute Kidney Injury (Brown, et al., 2022).

A5. Contextual statement for Chapter 4.

Expanding on the work from our single centre outcome studies, the next three papers provide the final section of this thesis; Use of EPD to identify modifiable predictors of CPB practice on acute kidney injury and 30-day mortality using multicentre registry data.

The first paper in this section represents the progression of the single centre study which evaluated the role of hyperthermic perfusion in AKI. At the time of publication, a number of other modifiable CPB related factors had been identified to be associated with AKI, including oxygen delivery and CO_2 production (De Somer, et al., 2011; Ranucci, et al., 2005), hemodilution and red blood cell transfusion (Habib, et al., 2005; Ranucci, et al., 2015; Rasmussen, et al., 2020), and mean arterial pressure (Kanji, et al., 2010; Haase, et al., 2012). Although our single centre study reported that the duration of hyperthermic perfusion during CPB was found to be a predictor of AKI, the influence of temperature ranges below 37°C had not been reported, nor had the study been reproduced. Using multicentre data from the collaborative database provided the opportunity to test the hypothesis that patients exposed to higher rewarming temperatures during CPB would have an increased incidence of AKI following cardiac surgery with an increased sample size and generalizability. The methodological approach in this study was to firstly to estimate a propensity score for each patient using logistic regression to determine the predicted probability of hyperthermic perfusion to create a subgroup of propensity matched patients. Secondly, to determine the

influence of hyperthermic perfusion on AKI, two multivariate logistic regression models were created that included the duration of hyperthermic perfusion. In model 1, 6904 patients with complete datasets were analysed in a mixed effects model panelled by centre, with adjustment for the propensity-score. In model 2, propensity-matched patients were analysed (n=2044) clustered by centre. Since patients routinely undergo rewarming during CPB, this study also provided the opportunity to evaluate whether temperature ranges below 37°C may be relevant to AKI, which could provide a unique understanding of the role of the CPB rewarming process. The study found that duration of rewarming temperature > 37°C (hyperthermic perfusion) was independently associated with RIFLE stage Risk or greater (OR, 1.42; 95% CI, 1.09-1.77; p=0.012) and Injury or greater AKI (OR, 1.52; 95% CI, 1.09-1.97; p=0.016) in the entire cohort, and Injury or greater AKI (OR, 1.51; 95% CI, 1.18-1.84; p=0.002) in propensity-matched patients. Arterial outlet temperatures between 36 and 37^{o}C were not found to be associated with AKI. In this study we observed that for every 10 minutes of hyperthermic perfusion, there was an associated 42% increase in the incidence of AKI which was a similar effect size to that previously reported in the single centre study. These multicentre findings supported the adoption and compliance with the recommendation of limiting arterial line temperature to 37°C, from the context of providing further evidence for a reduction in the risk of developing AKI. The objective of undertaking this work utilizing the collaborative registry has been to improve the understanding of the impact of CPB on patients and to develop quantitative quality indicators to support clinical improvement through benchmarking. In 2010 we reported that 77% of cases performed within the collaboration complied with the recommendation to avoid arterial outlet temperatures greater than 37°C. Compliance with this recommendation had improved to 93% in 2014 at the time of publication, demonstrating the impact of this work on clinical practice. Although CPB rewarming has been implicated in AKI in other studies, the duration of measured temperatures during these studies was not reported (Delbridge, et al., 2007; Boodhwani, et al., 2009). A unique contribution of this study to the understanding of CPB was that limiting rewarming temperatures to <37°C may be more beneficial than avoidance of rewarming per se. This paper was cited in The Society of Thoracic Surgeons/Society of Cardiovascular Anesthesiologists/American Society of Extracorporeal Technology Clinical Practice Guidelines for the Prevention of Adult Cardiac Surgery-Associated Acute Kidney Injury (Brown, et al.,

2022), and the Guidelines for Perioperative Care in Cardiac Surgery - Enhanced Recovery After Surgery Society Recommendations (Engelman, et al., 2019).

The second paper in this section also focuses on AKI as an outcome measure following CPB, examining the role of oxygen delivery, which has been an ongoing topic of interest to the perfusion community. Following the identification of a prediction threshold of DO_2i for the development of AKI, the randomised goal-directed perfusion trial (GIFT) was conducted to test the hypothesis that a goal directed approach to target DO_2i during CPB > 280 ml/min/m2 compared with the traditional approach of whole-body flow indexed on body surface area (1.6 – 2.4 l/min/m2). Flinders Medical Centre was chosen as one of the participating sites based on its recognition as a centre of significant research contribution and its application of electronic data integration. The GIFT trial demonstrated increased AKI with a nadir DO_2i during CPB below 280 ml/min/m^2 in 326 patients (Ranucci, et al., 2018). We recognized that by conducting an analysis using a rigorously defined large multicentre clinical registry dataset (the ANZCPR), we could aim to confirm the findings of the GIFT trial using a broader risk patient population. Furthermore, using a large multicentre population we could identify the optimal threshold for AKI following cardiac surgery. Using data from 19,410 CPB procedures randomly divided into equal sized (n=9,705) training and validation datasets multivariate logistic regression was used to determine the best predictive model for AKI (RIFLE class ≥R and ≥I) and the incremental predictive value of minimum DO_2i during CPB. Minimum DO_2i was significantly associated with the odds of RIFLE class ≥R and ≥I AKI in both datasets (validation dataset class ≥R OR 0.993, 95% CI=0.991-0.995, p<0.001; class ≥I 0.993, 95% CI=0.991-0.996, p<0.001), representing on average a 7% increase in the likelihood of AKI for every 10 ml/min/m^2 decrease in DO_2i. Diagnostic accuracy was similar for both datasets with an optimal DO_2i threshold of 270 ml/min/m^2. The significance of these findings was that the results of the GIFT trial were supported in a broader risk, multicentre cohort, and that the threshold value associated with AKI was also confirmed. This was an important contribution to the understanding of oxygen delivery and CPB practice given the size and risk profile of the patient cohort in comparison to the GIFT trial. This paper was cited in The Society of Thoracic Surgeons/Society of Cardiovascular Anesthesiologists/American Society of Extracorporeal

Technology Clinical Practice Guidelines for the Prevention of Adult Cardiac Surgery-Associated Acute Kidney Injury (Brown, et al., 2022).

More recently, Mukaida et al reported the use of DO_2i during CPB to develop receiver operating characteristic curves and measures of the time that DO_2i was below a critical value to determine association between DO_2i and AKI (Mukaida, et al., 2019). In qualitative terms, the authors found that the longer that the DO_2i during CPB was below a critical threshold, the greater the chance of developing AKI. This study was relatively small (n=112), however interesting in that the metric of time below a threshold (<300 mL/min/m^2) was a better indicator of AKI than the lowest CPB DO_2i, which links back to our initial single centre study in this thesis which reported the association of the area under the DO_2i curve and AKI. Notably, in the Mukaida et al study, they performed CPB at normothermia. Oxygen dissociation curves depend on temperature, and therefore hemoglobin delivery in their study is likely to be different from oxygen delivery for the vast majority of patients who undergo hypothermia for CPB (Ferraris, 2019). This may be consistent with the lower threshold value of 270 mL/min/m^2 that was utilized in our initial study in patients undergoing more traditional mild hypothermic (32-35^{O}C) CPB. Importantly, the Mukaida et al study adds weight to the evidence for the use of the area under the DO_2i curve as a metric for the prediction of AKI following CPB.

The final paper in this section and for the thesis represents the culmination of many years of development of electronic data collection techniques, registry application of integrated electronic data, understanding of how to analyse the collected data, and application of statistical methodology. For many years the intention had been to utilize the collected intraoperative data from the heart lung machines and physiological monitoring in such a way that would identify areas of CPB conduct that are relevant to patient outcome. It was envisaged that identification of relevant parameters could help guide CPB practice by gaining further understanding of the limited existing relationships between practice and outcome, and this may lead to the development of randomized trials to evaluate the effect of interventions based on these parameters. Since 30-day mortality is commonly used as a quality indicator for cardiac surgery and prediction models have not included CPB parameters, we hypothesized that reproducing a currently utilised regional prediction model of 30-day mortality using the ANZCPR variables would identify relevant CPB predictors. Billah et al

reported a statistical model which includes 18 preoperative risk factors to calculate predicted risk for 30-day mortality following cardiac surgical procedures utilising data from the Australian and New Zealand Society of Cardiothoracic Surgeons (ANZSCTS) registry (Billah, et al., 2010). This model was used until 2020 to calculate risk adjusted mortality in the ANZSCTS registry reporting and has now been updated by the ANZSCORE. Since the ANZCPR data definitions for preoperative risk factors and outcomes are consistent with the ANZSCTS registry and the ANZCPR is unique in its integration of EPD collected intraoperatively from the heart lung machine (HLM) and patient physiological monitoring systems, this allowed the model to be reproduced with the inclusion of CPB parameters. In total, 30,145 patients were included in the study (15,073; creation dataset, 15,072; validation). The area under the ROC for the model including CPB parameters was significantly greater than using the previously published model of preoperative risk factors only (0.829 vs 0.783, $p<0.001$). Modifiable CPB parameters identified in the predictive model were CPB time, red blood cell transfusion, mean arterial pressure <50mmHg, minimum oxygen delivery, cardiac index <1.6 l/min/m^2. This is the first predictive model to be reported which incorporates CPB parameters using 30-day mortality as the primary outcome. By reproducing the approach taken by Billah et al to identify predictors of 30-day mortality we demonstrated generalisability of their model (Billah, et al., 2010) whilst also identifying relevant CPB predictors. This demonstrates the importance of CPB parameters in the prediction of 30-day mortality. Furthermore, we were able to demonstrate that the estimates of risk compared with observed values were highly consistent as risk increases. Application of these parameters as CPB quality indicators will facilitate development of improvement initiatives, however randomised trials designed to evaluate modification of these parameters will determine their impact on mortality. This paper links back to the previous studies in this thesis in which we reported the use of CPB quality indicators to improve process outcomes through feedback to clinicians at an institution level, and through multicentre registry reporting using benchmarking. The inclusion of intraoperative variables in a cardiac surgery 30-day mortality risk prediction model provides additional information to guide postoperative management, which can be calculated for an individual patient as;

$$predicted\ risk\ (\%) = 100\ \times \frac{e^{(\Sigma\beta)}}{1 + e^{(\Sigma\beta)}}$$

$$Where\ e = exponential;\ \sum\beta = sum\ of\ the\ relevant\ model\ beta\ coefficents\ for\ the\ patient$$

If we consider the modifiable CPB parameters identified in the predictive model (CPB time, red blood cell transfusion, mean arterial pressure <50mmHg, minimum oxygen delivery, cardiac index <1.6 l/min/m^2) this model may be of value to specialists caring for these patients after surgery, providing an additional understanding of intraoperative course upon recovery and providing the opportunity for future studies to evaluate optimisation of postoperative management.

As previously discussed, there is a paucity of knowledge regarding the relationships between CPB practice and outcome due to a lack of randomised studies. More specifically, the identification of modifiable CPB parameters associated with mortality are limited due to the large sample size required to reach adequate statistical power, and this study highlights the benefit of multicentre perfusion registries. The ANZCPR is unique in its integration of electronic perfusion data which have been collected in sites throughout Australia and New Zealand over a considerable period, and this study provided the opportunity to define and report which of these parameters play an important role in patient outcome. The methodology of statistical modeling can be categorized into three primary types: descriptive, explanatory, and predictive. Descriptive modeling is typically confined to establishing associations between individual variables and outcomes. In contrast, explanatory modeling is frequently employed to test causal hypotheses using multiple variables. Predictive modeling employs statistical models or algorithms to forecast future observations. Predictive modeling serves multiple purposes, including: 1) uncovering potential new causal mechanisms and generating new hypotheses, 2) suggesting improvements to existing explanatory models by capturing underlying complex patterns and relationships, 3) facilitating the comparison of competing theories by assessing their respective predictive power, and 4) possessing explanatory ability (Shmueli, 2010). The predictive modeling approach employed in this study allowed us to assess the relative importance of the cardiopulmonary bypass (CPB) variables

collected in our registry from an explanatory standpoint. This assessment was conducted through the bootstrap selection and ranking process, model validation, as well as by comparing the predictive ability of the model with and without the inclusion of CPB variables. This was a novel methodological approach and solution to address the challenge that we had grappled with for many years - to define and report which of the EPD parameters uniquely collected in the ANZCPR play an important role in patient outcome.

An important perspective gained from undertaking this analysis concerning modelling of CPB related data was the inclusion of CPB time as quintiles to separate the impact of long bypass times. CPB duration has been previously identified as an independent predictor of morbidity and mortality after cardiac surgery (Salis, et al., 2008). This may be attributed to denoting technical difficulties in executing the planned operation because of unfavorable anatomy or intraoperative complications, the effect of which may be ameliorated by including the procedure type in the model. Other factors that have been implicated in this relationship are the inflammatory response, neurological and abdominal organ complications, blood loss and respiratory dysfunction (Salis, et al., 2008). If CPB time was included in the model as a continuous variable, the effect of longer bypass times would be averaged across all patients, thereby overestimating the effect in patients undergoing shorter CPB times. Given that CPB time was selected in 100% of the bootstrap models, this has a considerable influence on determining the influence of other variables in the final model. Finally, a reassuring finding in this study was the consistency in the reliability between the predicted and actual risk performance across the spectrum of risk, as indicated by the calibration plot and goodness of fit statistics from the predictive model.

The publications in the final section of this thesis make a significant contribution to the evidence base underpinning the use of intraoperative EPD for quality improvement, and the identification of modifiable CPB factors that impact acute kidney injury and 30-day mortality following cardiac surgery. Overall, of the 10 publications included in this thesis, 8 of these contributed to the development of international CPB and cardiac surgical practice guidelines.

Over the period of ANZCPR data collection, we have seen a reduction in the rate of mortality and AKI (Figures 4 and 5). Whilst we recognize that the contributing factors to these outcomes are multifactorial and we cannot infer causality in CPB practice and outcome in these results, it is simply encouraging to observe a trend in a positive direction.

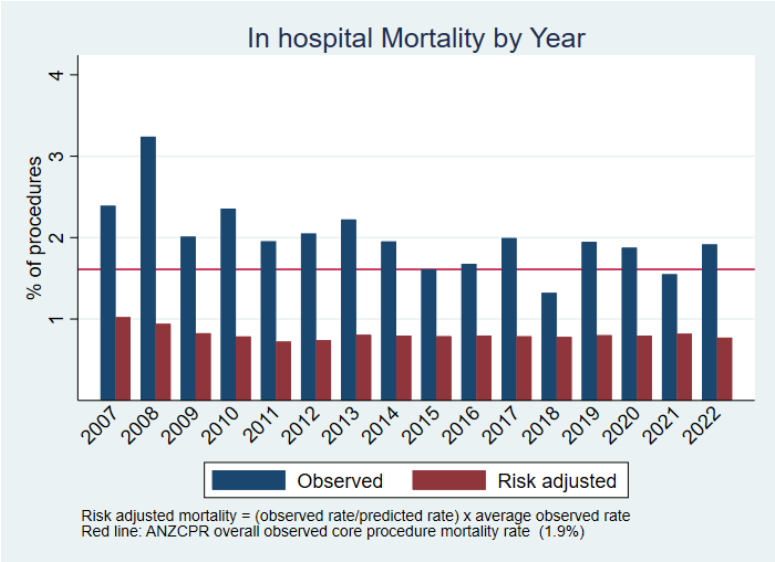

Figure 4. Overall rates of in-hospital observed, and risk adjusted mortality in sites contributing to the ANZCPR between 2007-2022.

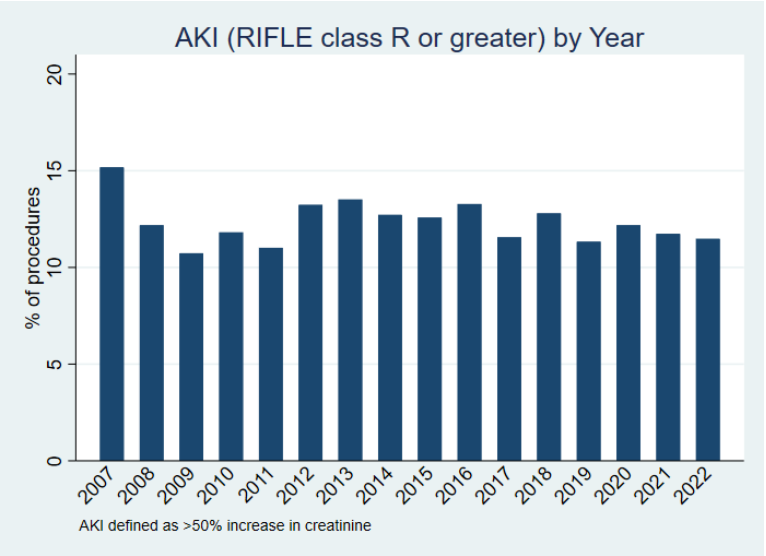

Figure 5. Overall rate of acute kidney injury (RIFLE classification Risk or greater) in sites contributing to the ANZCPR between 2007-2022.

A6. Challenges encountered throughout the research.

Throughout the journey of undertaking the studies included in this thesis, there were a number of challenges encountered;

The nature of the work was pioneering in our field, together with the unique environment of cardiac surgery and CPB meant that there were limited resources and/or literature for guidance. Particularly in the early days of developing the fundamental concepts and processes required to implement a data collection platform and expand upon research directions, there was limited opportunity to interact with collaborative researchers and discuss adoption of data processing techniques. Since I had no formal education or training in IT, database development, or device data communication, significant self education was required.

One of the system challenges in the development and application of this work is the healthcare/hospital recognition of the application of information technology at the point of care. Since the CPB software utilised on the heart lung machines has a cost for purchase and/or licences and for ongoing IT support, an appreciation of the value of the software as a clinical tool is required by the organisation. Furthermore, a risk is created to patient privacy in the electronic collection of identifying data, which requires mitigation through establishment of secure data access and storage. Thankfully both Flinders Medical Centre and Flinders Private Hospital have been extremely supportive of the integration of this technology into clinical practice which has required a cohesive approach from administrative, IT and biomedical engineering departments. Being and early adopter of CPB software implementation, together with pioneering registry integration at our hospital provided a working model which was beneficial in leveraging other hospitals support services participating in the multicentre registry. The platform that we developed to support the ANZCPR had to be available at each hospital and allow for variation in different hospital IT requirements, operating system versions, and IT hardware configurations. We chose Microsoft Access as a commonly deployed database application, which allowed implementation at each hospital, simplicity in development of the front-end registry

application, and usability for clinicians at the point of care. Although this platform has been robust and met the objectives of the registry during the period of this work, the registry is now at a point at which a significant infrastructure change is required to support the volume of data collected.

Throughout the period of undertaking this work, there was considerable regional and clinician variation in perfusionist's perceptions regarding the use of electronic data in clinical litigation particularly in the early 2000's in the USA at which time 'discoverability' was a real concern. A legal opinion from the Australian and New Zealand College of Perfusionist's lawyer suggested that "more data = more defence". This provided the basis to reduce one of the perceived barriers to the adoption of CPB data collection software and to promote its benefits. With the implementation of government incentives to adopt electronic medical records (EMR) in many countries, and the recognition of EMR's in reducing medical errors and costs such initiatives have improved adoption of electronic recording.

Over the period that this work was undertaken, it has been a challenge to demonstrate to vendors of CPB technology the value and need for CPB software development for clinicians and its role in the market. This is most likely attributed to the attitudes and factors associated with adoption of the software as described above, having an impact on customer concerns and demands. Ultimately both clinicians and vendors respond to the evidence, and it has been encouraging to see the trajectory of perception change as the evidence base has expanded. Since the ANZCPR remains to date as the only CPB registry to have integrated electronic data from the heart lung machine, there are some further barriers that need to be addressed in expanding the evidence base further.

A7. Future directions of this work and summary

In December 2023 I had the opportunity to participate in a global advisory board to discuss and identify the current and future data management needs of the CPB community. This meeting was facilitated by Livanova (London, UK) demonstrating the increasing recognition of value of data collection and its application by CPB vendors.

This meeting engaged a multidisciplinary group including perfusion, anaesthesia and surgeon stakeholders that identified the importance of vendor engagement in facilitating registry

participation through CPB software integration and functionality. An important outcome for the meeting was the strong consensus for the development of an international CPB registry that leverages the platform already achieved by the ANZCPR. Furthermore, the international registry should include a novel dataset for paediatric cardiac surgical patients to bridge the gap in the support provided for understanding and improving CPB practice between adults and children.

Currently the ANZCPR is seeking funding for transformation of the registry to establish a cloud-based platform to revolutionize cardiac surgery research by creating a sustainable registry platform that integrates clinical registries and heart-lung machine data. The project will harness the success of the ANZCPR, and through transformation of the existing registry infrastructure will provide the opportunity to address knowledge gaps, optimise quality improvement and benchmarking, and enhance translational research capabilities to improve patient outcomes.

Translation research will be optimised by linking datasets to create the opportunity for large multicentre observational studies to be published that will inform ongoing trials. The infrastructure will provide a cost and time effective platform for the conduct of randomised clinical trials (RCT's), addressing critical unmet research questions in the CPB field to significantly contribute to the scientific knowledge base and bridge the gap between research findings and clinical practice.

The project will allow for exploration of opportunities for commercialization of research outcomes, particularly in AI and innovative technologies and through collaboration with industry partners to facilitate the application and dissemination of marketable health solutions. This infrastructure will facilitate deployment of machine learning models to predict outcome and provide personalization of practice based on interaction of individual patient risk factors and CPB interventions.

In summary, this thesis demonstrates a considerable undertaking of the development of intraoperative EPD processing to improve the understanding and practice of CPB. This was achieved through the development of:

- Automated generation of CPB quality indicators from electronic perfusion data to provide a process for continuous quality monitoring.

- A multicentre CPB registry to facilitate reporting and quality improvement through benchmarking.
- Determining the impact of CPB practice on patient outcome (acute kidney injury) at Flinders Medical Centre.
- Identification of modifiable predictors of CPB practice on patient outcome (acute kidney injury and 30-day mortality) using multicentre registry data.

This combined body of work has contributed to international guidelines for CPB best practice, recognizing the role of electronic data collection for quality improvement in CPB, and the importance of integration of EPD into registries to improve understanding and practice through identification of modifiable factors associated with patient outcome, facilitation of continuous quality monitoring, benchmarking and improvement. This work also provides the foundation for future development of registry-based randomized trials designed to further the understanding and improvement of CPB practice, using the multicentre registry as a platform for data collection, randomization, and follow-up.

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Chapter 1: Development of a novel method to facilitate automated generation of cardiopulmonary bypass quality indicators from electronic perfusion data and to provide a process for continuous monitoring of quality parameters.

1.1 Electronic data processing: the pathway to automated quality control of cardiopulmonary bypass.

Newland RF, Baker RA, Stanley R.

J Extra Corpor Technol. 2006 Jun;38(2):139-43. PMID: 16921687; PMCID: PMC4680750.

ABSTRACT

Electronic data collection during cardiac surgery creates an enormous data source that has many potential applications. After the introduction of the Stockert Data Management System (DMS; Munich, Germany) to our perfusion practice, we recognized that the data could be used for the purpose of quality control (QC). Our aim was to create an automated technique of data analysis and feedback for cardiopulmonary bypass (CPB) procedures. Using visual basic programming, we created a process by which data from the DMS is analyzed and processed in a Microsoft Access database after a CPB procedure. The processing is designed to transfer the collected data to a research database and create a number of CPB quality indicator (QI) parameters, such as mean arterial pressure being less than 40 mmHg for more than 5 minutes or a venous saturation of less than 60% for more than 5 minutes. In the event of QI parameter detection, a QC report is generated and e-mailed to the senior perfusionist and the perfusionist performing the procedure. The introduction of electronic data collection and subsequent development of electronic data processing techniques has enabled us to transfer the data into a readily accessible database and create a data set of perfusion variables and quality indicators for CPB procedures. This data set may be used for immediate automated QC feedback after CPB procedures and direction of performance improvement initiatives through retrospective or prospective data analysis as part of a continuous quality improvement process.

INTRODUCTION

Cardiac surgery has advanced at enormous rates over the last 50 years, and most recently the outcomes have been examined in greater detail with the advancement of alternative surgical and nonsurgical intervention strategies. Outcomes are usually multifactorial in origin; optimal

management systems intraoperatively contribute significantly to improving patient outcomes. The perception of data management as an integral component of modern clinical practice has in some areas been slow to evolve, and the potential value of automated data management systems has certainly been underrecognized. Historically, early perfusion electronic data collection systems have offered limited data integration or management (e.g., Cardio Link; Cobe Cardiovascular Inc., Arvada, CO). More recently, however, a number of data management systems have been developed that have facilitated integration of data not only from the heart lung machine (HLM), but also from anesthetic machines and other patient monitors, laboratory data, on-line blood gas measurement devices, and other point of care devices, in addition to all of the mandatory information directly relating to the conduct of bypass (e.g., blood and gas flow rates, line pressures, temperatures). The collection of data in itself is only one component of the value that can be gained from these integrated systems. The generation of the perfusion record is an obvious example of what we are able to do with this type of system; however, it is important to recognize that this is just the tip of the iceberg of the true power associated with data collection. The data provide an enormous resource for ongoing research activities, and we have previously showed that the use of automated data collection systems provides the opportunity to minimize transcription error and bias and provide a more detailed information base for the clinical procedure (1). Potentially, the most important influence that data management may have on clinical practice is with respect to quality management. The importance and benefits of quality assurance and quality control (QC) in health care delivery are well recognized. In our institution, although quality assurance processes were implemented, our QC processes were not as fully developed. Riley (2), in a recent editorial in the Journal of Extracorporeal Technology, promoted the role of the perfusion profession in recognizing the importance of quality improvement and reporting in perfusion. In a similar editorial, Groom et al. (3) highlighted the value of data collection and analysis in the improvement and management of cardiopulmonary bypass (CPB). We recognized that in addition to the data being a valuable research tool, additional benefits would be gained if we were able to use the information we collected to improve our day to day perfusion practices via electronic data processing—to develop an automated QC process. Quality control is defined as a set of activities or techniques whose purpose is to ensure that all quality requirements are being met. To achieve this purpose, processes are monitored and

performance problems are solved (4). To implement the QC process requires the identification of quality indicator (QI) variables that can be used to define specified quality outcomes. The routine analysis of the quality indicators is essential in achieving a continuous quality improvement (CQI) process. Rath and Strong (5) have described a five-step structured process (DMAIC) as an approach to standardizing the CQI process. The steps they identified were as follows: define the problem; gather information on the problem; identify root causes of the problem and confirm with the data; try out and implement solutions that address root cause(s) of the problem; and evaluate the solutions and outline and maintain the gains by standardizing the process. This can be coupled with six sigma reporting to also allow standardization of measurement. Outcome, which in the perfusion setting may be defined as the occurrence of an event (e.g., an accident, an observation, a protocol deviation), is able to be defined as number of events per million opportunities (DPMO). Riley (2) has proposed that six sigma DMAIC methodology be adopted by perfusionists, to allow them to study and meaningfully report and compare improvements in their clinical processes. Dickinson et al. (6) examined the use of perfusion data for QC purposes. They were able to show that compliance with the majority of perfusion quality indicators correlates with external validation of superior unit performance. One limitation of this study was that the original perfusion data was manually collected; more recently electronic data collection has been shown to be more accurate than manual data collection during surgery (1,7). Our unit has embraced a strong ethos toward quality of care; however, we recognized that we needed to develop a CQI process, and we identified the need to use a DMAIC process, and eventually six sigma reporting, to achieve our goals. To facilitate the process, we recognized the need to overcome one of the clear limitations of many of the commercial data management systems, that is, the lack of easy access to the raw data that was being collected, for the purpose of data processing. Therefore, the aim of this work has been to develop a method of easy access to the data collected by the data management system and to develop an automated technique of data analysis and feedback for CPB procedures, which may be used as part of a CQI process for our perfusion practice.

MATERIALS AND METHODS

Data Collection Technique

Since the inception of the Flinders Cardiothoracic Surgical Unit in 1992, we used Microsoft Access (Microsoft Corporation, Redmond, WA) to create a cardiac surgery database (CSD) for storing perfusion data, in addition to a comprehensive data set for each cardiothoracic patients clinical course. The perfusion record was created manually on a paper chart and data were manually entered into the CSD. We therefore needed to introduce a medium for the capture of perfusion data electronically and automated transfer to the CSD. In 2000, we implemented the Data Management System (DMS; Stockert, Munich, Germany) to routinely record and generate our CPB records. The data integration hub of the S3 heart-lung machine (Stockert) is a serial interface that provides the facility to communicate data with peripheral devices through an RS-232 connection. Data from these devices are transmitted from the serial interface in one signal to the laptop computer or touchscreen monitor on the HLM (Figure 1). This is a significant advantage because the data from these devices are able to be integrated into the perfusion record. However, this may also be a limitation because it requires multiple communication ports on the HLM and the ability of the devices to communicate with the HLM. It is important for manufacturers to recognize the new generation of interconnectivity required in the marketplace and to recognize the need to be able to establish communications between the different devices in the operating room.

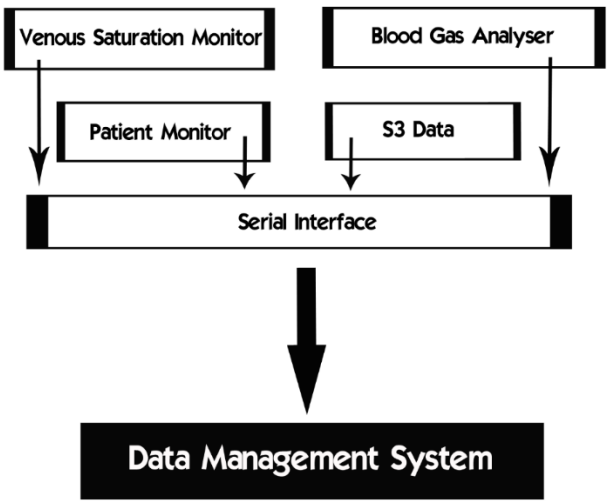

Figure1: Integration of data communication – peripheral monitoring devices are connected to the serial interface of the S3 heart-lung machine, and the integrated data is collected by the DMS software on the laptop computer.

Data are currently collected from the following peripheral devices: AS3 (Datex-Ohmeda, Helsinki, Finland) and Solar 8000 (GE Healthcare, Waukesha, WI) anesthetic machines, SAT/HCT monitor (Cobe Cardiovascular, Arvada), and the ABL700 blood gas analyser (Radiometer, Bronshoj, Copenhagen, Denmark). Data are collected and stored at 20-second intervals.

Data Integration

The initial step in allowing full data integration was to move the existing CSD from an Access platform to a SQL server platform, requiring conversion of existing database tables (Access) to SQL tables, while retaining the Access user interface. This provided a stable multiuser environment, allowing procedural data to be entered onto the CSD in real time by the perfusionist in the theater on the HLM laptop/touchscreen computers, which are connected through wireless local area network access. After a perfusion procedure, the DMS data are exported from the HLM computer to the perfusion server computer for report storage and printing. During this process, the data are stored as text files on the hospital network. Located on the hospital network is a processing database (transfer database) that was created to process and transfer data from the DMS text files into the CSD. The transfer database is linked to the CSD through open database connection (ODBC). The importing process relies on import specifications that are set using the Access importing wizard. To initiate the automated data transfer process, a button is clicked on the CSD that calls a visual basic programming module in the transfer database to perform the following functions. 1) import DMS text files into the transfer database, according to the import specifications. At the start of the import process, the import tables are empty so that patient records are processed individually. 2) Append the imported data in the transfer database to the CSD and run queries to process and update specific data variables to the CSD. 3) Delete the data in the transfer database tables, ready for the next import process.

Creation of Custom Perfusion Quality Indicator Variables

The data collection and data integration processes allowed us to achieve our goals of collecting and processing the data. To progress to data analysis and feedback, we recognized

the need to define what we wished to report from the CSD. To achieve this, we created a customized set of perfusion data variables such as the number of transfusions, minimum and maximum values, fluid balance, and pressure and temperature cumulative time values. We defined a number of QI parameters, based on the unit perfusion protocols. Our QI parameters were activated clotting time (ACT) less than 400 seconds, cardiac index less than 1.6 L/min/m^2 for more than 5 minutes, mean arterial pressure less than 40 mmHg for more than 5 minutes, venous saturation less than 60% for more than 5 minutes, hemoglobin less than 7 g/dL, pCO_2 less than 35 or more than 45 mmHg, pO_2 less than 100 mmHg, and arterial blood temperature of less than 37.5°C for more than 2 minutes. Time for all QI parameters are defined as cumulative time. The QI parameters have also been used in conjunction with data from procedural events to identify inappropriate responses from the perfusionist according to our unit protocols, such as when a blood transfusion is given when the patient hemoglobin is more than 7 g/dL or if no blood transfusion occurred when the hemoglobin was less than 7 g/dL. These parameters allow us to monitor a broad range of clinical responsibilities, including anticoagulation, blood gas management, hemodilution, rewarming, and perfusion adequacy.

Automated Quality Control Feedback

The automated feedback process was created by generating a report template in the transfer database and modification of the visual basic programming module so that in the event that any of the QI parameters are detected, a QC report was generated. The report was automatically e-mailed to both the senior perfusionist and the perfusionist performing the CPB procedure. Figure 2 is an example of a perfusion quality control report and shows the data variables currently included.

Report Interpretation

The quality control report is designed to highlight the QI parameters and display related data and certain procedural events such as a whether there was a low flow request from the surgeon, which makes interpretation of the report more meaningful (Figure 2). The report shows that there was an arterial pressure reported of less than 40 mmHg for more than 5 minutes; this is also reflected in the cardiac index and venous saturation. There is a qualifying comment, “low flow request from the surgeon” that accompanied these parameters, which

may assist in interpreting the context in which these variations occurred. The intraoperative comment verifies that a low flow period was required during aortic suturing. As indicated, the arterial pressure for the majority of the case was between 40 and 70 mmHg. An ACT of less than 400 seconds is also reported, along with the event, administration of 10,000 units of heparin. In this particular example, the perfusionist should consider why these QI parameters occurred, and how to improve performance in the future. From an administrative point of view, although, there is sufficient information to suggest that no immediate action is required; feedback and guidance could assist the performance improvement process.

Perfusion Quality Control Report

Perfusionist **Example**

Procedure Number	*Date*	*Urgency*	*Weight*	*Age*	*Redo*	*Consultant*
Example	xx/xx/20xx	Elective	89	67	No	Example

CPB Time: 71 Cross Clamp Time: 37

Intra-operative Comment: Low flow period during aortic suturing

QI Values (detection displayed as Yes): **Perfusion Data:**

Flow/Pressure: **Arterial Pressure Values(mmHg): (min)**

Arterial Pressure<40mmHg (>5 min): **Yes** <30: 0.99 <40: 8.25 <50: 17.49 <60: 22.77 <70: 16.5 >70: 3.3

Cardiac Index<1.6 $Lmin^{-1}/m^2$ (>5min): **Yes** 9.9

Venous Saturation <60% (>5min): **Yes** 6.6 Low flow request from surgeon?: Yes

Temperature:

Arterial Temperature >37.5ºC (>2min): No 0.33

Blood Gases:	**First sample:**	**Last sample:**
pO_2 <100: No	281	233
pCO_2 <35 or >45: No	38	42.3

Blood usage:

Haemoglobin <7: No 9 9.1

Preoperative Haemoglobin: 13.8

Blood Units in Prime: 0

Blood Units on CPB: 0

Anticoagulation:

ACT <400: **Yes** Heparin on CPB: 10000

1st ACT post heparin: 421

Wednesday, xx May 20xx ***Page 1 of 1***

Abbreviations: CPB – Cardiopulmonary bypass, ACT – activated clotting time.

Figure 2: Perfusion Quality Control Report.

Quality Indicator Data Analysis

In addition to individual feedback, group analysis of the incidence of QI parameters can be performed. This can be done in both a prospective and retrospective manner, allowing data analysis to monitor compliance of quality standards. Retrospective analysis enables identification of practice areas where performance improvement initiatives should be directed (root cause analysis), while prospective analysis provides assessment of the efficacy of these initiatives (root cause analysis solutions).

DISCUSSION

The processes that we have described have allowed us to achieve our goals of developing a method of easy access to the data collected by the DMS and to develop an automated technique of data analysis and feedback for CPB procedures, thereby achieving the first three steps of the DMAIC process; the ability to define the areas or problems that we wish to look at, the ability to gather the appropriate information, and the ability to analyze the data to allow root causes to be identified. Thus, we are well positioned to fulfill our goal of a DMAIC-guided CQI process.

This undertaking has shown the enormous advantage of creating and storing perfusion data in a separate database that is purpose designed to allow immediate access to the data, thus providing advantages from both an administrative and a research perspective. In addition to facilitating access to the created variables, it provides immediate access to the data collected by the DMS including all data obtained from the patient monitor. In contrast, accessing the perfusion data in the DMS requires the data to be exported into another application and linked before it can be analyzed and/or processed. One of the unplanned benefits that we identified has been in relation to the data processing technique that we established, because this has enabled us to analyze QIs on CPB procedures performed before the introduction of the automated feedback process. Therefore, we will be able to ask the question “is there a performance improvement effect caused by automated feedback alone?”

The data obtained from our technique can provide us with valuable feedback on perfusionist performance and adherence to protocols and also provides us with data to challenge the adequacy of our protocols. Even though we may attempt to practice an evidence-based

medicine approach, not all aspects of perfusion management have sufficient evidence available to support all of our protocols. The analysis and interpretation of our QI data has become a routine part of our clinical practice and will assist us in the process of protocol evaluation and modification. Furthermore, this implements the final stages of the DMAIC process because it allows us to undertake a professional performance improvement strategy and a new direction for the further development of new clinical processes. Prospective analysis of these variables after the introduction of the automated report generation feedback process is currently in progress. Our final challenges with this project will be to introduce six sigma reporting. Through the application of this methodology, we look forward to reporting our CQI process. The technology that we have used to achieve this is available to all users of HLM systems that allow collection and integration of electronic data; however, to simplify the process and promote broader use of perfusion QC, we are assisting the Stockert program development team with including similar quality management features within their DMS software.

CONCLUSIONS

The introduction of electronic data collection and subsequent development of electronic data processing techniques has enabled us to transfer the data into a readily accessible database and create a data set of perfusion variables and QIs for CPB procedures. This data set may be used for immediate automated QC feedback after CPB procedures, and direction of performance improvement initiatives through retrospective or prospective data analysis as part of an evolving CQI process.

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1.2 Continuous quality improvement of perfusion practice: the role of electronic data collection and statistical control charts.

Baker RA, **Newland RF**.

Perfusion. 2008 Jan;23(1):7-16. doi: 10.1177/0267659108093853. PMID: 18788212.

ABSTRACT

In-hospital data collection may be used to improve the selection, operative techniques, and process of care for cardiac surgical patients. The aim of this report is to demonstrate the influence of the automated generation of quality indicators (QI) for cardiopulmonary bypass (CPB) and the implementation of a continuous quality improvement (CQI) programme on the CPB process of care. Adult patients undergoing CPB were divided into three consecutive groups: Group 1 (n=363); no QI data feedback, Group 2 (n = 253); automated QI data feedback alone, and Group 3 (n = 363) data feedback and implementation of CQI. There were no significant differences in demographic, procedural or clinical outcomes for each group. Significant improvement, as determined by adherence to practice protocols and reduction in practice variation, was observed for cardiac index < 1.6 L/min/m2 (min), mean arterial pressure < 40 mmHg (min), venous saturation < 60% (min), arterial blood temperature of > 37.5^0C (min), minimum pCO_2 (mmHg), maximum pCO_2 (mmHg), and minimum pO_2 (mmHg). There was no change in the minimum haemoglobin (g/dl) on bypass.

Automated generation of QI resulted in improved adherence to process of care guidelines, highlighting the potential of electronic data collection. This technique is optimized in a CQI programme, utilising statistical control charts for data interpretation.

INTRODUCTION

In-hospital data collection may be used to improve the selection, operative techniques, and perioperative care of patients in the cardiac surgical setting. Analysis of risk-adjusted clinical outcomes (e.g. mortality, morbidity) has typically been the focus of attempts to quantify the quality of cardiac surgical care and quality improvement; however, these endpoints are only one measure of the overall care process. Comprehensive quality indicators that quantify

specific processes of care are an important component of the assessment of quality of care (1). Continuous quality improvement (CQI) is a method of quality control that uses repeated data collection to review and improve processes. Use of CQI and compliance with process of care guidelines in the clinical setting has been used to improve both the health care process (2,3) and patient outcomes (4). Underpinning the process of performance improvement is the requirement for reliable, accurate data collection. We, and others, have previously demonstrated the advantages of electronic data collection technology compared to manual intra-operative data collection (5–7). Utilising this technology, we have developed a method of automated generation and feedback of cardiopulmonary bypass (CPB) quality indicators (QI) (6). However, an initiative to audit these indicators was required in order to implement a CQI programme.

Providing clinicians with feedback on their performances is a fundamental component of a clinical quality improvement programme (2), which involves the translation of collected data into knowledge and understanding. Statistical process control (SPC) is a method of monitoring a process through statistical analysis (8). Originally described by Walter Shewart (Bell Laboratories) in the 1930s, the method has been more recently reported for its application in healthcare (8) to provide a mechanism for data interpretation in CQI. A typical control chart is a graphical representation of a quality indicator, either as individual values or calculated subgroups, with the data displayed in sequential order. Horizontal lines represent the central tendency or mean, the upper control limit (UCL) and the lower control limit (LCL). These control limits are used to assist in the interpretation of the control state or variation of the process and are typically set at ±3 standard deviations. Groom, et al (9) have described the application of SPC as a tool in the understanding of variation in CPB processes, through the translation of data into clinician feedback. The aim of this report is to demonstrate the influence of implementing a CQI initiative for CPB based on automated generation of quality indicators and the use of statistical control charts as a performance feedback method.

METHODS

Study population and CPB technique

Our study population was an observational cohort of three consecutive adult patient groups. The first group consisted of 363 patients who had CPB procedures immediately prior to the introduction of automated QI feedback (Group 1). The second group underwent surgery in the period between the introduction of automated QI feedback and the introduction of our CQI programme (Group 2 = 253 patients), and Group 3 (n=363 patients) were operated on after the introduction of the CQI programme. All patients underwent cardiac surgery with CPB (Table 1) using a S3 roller pump (Stockert, Munich, Germany). Cardiopulmonary bypass was instituted after positioning of either a single 36/51 Fr two-stage atrial cannula (SarnsTM, Terumo Corporation, Tokyo, Japan), or 32–36 Fr bicaval cannulation (SarnsTM), and a 22 Fr ascending aortic cannula (DLP, Medtronic, Minneapolis, MN, or Argyle, St Louis, MO). The CPB circuit included a hard-shell membrane oxygenator (SX25RX, Terumo Corporation, Japan), biopassive tubing (SMARxT®, Cobe Cardiovascular, Arvada, CO) and a 40-micron arterial line filter (D703, Dideco, Mirandola, Italy). Routine CPB protocol included arterial flow rate of 1.8-2.4 L/min/m2, alpha-stat pH management, gravity venous drainage, and tepid systemic temperature management (32-35°C). After placement of the aortic crossclamp, cardioplegic arrest was induced with blood cardioplegia (32-34°C), 25-30mmol/l at induction and intermittent bolus (16-25 mmol/l) as required. Patients were separated from bypass when nasopharyngeal temperatures in excess of 36.5°C were achieved. Rewarming rates did not exceed 1°C per min.

Data management

We have described the process for data collection in our institution previously (6). In summary, a Cardiac Surgery Research (CSR) database located on our hospital database server (SQL) is accessed via a Microsoft Access (Microsoft Corporation, Redmond, USA) user interface. Intraoperative data collected using the Stockert Data Management System (DMS) (Munich, Germany) is processed via a number of queries and integrated into our CSR database (6).

We generate cardiopulmonary bypass quality indicators (QI) designed to measure compliance with our process of care guidelines. We chose eight QI to determine process of care compliance:

cardiac index < 1.6 L/min/m2 (min),

mean arterial pressure < 40 mmHg (min),

venous saturation < 60% (min),

arterial blood temperature of > 37.5^0C (min)

minimum haemoglobin (g/dl),

minimum pCO_2 (mmHg),

maximum pCO_2 (mmHg),

minimum pO_2 (mmHg).

For timed QI parameters, the time interval reported is the cumulative time. The DMS software also continuously measures the timed QI parameters, and this information is available to the perfusionist during CPB. Haemoglobin and blood gas concentrations were measured intermittently during CPB using an ABL 700 blood gas analyser (Radiometer, Copenhagen, Denmark). Generation of retrospective QI data was performed for patients in Group 1.

Quality improvement programme

The initial phase (Group 2) of our improvement programme involved automated generation of an electronic quality control (QC) report (6). The QC report was emailed to both the perfusionist performing the procedure and to the chief perfusionist. The final phase (Group 3) of our programme involved the establishment of a feedback mechanism to promote group discussion. Quality performance review meetings were introduced to discuss variation in practice and possible practice changes that were identified from the QI data. This provided the mechanism to create a process of continuous quality improvement. Both DMAIC (define, measure, analyse, improve, control) methodology (6) and control charts were applied in the process of quality improvement. Clinical improvement initiatives were focused on improving the perfusionist's performance, including increased vigilance in monitoring and response to physiological variables, increased awareness and understanding of institutional process of care guidelines and improved communication with cardiac surgical team members.

Statistical analysis

Patient baseline demographic, clinical and surgical characteristics were analysed using the Kruskal- Wallis test for multiple groups for non-normally distributed data and ANOVA for normally distributed data. Categorical data were analysed with the $\chi 2$ statistic. A p-value of < 0.05 was considered significant.

Statisitical process control charts were created using SPCXL software (Air Academy Associates, Colorado Springs, CO) and Microsoft Excel (Microsoft Corporation, Redmond, WA) with Shewhart control limits set at ±3 standard deviations. In the control charts, the data are represented either as individual points (Figures 6–8) or as subgroups of 20 procedures and the average plotted to facilitate interpretation of the charts (Figure 1–5). Analysis of nonnormally distributed data presented on the control charts was performed using the Kruskal-Wallis test for multiple groups and the Mann-Whitney U-tests for two groups for one-way between group comparison. For normally distributed data, the ANOVA was used. Where differences were significant, multiple post hoc comparisons were performed using Tukey's HSD. All statistical comparisons were performed on the raw data set, not on average data displayed. The p value for significance was adjusted to $p<0.005$ for multiple comparisons (Bonferroni correction). All data were analysed using SPSS® 12.0.1 statistical software package (SPSS Inc., Chicago, IL).

This work was performed as part of our ongoing quality improvement process and recognised by the Clinical Governance Unit of Flinders Medical Centre.

RESULTS

Basic demographic and procedural data on the 979 patients are displayed in Table 1. The data demonstrated that there were no significant differences in the demographic, procedural or mortality outcomes reported for each group.

Table 1 Demographic and Surgical Variables for all Patients

	Group 1 (n=363)	**Group 2 (n=253)**	**Group 3 (n=363)**	**p**
Age (years, mean (SD))	61.6 (14)	60.3 (15.2)	62.5 (14.7)	.178
Sex (% male)	69.8	65.6	70.8	.366
Euroscore (median (range))	2.9 (0.9-69.2)	2.9 (0.9-70.8)	3.2 (0.9-72,5)	.222
Procedure Type (%)				
CABG	68.4	68.8	64.2	.359
CABG/Valve	6.6	6.7	6.9	
Valve only	17.6	18.6	24.0	
Other combined	7.4	5.9	5.0	
CPB Time (min, mean (SD))	68.9 (30.7)	65.9 (29.0)	65.7 (27.4)	.296
X-Clamp Time (min, mean (SD))	42.7 (19.9)	40.2 (16.2)	43.0 (20)	.16
ICU Time (hrs, median (range))	25 (1-1298)	25(4.3-2341)	25(2.5-799)	.571
LOS (days, median (range))	6(2-54)	6(3-99)	6(2-48)	.105
Mortality (%)	1.1	1.6	0.8	.681

P value - difference between all three groups; LOS, length of stay.

The QI data for each group is presented as control charts in Figures 1–8.

The control chart for the average amount of time that the cardiac index was <1.6 L/min/m2 is displayed in Figure 1 for each of the 3 groups of patients. The control chart shows the mean (central tendency) and variation in measurement (upper and lower confidence limits) for each group, and demonstrates the significant reduction in the amount of time the cardiac index was <1.6 after the introduction of the quality control measures (Groups 2 and 3) (chi-square

12.829, df 2, p=0.002). The reduction in the variation in the amount of time spent with low cardiac indices is evident with the reduced confidence limits.

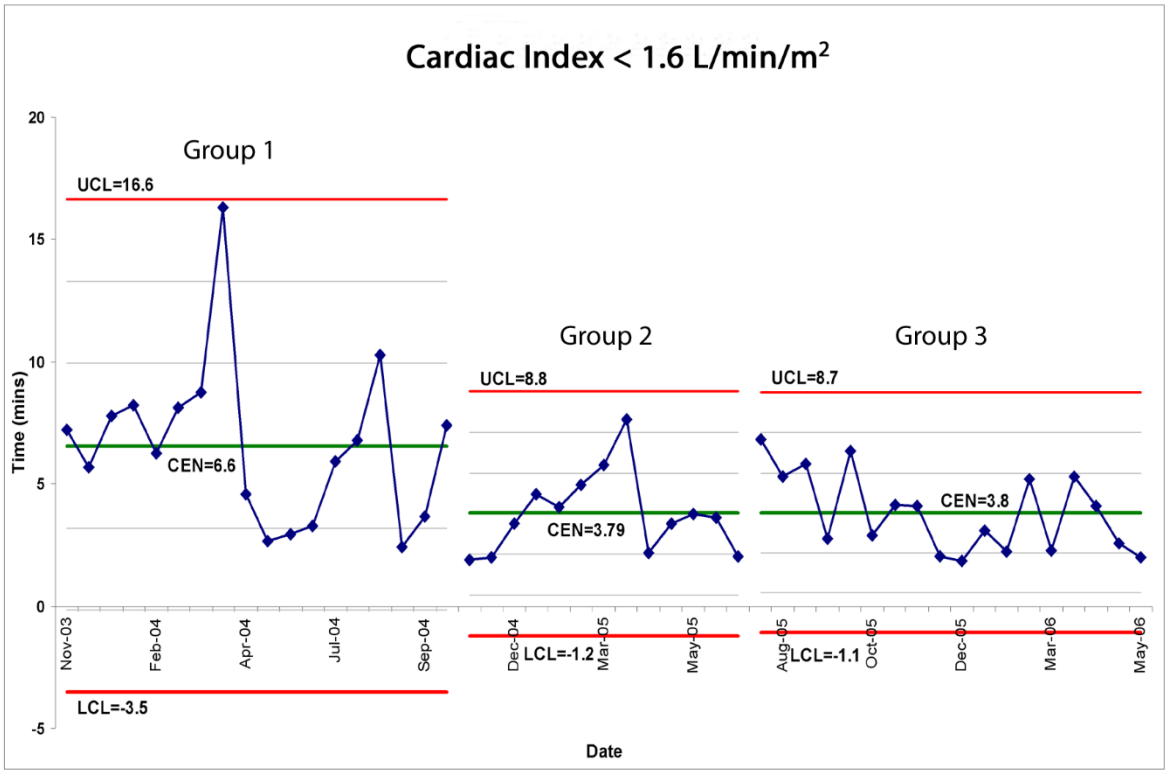

Figure 1: Xbar control chart of the average amount of time the cardiac index was < 1.6 L/min/m2 for each group of patients, group 1 (pre-QC), group 2 (QC), group 3 (CQI) are displayed as split data. The vertical axis is the average time in minutes that the cardiac index was < 1.6 L/min/m2. The horizontal axis shows the time period in calendar month and year. Each dot represents 20 cases. The central tendency for each group is shown (CEN), as is the upper confidence limit (UCL) and lower confidence limits (LCL). The decrease in variance is evident for groups 2 and 3 compared to group 1. Between group analysis (Kruskall Wallis) demonstrated a significant reduction in the amount of time the cardiac index was <1.6 L/min/m2 in groups 2 and 3 compared to 1 is shown between the groups (chi-square 12.829, df 2, p=0.002). Between group analysis for group 2 and 3 demonstrated group 2 demonstrated no difference between groups 2 and 3 (z -0.311, asymptomatic p value (2 tailed) p=0.756).

Figure 2 is a control chart looking at the average amount of time the mean arterial pressure <40 mmHg (min) for each group of patients. There was a significant reduction in the amount of time the pressure was <40mmHg after the introduction of the QC measures (Groups 2 and 3) (chi-square 36.165, df 2, p<0.000). Between group analysis demonstrated that Group 2

spent significantly less time than Group 3 with a mean arterial pressure <40mmHg (z -2.892, asymptomatic p-value (2 tailed) =0.004). The point lying above the UCL in Group 2 (time value of 167 min) was examined for accuracy and found to be legitimate. Exclusion of the value did not influence the distribution of the data (non-normally distributed) nor the analyses, therefore, it was not excluded from the analysis.

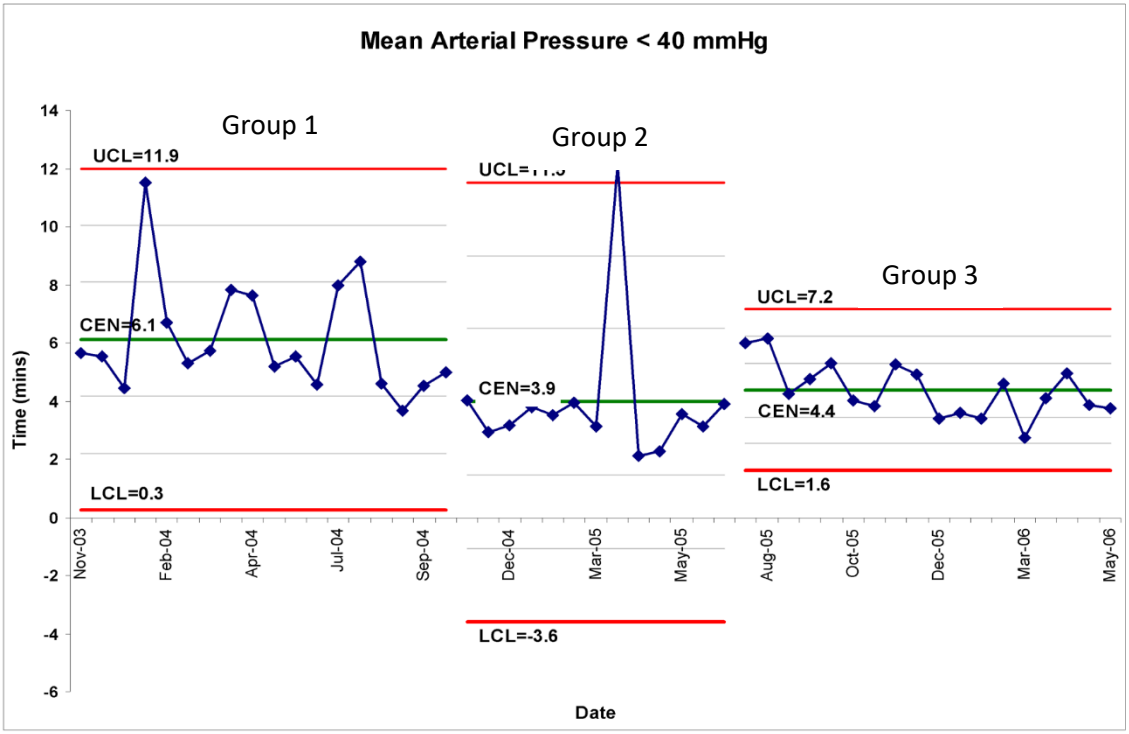

Figure 2: Xbar control chart of the average amount of time the mean arterial pressure was < 40 mmHg (min) for each group of patients, group 1 (pre-QC), group 2 (QC), group 3 (CQI) are displayed as split data. The vertical axis is the average time in minutes that the mean arterial pressure was < 40 mmHg (min). The horizontal axis shows the time period in calendar month and year. Each dot represents 20 cases. The central tendency for each group is shown (CEN), as is the upper confidence limit (UCL) and lower confidence limits (LCL). The decrease in variance is evident for group3 compared to group 1 or group 2. Between group analysis (Kruskall Wallis) demonstrated a There was a significant reduction in the amount of time the pressure was <40mmHg in group 2 and 3 compared to group 1between the groups, with group 1 the most time, and group 2 the least (chi-square 36.165, df 2, p<0.000). Between group analysis for group 2 and 3 demonstrated group 2 to have the least time with mean arterial pressure less than 40 mmHg Group 2 spent significantly less time than group 3 at MAP <40 (z -2.892, asymptomatic p value (2 tailed) p=0.004).

Control charts for the time the venous saturation was < 60%, the time arterial blood temperature was > 37.5^{0}C and the minimum haemoglobin (g/dl) on bypass are shown in Figures 3–5, respectively. There was a significant decrease in both the time the venous saturation was below 60% and arterial outlet temperature above 37.5^{0}C in the 2 groups representing periods after the introduction of the QC measures (chi-square 21.606, df 2, p<0.001; chi-square 338.132, df 2, p<0.001). Following the introduction of the third phase of our programme (Group 3), there was a further improvement in minimising the time the arterial outlet temperature was below 37.5^{0}C. There was no difference in the minimum haemoglobin value recorded on bypass after the introduction of the QC measures (chi-square 2.557, df 2, p=0.278).

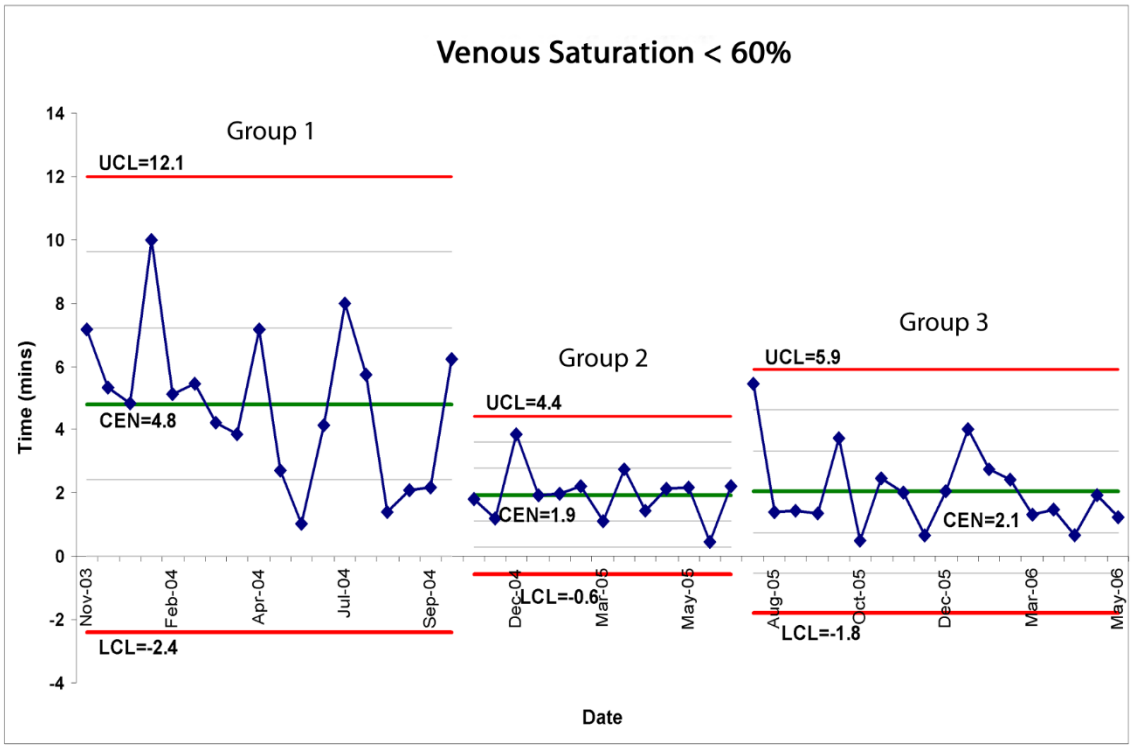

Figure 3: Xbar control chart of the average amount of time the venous saturation was < 60% (min) for each group of patients, group 1 (pre-QC), group 2 (QC), group 3 (CQI) are displayed as split data. The vertical axis is the average time in minutes that the venous saturation was < 60% (min). The horizontal axis shows the time period in calendar month and year. Each dot represents 20 cases. The central tendency for each group is shown (CEN), as is the upper confidence limit (UCL) and lower confidence limits (LCL). The decrease in variance is evident for groups 2 and 3 compared to group 1. Between group analysis (Kruskall Wallis) demonstrated There was a significant reduction in the amount of time the venous saturation was < 60% between the groups, with group 1 the most time, and group 2 the least in group 2 and 3 compared to group 1 (Kruskal-Wallis Test chi-square 21.606, df 2, p<0.0010). Between

group analysis for group 2 and 3 demonstrated no difference in the amount of time with venous saturation <60% (z -0.157, asymptomatic p value (2 tailed) p=0.875).

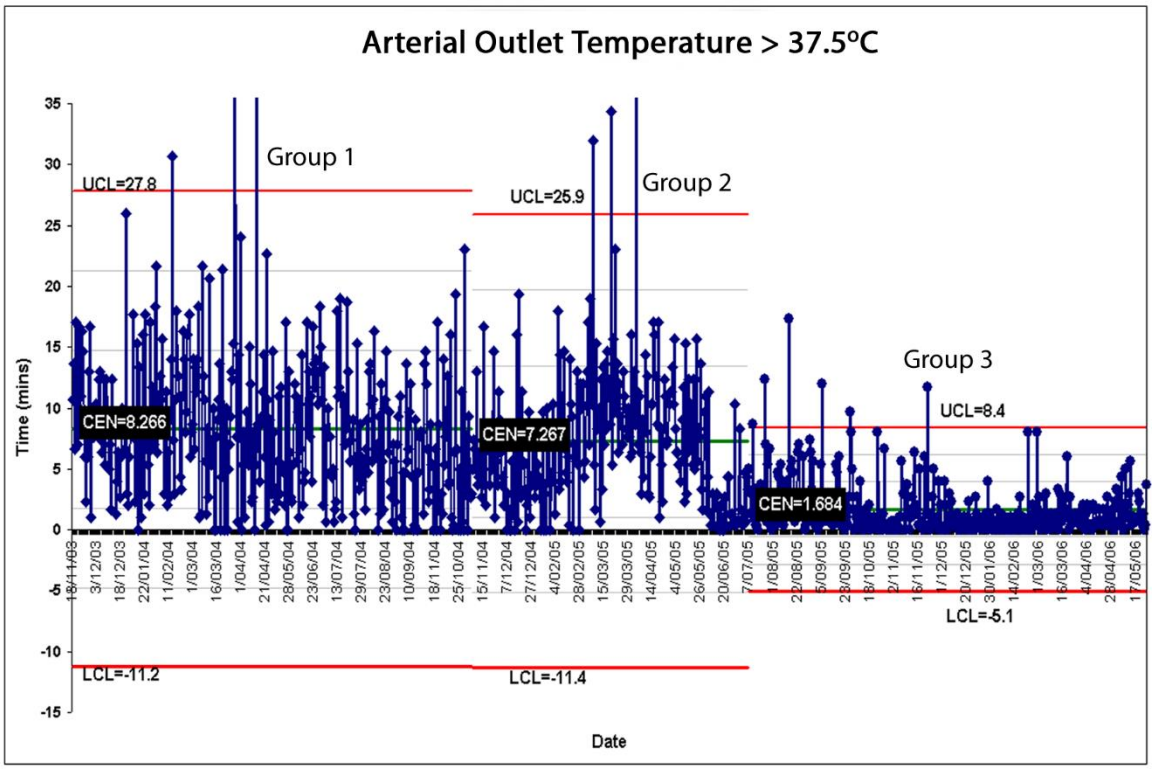

Figure 4: Xbar control chart of the average amount of time the arterial blood temperature was > 37.5^{0}C (min) for each group of patients, group 1 (pre-QC), group 2 (QC), group 3 (CQI) are displayed as split data. The vertical axis is the average time in minutes that the arterial blood temperature was > 37.5^{0}C (min). The horizontal axis shows the time period in calendar month and year. Each dot represents 20 cases. The central tendency for each group is shown (CEN), as is the upper confidence limit (UCL) and lower confidence limits (LCL). The decrease in variance is evident for groups 2 and 3 compared to group 1. Between group analysis (Kruskall Wallis) demonstrated There was a significant reduction in the amount of time the arterial blood temperature was > 37.5^{0}C (min) (Kruskal-Wallis Test chi-square 338.132, df 2, p<0.000). Group 3 spent significantly less time than group 2 (Mann Whitney z -14.226, asymptomatic p value (2 tailed) < 0.000001).

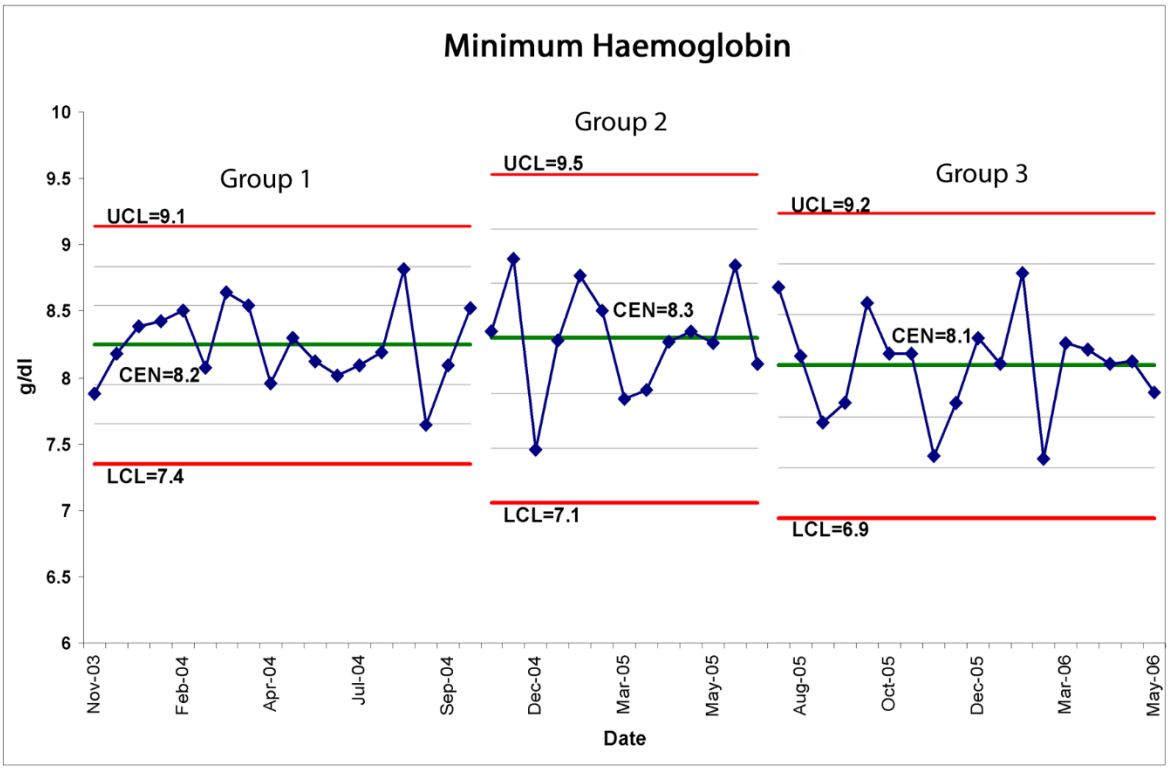

Figure 5: Xbar control chart of the average minimum haemoglobin (g/dl) for each group of patients, group 1 (pre-QC), group 2 (QC), group 3 (CQI) are displayed as split data. The vertical axis is the average minimum haemoglobin (g/dl). The horizontal axis shows the time period in calendar month and year. Each dot represents 20 cases. The central tendency for each group is shown (CEN), as is the upper confidence limit (UCL) and lower confidence limits (LCL). No change in the variance is evident between the three groups. Between group analysis (Kruskall Wallis) demonstrated no difference between groups (chi-square 2.557, df 2, p=0 .278)

Figure 6 shows the control chart of individual case data for the minimum pCO_2 (mmHg) on bypass. There was a significant increase in the average minimum pCO_2 between the groups following the introduction of the QC measures (ANOVA F (2,973) = 71.302, p<0.001); however, there was no difference between Groups 2 and 3.

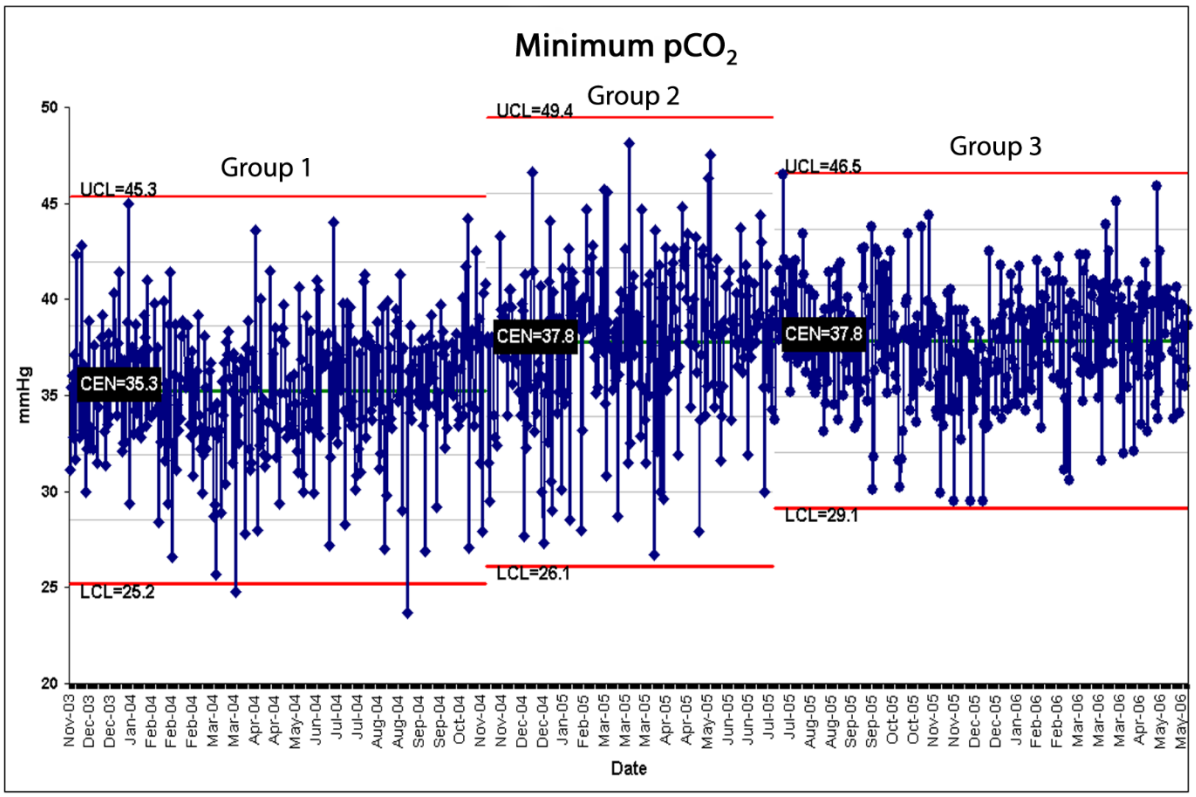

Figure 6: Individuals control chart of the average minimum pCO_2 (mmHg) for each group of patients, group 1 (pre-QC), group 2 (QC), group 3 (CQI) are displayed as split data. The vertical axis is the average minimum pCO_2 (mmHg) for each case. The horizontal axis shows the time period in calendar month and year. Each dot represents an individual case. The central tendency for each group is shown (CEN), as is the upper confidence limit (UCL) and lower confidence limits (LCL). The decrease in variance is evident for group 3 compared to group 1 and 2. Between group analysis (ANOVA) demonstrated There was a significant increase between the 3 groups ($F(2,973)=71.302$, $p<0.001$). Post hoc multiple comparison determination with the Tukey HSD revealed group 1 to be significantly different to group 2 and group 3 ($p<0.001$), whilst group 2 and 3 were not different ($p=0.990$).

Figures 7 and 8 demonstrate the maximum pCO_2 (mmHg) and minimum pO_2 (mmHg) for each group, showing a significant change between the 3 groups (ANOVA $F(2,972) = 43.759$, $p < 0.001$), ANOVA $F(2,969) = 11.262$, $p < 0.001$), respectively).

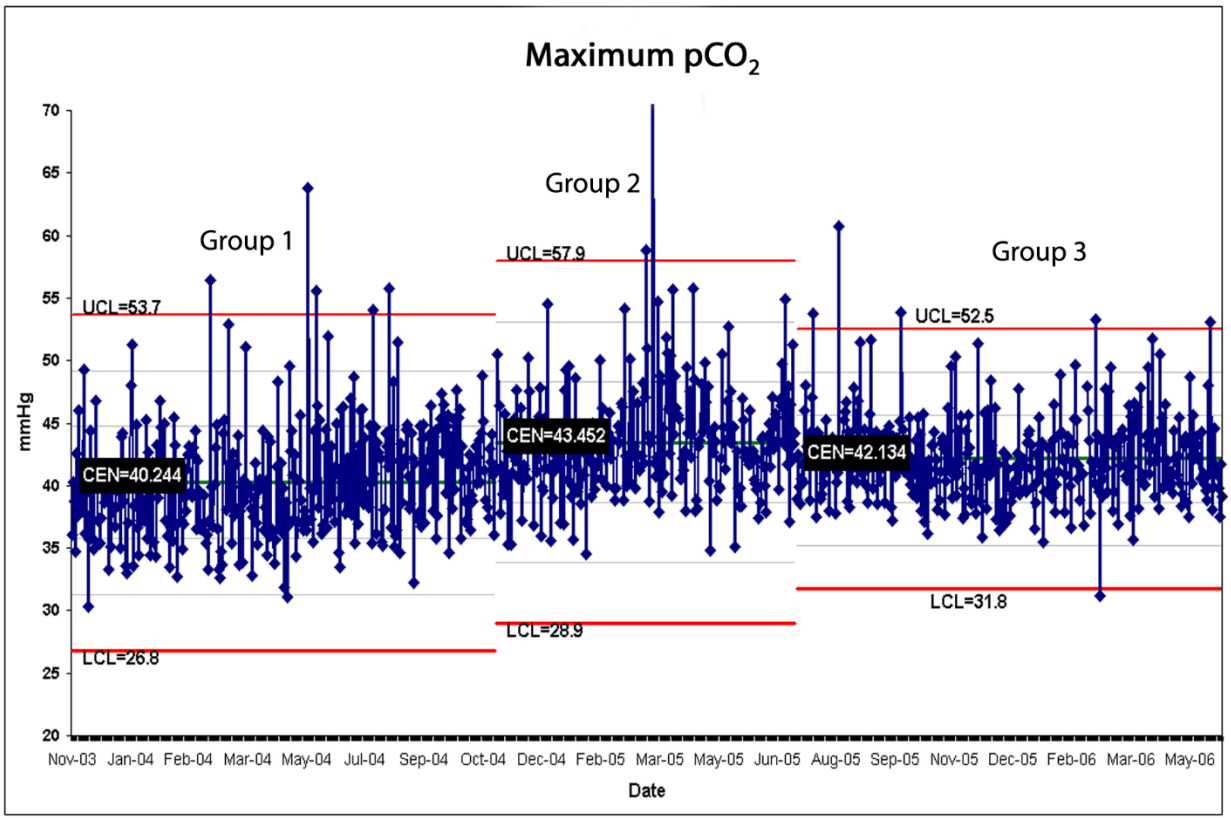

Figure 7: Individuals control chart of the maximum pCO_2 (mmHg) for each group of patients, group 1 (pre-QC), group 2 (QC), group 3 (CQI) are displayed as split data. The vertical axis is the average maximum pCO_2 (mmHg). The horizontal axis shows the time period in calendar month and year. Each dot represents 20 cases. The central tendency for each group is shown (CEN), as is the upper confidence limit (UCL) and lower confidence limits (LCL)). The decrease in variance is evident for group 3 compared to group 1 and 2. Between group analysis (ANOVA) demonstrated a significant change in maximum pCO_2 between the 3 groups ($F(2,972)=43.759$, $p<0.001$). Post hoc multiple comparison determination with the Tukey HSD revealed group 1 to be significantly different to group 2 and group 3 ($p<0.001$), group 2 and 3 to be significantly different ($p=0.001$).

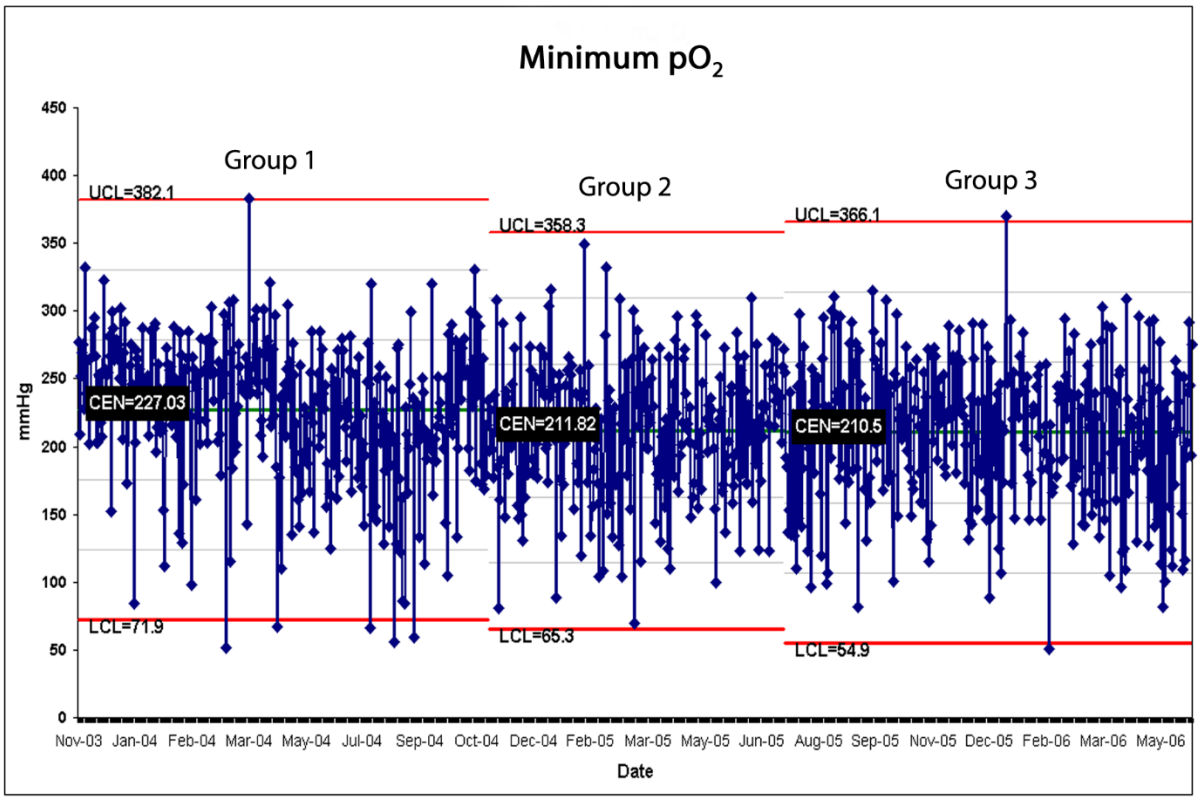

Figure 8: Individuals control chart of the average minimum pO_2 (mmHg) for each group of patients, group 1 (pre-QC), group 2 (QC), group 3 (CQI) are displayed as split data. The vertical axis is the average minimum pO_2 (mmHg). The horizontal axis shows the time period in calendar month and year. Each dot represents 20 cases. The central tendency for each group is shown (CEN), as is the upper confidence limit (UCL) and lower confidence limits (LCL). Between group analysis (ANOVA) demonstrated a significant difference between the 3 groups ($F(2,969)=11.262$, $p<0.001$). Post hoc multiple comparison determination with the Tukey HSD revealed group 1 to be significantly different to group 2 and group 3 ($p<0.001$), whilst group 2 and 3 were not different ($p=0.993$).

DISCUSSION

This report demonstrates that the implementation of a CQI process for CPB is able to improve adherence to institutional processes of care. We have demonstrated that the measurement of CPB quality indicators creates the opportunity for the perfusionist to improve the performance of CPB, as measured by QI, as a result of the availability of performance data. We have been able to show this, for example, with respect to blood gas management. In the absence of continuous in-line monitoring, blood gas measurement was routinely performed intermittently during CPB, analysis performed remotely, and data transmitted to the

operating room. Appropriate sweep gas flow rates were estimated by the perfusionist based upon both the arterial flow rate and oxygenator exhaust gas capnography values to estimate CO_2 concentration (10). The consistent improvement, seen by the increase in stability of the process, is demonstrated by the decrease in variability shown in the control charts in Figures 6 and 7. This was achieved by the perfusionist's awareness of practice outside of protocol gained by the generation of the QC report. Improvement in practice is evident with respect to the amount of time the CI was less than 1.6 L/min/m^2 or the number of minutes the arterial outlet temperature exceeded 37.5°C, as both the variability and the absolute amount of time decreased after the introduction of the QC process. This report is unable to demonstrate a clear benefit associated with the introduction of the second phase of our process; that is, the value of the quality performance review meetings, as only one QI showed further significant improvement.

Brush, et al. 2006 reported that the effectiveness of a clinical CQI program was maximised when the data was able to be reviewed in a manner that had an optimal effect on physician behaviour (14). Their aim was to create a committee framework for quality improvement within a cardiac operating centre, tasked with the implementation of a system of data measurement and feedback. They found that the provision of performance data to individuals and the introduction of performance review meetings induced buy-in to the concept of improving overall systems of care and were able to achieve both process and clinical outcome improvements. In our clinical setting prior to the introduction of our CQI programme, performance feedback occurred to the perfusionist at various intervals; intra-operatively via the data collection software in real time; postoperatively as an automatically generated report; in the CSR database when data were entered or reviewed. These data feedback methods alone

resulted in process improvement as seen for CI and arterial pressure in Figures 1 and 2. Although it is difficult to quantify the influence of the implementation of the quality review meetings as a single entity, the advantages of group discussion can be described in the context of promoting a culture of continuous practice improvement and by providing the opportunity to engage in the collective direction, implementation and monitoring of improvement initiatives. These findings are similar to those reported by Dickenson, et al. (11), who reported an autotransfusion quality indicator programme in which they highlighted the benefit of

collecting clinical performance data, revealing deficiencies in practice and creating the opportunity to implement change and improve practice. In this study, we have used statistical control charts to enable us to monitor and quantify changes in practice, and to help us translate our data into a format that made it more accessible to each member of the team. This may occur through the visualisation of trends and the calculation of control limits for the quantification of variation.

Variations in improvement between the various quality indicators may be related to the characteristics and nature of the information available to the perfusionist, such as whether the information is continuously or intermittently available. Cardiopulmonary bypass variables that are continuously monitored and available to the perfusionist include cardiac index, mean arterial pressure, venous saturation and arterial blood outlet temperature. We were able to achieve a highly significant reduction in the amount of time that the arterial outlet temperature was greater than 37.5^0C (as defined by our process of care guidelines) through the reinforcement of the importance of the compliance with this practice. The additional improvement seen in Group 3 may be the result of the reinforcement of the importance of monitoring arterial outlet temperatures as highlighted by Shann, et al (12). Improvement in process of care related to pressure, flow and venous saturation was also achieved, but associated with greater variation. Each of these latter variables is controlled by the interaction between surgeon and perfusionist working collectively to optimise the patient outcomes. To facilitate certain complex surgical manoeuvres, the surgeon may require a period of reduced flow or pressure, whilst the perfusionist may be aiming for a protocol-driven target. What is optimal will vary throughout a case, being a balance of patient-, surgeon- and perfusion-derived factors and the necessity to understand the need to collectively create the optimal environment for CPB is paramount. Improvement was found in blood gas management using intermittent analysis, although we may expect further improvement with the introduction of continuous monitoring (13,14). We did not observe a significant change in the minimum haemoglobin during CPB during the study period. This may be attributed to factors outside of the control of the perfusionist, or that, in order for us to make an improvement, a change in our practice is required. Groom, et al (9) provide an example in which improvement did occur following the introduction of smaller CPB circuits (for smaller patients), retrograde autologous priming and haemodilution prediction formula.

Our CPB quality indicators are based on our process of care guidelines which are, in turn, based on what we have determined to be the appropriate practice for the conduct of CPB based on the best available evidence and institutional practice. Quality indicators or, indeed, best practice recommendations for CPB, however, are not well described in the literature.

The American Heart Association in conjunction with the American College of Cardiology have published a guideline document in relation to coronary artery bypass graft surgery; however, this has little direct recommendations for the conduct of perfusion (15). The Society of Cardiovascular Anaesthesiology and the Society of Thoracic Surgeons have recently published broad-based guidelines related to blood conservation strategies in cardiac surgery (16). Specific perfusion recommendations were published by Shann, et al. However, they currently have a relatively narrow focus, and more work needs to be performed in this area (12). Perhaps this may be attributed to the lack of randomised studies specifically related to the management and outcomes of CPB, and the complexity of the pathophysiology related to patient morbidity and mortality.

Our technique of QI creation and analysis highlights the use of electronic data collection technology to improve process outcomes, but it also highlights the potential of this technology to determine associations between CPB variables and clinical outcomes. Although the measurement of clinical outcomes remains the “gold standard” of clinical improvement, the difficulty of demonstrating significant improvement in cardiac surgery is associated with the low frequency of adverse outcomes. The numbers required to achieve adequate statistical power in such studies may result in the introduction of bias associated with changes in practice over time. The use of mortality as a clinical endpoint is also associated with limitations, not only due to the low frequency of its occurrence, but also its value is limited unless reported as risk-adjusted or predicted versus actual mortality. The increasing adoption of electronic data collection technology and the amalgamation of collected data through national and international perfusion databases, such as the evolving Perfusion Downunder (17) or the International Consortium for Evidence Based Perfusion databases, (18) may provide us with the opportunity to reduce these limitations and evaluate clinical outcomes in greater detail. Trowbridge, et al. reported an improvement in clinical outcomes associated with the introduction of a multifactorial enhancement of CPB techniques, including the implementation of a quality improvement programme (19). This study illustrates a number of

difficulties inherent in reporting clinical outcomes improvement: firstly, the effect of the unusually high mortality rate reported in the control group; secondly, the confounding effects of multiple interventions; and finally, the statistical penalties required for analysing multiple endpoints in this manner. An issue relevant in reaching conclusions in observational studies is the inability to demonstrate cause and effect relationships. A consideration in the interpretation of the results in our current study is that changes to our practice were focussed on standardization of practice, rather than the introduction of alternative technology or techniques.

This study also has some clear limitations. We are reporting on the observed changes we have seen over time, but, whilst all of the data was collected prospectively, the data was queried in a retrospective manner. We were not able to report on a large enough sample to evaluate meaningfully any influence on clinical outcome, nor have we reported on all our processes of care, only those that we have included in our electronic QC process. Finally, the findings we have reported may not be generalised to other centres as the technology requirements of this process, whilst not overwhelming, may not be available to all centres.

We do not imply that there is a causal relationship between the QI reporting, CQI and improved practice. However, this observational study does provide supporting evidence of a benefit. This report highlights a number of important observations regarding the importance of the availability of data in CPB quality management, the importance of communication, and, hence, the inclusion of the entire cardiac team in providing information and assisting when appropriate in developing solutions to improve the process of CPB care. Although the demonstration of improvement in clinical outcomes as a result of CPB interventions has its inherent difficulties, participation in collaborative research projects based on electronic data collection may provide a fulcrum to attenuate some of these limitations and identify more definitively CPB quality indicators.

CONCLUSIONS

Measurement of CPB quality indicators creates the opportunity for the perfusionist to improve adherence to process of care guidelines as a result of the availability of performance data, highlighting the potential of electronic data collection technology in this setting. The use

of this technique is optimized when included as part of a CQI program, utilizing DMAIC methodology and statistical control charts for data analysis and interpretation.

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Chapter 2: Development of a multicentre cardiopulmonary bypass registry uniquely integrating electronic perfusion data to facilitate reporting and quality improvement through benchmarking.

2.1 The Perfusion Downunder collaborative database project.

Newland R, Baker RA, Stanley R, Place K, Willcox TW; Perfusion Downunder Collaboration. J Extra Corpor Technol. 2008 Sep;40(3):159-65.

ABSTRACT

The Perfusion Downunder Collaboration provides research infrastructure and support to the Australian and New Zealand perfusion community, with the objective of determining best practices and producing relevant research publications. The Perfusion Downunder Collaborative Database (PDUCD) has been created for the purpose of collecting a dataset for cardiopulmonary bypass (CPB) procedures that includes integration with commercially available CPB data collection software. Initial testing of the PDUCD involved collection of data from four Australian and New Zealand hospitals from March to July 2007.

Data from 513 procedures were compared with the concurrent Australasian Society of Cardiac and Thoracic Surgeons (ASCTS) database report to assess the validity of the collected data. Demographic, preoperative, and procedural variables were comparable between databases. Perfusion variables showed a median nasopharyngeal temperature of 36.7°C at separation from CPB (range, 35.3–37.5°C), which was similar to maximum nasopharyngeal temperature (median, 36.8°C). Median arterial flow and mean arterial pressure were 4.2 L/min and 57.2 mmHg, respectively. Control charts indicate a central tendency of 12.5 minutes for mean arterial pressure <50 mmHg and 3.5 minutes for arterial flow <1.6 L/min/m2 (cumulative time). There was no difference in median minimum and maximum blood glucose between diabetic and nondiabetic patients during CPB with 40% of patients receiving insulin. Median minimum and maximum activated clotting time (ACT) during CPB was 581 and 692 seconds, respectively. Outcome data for isolated coronary artery bypass grafting were similar for mortality (only) (both 1.8%). Initial data collection showed concurrent validity compared with the ASCTS database.

The inclusion of a large quantity of calculated CPB variables in the dataset highlights the benefits of electronic data collection as a research tool within a collaborative research

network and the potential for the evaluation of the relationships between patient risk factors, perfusion practice, and patient outcomes.

INTRODUCTION

The collection of data is an integral component of the research process since data management techniques may be used both in the development of a hypothesis and in the experimental technique and methodology. Analysis and processing of the data produced from the experimental method provide a means not only to evaluate the validity of the original hypothesis but also elucidate further observations relevant to the scientific manuscript. In the development of a research project, there are various methods available for data collection, and therefore, it is important that the method is chosen based on the aims, methods, and resources of the project. To ensure validity of the collected data, the data collection process must be replicable and accurate (1).

Increasingly, research studies have used electronic means rather than paper forms for data collection, and this provides a number of benefits, including a reduction in the error associated with transcription because data are entered directly and the ability of computer software to be configured to validate the data and perform skip logic [e.g., if a angina field is entered “no,” the subsequent unstable angina field automatically appears as “no” (2)].

Given that a vast quantity of data can potentially be collected during cardiac surgery and cardiopulmonary bypass (CPB) from patient monitors and clinical devices, electronic data collection during cardiac surgery provides a useful and accurate method of data acquisition. Another important consideration in the design of a research project is an accurate determination of the sample size required to make meaningful interpretation of the results possible. The creation of a research network facilitates the recruitment of observations for inclusion in studies. Research networks are a method for collection of clinical data from geographically dispersed institutions, with the advantage being that the statistical power of a particular study can be improved through an increase in sample size. Electronic data collection has been used successfully in these networks to improve the quality of data collection and reduce secondary data entry (3).

The Perfusion Downunder Collaboration aims to improve patient outcomes through its ability to provide research infrastructure and support to the Australian and New Zealand perfusion

community and to produce relevant and timely research publications (4). To support this aim, an electronic database has been created for the purpose of collecting a dataset for CPB procedures known as the Perfusion Downunder Collaborative Database (PDUCD). This report describes the development of the database and a comparison of the initially collected data with the data reported in the Australasian Society of Cardiac and Thoracic Surgeons (ASCTS) database.

MATERIALS AND METHODS

The PDUCD dataset is divided into five categories: demography, clinical (medical history, etc.), perfusion (CPB related data), procedural (surgical data), and outcome data. The complete database was designed to be comprised of three separate Microsoft Access (Microsoft, Redmond, WA) database files: a "Tables" database that stores the collected data at each institution; A "Server" database that serves as a front-end database and contains the data collection forms; and a "Transfer database" that performs the transfer and processing of the data from automated perfusion record software. The purpose of this design was to separate functionality and to provide a means of allowing multiple users to access the tables simultaneously through multiple copies of the server database. The Tables database file was developed through the creation of tables for each data category, with the majority of data fields stored in the format of coded variables. Development of the Server database file involved the creation of the data entry forms and development of automation of various tasks such as opening forms or exporting of data, through visual basic programming. The server forms provided an interface for data entry that facilitated skip logic, and a data dictionary was embedded in each form to provide definitions for each field. A frontend form was created to provide various options to the user, including the ability to create a new record, view existing records, access an administration console, or export the collected data. The administration console was created for the purpose of customizing certain default entries that would be routinely entered (such as use of arterial filter, arterial pump type, etc.), creation of usernames and passwords, and defining certain variables collected in other software (such as temperature probe locations). The database is locally protected by a user login form, which allows for security measures to be incorporated because patient identification data are

collected at the site of origin. The data export process, located within the Server database, was designed to transfer data that is nonidentifiable, in the format of text files, and involves assigning a new unique identifier for incorporation into the master PDUCD dataset. This creates anonymity of data within the master dataset but allows the data to be tracked at the point of origin by the data originators. A third database was created as a method of transferring the data from electronic perfusion record software (Stockert Data Management System; Stockert, Munich, Germany). This process allows the integration of a large quantity of data collected by automation in the operating theater, as previously described (5). During this process, a number of calculated parameters are generated from the CPB data; for example, timed quantification of mean arterial pressure, cardiac index, or arterial outlet temperature. The design of the database was intended to maximize flexibility of use to suit multiple institution's ability to access electronic data collection at the point of care. Where electronic data collection is not possible or available at the point of care, a paper form of the PDUCD dataset can be used to collect data, and data can be entered manually. The data collection workflow for the electronic data collection database is shown in Figure 1.

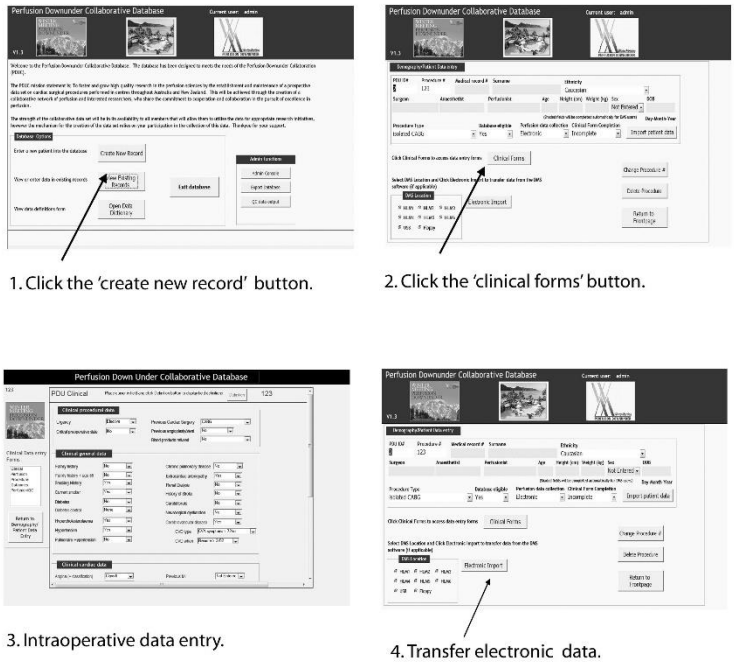

Figure 1. Data entry workflow for the database. Step 1; Click the 'create new record' button to enter the patient's demographic data. Step 2; Click the 'clinical forms' button to access the data entry forms for each category. Step 3; Clinical, perfusion, procedural and postoperative outcomes data may be entered via forms. The clinical form is shown. Step 4; Electronic data

is transferred from the electronic data management system of the heart lung machine into the database.

After appropriate clinical governance and ethics committee approval, initial testing of the PDUCDB involved collection of data from four Australian and New Zealand cardiac centers from March 2007 to July 2007. All centers used the Stockert Data Management System. A site coordinator was appointed from within each center with the responsibility of installation, configuration, and coordination of the database. In a preliminary analysis, PDUCD data were collected from 513 “data eligible” procedures. Procedures defined as eligible for inclusion were isolated on pump coronary artery bypass graft (CABG), isolated valve repair, and/or replacement and valve/CABG procedures. Both first time and redo procedures were included. A total of 179 data variables were collected in the following categories: demography (12), clinical (29), perfusion (115), and outcomes (23). The PDUCD data were compared with the Australasian Society of Cardiac and Thoracic Surgeons (ASCTS) database to assess the concurrent validity of the initial dataset. A subset of variables was selected from the PDUCD dataset to facilitate comparison with the most recently published ASCTS database data, which reported data collected from 2795 procedures in six cardiac surgical centers in Victoria, Australia (6). The most recent electronically available ASCTS database report was for the period July 2005–June 2006. The data in the ASCTS database are manually entered by medical staff into a purpose-designed database and stored electronically. The dataset has been reported annually since 2002. Continuous physiological and perfusion variables are not collected in the ASCTS database; only minimal operative nonprocedural data are collected.
Demographic and procedural variables included patient age distribution, procedure type, conduits used left internal mammary artery (LIMA), right internal mammary artery (RIMA) radial artery (RADG), gastroepiploic artery (GEPA)], and average number of grafts in CABG. Clinical variables included preoperative risk factors (smoking, recent myocardial infarction, hypertension, peripheral vascular disease, cerebrovascular disease, diabetes). A further subset of data to compare outcomes data in isolated CABG was comprised of mortality, new renal failure, stroke, cerebrovascular complication, return to theater, and red blood cell transfusion. Definitions for each variable were equivalent other than for recent myocardial infarction (MI), which is defined in the current dataset as a MI within 90 days before surgery compared with 21 days in the ASCTS data. Off-pump CABG procedures are included in the

isolated CABG group in the ASCTS data; however, they are grouped into the “other” category in the PDUCD. A small subset of variables related to CPB management was also included (activated clotting times and blood glucose concentrations both manually collected, and temperature, pressure, and flow management all collected continuously electronically). Because these data have not previously been reported as part of a registry, comparative data were not available. Statistical control charts were used to display the data obtained for CPB quality indicator variables mean arterial pressure (MAP) <50 mmHg and cardiac index <1.6 L/min/m2 (both cumulative time). Data for these two variables were collected every 20 or 30 seconds during CPB using the Data Management System. Pressure artefacts and periods of partial CPB were automatically excluded from analysis by programming techniques. Control charts of individual case data were created using SPCXL (Air Academy Associates, Colorado Springs, CO) with Shewhart control limits set at ±3 SD.

RESULTS

Comparison of PDUCD and ASCTS Database

Demographic and procedural variables for the PDUCD data eligible patients (CABG, isolated valve, and valve/ CABG) were closely comparable to the ASCTS database for procedure type and age distribution (Table 1). Internal thoracic arterial grafts for isolated CABG were similar for both datasets, but use of radial artery grafts was markedly different. Preoperative risk factors for both datasets were also comparable (Table 2). Preliminary outcome data collected to date for isolated CABG was similar to ASCTS for mortality only (Table 3).

Table 1. Demographic and procedural data

Procedure types	n	PDUCD (%)	ASCTS (6) (%)
Isolated CABG	339	50	63
Isolated valve	107	15	13
Valve CABG	67	10	10
Other	162	24	14
Total	675		
Eligible	513		
Age distribution			
< 40 yrs		4	4
40 - 49 yrs		7	6
50 - 59 yrs		17	18
60 - 69 yrs		30	30
70 - 79 yrs		31	34
80+ yrs		11	7
Conduit use (CABG)			
LIMA		93	85
RIMA		3	1
RADG		14	54
GEPA		0	0
Mean no. grafts		2.7	3.4

Abbreviations: PDUCD, Perfusion Downunder collaborative database; ASCTS, Australasian Society of Cardiac and Thoracic Surgeons; CABG, coronary artery bypass graft; LIMA left internal mammary artery; RIMA, right internal mammary artery; GEPA, gastroepiploeic artery.

Table 2. Patient preoperative risk factors

	PDUCD (%)	ASCTS (6) (%)
Current smoker	13	13
Recent myocardial infarct	26	19
Hypertension	65	71
Peripheral vascular disease	11	13
Cerebrovascular disease	7	12
Diabetes	27	29

Abbreviations: PDUCD, Perfusion Downunder collaborative database; ASCTS, Australasian Society of Cardiac and Thoracic Surgeons

Table 3. Clinical outcomes

	PDUCD (%)	ASCTS (6) (%)
Mortality	1.8	1.8
New renal failure	2.1	5.1
Stroke	2.1	0.7
Encephalopathy	4.7	1.4
Return to theatre	10.6	5.1
Red blood cell transfusion	33	43.4

Abbreviations: PDUCD, Perfusion Downunder collaborative database; ASCTS, Australasian Society of Cardiac and Thoracic Surgeons

CPB Variables

Perfusion variables showed a median nasopharyngeal temperature of 36.7°C at separation from CPB (range, 35.3–37.5°C), which corresponds with the maximum nasopharyngeal temperature (median, 36.8°C; range, 35.3–37.6°C). Median MAP was 57.2 mmHg and arterial flow was 4.2 L/min (Table 4). Control charts indicate a central tendency of 12.5 minutes for MAP <50 mmHg (Figure 2) and 3.5 minutes for arterial flow <1.6 L/min/m2 (Figure 3).

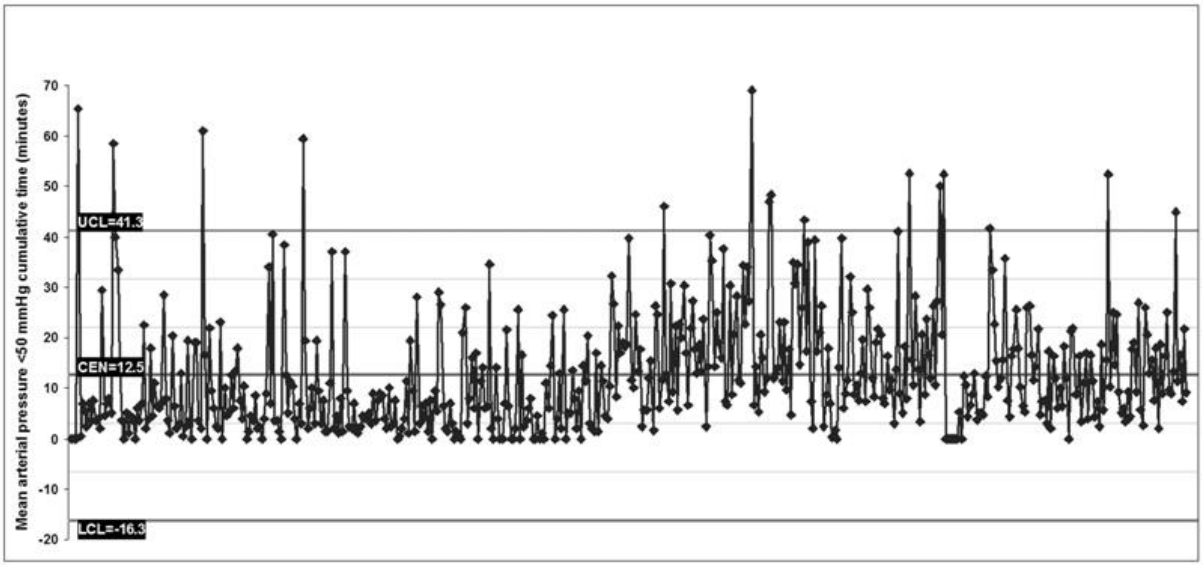

Figure 2. Control chart of individual case data (horizontal axis) for the amount of cumulative time that the mean arterial pressure was less than 50 mmHg (vertical axis). CEN = central tendency (mean), UCL = upper control limit, LCL = lower control limit. Cases are ordered chronologically.

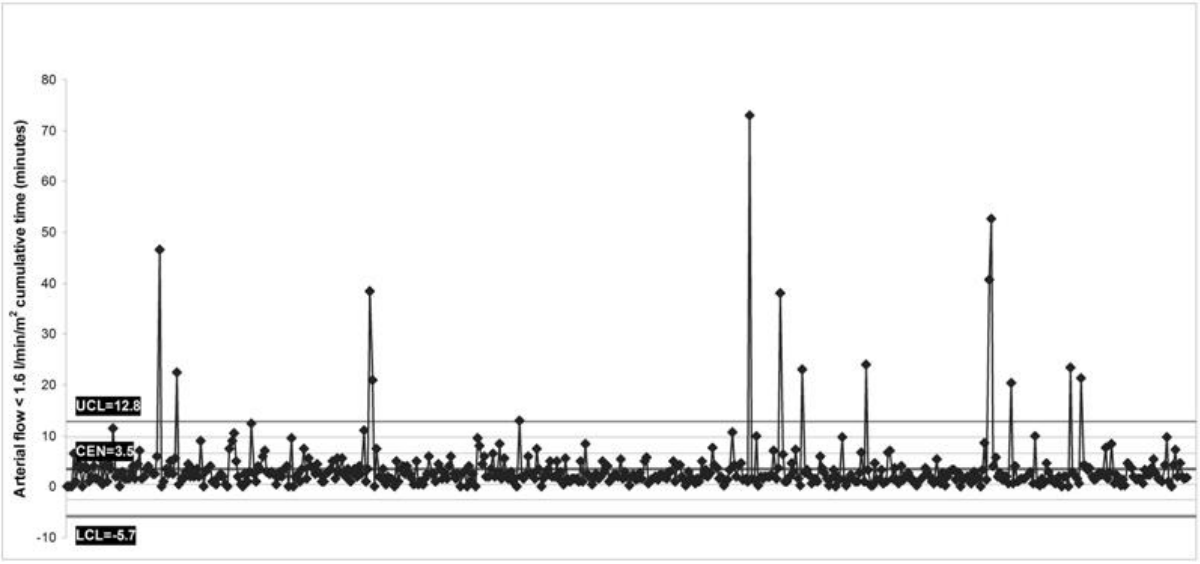

Figure 3. Control chart of individual case data (horizontal axis) for the amount of cumulative time that the arterial flow less than 1.6 L/min/M2 (vertical axis). CEN = central tendency (mean), UCL = upper control limit, LCL = lower control limit. Cases are ordered chronologically.

There was no difference in median minimum and maximum glucose between diabetic and nondiabetic patients during CPB, despite 40% of patients having glucose management with insulin (Figure 4).

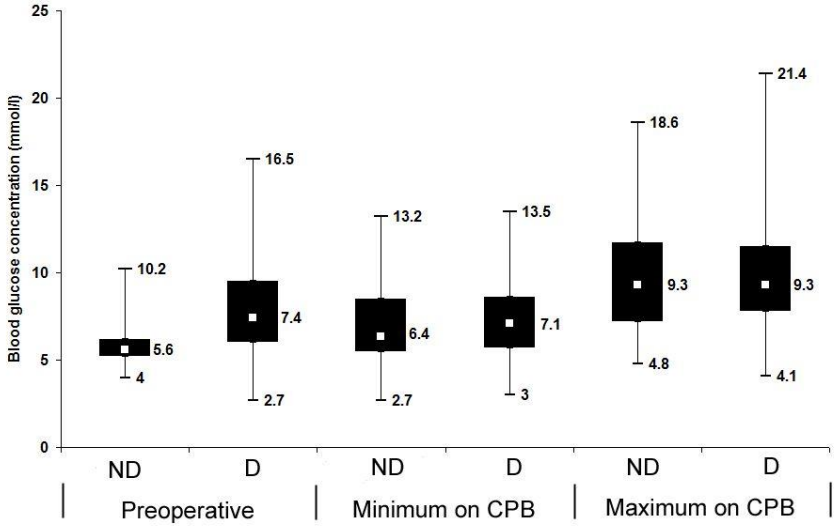

Figure 4. Box plot of blood glucose values comparing diabetic and nondiabetic patients, preoperatively and minimum and maximum values during CPB. ND = nondiabetic, D = diabetic. Displayed values indicate median and range.

Median minimum and maximum ACT during CPB were 581 and 692 seconds, respectively (Figure 5).

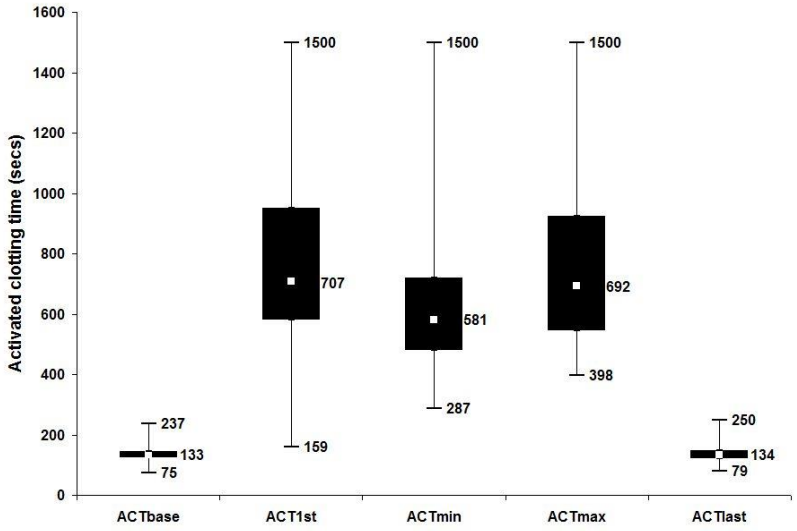

Figure 5. Box plot of activated clotting times. ACTbase; prior to heparinisation, ACT1st; 1st on CPB, ACTmin; minimum on CPB, ACTmax; maximum on CPB, ACTlast; post reversal of heparin. Displayed values indicate median and range.

DISCUSSION

The task of collecting high-quality research data in clinical environments provides a number of challenges, and therefore, it is important to match the method of data collection with the objectives of the research project. When considering electronic data collection as an option, the following questions need to be addressed (2). Do the study designs lend themselves to electronic data collection? Is the expertise available to implement electronic data collection? Can the development and administration of the database be supported and assistance be provided at the point of data entry?

The aim of the Perfusion Downunder Collaboration is to generate a prospectively collected dataset for the evaluation of hypotheses relating to CPB as it is conducted in Australia and New Zealand. Electronic data collection meets the needs of this endeavor because it provides a method of transferring data from multiple sites, integration of this data into a central database, and a means to generate calculated CPB parameters and perform complex data

analysis. Flinders Medical Centre has collected clinical data using this technology since 1992, and having dedicated personnel responsible for the development and administration of our database is well placed to support the PDUCD. Other centers contributing to PDUCD have found that establishment of a site coordinator role with appropriate time and resources are beneficial in the implementation, management, and coordination of the database.

The generation of a perfusion record is an integral part of CPB, and a number of electronic record systems have been developed to automate the majority of this process and improve the accuracy of the collected data (7,8). The Stockert Data Management System has been successfully integrated into a multicenter perfusion database, and the integration of alternative software is a major focus for current development to attract users of other systems. Integration has been achieved with the Jostra perfusion data collection software (Jocap XL; MAQUET Cardiopulmonary, Hirrlingen, Germany), and we look forward to incorporating data from multiple electronic perfusion data sources in the future.

Newland et al. (5) previously reported a technique in which the data collected by an automated CPB system can be integrated into a research database and during this process generate CPB quality indicators. However, a limitation of this process in relation to clinical practice is that measures of CPB "quality" have not been well described, and thus the definition of quality indicators may be considered subjective. It has been suggested that there is a need for the development of standards of practice for CPB obtained through the mandates of evidence-based medicine (9). One study designed to assess both the quantity and quality of the literature supporting principles currently applied to CPB concluded that the scientific data are insufficient on both counts to reliably serve as a basis for practical, evidence-based guidelines (10). One of the problems inherent in the interpretation of the clinical measures of outcomes from CPB is the low event rate of adverse events, resulting in the requirement of large cohorts to achieve adequate statistically powered studies. Amalgamation of collected data provides a means to increase cohort size and therefore reduce the confounding effects of practice changes over time. The PDU Collaboration and the PDUCD is a means to facilitate these objectives as may eventually be a recently established international consortium for evidence-based perfusion (11).

Such ventures are subject to rigorous ethical scrutiny. The most recent publication of the National Statement on Ethical Conduct in Human Research developed jointly by the National

Heath and Medical Research Council, the Australian Research Council, and the Australian Vice- Chancellors' Committee has for the first time included a chapter on databases (12). An important consideration in the ethical collection of patient information is whether data collected can be identified. The Statement has defined three levels to characterize how data are identified: individually identifiable data, where the identity of a specific individual can be ascertained; re-identifiable data, where identifiers have been removed and replaced with a code to facilitate re-identification of an individual; and nonidentifiable data, where there is no means to identify a particular individual, although it may be possible to link different datasets for the same individual. Currently, the data in the PDUCD will be individually identifiable at the site of collection, and on integration into the collaborative dataset, the data will be nonidentifiable to the custodians of the data and for research generated from the dataset. Other ethical concerns raised in the Statement include the requirement to conform to patient consent guidelines, the promotion of research through data accessibility, and that the use of the data by individual researchers must comply with any conditions relating to identification. The inclusion of this chapter in the national ethical research statement reflects the recognition of electronic data collection being increasingly adopted as a modality to facilitate the collection and dissemination of research information.

Concurrent validity may be defined as the ability of a newly developed measure to predict the results of an existing measure that represents a reference standard (13). The preliminary analysis of the initial PDUCD data collected from four centers showed concurrent validity in patient demographic and preoperative variables compared with the much larger ASCTS database from the same region. Differences in reported procedural variables could be attributed to regional surgical preferences, for example, use of the radial artery as a conduit for CABG. Future prospective collection will provide cumulative data for comparison; however, recruitment of additional contributing centers would provide a more representative dataset for comparative purposes. Some differences were observed in the outcomes data variables reported. These are likely to be related to the size of the datasets being compared. In this preliminary PDUCD report, we reported a 3-month period, whereas the ASCTS dataset is for a 12-month period from six centers. Alternatively, the differences in outcome data may reflect real differences introduced caused by the geographical separation of the hospitals, or the differences may reflect differences in methods of data collection. Another factor is that

offpump cases are reported in the ASCTS data set but not in the PDUCD data, which creates a limitation in the comparison of the outcomes data.

The variables included in this report show that those routinely recorded during CPB have been successfully integrated into a multicenter database. The inclusion of a large quantity of calculated CPB variables in the PDUCD dataset highlights the potential for the creation of a multicenter registry for the evaluation of the relationships between patient risk factors, perfusion practice, and patient outcomes: the cornerstones in the evaluation of perfusion best practices.

In conclusion, the advantage of this novel perfusion database is that it provides the benefits of electronic data collection as a research tool within a collaborative research network and has the ability to perform complex data processing techniques for the analysis of CPB parameters. Use of the PDUCD and participation in the PDUC has the potential to provide a multicenter perfusion registry for the evaluation of best practices and the testing of scientific hypotheses, ultimately benefiting all the perfusion community and most importantly our patients.

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2.2 Integration of Electronic Perfusion Data for Perfusion Registries.

Newland RF, Baker RA, Barratt CA.

J Extra Corpor Technol. 2018 Jun;50(2):102-112. PMID: 29921989; PMCID: PMC6002640.

ABSTRACT

Although the potential for the utilization of electronic perfusion data (EPD) from proprietary software to facilitate the understanding and improvement of cardiopulmonary bypass (CPB) has been recognized, the generalizability of previous reports of EPD integration are limited by superseded software or lack of sufficient detail for reproducibility. To date, the Australian and New Zealand Collaborative Perfusion Registry (ANZCPR) is the only multicenter perfusion registry to have reported the integration of EPD.

The inclusion of EPD in analyses of the impact of CPB on patient outcome is important to improve the understanding of CPB practice on outcome. Perfusion registries play an important role in this process, and the incorporation of EPD into perfusion registries could make a significant contribution towards this objective. By sharing the methodology used to integrate EPD from the CONNECT™ software into the ANZCPR, our intent is to diminish some of the barriers to adoption of EPD integration into other perfusion registries, by providing an example of how EPD integration may be achieved.

INTRODUCTION

The potential for the utilization of electronic perfusion data (EPD) from proprietary software to facilitate the understanding and improvement of cardiopulmonary bypass (CPB) has been recognized (1-3). We have previously reported how the integration of EPD into perfusion registries can facilitate quality improvement through benchmarking (4). To date, the Australian and New Zealand Collaborative Perfusion Registry (ANZCPR) is the only multicenter perfusion registry to have reported the integration of EPD. We reported a method for the automation of feedback of CPB quality parameters using the Data Management System (DMS) software (Stockert, Munich, Germany) (1); however, upgrades to this software have ceased and it has been replaced by CONNECT™ (LivaNova PLC, London, UK). Furthermore, our

previous work did not describe in sufficient detail the methodology used to transfer data from the DMS to our local registry. These limitations may be contributing factors for the non-integration of EPD into other registries. This paper describes, in detail, the methods used to integrate EPD from the CONNECT™ software into the ANZCPR.

DESCRIPTION

Database structure and connection

Microsoft Access (MS Access) (Microsoft Corporation, Redmond, USA) was chosen as the database platform to integrate EPD based on the availability of the software at participating ANZCPR hospitals, and our experience using MS Access in the integration of EPD in our own institution. CONNECT™ utilizes a Microsoft SQL Server database platform, which can be accessed via the Microsoft SQL Server Management Studio application. CONNECT™ is installed as two separate programs: the Manager program, which has access to all patient records, and the Recorder program, which is utilized on the heart-lung machine for collection of individual patient data during CPB. An open database connection (ODBC) was used to create a connection between MS Access and the CONNECT™ Manager database. The ANZCPR database structure consists of a Server database, a Tables database and a Transfer database (Figure 1). The clinical dataset for the ANZCPR is stored in the Tables data. The Server database provides a front-end to the dataset and provides data entry, data export, report generation and administrative functionality. The Transfer database provides connection and transfer of EPD from CONNECT™ to the Tables database.

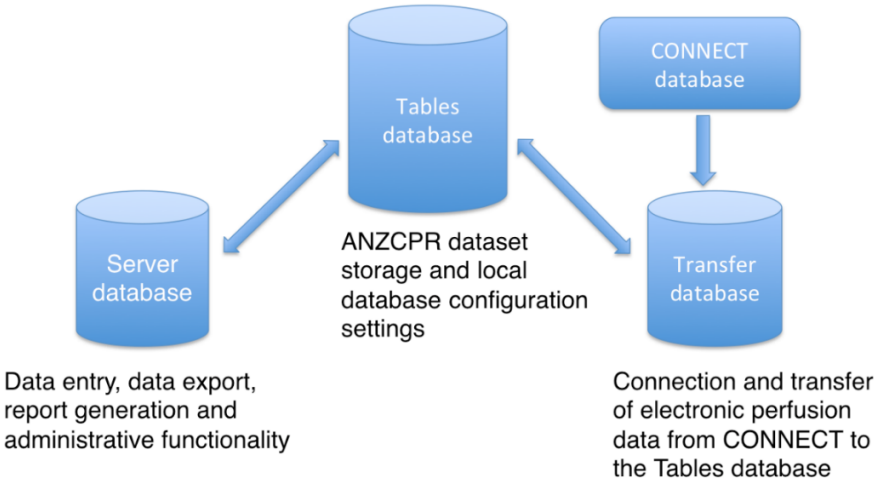

Figure 1. ANZCPR database structure and linkage to the CONNECT™ SQL database.

Each participating ANZCPR hospital has one Tables and Transfer database but may have multiple Server databases. In a local area network environment, this design allows access to the ANZCPR from either desktop or heart-lung machine computers by linking each instance of the Server database to the Tables and Transfer databases as linked MS Access tables. Using Microsoft Windows 7, ODBC connections were created using the ODBC Data Source Administrator window from the Administrative Tools tab to link the CONNECT™ tables to the Transfer database. Administrative rights may be required to achieve integration of EPD from CONNECT™ or perform other tasks as outlined in this document; therefore, consultation and assistance from Hospital IT departments is recommended.

CONNECT™ may either be installed on a local computer or on a hospital-based SQL server. During installation the authentication method is set as either integrated Windows authentication or SQL server authentication. Using the ODBC Data Source Administrator window, a connection to CONNECT™ is configured using the SQL Server Native Client 10.0 driver if the CONNECT™ database is installed on the local computer, or using the SQL Server driver if it is installed on the hospital SQL server. To add a new data source to a locally installed CONNECT™ database, the server name is localhost\sqlexpress. For SQL server connection, the hospital server name is required. Authentication using integrated Windows authentication or SQL server authentication is selected as appropriate. The default database is set to 'ConnectManager'. An ODBC connection is required for each computer on which the Server database is used for EPD integration.

Linking patient records, data encryption & de-identification of patient data

Patient data records in ANZCPR are linked to the corresponding patient data in CONNECT™ by entering the ANZCPR CPB procedure number into the 'Case record' field in CONNECT™. Each participating ANZCPR hospital may choose their own CPB procedure numbering system. Within the ANZCPR databases, the CPB procedure number is used as the primary key to link data between tables. Patient identifying data is transferred only to the participating ANZCPR hospital database, and are not exported as part of the collaborative ANZCPR data harvest as per the ethics requirements of the ANZCPR (386.15, Southern Adelaide Clinical Human Research Ethics Committee). Within the ANZCPR Server database, the 'demography' table is used to generate and store an auto-number that serves as the unique registry ID for each

procedure. A separate table stores a unique hospital ID value. When data is exported for the collaborative data harvest, the hospital ID and the registry ID are exported to create a combination of unique record identifiers without patient identification. CONNECT™ has the option of encrypting the patient identifying data (default) which is set as default in the ONNECT™ Manager configuration file. It is not possible to link records in CONNECT™ for integration of EPD without decryption of patient identification. Instructions for editing the configuration file can be found in the CONNECT™ service manual ((5), section 4.2, p 62). In the following command line, value="true" is changed to value="false" to enable decryption and linkage of patient data;

Encrypted: <add key="Database.PatientData.Encryption.Enabled" value="true" />

Decrypted: <add key="Database.PatientData.Encryption.Enabled" value="false" />.

Changing this command line will result in subsequent records being stored with decrypted data. Records already encrypted may be decrypted using the CONNECT™ Manager Configuration Studio application, as described in the Service Manual ((5), section 5.7.1, p 123).

CONNECT™ Electronic Perfusion Data structure

CONNECT™ has a number of tables dedicated to storage of various clinical data such as patient details, CPB equipment and disposables, priming solutions, laboratory biochemical data, cardioplegia delivery, procedural details, heart-lung machine and patient monitoring data. The CONNECT™ tables currently utilized for EPD transfer into the ANZCPR and description of clinical data contained therein are listed in table 1. The structure of the majority of the tables is in wide format, in which each different data variable is stored in a separate column; however, for the PerfusionStreamData table, the different variables from the physiological monitor are stored together in one column. In order to separate individual values, a specific process was developed using Visual Basic for Applications (VBA), the scripting language used within MS Access. The VBA script development to convert the physiological data stream into a data table in wide format was a key component of the EPD integration into ANZCP. The intraoperative data in the CONNECT™ tables is time-stamped, allowing linkage of the physiological data to the procedural and device data. The unique identifying value for each record within the CONNECT™ database is stored in the 'Guid' field

in the Surgery table. This value is stored in each table containing procedural data in the 'SurgeryGuid' field. In a relational database, this is known as the primary key.

Initiation of the Electronic Perfusion Data integration process

Not all data from each table is transferred to the ANZCPR. All heart-lung machine, cardioplegia, blood gas and physiological data are transferred; however, all other ANZCPR data-set variables that can be obtained from the CONNECT™ EPD are populated through the use of VBA programming contained within a module in the Transfer database. To activate the transfer of the EPD, the user clicks a button on the current patient record form in the Server database (Figure 2). Clicking the button activates a VBA sub-routine that initially checks whether the Transfer database is currently in use, to limit transaction to one record at a time. If the Transfer database is ready to begin a new transaction, the ANZCPR CPB procedure number of the current record is stored in a transaction table in the Tables database. A 'transaction in progress' indicator is set and remains in place until data processing and transfer is complete.

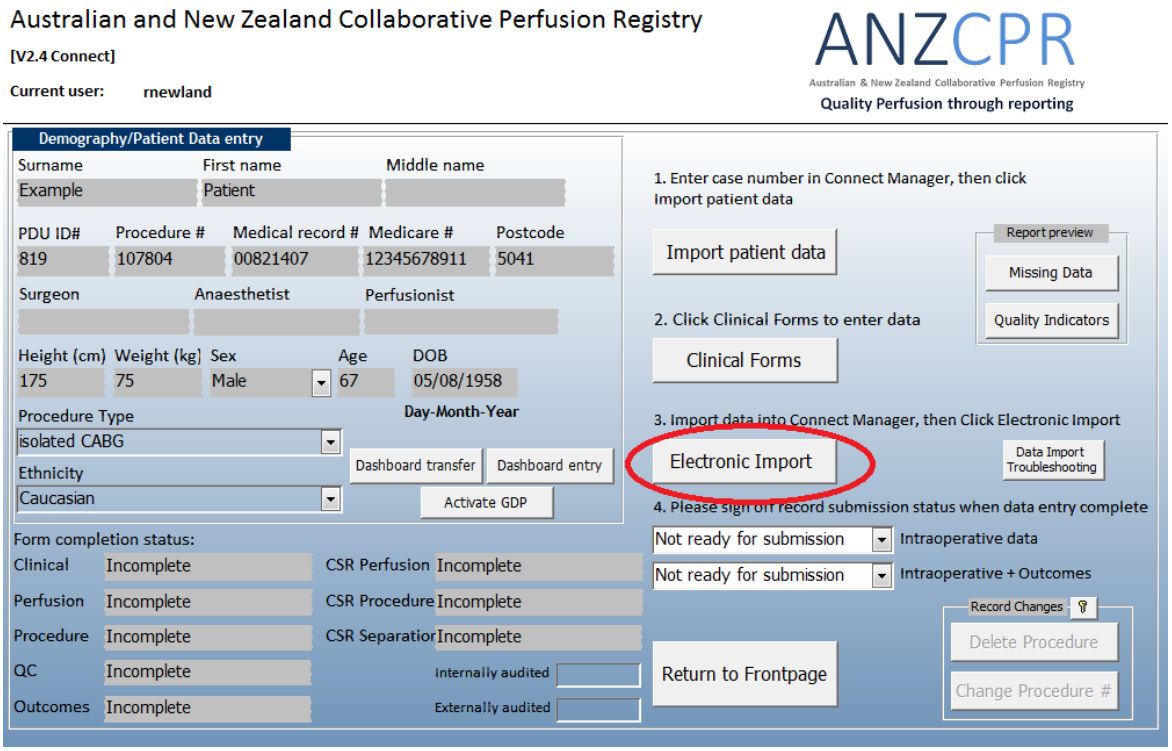

Figure 2. The current patient record form; to transfer data from CONNECT™ to the ANZCPR, the user clicks the electronic import button.

A configuration table is used to store the location of the Transfer and Tables databases at each participating hospital that can be referenced in the VBA sub-routine. The location of the Transfer database is determined, the database is opened and the EPD integration process is initiated. In order for the VBA subroutine to reference the appropriate libraries (listed in Appendix 1), these should be initialised in MS Access. The VBA subroutine for initiating the EPD process is reported in Appendix 2.

Electronic Perfusion Data integration process

The VBA subroutines and functions for the EPD integration process are contained within a module in the Transfer database. The overall process is controlled from a main subroutine that calls other sub-routines and functions to perform specific tasks. The sequence is executed as follows; initially, the ANZCPR CPB procedure number that was stored as part of the EPD initiation process is determined. Using structured query language (SQL) the CPB start and stop times are determined by searching for these data in the CPB event data table (EventData).

The physiological data stream is converted into a data table in wide format. This process activates a separate sub-routine for this purpose which:

- defines the labels of the fields' names to search for in the data stream.
- creates a record-set using an SQL query.
- evaluates each stream of data to extract the numerical values for each field name.
- populates a table in the Transfer database with the data.

Table 1. CONNECT™ tables utilised for transfer of data into the Australian and New Zealand Collaborative Perfusion Registry.

CONNECT table name	Data description	Storage frequency
CalculationData	Calculated CPB data variables eg; cardiac index, dP, dT, etc	Every 20 seconds
CardioplegiaData	Cardioplegia details; type, route, temperature, pressure, volume, etc	Per dose delivered
CoagulationData	Coagulation test results; ACT, INR, Pt, etc	Per sample
EventData	CPB events recorded automatically (alarms, timers, etc) and as entered by the Perfusionist	Per event
GasFlowData	Gas flow data recorded from the electronic blender; gas flows, FiO2, etc	Every 20 seconds
LaboratoryData	Blood gas machine data (external to heart lung machine)	Per sample
MetabolicData	Data for calculated oxygen delivery and carbon dioxide elimination	Every 20 seconds
Patient	Patient details; name, date of birth, gender, etc	Per patient
PerfusionData	Heart lung machine data; pump flows, pressures, temperatures etc	Every 20 seconds
PerfusionStreamData	Patient physiologic monitoring data; blood pressures, temperatures, heart rate, etc	Every 20 seconds
Surgery	Primary key field (SurgeryGuid), and procedural data for each record; date of operation, case record numbers (unique identifiers)	Per procedure
SurgeryAttributeValue	Reference table used to categorise system values	n/a
SurgeryCaseData	Patient and procedural details; height, weight, urgency of procedure, blood type, etc	Per procedure
SurgeryEquipment	CPB hardware, disposables, cannulae, implants, etc	Per procedure
SurgeryTeamMember	Operating team member names	Per procedure.
SurgeryTeamRole	Reference table used to categorise professions of team members	n/a
SurgeryVolume	Fluid and drug administration or loss values	Per event
TimerData	Timer values for the HLM (CPB, clamp, etc) and for events defined as having timer values	Per timer

Since the physiological variables collected at each participating hospital may be different, the sub-routine must include each CONNECT™ label used and these must also be fields in the Transfer database table. Consistency in labelling CONNECT™ physiological variables should be maintained across participating hospitals. This table is empty at the beginning of the EPD integration process. The data from each individual patient record is then used to generate calculated variables and then the complete physiological dataset appended to a registry table (ConnectPerfusionData) for storage of multiple patient records. Generating calculated variables creates a single record summary from the multiple data points collected during the

bypass period every 20-60 seconds for each procedure. For example, the average cardiac index during CPB is a single data value calculated from the patient's entire record. Storage of the entire physiological data stream in a dedicated table in wide format is an important step in the integration of EPD with the CONNECT™ system, since it provides storage of the EPD in a format that allows generation of additional calculated registry variables from the original data if required. The VBA script for the conversion of the physiological data stream is reported in Appendix 3.

EPD variables may be either transferred directly from CONNECT™ data fields (e.g., CPB time); however, the majority are calculated values during the CPB period, such as minimum haemoglobin, average cardiac index, duration that the mean arterial pressure < 50mmHg. SQL queries are then used to create record-sets along with VBA functions to determine the EPD variables according to the ANZCPR EPD data definitions. The main VBA sub-routine with examples of how various types of EPD variables are generated is reported in Appendix 4.

In order to make calculations on the data from electronic perfusion software, and to transfer certain data fields, some conventions, common to all participating sites are required, these include; "Rewarm" must be included as a comment during the procedure for calculation of temperature parameters during rewarming. "Heparin" and quantity must be entered to define heparin given during CPB. "Partial bypass" can be commented to remove the period of partial bypass from evaluation of cardiac index for quality indicator calculation purposes. The timer labels "Bypass Start" and "Bypass Stop" and "X-Clamp On" and "X-Clamp Off" must be used. In the coagulation table, the sample type "1st ACT post hep" must be used to define the 1st ACT measurement after heparin is administered. Blood gas, haemoglobin and glucose values transferred from an external blood machine (intermittent sampling) are used for blood gas and electrolyte quality indicator data. Continuous blood gas data is used for quantification of oxygen delivery if the Spectrum M4 monitor (Spectrum Medical, Gloucester, UK) is utilised. In this case, arterial flow data is obtained from the M4. Since not all centers use continuous blood gas monitoring with an arterial flow probe, the arterial flow rate from the heart lung machine is used for calculated cardiac index parameters.

The values returned from each query or function are updated to the appropriate field within the ANZCPR using a specific sub-routine reported in Appendix 5. Once the physiological stream data has been processed, the data in the Transfer database table is deleted in

preparation for the next patient record to be processed. Finally, the transaction table is reset to allow processing of the next EPD record.

Since CONNECT™ does not allow deletion of event data from the record, errors in manual data entry are marked with 'E' in the comment field for each event, which allows exclusion of these events from analysis. A configuration table in the ANZCPR allows for variation in units of haemoglobin measurement, blood gas pressure units and data collection interval.

ANZCPR database elements for Electronic Perfusion Data integration

The database tables and field names that are required within the ANZCPR are listed in table 2. The Tables database has four tables that are used for EPD integration;

- The Config table stores the data collection interval, and units of measurement for haemoglobin and blood gas values.
- The ItemLocations table stores the location of the Tables and Transfer databases.
- The sysFlags table stores the current status of the EPD integration process (whether a record is currently being processed).
- The ConnectPerfusionData table stores the perfusion stream data in wide format.

The Transfer database has one table (PerfusionStreamData) for temporary storage of the CONNECT™ perfusion data stream to facilitate conversion to wide format. The perfusion data stream is stored permanently in the ConnectPerfusionData table in the Tables database. All other tables accessed by the Transfer database are linked tables stored in the CONNECT™ database or the Tables database.

Currently, 88 of the 310 variables that comprise the ANZCPR dataset are generated from EPD integration. These variables are stored throughout each of the ANZCPR data-set tables. ANZCPR data-set variable definitions are available on the ANZCPR website (www.anzcpr.org).

DISCUSSION

This paper describes the process to integrate EPD from the CONNECT™ software into the ANZCPR. Whilst this method specifically applies to integration of data from the CONNECT™ software into a MS Access database, the principles of EPD integration can be generalized to other perfusion data collection systems and registry datasets. These principles include: creation of registry variables that can be populated with EPD either directly or derived

through calculation; procedural record data linkage between the registry and the EPD source database through a unique identifier; development of a process to query the EPD source database and update the registry variables; and additionally, store the EPD in a format that allows access generation of additional registry variables if required. We have reported the main VBA sub-routine used with examples of how various types of EPD variables are generated in the ANZCPR. These examples can be generalized to other perfusion registry variables through alteration of the SQL query structure to suit the registry variable definition and the EPD source. An important consideration in the automated collection of data is limiting the impact of erroneous data. For example, continuous data from online blood gas monitoring devices may be erroneous until a calibration sample has been performed. Similarly, errors in pressure or temperature measurements may occur. Data processing can be used to limit the influence of erroneous data through the development of specific approaches to each issue, for example; continuous blood gas data can be excluded from analysis until the time that the first calibration sample is received. Data that is clearly outside of normal physiological ranges can also be excluded. Furthermore, in a registry setting, some variation in the accuracy of certain data variables may occur. For example; variation in the accuracy of arterial outlet temperature may be influenced by differences in accuracy of oxygenator temperature probes. Variation in the accuracy of flow rates, used to calculate cardiac index and oxygen delivery may be introduced, either by using fixed arterial pump flow rates for all values irrespective of flow through arterial-venous shunts in the CPB circuit or due to the positioning of ultrasonic flow probes in relation to shunts. Although the potential for EPD to influence perfusion practice has been demonstrated (1-3), the generalizability of previous reports of EPD integration are limited by superceded software or lack of sufficient detail for reproducibility. The ANZCPR have utilized EPD to achieve multi-center process improvement as an example of how EPD can be used for generation of CPB quality indicators (QI) (4) to facilitate continuous monitoring of QI parameters and benchmark local performance to other hospitals. The inclusion of EPD in analyses of the impact of CPB on patient outcome is important in improving the understanding of CPB practice on outcome. Perfusion registries play an important role in this process, and the incorporation of EPD into perfusion registries could make a significant contribution towards this objective. By sharing the methodology used to integrate EPD from the CONNECT™ software into the ANZCPR, our

intent is to diminish some of the barriers to adoption of EPD integration into other perfusion registries, by providing an example of how EPD integration may be achieved.

Table 2. Australian and New Zealand Collaborative Perfusion Registry table structure.

Transfer Database

Local table	**Field name**	**Data type**	**Description**
PerfusionStreamData	ID	AutoNumber	Primary key
	CONNECT Perfusion stream data variables	Number	CONNECT perfusion stream data variables with one field per variable
Linked table	**Location**		
Config	Tables database		
ConnectPerfusionData	Tables database		
ItemLocations	Tables database		
sysFlags	Tables database		
ANZCPR dataset tables	Tables database		
CONNECT tables	CONNECT EPD tables as listed in Table 1.		

Tables Database

Local table	**Field name**	**Data type**	**Description**
Config	Datatype	Number	Data collection interval in seconds
	Hbunits	Number	Numeric code for either g/dl or g/l
	Gasunits	Number	Numeric code for either kpa or mmHg
ItemLocations	Item	Text	Database name (TablesDb, TranferDb)
	itemLoc	Text	Database file location & filename (eg c:\Tables.mdb)
sysFlags	Flagname	Text	Set to 'IsImporting' during EPD transfer
	Flag	Yes/No	Set to 'Yes' during EPD transfer
	Procnum	Text	ANZCPR procedure number during EPD transfer
ConnectPerfusionData	Procnum	Text	ANZCPR procedure number
	Timestamp	Date/Time	Time of data storage in CONNECT
	CONNECT perfusion stream data variables	Number	Storage of perfusion stream data in wide format. 1 field for each variable
ANZCPR dataset tables	Procnum	Text	ANZCPR procedure number

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2.3 Developing a benchmarking process in perfusion: a report of the Perfusion Downunder Collaboration.

Baker RA, **Newland RF**, Fenton C, McDonald M, Willcox TW, Merry AF; Perfusion Downunder Collaboration.

J Extra Corpor Technol. 2012 Mar;44(1):26-33. PMID: 22730861; PMCID: PMC4557436.

ABSTRACT

Background: Improving and understanding clinical practice is an appropriate goal for the perfusion community. The Perfusion Downunder Collaboration (PDUC) has established a multi-center perfusion focused database aimed at achieving these goals through the development of quantitative quality indicators for clinical improvement through benchmarking.

Methods: Data were collected using the PDUC database from procedures performed in 8 Australian and New Zealand cardiac centers between March 2007 and February 2011. At the Perfusion Downunder Meeting in 2010, it was agreed by consensus, to report quality indicator's (QI) for glucose level, arterial outlet temperature and pCO_2 management during cardiopulmonary bypass. The values chosen for each QI were: blood glucose ≥ 4 mmol/l and ≤ 10mmol/l; arterial outlet temperature ≤ 37°C; and arterial blood gas pCO_2 ≥ 35 and ≤45 mmHg. The QI data were used to derive benchmarks using the Achievable Benchmark of Care (ABC™) methodology to identify the incidence of QIs at the best performing centers.

Results: Five thousand four hundred and sixty-five procedures were evaluated to derive QI and benchmark data. The incidence of the blood glucose QI ranged from 37% to 96% of procedures, with a benchmark value of 90%. The arterial outlet temperature QI occurred in 16% to 98% of procedures with the benchmark of 94%; while the arterial pCO_2 QI occurred in 21 to 91%, with the benchmark value of 80%.

Conclusions: We have derived QI's and benchmark calculations for the management of several key aspects of CPB to provide a platform for improving the quality of perfusion practice.

INTRODUCTION

Improving and understanding perfusion practice is an appropriate goal for the perfusion community. Steps required to achieve this goal include the prospective collection and reporting of data that defines our practice, promotion of research and development in perfusion, the use of continuous quality improvement processes based on principles of evidence-based medicine, adoption of best practice guidelines, and development of perfusion practice benchmarks. The Perfusion Downunder Collaboration (PDUC) has established a multi-center perfusion focused database aimed at helping the Australian and New Zealand perfusion community to achieve these goals (1). Benchmarks provide a foundation for quality improvement, and have been adopted in cardiac surgery by professional organizations such as the Society of Thoracic Surgeons and the Australasian Society of Cardiac Thoracic Surgeons (ANZSCTS). The ANZSCTS published their early observations with their dataset and goals of developing performance indicators and benchmarks in 2004 (2); this early work has led to the development of the AUSCORE risk prediction model (3) and most recently an Australasian risk prediction model for aortic valve surgery (4).

What is Benchmarking?

Benchmarking involves using a structured method of measurement to identify standards of practice excellence. The purpose of which in the healthcare setting is to is to improve practice and quality. Benchmarking is a continuous process by which we can measure and compare our practice to those with best standards "leaders" (5,6). There are different measures that can be related to structure, process or outcome (7), we will focus in this paper on those which measure compliance with processes of care. These typically may reflect recommended practices, for example in a post myocardial infarct population, administration of various therapies could be measured such as thrombolytic therapy, use of beta blockers, or aspirin (5). In the domain of cardiopulmonary bypass (CPB) we may wish to look at process of care measures such the adherence to the conduct of bypass within an agreed physiological range).

What quality indicators should we use?

The choice and definition of benchmarks should be based on the following principles: they should be clinically relevant; the required information should be routinely (or at least readily) collected; and they should have the potential to be the focus for quality improvement initiatives. The development of collaborative datasets, such as the PDUC dataset or the International Consortium for Evidence Based Perfusion dataset will assist in providing one important aspect for this process, the generation of relevant and concurrently valid clinical practice data with tightly controlled data definitions.

The aim of this report is to define three quantitative quality indicators for perfusion practice and provide benchmark data as a platform for clinical practice improvement.

METHODS

Data collection

Data were collected using the PDUC Database (PDUCD) as previously described (1). The PDUCD dataset is divided into 6 categories; demography, clinical (medical history etc.), perfusion (CPB related data), procedural (surgical data), quality control (related to conduct of CPB), and outcome data. The database was designed to suit multiple institutions' ability to access electronic data collection at the point of care. With the approval of local ethics committees[1], data were collected from procedures performed in eight Australian and New Zealand cardiac centers between March 2007 and February 2011 (see appendix 1). A site coordinator was appointed from within each center with the responsibility of installation, configuration, and coordination of the database. The dataset for QI and benchmarking was generated from procedures performed in patients ≥ 18 years of age undergoing isolated on

[1] Flinders Clinical Research Ethics Committee 149/09; Human Research Ethics Committee (TAS) Network H0010158; Northern X Regional Ethics Committee NTX/07/78/EXP: Cabrini Health Research Ethics Committee CHREC 05-24-01-11: Westmead Scientific Committee and the Secretary of the SWAHS Human Research Ethics Committee. JH/TG HREC2010/4/5.10(3146)QA

pump coronary artery bypass graft (CABG), isolated valve repair and/or replacement and valve/CABG procedures. Both first time and redo procedures were included. Electronic data variables were collected every 20 or 30 s during CPB in 7 centers using the Data Management System (Stockert, Munich, Germany), and every minute at one center using the JOCAP XL (MAQUET, Rastatt, Germany). Blood gas, hemoglobin and glucose data were collected electronically with intermittent sampling. A subset of variables was selected to facilitate comparison with published ANZSCTS database data, which reported data collected from 8061 procedures in six cardiac surgical centers in Victoria, Australia (8). Continuous physiological and perfusion variables are not collected in the ANZSCTS database. Clinical data definitions were the same as those reported by ANZSCTS database, except for recent myocardial infarction (MI) which is defined in the PDUC dataset as a MI within 90 days prior to surgery compared to 21 days in the ANZSCTS dataset. The PDUC data are reported for periods March 2007-April 2008, May 2008- April 2009, May 2009-April 2010, and May 2010- February 2011, while ANZSCTS data is reported for financial years (1 July to 30 June) 2007-2008, 2008-2009, and 2009-2010.

Quality indicators and benchmarks

At the Perfusion Downunder Meeting in 2010[2], it was agreed by consensus amongst the attendees (see appendix 2) to report QIs for glucose, arterial outlet temperature and pCO_2 management. The values chosen for each QI were the number of procedures in which:

1. The blood glucose was ≥ 4mmol/l and ≤ 10mmol/l
2. The arterial outlet temperature was ≤ 37^oC
3. The arterial blood gas pCO_2 was ≥35 and ≤45 mmHg.

These values were chosen based upon published guidelines and regional practices (9, 10). A QI was reported when any of the above conditions were met for an individual procedure, so the best performing centers reported the highest incidence of the QI.

[2] Perfusion Downunder Winter Meeting, Queenstown, New Zealand 5th-8th August 2010

The QI data were used to derive benchmarks using the Achievable Benchmark of Care (ABC^{TM}) methodology which ranks sites performance according to the incidence of the QI (5, 6). For each quality indicator the Bayesian adjusted performance fraction (APF) for each site was calculated using the following formula:

$$APF = (x + 1) / (d + 2),$$

where x is the actual number of procedures in which the conditions of the quality indicator were met, and d is the total number of eligible procedures. Sites with small numbers of eligible procedures have the potential to skew the calculated benchmark (for example a site with 10 procedures and 100% incidence of the QI would artificially inflate the benchmark in comparison to sites with much larger numbers of procedures); the adjusted performance fraction is used to reduce this effect. This technique allows for inclusion of all sites regardless of the number of procedures, since as the number of eligible patients (d) increases, the adjusted performance fraction and the unadjusted mathematical percentage tend to the same number.

After ranking the sites according to performance for each QI (based on the APF), the benchmarks were defined by including the total number of eligible procedures from the highest ranked performing site(s) so that at least 10% of the total dataset was represented. The benchmarks were then calculated from this subset according to the formula:
Benchmark = number of procedures with the quality indicator / total number of procedures.
(See table 3 for an example of how the benchmark is calculated using this method).

RESULTS

The PDUCD has procedural data on 7385 cases, 5465 (74%) were eligible for developing QI's and benchmarks. Isolated coronary artery bypass graft procedures (CABG) were the most commonly performed procedure (60%), followed by isolated valve procedures (25%) of cases and combined valve and CABG (15%). Patient demographic and risk factor data are shown in table 1 with a comparison to data reported from the ANZSCTS database (8). Postoperative outcomes are reported in table 2.

Table1. Demographic and Risk Factors Data

	PDUC 2007-08	ANZSCTS 2007-08*	PDUC 2008-09	ANZSCTS 2008-09	PDUC 2009-10	ANZSCTS 2009-10*	PDUC 2010-11	PDUC Total
Number of patients	1191	2629	1286	2692	1530	2740	1458	5465
	%	%	%	%	%	%	%	%
Risk Factors								
Current Smoker	16	14	11	15	14	14	15	14
Diabetes	28	29	29	30	27	30	28	28
Hypertension	68	71	64	72	68	73	68	67
Cerebrovascular disease	9	13	10	13	10	14	10	10
Family history of heart disease	35		40		34		36	36
Hypercholesterolaemia	63		63		65		62	63
Previous cardiac intervention	17	19	17	21	19	21	18	18
Congestive heart failure	25	25	16	21	13	22	15	16
MI before surgery^	34	20	27	20	25	20	26	28
Male	74	75**	74	70	74	72	73	74
Age > 60	68	72	71	72	71	72	72	71
Euroscore	5.9		6.4		6.1		6.4	6.2

* Based on the ANZSCTS (Australia and New Zealand Society of Cardiothoracic surgeons) Cardiac surgery in Victorian public hospitals 2009–10 public report. **approximate

^ MI – myocardial infarction, <21 days (ANZSCTS) or <90days (PDUC)

PDUC- Perfusion Downunder Collaboration

Table 2. Postoperative Outcomes

	PDUC 2007-08	PDUC 2008-09	PDUC 2009-10	PDUC 2010-11	PDUC Total
	%	%	%	%	%
Stroke	1.6	1.1	1.8	1.7	1.6
New renal failure	2.6	2	2.1	2.5	2.3
Myocardial infarction	2.2	1.7	1.8	1	1.6
Reoperation	7.6	4.6	5.5	7.1	6.1
Ventilation > 24 hrs	11.3	13.8	15.7	15.7	14.2
30-day mortality	2.7	3.4	1.4	2.4	2.4

Quality indicator and Benchmark data

The minimum and maximum blood glucose concentrations during CPB for each site are shown in figures 1. The benchmark calculation for the glucose QI is shown in table 3, in which the number of procedures in which the QI is achieved is reported for each site (x (%)), the total number of procedures (d) and the APF. A benchmark value was calculated for the glucose QI of 89.7%.

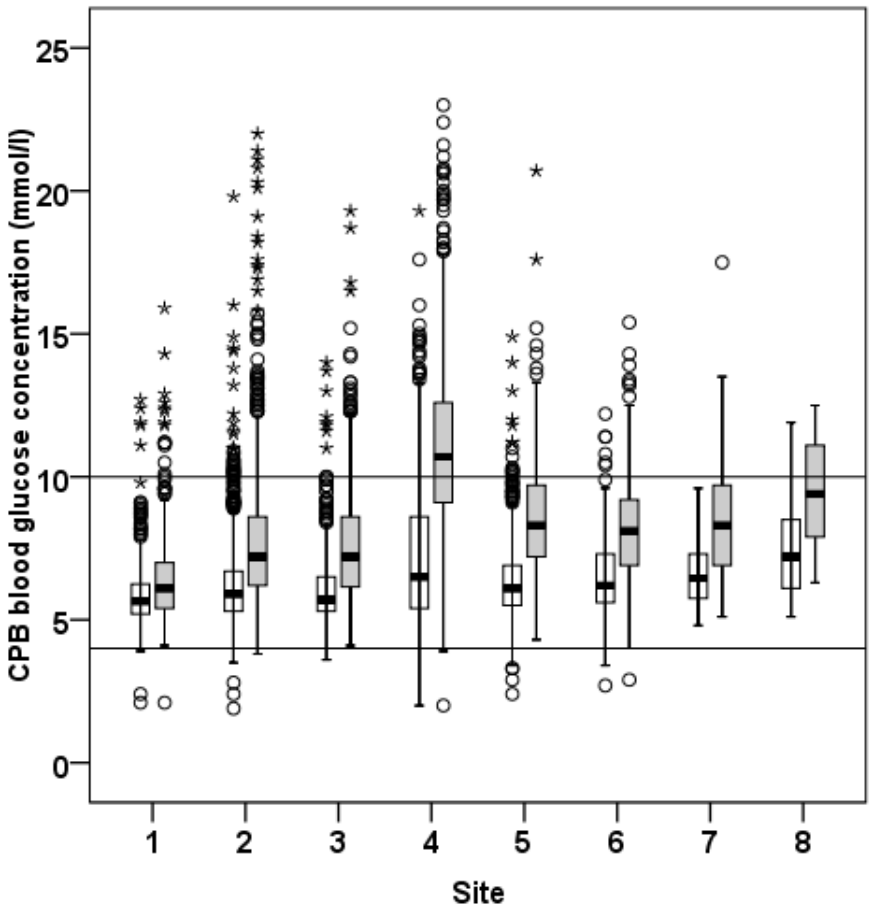

Figure 1. Box plot of minimum (white box) and maximum (grey box) blood glucose values during cardiopulmonary bypass for each participating site. The box indicates the interquartile range, error bars indicate the 95% confidence interval. o; outlier values outside of 95% confidence interval. *; outlier values more than three times the interquartile range. Horizontal lines indicate targets of 4 and 10 mmol/l.

Table 3. Glucose benchmark calculation.

QI: Blood glucose concentration ≥ 4 or ≤ 10mmol/l

Site	x (%)	d	APF	Rank
1	**399 (95.9)**	**416**	**0.957**	**1**
2	**1113 (87.7)**	**1269**	**0.877**	**2**
3	408 (86.8)	468	0.864	3
4	779 (37.3)	2089	0.373	8
5	683 (79.7)	857	0.795	6
6	211 (82.1)	257	0.819	4
7	49 (81.7)	60	0.806	5
8	22 (64.7)	34	0.639	7

Benchmark calculation: $\frac{399+1113}{416+1269}$ = 89.7%

Table 3: x is the number of procedures in which the quality indicator (QI), blood glucose concentration ≥4 or ≤10 mmol/l occurs, d is the number of eligible procedures at each site, APF is the adjusted performance factor, Rank is the ranking of performance from best to worst for the QI based upon the APF. The benchmark calculation combines the QI for sites 1 and 2 , so that the benchmark was represented by at least 10% of the eligible procedures.

The total time (cumulative) that arterial blood outlet temperature exceeded 37°C during CPB for each site are displayed in figure 2. A benchmark value of 93.8% was calculated for achieving the arterial temperature QI (table 4).

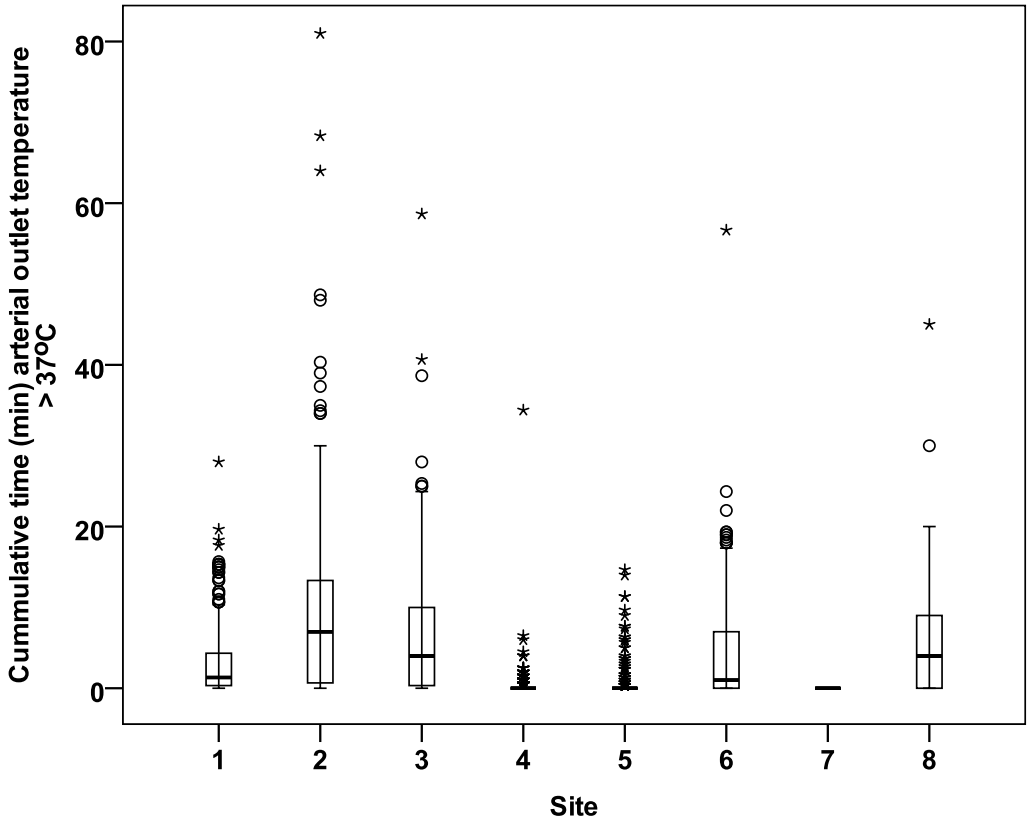

Figure 2. Box plot of arterial outlet temperature > 37°C during cardiopulmonary bypass for each participating site. The box indicates the interquartile range, error bars indicate the 95% confidence interval. o; outlier values outside of 95% confidence interval. *; outlier values more than three times the interquartile range.

Table 4. Arterial outlet temperature benchmark calculation.

QI: Arterial outlet temperature ≤ 37°C

Site	x (%)	d	APF	Rank
1	1016 (24.2)	417	0..243	6
2	197 (15.5)	1273	0.156	8
3	96 (20.5)	469	0.206	7
4	**1959 (93.6)**	**2093**	**0.936**	**2**
5	798 (93.1)	857	0.930	3
6	113 (43.1)	262	0.432	4
7	**60 (100)**	**60**	**0.984**	**1**
8	11 (32.4)	34	0.333	5

Benchmark calculation: $\frac{60+1959}{60+2093}$ = 93.8%

Table 4: x is the number of procedures in which the quality indicator (QI), arterial outlet temperature ≤37**°C** occurs, d is the number of eligible procedures at each site, APF is the adjusted performance factor, Rank is the ranking of performance from best to worst for the QI based upon the APF. The benchmark calcualtion combined sites 4 and 7.

The minimum and maximum arterial blood gas pCO_2 during CPB for each site are shown in figures 3. A benchmark value of 79.6% of procedures was calculated for achieving the pCO_2 QI.

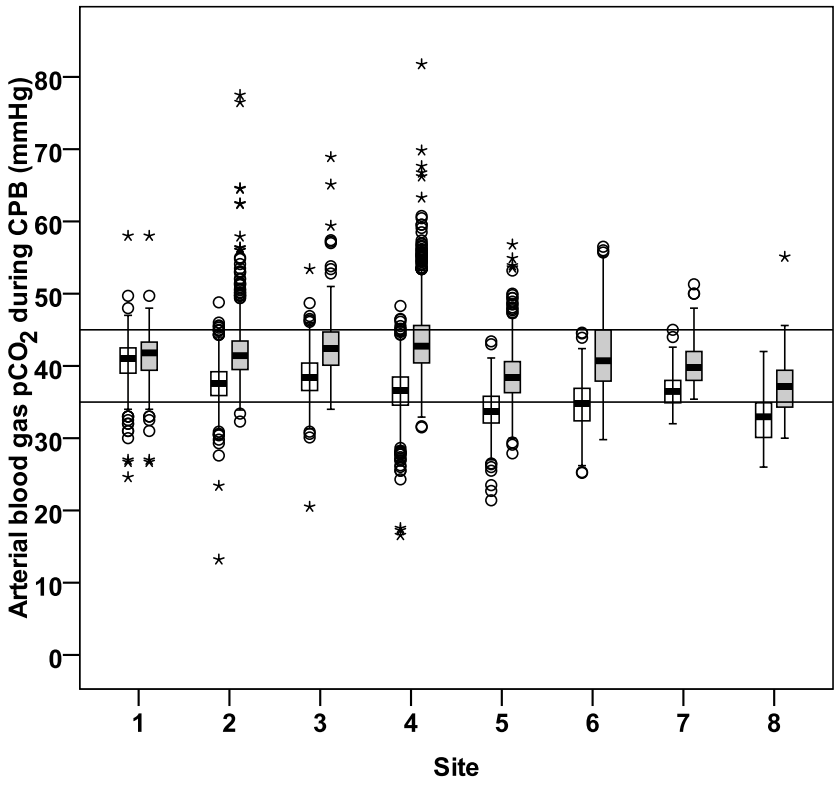

Figure 3. Box plot of minimum and maximum arterial blood gas pCO_2 during cardiopulmonary bypass for each participating site. The box indicates the interquartile range, error bars indicate the 95% confidence interval. o; outlier values outside of 95% confidence interval. *; outlier values more than three times the interquartile range. Horizontal lines indicate targets of 35 and 45 mmHg.

Table 5. CO_2 management benchmark calculation.

QI: Arterial pCO_2 ≥35 or ≤45 mmHg

Site	x (%)	d	APF	Rank
1	**378 (90.6)**	**417**	**0.904**	**1**
2	**967 (76)**	**1272**	**0.760**	**2**
3	333 (71)	469	0.709	3
4	792 (48)	1651	0.480	5
5	277 (32.3)	857	0.323	6
6	80 (31.1)	257	0.312	7
7	39 (66.1)	59	0.656	4
8	13 (20.6)	34	0.222	8

Benchmark calculation: $\frac{378+967}{417+1272}$ = 79.6%

Table 5: x is the number of procedures in which the quality indicator (QI), arterial pCO_2 is ≥35mmHg or ≤ 45mmHg, occurs, d is the number of eligible procedures at each site, APF is the adjusted performance factor, Rank is the ranking of performance from best to worst for the QI based upon the APF. The benchmark calcualtion combined sites 1 and 2.

Figure 4 displays the overall site performance in terms of compliance with each benchmark, demonstrating site 7 to have the overall highest benchmark achievement overall, and to be the best performing site on the temperature QI.

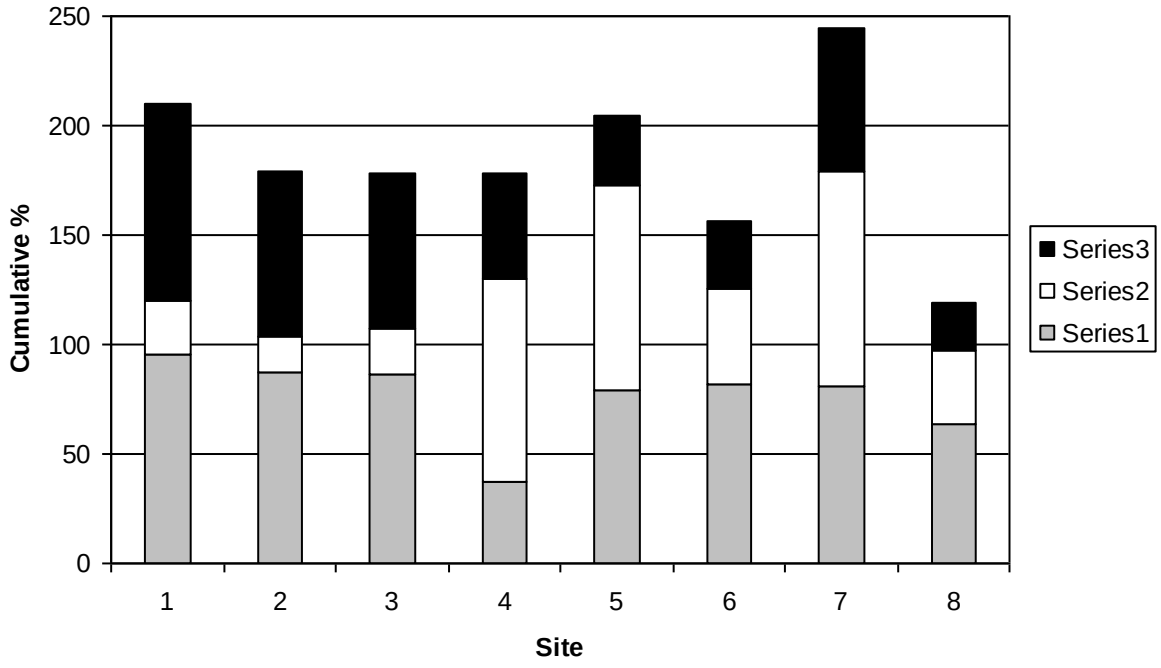

Figure 4. Cumulative percentage of the occurrence of each quality indicator (QI) for each participating site. Solid shading glucose QI; white pCO_2 QI; grey arterial outlet temperature QI.

DISCUSSION

We have defined three QI's for CPB, reported benchmarks for their rate of occurrence and reported the variation in relation to these benchmarks that occurs within the participating sites of the PDUC. These results provide a resource for quality improvement initiatives. The data for patient risk factors and outcomes highlights the opportunity to report risk adjusted outcomes in the future. Benchmarks of quality indicators are not direct measures of outcome, however it is reported that when processes of care are met there is a general association with improved outcomes. It follows that sites achieving standards of excellence as identified by benchmark performance may have better outcomes than those who do not (5,6). The

demographic data collected in the PDUC dataset were comparable to those reported by ANZSCTS for data from Victorian hospitals for similar time periods (8), demonstrating the maintenance of concurrent validity for the PDUC dataset which we had previously reported (1).

The frequency of the QI for blood glucose concentration (blood glucose ≥ 4mmol/l and ≤ 10 mmol/l) ranged from 37.3% to 95.9% of cases. We identified a benchmark value of 89.7%. Glucose management during CPB has been the focus of numerous studies as hyperglycemia during CPB has been shown to be an independent predictor of morbidity and mortality (11). Similarly, the risks of hypoglycaemia are well recognized (12). Guidelines for the management of perioperative blood glucose management during CPB have been reported; for example, Shann et al. (9) recommended the following: *Maintenance of Euglycaemia: The clinical team should maintain perioperative blood glucose concentration within an institution's normal clinical range in all patients, including non-diabetic subjects. (Class1, Level B).* More recently the STS published practice guidelines specifically addressing the management of blood glucose during adult CPB recommends, in both diabetic and non-diabetic patients, that blood glucose levels should be maintained <= 180 mg/dL (10mmol), while recognizing that hypoglycaemia must be avoided (10). In our collaboration, 1 site achieved a value less that this benchmark and 2 sites were close. DioDato et al (13) reported their regions comparison to the recommendation published by Shann et al (9). They reported a regional practice with respect to the maintenance of euglycemia of 55.1% (range 3.2-76.9%) of cases recording a maximum glucose ≤200 mg/dl. The overall practice within the PDUC registry of 67.2% (range 37.3% to 95.9%) occurrence of the glucose QI suggests a lower percentage of cases are not maintained within this range, however similar to Northern New England experience we report a wide range in the expression of the QI. Of note DioDato et al (13) reported practice from 2004 and early 2005, while the PDUC has reported contemporary data (2007-2011) and both hypoglycaemia and hyperglycaemia.

The PDUC QI for arterial outlet temperature not exceeding 37^{o}C produced a benchmark of 93.8%. Shann and co-authors (9) made the following recommendation in relation to the avoidance of hyperthermia during CPB *"Limiting arterial line temperature to 37C might be useful for avoiding cerebral hyperthermia. (Class IIa, Level B)".* The avoidance of hyperthermia was supported by the review by Grigore et al (14) albeit with their recognition of the lack of

randomized controlled data evaluating the adverse effects of hyperthermia following CPB. Our quality indicator suggested overall nearly 61% of cases maintained arterial outlet temperature ≤ 37°C, with a range of 15.5% to 98.4% of cases, this compared with DioDato's report in which temperatures maintained ≤ 37°C for 23.4% (1.5-83.2), i.e., highest blood temperature reached by the arterial inflow during re-warming was in excess of 37°C in nearly 67% of the cohorts reported cases (13). This was more recently investigated in the same region by Warren et al (15) who reported a regional quality improvement project looking at reducing the variation in arterial inflow temperatures. They reported after their improvement projects a reduction from 90% of procedures having arterial inflow temperatures >37°C to 69% (i.e., temperature maintained below 37C for only 10-31% of cases). The PDUC data is unique in that it uses the continuous data acquisition capabilities of the current heart lung machine data management systems to report continuous temperature output from the arterial outlet temperature port of the oxygenator, unlike the reports of DioDato et al and Warren et al who rely on manually recorded temperature data. The manual reporting of temperature has previously been shown to be less accurate than electronic temperature measurements (16).

The arterial outlet temperature results were not influenced by changes in oxygenators used at each site during the period of data reporting. We did not include a confirmation of the accuracy of arterial outlet measurements as an evaluation of all devices used by collaborating centers has not been reported to date. Warren et al in their report did evaluate the inaccuracy of the arterial outlet temperature probes however they have not reported these findings in detail to date. Interestingly while they reported a range of temperature variation from different sites, they only corrected data from one site (15).

The benchmark for procedures in which the arterial pCO_2 was maintained between 35 and 45 mmHg was 79.6%, with overall incidence ranging from 20.6% to 90.6%. Adoption of alpha stat blood gas management in adults undergoing CPB under mild hypothermia and tepid bypass is widely practiced, and the following recommendation that *"The clinical team should manage adult patients undergoing moderate hypothermic CPB with alpha stat pH management. (Class I, Level A)"* published (9). Measurement of pCO_2, in the range 35-45mmHg, allows monitoring of adherence to alpha stat management practices. Continuous online blood gas monitoring was only utilized at two sites (sites 1 & 6), with oxygenator

exhaust gas capnography being variably used at sites 2, 3, 4 and 8. Both DioDato et al (13) and the PDUC reported 100% adoption of the recommendation of alpha stat blood gas management; however, there are no reported comparisons of compliance to this blood gas management regime previously in the literature.

The cumulative performance of the sites in terms of compliance with each of these three benchmarks indicates that while some sites may be leaders for one particular QI, they may not perform as well across all practice areas, highlighting the potential for improvement of practice through sharing of collective experience; a fundamental principle of benchmarking. Further investigation of the barriers that have been encountered and the practices that have been found to be beneficial in the performance observed at each institution is required.

Limitations

The PDUC has developed since 2007, however we are still limited by the relatively small number of contributing sites. In addition, as with any registry accumulated data there will be some variation in the accuracy of the reported information, and the lack of specific detailed knowledge of each sites management protocols may account for variation in the incidence of the reported QI's. We recognize that there can be improvement in monitoring and data collection within our collaboration and we have introduced audit (17) as one mechanism to improve data quality. Our benchmark data has been created using data from CABG, Valve and Valve/CABG procedures, in the future procedure specific benchmark data will be able to be derived. Another area of consideration relates to the interpretation of the arterial outlet temperature data. We have presented raw data from participating sites; however, we recognize that there are limitations associated with the accuracy of these arterial temperature measurements (18). Industry could assist in this area by improving the accuracy of the arterial outlet blood temperature or through the hardware by providing built-in temperature off-set capability similar to that currently offered for pressure transducer measurements.

CONCLUSIONS

The PDUC has combined prospective data collection with a structured benchmarking process. We have defined process of care QI's and used these to calculate benchmarks for the management of blood glucose, arterial outlet temperature and blood gas management during CPB. These benchmarks provide a baseline for the implementation of multicenter continuous quality improvement processes for perfusion practice.

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Chapter 3: Use of electronic perfusion data to demonstrate impact of cardiopulmonary bypass practice on patient outcome (acute kidney injury) at Flinders Medical Centre.

3.1 Hyperthermic perfusion during cardiopulmonary bypass and postoperative temperature are independent predictors of acute kidney injury following cardiac surgery.

Newland RF, Tully PJ, Baker RA.

Perfusion. 2013 May;28(3):223-31. doi: 10.1177/0267659112472385. Epub 2013 Jan 11. PMID: 23314194.

ABSTRACT

Acute kidney injury (AKI) following cardiopulmonary bypass (CPB) is associated with increased mortality, requirement for dialysis, and longer intensive care unit (ICU) and hospital length of stay. Rewarming during CPB and poor oxygen delivery have been associated with AKI; however, the role of temperature management on AKI has not been clearly defined. This study aims to evaluate the role of hyperthermia during CPB and the temperature upon admission to the ICU on AKI following cardiac surgery using the RIFLE (renal Risk, Injury, Failure, Loss of renal function and End-stage renal disease) criteria.

To determine whether CPB hyperthermia (measured as the cumulative time arterial outlet temperature > 37^{o}C) and ICU admission temperature were independent risk factors for AKI, data from 1393 consecutive adult patients undergoing isolated on pump coronary artery bypass graft (CABG), valve repair and/or replacement and valve/CABG procedures was analysed using a logistic multivariate model. After testing for interaction, we incorporated covariates having a p value <0.1. AKI was defined according to the RIFLE criteria as an increase in serum creatinine > 50% from baseline to peak value postoperatively. Overall, 12.3% of patients developed AKI with a 4.5 fold increase in-hospital mortality. Variables found to be independent predictors of AKI included CPB hyperthermia (Odds ratio [OR] 1.03 per minute increase [95% confidence interval (CI) 1.01-1.05]; P = 0.01), ICU admission temperature ([OR] 1.44 per degree increase [(CI) 1.13-1.85]; P < 0.001), minimum CPB haemoglobin ([OR] 0.83 per g/dl increase [(CI) 0.71-0.97]; P = 0.02) use of intra-aortic balloon pump ([OR] 2.69 [(CI) 1.24-5.82]; P = 0.01) and ICU readmission ([OR] 3.13 [(CI) 1.73-5.64]; P < 0.001).

Avoiding arterial outlet hyperthermia may help decrease AKI following cardiac surgery using CPB. Both intraoperative and postoperative temperature management strategies should be the focus of future randomised studies to determine optimal interventions.

INTRODUCTION

Perioperative renal failure following cardiopulmonary bypass (CPB) is associated with increased mortality, requirement for dialysis, and longer intensive care unit (ICU) and hospital length of stay (1). Limitations in the prevention and treatment of perioperative renal failure have been caused by inconsistencies in defining the injury, and a lack of understanding of the pathophysiology in the clinical setting (2). In order to create a common definition and to improve risk stratification, the term *acute kidney injury* (AKI) has been adopted to reflect the spectrum of disease from minimal elevations in serum creatinine to anuric renal failure (2). A 5-stage classification system developed by the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) group defines AKI according to changes in serum creatinine and/or urine output using the acronym RIFLE (renal Risk, Injury, Failure, Loss of renal function and End-stage renal disease). The first 3 stages define grades of increasing severity of AKI (risk, injury, and failure) based on changes from baseline serum creatinine or glomerular filtration as well as a decline in urine output. The last 2 stages are outcome variables (loss of renal function and end-stage kidney disease) (3). This criterion is currently the most extensively used and validated consensus definition and method of classifying AKI (4).

Various pharmacological interventions aimed at manipulation of renal hemodynamics and glomerular filtration have failed to demonstrate significant clinical protection during cardiac surgery (1). A number of modifiable factors have been identified as predictors for AKI, including hemodilution, intraoperative transfusion, hypotension, and oxygen delivery (5, 6, 7). The role of temperature management on AKI has not been clearly defined. In animal models, hyperthermia has been shown to exacerbate ischemic renal injury, and hypothermia to have a protective benefit, however randomised clinical studies have not demonstrated a protective effect of hypothermia during cardiac surgery (1). Two trials reported by Boodwhani et al (1), designed to evaluate neurocognitive outcome following coronary artery bypass graft (CABG), also reported the influence of temperature management and rewarming on kidney injury after surgery defined as a 25% increase in serum creatinine from baseline. In the earlier trial, 223 patients were cooled to 32^{o}C during CPB and randomised to rewarm to 37^{o}C or 34^{o}C. The authors reported a higher (nonsignificant) incidence of renal injury in patients rewarmed

to 37°C than those rewarmed to 34°C (17% versus 9%, p = 0.07). In the second trial, 267 patients were randomised to sustained mild hypothermia at 34°C with postoperative rewarming or normothermia (37°C). The authors reported a comparable incidence of renal injury in both groups (20%: 34°C versus 15%: 37°C, p = 0.28). In a post hoc analysis of both trials to evaluate the influence of rewarming on AKI, they reported that rewarming was an independent risk factor for renal injury, however the influence of hyperthermic perfusion was not examined.

In a rat model of renal ischemia, prophylactic hypothermia was found to be effective when applied not only during ischemia but also during early reflow post-ischemia (8), however, there is a paucity of data regarding the renal effects of prophylactic hypothermia post injury (4). Although hypothermia upon ICU admission in CABG patients has been shown to be associated with an increase in mechanical ventilation time, transfusion requirements and hospital length of stay (9), the association between ICU admission temperature and AKI following cardiac surgery has not been reported.

This study aims to evaluate the role of hyperthermic perfusion during CPB and the temperature upon admission to the ICU on AKI, as defined by the RIFLE criteria following cardiac surgery.

METHODS

Data source & collection.

In an observational cohort study of consecutive adult patients undergoing isolated on pump CABG, isolated valve repair and/or replacement and valve/CABG procedures at Flinders Medical Centre between January 2007 to August 2011, data was analysed retrospectively. Study approval (411.11) was given and the requirement for written informed consent was waived by the Clinical Human Research Ethics Committee.

Preoperative, intraoperative and postoperative data was collected prospectively using the Flinders Medical Centre Cardiac Surgery Database. Continuous intraoperative variables were collected at 20 s intervals using the Data Management System (DMS) (Stockert, Munich, Germany). Arterial outlet temperature was measured at the outlet of the Capiox® SX25RX oxygenator (Terumo Corporation, Japan) using the oxygenator integrated thermistor

temperature probe without correction for inaccuracy of the thermistor. Intraoperative monitoring artefacts as defined by an arterial pressure <5 mmHg, nasopharangeal temperature < 10^{o}C or arterial outlet temperature < 10^{o}C were excluded from analysis. Haemoglobin data were collected electronically with sampling every 20-30 min during CPB using an ABL700 analyser (Radiometer, Copenhagen, Denmark). Patients with pre-operative chronic renal disease requiring dialysis, or operated off-pump were excluded.

CPB parameters including arterial outlet temperature > 37^{o}C, mean arterial pressure < 40mmHg, mean arterial pressure < 50mmHg, and cardiac index < 1.6 l/min/m^2 were calculated electronically as cumulative time as previously described (10).

Clinical management

General anaesthesia was induced with fentanyl (10–30 g/kg) and supplemented with sevoflurane and/or propofol. All patients underwent cardiac surgery with CPB using a S3 roller pump (Stockert, Munich, Germany). Arterial pressure was monitored via radial artery catheter. Cardiopulmonary bypass was instituted after positioning of either a single 36/51 Fr two-stage atrial cannula (Sarns^{TM}, Terumo Corporation, Tokyo, Japan), or 32–36 Fr bicaval cannulation (Sarns^{TM}), and a 22 Fr ascending aortic cannula (DLP, Medtronic, Minneapolis, MN), or 20 Fr FemFlex used in the ascending aortic position (Edwards Lifesciences, Irvine, CA). The CPB circuit included a hard-shell membrane oxygenator (Capiox® SX25RX, Terumo Corporation, Japan), biopassive tubing (SMARxT®, Cobe Cardiovascular, Arvada, CO) a 40-micron arterial line filter (D703, Dideco, Mirandola, Italy) and a 0.2 micron prebypass filter (Prebypass Plus®, Pall Corporation, Port Washington, USA). The circuit was primed with 1L Plasmalyte solution, 500ml of Gelofusine (isolated CABG procedures) or 4% albumin (other procedures), 50ml 8.4% sodium bicarbonate solution, 50ml Hartmann's solution and 10,000 iu heparin. Packed red blood cells were added if required to provide a predicted haemoglobin level of > 7 g/dl on initiation of CPB (determined by the algorithm of the DMS software). The CPB protocol included arterial non-pulsatile target flow rate of 1.8-2.4 L/min/m^2, alpha-stat pH management with target pO_2 100-250 mmHg, gravity venous drainage, and tepid systemic temperature management (nasopharyngeal temperature 34-35°C) with no active cooling. After placement of the aortic crossclamp, cardioplegic arrest was induced with blood cardioplegia (32-34°C), 30 mmol/l at induction and intermittent bolus (16 mmol/l) as

required. Mean CPB arterial pressure was controlled using metaraminol, phentolamine or isoflurane to achieve a target of 40-80 mmHg, Target nasopharyngeal temperature for separation from bypass was > 36°C with rewarming rate < 1°C per min. During the study period our protocol for maximum arterial outlet temperature during rewarming was reduced from 37.5°C to 37°C in October 2009.

Transfusion of red blood cells during CPB was triggered when haemoglobin level was measured to be <7 g/dL. Post-operative renal replacement therapy was initiated according to physician assessment based on oliguria unresponsive to fluid resuscitation measures, hyperkalaemia, severe acidaemia or clinically significant lung oedema.

Acute Kidney Injury

AKI was defined according to the serum creatinine criteria of the RIFLE classification as an increase in serum creatinine >50% from baseline to peak value postoperatively. Serum creatinine measurement was performed using the enzymatic method (Roche, Basel, Switzerland).

Statistical analysis

Statistical analysis was carried out using SPSS software version 19.0 (SPSS Inc., Chicago, IL). Variables were screened for normality using histograms, with normally distributed data presented as the mean ± SD, and non-normally distributed data as medians with interquartile range. Categorical data are presented as percentages. Continuous variables were analysed using the t-test or the Mann–Whitney U-test according to normality of distribution while categorical variables were compared using chi square statistic. Incident AKI after cardiac surgery was analysed with logistic regression showing the odds ratio (OR) and 95% confidence intervals (CI). Due to regression model overfitting constraints, all covariates were evaluated in univariable analyses for their association with AKI and only retained for further multivariable analysis when the univariable result indicated $p<0.1$. Logistic regression model discriminatory and fit indices included the Hosmer and Lemeshow χ^2 test and the c-index.

Due to our change in rewarming protocol during the study period, we dichotomised the dataset to procedures performed before or after the reduction in maximum arterial outlet temperature protocol from 37.5°C to 37°C. Chi square analysis was performed to compare

the incidence of AKI before and after the temperature protocol. In all analyses a two-sided P-value <0.05 was considered to be statistically significant and we did not adjust for multiple comparisons.

RESULTS

Data from 1885 consecutive adult patients undergoing cardiac surgery was initially retrieved. After exclusion of 492 patients (Figure 1), 1393 patients undergoing isolated on pump coronary artery bypass graft (CABG), isolated valve repair and/or replacement and valve/CABG procedures were analysed. We identified 171 patients with AKI (12.3%).

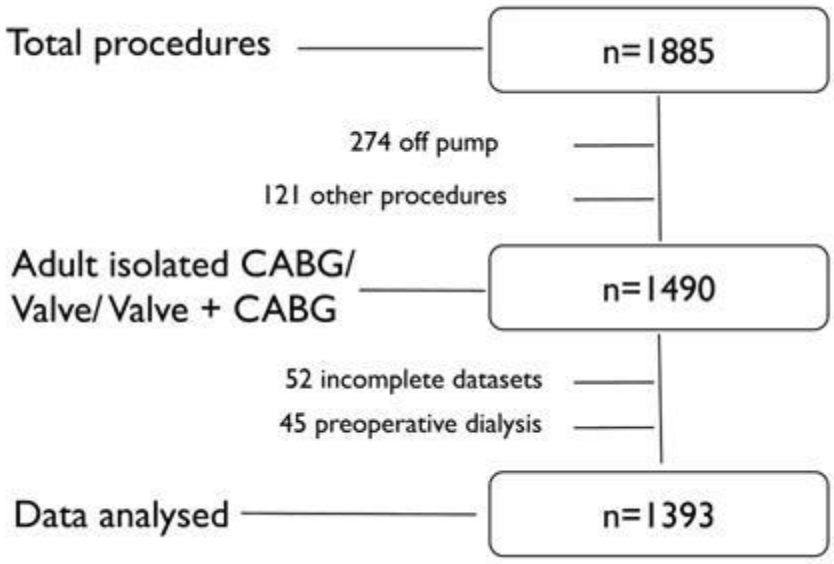

Figure 1. Flowchart showing patients included in the analysis.

Patient risk factors, intraoperative characteristics and outcomes

Patient baseline characteristics and outcomes are displayed in table 1. Patients with AKI had significantly greater incidence of chronic obstructive airway disease, peripheral vascular disease, chronic renal disease, diabetes, congestive heart failure, and significantly lower preoperative haemoglobin. AKI patients had significantly higher ICU admission temperature, increased postoperative use of intra-aortic balloon pump, inotropes, and transfusion of red blood cells, greater incidence of return to the operating room, and readmission to ICU. Patients with AKI had longer duration of hospital stay, and experienced greater in-hospital mortality.

Table 1. Baseline characteristics and postoperative outcome.

	No AKI (*N* = 1222)	AKI (*N* = 171)	P
Baseline			
Age, years	66 (55-74)	67 (57-76)	0.607
Female	353 (28.9%)	61 (35.7%)	0.069
Surface area, m^2	1.89 ± 0.22	1.89 ± 0.23	0.826
Chronic obstructive airway disease	312 (25.5%)	58 (33.9%)	0.02
Peripheral vascular disease	138 (11.3%)	26 (15.2%)	0.028
Previous cardiac surgery	44 (3.7%)	11 (6.4%)	0.075
Renal disease	109 (8.9%)	36 (21.1%)	<0.001
Diabetes	361 (29.5%)	67 (39.2%)	0.01
Hypertension	867 (70.9%)	121 (70.8%)	0.959
Congestive heart failure	520 (42.6%)	91 (53.2%)	0.021
Ejection fraction < 30%	58 (4.7%)	13 (7.6%)	0.112
Preoperative haemoglobin, g/dl	13.6 (12.2-14.7)	12.4 (10.8-13.9)	<0.001
Emergency surgery	18 (1.5%)	6 (3.5%)	0.055
Outcome			
ICU admission temperature, °C	35.1 (34.6-35.5)	35.3 (34.8-35.7)	0.02
Serum creatinine increase			
>50%	N/A	175 (100%)	
>100%	N/A	57 (32.6%)	
>200%	N/A	22 (12.6)	
Use of intra-aortic balloon pump	34 (2.8%)	19 (11.1%)	<0.001
Use of inotropes in ICU	409 (33.5%)	97 (56.7%)	<0.001
Atrial fibrillation	310 (25.4%)	49 (28.7%)	0.357
Units of red blood cells transfused	1 (1-2)	2 (0-5)	<0.001
Postoperative renal dialysis	33 (2.7%)	34 (19.9%)	<0.001
Return to operating room	51 (4.2%)	19 (11.1%)	<0.001
Intensive care unit readmission	45 (3.7%)	22 (12.9%)	<0.001
Length of stay in hospital, days	6 (5-9)	10 (7-21)	<0.001
Stroke	15 (1.2%)	4 (2.3%)	0.24
Mortality in hospital	16 (1.3%)	10 (5.8%)	<0.001

Values denote mean ±SD, median (25–75th percentiles) or proportion of patients in %.

Abbreviations: AKI, acute kidney injury; ICU, intensive care unit.

Intraoperative characteristics are displayed in table 2. Patients with AKI had significantly lower minimum CPB haemoglobin and greater amount of time with CPB MAP < 40mmHg.

Table 2. Intraoperative characteristics.

	No AKI (*N* = 1222)	AKI (*N* = 171)	P
Type of surgery			0.388
CABG	704 (57.6%)	89 (52%)	
Valve surgery	367 (30%)	58 (33.9%)	
Valve and CABG	151 (12.4%)	24 (14%)	
CPB time, min	69 (54-88)	74 (55-99)	0.085
Minimum CPB Haemoglobin, g/dl	8.3 (7.3-9.4)	7.5 (6.8-8.7)	<0.001
CPB cardiac index < 1.6 l/min/m^2, min	2.3 (1.3-3.6)	2.3 (1.3-5.9)	0.521
CPB MAP < 40mmHg, min	3 (1.6-5)	3.6 (2-6.7)	0.001
CPB MAP < 50mmHg, min	17 (9.6-25.3)	21 (10.3-36.3)	0.163
Minimum nasopharyngeal temperature, ^oC	34 (33.8-34.4)	34 (33.8-34.4)	0.99
Arterial outlet temperature > 37^oC, min	4.3 (0.6-12)	8 (0.6-15.7)	0.145
Last CPB nasopharyngeal temperature, ^oC	36.7 (36.4-36.9)	36.8 (36.5-37)	0.072

Values denote mean ±SD, median (25–75th percentiles) or proportion of patients in %.
Abbreviations: AKI, acute kidney injury; CABG, coronary artery bypass graft; CPB, cardiopulmonary bypass; MAP, mean arterial pressure.

Univariate and multivariate associations with AKI

The univariate and multivariate association between variables and AKI ascertained by logistic regression are shown in table 3. The variables meeting criteria for inclusion in the multivariate model (p<.10) were; female gender, chronic obstructive airway disease, peripheral vascular disease, previous cardiac surgery, renal disease, diabetes, congestive heart failure, cardiopulmonary bypass time, emergency surgery, minimum CPB Haemoglobin, CPB cardiac index < 1.6 l/min/m^2, CPB MAP < 40mmHg, arterial outlet temperature > 37^oC, ICU admission temperature, use of intra-aortic balloon pump, units of red blood cells transfused, return to operating room, and intensive care unit readmission. When such variables were subjected to multivariate logistic regression, only minimum CPB haemoglobin, arterial outlet temperature > 37^oC, ICU admission temperature, use of intra-aortic balloon pump and ICU readmission remained independently associated with AKI. Specifically, CPB haemoglobin (OR 0.83: CI 0.71-0.97; P = 0.02) translated to a 20% lower risk of AKI per g/dl increase in haemoglobin. With respect to arterial outlet temperature time >37^oC (OR 1.03: 95% CI 1.01-1.05; P = 0.01), the result translated to a 34% increase in odds for AKI with every ten minutes spent >37^oC. The ICU admission temperature results (OR 1.44: CI 1.13-1.85; P < 0.001) suggested that a 44% increase in odds for AKI was evident for every 1 degree increase in temperature. The use of intra-aortic balloon pump (OR 2.69: CI 1.24-5.82; P = 0.01) translated to a nearly three-fold

greater odds for AKI amongst patients receiving IABP. Finally, having an intensive care unit readmission (OR 3.13: CI 1.73-5.64; P < 0.001) was associated with more than three-fold greater odds for AKI.

Table 3. Results of univariate and multivariate logistic regression modelling of risk factors for AKI (n=1393).

	P univariate	P multivariate	Adjusted OR (95% CI)
Age, years	0.393		
Female	0.07	0.985	1 (0.65-1.53)
Surface area, m^2	0.826		
Chronic obstructive airway disease	0.021	0.69	1.08 (0.74-1.58)
Peripheral vascular disease	0.03	0.41	1.19 (0.79-1.78)
Previous cardiac surgery	0.079	0.34	1.44 (0.68-3.02)
Renal disease	<0.001	0.11	1.48 (0.91-2.4)
Diabetes	0.011	0.33	1.2 (0.83-1.73)
Hypertension	0.959		
Congestive heart failure	0.02	0.82	0.97 (0.77-1.23)
Cardiopulmonary bypass time, min	<0.001	0.18	1 (1-1.01)
Emergency surgery	0.063	0.26	0.47 (0.12-1.77)
Ejection fraction < 30%	0.115		
Minimum CPB Haemoglobin, g/dl	<0.001	0.02	0.83 (0.71-0.97)
CPB cardiac index < 1.6 l/min/m^2, min	0.002	0.28	1.01 (0.99-1.03)
CPB MAP < 40mmHg, min	<0.001	0.32	1.01 (0.99-1.04)
Minimum Nasopharangeal temperature, ^oC	0.435		
Arterial outlet temperature > 37^oC, min	<0.001	0.01	1.03 (1.01-1.05)
Last CPB Nasopharangeal temperature, ^oC	0.1		
ICU admission temperature, ^oC	0.016	<0.001	1.44 (1.13-1.85)
Use of intra-aortic balloon pump	<0.001	0.01	2.69 (1.24-5.82)
Use of inotropes in ICU	0.304		
Atrial fibrillation	0.358		
Units of red blood cells transfused	<0.001	0.13	1.03 (0.99-1.07)
Return to operating room	<0.001	0.08	1.85 (0.94-3.65)
Intensive care unit readmission	<0.001	<0.001	3.13 (1.73-5.64)

Hosmer and Lemeshow goodness-of-fit test x^2=5.89, *df*=8, *p*=0.66. *C*-statistic =74.2%.
Abbreviations: AKI, acute kidney injury; CPB, cardiopulmonary bypass; MAP, mean arterial pressure; ICU, intensive care unit.

Temperature and AKI

The cumulative time for the arterial outlet temperature > 37°C is shown for procedures performed before or after the change in rewarming protocol (Figure 2), demonstrating a significant decline (11 (0-89) vs 0.6 (0-19) minutes (P<0.001). The change in protocol was associated with a 31% reduction in the incidence of AKI (14% vs 9.6%, P=0.015).

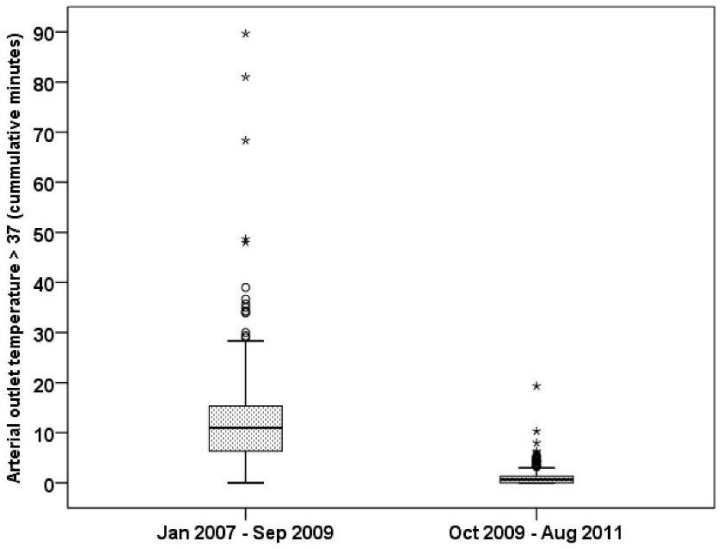

Figure 2. Hyperthermic perfusion during cardiopulmonary bypass, before and after our protocol for maximum arterial outlet temperature during rewarming was reduced from 37.5°C to 37°C in October 2009. Box plot of arterial outlet temperature >37°C during cardiopulmonary bypass before and after protocol change. The box indicates the interquartile range, error bars indicate the 95% confidence interval: o; outlier values outside of 95% confidence interval. *; outlier values more than three times the interquartile range.

DISCUSSION

In the development of AKI following cardiac surgery, this analysis found temperature management to be important, in particular we identified arterial blood temperature > 37°C and the ICU admission temperature to be independent predictors. Intraoperative minimum haemoglobin level and transfusion of red blood cells, and postoperative use of intra-aortic balloon pump and readmission to the ICU were also found to be independent predictors of AKI.

The confirmation of the hypothesis that hyperthermic perfusion during CPB, defined as the cumulative time >37°C, is associated with an increase in the incidence of AKI following cardiac

surgery is consistent with the observations of Boodhwani et al that reported exacerbation of AKI attributed to rewarming during CPB (1). In their study, arterial blood temperatures were reportedly kept <37.5^{o}C, suggesting that patients would have encountered some degree of hyperthermic perfusion, however a quantification of hyperthermia was not reported. An observational study of 1072 patients undergoing coronary artery bypass grafting (CABG) with target core temperatures between 24 and 36^{o}C found the lowest arterial perfusate temperature to be an independent predictor of AKI (11). Kourliouros et al proposed that the increase in AKI associated with lower CPB perfusate temperature may be related to injury associated with the need for increased rewarming, however an evaluation of the influence of hyperthermia or highest CPB temperatures was not performed. Given our ability to quantify oxygenator arterial outlet temperature during CPB, our study was performed to evaluate the relationship between hyperthermia and AKI since this data was not included in previous studies. Our analysis found that for every 10 minutes the oxygenator arterial outlet temperature exceeded 37^{o}C, there was an associated 34% increase in the incidence of AKI. Since we did not report the minimum perfusate temperature we are unable to make a comparison with the study reported by Kourliouros et al (11). We did not observe a relationship between the minimum patient temperature during CPB and AKI, patients were maintained between 33-35 ^{o}C in our study compared with 24-36 ^{o}C in the Kourliouros et al study (11).

The rationale for avoiding hyperthermia during CPB has focussed on reducing the risk of neurologic injury associated with CPB, as highlighted in the recommendation by Shann et al (12); *"Limiting arterial line temperature to 37C might be useful for avoiding cerebral hyperthermia. (Class IIa, Level B").* During the study period we observed a significant decline in the incidence of arterial outlet hyperthermia (figure 2) reflecting our change in rewarming protocol in compliance with the Shann et al guideline (12). Following the change in protocol our incidence of AKI fell significantly from 14% to 9.6%, suggesting the association that reducing the incidence of arterial hyperthermia may be beneficial in reducing AKI. The evidence reporting a relationship between hyperthermia and adverse outcome is largely derived from the association between cerebral hyperthermia in the setting of stroke with increased morbidity and mortality, however in the setting of CABG surgery both exposure to a faster rewarming rate during CPB and hyperthermia postoperatively have been

demonstrated to be associated with greater incidence of neuropsychologic dysfunction (12). In Boodwhani et al's (2009) retrospective report designed to evaluate neurocognitive outcome and kidney injury following CABG they reported a similarity in neurologic outcome and renal outcomes; with worse outcomes observed in patients that had greater rewarming (1). The authors reported arterial outlet temperatures to be limited to < 37.5 ^{o}C in these studies, however it is likely that patients experienced some degree of hyperthermia, as continuous electronic temperature data was not available. The results from our study therefore raise the question of the influence of arterial outlet hyperthermia on the results of previous studies of temperature management during CPB.

In our study patient temperature upon arrival to the ICU was also identified as an independent predictor of AKI. We found no correlation between arterial hyperthermia blood temperature > 37^{o}C and ICU arrival temperature, and that intraoperative patient temperatures (both minimum nasopharangeal, and nasopharangeal temperature at CPB separation) were not univariate predictors of AKI, therefore our results may suggest that ICU arrival temperature is a relevant measure to predict postoperative course. Grocott and associates have reported postoperative hyperthermia to be associated with greater neuropsychologic dysfunction following CABG surgery (13), however the relationship between ICU arrival temperature and postoperative hyperthermia in our practice, and the influence of postoperative temperature management and AKI are yet to be determined. Further evaluation of postoperative temperatures is required to determine whether higher ICU admission temperatures are associated with subsequent hyperthermia, or whether lower ICU admission temperatures are beneficial in reducing the incidence of AKI.

Various modifiable factors related to the conduct of CPB have been reported to be associated with AKI including red blood cell transfusion, combined anaemia and hypotension (6) and oxygen delivery (14). A recent analysis of 920 consecutive on-pump cardiac surgery patients reported by Haase et al (6), identified decreased haemoglobin concentration as an independent risk factor for AKI (defined by an increase in serum creatinine >50% from baseline to peak value within the first seven post-operative days), and the volume of transfused red blood cells represented a specific additional risk factor in patients with a haemoglobin concentration >8 g/dL. In their study, systemic hypotension alone (<50mmHg) was not independently associated with AKI, however, the combination of low haemoglobin

concentration and severe hypotension acted synergistically to increase the risk of AKI. Although our study found a univariate association between red blood cell transfusion, minimum haemoglobin during CPB, CPB cardiac index < 1.6 l/min/m^2, CPB MAP < 40 or 50 mmHg, and AKI, multivariate analysis failed to indicate the indices of pressure or flow reported to be independent predictors. Our study similarly identified minimum haemoglobin reported during CPB to have an independent association with AKI. Since measurements of hyperthermic perfusion and postoperative temperature have not been included in these previous studies, this highlights the importance of our findings from a pathophysiological perspective. In addition, our study supports the practice recommendations of published consensus guidelines for the conduct of CPB in relation to minimising anaemia during cardiac surgery (15) and limiting arterial outlet temperature to 37^{o}C during CPB (12). Postoperatively, use of intra-aortic balloon pump and readmission to the ICU were found to be independent predictors of AKI, most likely secondary to compromised haemodynamic function. The inclusion of these factors in the multivariate model highlights the role of the modifiable intraoperative predictors of AKI, since they remain significant even after controlling for these postoperative factors.

Renal dysfunction has been frequently used as a surrogate outcome measure for reporting renal outcomes, determining risk factors, and assessing treatment benefits, however varying definitions have been proposed (1). The ADQI group (3), made recommendations that the change from baseline in serum creatinine or estimated creatinine clearance be used whenever possible rather than single absolute values. According to the RIFLE criteria, as the categories of AKI progress according to change from baseline creatinine, sensitivity for the endpoint decreases and specificity increases. More recently, a modification to the RIFLE classification by the Acute Kidney Injury Network (AKIN) included a shorter time frame within which AKI has to occur (48 hours), a milder serum creatinine value increase from baseline to peak value, and the staging of patients receiving renal replacement therapy. A comparative study of the classification systems found that modification did not improve the clinical usefulness of the definition, the authors concluding that in the interest of meaningful comparison of study findings, it appears to be advisable that only 1 AKI classification system should be referenced (16).

The quantification of hyperthermia during CPB is limited by the accuracy of the measurement of arterial outlet temperature. We have determined previously that at a temperature of 37^{o}C measured at the arterial outlet of the Capiox® SX25RX oxygenators purports to actual blood temperature of approximately 37.5^{o}C (17). We have also previously reported under-reading of the arterial blood temperature by arterial outlet oxygenator thermistor probes in all other oxygenators we have evaluated (17, 18). Therefore, although we have defined hyperthermia in this study as an arterial outlet temperature of >37^{o}C as recorded by the heart lung machine, actual blood temperatures are likely to have been at least 0.5 ^{o}C higher. Although Shann et al suggest that *"Coupled temperature ports for all oxygenators should be checked for accuracy and calibrated"* (12), the ability to calibrate temperature measurement ports on our heart lung machine is not a feature provided by the manufacturer. To avoid actual arterial blood temperatures exceeding 37^{o}C when using the Capiox® range of oxygenators a measured arterial outlet temperature target of 36.5^{o}C should be used (18). As a result of this report, we have modified our protocol to limit the measured arterial outlet temperature to 36.5^{o}C. Prospective audit is required to determine whether this change in practice is associated with a further reduction in the incidence of AKI. This is a single-centre study therefore reproduction of these results using a larger multicentre dataset encompassing differences in management approaches to modifiable CPB factors affecting AKI such as anaemia, transfusion, pressure and flow during CPB, and rewarming may improve generalisabilty. Due to the change in rewarming protocol, there was a strong negative correlation (19) between the incidence of arterial outlet hyperthermia and year of operation (Pearson correlation coefficient *(r)* = -0.61, p <0.001), the year of operation was not included in the multivariate model. No significant changes were made to clinical practice during the study period other than the introduction of retrograde autologous priming during 2010. Minimum CPB haemoglobin was similar for each year of operation. This study was observational in nature and therefore associations identified cannot infer causality.

CONCLUSIONS

In conclusion, avoiding arterial outlet hyperthermia may help decrease AKI following cardiac surgery using CPB. Both intraoperative and postoperative temperature management strategies should be the focus of future randomised studies to determine optimal interventions.

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3.2 Low Oxygen Delivery as a Predictor of Acute Kidney Injury during Cardiopulmonary Bypass.

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ABSTRACT

Low indexed oxygen delivery (DO_2i) during cardiopulmonary bypass (CPB) has been associated with an increase in the likelihood of acute kidney injury (AKI), with critical thresholds for oxygen delivery reported to be 260-270 ml/min/m^2. This study aims to explore whether a relationship exists for oxygen delivery during CPB, in which the integral of amount and time below a critical threshold, is associated with the incidence of postoperative AKI.

The area under the curve (AUC) with DO_2i during CPB above or below 270 ml/min/m^2 was calculated as a metric of oxygen delivery in 210 patients undergoing CPB. To determine the influence of low oxygen delivery on AKI, a multivariate logistic regression model was developed including AUC<0, Euroscore II to provide preoperative risk factor adjustment, and incidence of red blood cell transfusion to adjust for the influence of transfusion. Having an AUC<0 for an oxygen delivery threshold of 270 ml/min/m^2 during CPB was an independent predictor of AKI, after adjustment for Euroscore II and transfusion (OR 2.74, CI (1.01-7.41), p=0.047).

These results support that a relationship exists for oxygen delivery during CPB, in which the integral of amount and time below a critical threshold is associated with the incidence of postoperative AKI.

INTRODUCTION

Acute kidney injury (AKI) is a recognized and serious complication of cardiac surgery that increases in-hospital mortality, morbidity, length of stay, and hospital costs after surgery (1). Low indexed oxygen delivery (DO_2i) and low ratio of oxygen delivery/carbon dioxide elimination (DO_2/VCO_2) during cardiopulmonary bypass (CPB) have been associated with an increase in the likelihood of AKI (2,3) together with a number of modifiable factors including hemodilution and red blood cell transfusion (4,5), mean arterial pressure (6,7), and hyperthermic perfusion (8, 9). Critical thresholds for oxygen delivery metrics associated with AKI have been reported to be 260-270 ml/min/m^2 for DO_2i and a ratio of 5 for DO_2/VCO_2 (5,6). The peak lactate during CPB has also been reported to increase below a DO_2i of 260 ml/min/m^2 (10), however further data supporting a critical threshold of oxygen delivery is lacking. This study aims to explore whether a time-dose relationship exists for oxygen delivery during CPB, in which below a critical threshold, is associated with the incidence of postoperative AKI.

METHODS

Data source & collection.

This was a single centre observational study of prospectively collected data during CPB procedures from Jan – Jul 2015 in which the M4 monitor (Spectrum Medical, Gloucester, UK) was routinely used which provided calculated DO_2i and DO_2i/VCO_2i parameters. The study was approved by our Institutional Ethics Review Committee (332.14). Average DO_2i for each minute of bypass was calculated from data stored on the M4 monitor, from which 10-minute rolling averages were calculated for DO_2i and DO_2/VCO_2 ratios. NADIR values for each patient were the lowest 10-minute rolling average values for DO_2i and DO_2/VCO_2. The area under the curve (AUC) with DO_{2i} during CPB above or below 270 ml/min/m^2 was calculated as a metric of oxygen delivery. The AUC represents the integral of amount and duration of oxygen delivery above or below 270 ml/min/m^2, therefore for each patient if the AUC was negative then they were exposed to a greater integral of amount and duration of oxygen delivery

below 270 ml/min/m^2 than above 270 ml/min/m^2. Data for each entire case from initiation to end of bypass was included. All oxygen delivery and hematocrit data were obtained from the M4 monitor.

Continuous intraoperative variables were collected at 20 s intervals during CPB from either an Intellivue (Koninklijke Philips, Amsterdam, Netherlands) or Datex (GE Healthcare, Chicago, USA) physiological monitor. Nadir haemoglobin data were collected every 20-30 min using an ABL700 analyser (Radiometer, Copenhagen, Denmark). Monitoring and blood gas data was stored using the CONNECT™ software (LivaNova, London, UK). Patient risk factors, perioperative data and outcomes were collected using the Australian and New Zealand Collaborative Perfusion Registry (ANZCPR) which integrates electronic data from CONNECT™ software as previously described (11).

Clinical management

General anaesthesia was induced with fentanyl (10-30g/kg) and supplemented with sevoflurane and/or propofol. All patients underwent cardiac surgery with CPB using a S5 roller pump (LivaNova, London, UK). Arterial pressure was monitored via radial artery catheter. Cardiopulmonary bypass was instituted after positioning of either a single 36/51 Fr two-stage atrial cannula (Sarns™, Terumo Corporation, Tokyo, Japan), or 32–36 Fr bicaval cannulation (Sarns™), and a 22Fr or 24Fr ascending aortic cannula (DLP, Medtronic, Minneapolis, MN). The CPB circuit included a hard-shell membrane oxygenator (Capiox® RX25, Terumo Corporation, Japan), biopassive tubing (Phisio, LivaNova, London, UK) a 40-micron arterial line filter (AL40, Pall Corporation, Port Washington, USA) and a 0.2 micron prebypass filter (Prebypass Plus®, Pall Corporation, Port Washington, USA). A ½" diameter venous line was utilised routinely. The circuit was primed with 1L Plasmalyte solution, 500ml of Gelofusine (isolated CABG procedures) or 4% albumin (other procedures), 50ml 8.4% sodium bicarbonate solution, 50ml Hartmann's solution and 10,000 iu heparin. Packed red blood cells (RBC) were added if required to provide a predicted haemoglobin level of > 7 g/dl on initiation of CPB (determined by the algorithm of the CONNECT™ software). Prior to initiation of CPB retrograde autologous priming was performed with a target RAP volume of 250ml if the predicted CPB haemoglobin level was < 11 g/dl. The routine CPB protocol included arterial

non-pulsatile target flow rate of 1.8-2.4 L/min/m^2, alpha-stat pH management with target pO_2 100-250 mmHg, gravity venous drainage, and tepid systemic temperature management (nasopharyngeal temperature 34-35°C) with no active cooling.). After placement of the aortic cross clamp, cardioplegic arrest was induced with tepid (34°C) hyperkalemic blood cardioplegia (30 mmol/l) at induction and maintained with intermittent doses (16 mmol/l) delivered either anterograde or retrograde as required. Mean CPB arterial pressure was controlled using metaraminol, phentolamine or isoflurane to achieve a target of 40-80 mmHg, Target nasopharyngeal temperature for separation from bypass was > 36°C with rewarming rate < 0.5°C per 2 min and arterial outlet temperature < 37°C. Transfusion of red blood cells during CPB was triggered when haemoglobin level was measured to be <7 g/dL. Hemoconcentration was used in the setting of hyperkalaemia or fluid overload. Restrictive IV fluid administration was utilised routinely intraoperatively. For the 4 surgeons in our team, one used cardiotomy suction to collect shed mediastinal blood without cell salvage routinely. For the other 3, shed mediastinal blood was collected using cell salvage (Xtra, LivaNova, London, UK) in isolated coronary artery bypass graft (CABG) procedures, and cardiotomy suction and cell salvage in procedures other than isolated CABG. Salvaged blood was processed if sufficient volume was available for processing or when residual CPB circuit blood was processed (if last CPB haemoglobin was < 9 g/dl), otherwise residual circuit blood was returned to the patient via IV infusion. Post-operative renal replacement therapy was initiated according to physician assessment based on oliguria unresponsive to fluid resuscitation measures, hyperkalaemia, severe acidaemia or clinically significant lung oedema.

Acute Kidney Injury

AKI was defined according to the serum creatinine criteria of the RIFLE (renal Risk, Injury, Failure, Loss of renal function and End-stage renal disease) classification at the Risk or greater level as any increase in serum creatinine >50% from baseline to peak value postoperatively (12). Serum creatinine measurement was performed using the enzymatic method (Roche, Basel, Switzerland).

Statistical analysis

STATA® SE version 14.0 (StataCorp LP, College Station, Tx, USA) was used for the statistical analyses. Patient preoperative and intraoperative characteristics were compared in 210 patients with an AUC >0 (greater proportion of CPB with DO_2>270 ml/min/m) or an AUC <0 (greater proportion of CPB with DO_2<270 ml/min/m). The Kolmogorov–Smirnov test was used to check for normality of data before further analysis. P values were calculated for continuous variables using the student t test or the Wilcoxon rank sum test, as appropriate and the Pearson $\chi 2$ test for categorical variables. Group differences were considered statistically significant with a P value of <0.05. To determine the influence of low oxygen delivery and AKI, a multivariate logistic regression model was developed. Due to the size of the study population, to avoid overfitting, covariates selected for inclusion in the model were Euroscore II to provide preoperative risk factor adjustment, and incidence of red blood cell transfusion to adjust for the influence of transfusion on AKI. These covariates were tested for univariate association with AKI to confirm the assumption of their relevance to AKI. Logistic regression model discriminatory and fit indices included the Hosmer and Lemeshow χ^2 test and the c-index. A Lowess smoothing plot of the AUC DO_2i above or below 270 ml/min/m^2 was used to assess visually its relationship to the probability for AKI.

RESULTS

Data from 210 consecutive adult patients undergoing cardiac surgery was utilised. AKI was identified in 30 patients (14.3%). Having a greater integral of amount and duration of oxygen delivery during CPB above 270 ml/min/m^2 results in a positive value for the AUC and was observed in 42.4% (89/210) of patients. Conversely having a greater integral of amount and duration of oxygen delivery during CPB below 270 ml/min/m^2 results in a negative value for the AUC and was observed in 57.6% (121/210) of patients.

Patient baseline characteristics, intraoperative data and outcomes collected using ANZCPR are displayed in table 1. Patients with a negative AUC were significantly older, a greater proportion were female, lower BMI, had a higher incidence of diabetes, cerebrovascular disease, preoperative myocardial infarction, lower preoperative haemoglobin and greater predicted risk of mortality (Euroscore II). Intraoperatively, patients with a negative AUC underwent a greater proportion of coronary artery grafting and less proportion of other procedures, shorter CPB duration, lower CPB haemoglobin and CPB flow. Postoperatively they received greater exposure to red blood cell transfusion and had a greater incidence of AKI.

Calculated parameters are shown in table 2. Patients with a negative AUC had both lower CPB flow and haematocrit, resulting in lower average and nadir DO_2i. There was no difference in the nadir DO_2i/VCO_2i ratio between groups. In contrast, when comparing patients with or without AKI (table 3), patients with AKI had lower average and nadir DO_2i, greater negative AUC, however there was no difference in average CPB flow. There was no difference in the nadir DO_2/VCO_2 ratio for patients with or without AKI.

Figure 1 shows the LOWESS smoothing plot which allows visualisation of the relationship between the time-dose relationship of oxygen delivery above or below 270 ml/min/m^2 (AUC) and the probability of the incidence of AKI.

Table 1: Baseline demographic, procedural and outcome data obtained for patients undergoing cardiopulmonary bypass procedures with a positive or negative area under the curve for oxygen delivery index <270 ml/min/m^2.

	AUC + (89)	**AUC - (n=121)**	**p**
Preoperative			
Age, years	64 (52-71)	68 (60-77)	0.009
Female	7%	34%	<0.001
BMI	29 (26-32)	28 (24-31)	0.019
COPD	11%	19%	0.126
Previous cardiac surgery	6.8%	3.4%	0.252
Emergency surgery	2.3%	4.1%	0.452
Hypertension	49%	57%	0.276
Diabetes	15%	28%	0.020
Dialysis	1.1%	2.5%	0.478
Cerebrovascular disease	1.5%	13%	0.009
Myocardial infarction	15%	32%	0.003
Preoperative Hb, g/dl	148 (140-153)	131 (118-142)	<0.001
Preoperative creatinine, umol/l	90 (75-100)	88 (74-111)	0.531
Euroscore II	0.9 (0.7-1.7)	1.7 (0.9-3.4)	<0.001
Intraoperative			
CABG	33%	56%	0.001
Valve repair/replacement	12%	8%	0.328
Valve + CABG	35%	26%	0.148
Other procedure	20%	10%	0.035
CPB duration, min	87 (72-111)	80 (62-101)	0.026
Average CPB MAP, mmHg	64 (60-68)	62 (58-66)	0.071
Nadir CPB Hb, g/l	106 (101-112)	89 (76-96)	<0.001
Average CPB flow, l/min	4.0 (3.9-4.3)	3.8 (3.4-4.0)	<0.001
Average CPB CI, l/min/m^2	2.0 (1.9-2.1)	1.9 (1.8-2.1)	0.005
Nadir CPB Naso temperature, ^{O}C	33.2 (2.2)	33.2 (2.5)	0.525
RAP	16%	50%	<0.001
RAP volume	200 (200-400)	200 (200-300)	0.988
Maximum lactate, mmol/l	1.7 (1.5-2.1)	1.6 (1.3-2)	0.137
Postoperative			
Baseline creatinine %	107 (92-121)	110 (96-135)	0.076
Received RBC transfusion	8%	38%	<0.001
Postoperative renal dialysis	2.3%	4.9%	0.310
Postoperative stay, days	6 (5-9)	7 (5-10)	0.252
Acute kidney injury	7%	20%	0.007

Values denote median (25–75th percentiles), mean (SD), or proportion of patients in %. AUC +; greater integral of amount and duration of DO_{2i}>270 ml/min/m^2, AUC - ; greater integral of amount and duration of DO_{2i}<270 ml/min/m^2, CABG: coronary artery bypass graft; BMI: body mass index; COPD: chronic obstructive airway disease; Hb: haemoglobin; CPB: cardiopulmonary bypass; CI: cardiac index; Naso: nasopharyngeal ; MAP: mean arterial pressure; RAP: retrograde autologous prime; RBC: red blood cells.

Table 2: Calculated parameters utilising data obtained from the Spectrum M4, for patients undergoing cardiopulmonary bypass procedures with a positive or negative area under the curve for oxygen delivery index <270 ml/min/m^2.

Calculated M4 variables	AUC + (89)	AUC - (n=121)	p
Average CPB arterial flow, l/min	3.9 (3.7-4.2)	3.6 (3.3-3.9)	<0.001
Nadir CPB hct, %	29 (3.6)	25 (3.4)	<0.001
Nadir DO_2i, l/min/m^2	204 (179-232)	159 (125-182)	<0.001
Average DO_2i, l/min/m^2	297 (24)	228 (28)	<0.001
AUC DO_2i, 270 l/min/m^2	1960 (681-3507)	-3080 (-4968--1299)	<0.001
Nadir DO_2/VCO_2	4.4 (9.5)	3.6 (2.2)	0.817

Values denote median (25–75th percentiles), mean (SD), or proportion of patients in %. AUC +; greater integral of amount and duration of DO_{2i}>270 ml/min/m^2, AUC - ; greater integral of amount and duration of DO_2i<270 ml/min/m^2, Hct: hematocrit; CPB: cardiopulmonary bypass; DO_2: oxygen delivery; VCO_2: carbon dioxide elimination.

Table 3: Calculated parameters utilising data obtained from the Spectrum M4, for patients undergoing cardiopulmonary bypass procedures with or without acute kidney injury.

Calculated M4 variables	AKI (30)	No AKI (n=180)	p
Average CPB arterial flow, l/min	3.9 (3.4 - 4.3)	3.9 (3.6 - 4.2)	0.475
Nadir CPB Hct, g/l	25 (4)	27 (4)	0.002
Nadir DO_2i, l/min/m^2	170 (126-184)	180 (147-210)	0.08
Average DO_2i, l/min/m^2	233 (40)	261 (42)	0.001
AUC DO_2i, 270 l/min/m^2	-2956 (-6512 - -455)	-553(-3273 - 1835)	0.001
Nadir DO_2/VCO_2	3.2 (3)	4.2 (7.8)	0.258

Values denote median (25–75th percentiles), mean (SD), AKI: acute kidney injury; Hct: hematocrit; CPB: cardiopulmonary bypass; DO_2: oxygen delivery; VCO_2: carbon dioxide elimination.

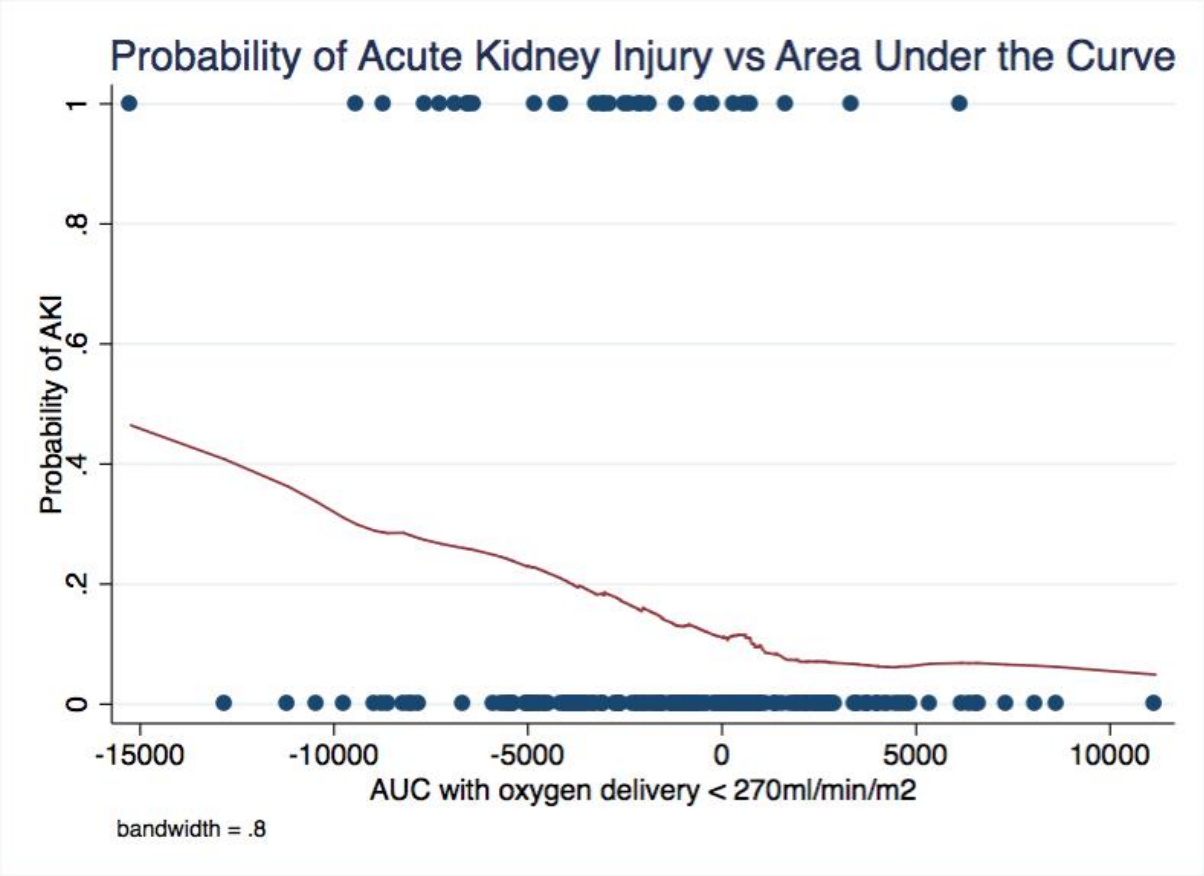

Figure 1: Lowess smoothing plot of the probability of AKI vs AUC with DO_2i <270 ml/min/m^2 during CPB. The Lowess is a smoothed scatterplot in which smoothed values are obtained by running a regression of the y-axis variable on the x-axis variable for each data point, and a few of the data near this point. In lowess, the regression is weighted so that the central point gets the highest weight and points that are farther away receive less weight. The procedure is repeated to obtain the remaining smoothed values, which means that a separate weighted regression is performed for every point in the data. This plot indicates an increase in probability of AKI for AUC values<0 (greater integral of amount and duration of DO_2i <270 ml/min/m^2 during CPB).

Figure 2, a contour interaction plot, indicates for patients with an overall negative AUC an increase in probability of AKI, and further increases in probability associated with each unit of red blood cells transfused.

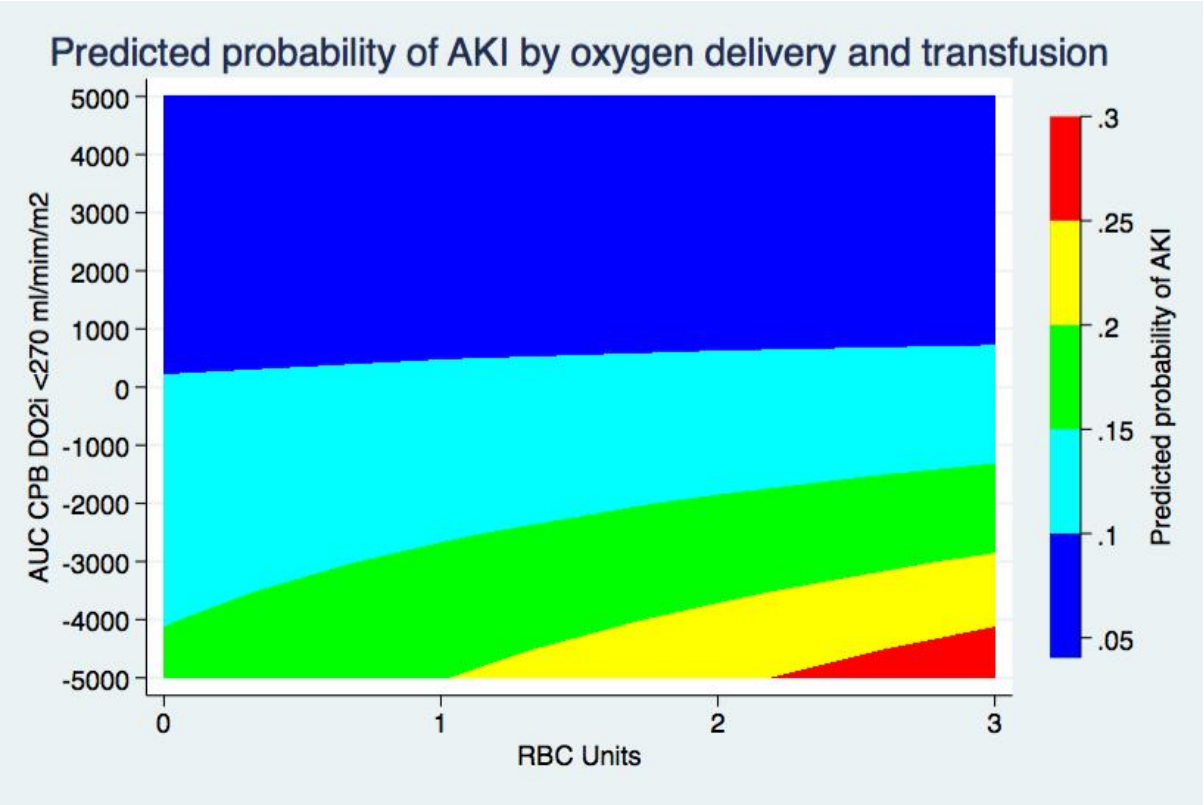

Figure 2: Contour interaction plot of the predicted probability of AKI, according to the interaction of the area under the curve for DO_2i <270 ml/min/m^2 during CPB and the transfusion of 0-3 units of red blood cells peri-operatively. The plot indicates that there is lowest probability for AKI and no interaction between oxygen delivery and number of units transfused with AUC values>0 (greater integral of amount and duration of DO_2i >270 ml/min/m^2 during CPB).

Since the relationship between AUC and the probability of AKI was non-linear (as shown by the Lowess plot), AUC was categorised as above or below 0 and entered into the multivariate model. Both Euroscore II and RBC transfusion were found to have a significant univariate association with AKI and were also included in the model. Having a greater proportion of CPB with DO_2i<270 ml/min/m^2 was an independent predictor of AKI, after adjustment for Euroscore II and RBC transfusion (OR 2.74, CI (1.01-7.41), p=0.047). Results of the multivariate model are summarised in table 4.

Table 4: Results of multivariate logistic regression modelling to identify predictors of acute kidney injury (n=210).

	P univariate	Adjusted OR (CI)	P multivariate
AUC < 0 for DO_2i<270 ml/min/m^2	<0.001	2.74 (1.01-7.41)	0.047
Euroscore II	<0.001	1.06 (0.96-1.18)	0.247
RBC transfusion	<0.001	1.4 (0.56-3.51)	0.468

Hosmer and Lemeshow goodness-of-fit test χ^2=7.34, *df*=10, *p*=0.5. AUC: area under curve; RBC red blood cell; OR: odds ratio; CI: confidence interval

DISCUSSION

The findings of this study support that for oxygen delivery during CPB, the integral of amount and time below a critical threshold (in this study a DO_{2i} of 270 ml/min/m^2) is associated with an increase in the incidence of postoperative AKI. The results of our multivariate model show that overall; patients that had an AUC that was negative (meaning that they had a greater integral of amount and duration of oxygen delivery during CPB below 270 ml/min/m^2) were 2.7 times more likely to experience AKI. These results support the previous work suggesting a critical threshold for oxygen delivery may be associated with an increase in the risk of AKI as previously reported (2,3). Ranucci et al (2), in a study involving 1048 patients undergoing coronary revascularization with CPB, reported a critical oxygen delivery threshold of 272 ml/min/m^2 for acute renal failure requiring renal replacement therapy and peak postoperative serum creatinine levels, within a multivariate model including serum creatinine, diabetes and chronic pulmonary disease. More recently De Somer et al (3) reported in 359 patients undergoing CPB that a nadir DO_{2i} level < 262 ml/min/m^2 was independently associated with AKI within a model including EuroSCORE and CPB duration. Both studies were characterised by relatively small sample sizes (in the context of multivariate modelling) and non-linearity in the relationship between oxygen delivery and the outcome variables. The non-linearity between oxygen delivery and AKI, as demonstrated in the Lowess plot (figure 1) provides visualisation of how the relationship between AUC and the probability

of AKI changes according to the whether CPB was performed with an overall positive or negative AUC. The plot indicates a clear inflection point where the probability of AKI increases. This relationship is also evident in the contour interaction plot (figure 2), which indicates for patients with an overall negative AUC an increase in probability of AKI, and further increases in probability associated with each unit of red blood cells transfused. Our results support previous findings that a threshold for critical oxygen delivery during CPB is relevant in the aetiology of postoperative AKI; however additional studies using larger datasets are warranted to confirm both the threshold value for oxygen delivery, its relationship to AKI, and the interaction of red blood cell transfusion.

De Somer et al identified a nadir DO_2/VCO_2 ratio < 5.3 to be associated with AKI (3), supporting the results of a small earlier study which identified a DO_2/VCO_2 ratio <5 to be a predictor of hyperlactatemia (13). Our study did not explore the relationship between DO_2/VCO_2 ratio and AKI, as we did not see a significant difference in the DO_2/VCO_2 ratio between patients with or without AKI (3.2 vs 4.2, p=0.258). A number of possible explanations may explain this difference, firstly the VCO_2 measurements in our study were obtained using the M4 monitor rather than a dedicated capnograph as described in the previous studies, secondly the formulae to calculate VCO_2 used by the M4 is different to that by De Somer, and thirdly it has been widely reported that the design of the oxygenator contributes to the measurement of exhaust CO_2 (14-16). We did not observe a significant difference in lactate levels during CPB, between patients with an AUC above or below 0.

A consideration in the reporting and understanding of the role of oxygen delivery during CPB is variation in the measurement of oxygen delivery and carbon dioxide production parameters and also how we utilise these parameters in analyses. Published formula exist for the calculation of DO_2 and VCO_2, however variation exists in the formula used by currently available monitoring devices. Variation can also be introduced through the devices used to measure the physiological parameters in the formula (see limitations). Equally important to consider is how we derive meaningful metrics that we can relate to outcome and how these metrics should be interpreted by the clinician. For example, in the studies reported by Ranucci et al (2) and De Somer et al (3) a metric of minimum DO_2i was used to relate oxygen delivery to outcome. In the Ranucci et al study, minimum DO_2i was calculated at the time when the lowest hematocrit was reached, with arterial oxygen tension recorded

simultaneously to lowest hematocrit, and pump flow as the mean value during 30 minutes of CPB around the time when the lowest hematocrit was recorded (2). In the De Somer study, data were collected at 10-minute intervals with the nadir DO_2 level defined as the lowest DO_2 value registered for at least two consecutive measurements during CPB (3). These calculations of minimum DO_2i were able to identify a threshold of oxygen delivery associated with outcome but do not provide quantification of the duration or quantity of oxygen delivery below the threshold. This study was designed to generate an AUC metric similar to that presented by Justison (17) in order to support previous findings.

There are a number of limitations of this study however they provide insight into reporting studies in this field. Firstly, this study is observational, from a single centre with data from only one oxygenator. Secondly, we only evaluated one oxygen delivery threshold to base the calculation of AUC, whilst this was evidence based, the inflection point in the Lowess plot occurs at a value around 2000 therefore the threshold at which oxygen delivery is associated with AKI may be higher than 270 ml/min/m^2. If a higher threshold were used the curve would move to the left. Thirdly, the DO_2i value we report was calculated by the M4 monitor that measures the flow in the arterial line of the CPB circuit ultrasonically. The positioning of the flow probe distal to any arterial to venous shunts is important to avoid overestimation of DO_2i, which is highlighted in our data in the average arterial flow rates reported for the arterial pump (Table 1) and the M4 (Table 2). Previous studies used arterial pump flow values to calculate DO_2i and may not have taken such shunts into account (2,3). Calculating DO_2i using the arterial pump flow value would tend to shift the Lowess plot to the left and would result in the inflection point being closer to an AUC of 0. Fourthly we have found that using the M4 to calculate DO_2i consistently results in a DO_2i value approximately 20 units less than the CONNECT™ GDP system which may be attributed to differences in the formula used to calculate DO_2. The formula used by the M4 to calculate DO_2 (18) is;

$$DO_2 = 10.Q_{blood}.\frac{SaO_2}{100}.Hb. \quad 1.34$$

whereas the formula used by CONNECT (18) is;

$$DO_2 = Q_{blood} \cdot \left(\frac{Hct}{2.94} \cdot 1.36 \cdot SaO_2 + PaO_2 \cdot 0.003\right) \cdot 10$$

Finally, the AUC value included the entire CPB period, and therefore included periods of partial CPB at the initiation of bypass and weaning from CPB where actual DO_2i values may be less than the calculated value in the presence of native cardiac output. In our practice these periods of partial bypass contribute only a small percentage of the total bypass period for which DO_2 is reported. To date, clear consensus definitions of how oxygen delivery and carbon dioxide production parameters should be calculated during CPB have not been developed. Multicentre studies using larger datasets would improve the generalisability of studies evaluating oxygen delivery and exhaust carbon dioxide derived parameters.

CONCLUSION

Having an AUC<0 for an oxygen delivery threshold of 270 ml/min/m^2 during CPB was an independent predictor of AKI. These results support that a relationship exists for oxygen delivery during CPB, in which the integral of amount and time below a critical threshold is associated with the incidence of postoperative AKI.

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Chapter 4: Use of EPD to identify modifiable predictors of CPB practice on acute kidney injury and 30-day mortality using multicenter registry data.

4.1 Rewarming Temperature During Cardiopulmonary Bypass and Acute Kidney Injury: A Multicenter Analysis.

Newland RF, Baker RA, Mazzone AL, Quinn SS, Chew DP; Perfusion Downunder Collaboration. Ann Thorac Surg. 2016 May;101(5):1655-62. doi: 10.1016/j.athoracsur.2016.01.086. Epub 2016 Mar 31. PMID: 27041450.

ABSTRACT

Background: Acute kidney injury (AKI) following cardiopulmonary bypass (CPB) is associated with dialysis requirement, longer intensive care and hospital length of stay and mortality. Oxygenator arterial outlet temperature > 37^{o}C has been reported to be associated with AKI, however the influence of other rewarming temperatures is unclear. Using multi-centre registry data, this study aims to evaluate the role of CPB rewarming temperatures on AKI.

Methods: Data from 8407 adult patients undergoing coronary artery bypass graft and/or valve repair or replacement was collected using the Perfusion Downunder Collaborative Database. Primary variables of interest were rewarming temperatures, defined as cumulative time the oxygenator arterial outlet temperature was >36°C >36.5°C or >37°C. Propensity scores were calculated to determine the predicted probability of hyperthermic perfusion (rewarming temperature >37°C). The influence of temperature on AKI was determined using separate multivariate models adjusting for propensity score; in the entire cohort (n=6904), and in propensity-matched patients (n=2044).

Results: Overall, 11.8% developed AKI. Duration of rewarming temperature > 36 or 36.5°C was not associated with AKI. Duration of rewarming temperature > 37°C (hyperthermic perfusion) was independently associated with RIFLE stage Risk or greater (OR, 1.42; 95% CI, 1.09-1.77; p=0.012) and Injury or greater AKI (OR, 1.52; 95% CI, 1.09-1.97; p=0.016) in the entire cohort, and Injury or greater AKI (OR, 1.51; 95% CI, 1.18-1.84; p=0.002) in propensity-matched patients.

Conclusions: Duration of hyperthermic perfusion, rewarming temperature >37°C, was an independent predictor of AKI. Avoidance of hyperthermic perfusion may be more beneficial in reducing AKI rather than avoidance of rewarming.

INTRODUCTION

Acute kidney injury (AKI) is a recognized and serious complication of cardiac surgery that increases in-hospital mortality, morbidity, length of stay, and hospital costs after surgery (1). Standardized definitions of AKI have been reported and include the RIFLE (risk, injury, failure, loss, end-stage renal disease) consensus definition of acute renal failure (2), AKIN (Acute Kidney Injury Network) (3), and the KDIGO (Kidney Disease: Improving Global Outcomes) (3) definitions. Pickering et al recently reported a meta-analysis of cohort studies comparing over 240,000 patients demonstrating cardiopulmonary bypass (CPB)-related AKI to be associated with a more than 2-fold increase in early and late mortality and stroke, regardless of AKI definition (4).

A number of modifiable CPB related factors have been identified to be associated with AKI, including oxygen delivery and CO2 production (5, 6), hemodilution and red blood cell transfusion (7, 8), mean arterial pressure (9, 10), and hyperthermic perfusion (11). Newland et al, in a single centre study reported that hyperthermic perfusion, defined as the duration of oxygenator arterial outlet temperature > 37°C was found to be a predictor of AKI (11), however the influence of temperature ranges below 37°C has not been reported, nor has the study been reproduced. In August 2015 the Society of Thoracic Surgeons (STS), The Society of Cardiovascular Anesthesiologists (SCA), and The American Society of ExtraCorporeal Technology (AmSECT) published Clinical Practice Guidelines for CPB focusing on temperature management during CPB, and made a class 1, level C recommendation that arterial outlet temperature should be limited to below 37°C to avoid cerebral hyperthermia (12).

To examine the influence of rewarming temperature on AKI we undertook a multi-centre study using prospectively collected perfusion registry data to test the hypothesis that patients exposed to higher rewarming temperatures during CPB would have an increased incidence of AKI following cardiac surgery.

METHODS

Study setting and data collection

Nine cardiac surgical centres in Australia and New Zealand participated in this observational study (see Appendix B). Institutional Ethics Review Board approval was obtained at all centres for participation in the Perfusion Downunder Collaborative Database project, and this study was approved by the Southern Adelaide Clinical Human Research Ethics Committee (297.14). Participating centres collected data on 8407 consecutive adult patients undergoing isolated coronary artery bypass graft (CABG), valve repair and/or replacement and valve/CABG procedures undergoing CPB. This cohort of patients included procedures in which rewarming temperatures were prospectively quantified from January 2011 to February 2014. Patients were excluded if they underwent dialysis preoperatively, had a chronic kidney disease classification of class 5 (estimated glomerular filtration rate <15 ml/min/1.73 m2 or on dialysis) or were missing pre or post-operative creatinine measurements (Figure 1).

Data was collected prospectively using the Perfusion Downunder Collaborative Database as previously described (13, 14), which integrates intraoperative data from the Data Management System® (Sorin) and JOCAP® (Maquet) heart lung machine data collection software, including patient, and blood gas monitoring systems. All perfusion related parameters and temperature measurements were collected continuously electronically at 20-60 s intervals. Clinical data definitions were based on those reported by the Australian and New Zealand Society of Cardiothoracic Surgeons database (15).

Independent variables

The primary variables of interest were rewarming temperatures, defined as the cumulative time that the oxygenator arterial outlet temperature was >36°C, >36. 5°C or > 37.0°C.

Dependent variables

The RIFLE criteria for AKI were used for the definition of the primary outcome variables. AKI was defined as meeting the criteria for RIFLE Risk class or greater, defined as an increase in serum creatinine to 150% (1.5 fold) from baseline during the postoperative period. RIFLE Injury class or greater defined as an increase in serum creatinine to 200% (2.0 fold) from baseline during the postoperative period was also analysed.

Statistical analyses

STATA® SE version 14.0 (StataCorp LP, College Station, Tx, USA) was used for the statistical analyses. Initially we examined the univariate association of the duration for which rewarming times were above each of the predefined rewarming temperatures and their association with AKI using logistic regression, then furthermore assessed visually the relationship between mean arterial outlet temperatures above 36°C and the probability of AKI using a lowess plot.

Hyperthermic perfusion was defined as exposure to an oxygenator arterial outlet temperature > 37.0°C. Patient preoperative and intraoperative characteristics were compared in 6904 patients with or without hyperthermic perfusion. Group differences were considered statistically significant with a p value of <0.05. p values were calculated for continuous variables using the median and Fisher exact test, and the $\chi 2$ test for categorical variables. To minimise the influence of selection bias according to preoperative and intraoperative factors that could influence whether patients underwent hyperthermic perfusion, propensity scores were estimated using logistic regression to determine the predicted probability of hyperthermic perfusion for each patient. Preoperative and intraoperative characteristics, and the number of perioperative red blood cell transfusions were evaluated for univariate association with hyperthermic perfusion, and those found to be significant predictors were included in the propensity-score model. Variables used in the calculation of the propensity score are reported in table 2. Patients were matched in a 1:1 ratio using nearest-neighbor matching (caliper 0.01) without replacement of subjects resulting in 1022 matched pairs.

To determine the influence of hyperthermic perfusion on AKI, multivariate logistic regression models were created that included the duration of hyperthermic perfusion. Variables not already included in the calculation of the propensity score were tested for univariate association with AKI using logistic regression, including the year of operation to evaluate temporal variation. Variables found to have a significant association with AKI ($p<0.05$) were included in the multivariate models. In model 1, 6904 patients with complete datasets were analysed in a mixed effects model panelled by centre, with adjustment for the propensity-score. In model 2, propensity-matched patients were analysed (n=2044) clustered by centre.

RESULTS

6904 patients undergoing cardiac surgical procedures with CPB were eligible for inclusion in this study (figure 1). 5042 (73%) were subjected to arterial outlet oxygenator temperatures >36oC, 3900 (56%) were subjected to arterial outlet oxygenator temperatures >36.5°C, and 1014 (15%) patients were subjected to arterial outlet oxygenator temperatures > 37°C.

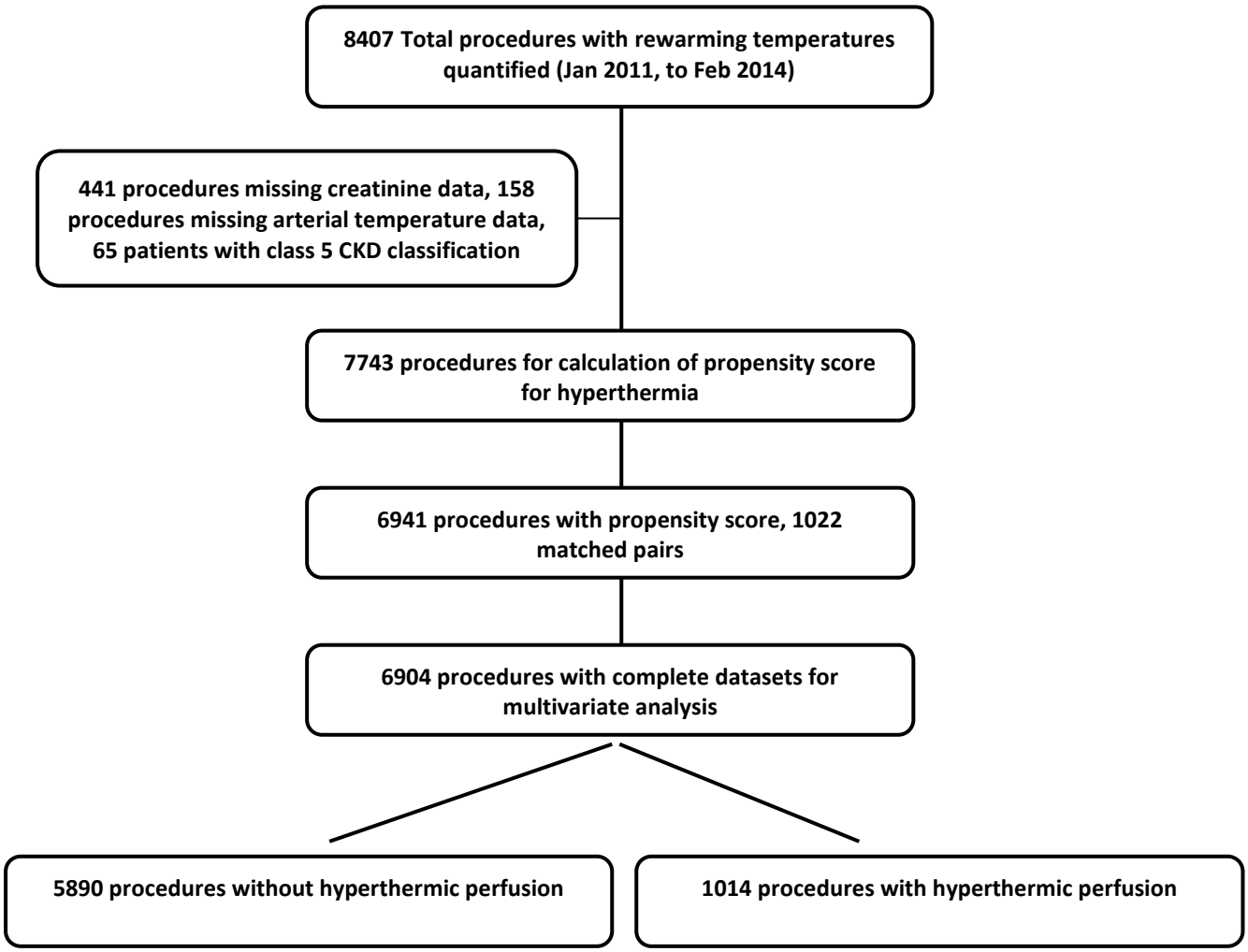

Figure 1. Flowchart showing patients extracted from the Perfusion Downunder Collaborative Database included in analysis.

A comparison of the duration of rewarming temperatures at 36°C, 36.5°C and 37°C is shown in Figure 2.

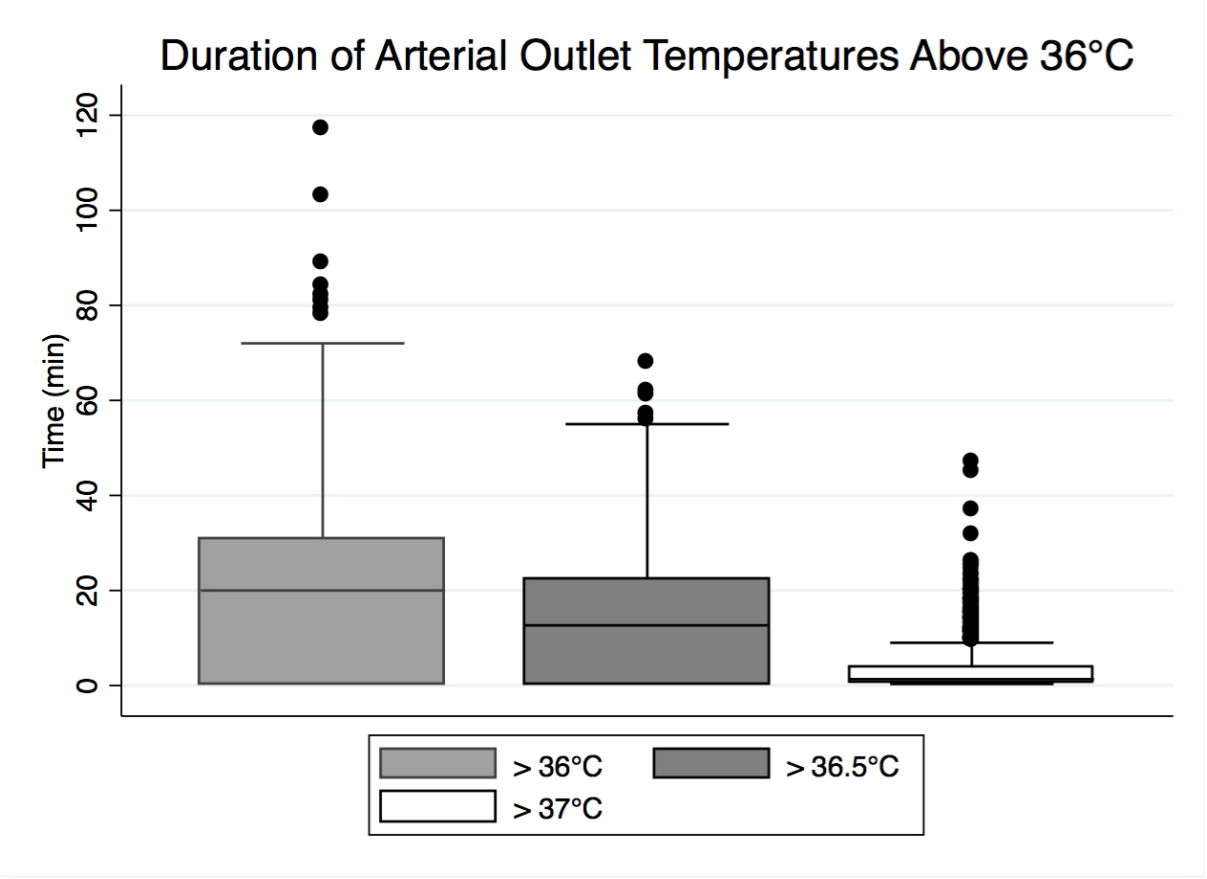

Figure 2. Duration of arterial perfusion temperatures during cardiopulmonary bypass rewarming. Box and whisker plot of cumulative time during CPB that the arterial outlet temperature was >36 °C, >36.5°C and >37°C. The box indicates the median and interquartile range, upper whisker indicates highest value <= (upper quartile + 1.5*interquartile range), values greater than this are outliers. The number of patients in each group is indicated (N).

The duration of oxygenator arterial outlet temperature >36°C and >36.5oC were not found to have a univariate association with AKI (p=0.113, p=0.208 respectively), only the duration of arterial outlet temperature > 37°C was associated with AKI (p=0.019). The relationship between mean rewarming temperature above 36°C and incidence of AKI was assessed visually using a lowess smoothing plot to further validate that temperature less than 37°C should not be included in the multivariate models (Figure 3).

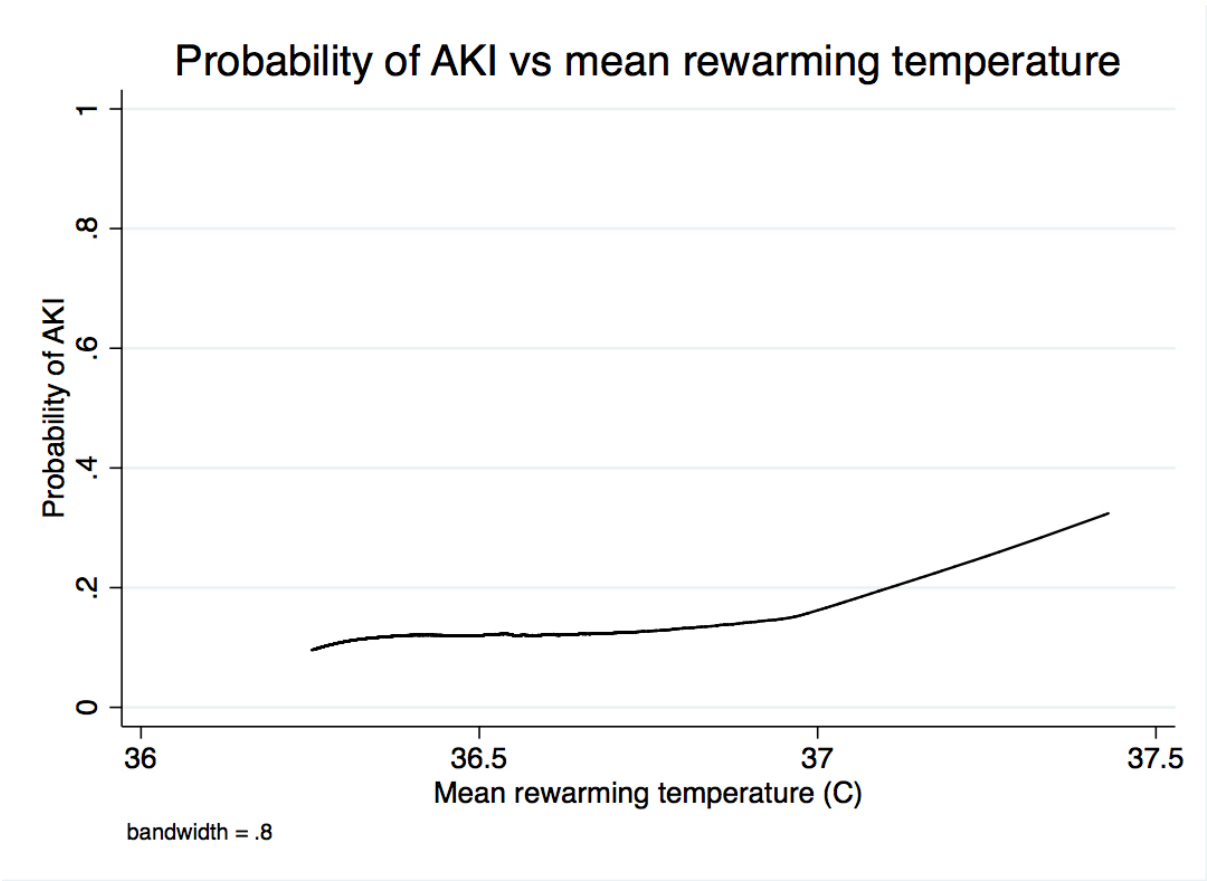

Figure 3. Lowess smoothing plot of mean rewarming temperature above 36°C and incidence of AKI. The plot confirms that there is an increase in probability of AKI only for temperatures above 37 °C.

Perioperative characteristics and outcomes of patients with or without hyperthermic perfusion (duration of arterial outlet temperature > 37°C) are compared in Table 1. Overall, 11.9 % of patients developed AKI, with a 9-fold increase in-hospital mortality (mortality 0.7% without AKI, 6.8% with AKI). Perioperative characteristics and outcomes of the 2044 successfully propensity matched patients are shown in Table 2.

Variables found to have a univariate association with AKI not already included in the calculation of the propensity score were the duration of hyperthermic perfusion, age, preoperative haemoglobin, infective endocarditis, emergency procedures, procedures undertaken during 2011, and CPB duration as shown in Table 3. Duration of hyperthermic

perfusion was found to be independently associated with any AKI (Table 3) and Rifle Injury class or greater (Table 4) after adjusting for the propensity score. For every 10 minutes of hyperthermic perfusion, there was an associated 42% increase in the incidence of any AKI (OR, 1.42; 95% CI, 1.09-1.77; P=0.012) and a 52% increase in the incidence of Rifle Injury class or greater (OR, 1.52; 95% CI, 1.09-1.97; P=0.016).

In the propensity-matched patients, duration of hyperthermic perfusion was found to be independently associated with Rifle Injury or greater class AKI (OR, 1.51; 95% CI, 1.18-1.84; P=0.002), with a 51% increase in the incidence for every 10 minutes of hyperthermic perfusion.

Table 1. Preoperative, intraoperative characteristics and outcomes of all patients (n= 6904).

	Without hyperthermic perfusion (N = 5890)	With hyperthermic perfusion (N = 1014)	P
Baseline			
Age, years	68 (60-76)	67 (58-75)	0.174
Female	26%	27%	0.471
BMI	28 (25-31.8)	27.9 (24.8-31. 6)	0.825
Chronic obstructive airway disease	10.1%	13.1%	0.026
Previous cardiac surgery	5.5%	7.5%	0.010
Diabetes	28.9%	32.9%	0.010
Hypertension	69.6%	73.3%	0.018
Congestive heart failure	14.1%	17.8%	0.002
Ejection fraction < 30%	3.6%	4.9%	0.047
Emergency surgery	1.8%	1.7%	0.871
Infective endocarditis	1.8%	2.1%	0.475
Preoperative haemoglobin, g/dl	13.3 (12-14.4)	13.2 (11.8-14.3)	0.454
Preoperative creatinine, umol/l	86 (74-102)	85 (73-103)	0.563
Euroscore	3.2 (1.6-6.2)	3.5 (1.7-6.9)	0.038
Procedure			
Coronary artery graft (CABG)	59.6%	51.2%	<0.001
Valve repair/replacement	26.2%	33.4%	<0.001
Valve + CABG	14.2%	15.4%	0.318
CPB duration, min	86 (67-109)	84 (65-108)	0.377
Min CPB Naso temp, ^{O}C	33.7 (32.4-34.2)	33.8 (33.1-34.2)	<0.001
Last CPB Nasopharangeal temp, ^{O}C	36.5 (36.3-36.7)	36.6 (36.3-36.9)	<0.001
Min CPB haemoglobin, g/dl	86 (75-97)	84 (73-95)	0.096
Avg CPB cardiac index, l/min/m^2	2.29 (2.05-2.42)	2.1 (1.93-2.3)	<0.001
Avg CPB MAP, mmHg	61.7 (57-66.8)	60.5 (56.2-65)	<0.001
CPB MAP < 50mmHg, min	8.9 (4-17)	9.9 (5-17)	0.013
Arterial temp >36 ^{O}C, min	15 (0-26)	18.4 (0-21.3)	0.003
Arterial temp >36.5 ^{O}C, min	1.5 (0-10)	10.6 (0-22.3)	<0.001
Arterial temp >37 ^{O}C, min	0	1.3 (0.5-4)	<0.001
Outcome			
Serum creatinine increase			
>50%	11.7%	12.9%	0.288
>100%	3.5%	5.3%	0.004
>200%	0.8%	1.7%	0.004
Use of intra-aortic balloon pump	1.2%	0.8%	0.285
Units of red blood cells transfused	0 (0-2)	0 (0-2)	0.047
Postoperative renal dialysis	1.6%	2.2%	0.161
Return to operating room	5.4%	6.7%	0.085
Intensive care unit readmission	3.4%	3.1%	0.741
Length of stay in hospital, days	7 (6-10)	7 (6-11)	0.160
Mortality in hospital	1.3%	2.0%	0.086

Values denote median (25–75th percentiles) or proportion of patients in %.
BMI: body mass index; CPB: cardiopulmonary bypass; MAP: mean arterial pressure.

Table 2. Propensity score variables and outcome variables of matched patients.

	No Hyperthermia (*N* = 1022)	Hyperthermia (*N* = 1022)	*P*
Propensity score variables			
Chronic obstructive airway disease	12.7%	13.1%	0.792
Previous cardiac surgery	6.4%	7.4%	0.337
Diabetes	33.9%	33.1%	0.673
Hypertension	72%	73.3%	0.519
Congestive heart failure	18.4%	17.6%	0.645
Ejection fraction < 30%	5.7%	4.9%	0.491
Euroscore	3.7 (1.9-7)	3.5 (1.7-6.9)	0.376
Coronary artery graft	51.1%	51.4%	0.894
Valve repair/replacement	33.2%	33.2%	1
Min CPB Naso temp, ^{O}C	33.8 (32.7-34.4)	33.8 (33.1-34.2)	0.070
Min CPB haemoglobin, g/dl	85 (73-96)	85 (74-95)	0.319
Avg CPB cardiac index, l/min/m^2	2.1 (1.9-2.3)	2.1 (1.9-2.3)	0.507
Units of red blood cells transfused	0 (0-2)	0 (0-2)	0.950
Outcome variables			
Serum creatinine increase			
>50%	12.1%	12.9%	0.574
>100%	3.6%	5.4%	0.055
>200%	1.2%	1.7%	0.350
Use of intra-aortic balloon pump	1.7%	0.8%	0.071
Units of red blood cells transfused	0 (0-2)	0 (0-2)	0.950
Postoperative renal dialysis	2.0%	2.3%	0.646
Return to operating room	7.0%	6.8%	0.861
Intensive care unit readmission	4.3%	3.2%	0.192
Length of stay in hospital, days	7 (6-10)	7 (6-11)	0.866
Mortality in hospital	1.6%	2.0%	0.499

Values denote median (interquartile range) or proportion of patients in %.
Abbreviations: CPB cardiopulmonary bypass; Naso nasopharyngeal; min minimum; avg average

Table 3. Results of multivariate model of risk factors for any AKI adjusting for the propensity score (n=6904).

	P univariate	Adjusted OR (CI)	*P* multivariate
Hyperthermic perfusion time, 10 min	0.019	1.42 (1.09-1.77)	0.012
Age, yrs	<0.001	1.02 (1.01-1.03)	<0.001
Preoperative haemoglobin, g/dl	<0.001	0.98 (0.97-0.99)	<0.001
Infective endocarditis	<0.001	1.32 (0.82-2.15)	0.248
Emergency surgery	<0.001	3.09 (2.04-4.69)	<0.001
Year of operation 2011	0.025	0.89 (0.74-1.07)	0.245
Cardiopulmonary bypass time, 10 min	<0.001	1.05 (1.03-1.07)	<0.001
Propensity score	<0.001	30.29 (8.15-112.57)	0.024

Table 4. Results of multivariate model of risk factors for RIFLE stage Injury or greater AKI adjusting for the propensity score (n=6904).

	Adjusted OR (CI)	*P* multivariate
Hyperthermic perfusion time, 10 min	1.52 (1.09-1.97)	0.016
Age, yrs	1.02 (1.01-1.03)	0.001
Preoperative haemoglobin, g/dl	0.99 (0.98-0.99)	<0.001
Infective endocarditis	1.36 (0.65-2.87)	0.414
Emergency surgery	2.42 (1.26-4.67)	0.008
Year of operation 2011	0.76 (0.55-1.05)	0.099
Cardiopulmonary bypass time, 10 min	1.05 (1.02-1.07)	<0.001
Propensity score	26.42 (3.99-174.69)	0.001

Table 5. Results of multivariate model of risk factors for RIFLE stage Injury or greater AKI in the propensity-matched patients (n=2044).

	Adjusted OR (CI)	*P* multivariate
Hyperthermic perfusion time, 10 min	1.51 (1.15-1.90)	0.006
Age, yrs	1.02 (1.01-1.04)	0.014
Preoperative haemoglobin, g/dl	0.98 (0.97-0.99)	<0.001
Infective endocarditis	0.91 (0.22-3.86)	0.900
Emergency surgery	1.57 (0.36-6.82)	0.547
Year of operation 2011	0.59 (0.32-1.08)	0.088
Cardiopulmonary bypass time, 10 min	1.08 (1.03-1.14)	0.001
Propensity score	19.25 (1.32-279.87)	0.03

DISCUSSION

This study investigated the role of rewarming temperatures during CPB on AKI using multi-centre perfusion registry data, and found that the duration of hyperthermic perfusion, defined as the duration of arterial outlet temperature >37 ^{o}C, was found to be an independent predictor of Rifle Risk class or greater AKI after adjustment for the propensity score, and an independent predictor of Rifle Injury class or greater AKI in the propensity-matched cohort. Arterial outlet temperatures between 36 and 37^{o}C were not found to be associated with AKI. These results confirm Newland et al's single center study that identified hyperthermic perfusion to be associated with AKI (11), demonstrating reproducibility of these findings and

increasing their generalisability. Furthermore, the current findings are strengthened by the availability of a large multicentre dataset, and the use of propensity scoring to adjust for clinical factors that may be associated with the exposure to hyperthermic perfusion. In the first model, in which 6904 patients with a propensity score were analysed, we observed that for every 10 minutes of hyperthermic perfusion, there was an associated 42% increase in the incidence of AKI; a similar effect size to that previously reported (11). Other independent predictors of AKI identified in the multivariate model (age, emergency surgery, CPB time) are consistent with those previously reported by Ng et al (1), and Ranucci et al (16) (preoperative haemoglobin). The calculation of the propensity score provided a cohort of 1022 successfully matched patient pairs, in which we observed that for every 10 minutes of hyperthermic perfusion, there was an associated 42% increase in the incidence of any AKI and a 52% increase in the incidence of Rifle Injury class or greater AKI. The two models provided firstly the opportunity to reproduce the findings in the single centre study, and secondly to further validate those findings in the propensity-matched cohort only.

Our results suggest that although it has been recognised that oxygenator temperature measurements are subject to some degree of inaccuracy resulting in under-reading of arterial temperature during rewarming (17, 11), monitoring and maintaining arterial outlet temperatures < 37°C as measured by the oxygenator and heart lung machine is beneficial in the conduct of CPB (12). Although arterial outlet temperatures during rewarming would have been higher than the reported temperatures, an association between measured temperature and AKI was only observed for the duration for which the arterial outlet temperature was above 37ºC. Overall, 15% of patients in this study experienced hyperthermic perfusion. The recent STS/SCA/AmSECT temperature guidelines state, “Surgical teams should limit arterial outlet blood temperature to <37°C to avoid cerebral hyperthermia. (Class I, Level C)” building on earlier evidence-based recommendations by Shann et al (18). Much of the evidence in the literature regarding the effect of hyperthermia during CPB is focused on reducing the risk of neurologic injury in contrast to the effect of hyperthermia on the kidney. Grocott et al (19) have reported increased rate of cognitive dysfunction in patients experiencing postoperative hyperthermia and Groom et al (20) reported the association between highest core temperature during CPB and an increase in the incidence of mediastinitis. These multicentre findings support the adoption and compliance with the recommendation of limiting arterial

line temperature to 37°C, from the context of providing further evidence for a reduction in the risk of developing AKI.

The Mission of the Perfusion Downunder Collaboration has been to improve the understanding of the impact of CPB on patients and has developed quantitative quality indicators to support clinical improvement through benchmarking. In 2010 we reported that 77% of cases performed within the collaboration complied with the recommendation to avoid arterial outlet temperatures greater than 37°C (14). Compliance with this recommendation has improved to 93% in 2014 during the period of our study (Figure 4).

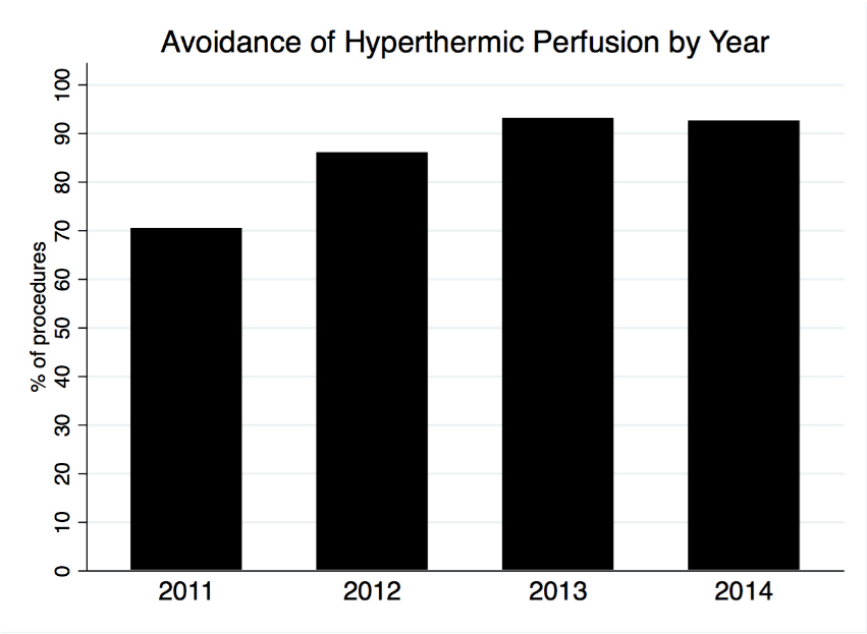

Fig 4. Improvement in compliance with the recommendation by Shann et al (2006) to limit arterial outlet temperature to 37°C during the study period in sites contributing to the Perfusion Downunder Collaboration.

To date, the incorporation of intraoperative electronic data is unique to the Perfusion Downunder Collaboration and this report highlights the value of collection of this data for improvement in the quality and understanding of CPB practice.

In a series of experiments of renal ischaemia-reperfusion injury models in the rat, Delbridge et al (21) found that hyperthermia, resulted in a significant rise in creatinine levels during the ischaemic and early re-flow post ischaemic phases. The study illustrated the potential role of temperature in kidney injury, as increasing temperature correlated with the severity of injury and unrecoverable loss of kidney function (21). We report that in cardiac surgical patients that the temperature associated with an increase in serum creatinine of >50% was

an arterial outlet temperature exposure of >37°C. Boodhwani et al reported the influence of rewarming on postoperative renal function after CPB in two separate randomised studies. In the first study, patients were cooled to 32°C during CPB and randomly assigned to rewarming to 37°C or 34°C, and second study patients underwent either sustained mild hypothermia at 34°C or normothermia 37°C without rewarming (22). The authors concluded that rewarming was found to be an independent risk factor for significant renal dysfunction, however the duration of measured temperatures during these studies was not reported. Our data suggests that since the duration of arterial temperatures at 36°C and 36.5°C were not found to be associated with AKI, that limiting rewarming temperatures to <37°C may be more beneficial than avoidance of rewarming per se.

The association between AKI and mortality has been recognised (23) and was observed in our study population; patients that deleveloped AKI had a 9-fold increase in-hospital mortality (mortality 0.7% without AKI, 6.8% with AKI). The difference in mortality rates between patients with or without hyperthermic perfusion did not reach statistical significance (mortality 1.8% without hyperthermic perfusion, 2% with hyperthermic perfusion, p=0.086).

Study limitations

The study was observational and the analysis retrospective, therefore causality could not be determined. We cannot exclude the possibility that other confounding factors may have existed, which, if adjusted for, may have influenced the association found between hyperthermic perfusion and AKI. The accuracy of the arterial temperature measurement has not been verified for some of the oxygenators utilised in the different centers. Despite these limitations, the strengths of our study include carefully applied regression and propensity analyses to a large multicentre CPB focussed dataset collected prospectively incorporating continuously recorded intraoperative electronic data. Although we were able to identify the duration of hyperthermic perfusion as an idependent predictor of RIFLE stage Injury or greater AKI in the propensity-matched cohort, the power to detect any AKI class was reduced both by the sample size and the lack of difference in rates of this AKI class (12.1% with hyperthermic perfusion, 12.9% without hyperthermic perfusion).

CONCLUSION

Hyperthermic perfusion defined as the duration of rewarming temperature > 37°C was found to be an independent predictor of AKI. These findings from multi-centre data support our previous results, that avoiding an arterial outlet temperature > 37^{o}C may help decrease AKI following cardiac surgery using CPB.

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4.2 Predictive Capacity of Oxygen Delivery During Cardiopulmonary Bypass on Acute Kidney Injury.

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ABSTRACT

Background: The randomised goal-directed perfusion trial (GIFT) confirmed retrospective findings that a goal directed perfusion strategy to maintain oxygen delivery index (DO_2i) during cardiopulmonary bypass (CPB) >280 ml/min/m^2 reduces the incidence of acute kidney injury (AKI). We developed a predictive model for AKI using data from the Australian New Zealand Collaborative Perfusion Registry to determine whether these findings could be validated in a real-world clinical setting and used to identify an optimal DO_2i threshold for predictive diagnostic accuracy.

Methods: Data in 19,410 CPB procedures was randomly divided into equal sized (n=9,705) training and validation datasets. Univariate and multivariate logistic regression was used to determine the best predictive model for AKI (RIFLE class ≥R and ≥I) and the incremental predictive value of minimum DO_2i during CPB. The optimal threshold for DO_2i was determined.

Results: Minimum DO_{2i} was significantly associated with the odds of RIFLE class ≥R and ≥I AKI in both datasets (validation dataset class ≥R OR 0.993, 95% CI=0.991-0.995, p<0.001; class ≥I 0.993, 95% CI=0.991-0.996, p<0.001), representing on average a 7% increase in the likelihood of AKI for every 10 ml/min/m^2 decrease in DO_2i. Diagnostic accuracy was similar for both datasets with an optimal DO_2i threshold of 270 ml/min/m^2. The odds of RIFLE class ≥R AKI were increased by 52% in those below the threshold (OR=1.52, 95% CI=1.29-1.77, p<0.001).

Conclusion: This study confirms previous findings that minimum DO_2i during CPB is independently associated with AKI supporting the findings of the GIFT trial in a broader risk, multicentre cohort.

INTRODUCTION

Acute kidney injury (AKI) is a serious complication of cardiac surgery increasing in-hospital mortality, morbidity, length of stay, and hospital costs (1). A recent meta-analysis of cohort studies including over 240,000 patients demonstrated cardiopulmonary bypass (CPB)-related AKI to be associated with a more than 2-fold increase in early and long-term mortality and stroke, regardless of AKI definition (2). Cardiac surgical risk factors for AKI include age, female gender, preoperative renal insufficiency, low ejection fraction, emergency surgery and diabetes (1,3), whilst modifiable intraoperative factors include hemodilution, red blood cell transfusion, mean arterial pressure, hyperthermic perfusion and surgical re-exploration (3-6, 7). The minimum oxygen delivery index (DO_2i) during CPB has been reported as an independent predictor of renal replacement therapy (8) and Acute Kidney Injury Network class II injury (9), with optimal diagnostic thresholds of DO_2i identified as 272 and 260 ml/min/m2 respectively. Further evidence of increased risk of AKI following CPB has been demonstrated in a study that identified the integral of amount and time for DO_2i below 270 $ml/min/m^2$ as an independent predictor of AKI (10) and when included as part of a quality improvement measure (11). The recent randomised goal-directed perfusion trial (GIFT) demonstrated that a goal directed perfusion strategy, designed to avoid nadir DO_2i less than 280 ml/min/m2 reduced the rate of AKI in patients undergoing moderately hypothermic CPB (12).

To determine the applicability of increased risk associated with lower DO_2i and to identify the optimal threshold for AKI following cardiac surgery, we used Australian and New Zealand Collaborative Perfusion Registry (ANZCPR) data to develop a risk prediction model for AKI. From these findings, we examined whether the results of the GIFT trial could be extrapolated to a large multicentre population.

METHODS

Nine cardiac surgical centres in Australia and New Zealand prospectively collected data using the ANZCPR as previously described (13). Institutional Ethics Review Board approval was obtained at each participating centre, and this study was approved by the Southern Adelaide Clinical Human Research Ethics Committee (333.14) and the ANZCPR Steering Committee.

Centres collected data on 21,230 adult patients undergoing isolated coronary artery bypass graft (CABG), or valve repair/replacement +/- CABG using CPB between January 2008 and December 2016. Patients were excluded if they underwent dialysis preoperatively, had chronic kidney disease class 5 or missing perioperative creatinine, CPB haemoglobin or cardiac index data (Figure 1). A total of 19,410 patients were included in the study.

The ANZCPR meets the Australian Commission on Safety and Quality in Health Care National Operating Principles for Australian Clinical Quality Registries; http://www.safetyandquality.gov.au/our-work/information-strategy/clinicalquality-%20%20registries/strategic-operating-principles-for-clinical-quality-registries/. Clinical data definitions were based on the Australian and New Zealand Society of Cardiothoracic Surgeons registry (14). Complete ANZCPR variable definitions are available at www.anzcpr.org. Combined morbidity, excluding renal injury was defined as the incidence of postoperative ventilation >48hrs, stroke or return to theatre.

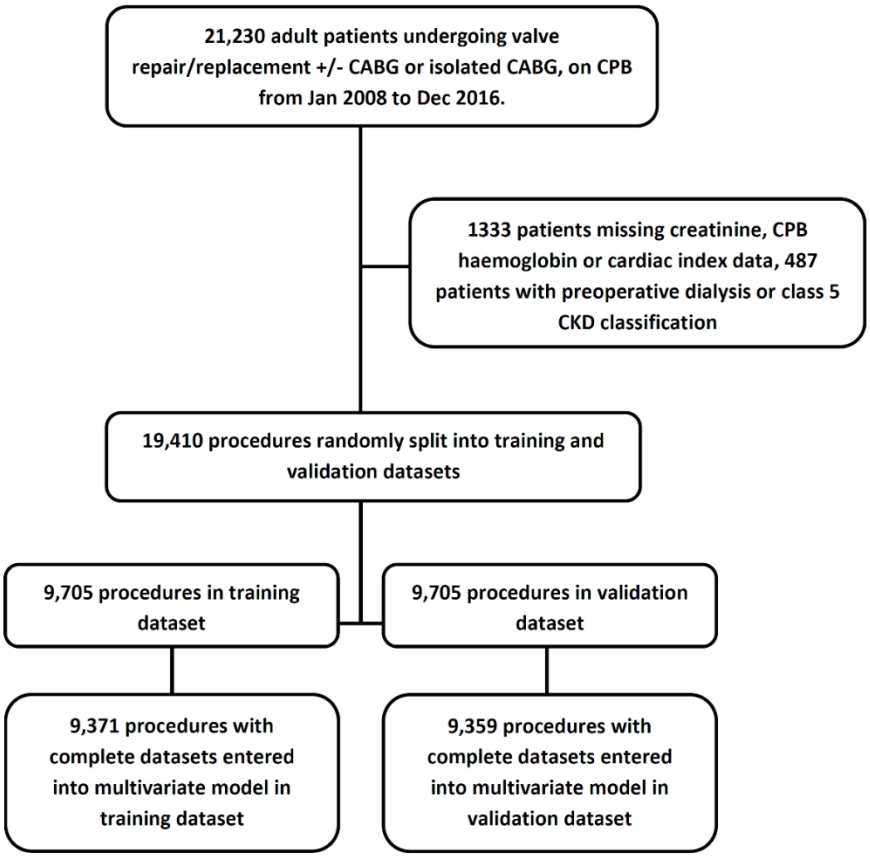

Figure 1. Flowchart showing patients extracted from the ANZCPR included in the analysis.

Dependent variables

The primary endpoint was AKI defined according to the serum creatinine criteria of the RIFLE (renal Risk, Injury, Failure, Loss of renal function and End-stage renal disease) classification. Specifically, AKI is reported as Risk (creatinine greater than 150% baseline) or Injury (creatinine greater than 200% baseline). Change in creatinine was measured from preoperative value to maximum postoperative value.

Independent variables

Potential predictors of AKI included patient demographic, preoperative and intraoperative factors (Table 1).

Oxygen delivery was calculated using the formula:

DO_2i = 10 x cardiac index (CI, l/min/m^2) x oxygen content (ml/min/m^2)

Oxygen content = (haemoglobin (g/dL) x 1.34 x oxygen saturation (%)) + (0.003 x pO_2 (mmHg))

where haemoglobin, O_2 saturation and pO_2 were measured during CPB using blood gas analysis. Based on the same formula, the estimated minimum DO_2i for each patient was determined using the average of the real time CI during CPB, the minimum haemoglobin, and the minimum pO_2. Imputation using mean replacement was performed for procedures missing minimum pO_2 (4% of values imputed). Oxygen saturation was estimated at 99% for arterial blood.

Statistical Analysis

Before constructing the risk prediction models the complete dataset was split into training and validation cohorts using 50% random sampling. STATA version 15.0 (StataCorp LP, College Station, Tx, USA) was used for all analyses. Patient preoperative and perioperative characteristics were compared between cohorts and in patients with or without AKI. The Kolmogorov–Smirnov test was used to check for normality of continuous data. Differences between groups were assessed using the student t-test for continuous data or the Wilcoxon rank sum test, as appropriate, and the Pearson $\chi 2$ test was used for categorical variables. Perioperative characteristics including operation year were evaluated for univariate

association with AKI using binary logistic regression with the training dataset. Significant predictors ($p<0.10$) were included in the multivariate logistic regression training model. The admission hospital was included in the multivariate models as a main effect a priori. Minimum haemoglobin and red blood cell transfusion were not included in the multivariate model as they were considered to be on the causal pathway between DO_2i and AKI. Variables that were significant independent predictors ($p<0.05$) were retained in the final model.

To validate the influence of minimum DO_2i on AKI, the final multivariate model obtained from the training data was applied to the validation data. The final model was also utilised to evaluate the relationship between minimum DO_2i and RIFLE class Injury AKI in both training and validation datasets.

To assess the diagnostic accuracy of each model we calculated the area under the receiver operating characteristic curve (AUROC). Similarity of diagnostic accuracy for AKI of the models was determined by using the chi-squared test to compare the 2 AUROC's.

The identification of an optimal threshold for minimum DO_2i associated with AKI was determined by generating residual values from regressing mean-centered independent predictors of AKI on minimum DO_2i. Sensitivity, specificity and residuals were then generated from the logit of AKI and the residuals from the regression. The residual value corresponding to the optimal coupling of sensitivity and specificity values was used to calculate deviation from the mean, which was then applied to the mean of the DO_2i values to provide a value of 270 ml/min/m^2. Since previous studies have reported models of minimum DO_2i and AKI using exposure to DO_2i below a cut-off level rather than a continuous variable (8,9), a sensitivity analysis for the AUROC was performed by including minimum DO_2i in the model as a binary variable with a cut-point at 270 ml/min/m^2 (based upon our identification of this value as the optimal cut-point). Goodness of fit was evaluated using the Hosmer-Lemeshow goodness of fit test. Linearity of the relationship between adjusted minimum DO_2i and AKI was assessed by plotting the log-odds of the probability of AKI vs minimum DO_2i. Multicollinearity was assessed by the variance inflation factor.

RESULTS

19,410 cardiac surgery patients were included in this study, with 9,705 included in both the training and validation datasets. The rate of AKI observed in training and validation cohorts was similar; 1175 (12.1%) patients with RIFLE Risk criteria (training) vs 1182 (12.2%) (validation), and 385 (3.9%) with RIFLE Injury vs 399 (4.1%) respectively.

Demographics and perioperative data

There were no differences between training and validation cohorts (table 1). Patients with AKI were more likely to be co-morbid, have lower haemoglobin and DO_2i, and longer CPB time, greater incidence of RBC transfusion, and mortality risk.

Patient outcomes

In-hospital mortality was 2% and combined morbidity 11%, similar in both training and validation cohorts. Patients with AKI had a greater incidence of in-hospital mortality (7% with AKI vs 0.8% without AKI, $p<0.001$) and combined morbidity (27% with AKI vs 9% without AKI, $p<0.001$).

Multivariate models of DO_2i and AKI

The final multivariate model for DO_2i and AKI is reported in Table 2. The analysis included 9,371 patients (334 patients excluded for missing data). Decreasing DO_2i was significantly associated with the odds of RIFLE Risk or greater AKI (OR=0.993, 95% CI=0.992-0.995, $p<0.001$). Other independent predictors of AKI are shown in table 2.

Table 1. Preoperative demographics and perioperative data in the training and validation cohort, and patients with or without AKI in the training dataset.

	Training cohort	Validation cohort	p	Without AKI	With AKI	p
N	9705	9705		8530	1175	
Preoperative						
Age, years	68 (59, 75)	68 (59, 75)	0.69	67 (59, 75)	70 (62, 77)	<0.001
Body surface area, m^2	2 (2, 2)	2 (2, 2)	0.1	2 (1.8, 2.1)	2 (1.8, 2.2)	0.002
Female	2379 (25%)	2441 (25%)	0.3	2047 (24%)	332 (28%)	0.002
Diabetes	2951 (30%)	2944 (30%)	0.93	2507 (29%)	444 (38%)	<0.001
Severe left ventricular dysfunction	372 (4%)	383 (4%)	0.68	310 (4%)	62 (5%)	0.007
Congestive heart failure	1340 (14%)	1313 (14%)	0.57	1096 (13%)	244 (21%)	<0.001
Infective endocarditis	181 (2%)	182 (2%)	1.0	132 (2%)	49 (4%)	<0.001
Chronic obstructive pulmonary disease	1297 (13%)	1267 (13%)	0.52	1082 (13%)	215 (18%)	<0.001
Pulmonary hypertension	1406 (16%)	1342 (15%)	0.24	1230 (16%)	176 (18%)	0.12
Hypertension	6912 (71%)	6929 (71%)	0.81	6016 (71%)	896 (76%)	<0.001
Smoking history	5048 (54%)	5114 (55%)	0.35	4437 (54%)	611 (56%)	0.2
Redo procedure	560 (6%)	555 (6%)	0.88	467 (6%)	93 (8%)	<0.001
Emergency procedure	179 (2%)	178 (2%)	0.96	122 (1%)	57 (5%)	<0.001
Cerebrovascular disease	835 (9%)	811 (8%)	0.54	715 (8%)	120 (10%)	0.04
Previous myocardial infarction	3331 (34%)	3458 (36%)	0.058	2908 (34%)	423 (36%)	0.2
Euroscore is this I or II	3 (2, 6)	3 (2, 6)	0.31	3 (2, 6)	5 (2, 9)	<0.001
Preoperative haemoglobin, g/L	134 (121, 145)	134 (120, 145)	0.42	135 (122, 145)	126 (111, 139)	<0.001
Preoperative creatinine, mmol/L	86 (74, 102)	87 (74, 103)	0.057	86 (74, 102)	87 (72, 111)	0.053
Intraoperative						
Cardiopulmonary bypass time, minutes	86 (67, 109)	86 (67, 110)	0.25	85 (66, 108)	93 (70, 120)	<0.001
Procedure						
Coronary bypass graft	5803 (60%)	5764 (59%)	0.37	5208 (61%)	595 (51%)	<0.001
Valve replacement	2564 (26%)	2536 (26%)		2208 (26%)	356 (30%)	
Combined valve/coronary	1337 (14%)	1405 (14%)		1113 (13%)	224 (19%)	
Min nasopharyngeal temperature, ^oC	34 (32, 34)	34 (32, 34)	0.69	34 (32, 34)	34 (32, 34)	0.64
Mean arterial pressure, mmHg	62 (57, 66)	62 (57, 66)	0.55	62 (57, 67)	61 (56, 66)	0.16
Min oxygen delivery, ml/min/m^2	273 (238, 309)	272 (237, 308)	0.18	275 (240, 311)	259 (223, 295)	<0.001
Min haemoglobin, g/L	87 (76, 99)	87 (75, 99)	0.53	88 (77, 99)	82 (71, 95)	<0.001
Red blood cell transfusion	1189 (12%)	1219 (13%)	0.021	916 (11%)	273 (23%)	<0.001

Categorical data is represented as n (%); continuous data as median (interquartile range). Min; minimum.

Table 2. Association between preoperative and intraoperative factors and AKI using logistic regression in the training dataset (n=9,371).

		P	Multivariate OR (95% CI)	P
Preoperative				
Age, years	1.02 (1.02-1.03)	<0.001	1.02 (1.02-1.03)	<0.001
Body surface area, m^2	1.6 (1.2-2.01)	0.001	2.9 (2.1-3.9)	<0.001
Female	1.2 (1.1-1.4)	0.001	1.1 (0.9-1.3)	0.26
Diabetes	1.5 (1.3-1.7)	<0.001	1.2 (1.1-1.4)	0.008
Severe left ventricular dysfunction	1.5 (1.1-1.9)	0.005	1.3 (0.9-1.8)	0.085
Congestive heart failure	1.8 (1.5-2.1)	<0.001	1.4 (1.2-1.7)	<0.001
Infective endocarditis	2.8 (1.9-3.9)	<0.001	2.5 (1.7-3.7)	<0.001
Chronic obstructive pulmonary disease	1.5 (1.3-1.8)	<0.001	1.4 (1.1-1.6)	0.001
Pulmonary hypertension	1.2 (0.9-1.4)	0.110		
Hypertension	1.3 (1.2-1.5)	<0.001	1.1 (0.9-1.3)	0.096
Smoking history	1.1 (0.9-1.2)	0.191		
Redo procedure	1.5 (1.2-1.9)	<0.001	1.03 (0.8-1.3)	0.847
Emergency procedure	3.5 (2.5-4.8)	<0.001	3.1 (2.2-4.4)	<0.001
Cerebrovascular disease	1.2 (1.0-1.5)	0.036	0.9 (0.8-1.2)	0.562
Previous myocardial infarction	1.1 (0.9-1.2)	0.201		
Preoperative creatinine, per 10 mmol/L	1.05 (1.04-1.07)	<0.001	1.01 (0.99-1.03)	0.187
Intraoperative				
Cardiopulmonary bypass time, per 10 minutes	1.06 (1.04-1.07)	<0.001	1.04 (1.02-1.05)	<0.001
Procedure				
Coronary bypass graft (reference category)				
Valve replacement	1.4 (1.2-1.6)	<0.001	1.35 (1.1-1.6)	0.001
Combined valve/coronary	1.8 (1.5-2.1)	<0.001	1.2 (0.9-1.4)	0.127
Year of operation				
2008 (reference category)				
2009	0.9 (0.7-1.4)	0.89	1.04 (0.7-1.5)	0.81
2010	1.1 (0.8-1.6)	0.539	1.2 (0.8-1.7)	0.366
2011	0.9 (0.7-1.2)	0.497	1.1 (0.8-1.5)	0.641
2012	1.3 (0.9-1.7)	0.131	1.4 (0.9-1.9)	0.056
2013	1.4 (1-1.8)	0.03	1.5 (1.1-1.9)	0.019
2014	1.1 (0.8-1.5)	0.451	1.2 (0.9-1.7)	0.237
2015	1.1 (0.8-1.5)	0.435	1.2 (0.9-1.7)	0.194
2016	1.4 (1-1.9)	0.029	1.6 (1.1-2.2)	0.007
Minimum nasopharyngeal temperature, ^oC	0.99 (0.96-1.02)	0.504		
Hospital site				
1 (reference category)				
2	1.1 (0.8-1.4)	0.657	0.9 (0.7-1.4)	0.882
3	1.3 (0.9-1.9)	0.128	1.3 (0.9-1.9)	0.211
4	1.1 (0.9-1.5)	0.369	1.5 (1.1-2.1)	0.007
5	0.7 (0.5-0.9)	0.017	0.8 (0.6-1.1)	0.224
6	1.4 (0.9-2)	0.052	1.3 (0.9-1.9)	0.192
7	0.8 (0.6-1)	0.079	0.9 (0.6-1.2)	0.465
8	0.9 (0.7-1.2)	0.418	0.7 (0.5-1.03)	0.08
9	2 (1.5-2.7)	<0.001	2.9 (2.1-4.1)	<0.001
Arterial outlet temperature>37^oC, per 10 minutes	1.2 (1.1-1.4)	0.001	1.4 (1.1-1.6)	0.006
Mean arterial pressure, mmHg	0.99 (0.99-1.002)	0.182		
Minimum oxygen delivery, ml/min/m^2	0.94 (0.93-0.95)	<0.001	0.993 (0.92-0.95)	<0.001

Hosmer and Lemeshow goodness-of-fit test χ^2=9162, *df*=9336, *p*=0.899. C-statistic=0.701

The DO_2i AUROC was 0.70 (95% CI: 0.69-0.72) for the training dataset showing moderate overall diagnostic accuracy. The optimal cut-point for the minimum DO_2i was 270 ml/min/m^2. Sensitivity and specificity values are shown according to cut points of DO_2i in figure 2.

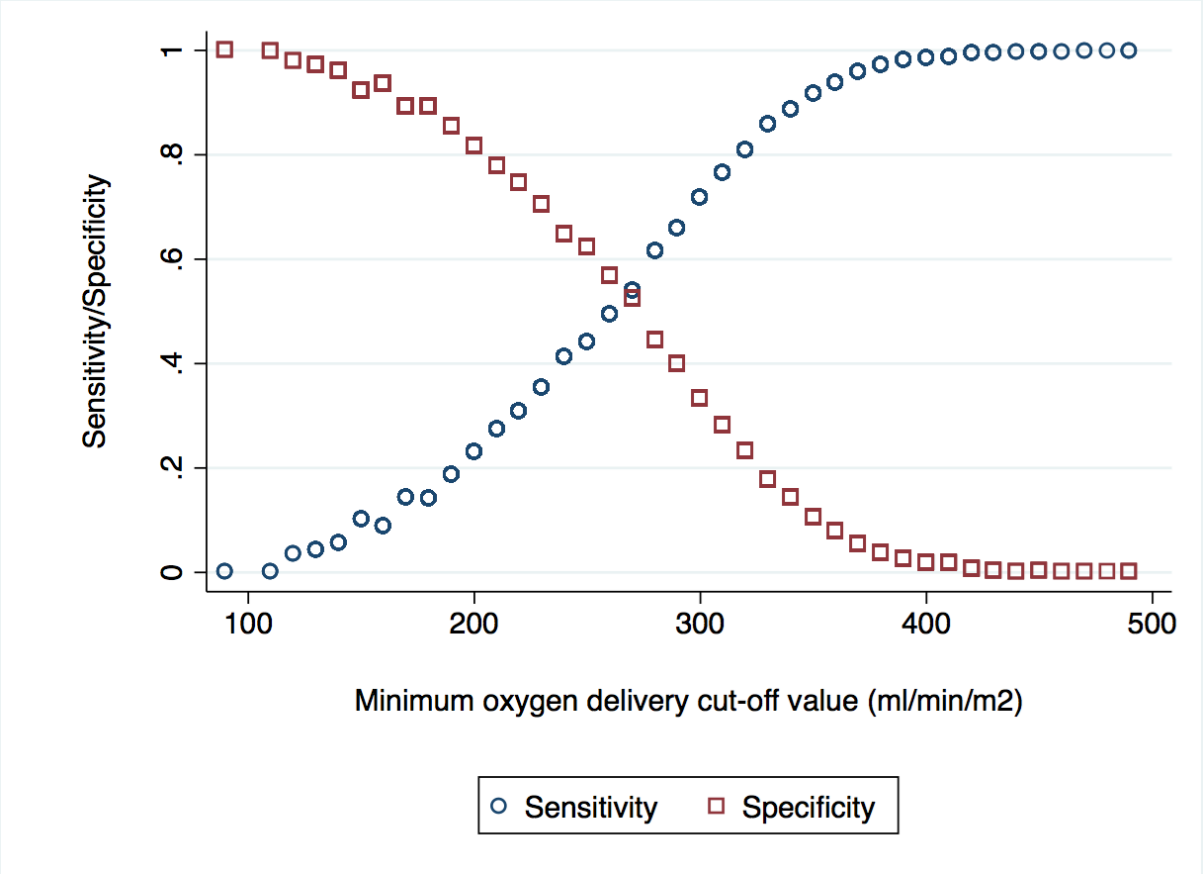

Figure 2. Sensitivity and specificity values according to cut points of minimum CPB DO_2i, based on the predicted values from the model of AKI and minimum DO_2i. The plot shows that there is an optimal balance of probability of false negative vs probability of false positive diagnosis of AKI at a DO_2i value of 270ml/min/m^2. Below 270ml/min/m^2 threshold the ability to correctly identify patients with AKI increases. Above 270ml/min/m^2 the ability to correctly identify patients without AKI increases.

When the same predictors for the model based on the training data were applied to the validation dataset, minimum DO_2i was similarly associated with the odds of RIFLE Risk or greater AKI (OR=0.993, 95% CI=0.991-0.995; p<0.001). The diagnostic accuracy was also similar to the training model; AUROC 0.68 (CI: 0.66-0.69); p=0.07. In sensitivity analysis, with DO_2i included as a binary variable with a cut-point of 270 ml/min/m^2, the odds of RIFLE Risk

or greater AKI were increased by 52% (OR=1.52, 95% CI=1.29-1.77, p<0.001) in those below the threshold. The corresponding incidence of AKI was 14.8% in patients below 270 ml/min/m^2, and 9.8% in patients above 270 ml/min/m^2 (p<0.001). The AUROC curve was 0.69 (95% CI=0.68-0.71) which was comparable to the training model in which minimum DO_2i was included as a continuous variable.

Decreasing minimum DO_2i was also significantly associated with the odds of RIFLE Injury or greater AKI in both the training dataset (OR 0.994, CI (0.992-0.997), p<0.001) and the validation dataset (OR 0.993, CI (0.99-0.996), p<0.001). With DO_2i included as a binary variable below 270 ml/min/m^2, the odds of RIFLE Injury or greater AKI were increased by 43% (OR=1.43, 95% CI=1.09-1.86, p=0.008) in those below the threshold. The corresponding incidence of AKI was 4.8 % in patients below 270 ml/min/m^2, and 3.2 % in patients above 270 ml/min/m2 (p<0.001). The area under the ROC curves was similar between dataset models: training; AUROC=0.72 (95% CI=0.69-0.75) versus validation AUROC=0.72 (0.7-0.75); p=0.707.

DISCUSSION

The findings of this study using a rigorously defined large multicentre clinical registry dataset demonstrated that oxygen delivery during CPB is an independent risk factor for AKI. Our results confirm the findings of the GIFT trial and can be extrapolated to a broader risk patient population, providing high-level evidence that a perfusion strategy to avoid a minimum DO_2i below 270 ml/min/m^2 is associated with a reduced rate of AKI. The odds of RIFLE Risk or greater AKI increase by 52% when minimum DO_2i is below this threshold.

The clinical implication for the minimum DO_2i during CPB having an odds ratio of 0.993 in the model translates on average to 7% decrease in the likelihood of AKI for every decrease in DO_2i of 10 ml/min/m^2. The sensitivity analysis with patients above or below the threshold of 270 ml/min/m^2 provided quantification of the validity of a goal directed perfusion approach, supporting previous findings (8-12). The odds of RIFLE Risk or greater AKI were increased by 52% below the threshold (14.8% in patients below compared with 9.8% in patients above) with similar diagnostic accuracy to the model using DO_2i as a continuous value. These results

show a similar increase in AKI to the GIFT trial, in which a 60% higher rate was seen (24.7%; 15.4% respectively) (12).

Blood flow rates during CPB to achieve adequate whole-body perfusion have typically used flow indexed on body surface area of 1.6 – 2.4 l/min/m^2 (15). Attention has turned to a patient specific approach to flow indexed on oxygen delivery as an attempt to reduce the incidence of post-operative AKI. The first reported study identifying a threshold for DO_2i involved 1048 patients undergoing coronary revascularization with CPB, identifying a critical oxygen delivery threshold of 272 ml/min/m^2 for acute renal failure requiring renal replacement therapy and peak postoperative serum creatinine levels (8). De Somer et al (9) subsequently demonstrated a nadir DO_2i level < 262 ml/min/m^2 was independently associated with AKI. The randomised controlled GIFT study demonstrated increased AKI with a nadir DO_2i during CPB below 280 ml/min/m^2 in 326 patients (12).

We identified the threshold of oxygen delivery associated with AKI to be 270 ml/min/m^2. Figure 2 demonstrates for DO_2i values below 270, sensitivity decreases, and specificity increases. Below the threshold the ability to identify patients with AKI increases, and to identify patients without AKI decreases. The overall diagnostic accuracy of the model as defined by the AUROC was 0.7, meaning that a higher probability of AKI was predicted in 70% of patients that actually had AKI. Since the threshold value was based on the predicted risk of AKI after adjustment for other variables found to be associated with AKI, it should be interpreted as the cut point associated with the average value of the covariates. In reality, each patient is individual, and therefore although this study supports goal directed perfusion, further improvement may be achieved with the development of patient specific prediction of optimal DO_2i thresholds.

Patients with AKI had significantly lower CPB haemoglobin as may be expected given the contribution of haemoglobin to oxygen delivery. Higher rates of intraoperative RBC transfusion were observed in patients with AKI, consistent with lower haemoglobin values. We chose not to include RBC transfusion in the multivariate AKI model since doing so would have removed the indirect effect of low DO_2i on AKI via RBC transfusion in response to low haemoglobin. The potential confounding effect of RBC transfusion on AKI highlights the difficulties associated with independent effects of DO_2i and transfusion on AKI. In addition to minimum DO_2i, other independent predictors of AKI that we identified are consistent with

currently defined AKI risk factors (16) and in particular highlight the role of modifiable CPB factors related to AKI including duration of CPB, and the avoidance of hyperthermia during rewarming (7).

Patients in both the training and validation cohorts with AKI had significantly increased mortality, ventilation time, dialysis, intra-aortic balloon pump usage and length of stay, demonstrating that a modest increase in creatinine as defined by the RIFLE Risk level has a large impact upon patient outcomes and associated costs, demonstrating the importance of identifying modifiable factors that may reduce the burden of cardiac surgery associated AKI. DO_2i is modifiable during bypass by increasing blood flow rate or its oxygen carrying capacity. This provides further support for the continuation of practices to minimise hemodilution (17).

A limitation of this study and other observational studies is the lack of a consistency in the calculation of minimum DO_2i (17). We used electronic perfusion data available in the ANZCPR to calculate minimum DO_2i according to average pump flow index, minimum haemoglobin value (based on intermittent sampling), estimated arterial oxygen saturation and minimum recorded pO_2 during CPB. Other studies have included the mean oxygen delivery value during 30 minutes of CPB at the time when the lowest hematocrit was reached (8) or the lowest DO_2i value recorded for at least two consecutive 10 minute intervals during CPB (9). In each of these calculations the extent of exposure to the minimum DO_2i throughout CPB is not defined. This will be overcome when real time electronic acquisition of DO_2i during CPB becomes commonplace. The use of arterial pump flow values to calculate DO_2i, may not have taken into account the effect of arterial-venous shunts in the CPB circuit (such as sampling and purge lines) which would tend to over-estimate DO_2i. We used the maximum postoperative creatinine value to calculate AKI. This may lead to over estimation of the incidence of AKI however our rates of AKI are relatively low. In addition, although the description of our patients was detailed and allowed us to extensively control for confounding, we cannot exclude the possibility of residual confounding due to unobserved potential confounders. Despite these limitations, the strengths of our study include the use of a large and well described multicentre CPB registry of prospectively collected data. Furthermore, randomly splitting the dataset into two cohorts provided the opportunity to cross validate the performance of the model obtained from the first cohort when applied to the second cohort. Since the patient sample was large, selection of patients was randomly performed, patient

characteristics between cohorts were similar and the results of the model were validated, providing evidence that the model is robust.

CONCLUSION

Our results confirm previous findings that oxygen delivery during CPB is independently associated with AKI and that a minimum threshold for DO_2i during CPB of 270 ml/min/m^2 can be reasonably considered.

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4.3 The role of cardiopulmonary bypass parameters in risk prediction for 30-day mortality following cardiac surgery.

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ABSTRACT

Currently 30-day mortality is commonly used as a quality indicator for cardiac surgery; however, prediction models have not included the role of cardiopulmonary bypass (CPB). We hypothesized that reproducing currently utilised prediction model methods of 30-day mortality using the Australian and New Zealand Collaborative Perfusion Registry (ANZCPR) would identify relevant CPB predictors.

Nine centers in Australia and New Zealand collected data using the ANZCPR between 2011 - 2020. CPB parameter selection was determined by evaluating association with 30-day mortality. Data were divided into model creation (n = 15,073) and validation sets (n = 15,072). Bootstrap sampling and automated variable selection methods were used to develop candidate models. The final model was selected using prediction mean square error and Bayesian Information Criteria. and the average receiver operating characteristic (ROC), p-value for Hosmer—Lemeshow chi-squared test and MSE were obtained.

In total, 30,145 patients were included, of which 735 (2.4%) died within 30 days of surgery. The area under the ROC for the model including CPB parameters was significantly greater than preoperative risk factors only (0.829 vs 0.783, $p<0.001$). CPB parameters included in the predictive model were CPB time, red blood cell transfusion, mean arterial pressure <50mmHg, minimum oxygen delivery, cardiac index <1.6 l/min/m^2.

CPB parameters improve the prediction of 30-day mortality. Randomised trials designed to evaluate modifiable CPB parameters will determine their impact on mortality.

INTRODUCTION

Given the concern of perioperative mortality and morbidity and the demands on hospital resources, accurate assessment of preoperative risk is essential for patients and clinicians prior to cardiac surgery to provide informed consent and support medical management. Methods to assess preoperative risk have been developed for the Australian population. Billah et al reported a statistical model which includes 18 preoperative risk factors to calculate predicted risk for 30-day mortality following cardiac surgical procedures utilising data from the Australian and New Zealand Society of Cardiothoracic Surgeons (ANZSCTS) registry (1). 30-day mortality is commonly used as a standard performance metric for cardiac surgery, however as predictive models are designed to inform the patient and surgeon prior to surgery they have not included cardiopulmonary bypass (CPB) parameters.

We hypothesized that by reproducing the approach taken by Billah et al (1) to identify predictors of 30-day mortality we could potentially expand the model by identifying relevant CPB predictors. The Australian and New Zealand Collaborative Perfusion Registry (ANZCPR) data definitions for preoperative risk factors are consistent with the ANZSCTS registry allowing the model to be reproduced., The ANZCPR is unique in its integration of electronic perfusion data (EPD) collected intraoperatively from the heart lung machine (HLM) and patient physiological monitoring systems, together with patient preoperative risk factors and outcome data (2). As reporting of modifiable CPB predictors of mortality is limited, the identification of modifiable predictors that can be used as quality indicators will facilitate development of CPB improvement initiatives. Furthermore, the inclusion of intraoperative variables in a cardiac surgery risk prediction model may provide a unique additional source of information to help inform postoperative management. The aim of this study was to identify CPB parameters that impact upon the prediction of 30-day mortality following cardiac surgery.

METHODS

Nine cardiac surgical centers in Australia and New Zealand prospectively collected data using the ANZCPR as previously described (3). Intraoperative CPB and physiological data were

collected every 20-60 seconds during CPB. Periods of partial CPB were excluded from cardiac index calculations as part of the routine data collection process at each center. Institutional Ethics Review Board approval was obtained at each participating center, and this study was approved by the Southern Adelaide Clinical Human Research Ethics Committee (386.15), the ANZCPR Steering Committee and registered on the Southern Adelaide Local Health Network Quality Register Library (2327). Centers collected data on 34,687 adult patients undergoing cardiac surgery using CPB between January 2011 and December 2020. Data collected prior to 2011 was excluded to provide all ANZCTS variables required for the analysis. Patients were excluded if they were missing 30-day mortality data (1018), underwent circulatory arrest (932), had a minimum nasopharyngeal temperature <25^{o}C (729), or were missing intraoperative electronic perfusion (either blood flow, blood pressure or blood gas) data (1863). In total, 8.3% of the patients were excluded from the analysis because of missing observations. Imputation using mean replacement of 20 chained iterations was performed for residual missing values (<1% of dataset). A total of 30,145 patients were included in the study. The ANZCPR is listed in the Australian Commission on Safety and Quality in Health Care register of clinical registries (https://www.safetyandquality.gov.au/publications-and-resources/australian-register-clinical-registries). Clinical data definitions were based on the ANZSCTS registry (4). Complete ANZCPR variable definitions are available (http://www.anzcpr.org).

Statistical software package Stata (version 15) was used for the analyses. The a-priori selection of risk factors was made by including variables reported by Billah et al (1). CPB parameter selection was determined by evaluating each variables association with 30-day mortality. Variables were selected with a significant association ($p<0.05$) including; intraoperative red blood cell transfusion (pre, during or post CPB), minimum and maximum blood glucose, minimum nasopharyngeal temperature, minimum oxygen delivery, and minimum arterial pCO_2, and minute duration variables including oxygenator arterial outlet temperature >36.5^{o}C, CPB, aortic cross clamp, arterial flow <1.6 l/min/m^2, arterial flow < 1.8 l/min/m^2, venous oxygen saturation < 60%, mean arterial pressure <50mmHg and mean arterial pressure <40mmHg. The linearity of the relationship between continuous CPB variables and 30-day mortality was assessed using LOWESS plots. CPB duration and minimum oxygen delivery were converted to quintiles due to non-linearity.

Subsequent model development was performed according to the method described by Billah et al (1). Bootstrap methods along with automated variable selection procedures were used to develop a parsimonious model using multiple logistic regression (5). The data were randomly divided into two sets: model creation set (n = 15,073 50% of the total patients) and model validation set (n = 15,072). In all, 1000 bootstrap samples (each of size of 15,073) were selected from the model creation set and a multiple logistic regression model was developed for each of the 1000 samples. The number of times each variable was identified as significant in 1000 bootstraps was recorded and then ranked. In each bootstrap, a p-value of 0.05 or less was regarded as significant in the variable selection. Then we developed seven multiple logistic regression models with the variables selected in at least 100%, 90%, 80%, 70%, 60%, 50% and all variables of bootstrap samples. In the creation set, the Bayesian Information Criteria (BIC) (6) and the prediction mean square error (MSE) were calculated for each of these models and the final model was selected based on the value obtained for the BIC and MSE. The prediction performance of the selected model was assessed by calculating average ROC, Hosmer—Lemeshow p-value and MSE from a multifold (100) validation on the validation set. Multicollinearity was assessed by the variance inflation factor.

A base comparative model was created using the variables reported by Billah et al (1). To assess the diagnostic accuracy of each model, we calculated the area under the receiver-operating characteristic curve (AUROC) in the validation dataset. Similarity of diagnostic accuracy for 30-day mortality of the models was determined by using the chi-square test to compare the 2 AUROC curves. The extent of over and underestimation associated with the model was graphically described using calibration plots.

Results

In total, 30,145 patients were included in the study (15,073; creation dataset, 15,072; validation). Patient preoperative and intraoperative characteristics were similar between training and validation cohorts (table 1). Isolated CABG accounted for 50% of procedures, isolated valve repair or replacement 20%, valve repair or replacement + CABG 11%, and other procedures 19%. Most of the procedures were elective (70%) in patients <70 years of age (60%) with normal left ventricular function (82%). Predominant risk factors included

hypercholesterolemia (60%) and body mass index >25 kg/m^2 (70%). Overall, 735 (2.4%) patients died within 30 days of surgery with similar rates of 30-day mortality between training and validation datasets (2.3% vs 2.6% respectively). Rates of other major adverse outcomes were also similar (table 2).

Table 1

Preoperative and intraoperative risk factors for 30-day mortality in the creation and validation datasets.

Preoperative	Creation dataset n=15073	Validation dataset n=15072	*p*
Age group			
<70	9038 (60%)	8994 (60%)	0.27
70-79	4509 (30%)	4467 (30%)	
80+	1526 (10%)	1611 (11%)	
Female	3953 (26%)	4057 (27%)	0.17
Hypercholesterolaemia	9066 (60%)	9259 (61%)	0.022
Preoperative dialysis	248 (2%)	292 (2%)	0.056
Respiratory disease	1907 (13%)	1869 (12%)	0.51
Critical preoperative state	585 (4%)	580 (4%)	0.88
Peripheral vascular disease	1030 (7%)	969 (6%)	0.16
Cerebrovascular disease	1183 (8%)	1192 (8%)	0.85
Previous cardiac surgery	1269 (8%)	1244 (8%)	0.6
Cardiogenic shock	190 (1%)	189 (1%)	0.96
Ejection fraction estimate			
>60%	12434 (82%)	12415 (82%)	0.8
46-60%	42 (<1%)	34 (<1%)	
30-45%	1891 (13%)	1904 (13%)	
<30%	706 (5%)	719 (5%)	
Urgency of procedure			
Elective	10574 (70%)	10703 (71%)	0.44
Urgent	4005 (27%)	3891 (26%)	
Emergency	484 (3%)	469 (3%)	
Salvage	10 (<1%)	9 (<1%)	
NYHA class			
1	10970 (73%)	10970 (73%)	0.16
2	153 (1%)	144 (1%)	
3	3066 (20%)	3153 (21%)	
4	884 (6%)	805 (5%)	
Procedure type			
CABG	7484 (50%)	7449 (49%)	0.62
Valve repair/replacement	3059 (20%)	3150 (21%)	
Valve + CABG	1623 (11%)	1602 (11%)	
Other	2907 (19%)	2871 (19%)	
Body mass index >25 kg/m^2	10605 (70%)	10764 (71%)	0.043

Intraoperative			
CPB time, minutes	91 (70, 119)	91 (70, 119)	0.66
Aortic cross clamp time, minutes	64 (47, 88)	64 (46, 89)	0.83
Red blood cell transfusion			
0	13086 (87%)	13113 (87%)	0.54
1	612 (4%)	644 (4%)	
2	778 (5%)	743 (5%)	
3 or greater	597 (4%)	572 (4%)	
CPB minimum oxygen delivery, ml/min/m^2	282 (244, 321)	281 (244, 321)	0.52
CPB cardiac index <1.8 l/min/m^2, minutes	4.5 (2.3, 9.7)	4.5 (2.3, 9.7)	0.54
CPB cardiac index <1.6 l/min/m^2, minutes	3.0 (1.7, 6.0)	3.0 (1.7, 6.0)	0.7
CPB cardiac index average, l/min/m2	4.5 (2.3, 9.7)	4.5 (2.3, 9.7)	0.54
CPB mean arterial pressure <50 mmHg, minutes	7.7 (3.5, 15.0)	8.0 (3.5, 15.0)	0.74
CPB mean arterial pressure <40mmHg, minutes	1.5 (0.5, 3.5)	1.5 (0.5, 3.5)	0.27
CPB mean arterial pressure average, mmHg	63 (59, 68)	63 (59, 68)	0.43
CPB minimum blood glucose, mmol/l	6 (6, 8)	6 (6, 7)	0.33
CPB maximum blood glucose, mmol/l	8 (7, 10)	8 (7, 10)	0.44
CPB minimum hemoglobin, g/dl	91 (78, 103)	91 (79, 103)	0.4
CPB minimum nasopharyngeal temperature, ^oC	34 (32, 34)	34 (32, 34)	0.35
CPB arterial blood temperature >36.5^oC, minutes	1 (0, 14)	1 (0, 14)	0.088
CPB minimum arterial pCO_2, mmHg	37 (35, 39)	37 (35, 39)	0.058
CPB maximum arterial pCO_2, mmHg	41 (39, 44)	41 (39, 44)	0.29
CPB venous saturation <60%, minutes	0 (0, 1)	0 (0, 1)	0.98

Data presented as n (%) or median (IQR). NYHA: New York Heart Association; CPB: cardiopulmonary bypass.

Table 2

Postoperative outcomes in the creation and validation datasets.

	Creation dataset n=15073	Validation dataset n=15072	*p*
30-day mortality	349 (2.3%)	386 (2.6%)	0.17
Stroke	240 (2%)	213 (1%)	0.2
Acute kidney injury (RIFLE class risk or greater)	2030 (14%)	2121 (14%)	0.12
Mechanical ventilation > 48 hrs	1112 (8%)	1200 (8%)	0.052
Return to operating theatre	1045 (7%)	1128 (7%)	0.064
Intra-aortic balloon pump	163 (1%)	159 (1%)	0.82
Dialysis	444 (3%)	459 (3%)	0.61
Postoperative stay (days)	7 (6, 10)	7 (6, 10)	0.41

Data presented as n (%) or median (IQR). RIFLE: risk, injury, failure, loss or end stage.

A total of 15 preoperative and 14 intraoperative variables were included as covariates for the 30-day mortality logistic regression model. In 1000 bootstraps of the regression model, the number of times each variable appeared as significant was recorded (Table 3).

Table 3. Number of times each candidate variable was selected in 1000 bootstrap samples drawn from model creation dataset.

Risk factor	Frequency	%
Age group	1000	100
Red blood cell transfusion	1000	100
CPB time (quintiles)	1000	100
Ejection fraction estimate	997	99.7
Preoperative dialysis	982	98.2
Urgency of procedure	978	97.8
CPB mean arterial pressure <50 mmHg (minutes)	828	82.8
CPB minimum oxygen delivery (quintiles)	746	74.6
CPB cardiac index <1.6 l/min/m^2 (minutes)	641	64.1
Respiratory disease	614	61.4
Cardiogenic shock	578	57.8
NYHA class	554	55.4
Critical preoperative state	521	52.1
Peripheral vascular disease	441	44.1
Previous cardiac surgery	358	35.8
CPB mean arterial pressure <40mmHg (minutes)	329	32.9
Procedure type	325	32.5
Aortic cross clamp time	320	32
Cerebrovascular disease	256	25.6
CPB arterial blood temperature >36.5^oC (minutes)	224	22.4
CPB minimum arterial pCO_2	182	18.2
Female	176	17.6
CPB cardiac index <1.8 l/min/m^2 (minutes)	169	16.9
CPB minimum nasopharyngeal temperature	137	13.7
Hypercholesterolaemia	106	10.6
Body mass index >25 kg/m^2	97	9.7
CPB minimum blood glucose	94	9.4
CPB maximum blood glucose	93	9.3
CPB venous saturation <60% (minutes)	51	5.1

CPB; cardiopulmonary bypass, NYHA; New York Heart Association

Variables that were identified as significant in all bootstrap samples included age (group), red blood cell transfusion and CPB time (quintiles). Variables selected in at least 90% of the samples included ejection fraction estimate, preoperative dialysis and urgency of procedure. CPB mean arterial pressure <50 mmHg (minutes) was identified in 83%, CPB minimum oxygen delivery (quintiles) in 75%. CPB cardiac index <1.6 l/min/m^2 (minutes) and respiratory disease were selected in at least 60%. Cardiogenic shock, NYHA class and critical preoperative state were selected in at least 50%. Other variables were selected as independent predictors in less than 50%. Using the results in Table 3, we developed six plausible risk prediction models. The average ROC, Hosmer—Lemeshow p-value and prediction MSE for each candidate model are reported in Table 4. The model with variables selected in at least 60% of the samples was selected as our final model based on firstly the minimum MSE and then the lowest BIC. The average 100-fold cross validation ROC (0.8214, 95% CI: 0.8001—0.8425) and Hosmer-Lemeshow p-value (0.2882) show good discrimination and calibration.

Table 4

Average ROC, Hosmer-Lemeshow *p*-value and predictions MSE from 100-fold validation.

	Model building		Model validation (100-fold)		
% of time variables in the bootstrap models	BIC	MSE	ROC	H-L *p*-value	MSE
100% (Variables shown in Table 3 with frequency of 100%)	2931	0.0212	0.7654	<0.001	0.0234
At least 90% (Variables shown in Table 3 with frequency of >90%)	2849	0.0207	0.8061	0.0002	0.0231
At least 80% (Variables shown in Table 3 with frequency of >80%)	2842	0.0206	0.8112	0.2736	0.023
At least 70% (Variables shown in Table 3 with frequency of >70%)	2851	0.0205	0.8189	0.2113	0.0229
At least 60% (Variables shown in Table 3 with frequency of >60%)	2858	0.0203	0.8214	0.2882	0.0229
At least 50% (Variables shown in Table 3 with frequency of >50%)	2892	0.0203	0.8258	0.5111	0.023
All variables (All variables shown in Table 3)	3004	0.0207	0.8311	0.5439	0.023

BIC: Bayesian information criteria, MSE; mean square error, H-L; Hosmer—Lemeshow.

The validation comparison including CPB parameters had a ROC 0.8306, which was significantly improved in comparison to the base model of preoperative risk factors only (ROC 0.7833), p<0.001 (see Figure 1 for ROC curves). A calibration plot of the validation model (Figure 2) shows strong calibration (intercept 1.000, slope 1.000, calibration in the large; 0.000, AUC 0.831).

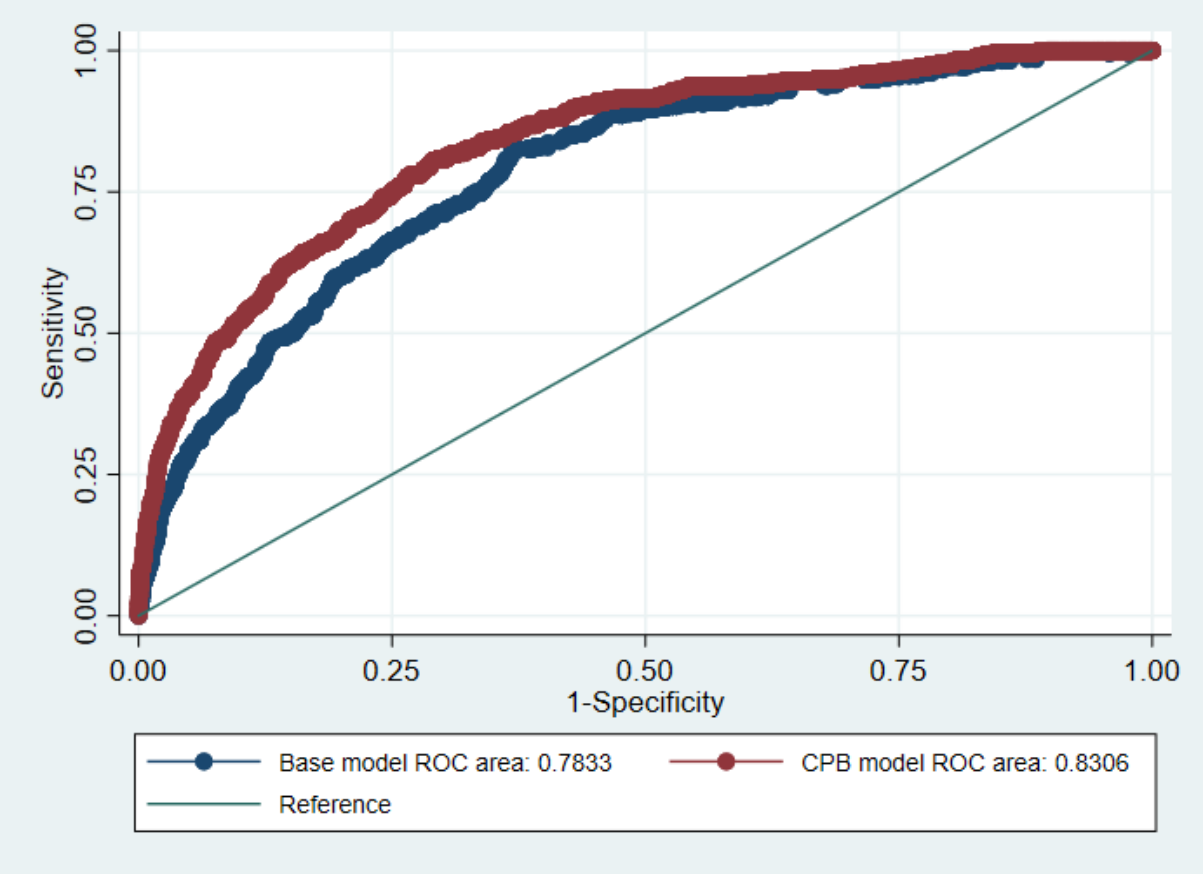

Fig 1. Receiver operating curves (ROC) for the risk prediction model including CPB parameters and the base model in the validation dataset (n = 15,072). The area under the ROC for the CPB parameter model was significantly greater than the base model (p<0.001).

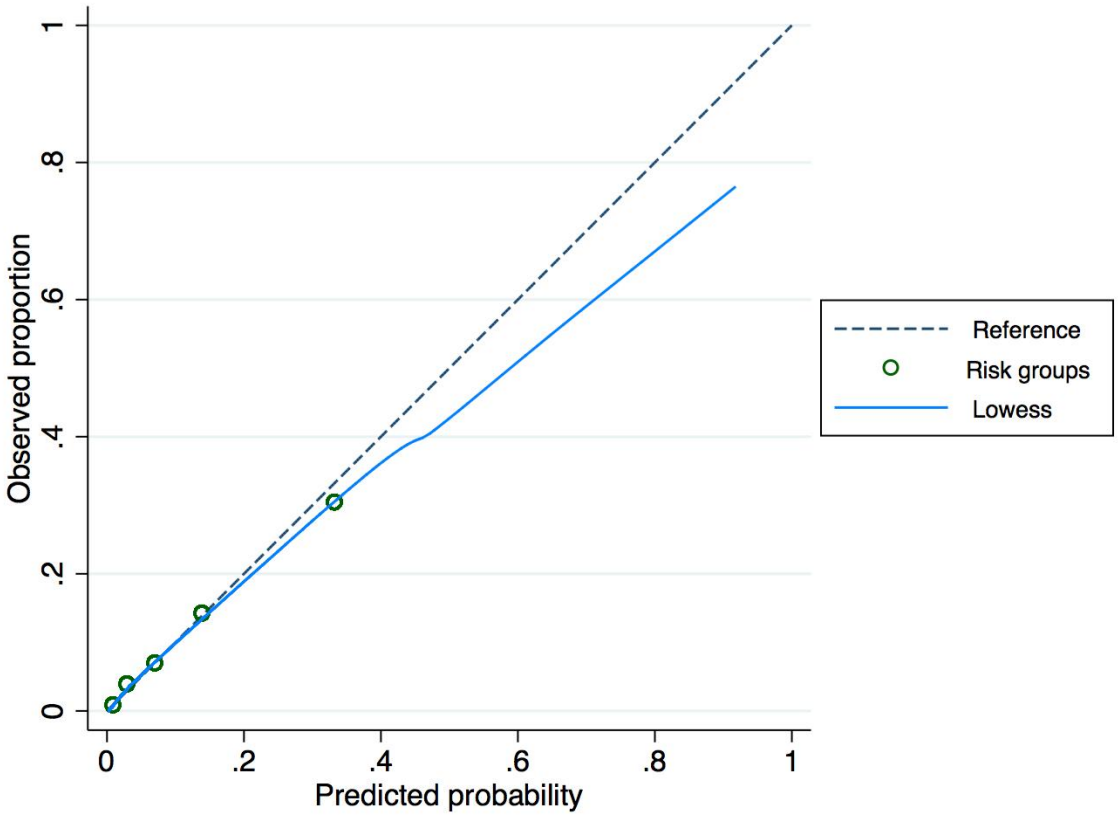

Figure 2. Calibration plot for the risk prediction model with the validation cohort with risk groups defined as <2%, 2-5%, 5-10%, 10-20% and >20%, demonstrating that the model is adequately fit (intercept 1.000, slope 1.000, calibration in the large; 0.000, AUC 0.831).

The beta coefficients and odds ratio for the variables included in the final model are reported in Table 5. Increasing age, respiratory disease, preoperative dialysis, ejection fraction estimate, urgency of procedure, were identified as independent patient risk factors. Modifiable CPB parameters included red blood cell transfusion, minimum oxygen delivery, duration of arterial pressure <50 mmHg, cardiac index <1.6 l/min/m^2, and CPB time.

Table 5. Preoperative risk and intraoperative management factors for predictive model for 30-day mortality for patients undergoing cardiac surgery.

Risk Factors	Coefficient	OR (95% CI)	p
Age (<60, reference group)			
60-69	0.4	1.5 (1.09 - 2.05)	0.012
70-79	0.56	1.75 (1.29 - 2.37)	<0.001
80+	1.07	2.91 (2.05 - 4.12)	<0.001
Respiratory disease	0.16	1.18 (0.88 - 1.57)	0.272
Preoperative dialysis	0.72	2.06 1.32 - 3.21)	0.001
Ejection fraction estimate (>60, reference group)			
46-60	0.78	2.18 (0.65 - 7.32)	0.209
30-45	0.21	1.23 (0.91 - 1.65)	0.176
<30	1.06	2.9 (2.08 - 4.03)	<0.001
Urgency of procedure (elective, reference group)			
Urgent	0.29	1.34 (1.05 - 1.7)	0.019
Emergency	1.01	2.74 (1.89 - 3.97)	<0.001
Salvage	3.06	21.4 (3.72 - 123.17)	0.001
CPB time (<65 , reference group) (minutes)			
66-83	-0.04	0.96 (0.61 - 1.52)	0.873
84-101	0.05	1.05 (0.67 - 1.65)	0.821
102-128	0.51	1.67 (1.11 - 2.51)	0.014
>128	1.11	3.03 (2.08 - 4.42)	<0.001
Red blood cell transfusions (0, reference category)			
1	0.6	1.82 (1.2 - 2.77)	0.005
2	0.9	2.47 (1.73 - 3.52)	<0.001
3+	1.66	5.26 (3.83 - 7.23)	<0.001
CPB mean arterial pressure <50 mmHg (minutes)	0.01	1.01 (1 - 1.01)	0.001
CPB minimum oxygen delivery (<235, reference group) (ml/min/m^2)			
236-267	-0.11	0.89 (0.67 - 1.19)	0.444
268-296	-0.14	0.87 (0.62 - 1.21)	0.411
297-331	-0.52	0.59 (0.4 - 0.89)	0.012
>331	-0.89	0.41 (0.26 - 0.67)	<0.001
CPB cardiac index <1.6 l/min/m^2 (minutes)	0.01	1.01 (1 - 1.02)	0.006
Constant	-5.15	0.01 (0 - 0.01)	<0.001

CPB; cardiopulmonary bypass

Discussion

In this study, we have shown an association between intraoperative CPB management and patient outcome (30-day mortality). This is the first predictive model to be reported which incorporates CPB parameters using 30-day mortality as the primary outcome. By reproducing the approach taken by Billah et al (1) to identify predictors of 30-day mortality we demonstrated generalisability of their model whilst also identifying relevant CPB predictors. This demonstrates the importance of CPB parameters in the prediction of 30-day mortality, significantly improving the ROC from 0.7833 to 0.8306 in comparison to the base model reported by Billah et al (1), from which 4 out of the 12 preoperative variables were retained. Furthermore, the estimates of risk compared with observed values were highly consistent as risk increases. Modifiable CPB parameters included CPB time, red blood cell transfusion, minimum oxygen delivery, duration of arterial pressure <50 mmHg, and cardiac index <1.6 l/min/m^2. Application of these parameters as CPB quality indicators will facilitate development of improvement initiatives. Previously we have reported the use of CPB quality indicators to improve process outcomes through feedback to clinicians at an institution level (7), and through multicentre registry reporting using benchmarking (8). Furthermore, the inclusion of intraoperative variables in a cardiac surgery 30-day mortality risk prediction model provides additional information to guide postoperative management, which can be calculated for an individual patient as;

$$predicted\ risk\ (\%) = 100\ \times \frac{e^{(\sum \beta)}}{1 + \ e^{(\sum \beta)}}$$

$$Where\ e = exponential;$$

$$\sum \beta = sum\ of\ the\ relevant\ model\ beta\ coefficents\ for\ the\ patient$$

If we consider the following hypothetical patient, a 75-year-old male with ejection fraction estimate of 40% and hypercholesterolaemia undergoing urgent CABG surgery, with a CPB time of 103 minutes, minimum oxygen delivery of 278 ml/min/m^2, 8 minutes of mean arterial pressure <50 mmHg and 5 minutes with cardiac index < 1.6 l/min/m^2 would have a predicted risk of 2.8% using our CPB parameter model, and 2.7% using the model reported by Billah et

al (1). However, if the CPB time was >128 min, predicted risk would increase to 5%. If 2 units of red blood cells were given intraoperatively predicted risk would increase to 6.6%. Predicted risk if both occurred would be 11.5%, highlighting the impact of these intraoperative predictors in comparison to the model of preoperative factors only in which predicted risk remains at 2.8%. This may be of value to specialists caring for these patients after surgery, providing an additional understanding of the intraoperative course upon recovery, and providing the opportunity for future studies to evaluate optimisation of postoperative management.

The association of red blood cell transfusion and CPB oxygen delivery with poor outcomes has been well recognised. Transfusion of as little as 1 or 2 units of red blood cells has been associated with increases in mortality and morbidity in patients undergoing CABG (9). Our study found an increase of 1.82 times likelihood of 30-day mortality with transfusion of 1 unit of red blood cells intraoperatively, 2.5 times increase with 2 units and 5.2 times with 3 or more units. However, it remains unclear the degree to which transfusion is the causal factor related to outcome given its association with surgical complexity and complications (10). This study confirms the rationale for blood conservation strategies consistent with the 2017 EACTS/EACTA Guidelines on patient blood management for adult cardiac surgery (10), and the importance of reducing hemodilution to reduce both the requirement for red blood cell transfusion and to maintain oxygen delivery. The minimum oxygen delivery during CPB has been identified as an independent predictor of acute kidney injury (AKI) (11, 12), with a goal directed approach to maintain CPB oxygen delivery >270 ml/min/m^2 shown to be beneficial in reducing the incidence of stage I AKI (13). Our model found that the 2 highest quintiles of oxygen delivery (> 297 ml/min/m^2) were significantly associated with lower incidence of 30-day mortality, compared with the lowest quintile (<235 ml/min/m^2).

The duration of cardiac index <1.6 l/min/m^2 independent of oxygen delivery was shown to be an important modifiable factor in our model, which we believe to be a novel finding. The identification of duration of mean arterial pressure <50 mmHg as an independent factor has been reported by Haase et al, who found that mean arterial pressure <50 mmHg recorded using electronic intraoperative data was an independent predictor of AKI in patients undergoing CPB, but only in conjunction with severe anemia (lowest haemoglobin concentration >75th percentile) (14). Studies evaluating the influence of CPB pressure

management have largely reported manually recorded and potentially incomplete and biased MAP values or lacked additional covariates (15-18). Thus, they may have had limited accuracy, precision and statistical power for their interpretation within a complex pathophysiological context, making the role of these intraoperative factors or their combination as modifiable predictors of post-operative AKI uncertain (14). Our study found a 10% increase in likelihood of 30-day mortality for every 10 minutes duration of cardiac index <1.6 l/min/m^2, and the same increase for every 10 minutes duration of mean arterial pressure <50 mmHg.

The relationship between the duration of CPB and postoperative morbidity and mortality in patients undergoing cardiac surgery has been demonstrated (19). Despite the continuous improvement and development of new CPB techniques, the blood's exposure to roller pumps, the air-blood interface, and its contact with artificial circuit components activates the coagulation and fibrinolytic system (20), platelets (21), complement system (22), and leukocytes with consequent degranulation and release of cytotoxic enzymes and inflammatory mediators (23). These sequalae increase the risk of postoperative multiorgan failure, infectious and bleeding complications (19). Factors such as operative planning and surgical team communication may modify risk of these outcomes if CPB time can be reduced. Since CPB duration is often related to the complexity of operation which itself may be related to postoperative outcome, we included both the procedure type and redo procedures in the variable selection process.

Not all preoperative variables in the model reported by Billah et al (1) were retained in our model. This reflects a change in the relative predictive value of these variables once the intraoperative variables were included in the bootstrap selection process.

In general, there is a paucity of knowledge regarding the relationships between CPB practice and outcome due to a lack of randomised studies. More specifically, the identification of modifiable CPB parameters associated with mortality are limited due to the large sample size required to reach adequate statistical power, and this study highlights the benefit of multicentre perfusion registries. The ANZCPR is unique in its integration of electronic perfusion data which have been collected in sites throughout Australia and New Zealand over a considerable period, and this study provided the opportunity to define and report which of these parameters play an important role in patient outcome.

Statistical modelling methodology can be described as either descriptive, explanatory or predictive. P Predictive modelling can suggest improvements to existing explanatory models whilst also have an explanatory ability (24). The predictive modelling approach taken in this study enabled us to evaluate the relative importance of the CPB variables collected in our registry from an explanatory perspective through the bootstrap selection and ranking process, and by comparing the predictive ability of the model with or without the inclusion of the CPB variables.

An important perspective gained from undertaking this analysis concerning modelling of CPB related data was the inclusion of CPB time as quintiles in order to separate the impact of long bypass times. If CPB time was included in the model as a continuous variable, the effect of longer bypass times would be averaged across all patients, thereby overestimating the effect in patients undergoing shorter CPB times. Given that CPB time was selected in 100% of the bootstrap models, this has a considerable influence on determining the influence of other variables in the final model. This may account for the inconsistency in findings reported by Turner et al who were unable to identify cardiac index <1.6 l/min/m^2 or mean arterial pressure <50 mmHg as predictors of AKI (25); as CPB duration was treated as a continuous variable the effect of long CPB time may have overestimated the effect of CPB duration in patients with shorter bypass times, thereby influencing the independent effect of the pressure and flow variables.

Limitations of this study include its use of observational data and although the description of our patients was detailed and allowed us to extensively control for confounding, we cannot infer causality, nor exclude the possibility of residual confounding from factors not collected or included in the model. The metrics of model discrimination and calibration were consistent with those reported by Billah et al (1), albeit our base model of preoperative risk factors had a slightly lower ROC of 0.7833, compared with 0.8131 reported by Billah et al in single validation. Differences may be partially attributed to data collection over different time periods and a difference in the number of contributing sites in each registry. ANZCPR does not collect data on preoperative inotropic, nitrate use or anticoagulant medication, rather collects critical preoperative state (ventricular tachycardia / ventricular fibrillation or aborted sudden death, cardiac massage, ventilation before anaesthetic room, inotropes or IABP, acute

renal failure) and this was included in development of the model. Given that the final model relies upon inclusion of intraoperative parameters, it cannot be used preoperatively.

Despite these limitations, the strengths of our study include the use of a large and well described multicentre CPB registry of prospectively collected data. Furthermore, randomly splitting the dataset into two cohorts provided the opportunity to both cross validate the performance of the model and to compare metrics of model performance with a similar model from an Australian dataset with comparable data definitions. Since the patient sample was large, selection of patients was randomly performed, patient characteristics between cohorts were similar and discrimination, calibration, and goodness-of-fit metrics were similar for the training and validation sets, we have provided evidence that the model is robust and did not suffer from overfitting.

CONCLUSION

The inclusion of CPB parameters augments the prediction of 30-day mortality following cardiac surgery. Modifiable CPB parameters including CPB time, red blood cell transfusion, mean arterial pressure <50 mmHg, minimum oxygen delivery and cardiac index <1.6 l/min/m^2 were identified. Randomised trials designed to evaluate modifiable CPB parameters will determine their impact on mortality.

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Appendices

Appendices A1-A6 relate to publication 2.1; Integration of Electronic Perfusion Data for Perfusion Registries.

Appendix A1

The following libraries should be initialised in MS Access through the Microsoft Visual Basic for Applications editing window;

Visual basic for applications

Microsoft Access 14.0 object library

Microsoft DAO 3.6 object library

OLE automation

Microsoft visual basic for applications extensibility 5.3

Microsoft scripting runtime

Microsoft activeX data objects 2.8 library

Microsoft activeX data objects recordset 2.8 library

Appendix A2

VBA sub-routine for activating EPD process for current patient record in ANZCPR.

Note: This process is activated upon clicking a button on the database form, stored in the server database.

```
Private Sub cmd_Import_CONNECT_Click()
Dim AccessApp As Object
Dim curProcnum As String
Dim con As ADODB.Connection
Dim fInTrans As Boolean 'flag for determining if we are currently in a transaction or not

‘This checks to see if the transfer database is currently in use
If IsImporting Then
MsgBox "Error, import already in progress, exiting", vbOKOnly + vbCritical, "Error"
Exit Sub
End If

Set AccessApp = CreateObject("Access.Application")
If SysCmd(acSysCmdAccessVer) >= 11 Then
Call AutomateSecurity(AccessApp)
```

```
End If

If MsgBox("Starting transfer", vbOKCancel) = 1 Then
SysCmd acSysCmdInitMeter, " Data Transferring ", 10
curProcnum = Me.Procnum
'preset the transaction flag
fInTrans = False
Set con = CurrentProject.Connection
' Start of transaction.
con.BeginTrans
fInTrans = True
con.Execute ("UPDATE sysFlags SET sysFlags.Procnum = '" & curProcnum & "' WHERE
sysFlags.FlagName='Importing'")
con.CommitTrans
fInTrans = False

AccessApp.OpenCurrentDatabase DLookup("[itemloc]", "[itemlocations]", "[item] =
'TransferDb'")
SysCmd acSysCmdUpdateMeter, 3
AccessApp.Run "Transfer_CONNECT", UserName
SysCmd acSysCmdUpdateMeter, 6
AccessApp.Quit
Set AccessApp = Nothing
SysCmd acSysCmdUpdateMeter, 10
MsgBox "Finished Transfer"
SysCmd acSysCmdRemoveMeter
Me.Refresh

Else
End If
End Sub
```

Appendix A3 – VBA script to extract CONNECT™ perfusion data stream

Note: This script is stored in the transfer database.

```
Private Sub Extract_StreamData(theGUID As String, bpStart As Date, bpEnd As Date, pnum
As String)
Dim FieldNameArray As Variant
FieldNameArray = Array("HeartRate", "StAlgorithm1", "StAlgorithm2", "StAlgorithm3", _
"ArtPress_sys", "ArtPress_dia", "MAP", "CVP", "NasoPharynigialTemp") ‘Note:  this list
should include all variable names in the PerfusionStreamData
Dim NumFields As Integer
NumFields = UBound(FieldNameArray) + 1
Dim SQLQuery As String
```

```
SQLQuery = "SELECT s.TimeStamp, s.StreamData,  d.Bsa " & _
"FROM dbo_PerfusionStreamData s left join dbo_SurgeryCaseData d  on d.SurgeryGuid =
s.SurgeryGuid " & _
"   WHERE s.SurgeryGuid = '" & theGUID & "' and  " & _
"        s.Timestamp >= #" & Format(bpStart, "yyyy-mm-dd hh:nn:ss") & "# and " & _
"        s.Timestamp <= #" & Format(bpEnd, "yyyy-mm-dd hh:nn:ss") & "# " & _
" ORDER BY s.TimeStamp; "

OutputLine ("Processing Perfusion stream data")
Dim stDataRset As DAO.Recordset
Dim stDataTable As Recordset
Set stDataRset = CurrentDb.OpenRecordset(SQLQuery)
stDataRset.MoveFirst
Set stDataTable = CurrentDb.OpenRecordset("PerfusionStreamData", dbOpenTable)

Do While Not stDataRset.EOF            ' read each record
stDataTable.AddNew
stDataTable("ProcNum").Value = pnum
stDataTable("Timestamp").Value = stDataRset!TimeStamp
Dim fcnt As Integer
For fcnt = 0 To (NumFields - 1)          ' parse out each of the fields and put in table
Dim fname As String
fname = FieldNameArray(fcnt)
If (GetFieldValue(fname, stDataRset!StreamData) <> "") Then
Dim fval As Variant
fval = CDbl(GetFieldValue(fname, stDataRset!StreamData))
If (fname = "ArtTemp") Then    ' ensure values are within a valid range
If (fval < 5) Or (fval >= 100) Then
fval = Null
End If
End If
If (fname = "Hb") Then    ' ensure values are within a valid range
If (fval < 1) Or (fval >= 100) Then
fval = Null
End If
End If
If fname = "pCO2Art_37" Then              ' as above
If (fval < 5) Or (fval >= 120) Then
 fval = Null
 End If
 End If
If Not IsNull(fval) Then                   ‘ if a value was found then
 stDataTable(fname).Value = fval          ‘store it in the perfusion data table field
 End If
 End If
 Next fcnt
```

```
 stDataTable.Update
 stDataRset.MoveNext
 Loop

End Sub

‘This function is to extract the field names from the perfusion data stream
‘The string containing the fields and their values is formatted such that an ASCII 30 character
‘(record separator) surrounds each record, within which an ASCII 31 character (field
separator) ‘separates the field name from its value
Public Function GetFieldValue(fldName As String, fldStr As String) As String
Dim namePos As Integer
Dim valPos As Integer
Dim valLen As Integer
Dim nextSep As Integer
Dim fldVal As String
namePos = InStr(1, fldStr, fldName + Chr(31))
If IsNull(namePos) Or (namePos <= 0) Then
GetFieldValue = ""
Else
valPos = namePos + Len(fldName) + 1
nextSep = InStr(valPos, fldStr, Chr(30))
valLen = nextSep - valPos
fldVal = Mid(fldStr, valPos, valLen)
GetFieldValue = fldVal
End If
End Function
```

Appendix A4
VBA subroutine for the EPD integration process in ANZCPR.
Note: This script is stored in the transfer database.

```
Public Sub Transfer_CONNECT(logusername As String)
Dim logProcnum As String

'lookup current CPB procedure number:
logProcnum = DLookup("Procnum", "sysFlags")

'check that the database is not currently processing data:
If IsImporting Then
MsgBox "Error, import already in progress, exiting", vbOKOnly + vbCritical, "Error"
Exit Sub
Else
CurrentDb.Execute ("UPDATE sysFlags SET sysFlags.Flag = True WHERE
sysFlags.Flagname='Importing'")
End If
```

```
'retrieve key values that we will need in queries:
Dim procGuid As String
Dim patientGuid As String
Dim surgDate As Date
'run subroutine to retrive the values:
Call GetSurgDetails(logProcnum, procGuid, patientGuid, surgDate)
If procGuid = "" Then
MsgBox "Procnum " & logProcnum & " cannot be found in CONNECT database - no update
done."
Exit Sub
End If
OutputLine ("GUID = " & procGuid)

' define CPB start and stop times
Dim bySQL As String
Dim byRSet As Recordset
Dim bypassStart As Date                    ' get time of first bypass start
Dim nullBypassStart As Boolean
extraData.bypassStartTime = Null
nullBypassStart = True
bySQL = "select  min(EventTime) as StartTime From dbo_EventData " & _
"where  SurgeryGuid = '" & procGuid & "' and " & _
"     ((CommentText is null) or (CommentText <> 'E')) and " & _
"     ((SourceLabel = 'Bypass' and EventLabel = 'Start') or (SourceLabel = 'Bypass Start'))"
Set byRSet = CurrentDb.OpenRecordset(bySQL)
If Not byRSet.EOF Then
If Not IsNull(byRSet![StartTime]) Then
bypassStart = byRSet![StartTime]
extraData.bypassStartTime = byRSet![StartTime]
nullBypassStart = False
End If
End If
byRSet.Close

Dim bypassEnd As Date                      ' get time that last bypass ends
Dim nullBypassEnd As Boolean
nullBypassEnd = True
bySQL = "select  max(EventTime) as EndTime From dbo_EventData " & _
"where  SurgeryGuid = '" & procGuid & "' and " & _
"     ((CommentText is null) or (CommentText <> 'E')) and " & _
"     ((SourceLabel = 'Bypass' and EventLabel = 'Stop') or (SourceLabel = 'Bypass End') or
(SourceLabel = 'Bypass Stop'))"
Set byRSet = CurrentDb.OpenRecordset(bySQL)
If Not byRSet.EOF Then
If Not IsNull(byRSet![endTime]) Then
bypassEnd = byRSet!endTime
```

```
nullBypassEnd = False
End If
End If
byRSet.Close

' clear the perfusion stream data table from last import
CurrentDb.Execute "delete * from [PerfusionStreamData];"
' now populate table
Call Extract_StreamData(procGuid, bypassStart, bypassEnd, logProcnum)

'This section contains examples of how to generate calculated EPD variables
'Here is an example of retrograde autologous prime volume
'The comment RAP is entered as a volume comment and the volume amount is retrieved
Dim RapVol As Integer
RapVol = 0
bySQL = "select Value as RapValue From dbo_EventData " & _
"where SurgeryGuid = '" & procGuid & "' and " & _
"     ((CommentText is null) or (CommentText <> 'E')) and " & _
"     (SourceLabel = 'RAP') and SourceType = 'Volume -' "
Set byRSet = CurrentDb.OpenRecordset(bySQL)
If Not byRSet.EOF Then
RapVol = Nz(byRSet!RapValue, 0)
End If
byRSet.Close

'Here are examples of how to extract minimum and maximum blood gas and electrolyte
data,
'incorporating different units of haemoglobin and blood gas pressure. Also a binary
'quality indicator is set for having a blood glucose <4 or > 10
Dim minHb As Single
Dim maxHb As Single
Dim minCO2 As Single
Dim maxCO2 As Single
Dim minGlucose As Single
Dim maxGlucose As Single
Dim Gluc As Integer

OutputLine ("Extracting Laboratory max/mins")
labSQL = "select Min(Hb_Ext)        as MinHb,   Max(Hb_Ext) as MaxHb, " & _
"      Min(pCO2Art_37_ext) as MinCO2,  Max(pCO2Art_37_ext) as MaxCO2, " & _
"      Min(Glucose_ext)    as MinGlu,  Max(Glucose_ext) as MaxGlu   " & _
"  from dbo_LaboratoryData " & _
"  where SurgeryGuid = '" & procGuid & "' and " & _
"       TimeStamp >= #" & Format(bypassStart, "yyyy-mm-dd hh:mm:ss") & "# and " & _
"       TimeStamp <= #" & Format(bypassEnd, "yyyy-mm-dd hh:mm:ss") & "#"
Set labRSet = CurrentDb.OpenRecordset(labSQL)
```

```
If Not labRSet.EOF Then
If Nz(DLookup("Hbunits", "Config")) = 1 Then
minHb = labRSet!minHb * 10
maxHb = labRSet!maxHb * 10
ElseIf Nz(DLookup("Hbunits", "Config")) = 2 Then
minHb = labRSet!minHb
maxHb = labRSet!maxHb
Else
MsgBox ("Bad config value for HbUnits")
Exit Sub
End If
If Nz(DLookup("Gasunits", "Config")) = 1 Then
minCO2 = labRSet!minCO2
maxCO2 = labRSet!maxCO2
ElseIf Nz(DLookup("Hbunits", "Config")) = 2 Then
minCO2 = labRSet!minCO2 * 7.5
maxCO2 = labRSet!maxCO2 * 7.5
Else
MsgBox ("Bad config value for HbUnits")
Exit Sub
End If
minGlucose = labRSet!minGlu
maxGlucose = labRSet!maxGlu
If minGlucose < 4 Or maxGlucose > 10 Then
Gluc = 1
Else
Gluc = 2
End If
End If
labRSet.Close

'Here are examples of how to extract min and max values from the perfusion stream data
table
Dim perfSQL As String
Dim perfRSet As Recordset
OutputLine ("Extracting Perfusion min/max/avgs")
perfSQL = "SELECT Min([NasoPharynigialTemp]) AS [MinOfNaso temp], " & _
"Max([NasoPharynigialTemp]) AS [MaxOfNaso temp], " & _
"Max([ArtTemp]) AS [MaxOfArt temp], " & _
"Min([ArtTemp]) As [MinOfArt temp], " & _
"Min(Nz([MAP])) AS [MinOfArt P], " & _
"Avg([MAP]) AS [AvgOfArt P] " & _
"FROM PerfusionStreamData  " & _
"WHERE ProcNum = '" & logProcnum & "'"

Dim Nasomin As Single
```

```
Dim Nasomax As Single
Dim MAPavg As Double
Dim Artmax As Single
Dim Artmin As Single
Set perfRSet = CurrentDb.OpenRecordset(perfSQL)
If Not perfRSet.EOF Then
Nasomin = perfRSet![MinOfNaso temp]
Nasomax = perfRSet![MaxOfNaso temp]
MAPavg = perfRSet![AvgOfArt P]
Artmax = perfRSet![MaxOfArt temp]
Artmin = perfRSet![MinOfArt temp]
End If
perfRSet.Close

'Here is an example of how to extract an average value from the perfusion data table
perfSQL = "SELECT Avg([ArtFlow]) AS [AvgOfArt Flow] " & _
"FROM dbo_PerfusionData  " & _
"WHERE SurgeryGuid = '" & procGuid & "' and " & _
"       TimeStamp >= #" & Format(bypassStart, "yyyy-mm-dd hh:mm:ss") & "# and " & _
"       TimeStamp <= #" & Format(bypassEnd, "yyyy-mm-dd hh:mm:ss") & "#"
Dim Flowavg As Double
Set perfRSet = CurrentDb.OpenRecordset(perfSQL)
If Not perfRSet.EOF Then
Flowavg = perfRSet![AvgOfArt Flow]
End If
perfRSet.Close

'To update the values returned from the queries into a registry table, use this syntax,
'according to the registry table and field name;
'eg updSQL = "UPDATE [Registry table name] SET [Registry field name] = " & [vba variable
name] & "
Dim updSQL As String
updSQL = "UPDATE ANZCPR_Perfusion SET Hbmin = " & minHb & ", " & _
"Hbmax = " & maxHb & ", " & _
"Nasomin = " & Nasomin & ", " & _
"Nasomax = " & Nasomax & ", " & _
"Artmax = " & Artmax & ", " & _
"Artmin = " & Artmin & ", " & _
"MAPavg = " & MAPavg & ", " & _
"Flowavg = " & Flowavg & ", " & _
"Glucmin = " & minGlucose & ", " & _
"Glucmax = " & maxGlucose & _
" WHERE Procnum = '" & logProcnum & "'"
doUpdate (updSQL)
```

```
'Here is an example of how to calculate cumulative time variables and then taking into
account the data collection interval
'This is the cummulative time that the MAP was < 40 mmHg;
Dim artP40 As Single
countSQL = "SELECT COUNT(TimeStamp) As TheCount from PerfusionStreamData where
(MAP >= 30) and (MAP < 40) and procnum = '" & logProcnum & "'"
artP40 = getCount(countSQL)   ' Note: getCount is a function decribed later on

'This is the cummulative time that the arterial outlet temperature was >37 degrees;
Dim ATemp37 As Single
countSQL = "SELECT COUNT(Timestamp) As TheCount from PerfusionStreamData where
(ArtTemp > 37) " & " and procnum = '" & logProcnum & "'"
ATemp37 = getCount(countSQL)

'Determining the data collection interval from the configuration table;
Dim BDQCfactor As String
If Nz(DLookup("Datatype", "Config")) = 2 Then
BDQCfactor = "0.5"
Else
OutputLine ("BD - QC Update 20 sec")
BDQCfactor = "0.33333333"
End If
Dim countSQL As String
'Updating the data taking into account the data collection interval;
updSQL = "UPDATE ANZCPR_PerfQC set artP40 = " & artP40 & "*" & BDQCfactor & ", " & _
"[ATemp>37] = " & ATemp37 & "*" & BDQCfactor & _
"  WHERE Procnum = '" & logProcnum & "'"
doUpdate (updSQL)

'append physiological stream data to multiple record table
If IsNull(DLookup("[ProcNum]", "ConnectPerfusionData", "[ProcNum] = '" + logProcnum +
"'")) Then
CurrentDb.Execute "Append Stream data"
End If

'now clear out the temporary stream data table and reset the transaction table
CurrentDb.Execute "delete * from [PerfusionStreamData];"
Dim MySQL As String
CurrentDb.Execute ("UPDATE sysFlags SET sysFlags.Procnum = Null WHERE
sysFlags.FlagName='Importing'")
CurrentDb.Execute ("UPDATE sysFlags SET sysFlags.Flag    = false WHERE
sysFlags.FlagName='Importing'")
MsgBox "Transfer complete"
Exit Sub
End Sub
```

Appendix A5
VBA subroutine to update values returned in the SQL queries to the database fields
Note: This script is stored in the transfer database.

```
‘This sub-routine is used to update values returned in the SQL queries to the database fields
Public Sub doUpdate(SQLtoUse As String)
Dim updTable As String
If Len(SQLtoUse) > 50 Then
Dim wordArray() As String
wordArray() = Split(SQLtoUse)
Select Case wordArray(0)
Case "UPDATE"
updTable = wordArray(0) + " " + wordArray(1) + " ..."
Case "INSERT"
updTable = wordArray(0) + " " + wordArray(1) + " " + wordArray(2) + " ..."
End Select
End If
With CurrentDb
.Execute SQLtoUse
If .RecordsAffected <= 0 Then
Call OutputLine("Update was not successful: " & SQLtoUse, True, updTable)
End If
End With
End Sub
```

Appendix A6
Miscellaneous specific VBA subroutines
Note: These scripts are stored in the transfer database.
‘this function finds the Connect unique record identifier for the corresponding ANZCPR unique procedure identifier, together with the date of surgery

```
Public Sub GetSurgDetails(Procnum As String, ByRef procGuid As String, ByRef patientGuid
As String, ByRef surgDate As Date)
Dim guidSQL As String
Dim guidRset As Recordset
guidSQL = "Select * from dbo_Surgery where CaseNumberDec = '" & Procnum & "'"
Set guidRset = CurrentDb.OpenRecordset(guidSQL)
If guidRset.RecordCount > 0 Then
procGuid = Mid(StringFromGUID(guidRset!Guid), 8, 36)            ' get the Connect GUID for
this procedure and chop off extraneous characters added by routine
patientGuid = Mid(StringFromGUID(guidRset!patientGuid), 8, 36)    ' The CONNECT identifier
for the patient
surgDate = guidRset!SurgeryDate
Else
Call OutputLine("Error finding procnum " & Procnum & " in CONNECT database", True)
procGuid = ""
```

```
End If
guidRset.Close
End Sub

 'This function determines if the transfer database is currently in use
Public Function IsImporting() As Boolean
If DLookup("[Flag]", "[sysFlags]", "[FlagName]='Importing'") = True Then
IsImporting = True
Else
IsImporting = False
End If
End Function

'This function is used to return the number of records for a certain criteria (e.g., count
number of times pressure <40)
Private Function getCount(SQLtoUse As String) As Integer
Dim cntRset As Recordset
Dim retcount As Integer
Set cntRset = CurrentDb.OpenRecordset(SQLtoUse)
If cntRset.RecordCount > 0 Then
retcount = cntRset!theCount
Else
retcount = 0
End If
cntRset.Close
Set cntRset = Nothing

getCount = retcount

End Function
```

2022

ANZCPR Annual Multicentre Data Report

ANZCPR

Australian & New Zealand Collaborative Perfusion Registry

Quality Perfusion through reporting

Authors: Rob Baker, Richard Newland

VISION:

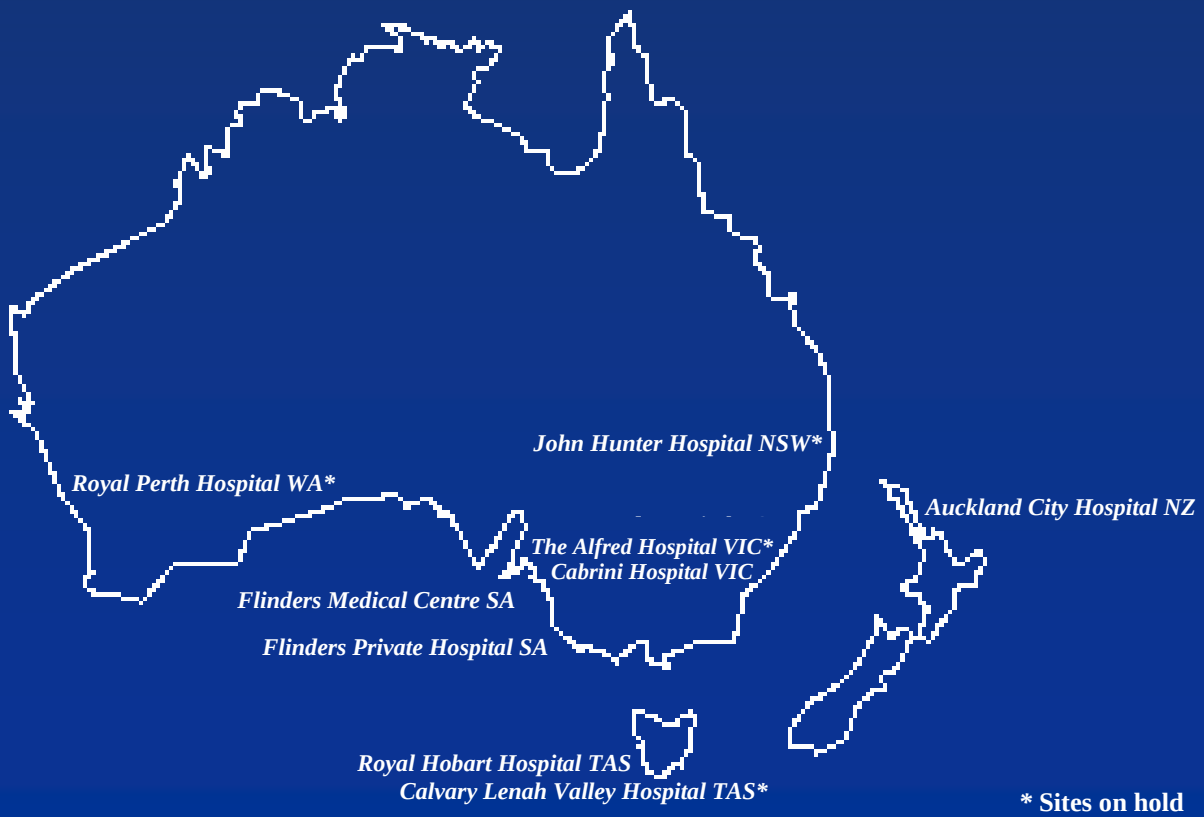
Empower all Cardiac Surgery Team Members to improve the understanding and practice of cardiopulmonary bypass to improve cardiac surgical patient outcomes.

MISSION:

Maintain and develop the Australian and New Zealand Collaborative Perfusion Registry for cardiac surgical procedures performed throughout Australia and New Zealand.

Promote the reporting and understanding of the effect of cardiopulmonary bypass on patient outcomes through encouraging evidence based practices, quality assurance, quality improvement and research.

CONTRIBUTING SITES:



*** Sites on hold**

(non-contributing sites)

Data Harvest Jan-Dec 2022. Published July 2023.

Table of Contents

Foreword

The Executive Summary Report of the Australian and New Zealand Collaborative Perfusion Registry (ANZCPR) shares an outline of the activity of the registry during the calendar year 2022.

The ANZCPR aims to empower cardiac surgical team members through the collection and reporting of data relevant to the practice of cardiopulmonary bypass. This is achieved through utilization of the data to understand clinical practice, provide a foundation for research, and to facilitate quality improvement.

We have collected data from over 46,000 patients undergoing CPB over 9 different hospitals, since our beginnings in 2007. We are unique in that we currently collect data from New Zealand and from 4 Australian States. We are the only registry of this kind in the world, as we prospectively capture and analyse electronic heart-lung machine data and combines these with demographic, pre-operative risk factors and post-operative complications and patient outcome data.

Unit activity is provided to enable individual units to review their activity across all aspects of the collaboration dataset allowing a contemporary view of practices compared to other collaboration partners. Data is presented for each site for the collection period, and all sites are de-identified, with each site having a unique site code and colour.

The benefits of measuring clinical practice and reviewing performance have recently been highlighted by the Australian Commission on Safety and Quality in Health Care demonstrating the need for clinical registries such as the ANZCPR. The success of the registry can be quantified by the questions that our work generates, the interest that we gain from colleagues, both perfusion, surgical, anaesthetic, nursing, intensive care and administrative, which will help us understand and improve clinical practice, and most importantly improve the outcomes for the patients who have entrusted us with their care.

We ask you to share these reports with your clinical teams and your hospital leadership such that every person in your institution can learn from our collective work.

2023 poses a unique challenge for our Registry, one we are approaching front on – we need to achieve our long-term goal of becoming truly encompassing of practice in our region and making the registry accessible to all Cardiac Surgery centres, whilst simultaneously developing a funding framework to support these initiatives.

We challenge you to improve your practice.

Rob Baker,
Chair, Australian and New Zealand Collaborative Perfusion Registry

Introduction

Australian and New Zealand Collaborative Perfusion Registry:

This report describes the data collected in the most recent data harvest year for core procedures (coronary artery bypass graft (CABG), isolated valve surgery and combined valve/CABG) performed utilising cardiopulmonary bypass to support cardiac surgical procedures.

The following institutions have contributed data in the 2022 data harvest:

Ashford Community Hospital, South Australia (2009-current)
Auckland City Hospital, New Zealand (2007-current)
Cabrini Hospital, Victoria (2011-current)
Flinders Medical Hospital, South Australia (2007-current)
Flinders Private Hospital, South Australia (2007-current)
Royal Hobart Hospital, Tasmania (2008-current)
Westmead Hospital, New South Wales (2010-current)
Calvary Lenah Valley Hospital, Tasmania (2019-current)

Royal Perth Hospital, Western Australia contributed data from 2009-14. The Alfred Hospital contributed data from 2012-2018 and will recommence contributing data upon completion of a transfer process from the Vision data management software.

For a complete list of the individuals who have contributed to the ANZCPR and made this work possible please see appendix 1. If your site has additional contributors who should be acknowledged, please forward their names to richard.newland@sa.gov.au

This report provides an overview of the patients who underwent surgery, the types of surgery performed, the complications encountered, and the outcomes of their surgery, and uniquely presents data on the intra-operative period, and specifically relating to the extracorporeal support they received. All figures relate to the CORE procedures of the collaboration (coronary artery bypass graft / aortic or mitral valve /valve coronary cases) except figure 1a, 2a and 3a which are for all procedures reported from each institution.

Data Quality and Purpose Statement

All data presented in this report is presented in good faith and as part of the Collaborations goals of improving cardiac surgical outcomes in our region. Data is presented as a quality improvement resource for all collaborators.

Data Preparation & Reporting Period

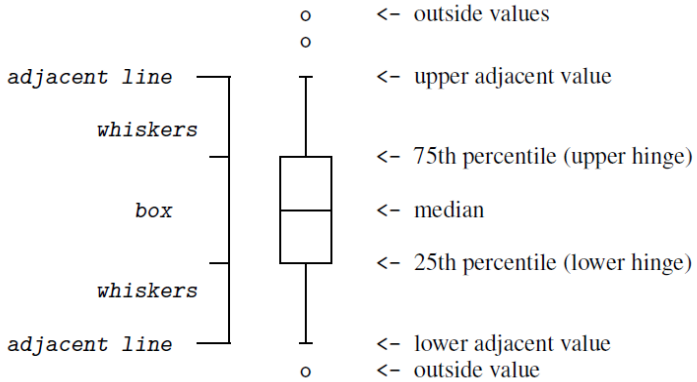
ANZCPR currently harvests data annually, with a harvest date in the first yearly quarter, making our data harvest for the previous calendar year. This report represents data collected for the last harvest period (2022).

Final data related to this report was received by the ANZCPR up to May 2023. Prior to submission Data Managers were given the opportunity to check and amend any errors in their Unit's data.

The current data harvest (all cases reported to ANZCPR since inception) yielded 50,084 procedures - cases that are missing the age of the patient, or the patient is age <18 (423), are excluded from reporting. Where obvious data errors have been identified, these values have been replaced with missing values (including values less than 0, representing typographical errors or where the data is identified as biologically not plausible (e.g., age = 120 years). The final dataset includes 46,296 records where CPB was utilised, of which 36,299 were core procedures. 2,060 records from core procedures are reported for the period Jan - Dec 2022. Where the incidence of missing postoperative data for a site exceeds 10%, the variable is omitted from reporting for that site. Furthermore, sites that contribute to the Australian and New Zealand Society of Cardiothoracic Surgeons (ANZSCTS) Registry may elect to populate their clinical and outcomes data in the ANZCPR by transferring their data from the ANZSCTS registry. ANZCPR collect additional clinical and outcome variables which will be missing for these sites for the current reporting period. This is being addressed prospectively.
All data in this report relates to events and practices occurring during the patient's hospital admission, mortality data includes all deaths in hospital prior to discharge.

Percentage data is presented as the percentage of total caseload for a year or Hospital.

Box and whisker plots are used to show variation within the data. To interpret these, the middle bar is the median value, the top and bottom of the box represent the 75th and 25th percentile (interquartile range). Outside values are greater than 1.5 times the upper or lower quartile. Upper and lower adjacent values are the closest data points to the first outside value.



Patient and Procedural Demographics:

ANZCPR 2022 – All comers

2,692

Total procedures in 2022

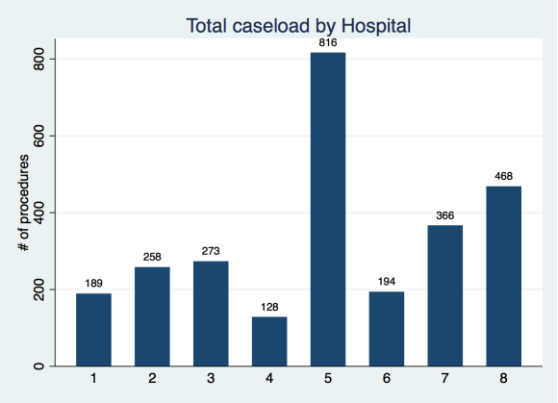


Figure 1a. The Total caseload of all procedures by calendar year January – December 2022.

ANZCPR 2022 – Core procedures

2,060

Core Procedures in 2022

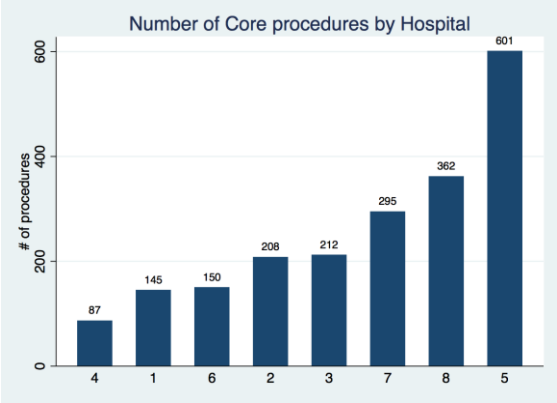


Figure 1b. The Number of core procedures January – December 2022.

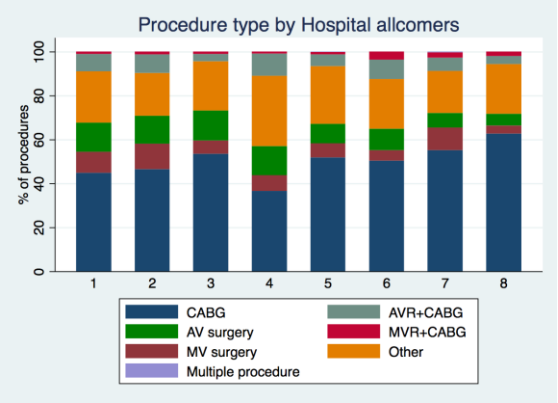


Figure 2a. All procedure types by Hospital.

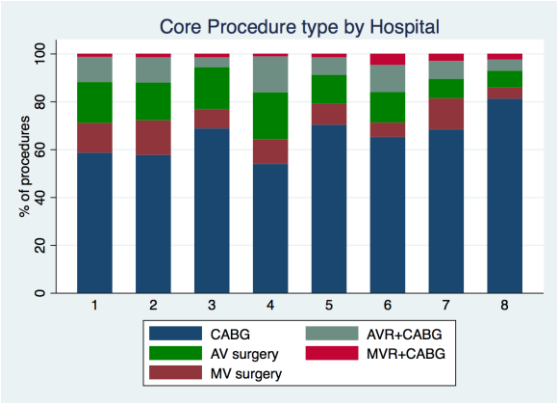


Figure 2b. Core Procedure type by Hospital.

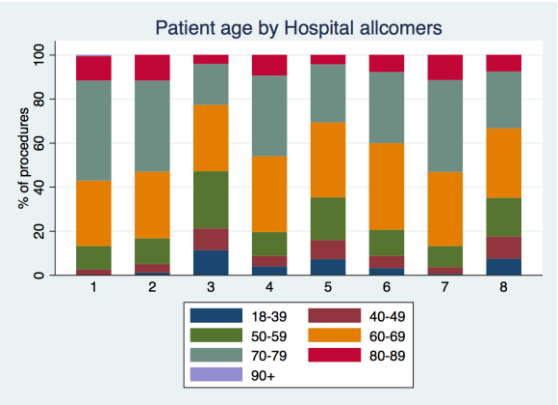


Figure 3a. Patient age by Hospital in all procedures.

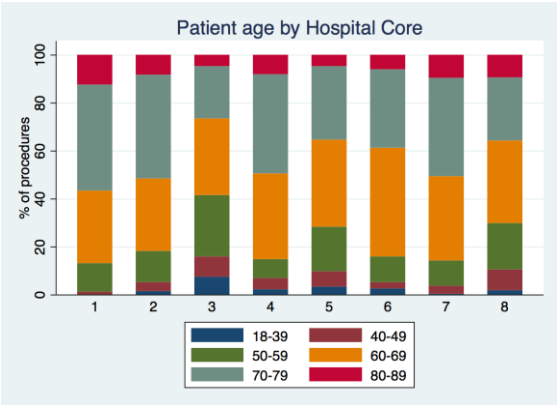


Figure 3b. Patient age by Hospital in core procedures.

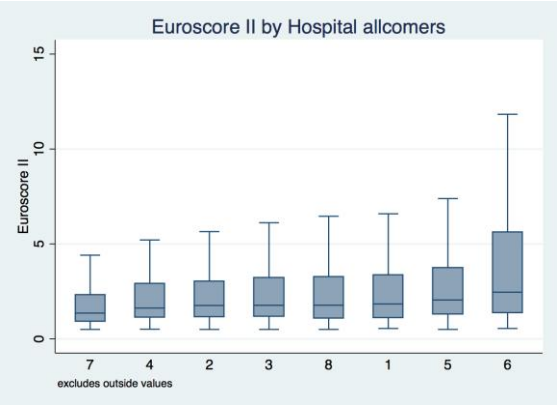


Figure 3c. Euroscore II by Hospital in all procedures.

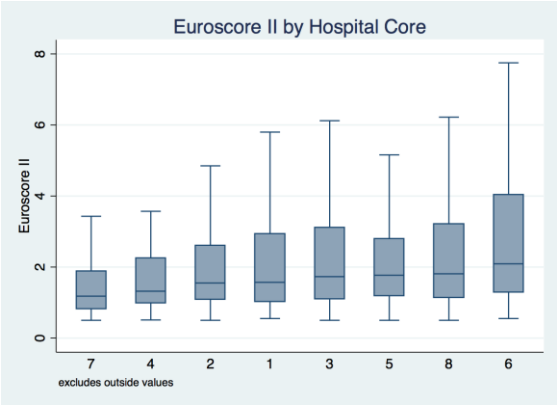


Figure 3d. Euroscore II by Hospital in core procedures.

Core Procedures (n=2,060)

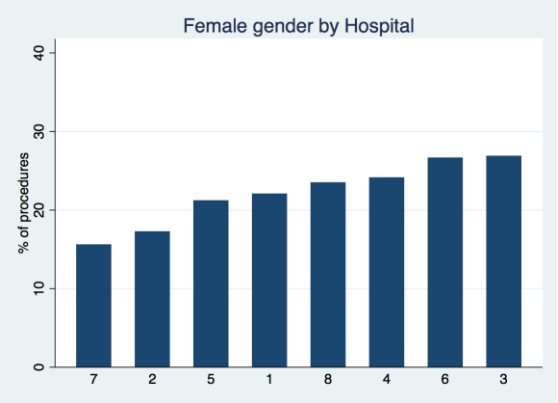


Figure 4. Female gender by Hospital. Note the vertical axis is truncated at 40%.

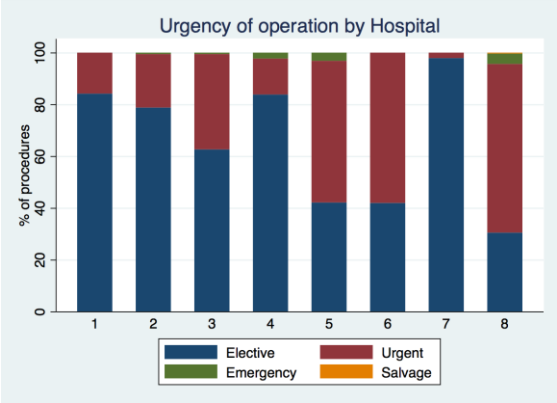


Figure 5. Urgency of operation by Hospital. There is variation between Hospitals with respect to the amount of elective and urgent procedures.

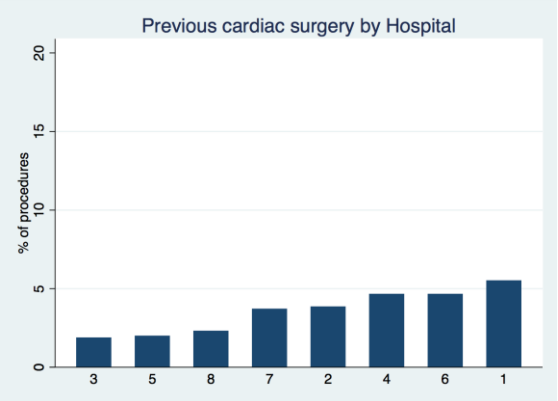


Figure 6a. Patients that have undergone previous Cardiac Surgery by Hospital. Note the vertical axis is truncated at 20%.

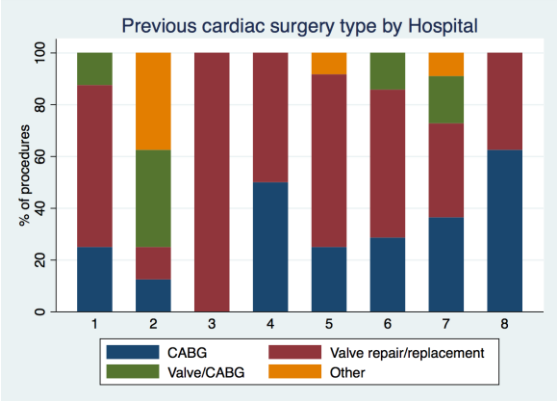


Figure 6b. Previous cardiac surgery type by Hospital.

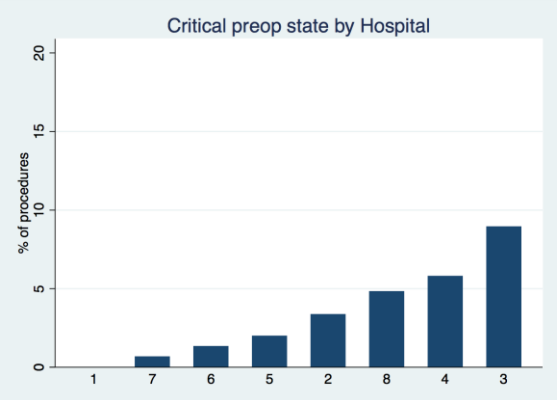


Figure 7. Critical preoperative state by Hospital. Incidence is very low at all sites this may reflect that this variable is not being collected correctly. Note the vertical axis is truncated at 20%.

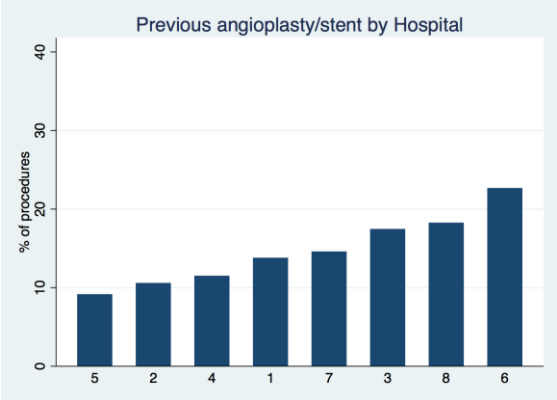


Figure 8. Previous angioplasty/stent by Hospital. Note the vertical axis is truncated at 40%.

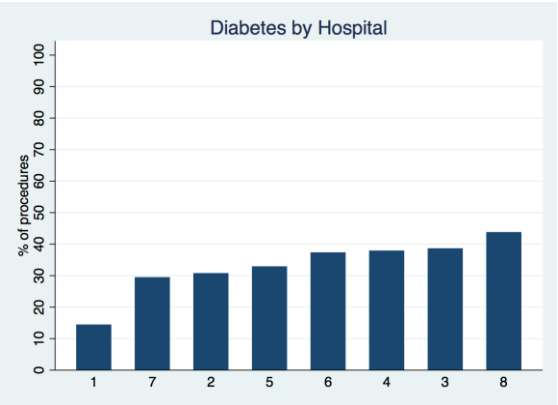


Figure 9a. Incidence of diabetes by Hospital.

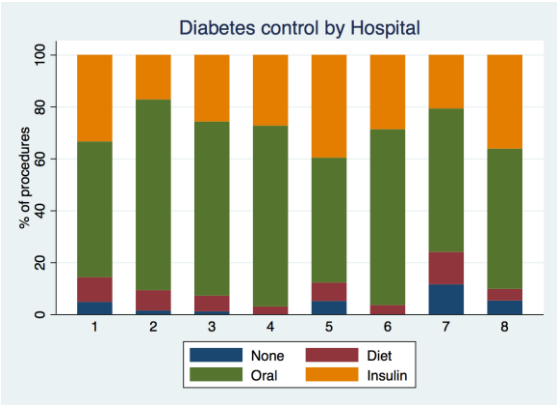


Figure 9b. Diabetes control by Hospital.

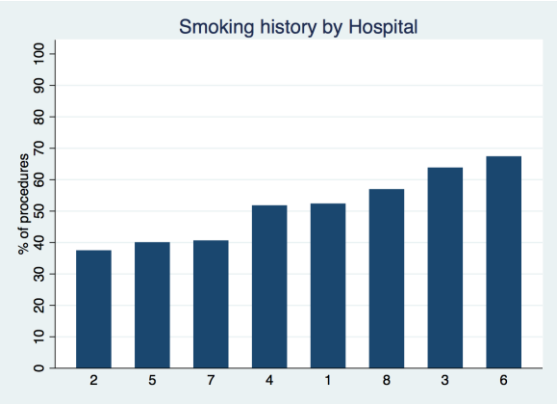


Figure 10a. Smoking history by Hospital. Wide variation exists between Hospitals with respect to smoking history.

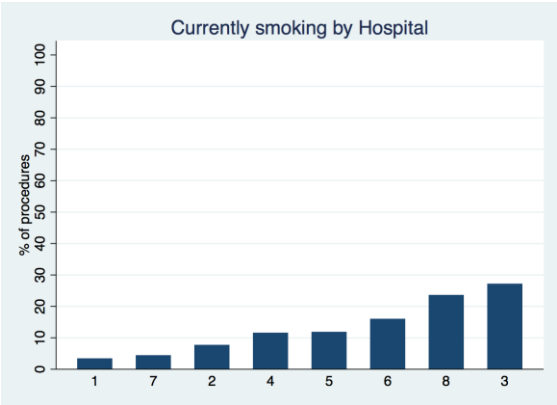


Figure 10b. Currently smoking by Hospital.

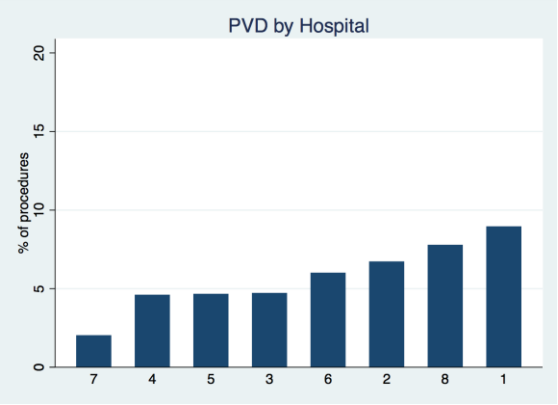


Figure 11. Peripheral Vascular Disease by Hospital.

Note the vertical axis is truncated at 20%

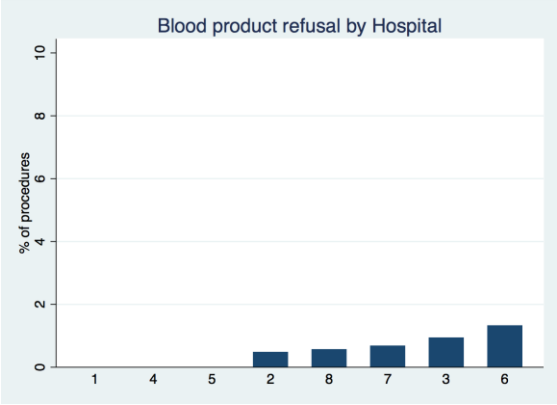


Figure 12. Blood product refusal by Hospital

Note the vertical axis is truncated at 10%.

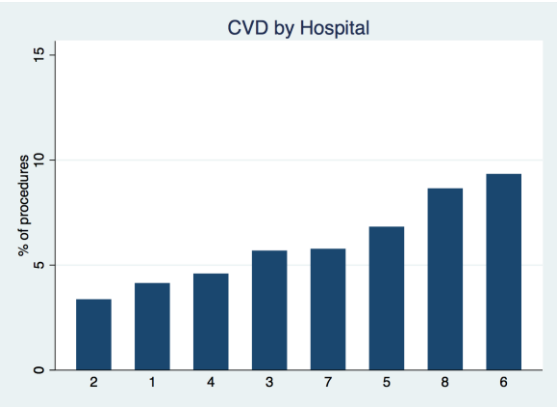


Figure 13. Preoperative Cerebrovascular Disease by Hospital.

Note the vertical axis is truncated at 15%.

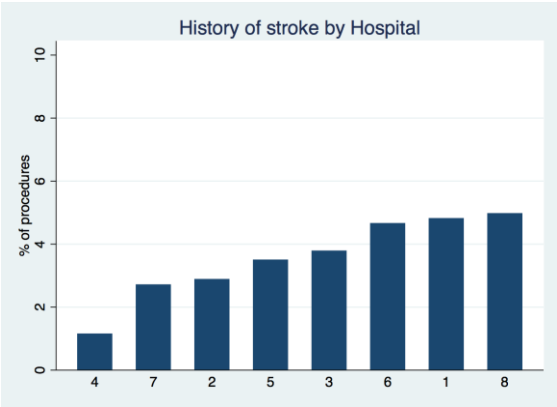


Figure 14. History of stroke by Hospital.

Note the vertical axis is truncated at 10%.

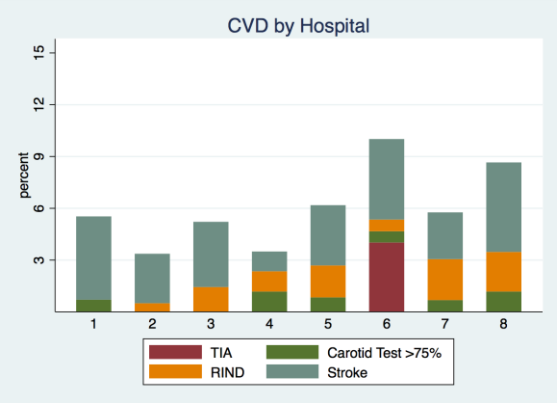


Figure 15. Preoperative Cerebrovascular Disease type by Hospital.

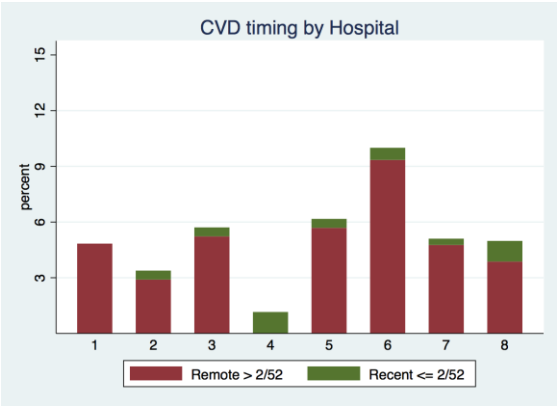


Figure 16. Preoperative Cerebrovascular Disease timing by Hospital.

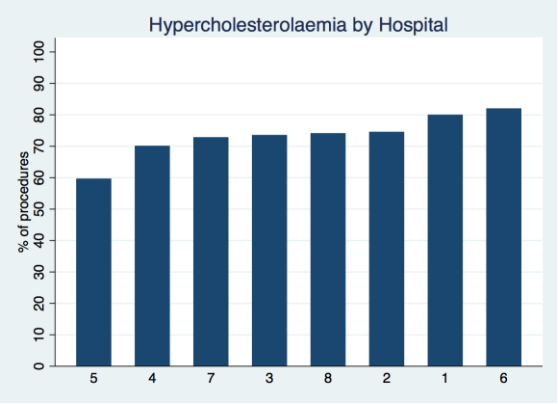


Figure 17. Preoperative hypercholesterolaemia by Hospital.

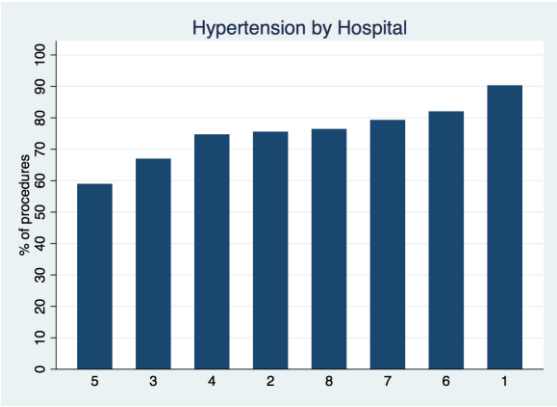


Figure 18. Preoperative hypertension by Hospital

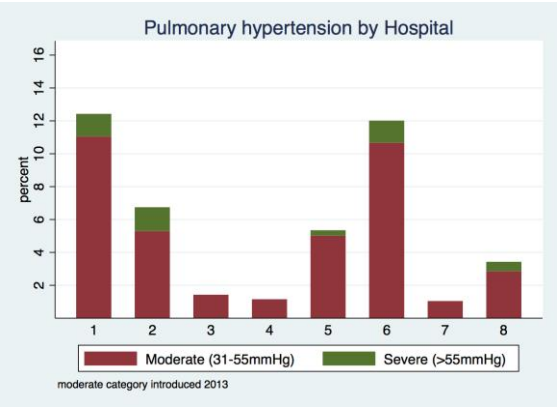


Figure 19. Preoperative pulmonary hypertension by Hospital. Note the vertical axis is truncated at 16%.

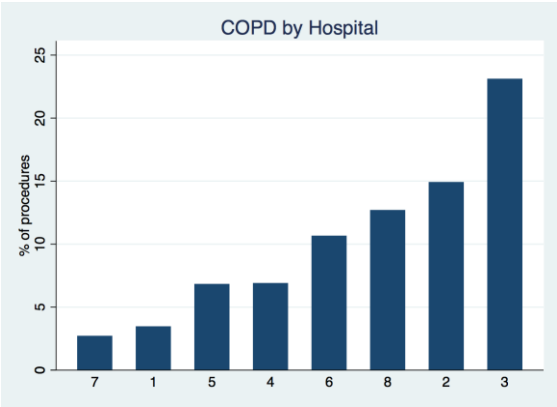


Figure 20 Preoperative chronic obstructive pulmonary disease by Hospital.
Note the vertical axis is truncated at 25%.

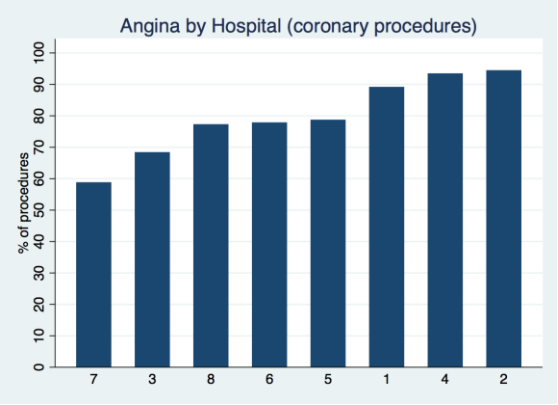


Figure 21. Preoperative presence of angina by Hospital.

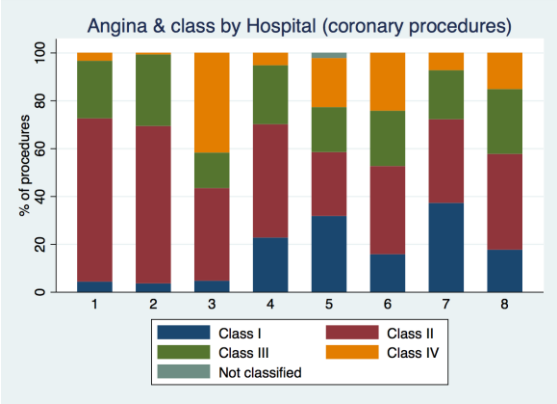


Figure 22. Angina class by Hospital

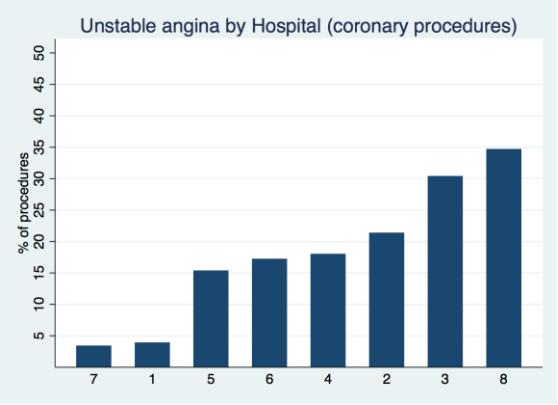


Figure 23. Preoperative unstable angina by Hospital.
Note the vertical axis is truncated at 50%.

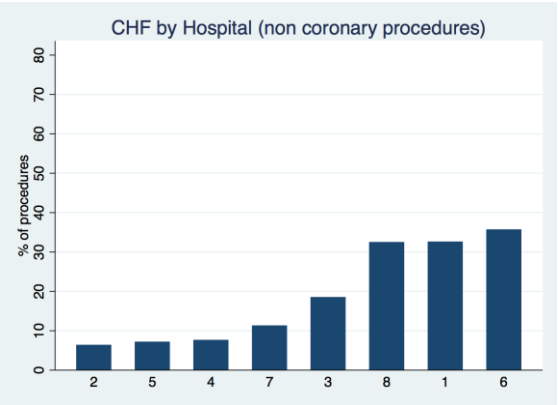


Figure 24. Preoperative congestive heart failure by Hospital in non-coronary core procedures. Note the vertical axis is truncated at 80%.

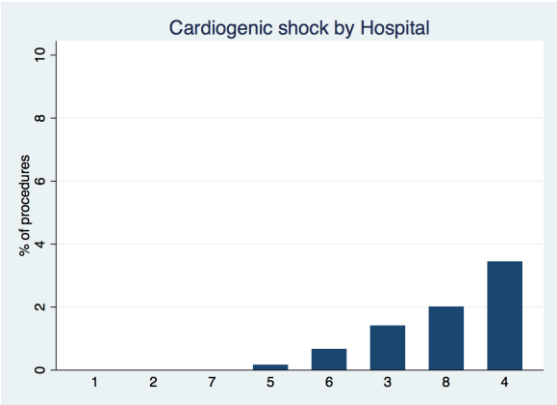


Figure 25. Preoperative cardiogenic shock by Hospital. Note the vertical axis is truncated at 10%.

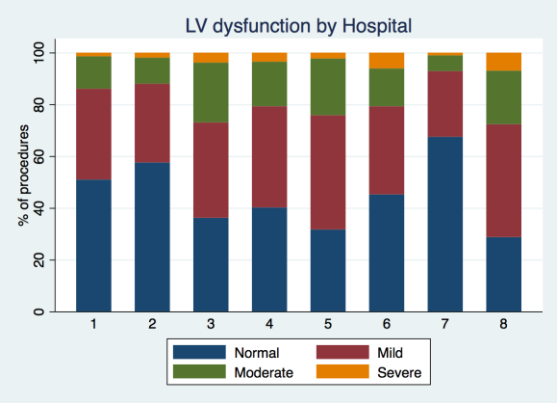


Figure 26. Preoperative left ventricular dysfunction by Hospital.

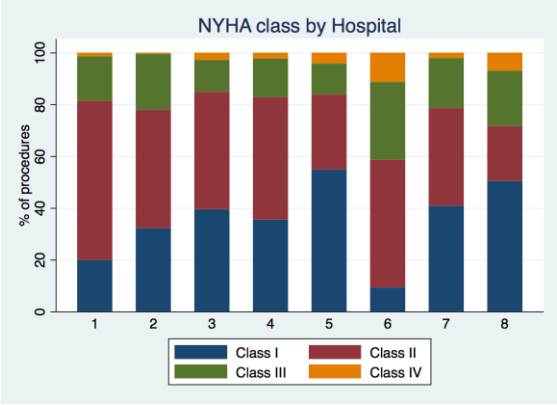


Figure 27. New York Heart Association class by Hospital.

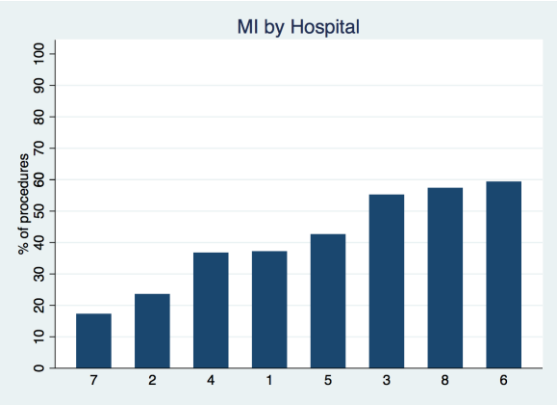


Figure 28. Previous myocardial infarct by Hospital. Rate of history of MI varies from 18-50%

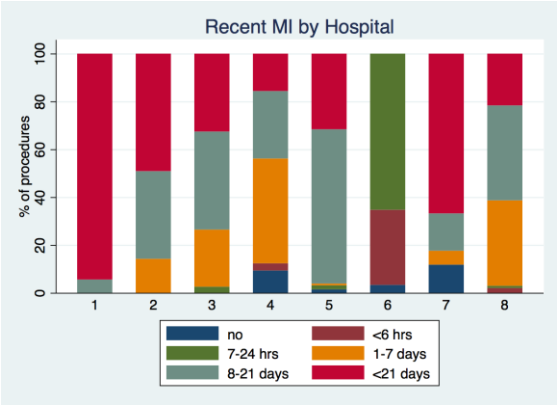


Figure 29. Recent myocardial Infarction by Hospital.

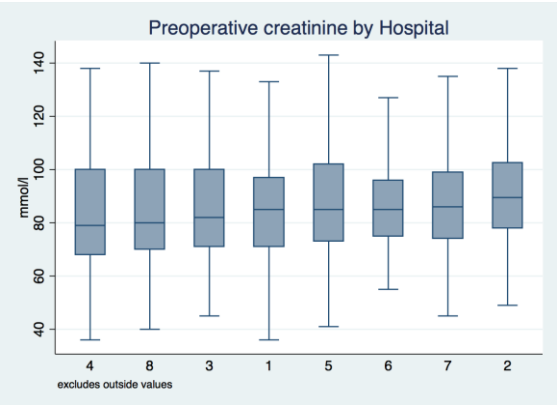


Figure 30. Preoperative creatinine by Hospital

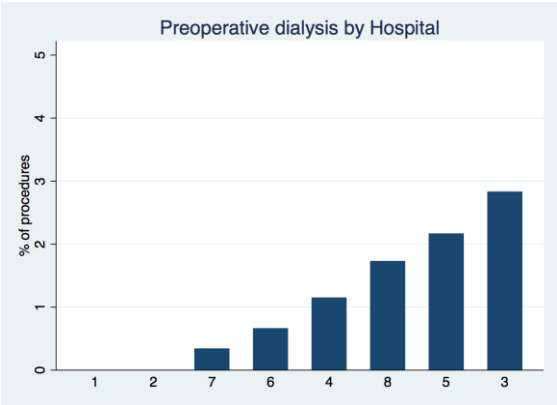


Figure 31. Preoperative dialysis by Hospital.

Note the vertical axis is truncated at 5%.

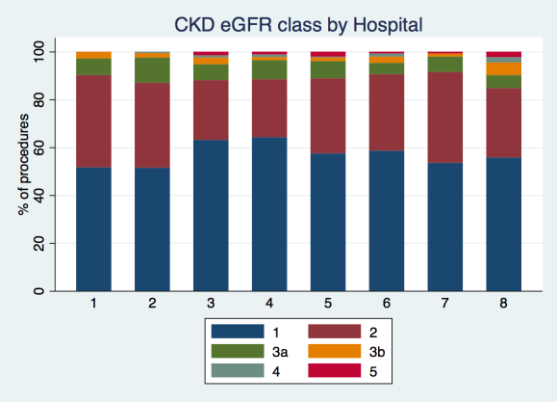


Figure 32b. Preoperative chronic kidney disease classification by Hospital. eGFR is calculated using the CKD-EPI equation. CKD class 1 and 2 require a diagnosis of albuminuria, haematuria or a pathological or structural kidney abnormality (we do not collect this data), CKD classification applies to stages 3a or greater only. Stages 1 and 2 refer to eGFR class only.

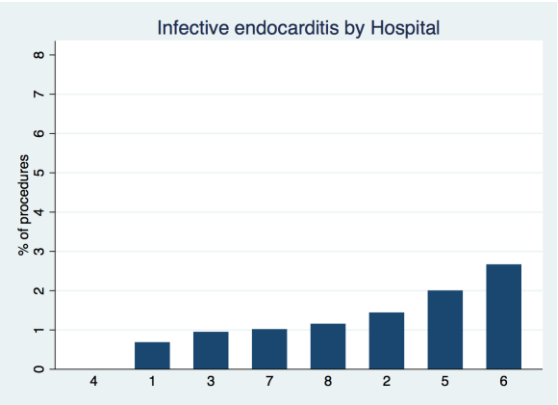


Figure 33. Infective endocarditis by Hospital

Note the vertical axis is truncated at 8%.

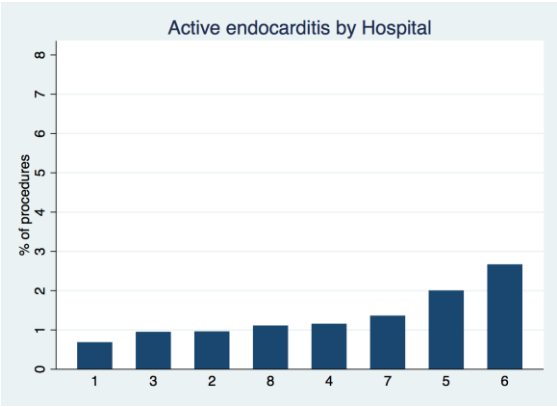


Figure 34. Active endocarditis by Hospital

Note the vertical axis is truncated at 8%.

Procedural Demographics – Core Procedures

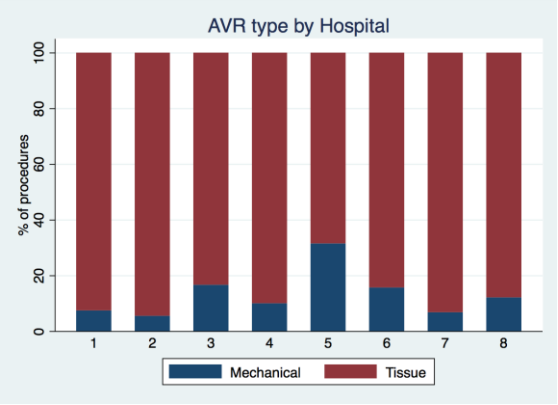


Figure 36a. Aortic valve type by Hospital.

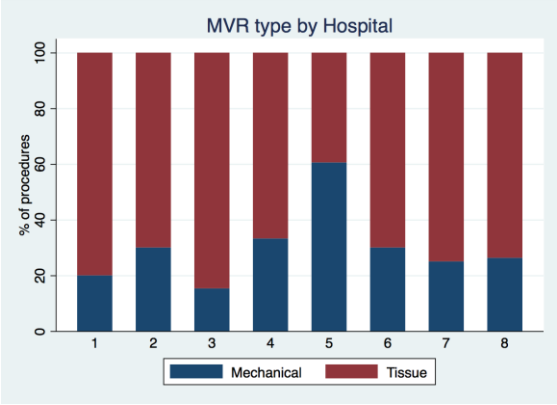


Figure 36b. Mitral valve type by Hospital.

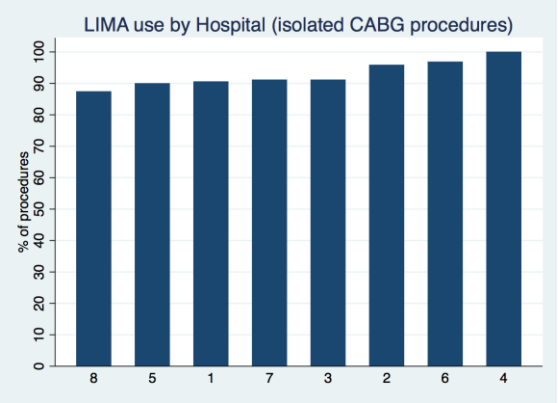


Figure 36c. Left internal mammary artery use by Hospital in isolated CABG procedures.

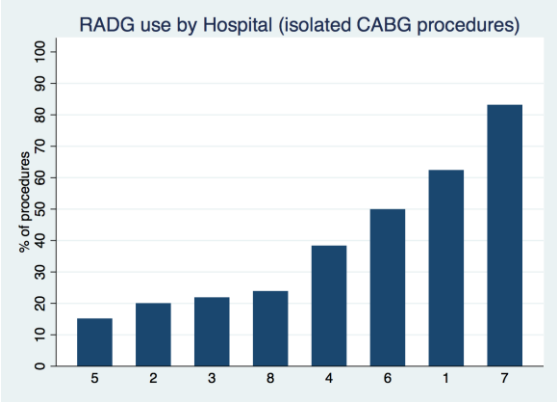


Figure 36d. Radial artery use by Hospital in isolated CABG procedures.

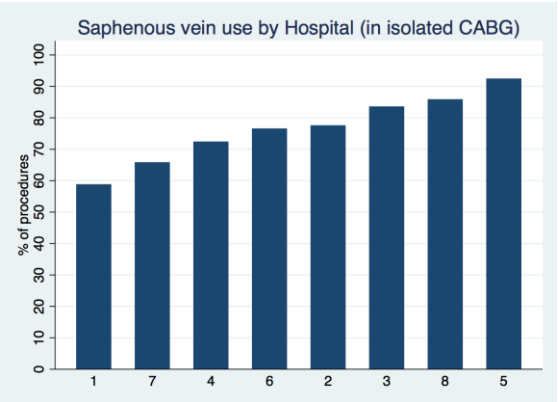


Figure 36e. Number of saphenous vein graft distal anastomoses by Hospital in isolated CABG procedures.

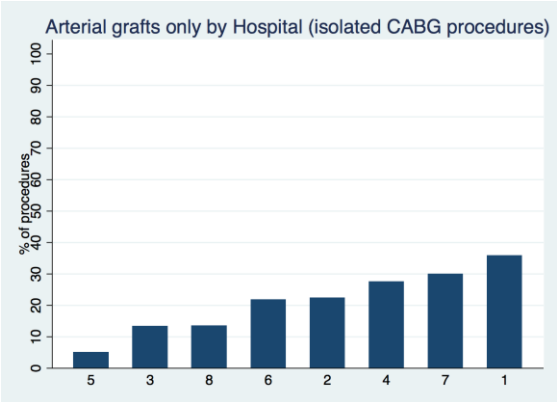


Figure 36f. Use of arterial graft conduit only by Year in isolated CABG procedures.

Perfusion Equipment - Core Procedures

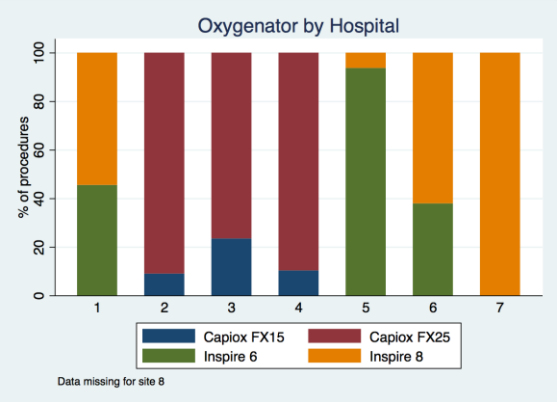


Figure 37. Oxygenator by Hospital.

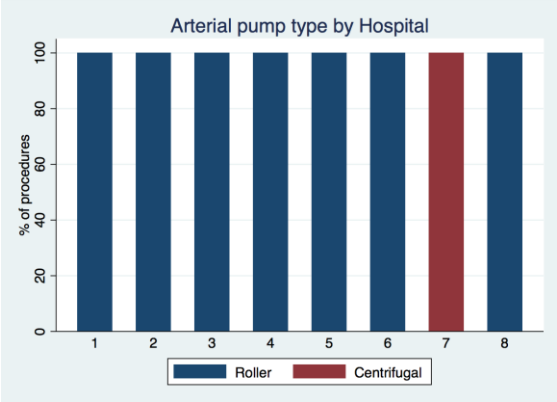


Figure 38. Arterial pump type by Hospital.

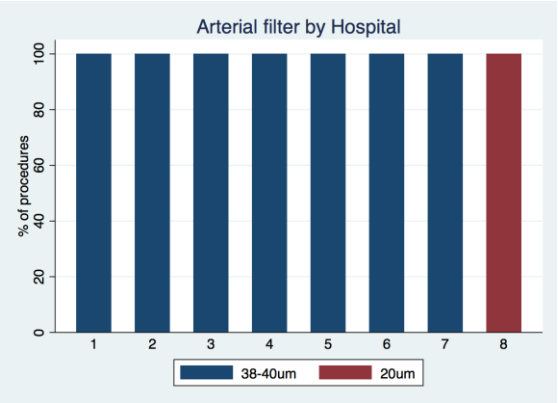


Figure 39. Arterial filter by Hospital.

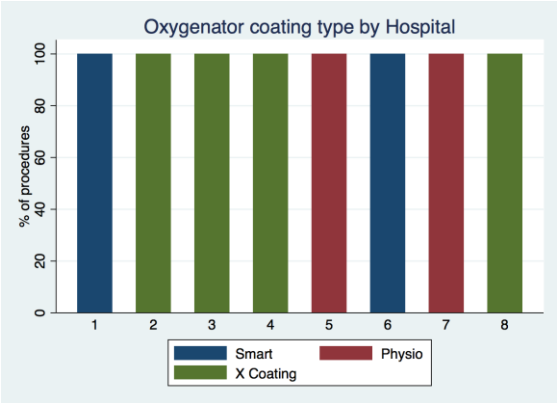


Figure 40. Oxygenator coating type by Hospital.

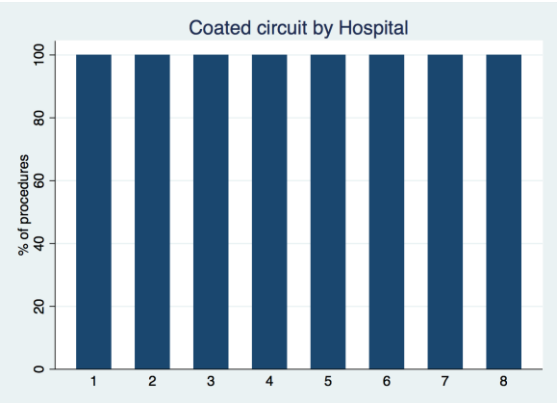


Figure 41. Coated circuit by Hospital. All sites use 100% coated circuits.

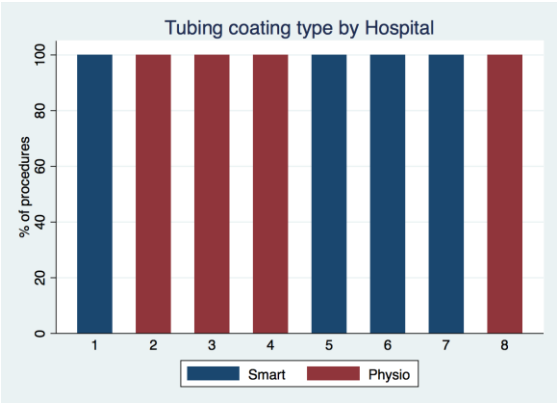


Figure 42. Tubing coating type by Hospital.

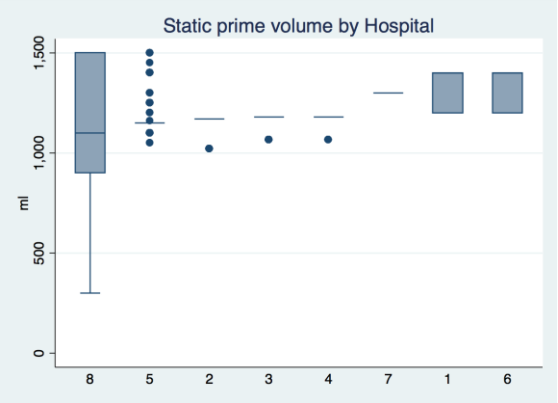


Figure 43. Static prime volume by Hospital.

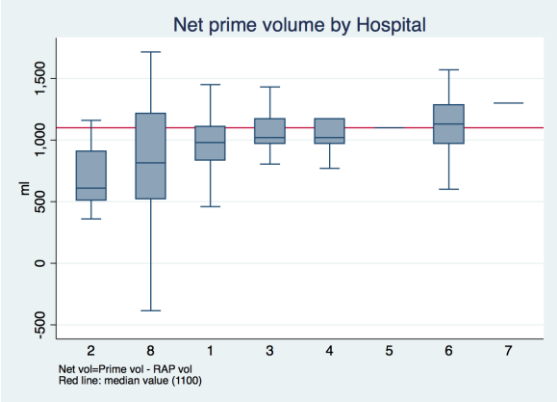


Figure 44. Net prime volume by Hospital. The volume of prime the patients is exposed to varies significantly between sites.

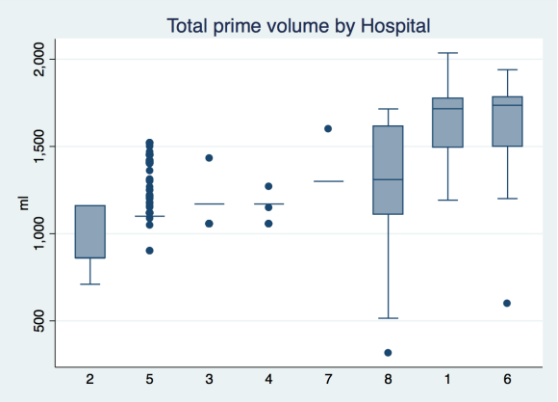


Figure 45. Total prime volume by Hospital. Large variation exists between different sites with respect to total prime volume.

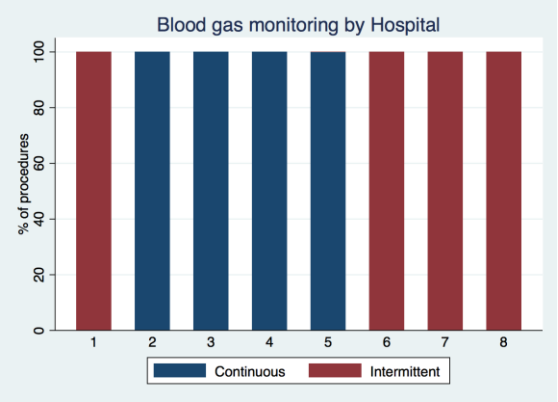


Figure 46. Blood gas monitoring by Hospital

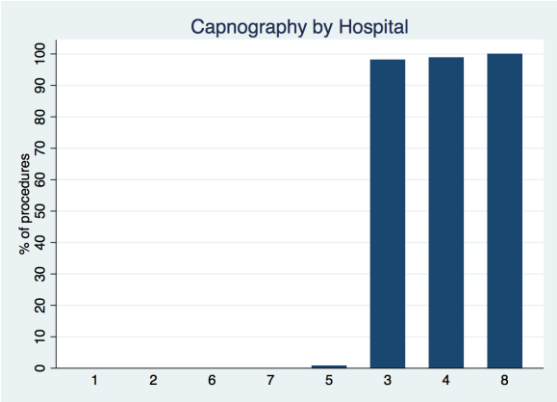


Figure 47. Capnography by Hospital.

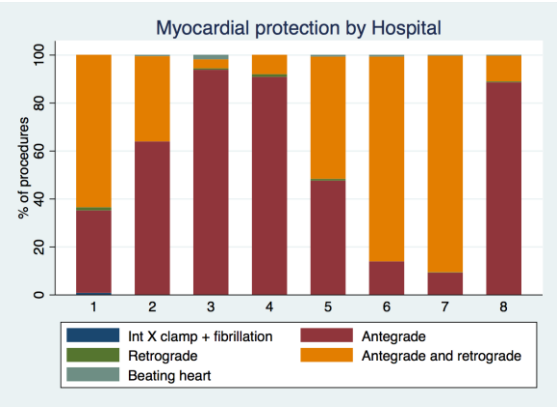


Figure 49. Myocardial protection by Hospital. Wide variation exists in the route of administration of blood cardioplegia. Most commonly an anterograde and retrograde delivery is used.

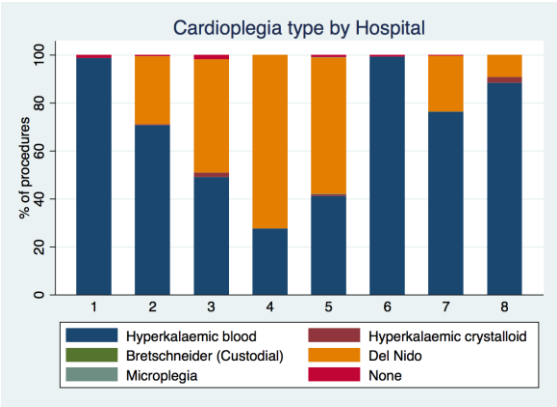


Figure 50. Cardioplegia type by Hospital.

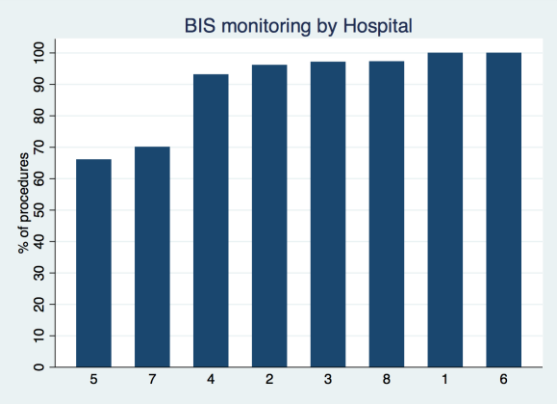


Figure 51. Bispectral monitoring by Hospital. One Hospital does not routinely use BIS, this unit routinely uses entropy

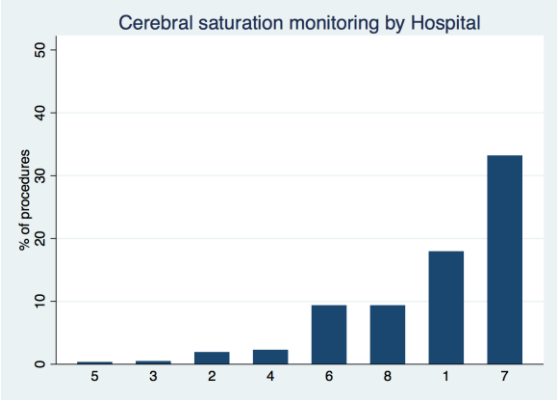


Figure 52. Cerebral saturation monitoring by Hospital. Note the vertical axis is truncated at 50%.

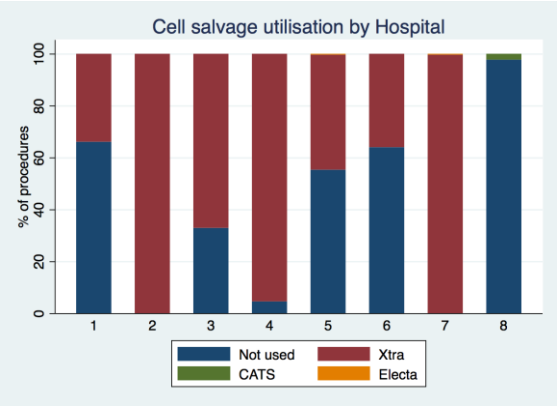


Figure 53. Cell salvage utilisation by Hospital. Large variation in use of cell salvage for core procedures.

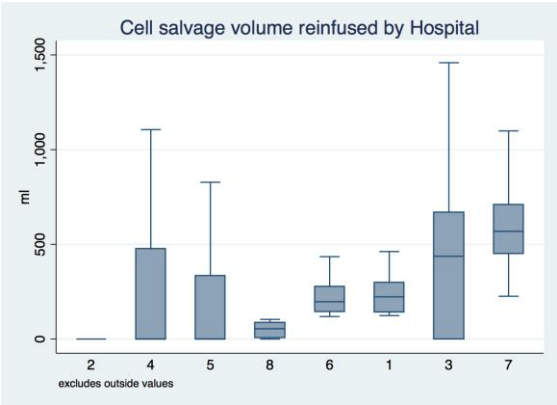


Figure 54. Volume of cell salvage blood reinfused by Hospital

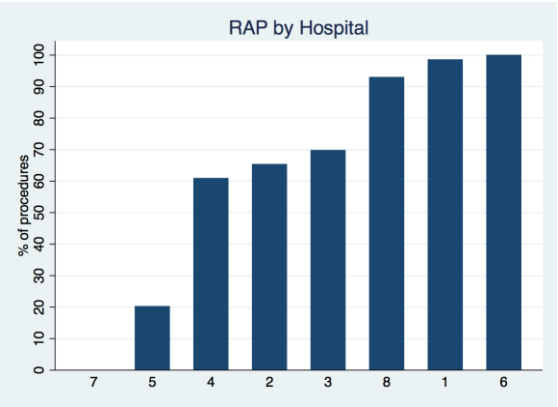


Figure 55. Retrograde autologous prime by Hospital. Large variation exists with the adoption of RAP.

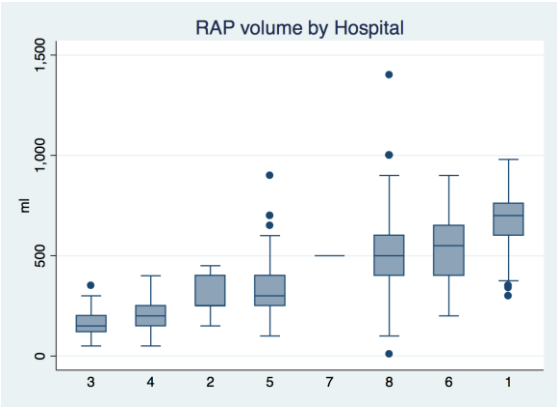


Figure 56. Retrograde autologous prime by Hospital. A similar variation exists in the volume removed. Note data displayed lowest volume to highest, not by Hospital number.

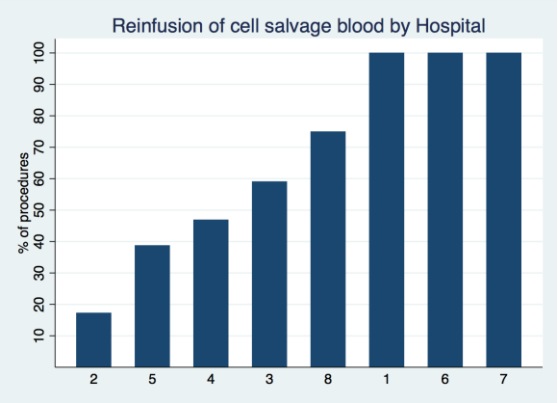


Figure 57. Cell salvage blood reinfusion by Site (in cases where cell salvage used).

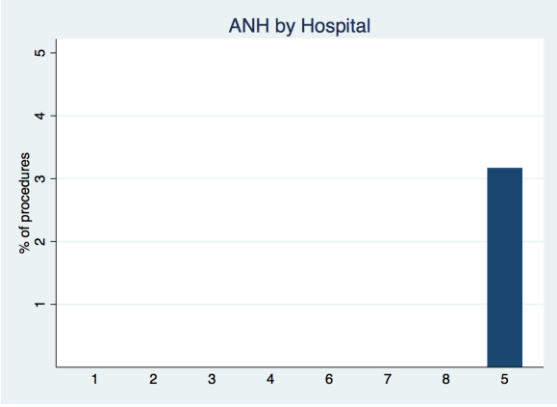


Figure 58. Acute normovolaemic haemodilution by Hospital

Note the vertical axis is truncated at 5%.

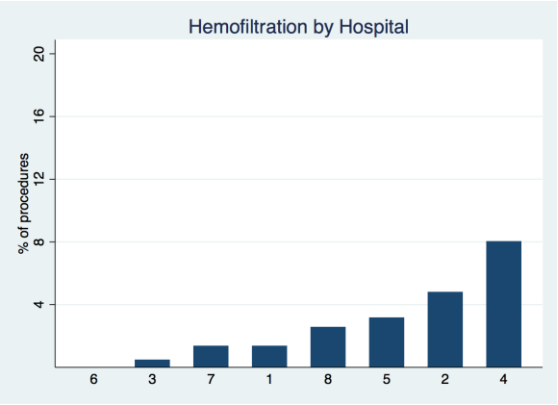


Figure 59. Hemofiltration by Hospital

Note the vertical axis is truncated at 20%.

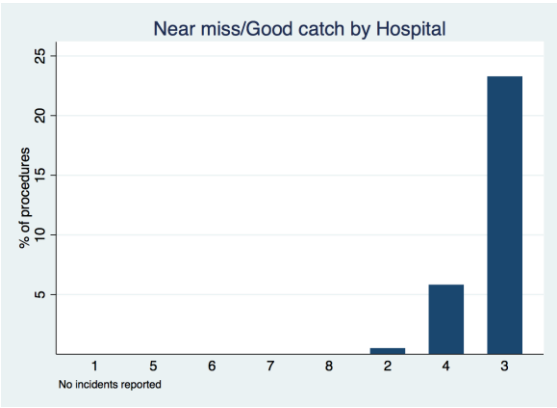


Figure 60. Incident by Hospital. The reporting rate for perfusion incidents remains very low.

Note the vertical axis is truncated at 10%.

Cardiopulmonary Bypass - Core Procedures

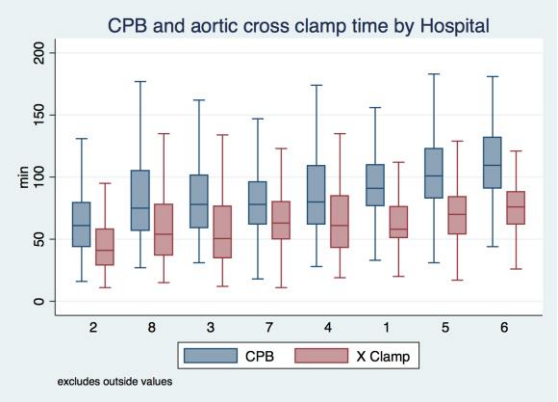


Figure 62. Cardiopulmonary bypass and aortic cross clamp time by Hospital

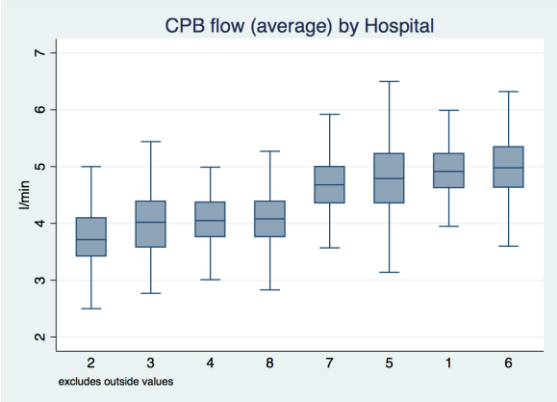


Figure 63. CPB flow (average) by Hospital.

The average flow varies considerably between high flow and lower flow units. This is reflected in average cardiac index, figure 75 and minimum DO_{2i} figure 76.

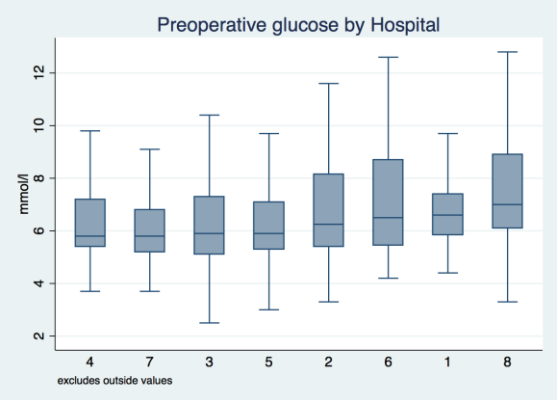


Figure 64. Preoperative glucose by Hospital

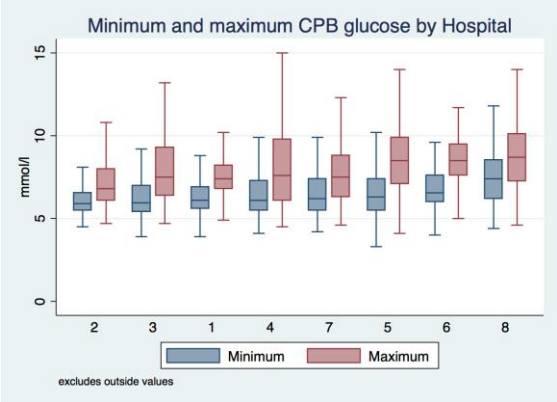


Figure 65. Minimum and maximum CPB glucose by Hospital.

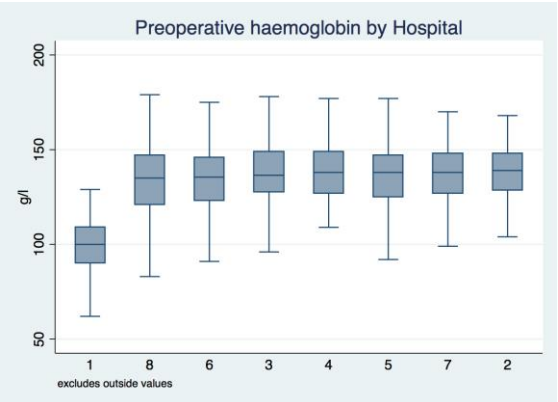


Figure 66. Preoperative haemoglobin by Hospital

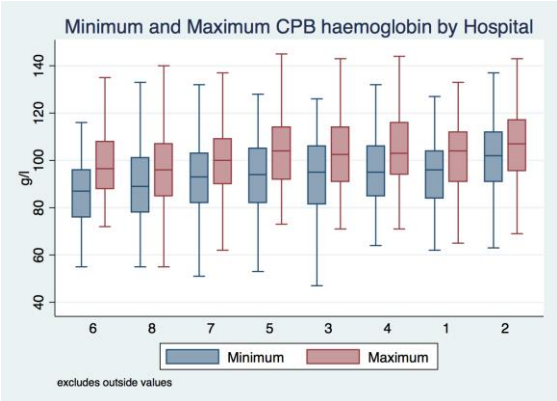


Figure 67. Minimum and maximum CPB haemoglobin by Hospital.

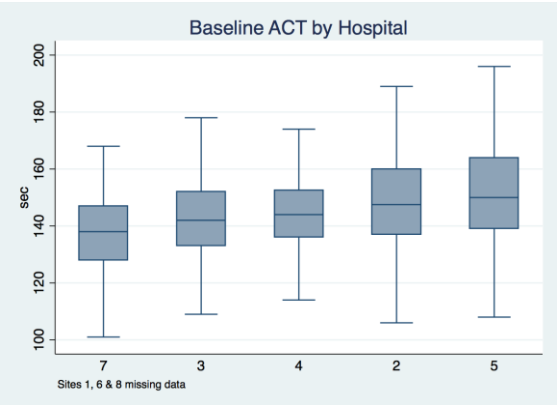


Figure 68. Baseline ACT by Hospital.

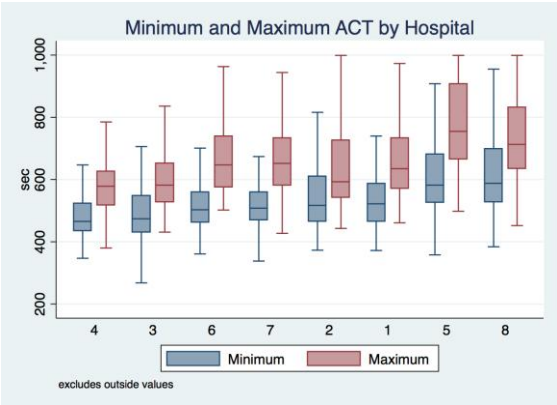


Figure 69. Minimum and maximum ACT by Hospital.

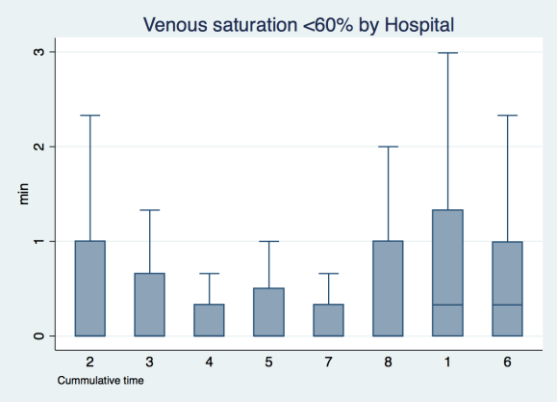


Figure 70. Venous saturation <60% by Hospital (cumulative time).

The number of minutes that cases are perfused with venous saturations less than 60% is small.

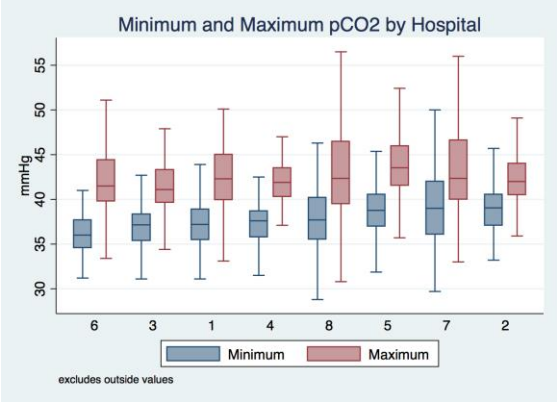


Figure 71. Minimum and maximum CPB pCO_2 by Hospital (intermittent blood gas measurements)

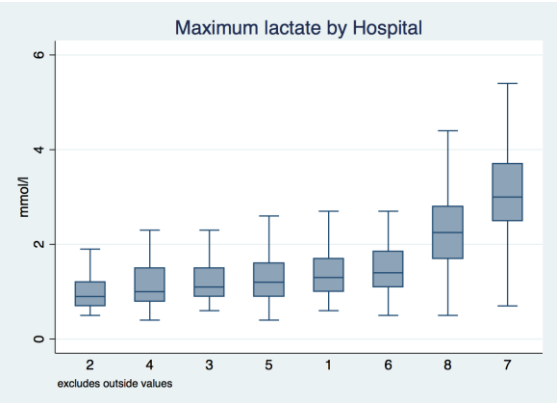


Figure 72. Maximum lactate by Hospital.

There is a large variation in the maximum lactate on bypass between Hospitals.

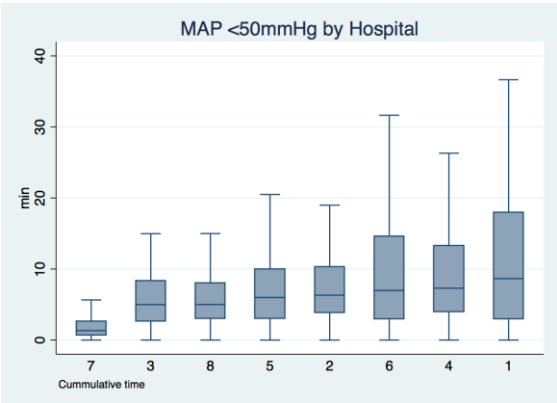


Figure 73. Mean arterial pressure <50mmHg by Hospital (cumulative time).

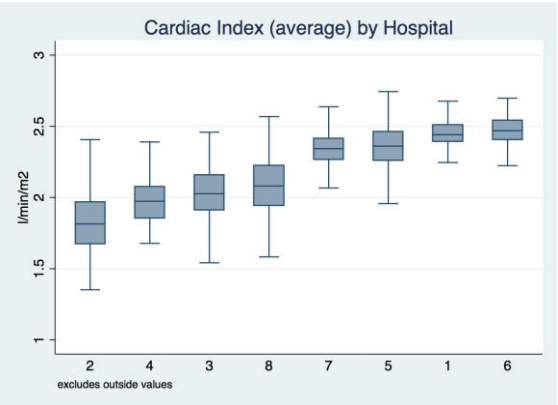


Figure 74. Average CPB cardiac index by Hospital.

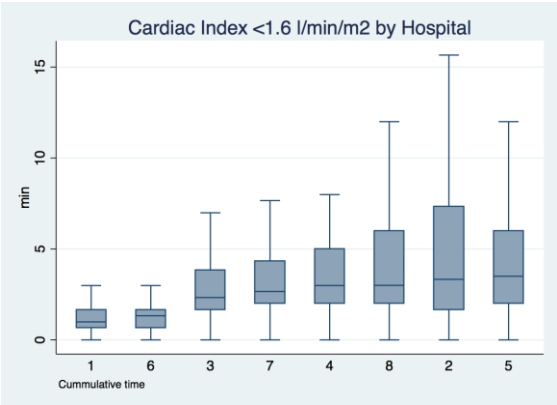


Figure 75. Cardiac index <1.6 l/min/m^2 by Hospital (cumulative time).

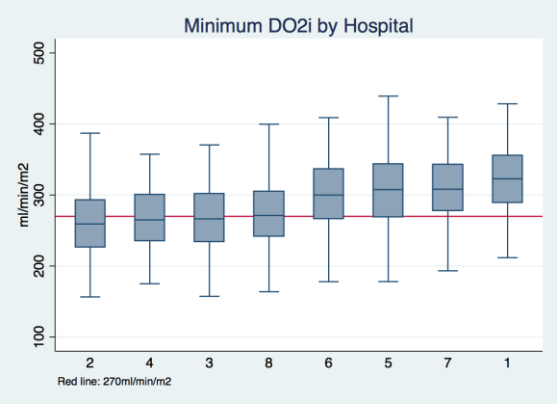


Figure 76. Minimum DO_{2i} by Hospital.

The calculated median DO_{2i} varies from a median value of approximately 250 to 320mmHg.

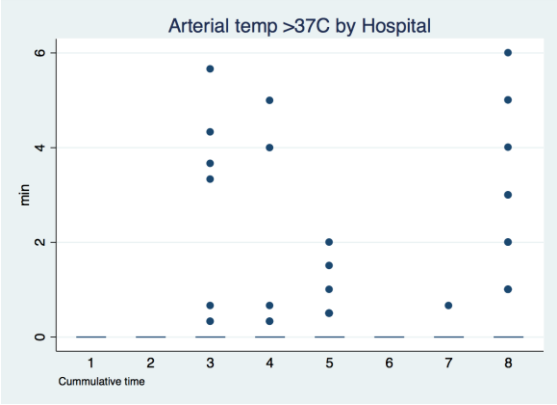


Figure 77. Arterial temperature >37C by Hospital (cumulative time).

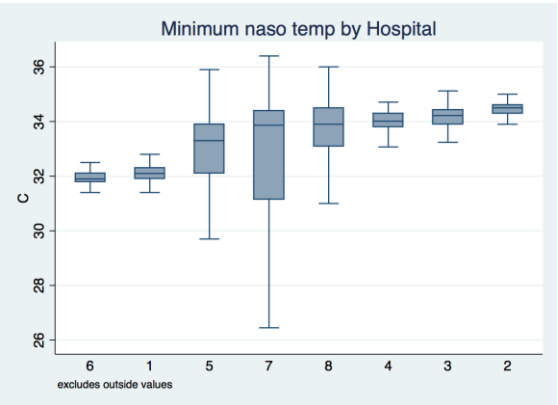


Figure 78. Minimum nasopharyngeal temperature for all core procedures by Hospital.

Min NP temperature on bypass varied from about 32°C to nearly 35°C.

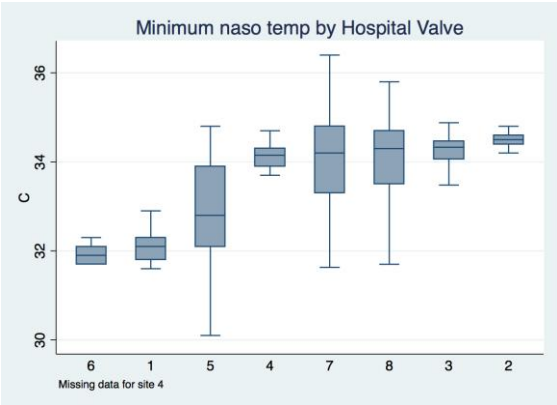


Figure 79. Minimum nasopharyngeal temperature by Hospital in isolated aortic and mitral valve procedures

Quality Indicators - Core Procedures

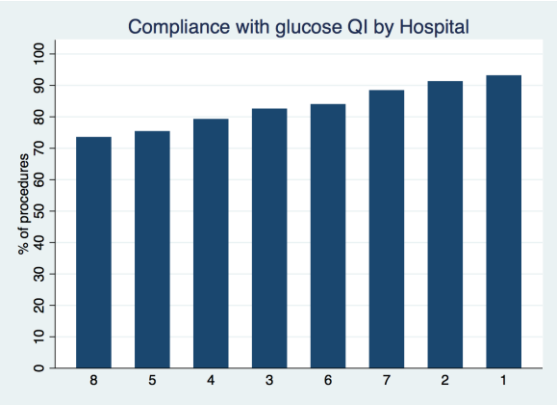


Figure 80a. Compliance with glucose QI by Hospital.

The quality indicator for blood glucose is measured as the compliance to maintaining a blood glucose level between 4 and 10 mmol/l.

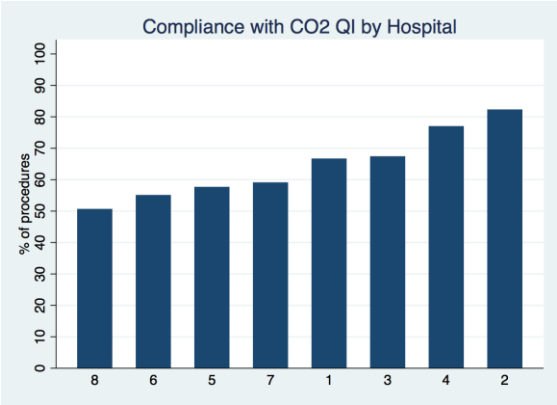


Figure 80b. Compliance with CO2 QI by Hospital

The quality indicator for CO2 management is measured as the compliance to maintaining a pCO2 during bypass of >=35 mmHg and <= 45 mmHg.

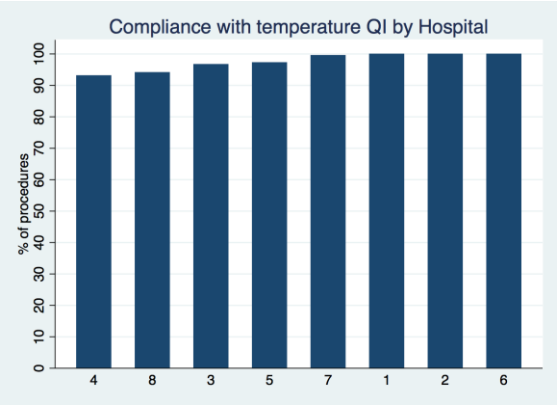


Figure 80c. Compliance with temperature QI by Hospital.

The quality indicator for temperature is measured as the compliance to maintaining an arterial outlet temperature less than 37°C.

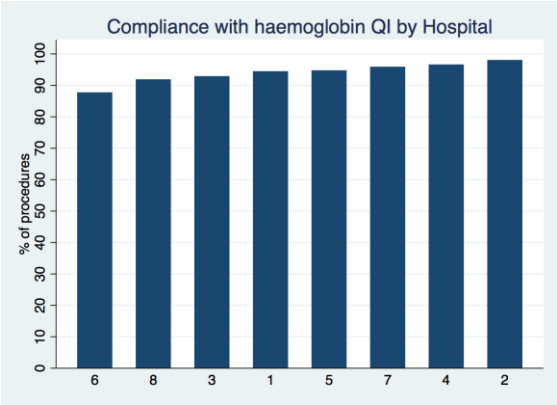


Figure 80d. Compliance with haemoglobin QI by Hospital.

The quality indicator for Hb management is measured as the compliance to maintaining Hb during bypass > 70g/l.

Outcomes - Core Procedures

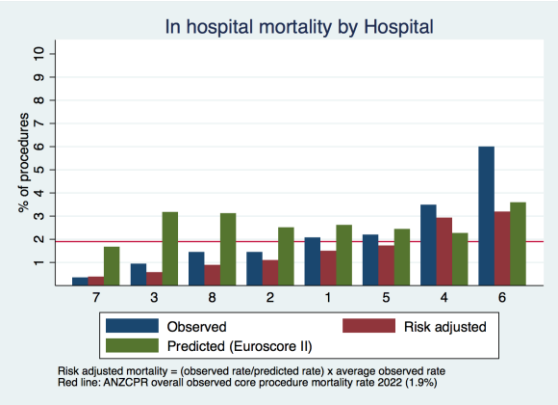


Figure 81. In hospital mortality by Hospital.
Note the vertical axis is truncated at 10%. Mortality data was missing for 0 patients. Predicted mortality is dependent on accuracy of collection and reporting of the risk factors that make up the risk model, when risk factors are missed the predicted mortality may be an underestimate of the risk score.

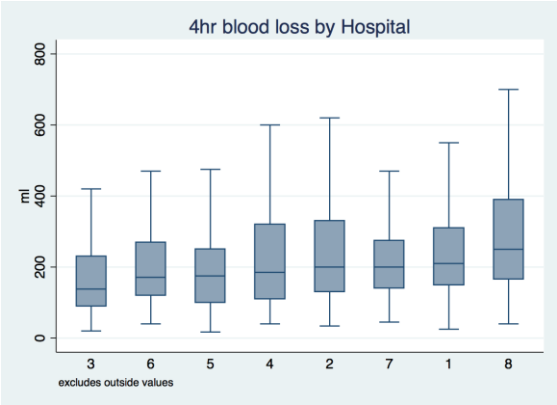


Figure 82. 4hr blood loss by Hospital

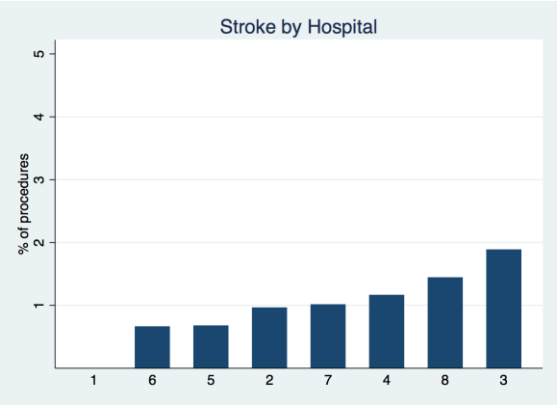


Figure 83. Postoperative Stroke by Hospital.
Note the vertical axis is truncated at 5%.

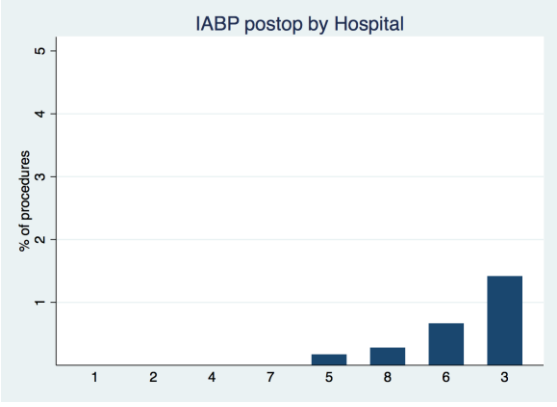


Figure 84. Intra-aortic balloon pump postop by Hospital. Note the vertical axis is truncated at 5%.

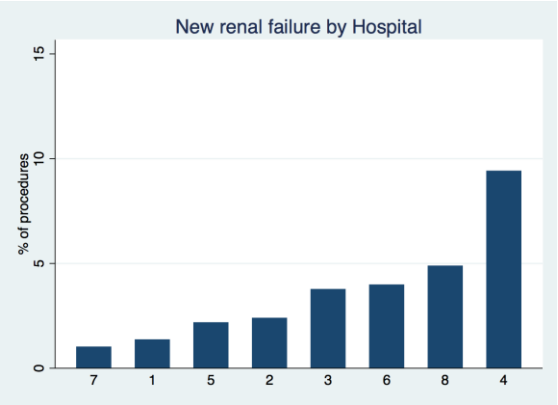


Figure 85. New renal failure by Hospital (ANZSCTS definition).

Defined as two or more of the following - a: Increased serum creatinine to >0.2mmol/l (>200mmol/l), b: A doubling or greater increase in creatinine over baseline pre-operative value, c: A new requirement for dialysis/haemofiltration. Note the vertical axis is truncated at 15%.

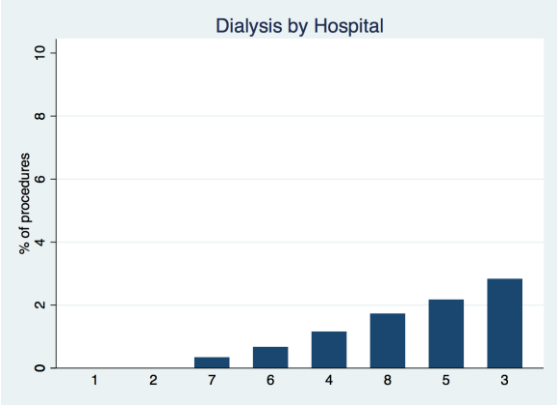


Figure 86. Postoperative dialysis by Hospital.

Note the vertical axis is truncated at 10%.

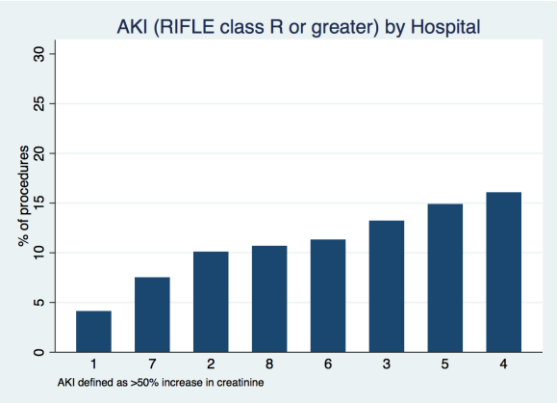


Figure 87a. Acute kidney injury by Hospital.

Note the vertical axis is truncated at 30%.

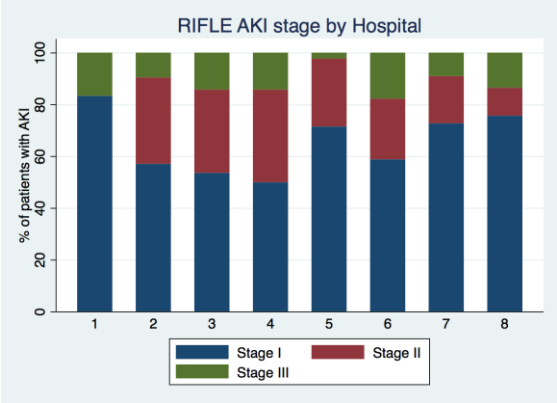


Figure 87b. Acute kidney injury stage by Hospital (in patients with AKI).

Transfusion - Core Procedures

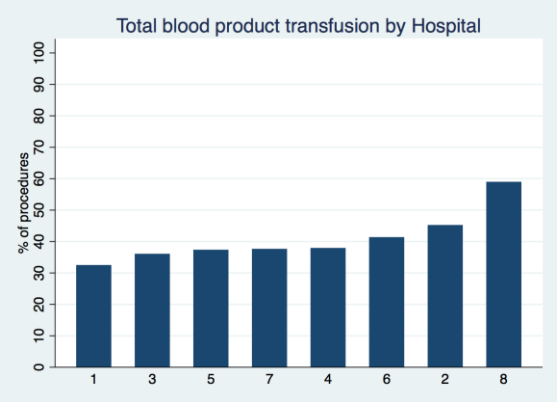


Figure 88. Total blood product transfusion by Hospital (RBC, FFP or platelets, intra or postop).

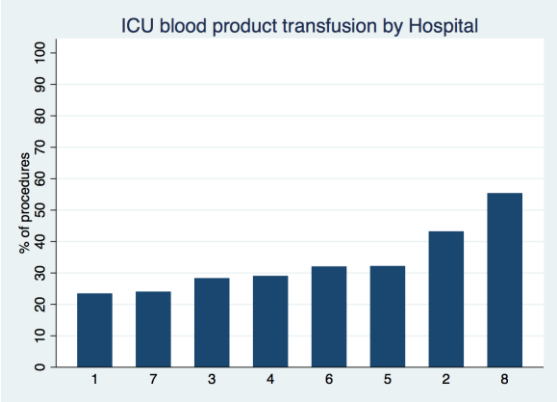


Figure 89. ICU blood product transfusion by Hospital (RBC, FFP, platelets).

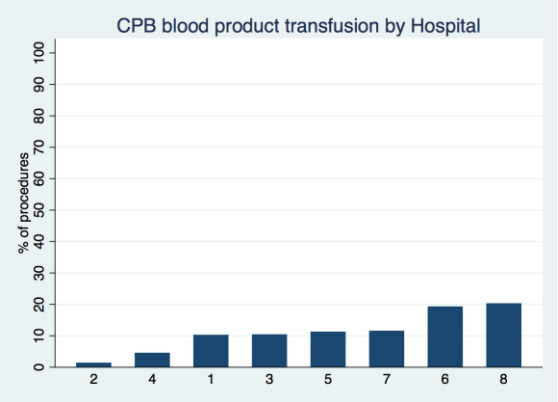


Figure 90. Perfusionist blood product transfusion by Hospital (RBC or FFP, prime or during CPB).

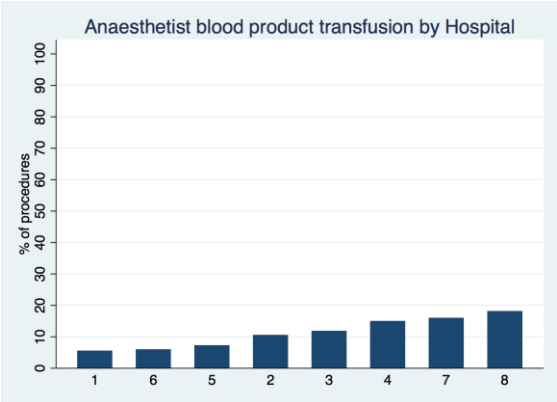


Figure 91. Anaesthesia blood product transfusion by Hospital (RBC, FFP, platelets).

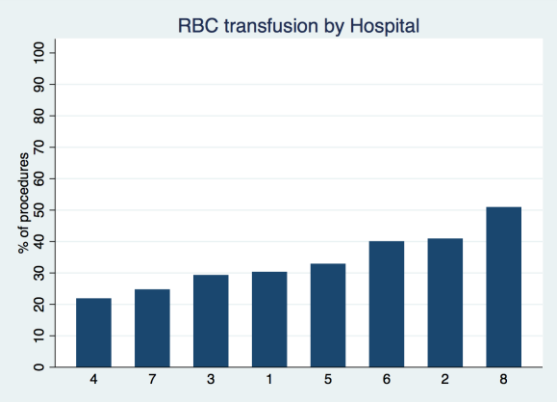


Figure 92. Total RBC transfusion by Hospital (intra or postop).

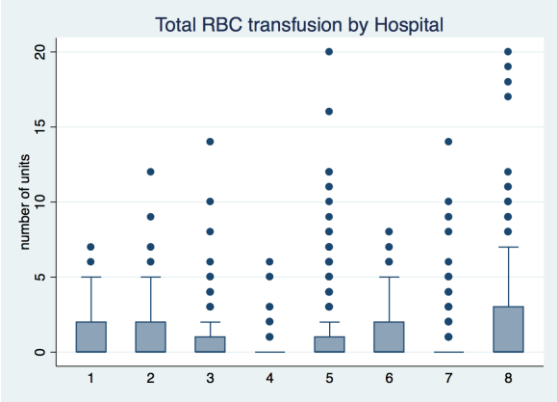


Figure 93. Total number of RBC transfusions by Hospital (intra or postop). Values >20 not shown.

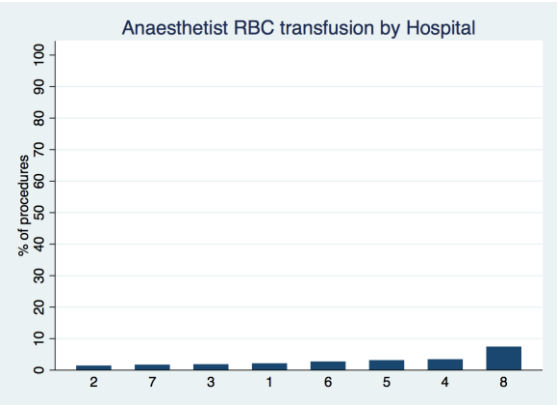


Figure 94. Anaesthesia RBC transfusion by Hospital.

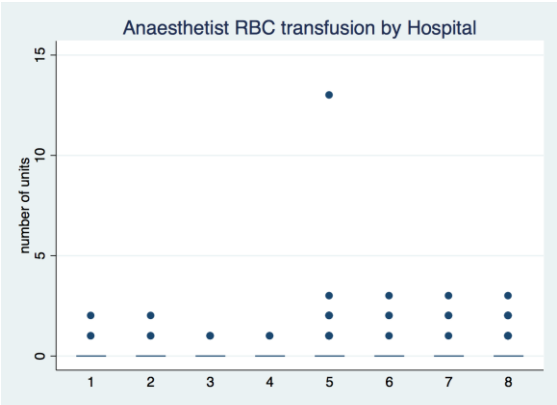


Figure 95. Anaesthesia number of RBC transfusions by Hospital.

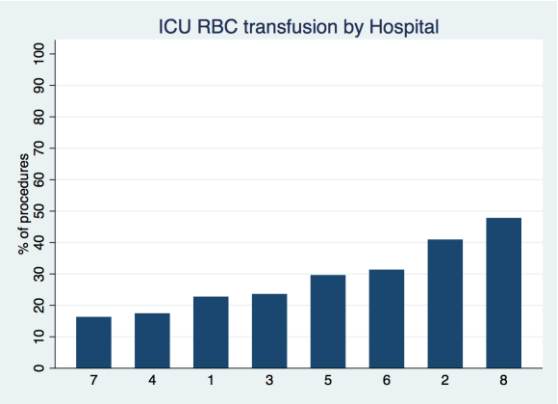


Figure 96. ICU RBC transfusion by Hospital.

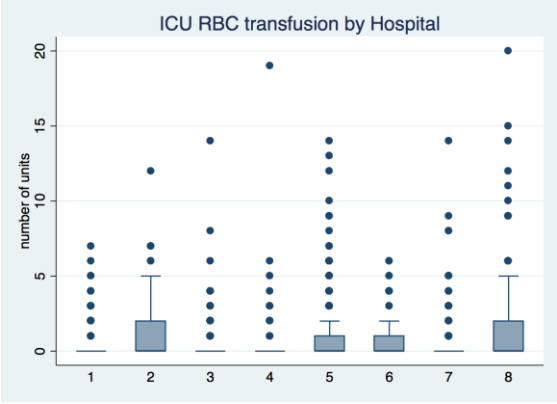


Figure 97. ICU number of RBC transfusions by Hospital. Values >20 not shown.

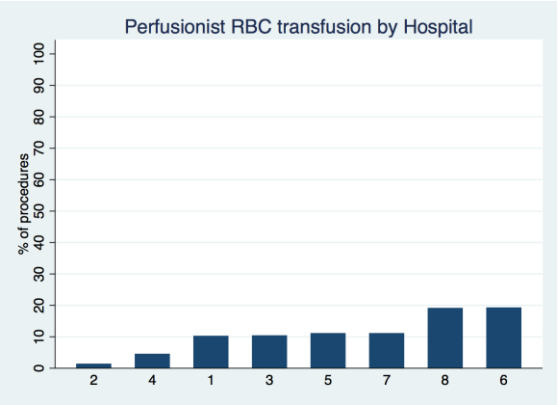


Figure 98. Perfusionist RBC transfusion by Hospital (prime or during CPB).

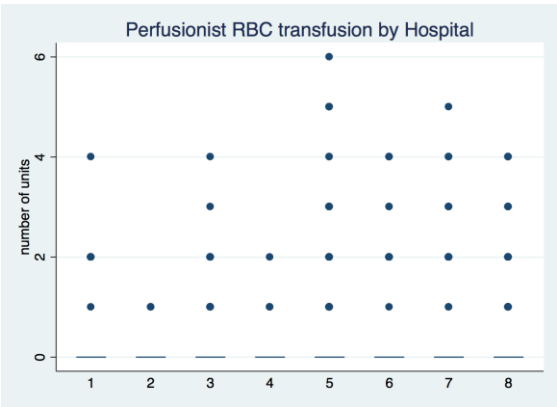


Figure 99. Perfusionist number of RBC transfusions by Hospital. Values >20 not shown.

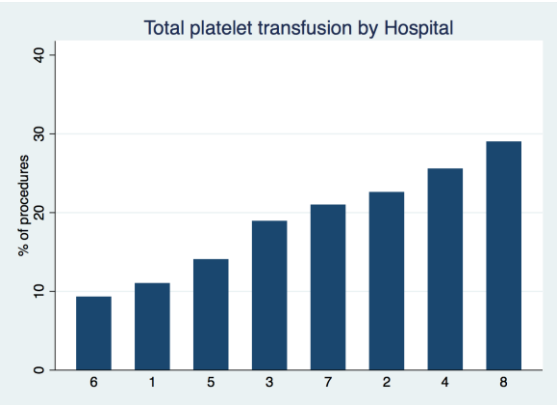


Figure 100. Total platelet transfusion by Hospital (intra or postop). Note the vertical axis is truncated at 40%.

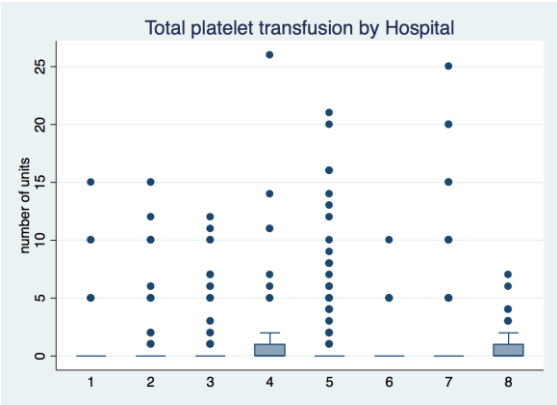


Figure 101. Total number of platelet transfusions by Hospital.

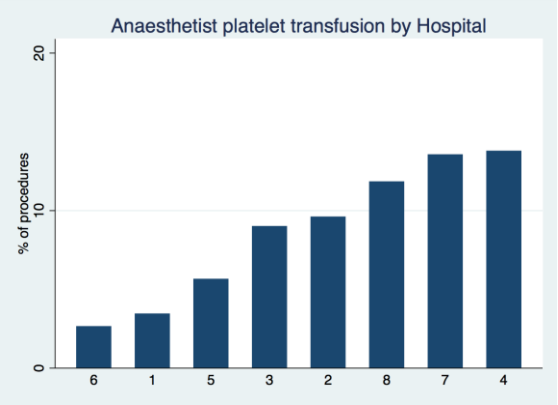


Figure 102. Anaesthesia platelet transfusion by Hospital.
Note the vertical axis is truncated at 20%.

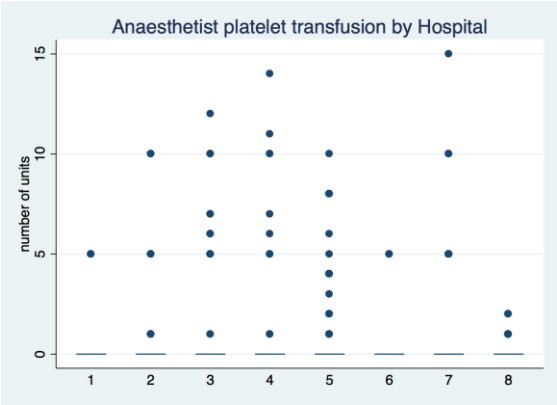


Figure 103. Anaesthetist number of platelet transfusions by Hospital.

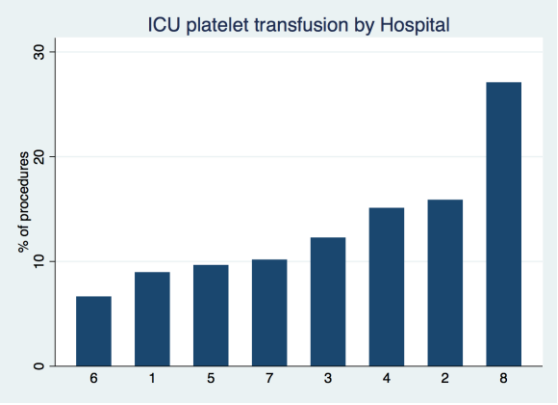


Figure 104. ICU platelet transfusion by Hospital. Note the vertical axis is truncated at 30%.

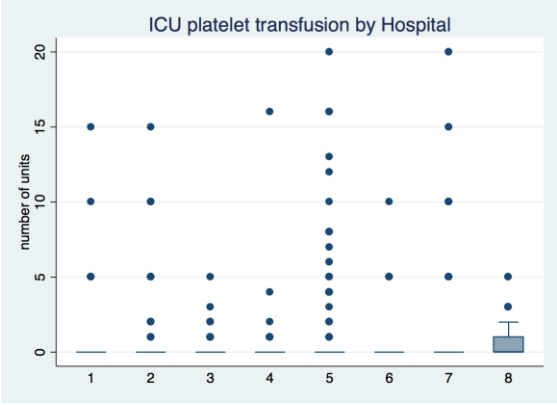


Figure 105. ICU number of platelet transfusions by Hospital.

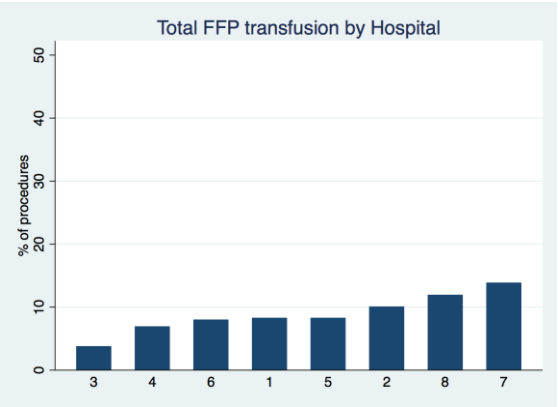


Figure 106. Total FFP transfusion by Hospital (intra or postop).

Note the vertical axis is truncated at 50%.

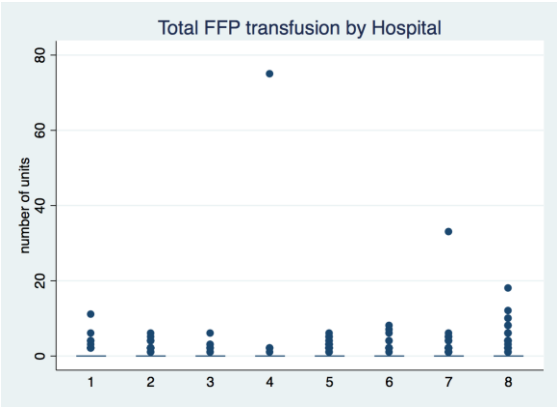


Figure 107. Total number of FFP transfusions by Hospital.

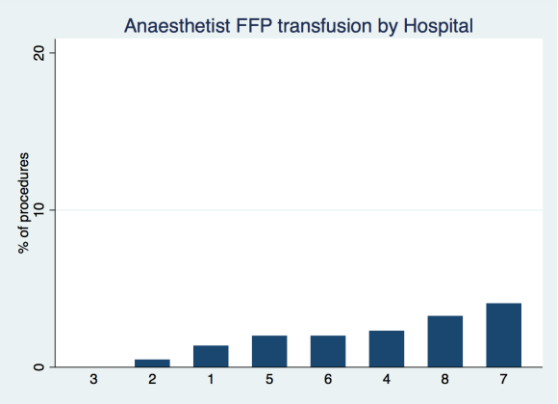


Figure 108. Anaesthesia FFP transfusion by Hospital.

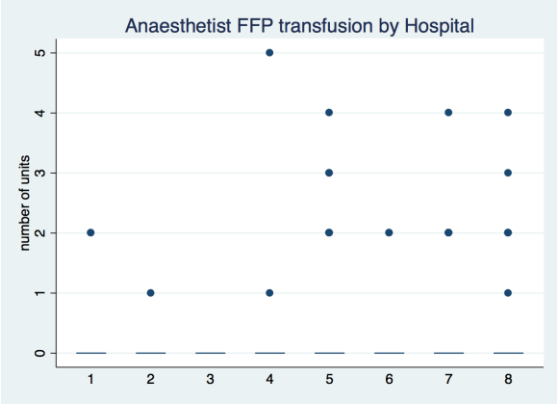


Figure 109. Anaesthesia number of FFP transfusions by Hospital.

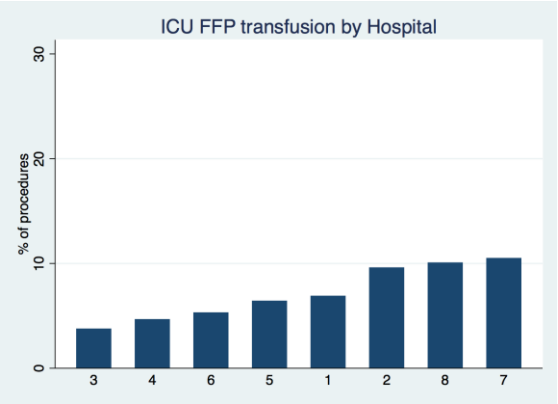


Figure 110. ICU FFP transfusion by Hospital.

Note the vertical axis is truncated at 30%.

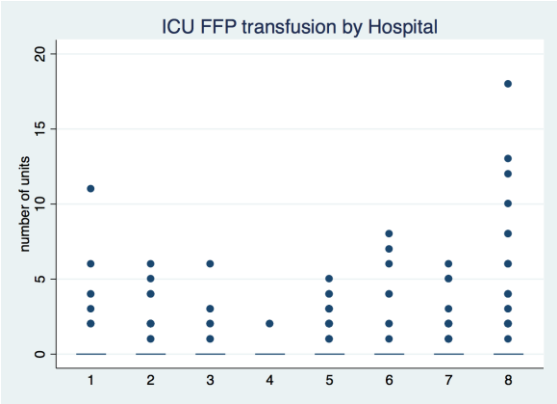


Figure 111. ICU number of FFP transfusions by Hospital.

Appendix 1

The following individuals have contributed to the ANZCPR as Perfusionists (P), Data Managers (DM) and/or Investigators (I) at each participating site as follows;

Ashford Hospital; Jane Ottens (I, P), Andrew Sanderson (DM, P);

Auckland City Hospital; Misty Bean (DM, I), Jude Clark (I), Taryn Evans (I), Nathan Ibbott (I), Alan Merry (I), Kathrine Morris (DM, I), Rachael van Uden (I), Timothy Willcox (I), Shuja Zahidani (I), Jill Chase (I), Luise van Wijk (I), Daryl Birchler (I), Alex Peterson (I), Danielle Blackie (I), Mark Greaves (I), Thomas Hick (I), James Holder (I), Hina Solanki (I), Ghaz Jabur (I), Cynthia Riddell (I), Camilla Hand (DM, I), Kate Rawlings (I), Maddie Dobier (DM, I);

Cabrini Private Hospital; James McMillan (P), Michael McDonald (DM, I, P), Smita Gavande (P), Kyriakos Angus-Anagnostou (P), Kamala Garfield (P), Vanessa Perafan (P), Emerson Sgammotta (P), Sreenivasulu Galaeti (P), Vijaykumar Valiyapurayil (P), Gil Giovinazzo (P), Adam Wells (P), Ravi Kapoor (P), Rowan Carpenter (P);

Flinders Private Hospital; Robert Baker (I, P), Kuljeet Farrar (DM, P), Richard Newland (I, DM, P), Jane Ottens (P), Andrew Sanderson (P), Annette Mazzone (P), Vijaykumar Valiyapurayil (P) ;

Flinders Medical Hospital; Robert Baker (I, P), Kuljeet Farrar (P), Roy Romanowicz (P), Richard Newland (DM, I, P), Vijaykumar Valiyapurayil (P), Annette Mazzone (P), Aidan Singh Howard (P), Jessica Betts (P);

Royal Hobart Hospital; Carmel Fenton (DM, I, P), Nick Carr (P), YiYi Huang (DM, P);

Royal Perth Hospital; Samantha Bizzell (P), Stuart Prince (DM, I, P), Viji Vincent (P), Brian Wright (P);

The Alfred Hospital; James Anderson (P), Robin McEgan (P), Mark Mennen (P), Jessica Underwood (P), Wendy Saad (P), Nicholas Carr (DM, P), Joshua Byrne (DM, P, I);

Westmead Hospital; Grace Agbulos (P), Orison Kim (P), Monique Brouwer (P), Rona Steel (DM, I, P), Ray Miraziz (P) Peter Klineberg (I), Jeremy Field (I):

Appendix 2

2023 Missing data report (Data 2022)								
Site	1	2	3	4	5	6	7	8
Variable	% missing	% missing	% missing	% missing	% missing	% missing	% missing	% missing
Clinical								
Sex	0.0	0.0	0.0	0.0	0.5	0.0	0.0	1.4
Ethnicity	0.7	0.0	3.8	0.0	0.2	0.0	0.3	missing
Resp_dis	0.0	0.0	0.0	0.0	0.2	0.0	0.0	4.1
Prev_cards~g	0.0	0.0	0.0	1.2	0.2	0.0	0.0	4.1
Inf_endo	0.0	0.0	0.0	0.0	0.2	0.0	0.0	4.1
Act_endo	0.0	0.0	0.0	0.0	0.2	0.0	0.0	0.0
Crit_preop	0.0	0.0	0.0	1.2	0.2	0.0	0.0	2.8
Unst_ang	0.0	0.0	0.0	1.2	0.2	0.0	0.0	0.0
LV_func	0.0	0.0	0.0	0.0	0.2	0.0	0.0	4.7
MI	0.0	0.0	0.0	0.0	0.2	0.0	0.0	4.1
MIrecent	0.0	0.0	0.0	0.0	0.2	0.0	0.0	4.1
Emerg	0.0	0.0	0.0	0.0	0.2	0.0	0.0	4.1
Pulm_hyp	0.0	0.0	0.0	0.0	0.2	0.0	0.0	2.8
Smokhist	0.0	0.0	0.9	0.0	4.5	0.0	0.0	10.2
Smokcurr	0.0	0.0	0.9	0.0	2.8	0.0	0.0	11.1
Diabet	0.0	0.0	0.0	0.0	0.2	0.0	0.0	4.1
Diabcont	0.0	0.0	0.0	1.2	0.2	0.0	0.0	4.1
Hypchol	0.0	0.0	0.0	0.0	0.2	0.0	0.0	4.1
Hypert	0.0	0.0	0.0	0.0	0.2	0.0	0.0	4.1
Strokhist	0.0	0.0	0.5	1.2	0.2	0.0	0.0	0.0
Angina	0.0	0.0	0.0	1.2	0.2	0.0	0.0	4.1
CVD	0.0	0.0	0.5	0.0	0.2	0.0	0.0	4.1
CVDtype	0.0	0.0	0.5	1.2	0.2	0.0	0.0	4.1
CVDwhen	0.0	0.0	0.5	0.0	0.2	0.0	0.0	0.0
PVD	0.0	0.0	0.0	0.0	0.2	0.0	0.0	4.1
Dialysis_pre	0.0	0.0	0.0	0.0	0.2	0.0	0.0	4.1
Prev_card	0.0	0.0	0.0	0.0	0.2	0.0	0.0	0.0
CHF	0.0	0.0	0.0	0.0	0.2	0.0	0.0	4.1
JW	0.0	0.0	0.0	0.0	0.2	0.0	0.0	3.6
NYHA	0.0	0.0	0.0	0.0	0.2	0.0	0.0	4.1
Procedure								
Proctype	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
LIMA	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
RIMA	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
RADG	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
GEPA	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
AVR	0.0	0.0	0.0	0.0	0.2	0.0	0.0	2.8
MVR	0.0	0.0	0.0	0.0	0.2	0.0	0.0	3.0
Mvrep	0.0	0.0	0.0	0.0	0.2	0.0	0.0	3.0
AortOcc	0.0	0.0	0.5	1.2	0.3	0.0	0.0	2.8
CCAB	0.0	0.0	0.0	0.0	0.0	0.0	0.0	4.1
Perfusion								
Myo_prot	0.0	0.0	0.5	0.0	0.0	0.0	0.0	2.8
HotShot	0.0	0.0	0.5	0.0	0.0	0.0	0.0	0.0
pH_strat	0.0	0.0	0.0	0.0	0.0	0.0	0.0	5.0
PSB_all	0.0	0.0	0.9	0.0	0.0	0.0	0.0	0.0
Artfilt	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Reserv	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Pump	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Coat	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Coattype	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
CoatOx	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Bgmon	0.0	1.9	1.9	1.2	0.0	0.0	0.0	0.0
SVo2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
rCRMO2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
BIS	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Hemofilter	0.0	0.0	0.0	0.0	0.0	0.0	0.0	3.0
AortCan	0.0	0.0	0.5	0.0	0.2	0.0	0.0	2.8
FemartCan	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
AxilCan	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
AtrCan	0.0	0.0	0.5	0.0	0.0	0.0	0.0	2.8
VothCan	0.0	0.0	0.5	0.0	0.0	0.0	0.0	2.8
ACTtype	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
ACTdevice	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Incident	0.0	0.0	4.7	1.2	0.3	0.0	0.0	3.3
PIRSrep	0.0	0.0	4.7	1.2	0.3	0.0	0.0	41.2
Csaver	0.0	0.0	0.0	0.0	0.7	0.0	0.0	2.8
Flowtype	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
RAP	0.0	0.0	0.0	0.0	0.3	0.0	0.0	5.0
Oxygenator	0.0	0.0	0.0	0.0	0.0	0.0	0.0	missing
Flowtype	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
PrimeVol	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.3
PrimeTot	0.0	0.0	0.0	0.0	0.3	0.0	0.0	0.3

Site	1	2	3	4	5	6	7	8
Variable	% missing	% missing	% missing	% missing	% missing	% missing	% missing	% missing
Perfusion (continued)								
NetPrime	0.0	0.0	0.5	0.0	0.3	0.0	0.0	5.0
Artmax	2.1	1.4	0.9	0.0	0.8	1.3	28.8	2.2
Cptype	0.0	0.0	0.0	0.0	0.0	0.0	0.0	3.3
Csaver	0.0	0.0	0.0	0.0	0.7	0.0	0.0	2.8
RAP	0.0	0.0	0.0	0.0	0.3	0.0	0.0	5.0
RapVol	0.0	0.0	0.5	0.0	0.0	0.0	0.0	4.7
ANH	0.0	0.0	0.0	0.0	0.2	0.0	0.0	0.0
Incid	0.0	0.0	4.7	1.2	0.3	0.0	0.0	3.3
CPB_time	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
X_time	0.0	0.5	1.9	0.0	0.7	0.7	0.7	0.3
Creatpre	0.0	0.0	0.0	0.0	0.0	0.0	0.7	4.1
Glucpre	0.7	0.0	0.9	0.0	1.8	20.0	1.0	4.4
Glucmin	0.0	0.0	0.0	0.0	0.5	0.0	0.0	20.4
Glucmax	0.0	0.0	0.0	0.0	0.5	1.3	0.0	20.4
Hbpreop	0.0	0.0	0.0	0.0	0.0	0.0	0.0	4.1
Hbmin	0.0	0.0	0.0	0.0	0.3	0.0	0.0	20.7
Hbmax	0.0	0.0	0.0	0.0	0.3	0.0	0.0	20.7
ACTmin	0.0	1.0	0.9	1.2	1.5	0.0	0.0	21.3
ACTmax	0.0	1.0	0.9	1.2	0.5	0.0	0.0	1.9
Lacmax	0.7	0.0	0.0	0.0	0.8	1.3	0.7	20.4
venSat	2.1	0.0	0.0	0.0	0.0	0.0	0.0	2.2
Flowavg	2.1	0.0	0.5	0.0	1.0	1.3	20.3	3.0
MAPavg	2.1	0.0	1.9	0.0	2.2	1.3	9.2	6.4
Hypoten50	2.1	0.0	0.0	0.0	0.0	0.0	0.0	6.4
minDO2	2.1	0.0	0.9	0.0	1.0	1.3	20.3	3.0
ArtGt37	2.1	0.0	0.0	0.0	0.7	0.7	0.7	6.1
Nasomin	2.8	0.5	3.3	0.0	4.2	1.3	8.5	7.2
GlucY	0.0	0.0	0.0	0.0	0.5	0.0	0.0	20.4
TempY	2.1	0.0	0.0	0.0	0.7	0.7	0.7	6.1
CO2Y	0.7	0.0	0.0	0.0	1.3	0.7	0.7	20.4
ACTbase	97.9	0.0	0.5	3.5	0.3	92.0	26.1	83.2
Antifibtype	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
PCO2min	0.7	0.0	0.0	0.0	1.3	0.7	1.0	20.4
PCO2max	0.7	0.5	0.0	0.0	1.5	0.7	1.7	20.4
Clavg	2.1	0.0	0.9	0.0	1.0	1.3	20.3	3.0
Cl	2.1	0.0	0.0	0.0	0.0	0.0	0.0	0.3
HbY	1.4	0.5	1.4	0.0	1.5	2.0	2.0	22.1
Outcomes								
postIABP	0.0	0.0	0.0	0.0	1.5	0.0	0.0	0.0
Creat50	0.0	0.0	0.0	0.0	1.8	0.0	1.0	4.4
ICUBloss	3.5	0.5	2.4	1.2	3.3	2.7	0.3	4.1
Stroke	0.0	0.0	0.0	1.2	1.7	0.0	0.0	4.1
Death	0.0	0.0	0.0	1.2	1.5	0.0	0.0	4.1
Newrenal	0.0	0.0	0.0	2.3	1.5	0.0	0.0	4.1
Dialysis_pre	0.0	0.0	0.0	0.0	0.2	0.0	0.0	4.1
CKD	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
AnyTrans	0.0	0.0	0.5	0.0	1.7	0.0	0.0	5.3
CPBTrans	0.0	0.0	0.0	0.0	0.0	0.0	0.0	3.0
ANTrans	0.0	0.0	0.5	0.0	0.2	0.0	0.0	7.2
ICUTrans	0.0	0.0	0.0	1.2	1.7	0.0	0.0	4.1
AnyRCC	0.0	0.0	0.5	0.0	1.7	0.0	0.0	5.5
ORRCC	0.0	0.0	0.5	0.0	0.0	0.0	0.0	3.6
ANRCC	0.0	0.0	0.5	0.0	0.2	0.0	0.0	6.9
ICURBC	0.0	0.0	0.0	1.2	1.7	0.0	0.0	4.1
AnyFFP	0.0	0.0	0.5	0.0	1.7	0.0	0.0	9.7
CPBFFP	0.0	0.0	0.0	0.0	0.0	0.0	0.0	3.0
ANFFP	0.0	0.0	0.5	0.0	0.2	0.0	0.0	6.6
ICUFP	0.0	0.0	0.0	1.2	1.7	0.0	0.0	4.1
AnyPlate	0.0	0.0	0.5	1.2	1.8	0.0	0.0	7.7
ANPlate	0.0	0.0	0.5	0.0	0.2	0.0	0.0	6.6
ICUPlt	0.0	0.0	0.0	1.2	1.7	0.0	0.0	4.1
RBCnum	0.0	0.0	0.5	1.2	1.8	0.0	0.0	11.3
ANRBCnum	0.0	0.0	0.5	0.0	0.2	0.0	0.0	6.9
ORRBCnum	0.0	0.0	0.0	0.0	0.0	0.0	0.0	3.0
ICURCC	0.0	0.0	0.0	1.2	1.7	0.0	0.0	4.1
FFPnum	0.0	0.0	0.5	1.2	1.8	0.0	0.0	10.8
FFPUnitsCPB	0.0	0.0	0.0	0.0	0.0	0.0	0.0	3.0
FFP	0.0	0.0	0.5	0.0	0.2	0.0	0.0	6.6
ICUFFP	0.0	0.0	0.0	1.2	1.7	0.0	0.0	4.1
Platenum	0.0	0.0	0.5	1.2	1.8	0.0	0.0	10.8
Platelets	0.0	0.0	0.5	0.0	0.2	0.0	0.0	6.6
ICUPlate	0.0	0.0	0.0	1.2	1.7	0.0	0.0	4.1

Data Harvest Jan-Dec 2022. Published July 2023.