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Creating a Multivariable Model to Predict Primary Graft Dysfunction after Heart Transplantation in the United Kingdom using the 2014 International Society of Heart and Lung Transplantation Consensus Definition

A Thesis submitted to

The University of Glasgow

for the degree of

DOCTOR OF PHILOSOPHY

Student GUID:

Sanjeet Singh Avtaar Singh

Abstract

Heart failure places a global strain on healthcare provision. It has an increasing incidence and represents the endpoint of a variety of cardiovascular diseases. The preceding decades have carved out a clear management algorithm for the use of pharmacotherapies (neurohormonal antagonists), device-based therapies (Implantable Cardioverting Defibrillator (ICD) and Cardiac Resynchronisation Therapy (CRT)) and mechanical therapies including left ventricular assist devices and heart transplantation. While heart transplantation remains the gold standard for the suitable few, the advancement of healthcare systems and improved working conditions and safety regulations have changed the demographics of the typical organ donor which traditionally were young brainstem death donors (DBD) with minimal other comorbidities. Nevertheless, transplantation confers a substantial survival benefit for selected patients with advanced heart failure, achieving a 1-year survival rate of ≥80%.

The primary cause for early mortality in recipients remains primary graft dysfunction (PGD). The incidence of PGD throughout the UK and the world are variable due to the lack of a standardised definition until 2014.

My research explored the true incidence of PGD throughout the UK using data collected from each of the 6 transplant centres alongside the National Health Service Blood and Transplant database. I then looked at risk factors for PGD which culminated in the largest PGD study recorded at the time of writing. I also looked into the role of mechanical circulatory support to bridge patients in cardiogenic shock post-myocardial infarction in Scotland. I finally developed 2 scoring systems, 1 for Primary Graft Dysfunction (PREDICTA) and 1 using the modified Delphi Method of a consensus agreement (GTS) to factor in elements of frailty which had been garnering increasing interest at conferences I had attended.

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Acknowledgement

I wish to thank my supervisors Professor Nawwar Al-Attar and Professor Colin Berry for their continuous support and guidance throughout the past few years. Professor Al-Attar has been instrumental as a mentor both surgically and academically, entrusting me with several responsibilities in ensuring that the journey of these research years was fulfilling and rewarding.

Professor Colin Berry was constantly available whenever help was sought, from the initial setting of selecting a research question to review every manuscript and providing additional resources afforded by the University of Glasgow.

I also wish to extend my sincerest gratitude to Dr. Nicholas Banner and Mrs. Sally Rushton, who were instrumental in steering the Cardiothoracic Advisory Group (CTAG) Audit Committee, which allowed me to access resources available to NHS Blood and Transplant.

The transplant teams at all 6 cardiothoracic transplant centres played a major part in ensuring I was well supported and had the resources to collect the data required for this thesis. They include

1) Freeman Hospital (Professor John Dark, Mr. Tanvir Butt, Dr Gareth Parry)

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3) Papworth Hospital (Mr. Steve Tsui, Dr. Jayan Parameshwar, Mr. Pedro Catarino)

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5) Wythenshawe Hospital, Manchester (Mr. Rajamiyer Venkateswaran, Mrs. Joanne Hasan)

6) Golden Jubilee National Hospital (Professor Nawwar Al-Attar, Mr. Philip Curry)

I wish to also thank all the transplant coordinators for their diligent efforts in procuring patient notes for data collection.

On a personal note, I wish to thank my wife, Manreet for her endless support and insightful reviews. I also wish to thank my entire family, Mum and Dad alongside my sisters, Sangeeta and Kaveeta who have supported me through every milestone in life.

Author's Declaration

The Primary Graft Dysfunction study was conceived and developed by Professor Al-Attar, Dr. NR Banner and Dr. Jennifer Mehew (nee Lannon) and funded by a grant from NHS Scotland. I was appointed as a Cardiothoracic Advisory Group (CTAG) Audit Fellow for the study through a competitive application process.

From May 2015 I became responsible for all aspects of the conduct of the study. This included adapting and implementing the study design, liaising with all 6 recipient centres and NHS Blood and Transplant. I ensured that Research Sponsorship was maintained and that the regulatory requirements of the University of Glasgow were met. I conducted a literature review on Primary Graft Dysfunction based on the International Society of Heart and Lung Transplantation (ISHLT) 2014 consensus statement. Using this, I reported back to my supervisors with a list of variables of interest. We obtained some of these data from NHS Blood and Transplant. Other important details were collected from each centre individually. I also developed a programmed Excel sheet to assist in the classification of PGD for each centre to allow prospective analysis of PGD for future use.

I designed the data collection forms and provided teaching updates to staff regarding the ISHLT 2014 consensus statement of PGD. I provided them with direct access to me via email and phone from September 2015 through to close of recruitment in November of 2018.

I reported progress on recruitment, data quality, data analysis and study conduct to the audit team on a monthly basis and compiled a 6-monthly update for the Cardiothoracic Transplant Advisory Group at NHSBT. I was responsible for identifying any problems at an early stage, proposing solutions through discussion with my supervisors and then implementing them. My-day to-day work was assisted by the specialist nurse practitioners for organ donation and recipient co-ordinators, transplant fellows and database managers.

I designed a password protected spreadsheet that stored data on 613 donors with >18000 data fields. I validated the data and identified missing data for follow up.

Statistical analysis was performed by myself under the supervision of Dr. Mehew, and then Mrs. Sally Rushton who later took over.

I learnt how to use SPSS and MINITAB alongside the statistical methodology required under the supervision of a statistician (Mrs. Rushton) and undertook all the data analysis and reporting.

I received support from my supervisors and other key people and this is illustrated throughout the thesis.

I was nominated for the European Association of Cardiothoracic Surgery (EACTS) Young Investigator award in 2017(Semi-finalist) and 2018 for some of the work in this thesis. Chapters that have been published and/or presented are indicated in the Publications and Presentations section.

Presentations and Publications

Presentations

2019

19th Annual Congress of the European Society of Organ Transplantation (ESOT)

- Cold Antegrade Myocardial Perfusion to Reduce Primary Graft Dysfunction After Heart Transplantation

39th International Society of Heart and Lung Transplantation (ISHLT) Annual Meeting Orlando, USA

- Keeping It Cool: Extended Myocardial Protection with Topical Cooling to Reduce PGD
- Survival after Primary Graft Dysfunction (PGD) in Heart Transplantation
- Can Donor Step Up Pressure Predict Primary Graft Dysfunction in Recipients Post Heart Transplantation

Society of Cardiothoracic Surgery of Great Britain and Ireland (SCTS) Annual Meeting, London, UK

- Are Donor Step-Up pressures reliable markers for post-operative Primary Graft Dysfunction in recipients?
- Survival after Primary Graft Dysfunction (PGD) in Heart Transplantation.
- Cool Aid: extended myocardial protection with topical cooling to reduce PGD

2018

32nd European Association of Cardiothoracic Surgery (EACTS) Annual Meeting 2018, Milan, Italy

- The Glasgow Experience of extended myocardial protection: A novel method of implantation to reduce primary graft dysfunction after heart transplantation
  (Nominated for Young Investigator of the Year)

- Validation of a model to predict Primary Graft Dysfunction after adult heart transplantation in the United Kingdom
  (Nominated for Young Investigator of the Year)

2018 **38th International Society of Heart and Lung Transplantation (ISHLT) Annual Meeting, Nice, France**

- Donor Right Ventricular Stroke Work Index (RVSWI) is a poor predictor of Primary Graft Dysfunction (PGD) after heart transplantation

- Validation of a model to predict Primary Graft Dysfunction (PGD) after adult heart transplantation in the United Kingdom

- The impact of gender mismatch on survival in heart transplantation

2018 **Society of Cardiothoracic Surgery of Great Britain and Ireland (SCTS) Annual Meeting, Glasgow, UK**

- The impact of gender mismatch on survival in heart transplantation

- Validation of a model to predict Primary Graft Dysfunction (PGD) after adult heart transplantation in the United Kingdom

- The Role of Mechanical Circulatory Support (MCS) as a Bridge to Decision in Cardiogenic shock (CS) after ST-Elevation Myocardial Infarction (STEMI) at a National Referral Centre

2017 **European Association of Cardiothoracic Surgery (EACTS) Annual Meeting 2017, Vienna, Austria**

- Mechanical circulatory support for post-acute myocardial infarction with refractory cardiogenic shock – A decade of lessons
  (Semi-finalist for Young Investigator of the Year)

2017 **37th International Society of Heart and Lung Transplantation (ISHLT) Annual Meeting 2017, San Diego, USA**

- The incidence and outcome of Primary Graft Dysfunction after adult heart transplantation in the United Kingdom.

- The Post- Operative Glasgow Transplant Score

2017 **Society of Cardiothoracic Surgery of Great Britain and Ireland (SCTS) Annual Meeting, Belfast, UK**

- The incidence and outcome of Primary Graft Dysfunction after adult heart transplantation in the United Kingdom.

- The Post- Operative Glasgow Transplant Score

2016 **Scottish Cardiac Society, Doubletree Hotel, Dunblane**

- The Post-operative Glasgow Transplant Score (Post-GTS™) initial pilot data

2016 **Association of Cardiothoracic Anaesthetists of Great Britain and Ireland Annual Meeting, Belfast, UK**

- The Post-operative Glasgow Transplant Score (Post-GTS™)

2016 **EuroELSO 5th International Congress, Glasgow, UK**

- Successful bridging to transplant with Levitronix Centrimag in two patients with cardiogenic shock following severe myocardial infarction

- Mechanical Circulatory Support with the Levitronix Centrimag- from bridging to decision.

2016 **Society of Cardiothoracic Surgery of Great Britain and Ireland (SCTS) Annual Meeting, Birmingham, UK**

- Glasgow Transplant Score: a visual qualitative and quantitative scoring tool

Published Abstracts

Keeping It Cool: Extended Myocardial Protection with Topical Cooling to Reduce PGD.
Singh SA, De SD, Morcos K, Hegazy Y, Al-Haideri H, Nair S, Doshi H, Al-Attar N, Curry P
The Journal of Heart and Lung Transplantation. 2019;38(4): S43-S4.

Survival after Primary Graft Dysfunction in Heart Transplantation: Outcomes of the National UK Data.
Singh SA, De SD, Rushton S, Banner N, Berry C, Al-Attar N.
The Journal of Heart and Lung Transplantation. 2019;38(4): S186-S7.

Can Donor Step Up Pressure Predict Primary Graft Dysfunction in Recipients Post Heart Transplantation?
De SD, Singh SA, Morcos K, Hegazy Y, Barton A, McGowan M, Dalzell J, Curry P, Al-Attar N
The Journal of Heart and Lung Transplantation. 2019;38(4): S272**.**

Donor Right Ventricular Stroke Work Index (RVSWI) is a Poor Predictor of Primary Graft Dysfunction (PGD) After Heart Transplantation.
S. Das De, S. Avtaar Singh, J. Dalzell, H. Doshi, P. Curry, N. Al-Attar, S. Nair
The Journal of Heart and Lung Transplantation 04/2018; 37(4): S349,

Validation of a Model to Predict Primary Graft Dysfunction (PGD) after Adult Heart Transplantation in the United Kingdom.
S. Avtaar Singh, N. Banner, S. Rushton, C. Berry, N. Al-Attar
The Journal of Heart and Lung Transplantation 04/2018; 37(4): S103

The Impact of Gender Mismatch on Survival After Heart Transplantation
S. Avtaar Singh, S. Das De, C. Berry, N. Banner, N. Al-Attar
The Journal of Heart and Lung Transplantation 04/2018; 37(4): S436

Novel Technique to Reduce Warm Ischemic Time During Cardiac Implantation.
K. Morcos, S. Singh, S. Das De, H. Haidari, Y. Hegazy, J. Dalzell, S. Nair, H. Doshi, N. Al-Attar, P. Curry
The Journal of Heart and Lung Transplantation 04/2018; 37(4): S425

The Incidence and Outcome of Primary Graft Dysfunction After Adult Heart Transplantation in the United Kingdom.
Singh SA, Banner NR, Rushton S, Al-Attar N.
The Journal of Heart and Lung Transplantation.36(4): S146-S7.

A Pilot Evaluation of the Post-Operative Glasgow Transplant Score (Post-GTS ™) for Heart Transplants.
Avtaar Singh S, Vassalos T, Nolan F, Sharp J, Young AM, Al-Attar N.
The Journal of Heart and Lung Transplantation.36(4): S398-S9.

Full Publications

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Journal of cardiac failure (Article in Press)

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Heart Failure Reviews 04/2019;
DOI:10.1007/s10741-019-09794-1

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DOI:10.20517/2574-1209.2018.27

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Sanjeet Singh Avtaar Singh, Nicholas R Banner, Sally Rushton, Andre R Simon, Colin Berry, Nawwar Al-Attar
Transplantation 05/2018;
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Singh, S., Das De, S., Spadaccio, C., Berry, C., & Al-Attar, N.
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Capoccia, M., Avtaar Singh, S., Hegazy, Y., Sinclair A, Al-Attar N, Balakrishnan M.
Indian J Thorac Cardiovasc Surg (2017) 33: 303.
DOI: 10.1007/s12055-017-0582-2

Definitions/Abbreviations

AMI	Acute myocardial infarction
ATG	Anti-Thymocyte Globulin
BMI	Body mass index
BNP	Brain-type natriuretic peptide
CASUS	Cardiac Intensive Care Score
CTAG	Cardiothoracic Advisory Group
NT-proBNP	N-terminal pro-brain natriuretic peptide
BSA	Body surface area
DBD	Donation after brainstem death
DCD	Donation after circulatory death
ECG	Electrocardiogram
ECHO	Echocardiogram
ECMO	Extracorporeal Membranous Oxygenation
Euroscore	European System for Cardiac Operative Risk Evaluation
HTx	Heart transplant
IABP	Intra-aortic balloon pump
ICU	Intensive care units
IL	Interleukin
LT-LVAD	Long-term(implantable) Left Ventricular Assist Device
LV	Left Ventricle
LVEF	Left ventricular ejection fraction
MTOR	Mammalian/ Mechanistic target of rapamycin
NHSBT	National Health Service Blood and Transplant
Nt-proBNP	N-terminal pro-brain natriuretic peptide
OCS	Organ Care System ™

PCWP	Pulmonary capillary wedge pressure
PGD	Primary graft dysfunction
PVR	Pulmonary vascular resistance
RV	Right ventricle
SNOD	Specialist Nurse for Organ Donation
SOFA	Sequential Organ Failure Assessment
TNF	Tumour necrosis factor

1 Introduction

1.1 Thesis overview

The primary aim of this thesis is to provide an overview of heart transplantation in the United Kingdom in the recent era (2012-2018) with an in-depth focus on Primary Graft Dysfunction(PGD) as defined by the International Society of Heart and Lung Transplantation (ISHLT) in a consensus statement (2014)(Jon Kobashigawa *et al*. 2014). A detailed overview of PGD is provided in 1.12. The lack of a consensus statement made identification and comparison of PGD difficult. The first aim of the thesis was to ascertain the true incidence of PGD in the UK. The findings of these were included in chapter 3. This represents the largest multicentre study of its kind at the time of writing and was presented as an oral presentation at the PGD plenary session at ISHLT's annual meeting in 2017. This study also identified risk factors that were considered based on the consensus statement from previous studies with centre-specific defined criteria for PGD.

The consensus definition currently permits comparison studies to be performed. The 2nd aim of this thesis was to, therefore, propose a scoring system for PGD. The scoring system had to be ubiquitous, easy to use and reproducible to allow benchmarking of PGD rates using observed vs expected analysis as a statistical quality control assessment. The utility in the scoring system would be to replace conventional, retrospective assessment of PGD outcomes that lacked continuous monitoring resulting in delayed recognition of practices/therapeutic options that lead to better than expected outcomes. One method that could be used would be variable life adjusted displays (VLAD)(Lovegrove *et al*. 1997), which is a relatively straightforward depiction of data that permits continuous surveillance of PGD outcomes. VLAD was established to highlight differences between observed and expected mortality in cardiac surgery using the Parsonnet score. It is sometimes referred to as the expected-observed cumulative sum (CUSUM) plot. In its original iteration, it plots the cumulative difference in observed mortality from expected mortality on the y-axis against individual cases in the chronological order that they occur on the x-axis. Hence if the expected outcome rate is equal to the observed rate(actual rate), it is seen as zero and a

rising line is indicative of an observed rate being lower than the expected rate and vice versa.

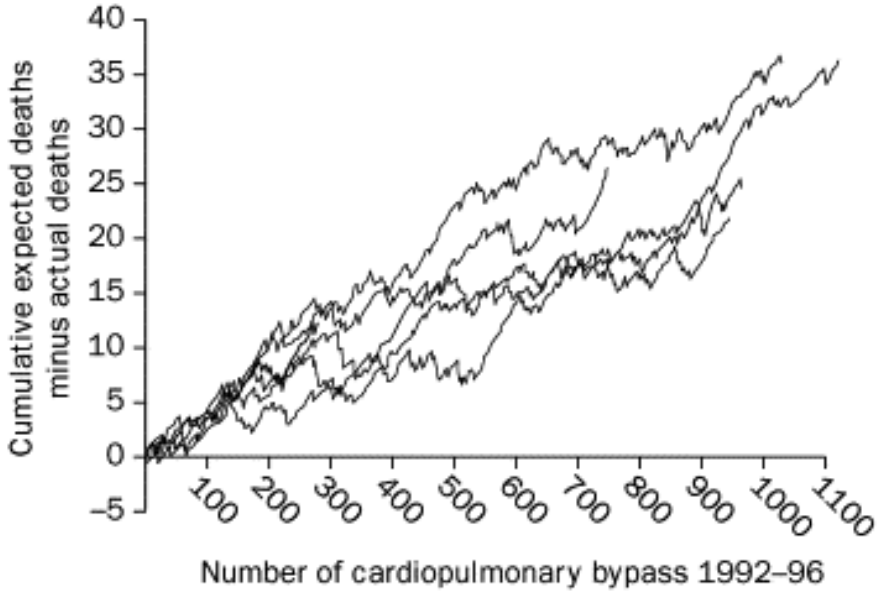


Figure 1-1 5000 operations between 1992 and 1996 divided into six contemporaneous series according to the perfusion technician running the bypass.
Reproduced with permission from 'Lovegrove J, Valencia O, Treasure T, Sherlaw-Johnson C, Gallivan S. Monitoring the results of cardiac surgery by variable life-adjusted display. The Lancet. 997;350(9085):1128-30'.

Figure 1-1 is an example of the VLAD plot in practice. While regional variations in practices that are unaccounted for remain, the VLAD plot could serve as a useful centre specific tool for monitoring performance. The PREDICTA score described in chapter 4 highlights the scoring system developed based on this study which will permit the VLAD analysis once it has undergone further multicentre validation.

The next aim of this thesis is to identify candidates that may be potentially at risk. Adverse donor and recipient profiles are highlighted in section 1.12.3 of the Introduction. There are however limitations to candidate selection due to the limited availability of organs. However, identifying candidate factors allows identification of high-risk patients to allow resource allocations such as the early institution of advanced Mechanical Circulatory Support(MCS), adequate provision of trained staff and appropriate tailoring of early post-transplant management strategies, such as using nitric oxide or inhaled prostaglandins prophylactically. Transplants frequently occur outwith 'normal' working hours, hence the importance of identifying high-risk combinations to permit the best possible care

within the settings of a nationally-funded healthcare system such as the National Health Service (NHS).

Chapter 5 incorporates the clinical findings of a single centre study compared to the national cohort. The aim of this study was to highlight the role of amelioration of warm ischaemic time to reduce the rate of PGD. This innovative yet cost-effective strategy was presented at several meetings with encouraging feedback.

The Glasgow Transplant Score (GTS) in Chapter 7 is an inventive depiction of individualised facets of care for patients. It employs a modified Delphi method to identify factors that were not identified in the ISHLT consensus statement such as frailty assessment. The aim of this study was to highlight the modified Delphi method as a tool for achieving a consensus-based on expert opinion, in the absence of other levels of evidence.

1.2 Core Methodology

The PGD incidence study approved by the Cardiothoracic Advisory Group(CTAG) Audit Committee headed by Dr. Nicholas Banner. A previous study on PGD was performed by Dr. Vamsidhar Dronavalli which looked at a locally derived PGD definition. The aims of our study are highlighted in section 1.1. The study was approved by CTAG. I obtained an honorary contract with NHSBT and each respective transplant centre for access to data. The study was supported by each of the 6 adult heart transplant centres in the UK. As the study was approved by the audit department of NHSBT, I was restricted to clinical data that were routinely collected by NHSBT.

I first performed a literature review to identify candidate variables of interest. The project proposal with all the variables of interest was submitted to the CTAG audit committee. I then liaised with NHSBT to identify variables that were routinely collected. I then formulated a password protected spreadsheet and obtained an encrypted USB stick. Following this, I arranged site visits for data collection with the heads of departments and the transplant coordinators at each site. Source data were collected from a combination of patient notes, operative and perfusion charts, ICU patient management systems and electronic

patient records. I underwent training at each centre to familiarise myself with the different platforms. I also consulted Human Tissue Authority Forms A and B stored in the medical records departments at each transplant centre to identify different timings for accurate accrual of ischaemic times. Data were interrogated at the source to ensure no missing data was recorded in the final spreadsheet. I performed data collection and entry myself to ensure data collection was consistent. PGD was defined either by echocardiographic parameters or pulmonary artery catheter measurements and had to be evident for at least 1 hour within the first 24 hours in the absence of secondary graft dysfunction (other causes highlighted in section 1.12.1). The raw data was then validated using the collected data on the NHSBT database, during my visit to the NHSBT statistical office in Bristol at the end of each data collection run. I performed a total of 3 data collection cycles and visited the NHSBT office on 5 occasions. The data collected was also used to supplement missing data within the NHSBT database itself.

1.2.1 Statistical Methodology

I attended lectures on statistical methodology and Endnote referencing at the University of Glasgow hosted by the Information Technology (IT) department. My statistical supervisor, Ms. Sally Rushton also provided lecture notes and supervised my analysis. To ensure the analysis was robust and reproducible, I performed the analysis on Minitab and this was replicated by Ms. Rushton using the SAS/STAT software, Version 14.1 of the SAS System for Microsoft Windows Copyright © 2015 SAS Institute Inc, Cary, NC, USA.

To generate the receiver operating characteristic (ROC) curves as seen in Chapters 4 and 7, I used the SPSS software package, IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp. IBM Corp.

1.3 Organ transplantation and ancient history

One of the notable advances in modern-day medicine is organ transplantation. None more so than the heart. A complex interaction between physiology, surgery, and immunology that spanned decades, involving the hard work of many pioneers in their fields. We revisit the contributions of the pioneers as well as marvel at the paradigm shifts in medicine that have made heart transplantation safe and reproducible with more than 4000 transplants done yearly today.

Organ transplantation initially stemmed from historical experimentation to become a mainstay of treatment for many chronic conditions and continues to do so in spite of improvements in device technology. Organ donation, however, underwent several challenges initially with cultural acceptance, ethics and legality, and political pressure. It has since evolved with the merging of improvements in the donation-allocation-procurement process, advances in technology, refinement of surgical technique, scientific breakthroughs in organ preservation, cognitive and methodical improvements in immunology and immunosuppression alongside expertise in managing adherent complications of organ transplantation.

In ancient civilisations, the practice of removal of organs/tissues for a multitude of reasons (beautification or therapeutic) was initiated. Hindu texts from 3 millennia ago provided detailed accounts of skin grafting from fatty regions (buttocks) or protrusions (chin) for the reconstruction of mutilated noses incurred during wars or punishments (Bergan 1997).

One of the earliest records of organ transplantation, Bian Que, a reported clairvoyant during the Han Dynasty in ancient China reportedly performed an exchange of hearts. He felt that the attainment of balance was possible by exchanging organs between men of ‘strong will’ but ‘weak spirit’ with that of one with opposite traits by intoxicating a ‘patient’ with fortified wine prior to “cutting their breasts removing their hearts and applying numinous medicine”(Salguero 2014).

The New Testament describes several cases of auto-transplantation by today’s definition; Jesus of Nazareth reattached the ear of a servant after it had been

cut by Simon Peter's sword. It also describes how Saint Mark re-implanted an amputated hand of a soldier (Linden 2009). Archaeological records have revealed that in the Bronze age, the term 'trephination' was first revealed whereby bone segments were temporarily removed to decompress brain swelling(Goodrich 2014).

Jacopoda Varagine (348 AD) described the 'miracle of the black leg' where a gangrenous leg of Justinian (Roman deacon) was replaced with that of a dead Ethiopian man (Gutkind 1988).

In 1688, Job van Meeneren successfully grafted a segment of bone from the skull of a dog to a defect in a human patient's cranium (Hewitt *et al*. 2008). A Russian aristocrat had a fragment of canine skull tissue inserted during a repair after an injury. He had it explanted due to threats of excommunication from the church(Hewitt *et al*. 2008). Such accounts of events highlighted the initial inquisitiveness with the concept of transplantation.

1.4 The pre-transplant era

Although organ transplantation had not taken place yet, the early 20th century witnessed the first skin and corneal transplants. The initial work behind corneal transplant is attributed to Franz Reisinger who experimented with 'keratoplasty' in 1818 (Crawford *et al*. 2013). 20 years later, Samuel Bigger performed the first successful corneal transplant in a gazelle. The first attempted corneal xenotransplantation on a human was performed in 1838 was unsuccessful. Improvements in antisepsis, anaesthesiology and surgical technique played a pivotal role, alongside ongoing animal experimentation. This subsequently led to the first successful human corneal transplant in 1905 by Eduard Zirm (1887-1948) in Olmutz near Prague (Crawford *et al*. 2013). The first successfully grafted tissue, however, was performed by Jacques-Louis Reverdin, who transplanted small detached skin grafts onto a wound and noted hastened granulation of wounds on 8th December 1869 (Davis 1941). Solid-organ transplantation would follow a similar path with years of experimentation before successful results were noted.

French President Marie François Sadi Carnot died from a severed portal vein in 1894. This had a profound effect on a young surgeon, Alexis Carrell (Merchant and Tan 2013). He mastered vascular anastomotic suturing methods and introduced smaller needles. Carrel coated his needles, instruments, and thread with petroleum jelly to reduce the thrombogenicity of the foreign material. He also perfected the concept of eversion thereby allowing blood within the vessels' continuous endothelial contact. He also revolutionised antisepsis in surgery and pioneered methods of extracorporeal tissue preservation, by using salt solution at freezing point (Aida 2014).

In 1902, he successfully performed the first heterotopic kidney transplant by inserting a dog's kidney into its own neck. He noted that the kidney began producing urine immediately (Merchant and Tan 2013). He later successfully transplanted organs, including kidneys, ovaries and thyroid glands between different dogs. In 1912, he became the first surgeon to win a Nobel Prize "in recognition of his work on vascular sutures and the transplantation of blood vessels and organs" (Sade 2005).

Carrell famously noted that despite success in the technical aspects of transplantation, there were consistent hostile host responses to the foreign allografts especially during xenotransplantation(Shayan 2001)

> *"Should an organ, extirpated from an animal and replanted into its owner by a certain technique, continue to functionate normally, and should it cease to functionate normally when transplanted into another animal by the same technique, the physiologic disturbance could not be considered as brought about by the organ but would be due to the influence of the host, that is, the biological factors"*

Despite Carrell's observations, between 1905-1910, several surgical peers such as M Princeteau, Mathieu Jaboulay, and Ernst Unger in this era attempted xenotransplantation of rabbit, pig and macaque kidneys to humans with disastrous results(Cooper *et al*. 1997).

1.5 Pre-immunosuppression era

Leo Loeb first noted that the strength and timing of rejection in skin homografts on rodents were potentially caused by the genetic disparity between donor and recipient and highlighted the involvement of lymphocytes in the 1930s (Barker and Markmann, 2013). He theorised that this genetic disparity did not occur in identical twins thus they would accept exchanged skin grafts. Unfortunately, his findings were ridiculed due to his inbreeding of mice. Contemporaries such as Peter Medawar dismissed the importance of lymphocytes and adopted the humoral theory of rejection (Barker and Markmann, 2013). The ensuing two decades were fraught with failed attempts at kidney transplantation in both human and animal models by Voronoy (1937), Simonsen (1953) and Dempster (1953) who even used radiation in organ transplant recipients (Dempster, 1953). Medawar's renewed interest in transplant rejection brought him to the Burns Unit at Glasgow Royal Infirmary (Gibson and Medawar, 1943) with Thomas Gibson. He remained convinced that skin grafts in burn victims failed because of humoral rather than cellular immunity (Brent, 2005). His work with Rupert Billingham and Hugh Donald revealed that even fraternal twin cows accepted skin grafts, not just identical twin cows (Anderson et al., 1951). Across the Atlantic, Ray Owen at the University of Wisconsin noted a hybrid of blood cell types in fraternal twins. He concluded that there was a persistence of chimerism from the intrauterine transfer of stem cells was probably responsible for this (Barker and Markmann, 2013). Medawar, Billingham, and Leslie Brent induced chimerism and homograft acceptance in mice by injecting inoculating intrauterine foetuses with donor strain spleen cells (Billingham et al., 1953). This was ultimately successful and resulted in a Nobel Prize in 1966 for Peter Medawar. They later discovered that some of the immunocompetent cells from the splenic tissues 'attacked' the lymphoid tissue of the host (Graft-Versus-Host-Disease), thereby proving the role of cellular immunity as first theorised by Loeb (Barker and Markmann, 2013).

Meanwhile, Joseph Murray and his team performing the first successful kidney transplant in 1954 using as a donor the recipient's identical twin bypassing the issues with immunity (Harrison et al., 1956). This generated a lot of interest in the field of transplantation. Joan Main and Richmond Prehn attempted to recreate Medawar's stem cell inoculation. They radiated mice to allow induction

of bone marrow from a donor. Murray's team used this method with poor outcomes as 11 of the 12 patients who underwent kidney transplantation with total body irradiation died within a month (Barker and Markmann, 2013). The survivor maintained adequate function of his fraternal twin's kidney for 20 years thereby becoming the first successful non-identical twin kidney transplantation. Jean Hamburger and René Küss from Paris performed 4 successful kidney transplants using total body irradiation without marrow inoculation (Dempster, 1953).

1.6 Early Immunosuppression

Robert Schwartz and William Dameshek discovered that 6-mercaptopurine (6-MP), which was primarily used for the treatment of malignancies, also reduced the antibody response of rabbits to bovine albumin (Barker and Markmann 2013). Roy Calne used 6-MP on canine kidney homografts and noted that it significantly prolonged survival (Calne 1960). His findings, however, were not replicated when 3 kidney transplant recipients treated with 6-MP died. Calne began a research fellowship with Joseph Murray and despite the ongoing trend of total body irradiation, pursued work with 6-MP and later azathioprine (Barker and Markmann 2013).

In 1963, at a National Research Council conference in Washington, the preliminary results of total body irradiation versus immunosuppressive drugs had reached equipoise with few patients surviving beyond 1 year. The practice of transplantation was questioned due to its poor long-term survival. Every represented centre demonstrated poor survival bar one. Thomas Starzl, combining azathioprine with prednisone achieved >70% survival kidney graft survival at 1-year follow up (Hamilton *et al*. 2012). He noted that large doses of prednisone could reverse early rejection that occurred and this could then be tapered down. This led to the formation of 50 new transplant centres in the United States alone that year (Brent 2005) and remained the mainstay of immunosuppression for the next 20 years. Immunosuppression also brought a new pathology, opportunistic infections, and malignancy. Starzl himself noted that there was a high rate of bacterial, viral, fungal and protozoal infections found in post-mortem examination (Hill *et al*. 1967).

Antilymphocyte serum (ALS) was first discovered by Elie Metchnikoff in 1899. In 1961, Byron Waksman identified that lymphocytic depletion could suppress delayed hypersensitivity reactions(Waksman *et al.* 1961). Combining the two concepts, Michael Woodruff demonstrated that ALS administration alongside thoracic duct drainage via a fistula extended skin allograft survival in rodents, a finding later replicated by Medawar (Woodruff and Anderson 1963; Levey and Medawar 1966). In 1966, Polyclonal antilymphocyte globulin(ALG) was successfully synthesized from human leukocyte inoculated horses and became the staple of a triple regimen alongside steroids and azathioprine (Starzl *et al.* 1967).

1.7 History of Cardiac Surgery and Transplantation

Unlike its other surgical counterparts, cardiac surgery was a relatively unknown subspecialty in the early 20th century. In 1881 at the Vienna Medical Society, Theodore Billroth once proclaimed.

"*No surgeon who wished to preserve the respect of his colleagues would ever attempt to suture a wound of the heart.*" (Weisse 1991)

The first cardiac procedure of the modern era was performed by Henry C. Dalton in St. Louis to repair a pericardial wound in a victim of a stabbing (Weisse 2011). In 1923, Elliot Carr Cutler and Samuel A. Levine successfully relieved a stenotic mitral valve in a 12-year-old girl. F. John Lewis, performed the first successful repair of an atrial septal defect in 1952 using hypothermia to protect the myocardium(Lewis and Taufic 1953). C. Walton Lillehei performed 45 open heart surgeries utilizing a technique called controlled cross-circulation using parents of the children as 'pump oxygenators'(Lillehei *et al.* 1986).
The introduction of the cardiopulmonary bypass circuit revolutionised cardiac surgery. John Gibbon perfected the device in 1953 and subsequently performed the successfully performed an atrial septal defect closure(Gibbon 1978). John Kirklin modified the pump and achieved relative success in small series of patients at the Mayo Clinic(Kirklin *et al.* 1955). However, it was Richard DeWall's cardiopulmonary bypass device with a disposable bubble oxygenator and simple pump action that enabled the correction of cardiac conditions under direct vision (Dewall *et al.* 1956).

The ensuing period saw numerous attempts to correct myocardial ischaemia until Robert Hans Goetz successfully grafted the right internal mammary artery to the right coronary artery, thereby performing the first coronary artery bypass graft in 1960, much to the chagrin of the medical and surgical fraternity at the time (Konstantinov 2000).

Inspired by the work of Carrel and Loeb, Frank C Mann identified 2 techniques for heterotopic cardiac transplantation(Mann *et al.* 1933). In his experimental model, he described using either a distal or proximal end of a divided carotid artery to supply blood to the aorta and assist circulation. The coronary sinus blood returned to the right atrium with both the vena cavae closed off and drained into the right ventricle. The pulmonary artery was anastomosed to the jugular vein. They noted that the pulse generated by the heart gradually faded with the longest-lasting heart failing after 8 days.

Vladimir Demikhov, a visionary surgeon developed a mechanical device too large to be inserted entirely within the thorax of a dog, but it functioned as a substitute for the heart for as long as 5.5 hours. Till 1946, intrathoracic transplantation had never been accomplished in a warm-blooded animal. The first issue encountered was the ongoing nourishment of the heart using arterialised blood. Demikhov ligated the aorta, venae cavae, azygos vein, brachiocephalic and left subclavian arteries in succession to maintain adequate pressure in the isolated heart-lung model. He then perfused the heart with arterialised blood via the left atrium after passing through the pulmonary circuit and delivered by the left ventricle into the coronaries. He used this method in around 300 experiments and maintained the heart in good condition for up to 4 hours (Shumacker 1994).

Despite multiple initial failures of intrathoracic transplant of the heart, one dog survived for 32 postoperative days. Perhaps his greatest achievement was a series of orthotopic heart transplants that he performed without hypothermia or the use of a cardiopulmonary bypass machine. He performed and end-to-side anastomosis of the donor aorta, pulmonary artery and venae cavae to the corresponding recipient vessels and reattached the pulmonary veins to the recipient’s left atrium closed off with purse strings. He reported survival times of up to 15.5 hours, thereby creating the first model of an orthotopic heart

transplant providing the entirety of the pumping function (Cooper 1968). Demikhov's research was not published in English until 1962.

Interest in Frank C Mann's work was rekindled in 1951. Marcus et al created a technique using 3 dogs, a donor, a recipient and a receptacle for the donor heart when disconnected from the circulation (Marcus *et al*. 1951). The final model was not too dissimilar to the cross-circulation utilized by Lillihei. This "interim parabiotic perfusion," was used to place the heart in the 2 previously mentioned configurations as described by Mann. In 1953, Marcus and associates managed to achieve a survival time of 48 hours for heterotopic heart transplantation (Cooper 1969). Wilfred Neptune and colleagues were the first to utilise hypothermia with a heart-lung block and achieved a survival time of 6 hours in a canine model (Piciche and Carpentier 2013).

Webb, Howard, and Neely produced 12 successful orthotopic heart transplants surviving as long as 7.5 hours using a different method of anastomosing the pulmonary veins of the donor to recipient compared to Demikhov (Webb *et al*. 1959). The first involvement of British cardiac surgeons occurred in 1959 when Cass and Brock described a series of methods for autotransplantation while including leaving the recipients atria and septal crest behind to avoid pulmonary vein and vena cavae anastomosis(Cass and Brock 1959).

In 1960, Lower and Shumway published results of their experiments with orthotopic homotransplantations using an oxygenator and partial atrial preservation as described by Cass and Brock. They yielded excellent results with 5 of the 8 dogs experimented on surviving between 6-21 days(Lower and Shumway 1960). To date, the bi-atrial anastomosis is still noted as the Shumway Technique.

Shumway paid meticulous attention to surgical technique and myocardial protection using isotonic saline at 4^{0}C. In addition, they introduced the concept of assistance time whereby the recipient dogs were left on the cardiopulmonary bypass for a short period of time to ease the heart into assuming the circulatory load(Lower *et al*. 1961).

Shumway's group also described initial issues such as the incidence of complete atrioventricular block. On learning lessons from rejection in renal transplant patients, Reemtsma et al attempted to use methotrexate for heterotopic heart transplantation in 21 canines, and prolonged survival up to 26 post-operative days (Reemtsma *et al*. 1962). Blumenstock mimicked the findings of Reemtsma's group with one canine in their cohort surviving for up to 42 days in 1963 (Blumenstock *et al*. 1963).

The first ethical dilemma faced by the fraternity was the concept of the donor as "the definition of irreversible coma" was only established in 1968 by an Ad Hoc Committee of Harvard Medical School on Brain Death('A definition of irreversible coma. Report of the Ad Hoc Committee of the Harvard Medical School to Examine the Definition of Brain Death' 1968). A patient presented with a large thrombus that had embolised to the left side of the heart and placed on mechanical coronary perfusion. The likelihood of a potential donor dying at exactly the same time as the patient needing a heart was minute and a decision was made that the team would not halt ventilation of the patient in January 1964 but instead would utilise a chimpanzee as a donor (Hardy *et al*. 1964). The chimpanzee's heart was explanted and implanted into the patient. Despite initially beating well, it became apparent that the heart was not able to support the larger volume of human circulation and the patient died within an hour of weaning from cardiopulmonary bypass.

Dr. Christiaan Barnard had worked alongside Shumway in Minnesota. He had also performed the first successful kidney transplant in South Africa to understand transplant immunology and geared for heart transplantation. On 14 September 1967, Louis Washkansky was admitted to the Groote Schuur Hospital in Cape Town, South Africa. Dr. Velva Schrire (Chief Cardiologist) recommended Washkansky as the appropriate case for transplant. On December 2, 1967, a 24-year-old female, Denise Ann Darvall was pronounced dead after sustaining a massive cerebral injury following a collision. Both patients were brought to theatres A and B where and mutual consent was obtained (Kalra *et al*. 2016).

> "If you can't save my daughter, you must try and save this man."
> - Edward Darvall (Denise's Father)

On 3rd December 1967, Dr. Christiaan Barnard performed the first successful human-to-human orthotopic heart transplantation. Her heart was taken via the Shumway technique with the heart cooled to 10ºC. He used a combination of local irradiation, azathioprine, prednisone, and actinomycin C as his immunosuppression regime. Although the post-operative course of the patient was very promising, he contracted Pseudomonas pneumonia and died on the 18th post-operative day (Barnard 1967).

Dr. Adrian Kantrowitz and his team performed the 2nd heart transplant (the first in a paediatric patient) in Brooklyn. Kantrowitz was already well known for designing the first intra-aortic balloon pump and had conducted considerable laboratory experiments in puppy hearts believing that the immune system of a younger heart may offer less allogenic resistance. On 6 December 1967, He transplanted an anencephalic donor heart into a 3-week-old patient diagnosed with tricuspid atresia. He performed the operation in hypothermic conditions under circulatory arrest. Despite initial recovery into sinus rhythm, the recipient developed irreversible acidosis and died (Kantrowitz *et al*. 1968).

Norman Shumway and his team performed their first heart transplant a month after Kantrowitz. The recipient developed chronic and progressive heart failure after “post-viral myocardial fibrosis” and coronary artery disease. The procedure was complicated by size mismatch with the donor heart being much smaller than the recipient’s. The recipient received a combination of methylprednisolone and azathioprine preoperatively and post-operatively with the addition of prednisolone. However, the patient did not succumb to rejection. Shumway noted that in the initial post-operative period the patient was mildly hypotensive and oliguric into the second postoperative day despite administration of isoproterenol and temporary digitalization. The patient developed a consumptive coagulopathy before succumbing to multiorgan dysfunction and bronchopneumonia (Stinson *et al*. 1968).

Across the Atlantic, Dr. Donald Ross, who worked with Lord Russell Brock, performed the first heart transplant in the United Kingdom. The patient, a 45-year-old man, survived for 46 days before succumbing to infection. He performed 2 more unsuccessful transplants before a moratorium was declared (Cooley 2014).

Denton Cooley's group reported moderate success early on at Baylor with 7 of 10 patients surviving 4.5 months (Cooley *et al*. 1969). To reduce the risk of rejection, they used blood-group compatibility, lymphocyte crossmatch studies (histocompatibility) as described by Dr. Paul Terasaki, and developed a matching system to predict the likelihood of a good outcome post-transplant (Patel and Terasaki 1969). They also administered anti-lymphocyte globulin in addition to other anti-rejection medications.

1.8 Early Issues with Heart Transplantation

Within a year of Barnard's feat, 102 heart transplantations were performed internationally(Patterson and Patterson 1997). Shumway famously quipped

> "Suddenly heart transplants were being done in places where one would hesitate to have his atrial septal defect closed"

The early promise of heart transplantation however soon diminished as the number of transplants rapidly fell from 100(1968) to 18(1970), with many inexperienced units abandoning the procedure. Kantrowitz, who was on the review panel for the National Institute of Health agreed to support Shumway and his unit in their ongoing research (DiBardino 1999). In 1971, they identified several identifiers of acute rejection (Griepp *et al*. 1971).

1) Electrocardiographic findings

   i. Increased QRS voltage
   ii. Arrhythmia
   iii. Right axis deviation
   iv. ST-T wave changes

2) Clinical Findings

   i. Appearance of gallop rhythm
   ii. Decreased precordial activity
   iii. Hypotension

3) Echocardiography findings

   i. Increased thickness of left ventricular wall

ii. Increased right ventricular diameter

Using the above-mentioned criteria, they successfully treated 57 of 60 patients with methylprednisolone, actinomycin D and ALG. As the experience of long-term survival in heart transplants increased, Shumway noted a condition he titled ‘chronic rejection’(Clark *et al*. 1971). It manifested as diffuse allograft vasculopathy and led to episodes of sick sinus syndrome or myocardial infarction, usually proving fatal.

In 1962, Dr. Souji Konno developed the catheter-type endomyocardial biopsy (EMB) allowing samples of the myocardium of patients suspected of having intrinsic musculature abnormality to be taken using a bioptome inserted via a peripheral vein or arterial cutdown(Nishikawa *et al*. 2017). It was initially developed for diagnoses of cardiomyopathies as opposed to limited thoracotomy approaches. The bioptome usually provided samples containing endocardium and myocardium, usually sufficient for microscopic examination.

In 1971, a young cardiothoracic surgeon, Dr. Philip Caves undertook a British American Research Fellowship at Stanford to work with Shumway. While there, he worked with instrument maker Werner Schulz to create the Stanford-Caves Schulz bioptome which transformed the management of heart transplant patients. There were 2 Stanford bioptomes that differed in size and length. The longer and thinner bioptome was used for left ventricular biopsy and the shorter and thicker one for right ventricular biopsy (Caves *et al*. 1973; Melvin and Mason 1982). The samples obtained were between 1-3 mm in diameter. He noted that changes seen in endomyocardial specimens matched those seen in grafts at post-mortem examinations. The samples taken from the endomyocardial surface were also free of post-operative inflammatory changes that complicated sub-epicardial samples taken during thoracotomy. Finally, he noted that the pathologic changes of cardiac allograft rejection were more prominent in the endomyocardial surface (as the graft came in direct contact with the host’s circulation). Philip Caves also worked with Margaret Billingham who was a pathologist at Stanford. In 1974, they developed a standardised histological scale to pathologically grade the severity of cardiac rejection based on the extent of

infiltrates (Caves *et al*. 1974). This was incorporated into routine practice and significantly improved the survival of heart transplant recipients at Stanford.

1.9 Immunosuppression in Heart Transplantation

1.9.1 Cyclosporin

Another notable feat in transplantation during this era was the discovery of cyclosporin A. In 1976, J.F Borel reported the immunosuppressive effects of a fungal metabolite (*Tolypocladium inflatum*) isolated from Swiss soil samples. He noted that skin graft rejection in mice and graft-versus-host disease in mice and rats were considerably delayed by cyclosporin A. He also noted that it had a direct antilymphocytic effect by targeting an early stage of mitogenic triggering of the immunocompetent lymphoid cell and lacked the myelosuppressive effects of cytostatic drugs used at the time (Borel *et al*. 1976). Roy Calne, who previously worked on azathioprine, conducted in vivo immunosuppression with cyclosporin A on porcine cardiac allografts. His group stated that

"Cyclosporin A is more effective in suppressing rejection than any other drug that we have used in pigs with orthotopic cardiac allografts" (Calne *et al*. 1978)

Terence English, a South African born surgeon who previously worked with Lord Russell Brock and Donald Ross, nearly abandoned medicine to be a mining engineer. He visited Stanford on the advice of his friend Philip Caves in 1973 (Morris 2017). He was truly impressed with the outcomes of heart transplant recipients at the unit. In 1978, Dr. Terence English sought approval from the Transplant Advisory Panel of the Department of Health but was informed that there were no funds for a transplant programme (Newton 2015). Given the moratorium, the panel was not keen on 'one-off' operations. He duly persisted but his initial attempt was unsuccessful as the donor had arrested prior to implantation and sustained an irreversible brain injury. He persevered and in July 1979, performed the first successful heart transplant in the United Kingdom. The recipient, Keith Castle lived for 5 and a half years(English 2011).

> *"He subsequently became the best possible advertisement for cardiac transplantation except for his inability to give up smoking"*

- Sir Terence English on Keith Castle (English 2011)

Although initial reports on cyclosporin were favourable, the improvements came with a price. Cyclosporin was nephrotoxic when used over a long period (Myers *et al*. 1984). Other side effects include, including hypertension, hepatotoxicity, gingival hyperplasia, hypertrichosis, involuntary tremor, and an increased risk of malignancy (Patel and Kobashigawa 2007). With the improvements in survival after the initial transplantation, the recipients were at risk of nephrotoxicity and morbidities associated with immunosuppression primarily infections. These drawbacks, however, did not offset the positive impact cyclosporin offered over previous methods. Immunosuppression formed the initial challenges in cardiac transplantation with suboptimal immunosuppressive regimens either causing allograft rejection or infectious complications from over-immunosuppression.

A European Multicentre trial evaluating renal graft survival at 1-year showed that cyclosporin alone as a first-line immunosuppressive agent was more effective than with azathioprine and steroids (European Multicentre Trial 1983). Stanford's group meanwhile reported one- and 5-year survival rates of 83% and 55%, respectively using a 3-drug protocol of Cyclosporin A, azathioprine, and prednisone(Starnes and Shumway 1987).

1.9.2 Tacrolimus

Tacrolimus (Tradename: Prograf®, Astellas Pharma US, Inc. Northbrook, IL) a calcineurin inhibitor like cyclosporin was discovered from a soil sample from the foot of Mount Tsukuba in Tokyo in 1984. It was cultured from an actinobacter, *Streptomyces tsukubaensis* (Fung 2004). It suppresses interleukin-2 production associated with T-cell activation, thus inhibiting the differentiation and proliferation of cytotoxic T cells. Thomas Starzl once again led research into the safety and efficacy of Tacrolimus at the University of Pittsburgh Medical School (Starzl *et al*. 1989). Tacrolimus had a more limited adverse effect profile and comparative studies suggest superiority over cyclosporin in preventing allograft rejection while causing less antibody suppression (Behr *et al*. 1998; Jurcevic *et al*. 1998). The pharmacokinetics were far more predictable than for micro-emulsion cyclosporin (Wang *et al*. 2004).

Numerous randomized controlled trials comparing tacrolimus to cyclosporin have been done. Two multicentre studies comparing tacrolimus to oil-based cyclosporin (Tradename: Sandimmune® Oral Solution, Novartis Pharmaceuticals Corporation, East Hanover, New Jersey) showed no significant difference between the groups at 12 months. Graft survival, renal function, and infection rates were not significantly different between the groups although more patients in the cyclosporin group developed hypertension and hypercholesterolaemia (Reichart *et al*. 1998; Taylor *et al*. 1999).

A microemulsion formulation of cyclosporin (Tradename: Neoral® Oral Solution, Novartis Pharmaceuticals Corporation, East Hanover, New Jersey 07936) was developed and was shown to have a better bioavailability profile with more predictable pharmacokinetics compared to the oil-based preparations (Cooney *et al*. 1998). A multi-centre, randomized study of both preparations of cyclosporin revealed fewer episodes of rejection requiring antilymphocyte antibodies and fewer study discontinuations for treatment failures in the micro-emulsion based cyclosporin cohort of patients compared to those treated with oil-based cyclosporin without any adverse events (Eisen *et al*. 2001).

When compared to tacrolimus, micro-emulsion based cyclosporin (alongside cytolytic induction) and a tapered steroid regime showed equivalent patient and graft survival at 19 months. However, there was an increased incidence of biopsy-proven acute rejection in the cyclosporin group at 6 months. Tacrolimus was associated with a higher incidence of new-onset diabetes mellitus, lower rates of post-transplant hypertension and lower incidences of dyslipidaemia (Grimm *et al*. 2006). Similar findings were noted in another trial without cytolytic induction (Kobashigawa *et al*. 2006b).

1.9.3 Mycophenolate mofetil

Another agent that is commonly used is mycophenolate mofetil (MMF; CellCept, Roche Laboratories, Nutley, NJ). It is an effective anti-proliferative agent that improves rejection and survival when used as part of combination therapy. Its active metabolite, mycophenolic acid, is a non-competitive inhibitor of inosine monophosphate dehydrogenase (IMPDH) in the de novo pathway for purine synthesis (Allison and Eugui 2000). Therefore, MMF has some selectivity for

lymphocytes over other cell types as lymphocytes rely on this pathway for DNA replication and proliferation. Studies have shown that heart transplant patients receiving MMF therapy had lower levels of C-reactive protein, circulating B lymphocytes, activated T lymphocytes and natural killer (NK) cells compared to patients receiving azathioprine (AZA) (Eisen *et al*. 2005).

1.9.4 Mechanistic target of rapamycin (mTOR) inhibitors

Everolimus (Tradename: Certican, Novartis Pharma Schweiz AG, Bern, Switzerland) and Sirolimus (Tradename: Rapamune, Wyeth Europa Ltd., Maidenhead, UK) are mechanistic target of rapamycin (mTOR) inhibitors (MacKeigan and Krueger 2015). They work by inhibiting proliferation signals by suppressing the cytokine-driven T-lymphocyte proliferation, resulting in an arrest of the cell cycle. Unlike the calcineurin inhibitors, they demonstrate little or no nephrotoxic side effects. Recent studies have even shown a reduction in the incidence of chronic allograft vasculopathy (CAV) with Everolimus as measured by IVUS among heart-transplant recipients after 1 year (J.A. Kobashigawa *et al*. 2013; Andreassen *et al*. 2014). Sirolimus, however, is linked to an increase in total cholesterol and triglyceride levels (Lindenfeld *et al*. 2004; Wlodarczyk *et al*. 2005). Everolimus, on the other hand, is linked with an increase in total cholesterol levels, without increased triglyceride levels, but a significant increase in HDL which may explain its attenuation of CAV (Tenderich *et al*. 2007).

1.9.5 Cytolytic induction therapy

Cytolytic Induction therapy comprises of immunosuppressive drugs that have been introduced into clinical transplantation directed against human lymphoid cells. Several different forms of cytolytic induction therapy have been used as identified in Table 1-1.

Substance	Origin	Dosages Applied	Routes Investigated	Monoclonal/ Polyclonal
Horse Antilymphocyte-Globulin	Horse	Various 7–14 days	IM	Polyclonal
Rabbit Antithymocyte-Globulin	Rabbit	1–3 mg/kg per day 1–10 days	IM/IV	Polyclonal
Muromunab CD3 antibody (OKT 3 Antibody)	Mouse	5–10 mg/day 4–14 days	IV	Monoclonal
IL-2 receptor antagonists – (basiliximab or daclizumab)	Basiliximab-chimeric Daclizumab-Humanized Mouse/Human	Basiliximab - 20mg on day 0 and day 4 Daclizumab -1 mg/kg with repeated doses every 2 weeks for a total of 5 doses:	IV	Monoclonal
Anti-CD52 antibodies Alemtuzumab	Rat	30mg intraoperatively	IV	Mono clonal

Table 1-1 Different types of Cytolytic Induction Therapy Available (adapted with permission from "Cytolytic Induction Therapy in Heart and Lung Transplantation: The Protagonist Opinion, Transplantation Proceedings, Volume 30, Issue 4, 1100 – 1103" (Wahlers 1998)

In heart transplantation, kidney dysfunction has been demonstrated to be a risk factor for early death(Wahlers *et al*. 1989; Odim *et al*. 2006). Cytolytic induction allows post-operative renal recovery from a pre-renal aetiology without the negative impact of high nephrotoxic cyclosporine/tacrolimus levels. It effectively allows bridging of immunosuppression until a steady state is reached for the regular immunosuppression medications. Most centres use a combination of the abovementioned immunosuppressants to achieve adequate immunosuppression. In 2006, Kobashigawa led a trial comparing 3 different immunosuppression regimes, micro-emulsion cyclosporin with MMF, tacrolimus with MMF or tacrolimus with sirolimus (Kobashigawa *et al*. 2006a).

The 343 heart transplant recipients in this trial were randomized to receive corticosteroids and one of the mentioned regimes. Cytolytic induction therapy was used for up to 5 days. The primary endpoint of moderate rejection or haemodynamic compromise rejection requiring treatment showed no significant difference between the three groups at 6 months and 1 year. The probability of treated rejection was significantly lower in both the tacrolimus groups compared with the micro-emulsion cyclosporin/mycophenolate mofetil group. The

tacrolimus/sirolimus group had more fungal infections and more impaired wound healing.

On the other hand, recent trials involving combinations with everolimus have shown promising results including reduced cytomegalovirus infections(J. Kobashigawa *et al*. 2013), reduced cutaneous cancer incidence(Euvrard *et al*. 2010), and CAV attenuation effects (Eisen *et al*. 2013).

Other induction agents that have also been used include interleukin-2 receptor antagonists (Basiliximab)

Figure 1-2 shows the different targets of the immunosuppression medications alongside the initiation of the adaptive immune response against the donor graft. The step is initiated by recognition of an alloantigen by a naive T-cell, followed by T-cell activation, proliferation, and differentiation.

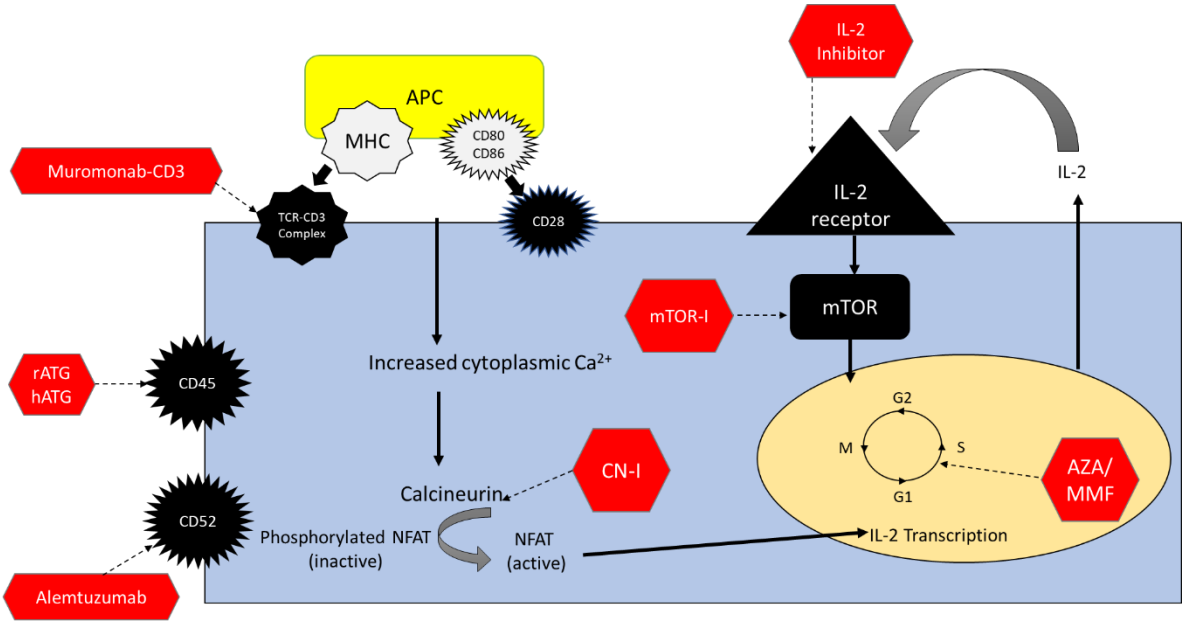
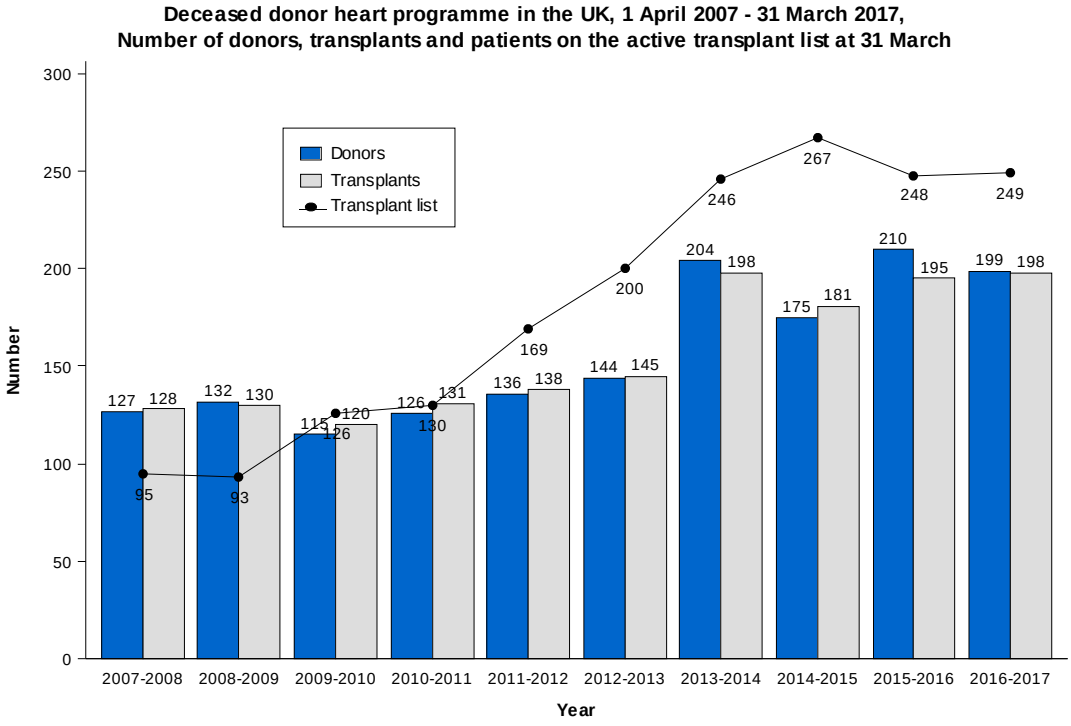


Figure 1-2 Immunosuppressive agents targeting stages of T cell differentiation and proliferation alongside selected cytokines.

APC-antigen-presenting cell, MHC – Major Histocompatibility Complex, rATG - rabbit antithymocyte globulin, hATG - horse antithymocyte globulin, CN-I – calcineurin inhibitors, G1-cell cycle gap phase 1, G2-cell cycle gap phase 2, IL-2 -interleukin-2, M-cell cycle mitosis phase, mTOR-mammalian target of rapamycin, mTORi - mammalian target of rapamycin inhibitor, AZA- Azathioprine, MMF-Mycophenolate Mofetil, NFAT-dephosphorylated nuclear factor of activated T-cells, NFAT-P-phosphorylated nuclear factor of activated T-cells, S-cell cycle synthesis phase, TCR- T-cell receptor. (dotted line indicates inhibition).

1.10 Current status of heart transplantation

Heart transplantation is considered to be the 'gold-standard treatment' for refractory advanced heart failure in carefully selected patients (Mehra *et al.* 2016; Ponikowski *et al.* 2016; Yancy *et al.* 2016). A major limiting factor of transplantation is the emerging gap between the number of donors (available grafts) and the number of patients on the waiting list. This issue is apparent even in neighbouring France (Dorent *et al.* 2017). The utilization of marginal donors or expanded-criteria donors has steadily increased over the decades. Part of the decision-making process currently between physician, surgeon, and patient includes discussing the potential options available. Currently, the choices include continued medical therapy (5% to 10% weekly mortality risk), mechanical circulatory support (10% to 15% operative risk), or a transplant which may or may not include a clause for marginal organs.



Source: Transplant activity in the UK, 2016-2017, NHS Blood and Transplant

Figure 1-3 Deceased donor heart programme in the UK, 1 April 2007 - 31 March 2017, Number of donors, transplants, and patients on the active transplant list at 31 March

The 'Standard Donor' or 'Traditional Criteria' for a donor as suggested by Copeland (Copeland 1995) is as follows

1. Age < 50 years
2. echocardiogram showing no important segmental abnormalities or global hypokinesis, ejection fraction greater than 50%, and normal valves
3. Inotropes less than 15 μg/kg/min of dopamine
4. Donor to recipient weight ratio of 1.5 to 0.7
5. Cold ischemic time less than 4 hours
6. No donor infection
7. Negative serology for hepatitis B, hepatitis C, and human immunodeficiency Virus
8. a normal electrocardiogram or minor ST-T wave abnormalities, with no conduction system disease.

The rising number of patients listed for heart transplantation has resulted in an increased number of donors from beyond the 'standard criteria' pool as a result of the undersupply of available organs. 'Marginal Donors' as they are termed would, under conventional transplant guidelines, be declined as potential organ donors (Brock *et al*. 2001). Median waiting times in the UK for hearts on the non-urgent list is currently 1280 days and 26 days for the urgently listed(NHSBT 2017d).

Forays into xenotransplantation as a potential pool of organs to solve the problem of donor-organ supply were also touted but to date, these remain in the experimental phase(Cooper *et al*. 2000).

The decision to accept a marginal donor organ is made on a recipient focused individualized basis rather than specific values, parameters or conditions. (Potapov *et al*. 1999; Blanche *et al*. 2002)

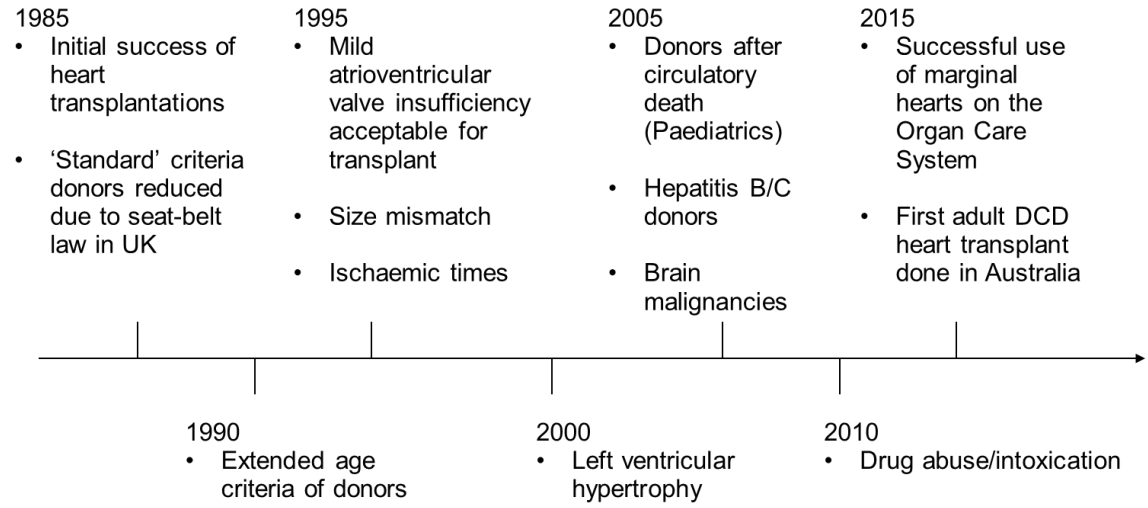


Figure 1-4 Timeline of events where modifications of 'Standard criteria' toward more marginal donors were implemented

The number of 'standard donors' for kidney transplants was first notably reduced after the implementation of the compulsory wearing of seat belts in the United Kingdom, which was approved by parliament in 1982 and became law on 1 February 1983 (Thompson *et al.* 1983). Other legislation includes zero-tolerance drinking-and-driving law resulting in fewer traffic accidents with fatal victims (Calil *et al.* 2009). During this time period, the United Kingdom Transplant Support Service Authority demonstrated a 12% increase in the number of cardiac donors aged greater than 41 years between 1988 and 1995 (Mercer *et al.* 1997). The initial reluctance to use organs from older donors especially the heart was due to longstanding dogma that older hearts were thought to more susceptible to the catecholamine flood that accompanies brain death (Young 1999). Internationally, gun crime has also been closely associated with donor organ availability. Studies in Brazil have shown a direct correlation between urban violence and gun crime to organ donors(Rodrigues *et al.* 2014; Silva *et al.* 2014).

Initial studies exploring the extended age criteria showed no significant difference in terms of left ventricular function and the incidence of infection and rejection (Drinkwater *et al.* 1996; Mercer *et al.* 1997). The risk of dying on the waiting list outweighed that of receiving an organ from an older donor (Bennett *et al.* 1998).

Some surgeons also opted to accept hearts with mild-to-moderate mitral or tricuspid insufficiency or secundum-type atrial septal defects as these could be repaired immediately or post-operatively with good results (Massad *et al*. 1996).

As our understanding of myocardial protection improved, the use of mildly hypertrophic left ventricles with short ischaemic times was also proposed with the caveat that there were no ECG changes (D. Marelli *et al*. 2000).

Patients with underlying malignancies were previously never considered donor candidates. However, the risk of metastasis from a primary intracranial tumour is low. A German study in one of the earliest studies evaluating the outcomes of recipients receiving organs from donors with intracranial malignancies showed good follow up outcomes of more than 5 years (Hornik *et al*. 2004).

Donation after circulatory death will be discussed in greater detail in later sections.

Transplantation also requires commitment from the patients and health care providers as it involves a long-term programme of treatment including pharmacological immunosuppression and regular surveillance (Banner *et al*. 2011). Clinical decisions, therefore, should consider a patient's ability to adhere to the demands of ongoing treatment. Alternatives to transplantation include the use of Ventricular Assist Devices (VADs). These are however limited in the National Health Service (NHS) due to the limited health care funding. In North America, the Food and Drug Administration recently approved VADs as destination therapy(Stewart and Mehra 2014). In its current form, heart transplantation confers a significant survival advantage with a 1-year survival of 84.5% and 5-year survival of 72.5% which is significantly improved as compared to the 76.9% 1-year survival and 62.7% 5-year survival in the 1980s. (Lund *et al*. 2014; Wilhelm 2015)

1.11 Primary Diagnostic Indications for Transplant

The most frequent indications for heart transplantation in adults are chronic heart failure secondary to dilated cardiomyopathy or ischaemic heart disease(Banner et al. 2011). There is also a significant number of

patients(approximately 3%) with adult congenital heart disease (ACHD) who present with advanced heart failure in adulthood (Burchill 2016). These patients are slightly more complex to manage both surgically (due to the abnormal anatomy, complex adhesions) and medically (due to human leucocyte antigen (HLA) sensitisation, potentially elevated pulmonary vascular resistance secondary to univentricular circulations and erythrocytosis secondary to cyanosis) (Banner et al. 2011; Burchill 2016). Coronary artery disease is the most important contributor to heart failure with a population-attributable risk of 65% in men and 48% in women(Lund et al. 2016). Most of the patients, however, can be classified into ischaemic or non-ischaemic cardiomyopathies.

1.12 Primary Graft Dysfunction after Heart Transplantation

Worldwide, more than 4000 adults undergo heart transplantation annually (Lars H. Lund *et al*. 2017a). It remains the closest resemblance to a 'cure' for end-stage heart failure. Whilst survival after cardiac transplantation has improved over the past four decades, primary graft dysfunction (PGD) is the leading cause of 30-day mortality post-transplant. The incidence of PGD is yet to be accurately delineated given the lack of an international consensus regarding its definition. Reports to date vary widely with respect to diagnostic criteria and definitions, therefore making incidence and outcomes difficult to compare between centres and regions. Prior to 2014, the International Society of Heart and Lung Transplantation (ISHLT) registry noted a 30-day mortality of 10 % in all heart transplants done since 1982 (Lund *et al*. 2013). The 90-day mortality was and 14 %. Almost 70% of these deaths were coded as 'graft failure' or 'multi-organ failure' for which a large majority would likely constitute contemporary PGD. Here, we provide a comprehensive overview of PGD in heart transplantation.

1.12.1 Definition

PGD presents as severe ventricular dysfunction of the donor graft which fails to meet the circulatory requirements of the recipient in the immediate post-transplant period. It may manifest as either single or biventricular dysfunction with low cardiac output and hypotension despite adequate filling pressures(Segovia *et al*. 1998; Russo *et al*. 2010; Iyer *et al*. 2011). In 2014,

Kobashigawa et al provided a consensus definition and grading system based on the modified Delphi method (Jon Kobashigawa *et al*. 2014). This agreement upon a uniform definition allowed subsequent studies to outline its true incidence and further explore and identify the potential multifactorial aetiologies underpinning PGD. `

PGD is defined as being a separate entity from secondary graft dysfunction, which is when a discernible cause for allograft dysfunction is identified. Such causes can include hyperacute rejection, graft dysfunction secondary to pulmonary hypertension or a recognised intra-operative complication. The diagnosis of PGD is made within 24 hours post-transplantation and is separated into PGD-LV, for PGD affecting the left ventricle or biventricular failure; and PGD-RV for isolated right ventricular involvement (Jon Kobashigawa *et al*. 2014). A severity scale applies to PGD-LV. For the mild and moderate categories, it relies on the requirement of inotropic support with a composite score as described by Wernovsky et al (<10 = mild, ≥10 = moderate) alongside either using echocardiography to identify ventricular dysfunction or right heart catheterisation to demonstrate haemodynamic compromise (Wernovsky *et al*. 1995b). For the echocardiography criteria, the left ventricular ejection fraction <40% is considered diagnostic for PGD (in the absence of secondary causes). With regards to haemodynamic parameters, high filling pressures i.e. a right atrial pressure (RAP) >15mmHg, and pulmonary capillary wedge pressure (PCWP) >20mmHg indicate PGD if occurring in the context of a low cardiac index (CI) (<2.0 L/min/m^2) lasting at least 1 hour. The requirement of an intra-aortic balloon pump signifies moderate PGD-LV, whereas requirement of extracorporeal short-term mechanical circulatory support in the form of extracorporeal membrane oxygenation (ECMO) or Ventricular Assist Devices (VADs) in any form (percutaneous/surgical) is diagnostic of severe PGD-LV (Jon Kobashigawa *et al*. 2014).

PGD-RV does not have a severity scale and is diagnosed based on the requirement of a Right-sided short-term VAD (RVAD) or right heart catheter measured haemodynamics in keeping with isolated right-sided dysfunction (RAP > 15 mm Hg, PCWP < 15 mm Hg, CI < 2.0 L/min/m^2, TPG <15 mm Hg and/or pulmonary artery systolic pressure < 50 mm Hg) (Jon Kobashigawa *et al*. 2014).

Previous studies had used the need for mechanical circulatory support as a criterion for diagnosis of primary graft dysfunction, however, the timing of initiation of therapy and endpoints differs from these studies, leading to significant variation in incidence reporting (2.3-32.4%) (Ibrahim *et al.* 2007; Oto *et al.* 2008; D'Alessandro *et al.* 2010; Russo *et al.* 2010; Dronavalli *et al.* 2015). With an increasing trend towards utilisation of extended criteria donor organs due to increasing waiting list pressures, a resultant reduction in threshold for initiation of ECMO support in certain patients to support the graft in the initial phase of reperfusion (first 24 hours) may result in an over-estimation of the incidence of PGD (Chew *et al.* 2014). This is especially true in high-risk recipients with a significant inflammatory milieu as a result of receiving a combination of in-hospital inotropic or short or long-term mechanical circulatory support pre-transplant.

1.12.2 Pathophysiology of PGD

The donor heart is exposed to a multitude of physiological insults at 4 specific time points; brainstem death, hypothermic ischaemia, warm ischaemia, and ischaemia-reperfusion injury.

1.12.2.1 Brainstem death

The first insult occurs during the declaration of brainstem death in donation after brainstem death (DBD). Raised intracranial pressure (ICP) invariably is the final pathway in DBD donors in which case the aetiology of death is usually a result of an intracerebral haemorrhage, hypoxia leading to oedema, inflammation or a space-occupying lesion in the cranium. The cerebral perfusion pressure is usually maintained by homeostatic mechanisms which result in increased arterial pressure. Due to the limited plasticity of the brain within the confines of the cranium, brain herniation ensues resulting in pontine ischaemia (Gordon and McKinlay 2012). This causes a surge in the adrenergic response, resulting in pulmonary and systemic hypertension which increases the afterload in both ventricles causing myocardial ischaemia. In some patients, stimulation of baroreceptors results in the classic Cushing's response characterised by hypertension and bradycardia (Shivalkar *et al.* 1993; Dictus *et al.* 2009).

Vasomotor tone is reduced to the loss of spinal cord sympathetic activity resulting in unopposed vasodilatation, further reducing preload and indirectly afterload, affecting coronary blood flow and reducing myocardial perfusion. In response, there is an intense release of myocardial noradrenaline immediately after brain death that results in mitochondrial and cytosolic calcium overload to increase contractility to counteract this unopposed vasodilatation (Shivalkar *et al*. 1993). Pituitary ischaemia may also result occur during brain herniation resulting in significant endocrine derangement (Souter *et al*. 2017).

These patients are also prone to metabolic disturbances due to acidosis, hypomagnesaemia or hypokalaemia secondary to mannitol initiation to reduce ICP, catecholamine administration, all of which contribute to increased myocardial oxygen demand or reduced myocardial perfusion(Souter *et al*. 2017). This initial surge may also cause catecholamine depletion leading to a vicious circle of impaired myocardial oxygenation and increasing myocardial oxygen demand (Gordon and McKinlay 2012).

Early donor management may reduce the deleterious effects of the abovementioned phenomenon. Early administration of vasopressors is aimed at reducing the unopposed vasodilatation (Rosendale *et al*. 2003). Methylprednisolone administration has been shown to reduce lung injury independently from its anti-inflammatory activity in animal studies as well as reduce extravascular lung water and reduce PCWP in DBD donors (Venkateswaran *et al*. 2008; Meers *et al*. 2011). It is also used in conjunction with insulin to ensure normoglycemia in the donor (Wood *et al*. 2004). The role of thyroid hormone replacement is uncertain during donor management with current consensus suggesting triiodothyronine(T_3) administration only in depleted donors (Venkateswaran *et al*. 2008; Novitzky *et al*. 2015; Kumar *et al*. 2017; Souter *et al*. 2017).

1.12.2.2 Hypothermic ischaemia

Despite advancements in normothermic ex-vivo perfusion devices, cold storage remains the mainstay of transportation after organ retrieval. Organ retrieval often has two distinct phases, a warm phase, and a cold phase. The warm phase involves dissection of the heart and exposure of the innominate artery and the

two cavae with variations in the degree of dissection depending on whether the lungs are to be retrieved as well. The retrieval surgeon also palpates the coronary arteries for potential disease. The aorta is prepared for administration of cold cardioplegia for the commencement of the cold phase.

Depending on the size of the patient and type of cardioplegic solution administered, the volume of administration may differ. The retrieval surgeon then performs a left atriotomy by lifting the heart. Once the aortic cross-clamp is applied, cold cardioplegia is infused via the aortic root at approximately 4ºC. The retrieval process is completed with the heart placed in a cold storage container. Cold storage induces hypothermic arrest of metabolism and maintains viability during this reduced metabolic state, therefore abating cellular swelling and minimalizing reperfusion injury (Schipper *et al.* 2016). At these temperatures, and with limited oxygenation, the heart switches from aerobic to anaerobic metabolism. This can have deleterious effects on the stored organs as ATP is slowly depleted. However, it should be noted that in the hypothermic state (0-4ºC), there is a 12-fold decrease in metabolic rate (Belzer and Southard 1988). The overall goal is to reduce the accumulation of mitochondrial by-products of metabolism such as oxygen-free radicals. Cold storage is also based on the assumption that there is no variation in temperature and the heart is uniformly cooled. In elderly patients whereby, pathologic LV hypertrophy may be noted, especially in those with a clinical history of hypertension, this may not be possible, possibly explaining why these hearts are more susceptible to ischaemic injury (D. Marelli *et al.* 2000; Russo *et al.* 2010). The length at which the hearts are kept in cold storage may also play a part in the formation of these free radicals. Cellular swelling and lactic acidosis occur in prolonged cold storage, causing a rise in intracellular H^+ ions (Anaya-Prado and Delgado-Vazquez 2008). The Na^+/H^+ exchanger is activated resulting in an increase in intracellular Na^+ which activates the Na^+/Ca^{2+} exchanger (Vigne *et al.* 1985; Karmazyn *et al.* 1999). The final pathway is the accumulation of cytosolic Ca^{2+}. This will play a major role in the pathogenesis of ischaemic-reperfusion injury.

1.12.2.3 Warm ischaemia

On arrival at the recipient centre, the heart is removed from cold storage and inspected. The period in which the heart is removed from cold storage or from

ex-vivo normothermic perfusion to the final release of the recipient aortic cross-clamp is termed warm ischaemic time. The heart is exposed to warmer temperatures which slowly increases its metabolic rate, resulting in increased formation of oxygen-free radicals. In a study by Marasco et al, warm ischaemic time and increasing donor age were independent predictors of early survival, suggesting an acceleration of the deleterious effects described during the cold ischaemic phase (Marasco *et al*. 2012). Similar findings were noted by Banner et al, despite a broader definition of warm ischaemic time termed surgical implant time (i.e. arrival of heart to the theatre to release of recipient aortic cross-clamp).

1.12.2.4 Ischaemia-reperfusion Injury (IRI)

IRI is defined as cardiomyocyte damage secondary to myocardial restoration of blood flow (Braunwald and Kloner 1985). On release of the recipient cross-clamp, the donor heart is re-perfused which leads to further calcium overload. This alongside the release of oxygen-free radicals activates the formation of mitochondrial permeability transition pores (MPTP) which are non-specific, thus allowing free movement of apoptotic factors across the cell membrane (Morciano *et al*. 2017). This causes a cascade of myocardial damage, causing loss of cardiomyocyte function and viability; all of which are most pronounced immediately after reperfusion (Penna *et al*. 2013). Post-conditioning may play a role in attenuating the effects of IRI by inhibiting MPTP formation. Cyclosporine A, a known MPTP desensitizer, has been shown to induce appreciable protection in acute myocardial infarction (Argaud *et al*. 2005). However, a recent metanalysis failed to show any benefit of Cyclosporine A post-infarction (Upadhaya *et al*. 2017). Other forms of preconditioning have also been suggested in an attempt to inhibit MPTP formation have shown some promise in animal studies (Liu *et al*. 1991; Birnbaum *et al*. 1997; Hausenloy *et al*. 2004). However, larger clinical trials in surgical revascularisation studies have revealed mixed results with some studies showing clinical improvements (Thielmann *et al*. 2013) and others showing minor biochemical improvements with no clinical benefit (D'Ascenzo *et al*. 2012; Hausenloy *et al*. 2015; Benstoem *et al*. 2017; Pierce *et al*. 2017; Meybohm *et al*. 2018). The proponents of ischaemic preconditioning have suggested that the duration of ischaemia in these studies probably limits the effect of preconditioning with prolonged ischaemia showing greater benefit

of preconditioning (Kleinbongard *et al*. 2016). To date, no studies have been performed in human heart transplants, with animal models of orthotopic heart transplants showing promising results potentially highlighting its benefits in prolonged ischaemia(Konstantinov *et al*. 2005).

Animal studies do however highlight attenuation of IRI using preconditioning in diabetics (Ishihara *et al*. 2001; Nieszner *et al*. 2002; Kristiansen *et al*. 2004), females (Crisostomo *et al*. 2006; Heinen *et al*. 2018), LV hypertrophied hearts (Moolman *et al*. 1997), obesity (Kristiansen *et al*. 2004), hypertensives (Ebrahim *et al*. 2007) and in the elderly (Bartling *et al*. 2003; Ebrahim *et al*. 2007; Heinen *et al*. 2018); all of which have been noted to be risk factors for PGD.

Another mechanism of IRI is hyper-contracture-mediated sarcolemmal rupture (HMSR). During the ischaemic phase, the low cytosolic ATP concentrations are quickly exhausted resulting in myofibrillar shortening that remains fixed as all cross-bridges between actin and myosin remain in an attached state (Nichols and Lederer 1990). This causes a moderate contracture with little structural damage but leads to cytoskeletal defects and increasing the cardiomyocytes fragility to mechanical damage which is reversible with early reperfusion (Schluter *et al*. 1996).

Reperfusion induced hyper-contracture occurs after prolonged ischaemia. There is greater myofibrillar shortening and cytoskeletal damage when compared to the ischaemic phase alone. It causes a marked rise in end-diastolic pressure with increased ventricular wall stiffness. It is shown to be due to Ca^{2+} overload which develops during ischaemia and is rapidly re-energised, as it would on release of the cross-clamp (Piper *et al*. 2004). In cellular studies, re-perfused infarcts consist almost exclusively of contraction band necrosis (Piper *et al*. 2004). Sarcolemmal rupture occurs due to the degradation of structural proteins like α-fodrin (Inserte *et al*. 2005) and ankyrin (Garcia-Dorado *et al*. 2006), impairing the Na^{+}/Ca^{2+} exchanger pumps. Sarcolemma rupture also results in increasing Na^{+} influx into cardiomyocytes via gap junctions and may propagate to adjacent cells (Garcia-Dorado *et al*. 2004).

Couchani (Chouchani *et al*. 2014) developed a comparative in vivo metabolomic analysis to identify pathways for mitochondrial ROS production during IRI. They

identified selective accumulation of the citric acid cycle (CAC) intermediate succinate as the metabolic signature of ischaemia in a range of tissues and as the driver for mitochondrial ROS production during reperfusion. Ischaemic succinate accumulation is caused by the reversal of succinate dehydrogenase, driven by other metabolic pathways (excessive fumarate from purine nucleotide breakdown and partial reversal of the malate/aspartate shuttle). Succinate is then rapidly oxidised by succinate dehydrogenase, perpetuating extensive ROS generation. The separate pathways driving succinate accumulation is highlighted in Figure 1-5.

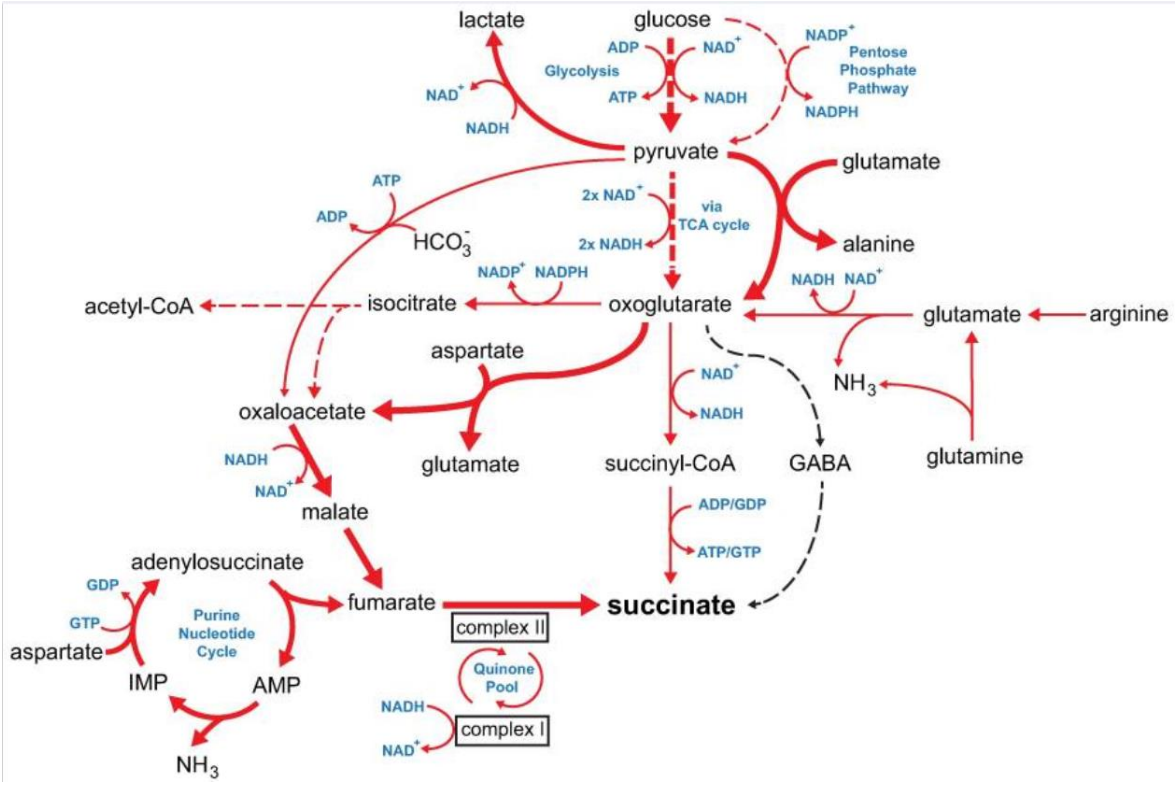


Figure 1-5 Metabolic model identifying pathways that can become activated by tissue ischaemia to drive succinate accumulation.
(GDP = Guanosine Diphosphate, GTP = Guanosine Triphosphate, NAD^+= Nicotinamide adenine dinucleotide (oxidised), NADH = Nicotinamide adenine dinucleotide (reduced), ADP = Adenosine Diphosphate, ATP= Adenosine Triphosphate, GABA=Gamma Aminobutyric Acid, TCA cycle = Kreb's cycle, $NADP^+$ = Nicotinamide adenine dinucleotide phosphate (Oxidised), NADPH = Nicotinamide adenine dinucleotide phosphate (reduced). Adapted with permission from ET Chouchani et al. Nature 000, 1-5 (2014) doi:10.1038/nature13909

Couchani et al demonstrated that succinate levels had a direct correlation with the extent of mitochondrial reperfusion injury by the addition of dimethyl succinate to ischaemic primary cardiomyocytes. Conversely, this may also serve as a future pharmacotherapeutic option with inhibition of certain pathways abolishing the level of ischaemic succinate, and in turn, ameliorated the IRI

effects. This was shown by infusing dimethyl malonate, a precursor of the succinate dehydrogenase inhibitor malonate, which reduced the extent of cardiac IR injury in an in vivo mice model(Chouchani *et al*. 2014). Figure 1-6 (next page) shows how the accumulation of ischaemic succinate drives this process from a mitochondrial to the cellular level and finally the myocardial stunning.

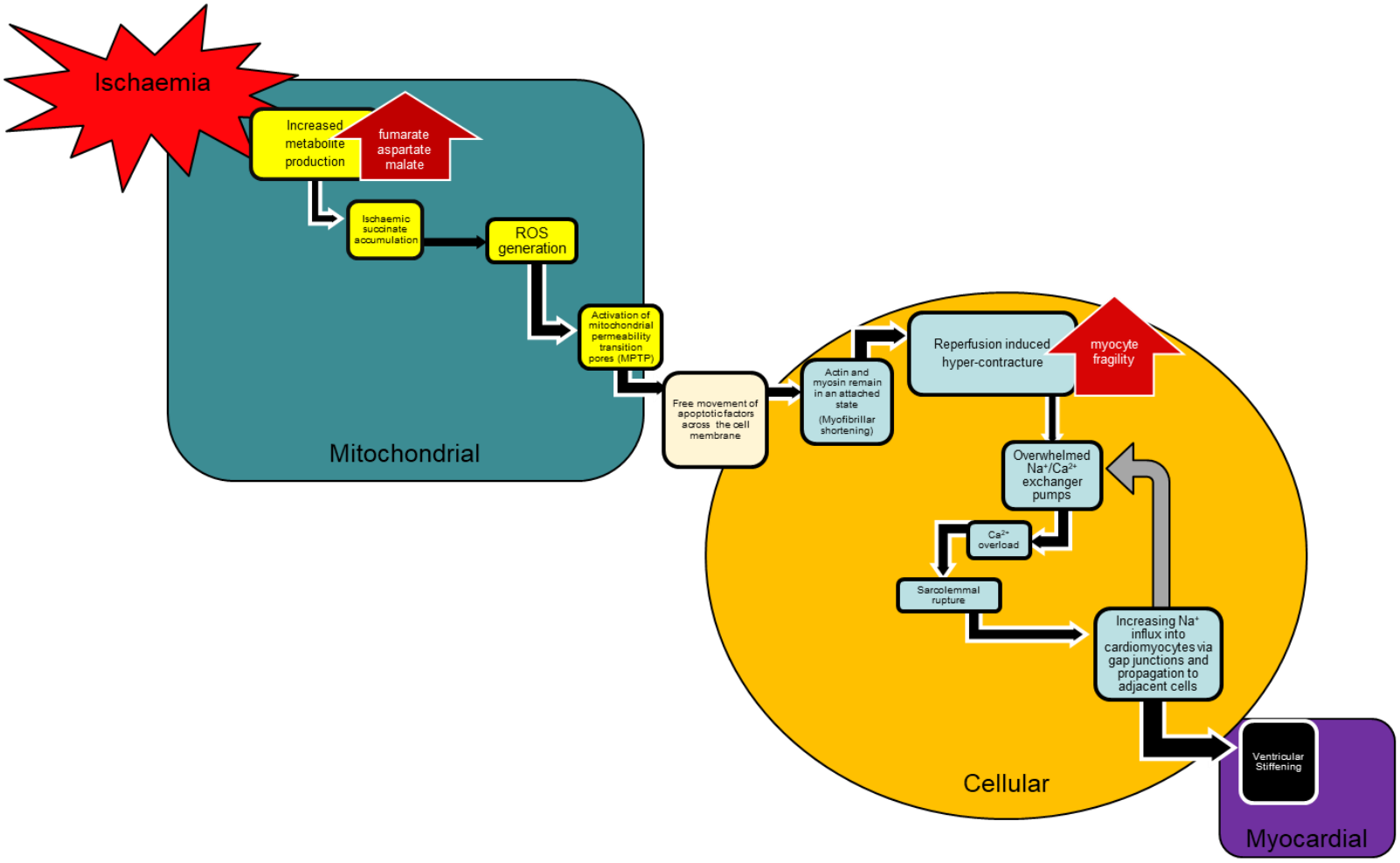


Figure 1-6 The pathophysiological mechanism of ischaemic reperfusion injury at mitochondrial, cellular and myocardial levels
Fumarate, aspartate, and malate rise during ischaemia resulting in accumulation of ischaemic succinate which drives Reactive Oxygen Species (ROS) generation. This, in turn, drives the movement of apoptotic factors across the cell membrane with cascading injuries as described.

1.12.2.5 Donation after Circulatory Death (DCD)

Donation after Circulatory Death (DCD) provides a different set of insults to the donor heart. The heart is placed in a hypoxemic and hypercarbic environment following the withdrawal of life support (White *et al*. 2018). This causes pulmonary vasculature constriction, with increased pulmonary vascular resistance imposed on the right heart (White *et al*. 2016). Although the catecholamine surge of brainstem death is not present, the hypoxemic environment induces an adrenergic response. This quickly depletes the myocardial energy stores – leading to circulatory arrest. A mandatory standoff period ensues as part of the guidelines for the declaration of circulatory death (Manara *et al*. 2012). The heart is exposed to a period of warm ischaemic time that is present until the institution of either normothermic regional perfusion (NRP) or ex-vivo normothermic perfusion using the Organ Care System device (TransMedics Organ Care System (OCS), Andover, MA, USA)(Page *et al*. 2018).

This prolonged ischaemic period causes intracellular acidosis which causes activation of the Na^+/H^+ exchanger in a pathway similar to the warm ischaemic period described above, with a net result of an accumulation of intracellular Ca^{2+} and follows the ischaemic-reperfusion pathway on reperfusion.

1.12.2.6 Recipient factors

Some recipient factors may also predispose a patient to PGD. Recipients, especially patients who have been on inotropic support and mechanical devices, have activation of their systemic inflammatory response, which causes intense vasodilation, thus lowering the systemic vascular resistance. The net result is a hypotensive state despite adequate filling and high cardiac output that is refractory to vasopressor support (Chan *et al*. 2017). The exact pathogenesis of this is poorly understood to date, some mechanisms have been postulated. Vasodilation is believed to be caused by the unopposed activation of vascular smooth muscle adenosine triphosphate-sensitive potassium channels (K_{ATP} channels). Endogenous nitric oxide, a potent vasodilator is also implicated in the pathogenesis alongside vasopressin deficiency (Omar *et al*. 2015).

Prolonged ischaemic time has been shown in previous studies to correlate with complications occurring after cardiopulmonary bypass(Chan *et al*. 2017). This association is thought to be due to the summative effect of the exposure of blood to synthetic surfaces of the cardiopulmonary bypass circuit which potentiates a cascading inflammatory response. This, in turn, could explain the increased incidence in recipients on advanced mechanical circulatory support (ECMO or Short-Term VAD). The ischaemic time may also be prolonged in some patients whereby careful dissection is necessitated following a previous sternotomy, highlighting the importance of communication with the retrieval team to potentially delay the retrieval procedure to minimise ischaemic time (Rylski *et al*. 2010).

Another pathogenic mechanism that has been suggested in the past is recipient pulmonary hypertension. The donor heart in its ischaemic state is exposed to a relatively high pulmonary vascular resistance, giving rise to right-sided heart failure. Due to the poor adaptability of the right ventricle to a sudden change in vascular resistance, biventricular dysfunction ensues due to a reduced left-sided preload, thereby reducing coronary perfusion and end-organ perfusion in the systemic circulation (Stobierska-Dzierzek *et al*. 2001).

1.12.3 Risk Factors for PGD

Several risk factors have been suggested that may contribute to PGD. These include donor factors, recipient factors, and procedural factors.

1.12.3.1 Donor factors

1.12.3.1.1 Donor Age

Donor age has been shown to be a risk factor in several different studies. This may have been due to the poorer tolerance for long ischaemic times in hearts from older donors (Mark J. Russo *et al*. 2007). They noted that among younger donors, there was no significant correlation between ischaemic time and survival. However, as the donor age increased, there was a statistically significant correlation between ischaemic times and survival in donor ages>20. Other studies have also shown a direct correlation between donor age and low cardiac output states post-operatively, which were likely PGD, however, were

not characterised as such due to the lack of a definition at the time of publication (Potapov *et al*. 1999; Loebe *et al*. 2000; Blanche *et al*. 2002; Lietz *et al*. 2004).

1.12.3.1.2 Gender Mismatch

Female-Donor to Male-Recipient gender mismatch has been suggested as a risk factor for PGD (J. Kobashigawa *et al*. 2014). The exact mechanism is poorly understood as this persisted despite organ size matching. Male-donor to female-recipients did not result in an increased PGD rate. Gender mismatched organs also had a poorer survival at up to 5 years(S. Avtaar Singh *et al*. 2018b). In liver transplantation recipients had poorer graft survival in female donor: Male Recipient cohorts compared with other donor-recipient gender groups despite adjustment for donor risk factors and recipient variables (Croome *et al*. 2014). The role of H-Y minor histocompatibility antigens has been implicated. Several haematopoietic stem cell studies have shown an increased relapse rate in patients undergoing stem cell transplants in female donor: male recipient cohorts (Gratwohl *et al*. 2001; Kongtim *et al*. 2015).

1.12.3.1.3 Cause of Death in the Donor

Intracranial haemorrhage is the most common cause of death for DBD donors in the UK (S. Avtaar Singh *et al*. 2018b). One study showed increased PGD rates in organs retrieved from donors with intracranial haemorrhage compared to donors with traumatic causes of death (Yamani *et al*. 2004). The exact mechanism is not clear, although it is thought to be due to prolonged exposure to the catecholamine surge (Yamani *et al*. 2004). Animal studies have shown a direct correlation between increased intracranial pressure and worsening myocardial function(Shanlin *et al*. 1988; Shivalkar *et al*. 1993). Another study showed an association with early mortality with a lower survival to discharge rate in patients transplanted with hearts from donors with atraumatic intracranial haemorrhage(Tsai *et al*. 2002).

1.12.3.1.4 Donor Left Ventricular Hypertrophy

Donors with hypertension often have a degree of left ventricular hypertrophy (LVH). This is more apparent across Europe where the average age of the donor

is older compared to North America(Lars H. Lund *et al.* 2017a). The use of donors with LVH has resulted in mixed results with some centres having favourable results (Daniel Marelli *et al.* 2000; Felker *et al.* 2005; B. Lima *et al.* 2006; Goland *et al.* 2008; Pinzon *et al.* 2011) but others reporting an increased incidence of early graft failure or poorer survival (Aziz *et al.* 1997; Kuppahally *et al.* 2007; Stehlik *et al.* 2010a). The reason for the varying results is likely due to the association of LVH to age, which is an independent predictor of PGD. Hypertrophied hearts with associated hypertension are more susceptible to ischaemic injury (Dunn and Pringle 1987). Therefore, the ischaemic time for donors with hypertrophied hearts should be kept to a minimum. The Harefield team reported their experience in using marginal donors with mild LVH with normothermic ex-vivo perfusion (García Sáez *et al.* 2014). They showed promising short-term outcomes when utilising marginal hearts with continuous normothermic perfusion using the OCS device. The ISHLT guidelines also cite the level of evidence C for a class IIa recommendation stating that "it would seem appropriate to use hearts from donors with LVH and LV wall thickness <14 mm provided that it is not associated with ECG findings of LVH" (Costanzo *et al.* 2010).

1.12.3.1.5 Donor Inotropic Requirement

Inotropic support is sometimes needed during the donor organ retrieval process due to the depletion of catecholamine and/or a systemic inflammatory phenomenon as described above. Noradrenaline use can cause left ventricular dysfunction in the absence of brain death (Movahed *et al.* 1994). It also has a dose-dependent detrimental effect on the right ventricle in DBD donors (Santise *et al.* 2009; D'Alessandro *et al.* 2011b; Segovia *et al.* 2011). The use of vasopressin and terlipressin is currently recommended as first-line treatment to reduce the noradrenaline requirement (McKeown *et al.* 2012). It treats two conditions that occur commonly in DBD donors, neurogenic diabetes insipidus and reduction in systemic vascular resistance (Yoshioka *et al.* 1986). Venkateswaran et al showed that vasopressin use could result in the elimination or reduction of noradrenaline use in more than 50% of donors (Venkateswaran *et al.* 2009b).

1.12.3.2 Recipient Factors

1.12.3.2.1 Pre-operative Mechanical Circulatory Support

Pre-operative recipient ECMO/VAD usage has also been linked to PGD post-operatively(Young *et al*. 2001; Russo *et al*. 2010; D'Alessandro *et al*. 2011b; Hong *et al*. 2011). Several factors have been suggested as potential causes which have been discussed under the pathophysiology section above.

A recent study by Truby and colleagues highlighted the role of continuous-flow LVAD (CF-LVAD) in recipients as a risk factor for severe PGD (Truby *et al*. 2018). This is of particular interest as CF-LVADs have contributed significantly to the growth and success of mechanical circulatory support for advanced heart failure for bridging to transplant and as destination therapy. CF-LVADs also currently account for more than 95% of VAD implants (Kirklin *et al*. 2017). 45 out of 56(80.4%) patients with severe PGD were bridged to transplant (BTT) using CF-LVADs in Truby's study (Truby *et al*. 2018). It should be noted however there were significant other contributory factors as the severe PGD patients were older, had a higher percentage of previous amiodarone exposure, had higher creatinine levels, spent longer time on the waiting list and had higher CVP/PCWP ratios which were possibly indicative of subclinical right ventricular dysfunction.

1.12.3.2.2 Recipient Diabetes Mellitus

The role of recipient diabetes as a predictor of PGD is evident in multiple studies(Segovia *et al*. 2011; Nicoara *et al*. 2017). However, Segovia's study was unable to account for recipient diabetes as a predictor of PGD when using robust statistical analysis (overfitting of regression models)(Foroutan and Ross 2019). However, recipient diabetes seems to be a predictor of graft loss within and beyond the first-year post-transplant (Foroutan *et al*. 2018). This may be due to direct glucose-mediated endothelial damage, oxidative stress from superoxide overproduction and production of advanced glycation end-products, which may result in changes in endothelial permeability, excessive vascular protein deposition and altered blood flow (Funk *et al*. 2012). Taghavi et al revealed diabetic recipients were older and would be more likely to receive organs from diabetic donors who were who themselves were more often females and older (Taghavi *et al*. 2013).

1.12.3.2.3 Recipient Age

Several studies have associated advancing recipient age with PGD and mortality (D'Alessandro *et al*. 2011b; Segovia *et al*. 2011). A risk prediction model assessing in-hospital mortality for post-heart transplant patients included recipient age but utilised it as a categorical variable. The c-statistic of less than 0.7, however, suggested poor performance (Singh *et al*. 2012). ISHLT registry data also highlighted advancing recipient age with having slightly higher long-term mortality. This may probably reflect the higher incidence of comorbidities such as hypertension and diabetes in this cohort of patients as well (Yeom *et al*. 2013). Some studies have attributed this to the increased fatal infection rate in the elderly (Bull *et al*. 1996; Tjang *et al*. 2008).

1.12.3.2.4 Recipient Re-sternotomy

A recipient re-sternotomy indicates previous surgery, most commonly for durable Ventricular Assist Device implantation, previous congenital cardiac surgery or previous coronary bypass or valvular surgery (Morales *et al*. 2010). The dissection process in the recipient who has undergone a previous sternotomy often is more complex and hazardous with the potential for significant injury (Kuralay *et al*. 2004). One study showed that patients with prior sternotomies had an almost 3-fold increase for PGD risk (S. Still *et al*. 2018). The increased technical difficulty of the surgery may result in longer ischaemic times and are associated with higher rates of blood transfusion and subsequent need for reoperation for bleeding (Kansara *et al*. 2014a; Awad *et al*. 2015; S. Still *et al*. 2018). Patients with prior sternotomies were also more likely be older (S. Still *et al*. 2018) and have spent longer time on the waiting list (S. Still *et al*. 2018), possibly indicating durable VAD implantation (Awad *et al*. 2015) in these patients as a bridge to candidacy/transplantation.

1.12.3.2.5 Recipient pre-operative amiodarone therapy

Amiodarone is a Class III antiarrhythmic used for a variety of arrhythmias including both ventricular, supraventricular and atrial tachyarrhythmias. Its mechanism of action is primarily by prolonging the refractory period myocardium. Arrhythmias are highly prevalent in advanced heart failure patients (Santangeli *et al*. 2017). The evidence regarding PGD and the use of amiodarone

in recipients appear to be conflicting. Studies have shown that patients who had received amiodarone before transplantation had significantly lower heart rates post-transplantation (Macdonald *et al*. 1991; Chelimsky-Fallick *et al*. 1992), required atrial pacing for a longer time after transplantation (Macdonald *et al*. 1991) but had no increased inotropic requirements (Macdonald *et al*. 1991) and no increased mortality post-operatively (Macdonald *et al*. 1991; Chelimsky-Fallick *et al*. 1992; Rivinius *et al*. 2016). Other studies have indicated a dose-dependent (Wright *et al*. 2017) or duration-dependent (Chin *et al*. 1999) link between amiodarone use and PGD post-transplant.

1.12.3.3 Procedural Factors

1.12.3.3.1 Ischaemic Time

In DBD donations, the ischaemic time consists of the placement of the donor aortic cross-clamp until the release of the recipient aortic cross-clamp (Halazun *et al*. 2007). For DCD donations, the ischaemic time is possibly under-estimated with a period of functional warm ischaemia (starting when systolic blood pressure is less than 50 mm Hg) till the heart is re-perfused on an ex-vivo perfusion device(OCS) (Page *et al*. 2018). The 2nd period of ischaemia ensues from the removal of the heart from the OCS till the release of the aortic cross-clamp from the recipient.

Cold ischaemic time consists of time spent in cold storage and warm ischaemia ensues once the heart is removed from cold storage or the OCS rig up to release of the aortic cross-clamp. Prolonged ischaemic time is associated with an increased rate of PGD (Russo *et al*. 2010; Segovia *et al*. 2011; Marasco *et al*. 2012; Squiers *et al*. 2017a). Banner et al noted that longer ischemia time was a risk factor for 30-day mortality after heart transplantation. They also noted that the surgical implant time (i.e. warm ischaemic time) was an independent risk factor for 30-day mortality (Banner *et al*. 2008). The direct ischaemic insult of warm ischaemia is explained in the pathophysiology above. Marasco et al also noted found that poorer survival with a warm ischemia time (WIT) of >80 minutes (Marasco *et al*. 2012). Ischaemic time is also closely related to donor age. Older donor organs are more susceptible to ischaemic injury compared to younger donor organs (Mark J. Russo *et al*. 2007; Wong *et al*. 2017).

1.12.3.3.2 Cardiopulmonary Bypass (CPB) Time

Prolonged CPB duration independently predicts postoperative morbidity and mortality after general cardiac surgery (Salis *et al*. 2008). Kirklin and colleagues alluded to a systemic inflammatory response following CPB (Kirklin 1980). The mechanism of injury from CPB and ischaemic-reperfusion of the myocardium is similar; both producing a hyperdynamic circulatory state due to a low systemic vascular resistance, platelet and coagulation factor dysfunction, inflammatory pathway activation triggered by leucocytes and endothelial cells and finally cytokine release and formation of oxygen-free radicals (Anselmi *et al*. 2004). It is also linked to an increased blood product requirement which is associated with both infection and ischaemic postoperative morbidity, increased hospital stay, increased early and late mortality, and increased hospital costs (Kuduvalli *et al*. 2005; Koch *et al*. 2006; Murphy *et al*. 2007). Therefore, prolonged CPB time may contribute to the worsening of the ischaemic injury caused by PGD.

1.12.3.3.3 Size Mismatch

The size of the donor graft has many implications for the recipient. It is a powerful predictor of survival with recipients receiving undersized grafts having an increased 1-year mortality, and a 36% increased mortality within the first 30 days (R. M. Reed *et al*. 2014). Smits showed inferior survival in donors who were undersized by more than 20% using data from the Eurotransplant database (Smits *et al*. 2003). This study however also showed an inferior survival amongst gender mismatched donors, which were more likely to be undersized in female donors to male recipients. Patel et al refuted the findings in an analysis of the UNOS database, suggesting increased pulmonary resistance as a confounder (Patel *et al*. 2008). Another analysis of the UNOS database several years later concluded that donor: recipient BMI ratio <0.75 was associated with an increase in post-transplant mortality in univariate analysis but not in multivariate analysis, highlighting gender mismatch as a confounder (Weiss *et al*. 2009). Other multi-institutional studies have also highlighted donor-recipient weight difference to be significant, but only in older grafts which were gender mismatched (Stehlik *et al*. 2010b). Jayarajan and colleagues noted that donor weight mismatching by up to 40% had no bearing on the outcome in non-gender mismatched patients (Jayarajan *et al*. 2013). The significance of size mismatching is hard to elucidate

from studies but smaller single centre data suggest poorer outcomes such as an increased length of stay(Murphy *et al*. 2016) and increased LV hypertrophy (Kertesz *et al*. 1995). The direct link between PGD and size mismatch, however, remains elusive.

1.12.3.4 Investigations and Biomarkers

The current definition for PGD is based on the treatment options utilised. Several biomarkers have been suggested as potential predictors of PGD, although to date none are used in routine care.

1.12.3.5 Inflammatory markers

The pro-inflammatory state accompanying PGD supports the use of inflammatory markers as potential predictive biomarkers. Tumor Necrosis Factor-α(TNF-α), Interleukin-6 (IL-6), Neutrophils and Procalcitonin (PCT) have all been suggested as potential biomarkers.

1.12.3.5.1 TNF-α (Donor)

Tumor necrosis factors are produced by lymphocytes and macrophages that cause cell lysis (Locksley *et al*. 2001). TNF-α has been implicated in the pathogenesis of numerous inflammatory conditions including arthritis (Cui *et al*. 2018), asthma, chronic obstructive pulmonary disease (COPD), acute respiratory distress syndrome (ARDS) (Mukhopadhyay *et al*. 2006), myocarditis (Sack 2002) and congestive heart failure (Levine *et al*. 1990).

Birks and colleagues noted increased expression of TNF-α in unused donor hearts due to poor function and compared them with donors with good ventricular function (used donors) pre-retrieval and in patients with advanced heart failure (HF) (Birks *et al*. 2000). In lung transplantation, a recent study highlighted the role of intravascular donor monocytes in the pathophysiology of IRI and PGD in lungs (Tatham *et al*. 2018). Another group showed a reduction in PGD rates post-lung transplantation after leukocyte depletion during implantation(Schnickel *et al*. 2006). Venkateswaran et al highlighted poorer biventricular function in donors with elevated levels of TNF-α using serum immunoassays (Venkateswaran *et al*. 2009a).

A Brazilian group showed recipients receiving grafts from donors expressing lower concentrations of plasma soluble tumour necrosis factor receptors 2 (sTNFR2) and IL-6, required more inotropic support post-transplantation (Braulio *et al*. 2016).

1.12.3.5.2 IL-6 (donor and recipient)

Interleukin 6 (IL-6), is produced in response to infections and tissue injuries by stimulation of acute-phase responses. It bridges the adaptive and innate immune responses and plays a major role in autoimmune conditions (Tanaka *et al*. 2014; Fontes *et al*. 2015). Birks et al noted IL-6 mRNA expression was 2.4-fold higher in the unused donor hearts than in those used for transplantation in pre-retrieval samples, with levels almost 5 times higher than in the potential recipients with advanced heart failure (Birks *et al*. 2000). The used donor hearts had an almost 2-fold increase of IL-6 mRNA levels compared to the recipients. These findings were also noted by Plenz and colleagues, who noted a significant rise in IL-6 and IL-6 receptors in DBD donors, comparable to patients with advanced heart failure in comparison with a control group not compromised by the sequelae of brain death. This may explain the close association of elevated IL-6 serum levels and acute allograft dysfunction in the early post-operative period (Plenz *et al*. 2002).

IL-6 was also shown to be associated with PGD post-lung transplantation. The serum and bronchioalveolar lavage concentrations of IL-6 were higher in transplant recipients with PGD than those without (Moreno *et al*. 2007).

Animal models have shown that ischaemic cardiac myocytes in watershed viable zones of a myocardial infarction exhibited reperfusion-dependent expression of IL-6 mRNA after reperfusion (Kukielka *et al*. 1995; Gwechenberger *et al*. 1999).

1.12.3.5.3 Procalcitonin (Donor)

Procalcitonin(PCT) is a 116 amino acid peptide that has an approximate molecular weight of 14.5 kDa and belongs to the calcitonin (CT) superfamily of peptides(Jin and Khan 2010). It is a biomarker that exhibits greater specificity than other proinflammatory markers in identifying patients with sepsis(Jin and Khan 2010).

In transplantation, PCT was used to differentiate bacterial infection from organ rejection. PCT levels are elevated in both conditions but significantly higher in the presence of infections (Yu *et al*. 2014; Sandkovsky *et al*. 2015). It has important prognostication value in heart transplantation with low levels signifying an uneventful course, and a higher value indicating increased mortality in the early post-operative period (Madershahian *et al*. 2008). Venkateswaran et al noted that elevated donor serum PCT levels were associated with poorer donor cardiac index and worse biventricular function despite early donor management during pre-retrieval optimisation (Venkateswaran *et al*. 2009a). The authors demonstrated that pre-optimisation baseline PCT levels of less than or equal to 2ngmL^{-1} was a potentially useful tool in predicting the end-management heart usability for transplantation. Similar findings were noted by Wagner and colleagues with increased 30-day mortality and early graft dysfunction in hearts utilised from donors with elevated PCT levels (Wagner *et al*. 2001). The increased early graft failure rate was also noted in renal (van Ree *et al*. 2009), but not in liver (Eyraud *et al*. 2008) or lung transplantation (Sammons and Doligalski 2014).

1.12.3.5.4 Neutrophil-to-lymphocyte ratio (NLR) (Recipient)

Both NLR and Platelet-to-Lymphocyte ratio (PLR) have been used as markers of inflammation with prognostic value in coronary artery disease (Bhat *et al*. 2013; Ucar *et al*. 2016) and other conditions. NLR ratios have been shown to be independently related to mortality in patients hospitalized for acute heart failure with LVSD (Huang *et al*. 2017). Implantation of LVAD in patients with heart failure showed reversibility of NLR which reflects the reversal of various HF mediated inflammatory processes (Yost *et al*. 2017).

A group in Argentina studied the relationship between the two ratios and survival after heart transplantation (Seropian *et al*. 2018). They noted NLR (baseline and at 6 hours) to be a good predictor of early mortality post-heart transplantation but not PLR. The number of patients in this single centre study was relatively small (n=111). A Polish single centre study noted similar findings in their renal transplant cohort, with NLR showing good predictive value of early graft dysfunction (Hogendorf *et al*. 2018). Another recent study showed a good correlation between NLR and survival after ECMO institution in non-transplant patients presenting with cardiogenic shock (Yost *et al*. 2018). However, patients

in the increased NLR ratio arm of this study were also significantly older with a higher blood urea nitrogen level.

1.12.3.5.5 Troponin (Donor)

Cardiac troponins are regulatory proteins that control the calcium-mediated interaction between actin and myosin. The measurements of serum cardiac troponin I (cTnI) and cardiac troponin T (cTnT) have been shown to be sensitive and specific markers of myocardial damage (Sharma *et al*. 2004).

The pathophysiology of brainstem death results in a catecholamine storm that is believed to cause transient myocardial ischemia and injury (Vamsidhar B. Dronavalli *et al*. 2010). Circulating cardiac troponin concentrations may, therefore, be elevated in the donor.

Several studies, however, have shown that elevated serum troponin levels in donors may predict adverse outcomes post-transplantation. Increasing cTnT levels have been shown to be associated with a reduction in left ventricular ejection fraction in the donor (Riou *et al*. 1995). Potapov et al showed in a single centre observational study that increased donor cTnT levels were associated with an increased rate of early allograft failure (Potapov *et al*. 2003). They showed a similar association with PCT indicating a coexistent proinflammatory state in these donors. PCT and cTnT levels, however, showed poor specificity. There was also no correlation between PCT and cTnT values and there was no significant interaction between the two markers using a logistic regression model (P=0.28). Vijay et al conducted a similar study, using endomyocardial biopsy-proven rejection at 1 year as the primary endpoint. They noted a linear correlation between the grade of rejection at 1-year and donor cTnT levels (Vijay *et al*. 1998). Another study by Potapov et al showed an association between increasing cTnI levels in donors to early graft dysfunction post-transplantation (Potapov *et al*. 2001).

In donors with subarachnoid haemorrhages, cTnI was a good indicator for left ventricular dysfunction, however, this was reversible, and did not affect outcomes post-transplant (Deibert *et al*. 2000; Deibert *et al*. 2003). Boccheciampe et al noted that cTnI values in donors were not associated with

PGD or post-transplant survival (Boccheciampe *et al*. 2009). Other larger studies of donor serum troponin have shown no association between elevated levels and PGD (Khush *et al*. 2007; Madan *et al*. 2016).

A recent study of cTnI in the preservation solution(University of Wisconsin solution and Custodiol) during transportation of heart grafts, however, showed that elevated cTnI (scaled to the corresponding LV mass) was predictive of post-transplant PGD (Schechter *et al*. 2016). They also noted a poor correlation between preservation fluid cTnI levels and donor serum cTnI levels. They raised the possibility that incomplete myocardial preservation may play a role in PGD pathogenesis. However, there were only 43 patients in the study, and only ischaemic time was noted to be a predictor of PGD in their logistic regression model.

1.12.3.5.6 Brain natriuretic peptide (BNP)/ N-terminal pro–B-type natriuretic peptide (NT-proBNP) (Donor)

BNP and its amino-terminal pro-fragment, NT-proBNP is commonly used for diagnosis and prognostication in heart failure (Yamamoto *et al*. 1996; Groenning *et al*. 2004). They are released by the myocardium in response to increasing ventricular wall stress (Krittayaphong *et al*. 2008). They have been shown to correlate well with ventricular dilation (Krittayaphong *et al*. 2008), adverse remodelling (Giallauria *et al*. 2008), and death after acute myocardial infarction (de Lemos and Morrow 2007). Dronavalli et al showed that elevated NT-proBNP correlated well with poor echocardiographic and haemodynamic findings of cardiac function in potential DBD donors (V. B. Dronavalli *et al*. 2010). Vorlat et al linked increased BNP levels to a lower cardiac output post-transplant and a prolonged hospital stay (Vorlat *et al*. 2012). They noted that a donor serum BNP of >160 pg/ml had 89% accuracy to predict poor cardiac performance in the recipient (cardiac index <2.2 litres/min/m^2). The authors, however, could not show a correlation between post-operative inotropic support and BNP levels.

1.12.3.6 Others

1.12.3.6.1 SWItch/Sucrose NonFermentable, a matrix-associated, actin-dependent regulator of chromatin subfamily a-like 1 (SMARCAL1) (Donor)

SMARCAL1 is an intracellular protein that acts as a DNA-dependent ATPase involved in transcription, DNA repair, and chromatin dynamics (Vamsidhar B. Dronavalli *et al*. 2010). Aharinejad et al noted that elevated serum SMARCAL1 levels in their cohort of 336 donors were predictive of recipient PGD (Aharinejad *et al*. 2009). In addition, SMARCAL1 levels correlated well with survival at 3 months, 1-year and 5-year survival. Using a donor serum cut off of ≥1.25 ng/ml, they demonstrated a 96% sensitivity and 88% specificity for predicting PGD. Pre- and post-aortic donor cross-clamp serum SMARCAL1 concentrations were the best markers of PGD risk. To date, no other validation studies have been performed.

1.12.3.6.2 Donor myocardial hypoxia inducible factor (HIF)-1α (Donor)

HIF-1 is a heterodimeric α, ß transcription factor that mediates tissue responses to hypoxia (Jiang *et al*. 1996). Aharinejad et al performed a series of assays using 857 donor LV myocardial biopsies obtained before and after aortic cross-clamping in the donor, and at 10, 30 and 60 min following reperfusion (Aharinejad *et al*. 2007). In the cDNA array, only HIF-1α mRNA expression after aortic cross-clamping in donors and at 10 min following the release of the aortic cross-clamp in the recipient were significant predictors of PGD. The authors hypothesize that the release of cytokines and inflammatory chemokines activated by ischemia and reperfusion injury reach the highest peaks prior to cross-clamping and just after reperfusion. Other studies have demonstrated the protective signalling of HIF-1 against ischemia-reperfusion injury in the heart (Loor and Schumacker 2008; Amaral and Okonko 2015). To date, however, there have been no further studies linked HIF-1α to PGD.

1.12.3.6.3 Heme-oxygenase-1 (Recipient)

The HOT study (NCT01430156) was a randomised placebo-controlled trial evaluating the effect of the drug human hemin (Heme Arginate [HA]) on heme oxygenase-1 (HO-1) upregulation and renal function in recipients of deceased

donor kidney transplants(Thomas *et al*. 2016). HO-1 is involved in the degradation of heme and plays a protective role in IRI. The objective of this Phase IIb trial was to ascertain if hemin could induce HO-1 and therefore potentiate its beneficial effects against IRI. The study showed that hemin successfully induced HO-1 upregulation safely. Larger studies are currently to identify if HO-1 upregulation translates to improved organ function and survival.

1.12.3.6.4 Serum exosome proteomics (Recipient)

Several published abstracts have highlighted the role of serum exosome proteomic analysis in the recipient as a potential biomarker for PGD (Giangreco *et al*. 2017; Fine *et al*. 2018). Giangreco et al noted that pretransplant serum exosome analysis revealed an inflammatory phenotype and complement activation in patients who later developed PGD which could be identified by the absence or presence of the biomarkers alone. Fine et al showed this could be further used to differentiate patients who would later develop PGD RV from PGD LV. In their study, significant upregulation of angiotensinogen (AGT) and adiponectin (ADIPOQ) signalling pathways were noted in the PGD LV group whereas hepatic growth factor activator (HGFAC) and insulin-like growth factor binding protein 3 (IGFBP3) pathways were both upregulated in the PGD RV group. The significance of these findings may hopefully shed light on the pathogenesis of PGD in the near future.

1.12.3.7 Prevention of PGD

A single administration of cold flush preservation fluid remains the gold standard for myocardial protection during transplantation. It confers reliable protection for a limited amount of ischaemic time in young donor hearts (Jon Kobashigawa *et al*. 2014). The increasing use of extended criteria donors, however, necessitate more aggressive protection strategies to attenuate the ischaemic effects on hearts. In a study conducted by the Hamburg group, they noted that the use of a leukocyte depleting filter alongside additional regular antegrade administration of Buckberg cold blood cardioplegia in intervals of 20 minutes resulted in a reduction of PGD rates (Wagner *et al*. 2013). Similar findings were noted by a group from the Czech Republic, utilising continuous cold blood cardioplegia followed by controlled reperfusion of warm blood (Cerny *et al*.

2002). The Glasgow group utilised a similar variation with continuous antegrade perfusion in a contemporary cohort of patients, resulting in a significant reduction in PGD rates compared to a historical group of patients and the national UK cohort (Morcos *et al.* 2018). The exact mechanisms by which additional cardioplegia administration reduces PGD remains uncertain. It may play a role in pre-conditioning, mitigating the impact of reperfusion or preventing generation and propagation of inflammatory pathways (Habertheuer *et al.* 2014).

1.12.3.8 Treatment and Management of PGD

Treatment of PGD thus far is still primarily supportive care. In a consensus statement by Kobashigawa et al, the treatment and management of PGD across 5 high volume transplant centres were evaluated. PGD is initially managed by using inotropic support using catecholamines and phosphodiesterase inhibitors. The most common escalation therapy that follows inotropic use is an intra-aortic balloon pump. Following this, advanced mechanical support is initiated which is usually directed by the expertise of the transplant units themselves. The most common mode of support is extracorporeal membranous oxygenation with both central and peripheral cannulation strategies utilised. The heart should be allowed to eject to prevent stasis and thromboembolic complications

For primary RV-PGD, nitric oxide may be used to reduce pulmonary vascular resistance. Following a period of support on ECMO, a short-term ventricular assist device is then implanted depending on the level of support needed (L-VAD, R-VAD, BiVAD ± oxygenator, Total Artificial Heart). Where possible, the patient is then re-evaluated for redo-orthotopic heart transplantation.

1.12.3.8.1 Levosimendan

Levosimendan is a calcium sensitizing agent and an inodilator which increases cardiac contractility. Its primary mode of action is by increasing the sensitivity of troponin-C to calcium during systole thereby increasing cardiac performance without increasing myocardial oxygen consumption. It also reduces peripheral vascular resistances by the opening of adenosine triphosphate–dependent K+ channels (Russ *et al.* 2007). It was initially used for treatment of cardiogenic shock post-acute myocardial infarction(Russ *et al.* 2007). However, SURVIVE, a

multicentre RCT evaluating levosimendan vs dobutamine in acute decompensated heart failure, revealed no differences in survival outcomes between the two groups (Mebazaa *et al*. 2007). There was an initial reduction in plasma B-type natriuretic peptide levels in patients in the levosimendan group compared with patients in the dobutamine group. Florian Weis and colleagues report a case series of 12 patients with PGD who received 0.1 µg/kg/min levosimendan for PGD with a centre specific definition of LVEF<30% on transoesophageal echocardiogram with a combination of adrenaline> 0.1 µg/kg/min and the milrinone > 0.3 µg/kg/min (Weis *et al*. 2009). 11 of the 12 patients survived beyond 30 days, with significant reductions in inotropic support without requiring mechanical circulatory support. However, follow-up studies by the same group showed significantly lower 1-year and 3-year survival rates (Beiras-Fernandez *et al*. 2011).

The inotropic effects of levosimendan may often take hours to develop, which may be offset by its potent vasodilation capacity (Sundberg *et al*. 1998). It may however also play a role in protecting cardiomyocytes against ischaemic/reperfusion injury by activating adenosine triphosphate-sensitive potassium channels in mitochondria as shown by numerous studies although to date, no studies have been done on pre-or post-conditioning in a heart transplant setting (Cammarata *et al*. 2006; Papp *et al*. 2006; Du Toit *et al*. 2008; Hönisch *et al*. 2010; Hasslacher *et al*. 2011).

1.12.3.8.2 Plasmapheresis

Plasmapheresis is a process by which whole blood is passed through a filter to separate the plasma components from the larger cellular components of red blood cells, white blood cells, and platelets(Nguyen *et al*. 2012). Its use in transplantation was primarily for hyperacute or acute humoral rejection, whereby adjunctive therapeutic plasma exchange has been used alongside immunosuppression and intravenous immunoglobulins to improve survival of incompatible organs compared to compatible organs. Plasmapheresis rapidly reduces the circulating antibodies and thereby improves cardiac function (Wang *et al*. 2006). Plasmapheresis was used for primary allograft dysfunction after liver transplantation with encouraging results(Mandal *et al*. 2000; Ince *et al*. 2013). A study by a group in Taiwan revealed treatment with pulsed steroid and

plasmapheresis improved the ejection fraction and NYHA status of >70% of the patients treated(Chou *et al.* 2012). However, the definitions of PGD in this cohort were not discernible from acute rejection due to the study methodology and lack of biopsy-proven rejection at the time of treatment as treatment was started empirically in all 35 patients who were in NYHA functional class III or IV requiring pharmacological or mechanical circulatory support. The Cedars-Sinai Heart Institute group performed a similar study in patients with severe PGD. In their cohort of 15 patients, 66% of whom underwent plasmapheresis post-transplantation had significantly improved outcomes compared to the 33% of severe PGD patients who did not. They concluded that the potential role of inflammatory molecule depletion in these patients may play a role in the pathophysiology of PGD(Chang *et al.* 2017). The exact role of plasmapheresis in PGD is still speculative and may potentially be clearer with ongoing research.

1.12.4 Conclusion

PGD is the leading cause of early morbidity and mortality following heart transplantation. It is thought to be multifactorial in origin and several risk factors implicated. The search for an accurate biomarker, however, remains elusive. Treatment options to date remain supportive with no definitive pharmacological agents identified as of yet. Plasmapheresis may have a role in the depletion of inflammatory chemokines and cytokines for the treatment of PGD.

2 The process of heart transplantation

2.1 The role of NHSBT in organ donation

There are 6 adult heart transplant centres and 2 dedicated paediatric heart transplant centres in the United Kingdom. In the preceding decade, around 150 hearts were implanted per year nationally.

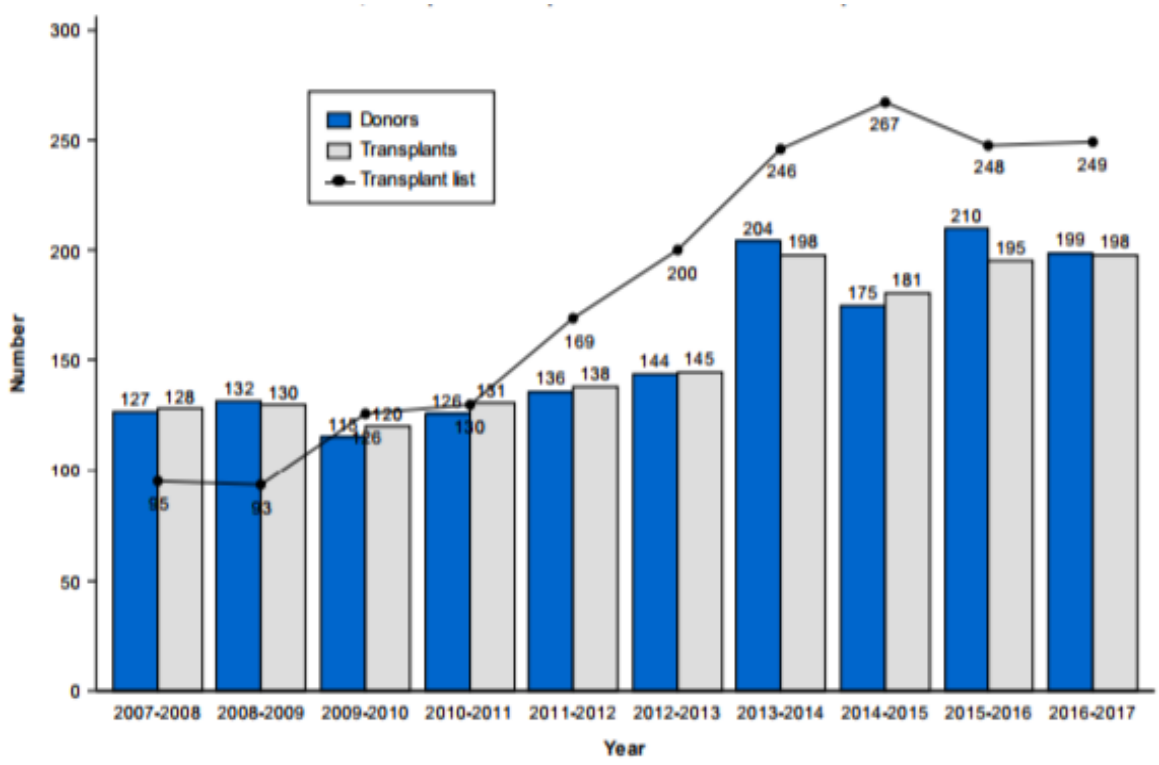


Figure 2-1 Deceased donor heart programme in the UK, 1 April 2007 - 31 March 2017 (source: NHSBT Annual Report 2017)

This represents a 50% reduction from the number of heart transplants performed in the early 1990s. This is commonly attributed to the decreasing number of patients dying from brain stem death as a consequence of improvements in health care provision and safety initiatives. (Kompanje *et al.* 2011)

Alongside limited organ pools, heart failure medical therapy has also improved in the past 20 years. This has significantly changed the listing criteria for patients and impacted transplant listing decision-making. A study of waiting list patients in the US over a 15-year period showed improved survival of urgently listed patients in the most recent era with transplantation compared to those not transplanted but similar survival of non-urgent candidates with or without transplants (Lietz and Miller 2007). This highlighted the benefits of optimal medical therapy, matching the benefits of transplantation in ambulatory patients. An exception in this study were patients with restrictive

cardiomyopathies, inherited cardiomyopathies from systemic diseases, and congenital heart diseases.

In 2008, an Organ Donation Taskforce was commissioned to implement recommendations to increase donor numbers. NHS Blood and Transplant (NHSBT) integrated the new Directorate for Organ Donation and Transplantation into its existing organisation. This involves organ allocation, audit, and maintenance of the Organ Donation Register (ODR) and centralising employment and staffing from individual transplant centres within the NHS. One of the recommendations was to develop a national organ retrieval service (NORS) and to revamp allocation and retrieval completely(Martin and Paul 2008).

NHSBT was also charged with supporting every acute hospital and health board in the UK (potential donor centres). This included appointing a liaison clinician to improve organ donation engagement within each organisation, allocating specialist nurses for organ donation (SNODs) to take on the role of donor transplant coordinators and serve as the bridge between local clinicians and NHSBT alongside establishing a local donation committee tasked with supporting organ donation within the organisation (Murphy and Smith 2012).

NORS was successfully implemented in 2010 to address the variability of organ retrieval support. Another key point in this time was the establishment of legal guidance concerning non-heart beating organ donation or donation after circulatory death (DCD). This was published in 2009 for England and Wales followed by Scotland and Northern Ireland in 2010 and 2011 respectively (Murphy and Smith 2012).

The net result of the implementation of these changes can be seen in Figure 2-2 where there has been a stark reduction in the number of patients on the waiting list with an increase in transplant activity and the number of organ donors.

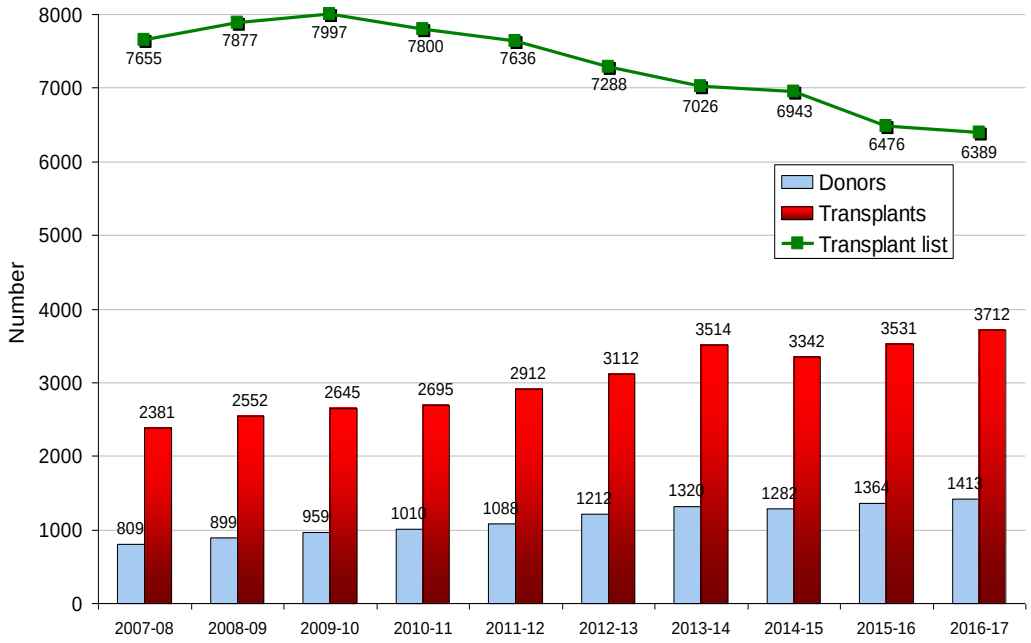


Figure 2-2 Deceased donors, transplants and the transplant waiting list 2007-2017 (NHSBT annual report 2016/2017)

2.2 Patient Listing for Transplantation

In the UK, current indications for referral for consideration of heart transplantation include:

1. Heart failure with impaired left ventricular systolic function or heart failure with reduced ejection fraction (HFrEF)

2. NYHA III or IV symptoms

3. Receiving optimal medical treatment (including target or maximum tolerated doses of ß-blockers, ACE inhibitors, and mineralocorticoid receptor antagonists)

4. cardiac resynchronisation therapy (CRT), implantable cardioverter device (ICD) or cardiac resynchronisation therapy defibrillator (CRT-D) (if indicated)

5. evidence of poor prognosis such as

    a. Cardio-Pulmonary Exercise Testing (CPET)

        i. VO2 max <12 ml/kg/ min if on ß-blockade, <14 ml/kg/min if not on ß-blockade with respiratory exchange ratio ≥1.05

b. Markedly elevated brain natriuretic peptide (BNP) or N-terminal pro-brain natriuretic peptide (NT-proBNP)) serum levels despite optimal medical treatment,

c. prognostic scoring systems such as the heart failure survival score (HFSS) or Seattle heart failure model (SHFM)

6. Other indications outside the above

a. Persistent haemodynamically compromising ventricular arrhythmias refractory to all usual therapy

b. refractory angina with evidence of recurrent significant myocardial ischemia not amenable to conventional treatment,

c. restrictive and hypertrophic cardiomyopathy with persisting NYHA III or IV symptoms refractory to conventional treatment and/or recurrent admissions with decompensated HF. (Aetiology should be clearly identified to ascertain the presence of systemic disease and the risk for recurrence following transplantation (Banner *et al*. 2011)

ISHLT guidelines from 2016 differ slightly from the UK guidelines (Mehra *et al*. 2016). It discourages listing patients solely based on cardiopulmonary stress test results or on heart failure survival scores, although it notes that combining both measures provides an important prognostic benefit. Given the large proportion of LVADs in North America, it also calls for a re-evaluation of haemodynamics in the bridge-to-candidacy patients to evaluate reversibility of elevated pulmonary pressures. It also highlights the need for frailty assessment by 3 of 5 possible of the following symptoms

1. unintentional weight loss of >4.5 kg within the past year
2. muscle loss
3. fatigue
4. slow walking speed
5. low levels of physical activity

Patients with significant cognitive impairment should be screened prior to listing due to potential issues with compliance to medication. Highly sensitized patients should be prioritized for listing due to potential difficulties in obtaining a

suitable donor. ISHLT has also removed amyloid heart disease as a contraindication to heart transplantation. Chronic infections in the recipient such as Human Immunodeficiency Virus (HIV) or hepatitis (B & C) are no longer listed as contraindications in the current guidelines (Mehra *et al*. 2016).

The current heart allocation systems are managed by NHSBT and the Cardiothoracic Advisory Group (CTAG). The ethos of heart allocation is to improve survival in selected patients with advanced heart failure prioritising the sickest patients at greatest risk of dying while ensuring the risk of transplantation is within acceptable limits. This meant that there were increasing patients who were transplanted on the urgent listing criteria vs the non-urgent listing criteria. In 2013/14, 15% of non-urgent heart patients were transplanted within 6 months of listing, compared with 69% transplanted on the urgent list. In 2006/7, only 28% of patients on the urgent waiting list were transplanted.

Urgent patients transplanted had a 1-year mortality of 16% compared to non-urgent patients of 23%, suggesting that urgent transplant outcomes were as good as non-urgent transplants (MacGowan *et al*. 2015). The use of Ventricular Assist Devices (VADs) has reduced the number of patients on the urgent waiting list as patients who are unable to wait or with less favourable demographics are undergoing VAD insertions as opposed to transplants precluding them from urgent listing.

Currently to qualify for the urgent listing is as follows(NHSBT 2017b)

1) Super Urgent Heart Allocation Scheme (SUHAS)
    a) Patients on short term mechanical circulatory support (MCS)- short-term VAD/Extracorporeal membrane oxygenation (ECMO)
    b) a patient meeting criterion for (UHAS) that is not suitable for a long-term left VAD. This requires the approval of an arbitration committee
2) Urgent Heart Allocation Scheme (UHAS)
    a) Patients with an intra-aortic balloon pump;
    b) inpatient dependent on intravenous inotropes.
    c) Adult long-term VAD or TAH patient with one of the following complications:
        i) o Right ventricular failure dependent on inotropes

ii) o Recurrent systemic infection related to VAD/TAH

iii) Other VAD/TAH issues including recurrent or refractory VAD/TAH thrombosis (after agreement by the arbitration committee)

d) Exceptionally sick adult patient with a high risk of dying or having an irreversible complication but does not meet urgent listing criteria. (after agreement by the arbitration committee)

e) ACHD arrhythmia patient with refractory arrhythmia (> 1 hospital admission over the last 3 months with haemodynamic instability or associated with kidney or liver dysfunction

f) ACHD patients with no option for conventional escalation of therapy. Inpatients unsuitable for inotropes and/or VAD with one of the following:

i) Bilirubin and transaminases > 2x normal

ii) Deteriorating renal function (eGFR <50ml/min/1.73m^3, or 20% reduction from baseline)

iii) The requirement for dialysis/CVVH for fluid or electrolyte management with recurrent admissions (>3 in preceding 3 months) with episodes of right heart failure or protein-losing enteropathy requiring ascites drainage

From NHSBT Policy 228//6

2.3 Donation after Brain Stem Death (DBD)

Diagnosis of death is a core skill required by medical practitioners in the UK (Oram and Murphy 2011). Improvements advanced resuscitation techniques and the need for cadaveric organ donation however may pose challenges primarily to intensive care staff. The majority of these do present themselves, however, the concept of death within the societal context of the distinction between life and death can pose a threat.

In 1967, when Christiaan Barnard carried out the first human heart transplant, there were no guidelines for the diagnosis of death of beating heart donors. Months later in 1968, the Harvard code of practice set the standard for which ‘whole brain death’ was defined based on ancillary testing('A definition of irreversible coma. Report of the Ad Hoc Committee of the Harvard Medical School to Examine the Definition of Brain Death' 1968). The committee agreed that withdrawal of life support was possible from patients diagnosed with “irreversible coma” or “brain death”. The timing of the report, just months after Christiaan Barnard’s feat raised suggestions that this provided the

necessary sanctions for organ retrieval and heart transplantation. It was therefore legally advised that patients who met the criteria of death via ancillary testing were certified dead prior to organ retrieval. These included

(1) Unreceptivity and Unresponsitivity

Lack of awareness or responses to externally applied stimuli (e.g. Lack of response to intensely painful stimuli-groan, withdrawal of limb, quickening of respiration)

(2) No Movements or Breathing.

No observed spontaneous muscular movement, respiration or response to stimuli. In patients on mechanical ventilatory support total absence of spontaneous breathing may be established by turning off the respirator for three minutes and observing whether there is any effort on the part of the subject to breathe (provided plasma carbon dioxide levels are within normal limits)

(3) No reflexes

Absence of elicitable reflexes. Fixed and dilated pupils irresponsive to a direct source of bright light. Negative caloric reflexes, no evidence of postural activity (decerebrate or decorticate).

(4) Flat Electroencephalogram (EEG)

In 1981, the US President’s commission declared that death depended on either irreversible cessation of circulatory and respiratory functions or irreversible cessation of all functions of the entire brain, leading to the formation of the Uniform Declaration of Death Act ('Guidelines for the determination of death. Report of the medical consultants on the diagnosis of death to the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research' 1981). As cessation of all functions of the brain is necessary, any residual electrical and neurohormonal activity in the brain of subjects who otherwise met the criteria of death precluded the declaration of death.

In contrast, the UK Conference of Royal Colleges defined brain death as the complete and irreversible loss of function of the brain stem ignoring the relevance of residual activity in the upper brain ('Diagnosis of brain death. Statement issued by the honorary secretary of the Conference of Medical Royal Colleges and their Faculties in the United Kingdom on 11 October 1976' 1976). This was based on the work of Mohandas and Chou in 1971 showing that brain stem damage was the crucial component of severe brain damage causing profound irreversible coma (Mohandas and Chou 1971). The simpler and more reliable UK definition is robust and has not evoked similar criticism (Capron 2001). Currently, the diagnosis of brainstem death (BSD) has to be made by two doctors who have been registered for more than five years and are competent in the procedure (at least one should be a consultant). Testing should be undertaken by the doctors together and must always be performed completely and successfully on two occasions in total. Following this, the following sequence of events is noted.

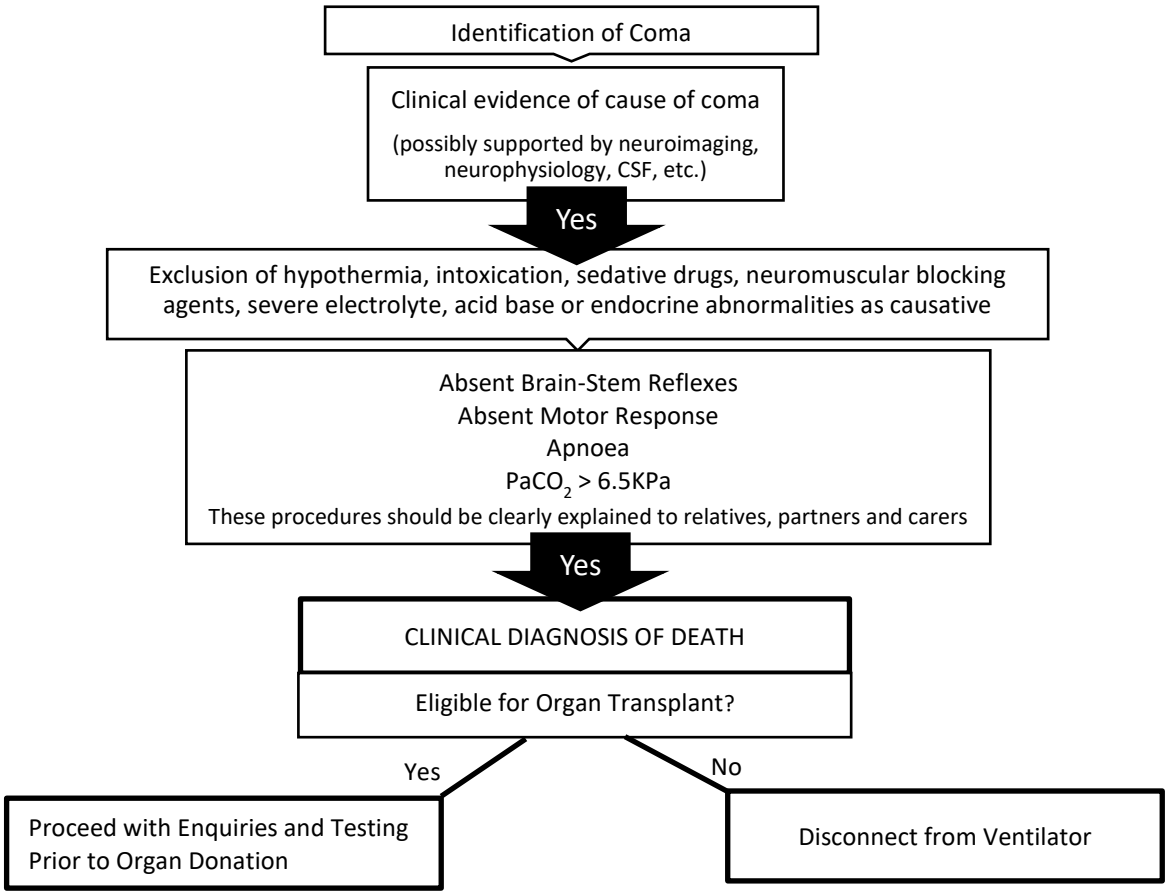


Figure 2-3 Diagnostic and management algorithm (from A Code of Practice for The Diagnosis and Confirmation of Death- Academy of Medical Royal Colleges)

2.3.1 Physiology of Brainstem Death

The number of DBD organ donations has plateaued (NHSBT 2017a). During BSD, there is an initial rise in intracranial pressure (ICP) usually as a result of intracranial haemorrhage or head injury. There is a progressive mass effect in the brain and worsening cerebral ischemia produces venous engorgement and brain swelling. This causes a rise in arterial blood pressure to maintain cerebral perfusion pressure resulting in a vicious positive feedback mechanism. The continued rise of ICP causes herniation of the brain through the foramen magnum (Smith 2004). This results in pontine ischaemia and a hyperadrenergic response with a catecholamine storm. The increased systemic vascular resistance and pulmonary hypertension increases the afterload of both ventricles resulting in myocardial ischaemia. A Cushing's reflex is noted in a third of patients by a combination of hypertension and baroreceptor and midbrain activation of the parasympathetic nervous system causing bradycardia (Gordon and McKinlay 2012). This progresses to the lower end of the medulla causing the vagal and cardiomotor nuclei to become ischaemic, resulting in unopposed sympathetic stimulation (Smith 2004).

Experiments in canine models recreating brain stem death have shown that during the catecholamine storm, circulating dopamine, adrenaline, and noradrenaline concentrations increased by almost 10-fold (Shivalkar *et al.* 1993; Chen *et al.* 1996). This is accompanied by unopposed vasoconstriction, thereby increasing myocardial oxygen demand. Coronary vasoconstriction also occurs, causing potentially causing sub-endocardial ischemia. The mismatch between myocardial oxygen demand and supply is associated with the initial impairment seen in BSD donors (Mikhova *et al.* 2013). It causes ventricular systolic dysfunction in even previously healthy young hearts devoid of any coronary vascular disease.

At the cellular level, animal models have shown BSD induces myocytolysis, contraction band necrosis, subendocardial haemorrhage, cell oedema and infiltration of mononuclear cells (Shivalkar *et al.* 1993). Catecholamines also induce increases in cytosolic calcium, causing impaired adenosine triphosphate (ATP) production. Impaired ATP production causes an increase in free radical formation, which directly causes cellular damage (Singal *et al.* 1998).

This phenomenon is similar to Takotsubo cardiomyopathy or stress-induced cardiomyopathy (Ako *et al*. 2006). In a case series by Ako et al, they noted a predominantly female patient cohort, presenting with a variety of ST-T segment changes and mildly elevated cardiac enzymes that mimic acute coronary syndrome. The LV dysfunction, characteristic of Takotsubo cardiomyopathy showed a hyperkinetic basal region and akinetic apical half of the ventricle, in the absence of CAD which resolved within weeks with a generally favourable prognosis.

The catecholamine surge is a common pathway in both pathologies noted above. Coronary vasospasm and subsequent myocardial stunning are believed to be an essential pathogenic factor. It does, however, differ from Prinzmental's angina as angiography findings are invariably normal. There is a role of adrenergic receptor blockade in treating Takotsubo cardiomyopathy and LVSD in DBD donors. Whether this LVSD in DBD donors is transient and therefore likely to recover is of interest for organ transplantation, as up to 20% of hearts were rejected for poor function (Liou *et al*. 2017). There have been numerous studies reporting good outcomes in recipients from young donors with poor LV function (Berman *et al*. 2010; Rao *et al*. 2015; Madan *et al*. 2017).

Myocardial injury after BSD is common with one study reporting up to 90% of patients with evidence of contraction band necrosis (Baroldi *et al*. 1997). BSD studies in the rabbit model also show changes in myocardial gene expression (Yeh *et al*. 2002). After the sympathetic storm, (usually<15 minutes) depletion of catecholamines occurs. This is followed by a rapid loss of sympathetic tone and loss of peripheral vasomotor activity (Zens *et al*. 2017). The net result is a negatively inotropic environment with a low systemic vascular resistance causing profound hypotension, affecting myocardial perfusion as well as other end-organ functions.

Anti-diuretic hormone (ADH)/Arginine Vasopressin (AVP) depletion is common post BSD, although the exact mechanism of not well understood. AVP is secreted by the supraoptic nucleus located within the magnocellular neurons of the hypothalamus. These osmoreceptors are sensitive to changes in the osmotic pressure of their extracellular environment (Leng *et al*. 1999). Excitatory glutamatergic input from circumventricular areas, particularly the organum

vasculosum of the lamina terminalis is involved in AVP secretion (Leng *et al*. 1999).

It was previously thought that the direct anatomical compression during coning may affect the posterior pituitary function. The inferior hypophyseal arteries supplying the posterior pituitary region, however, originate from extradural segments of the internal carotid arteries, therefore protected from increased intracranial pressure (Leclercq and Grisoli 1983). Autopsy studies have shown intact regions of the hypothalamus with relatively well-preserved neurons in patients with BSD refuting the anatomical compression theory (Walker *et al*. 1975; Wijdicks and Pfeifer 2008). One possible explanation is passive leakage of AVP from axonal terminals of ischaemic non-viable hypothalamic cells whose perikarya have been destroyed. This explains why some patients exhibit anuria prior to a polyuric phase (Michael *et al*. 2014).

Electrocardiogram (ECG) changes are also commonly seen in BSD donors. ST-segment changes, T-wave inversions, and arrhythmias are not uncommon(Smith 2004; Zens *et al*. 2017). They may reflect ongoing myocardial ischaemia, electrolyte imbalances or iatrogenically caused by the administration of inotropes. These patients may undergo asystolic cardiac arrest if unsupported. Less than 29% of hearts from donors who underwent aggressive cardiopulmonary resuscitation were transplantable in one study (Quader *et al*. 2014). Conventional measures to correct haemodynamic instability in these patients may worsen the myocardial injury. Excessive inotropic use has also been associated with increased myocardial injury in these donors. Around a quarter of potential donors may die prior to organ retrieval on maximal conventional support (Mackersie *et al*. 1991). Figure 2-4 highlights the potential factors that may result in the loss of a potential BSD donor.

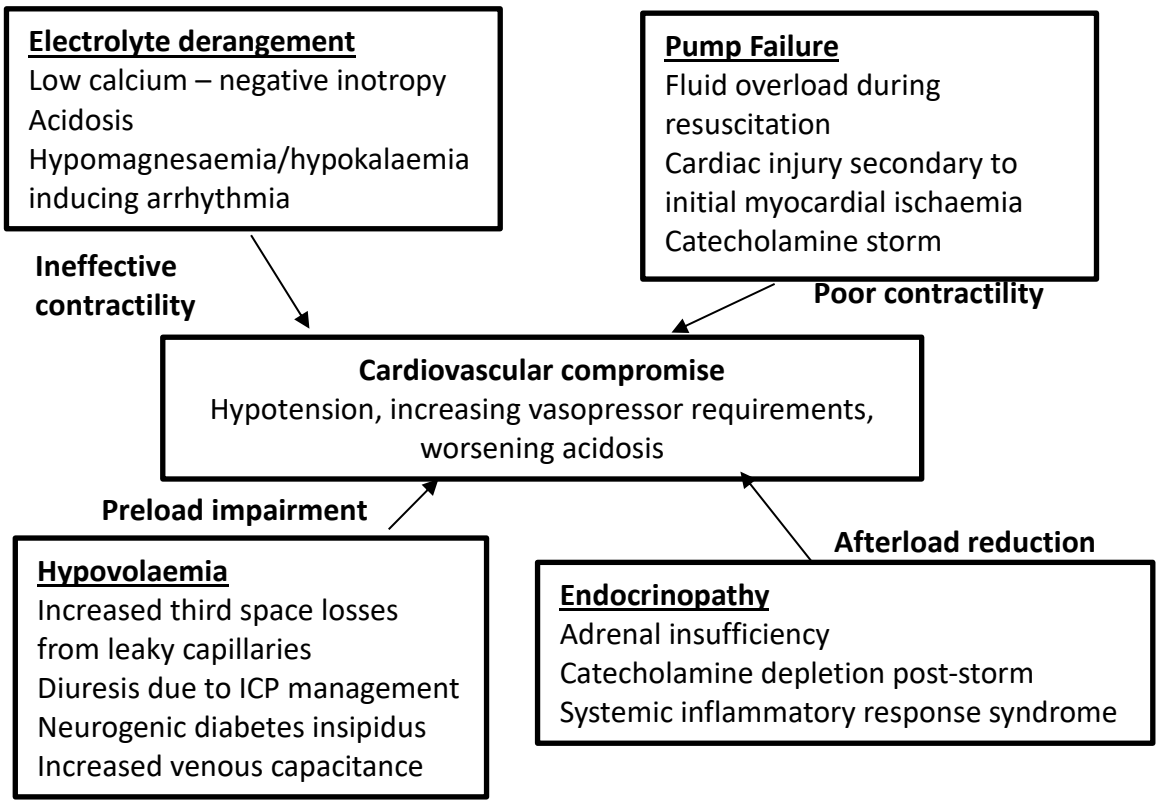


Figure 2-4 Factors contributing to haemodynamic instability in the potential organ donor.

2.3.2 Role of the SNOD

The regional SNODs are notified if there is a potential DBD donor prior to formal tests. The patient is then allocated a specific SNOD. His/her initial task is to identify if the patient is on the donor register. The next of kin is also approached and given information regarding the organ donation process and the families' wishes as well. This process may also be done by medical staff. Data from NHSBT however, is suggestive that the presence of the SNOD is significantly associated with consent(Vincent and Logan 2012).

Once consent has been obtained, the SNOD performs a clinical assessment in accordance with the Core Donor Data form designed by NHSBT. It contains demographic data, clinical findings, and investigation results and is accompanied by the collection of blood samples for tissue typing. This data is then relayed to all of the transplant centres nationally via an online database called the Organ Donation and Transplantation Electronic Offering System (EOS). The sequence of this process is determined by the waiting list prioritisation as mentioned in 2.2. Recipient transplant centres then decide on whether to provisionally accept or decline the donor heart before inspection. This decision is subjective as it is

made based on the history of the donor alongside demographic, geographic and tissue typing results. If the donor heart is declined by all centres at this stage, the cardiothoracic organ retrieval team is not mobilised.

2.3.3 The SCOUT Project

Some centres may elect to send a member of the retrieval team to optimise the heart prior to mobilising the team. The SCOUT project was piloted to increase the number of heart transplantations by increasing the number and quality of hearts procured.

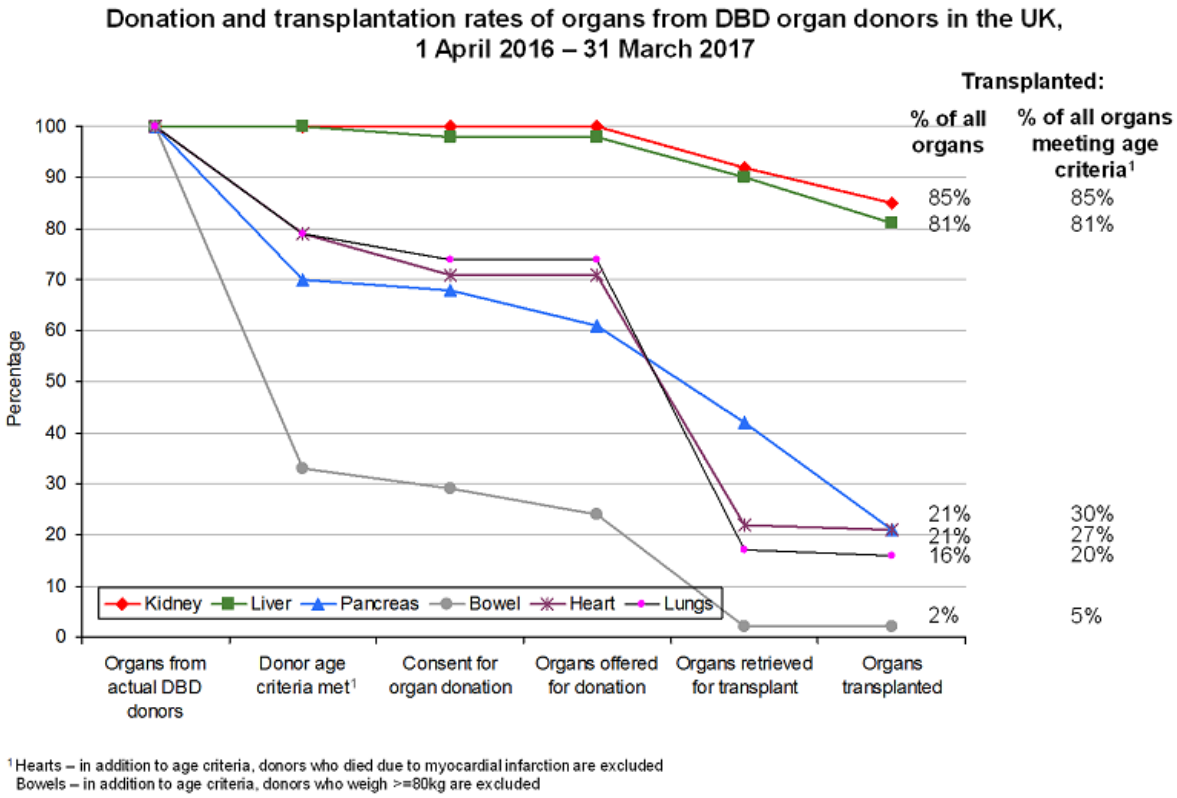


Figure 2-5 Use of organs from DBD donors in 2016-17 (numbers are organs transplanted as a % of total actual organ donors) Source: NHSBT - https://www.odt.nhs.uk/deceased-donation/best-practice-guidance/donor-optimisation/

The traditional model as detailed above lacks information and expertise in cardiovascular management for the average/marginal donor in ICUs across the UK. It was based on the premise that transplant centres would receive more detailed information regarding the function of the heart and if the donor was optimised to reduce myocardial damage induced by brainstem death.

Trained personnel from the transplant centre are sent to the donor ICU within 2 hours of road travel as soon as a potential heart donor becomes available. The Scout performs serial diagnostic and therapeutic procedures, including transoesophageal echocardiography, right heart catheterisation with a Swan-Ganz catheter and manages the titration of vasopressors, inotropes, and fluid resuscitation. Hormone replacement is also advocated if appropriate by the Scout. Early donor management was previously performed on an ad hoc basis prior to the centralisation of services as part of NORS. The current SCOUT project was designed as a feasibility study with a planned prospective trial soon after.

The feasibility study encountered limitations in data collecting and in scientific study design due to its retrospective nature and ad hoc basis of early donor management.

In previous iterations, the Scout project had shown promising results in increasing the yield of both heart and lung retrievals (Venkateswaran *et al.* 2008; Abuanzeh *et al.* 2015). Scouts initiated infusion of triiodothyronine(T3) in depleted donors (as a consequence of endocrinopathy of BSD in keeping with sick euthyroid) (Macdonald *et al.* 2012). Insulin and methylprednisolone infusions are also initiated to counteract the inflammatory process and hyperglycaemia that occurs post-brain death due to a drop in mentioned hormones levels (as elaborated in section 2.3.1). ADH/AVP depletion is commonly seen in BSD, hence the role of vasopressin in donor management instead of noradrenaline due to its potentially detrimental effects on myocardial function. Intravenous fluids and diuretic therapy are guided by the central venous pressure and urine output. There is also a lower threshold to administer blood transfusions to these potential donors as anaemia may temporarily be obscured by the haemoconcentration of neurogenic pulmonary oedema.

The profound drop in systemic vascular resistance after catecholamine depletion can also be misleading. To ensure accurate myocardial contractility and function, a donor practitioner will attempt to achieve a cardiac index >2.5 l/min/m^2, central venous pressure and pulmonary capillary wedge pressure <12 mmHg, mean arterial pressure between 65 and 85 mmHg, with a systemic vascular resistance from 800 to 1200 dyn/cm/s (Abuanzeh *et al.* 2015). The

preliminary findings of the Scout project showed a shorter mean duration between donor arrival in the operating room and skin incision compared to the non-scouted group. Donor hearts were also twice as likely to be accepted for transplantation in the scouted group (Barbero *et al*. 2017)

Currently, the Scout project has not been implemented across all the centres as it remains unfunded. Measures are currently being undertaken by NHSBT and CTAG to train potential scouts and allocate funding for this project.

2.3.4 DBD retrieval

Patient data is relayed to the transplant centres nationally in a sequence as shown in Figure 2-6. If the heart is accepted by one or more centres the regional NORS team on call is mobilised. The SNOD is present through the retrieval process and serves as the intermediary between the different organ retrieval teams as well as the recipient centres. The SNOD also serves as an advocate for the donor's family's wishes and ensures the relevant documentation is accurately completed.

A multi-organ retrieval takes place in the Donor Hospital as soon as possible after the offer has been received and accepted. The cardiothoracic retrieval team consists of, a suitably trained cardiac surgeon, a surgical assistant, a scrub nurse, and donor perfusionist. This team is supported by an anaesthetist, circulating theatre nursing staff from the donor hospital. Further, a separate liver, kidney, and pancreas transplant team will usually attend depending on which organs are being retrieved. This makes the process a multidisciplinary team exercise(NHSBT 2017c).

The cardiothoracic retrieval teams mobilise with their own equipment and sterile instruments including; organ storage bags and ice cool box containing all necessary perfusion fluids, blood bottles and specimen pots (for spleen and lymph nodes), drugs (antibiotics, steroids, and other relevant drugs), Invasive monitoring equipment (e.g. Swan Ganz Catheter), bronchoscopy, paperwork to document the cardiovascular and respiratory parameters during assessment and operation findings and procedure to travel with the organ to the recipient centre.

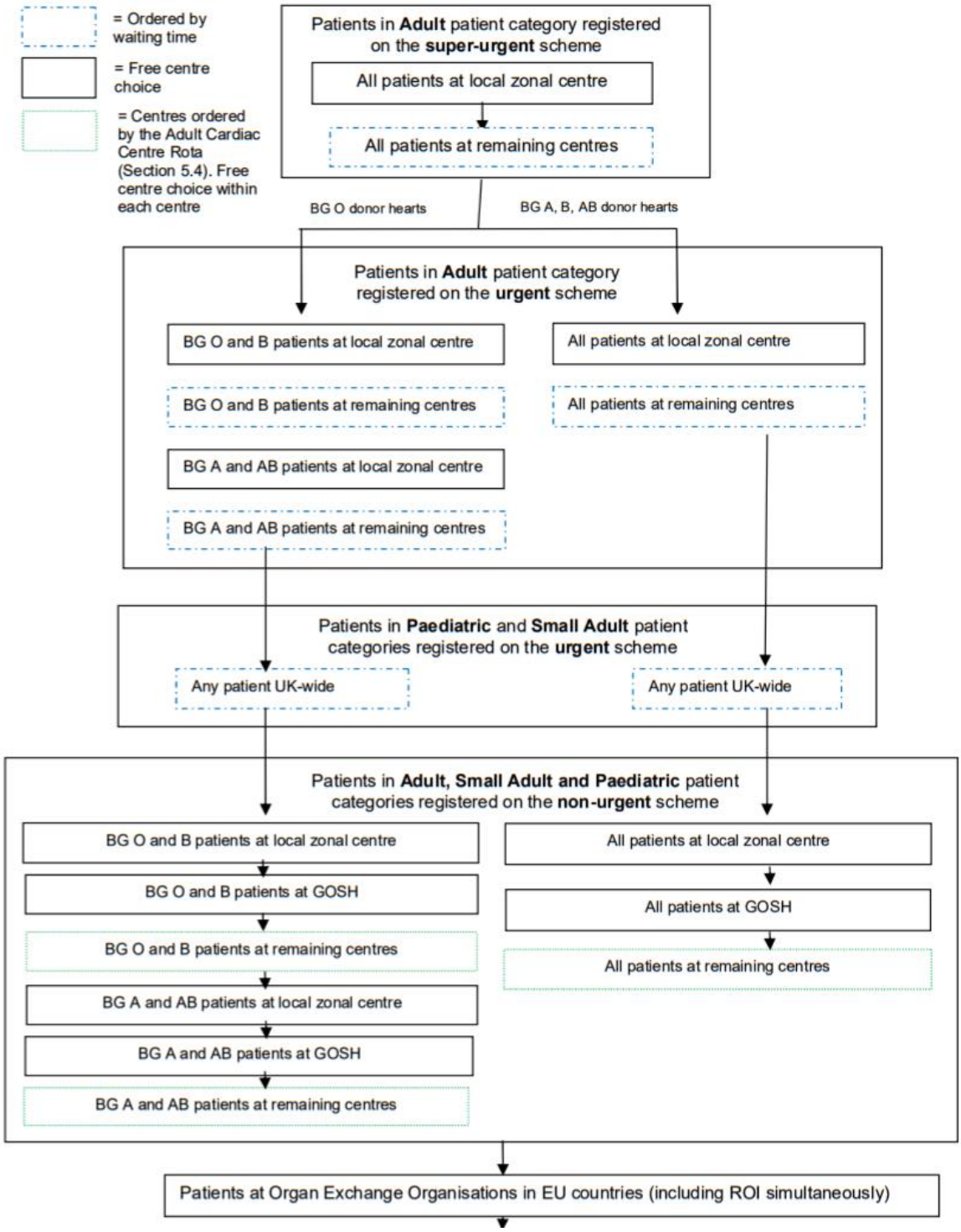


Figure 2-6 Allocation for an adult donor heart.
From NHSBT (http://odt.nhs.uk/pdf/heart_allocation_policy.pdf)

On arrival at the donor site, the cardiothoracic retrieval team contacts the SNOD, reviews the notes, investigations (including brain stem death testing) and consent. On arrival of the abdominal retrieval team, a discussion of the surgical strategies for each team is undertaken. This step is crucial especially as the anaesthetist and staff at the donor hospital may be inexperienced in the process of organ retrieval which requires careful coordination. Special requests are also noted during this period (e.g. the use of the Organ Care System^{tm}, the dose of

heparin, required length of Inferior Vena Cava for liver surgeons and venting of perfusion fluid). The anaesthetic requirements are also entailed by the retrieval teams. This includes correcting haemodynamic stability (boluses inotropes may be contraindicated if ex vivo perfusion of organs is done), gas exchange parameters for calibration of continuous cardiac output, lung compliance, amount of tracheal suction, blood testing/results, and blood loss and colloid replacement, alongside the administration of prophylactic antibiotics and steroids.

The donor is then transferred to the theatre for an initial assessment by the cardiothoracic retrieval team. Pulmonary artery catheterisation and TOE are performed where able. Currently, pre-retrieval TOEs are not offered by all retrieval teams. The results are relayed back to the recipient centre for further instructions or to synchronise the explantation process which may be prolonged in a donor on Mechanical Circulatory Support. If the organ is declined at this point, it is then offered to the next recipient centre according to Figure 2-6 once again. This process may delay the retrieval process and thereby affect the function of the other organs, thus careful communication with the abdominal team is vital.

2.3.4.1 Warm Phase

If the organ is accepted, the donor is prepped and draped. The surgical pause is also performed as part of the WHO safety checklist. The knife-to-skin time is noted and the warm phase of the organ retrieval process begins. The cardiac surgeon performs a sternotomy and opens the pericardium vertically from the diaphragm to its inflection at the ascending aorta or arch. Stay sutures are placed into the pericardium bilaterally to create a pericardial well (Camp 2010). This also prevents the expanding lungs from obscuring the surgeon’s view. The heart is visually inspected for function, chamber distension, coronary calcification, myocardial contusions, and other anatomic variations. Communication with the anaesthetist is vital as any cardiac manipulation may compromise cardiac output and cause haemodynamic instability which resolves on resting the heart in its anatomical position. Palpation of the coronaries is also done to assess subclinical coronary artery disease. Handling the heart may cause atrial fibrillation, thus internal defibrillator pads and a defibrillator should be

accessible at all times. The cardiac retrieval surgeon mobilizes the aorta from the main pulmonary artery. Care is taken during mobilization proximally into the root to avoid injury to the coronary arteries. The brachiocephalic vein is mobilized off the arch if needed. If concomitant lung retrieval is performed, the rest of the arch is dissected and the pulmonary artery mobilised to the bifurcation. Once complete, the surgeon isolates the aorta, superior vena cava, inferior vena cava using a combination of umbilical tape or vessel sloops. This is in preparation for the cold phase. At this point, the final readings of the cardiac output monitor are relayed to the recipient centre.

Once the recipient is in theatre the surgeon should be able to advise an approximate time for cross-clamp application. The abdominal dissection usually takes slightly longer depending on the number of organs harvested. The recipient centre will also advise on the preferred length of atrial cuff especially if both the heart and lungs are harvested.

At this phase, the anaesthetist withdraws the central lines from the patient. This includes the Swan Ganz catheter/pulmonary artery catheter (PAC) introduced and the central line that may have been inserted in the right internal jugular vein.

Prior to the cold phase commencing, sloops and umbilical tape should be in place. The azygous vein should also be identified and either tied off or clamped. Perfusion fluid should be prepared with the lines de-aired and passed to the surgeon or assistant. In the UK, the perfusion fluid of choice is primarily St Thomas's Solution with one centre using Custodiol® HTK (Histidine-Tryptophan-Ketoglutarate).

The volume of perfusion fluid to be administered is calculated based on the patient's body weight. Purse-string sutures are placed into the anterior ascending aorta prior to the systemic heparinization of the patient. The perfusion cannula is placed into the aorta as shown in Figure 2-7.

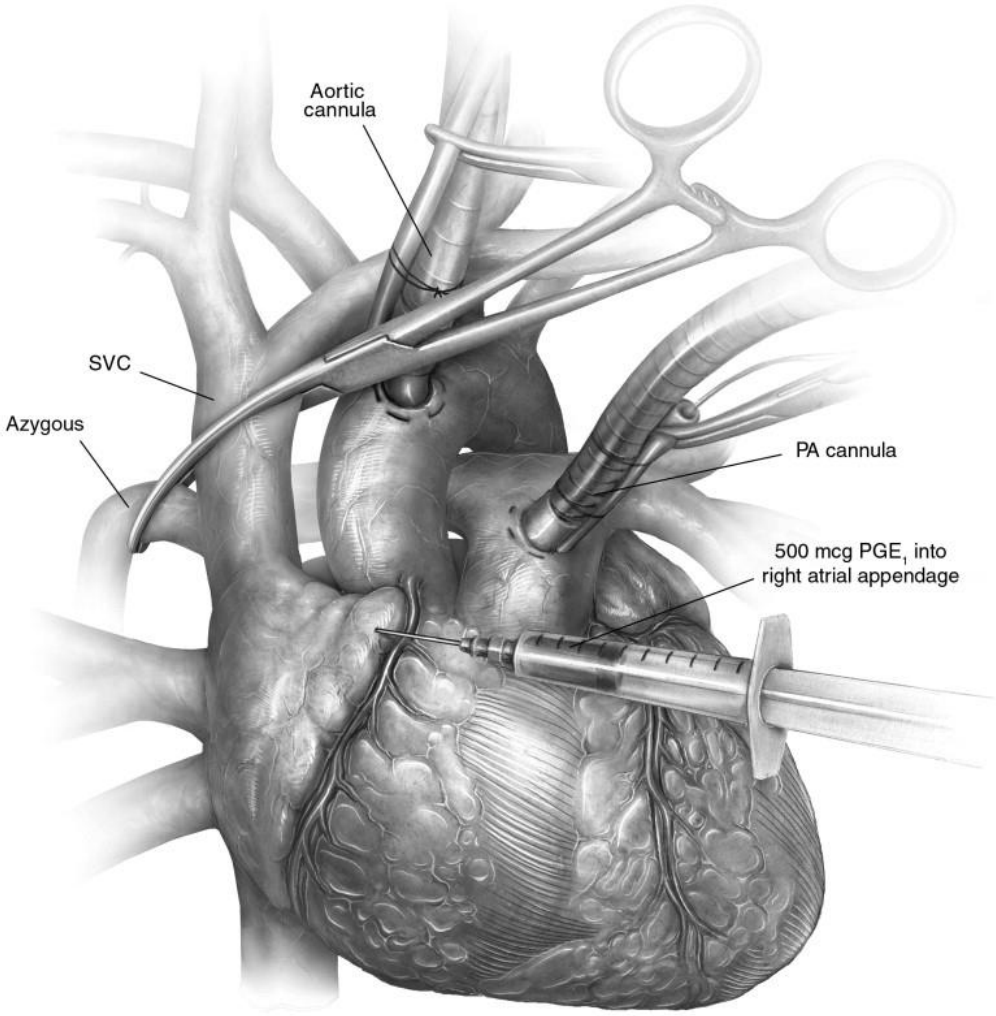


Figure 2-7 Heart in preparation for the cold phase with the aortic cannula in place, SVC and IVC clamped. Prostaglandin (PGE_1) may be administered if concomitant lung retrieval is performed. With permission from 'Heart Transplantation: Donor Operation for Heart and Lung Transplantation. *Operative Techniques in Thoracic and Cardiovascular Surgery,* 15, 125-137. (Camp 2010)'

2.3.4.2 Cold Phase

The heart is lifted out of the pericardium to expose the inferior aspect of the left atrium. The surgeon then performs a posterior left atriotomy, where a suction catheter is placed for when the cardioplegia is flushed. The IVC is also cut at this point to allow a healthy cuff for the abdominal retrieval team. This causes the heart to be released back into the pericardium. The aortic cross-clamp is applied to the distal ascending aorta. Cold Cardioplegia (approximately 4^0C) is delivered via the aortic root to the coronary arteries at a consistent pressure of around 150 mmHg by using a pressure bag. Topical cold saline or slush is also used for myocardial protection. If the flow of cardioplegia is sluggish, the perfusionist reports this back to the surgeon who checks the

position of the aortic cannula and aortic root pressure. Once cardioplegia administration is complete, the cardiectomy is completed. The aorta, SVC, right atrium, and left atrium are divided and the heart is then on the back table.

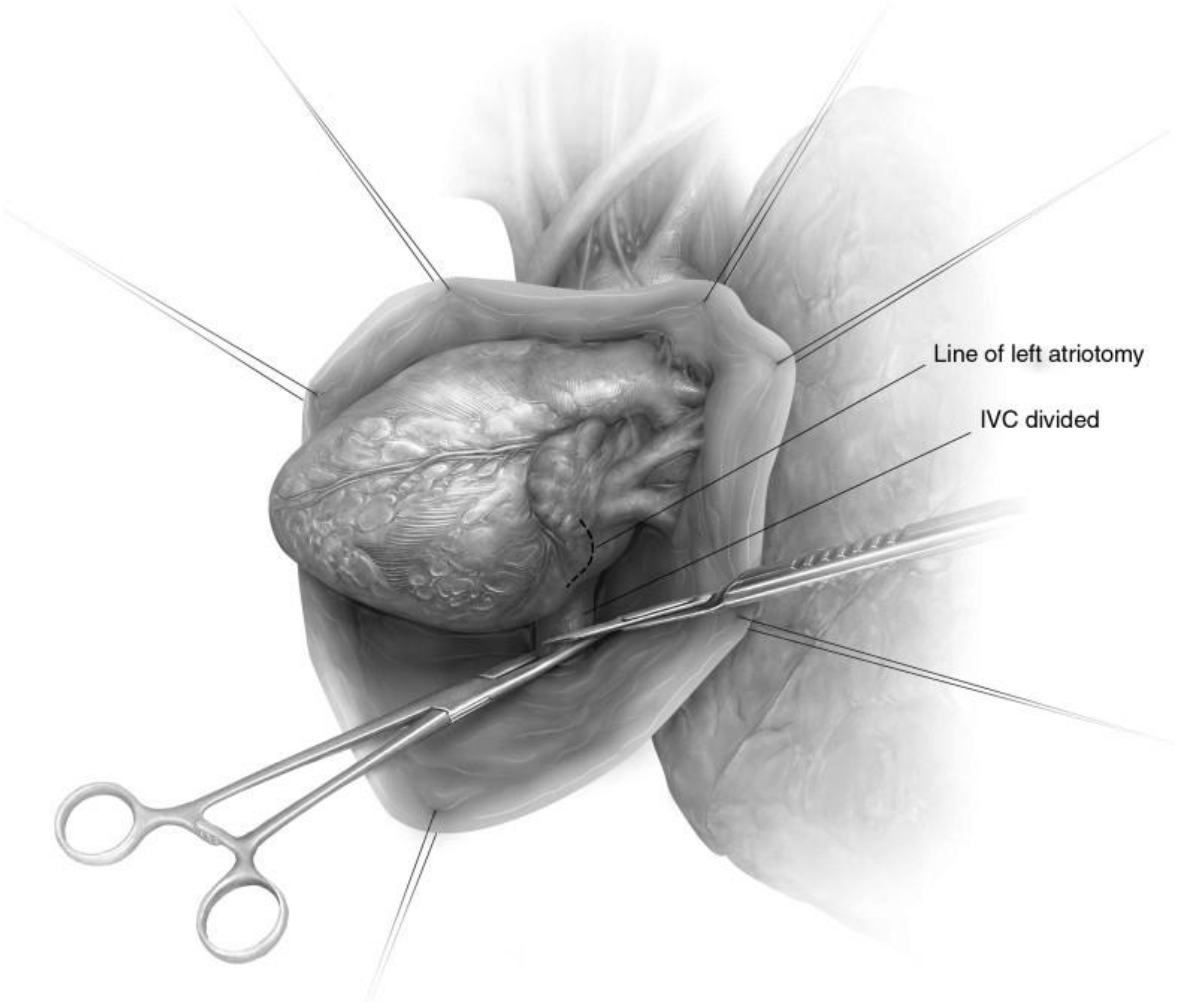


Figure 2-8 Left atriotomy prior to cardioplegia administration (heart lifted). With permission from 'Heart Transplantation: Donor Operation for Heart and Lung Transplantation. *Operative Techniques in Thoracic and Cardiovascular Surgery,* 15, 125-137. (Camp 2010)'

This step allows direct visualisation of the valves and interatrial septum for patent foramen ovale. The heart is brought to the back table where all the valves are carefully examined. Patent foramen ovale is ruled out or fixed and any additional surgical issues or anatomic findings are noted.

2.3.4.3 Standard cold storage

The heart is then packed in 3 organ storage bags, each filled with cold saline, before being packed in ice. A sample of lymph nodes and spleen is also supplied alongside the necessary paperwork from the SNOD. This is then sent to the

transporter to the recipient centre. The ischaemic time for a heart in cold storage should not exceed 4 hours.

2.3.4.4 Normothermic Ex-vivo Perfusion (Organ Care System^{tm})

Prior to the cold phase, approximately 1.5 litres of donor blood is removed to prime the console. To facilitate this, the patient is placed in a Trendelenburg position.

Instead of placing the heart in organ storage bags, the aorta is secured using the supplied cable ties and aortic tip cannula. Pledgeted sutures are sometimes used to prevent the aortic tip cannula from slipping.

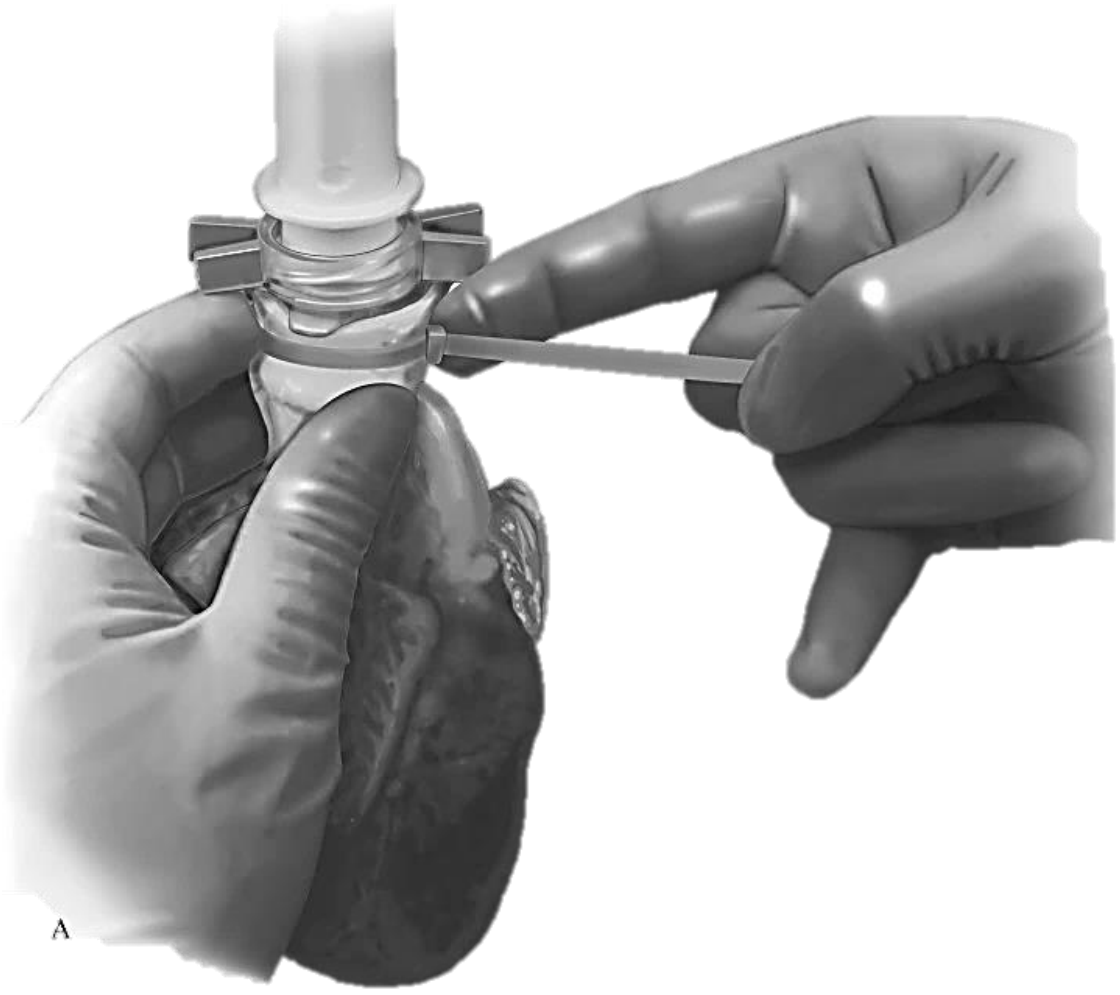


Figure 2-9 Application of supplied cable ties to aortic tip cannula for OCS retrieval.
With permission from 'Organ Care System for Heart Procurement and Strategies to Reduce Primary Graft Failure After Heart Transplant. *Operative Techniques in Thoracic and Cardiovascular Surgery,* 20, 322-334. (Tsukashita and Naka 2015)'

The pulmonary artery cannula is secured with purse-string sutures around the PA stump and an umbilical tie. The SVC is tied off.

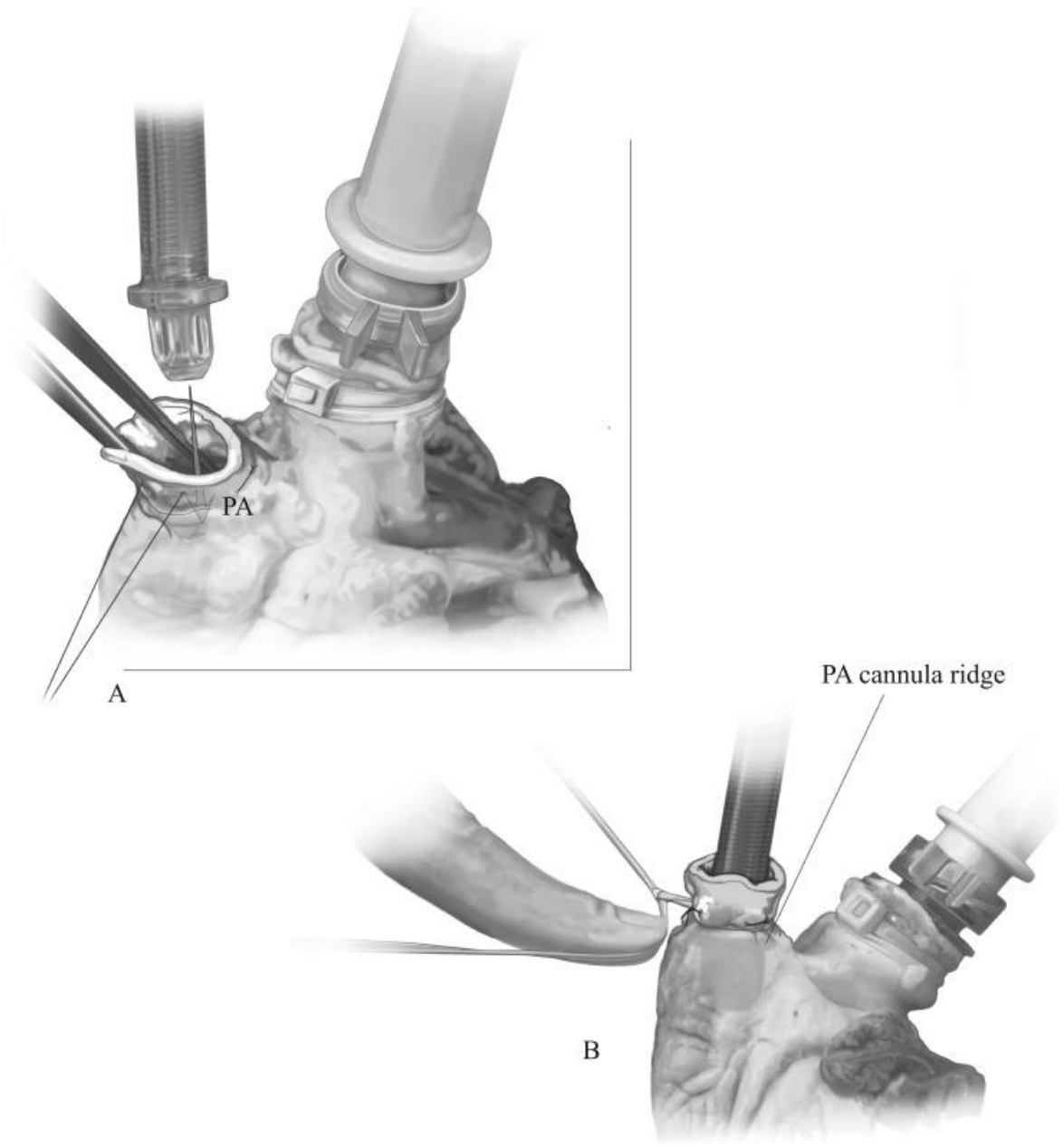


Figure 2-10 a) PA cannula inserted into PA stump b) Umbilical tie to secure PA cannula
With permission from 'Organ Care System for Heart Procurement and Strategies to Reduce Primary Graft Failure After Heart Transplant. *Operative Techniques in Thoracic and Cardiovascular Surgery,* 20, 322-334. (Tsukashita and Naka 2015)'

The heart is then placed on the console. Care is taken to reduce the flow of the console to permit the connection of the aortic tip cannula without any air being introduced into the circuit. The heart is placed with its posterior surface facing the surgeon with the IVC oversewn (Figure 2-11).

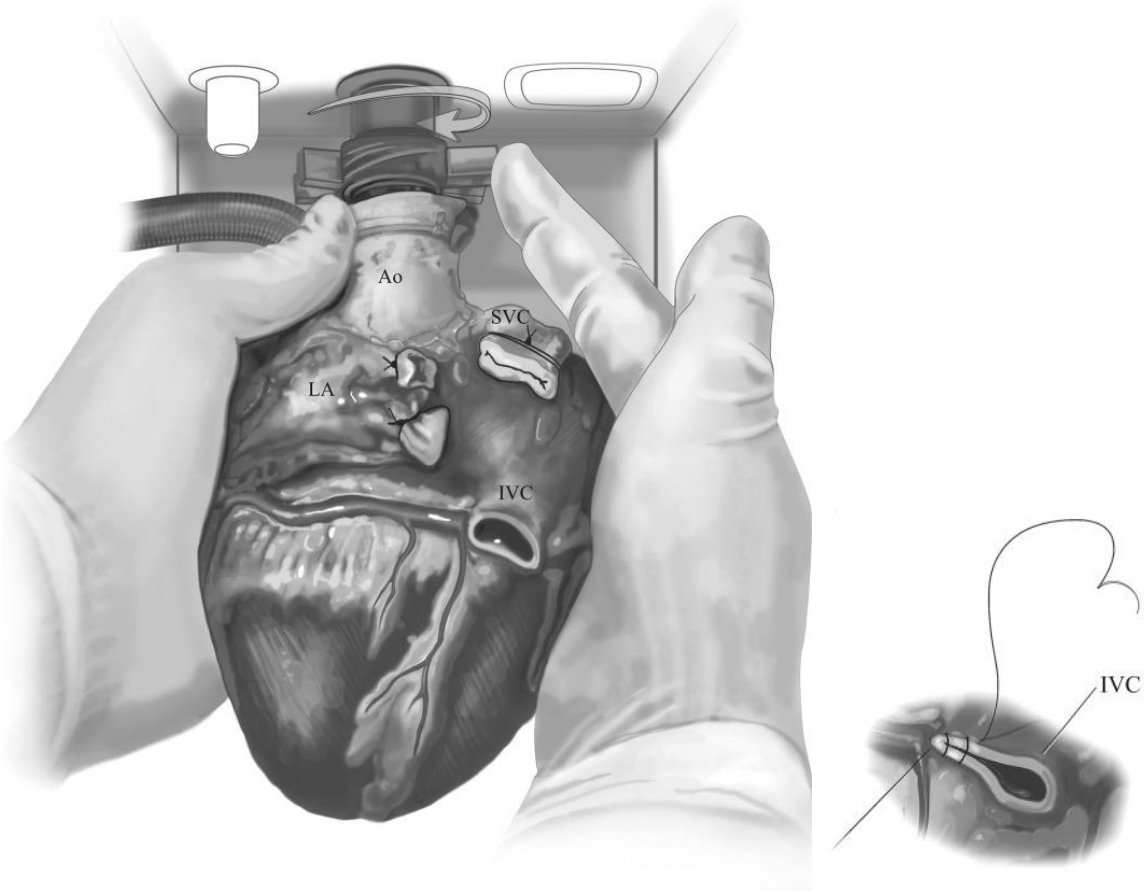


Figure 2-11 Placement of the heart on the OCS console(left). IVC oversewn (right)
With permission from 'Organ Care System for Heart Procurement and Strategies to Reduce Primary Graft Failure After Heart Transplant. *Operative Techniques in Thoracic and Cardiovascular Surgery,* 20, 322-334. (Tsukashita and Naka 2015)'

The heart is massaged to de-air the PA cannula. If the heart does not spontaneously contract, the attached defibrillator pads are aligned to the RA and the LV and a shock is delivered. The heart is kept at 34ºC and transported to the recipient site with interval sampling of blood to assess electrolytes, lactates, and acid-base balance. The flow can be remotely controlled via the console attachment. Epicardial pacing wires can also be attached to the surface of the right ventricle is pacing is required.

2.4 Donation after Circulatory Death (DCD)

Christiaan Barnard's pioneering work in 1967 utilised a heart after circulatory death as regulations regarding brainstem death had not been established. Once the criteria for declaring brainstem death was formed, the brain-dead patient became the ideal multiorgan donor for organ transplantation. Conditions that result in BSD are limited. In a review of 71 published series of brain dead patients (n=6317) subarachnoid haemorrhage (SAH), traumatic brain injury (TBI), or spontaneous intracerebral haemorrhage (ICH) caused BSD in 83% of patients(Kompanje *et al*. 2011). The number of DBD donors has plateaued over the years with referral rates reaching well above 90%.

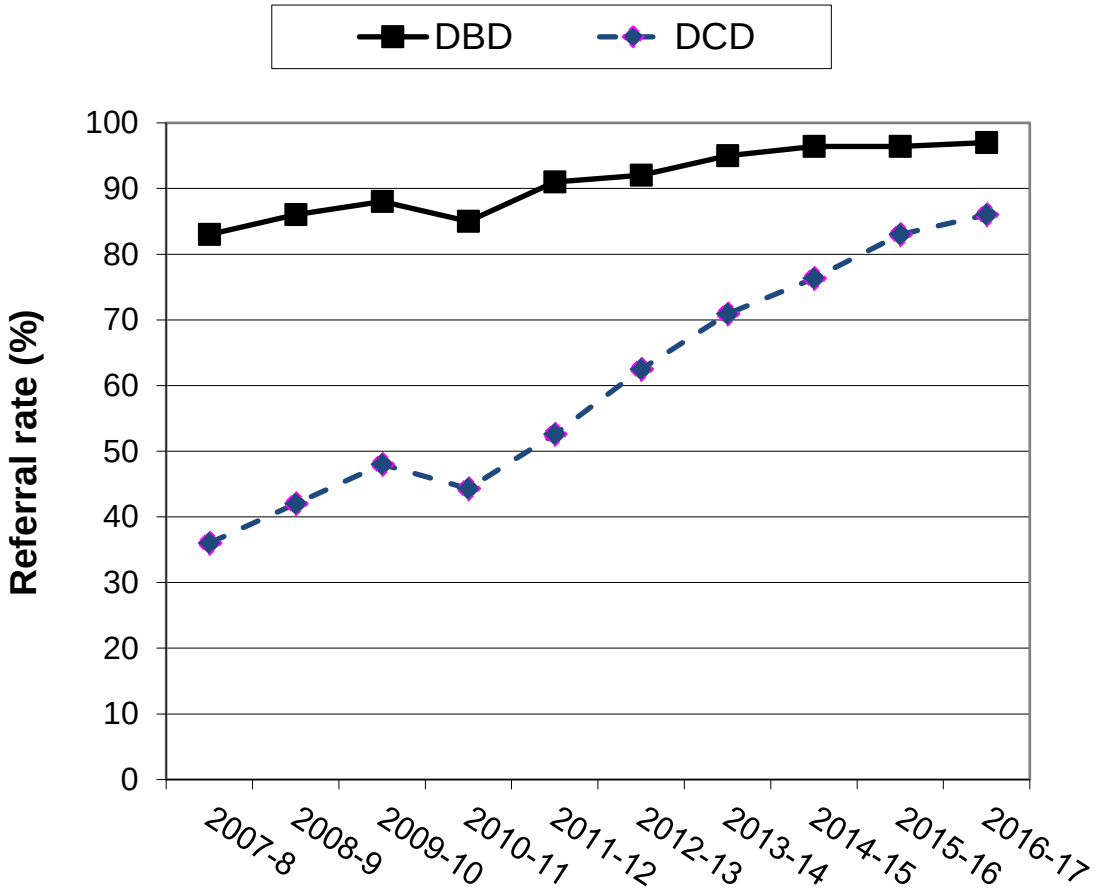


Figure 2-12 Referral rate for DBD vs DCD organ donations. Source: NHSBT

In DBD donors, the warm ischaemia and anaerobic metabolism were kept to a minimum, unlike DCD donors.

There are 4 categories of donation after circulatory death as defined by the Modified Maastricht Criteria.

I	dead on arrival and have not been resuscitated
II	unsuccessfully resuscitated
III	typical controlled DCD, with planned cardiac arrest
IV	planned donations following brain death (DBD) that suddenly arrest during or after the brain death determination.

Table 2-1 Modified Maastricht Classification of Donation after Circulatory Death
With permission from 'An overview of different methods of myocardial protection currently employed peri-transplantation'. *Vessel Plus; Vol 1, No 4 (2017)*(Singh *et al.* 2017)

Patients are declared 'dead by cardiorespiratory criteria following guidance from the Association of Medical Royal Colleges' (AoRMC 2016). Death can be diagnosed and confirmed after 5 minutes of continuous asystole usually by ECG and intra-arterial pressure monitoring. Echocardiography can be used as an alternative to determining the absence of pulsatility. Any return of cardiac or respiratory function necessitates a further observation period. After 5 minutes, the clinician confirms the absence of pupillary reaction and motor response to corneal stimulation and supra-orbital pressure, prior to recording the time of death (Manara *et al*. 2012).

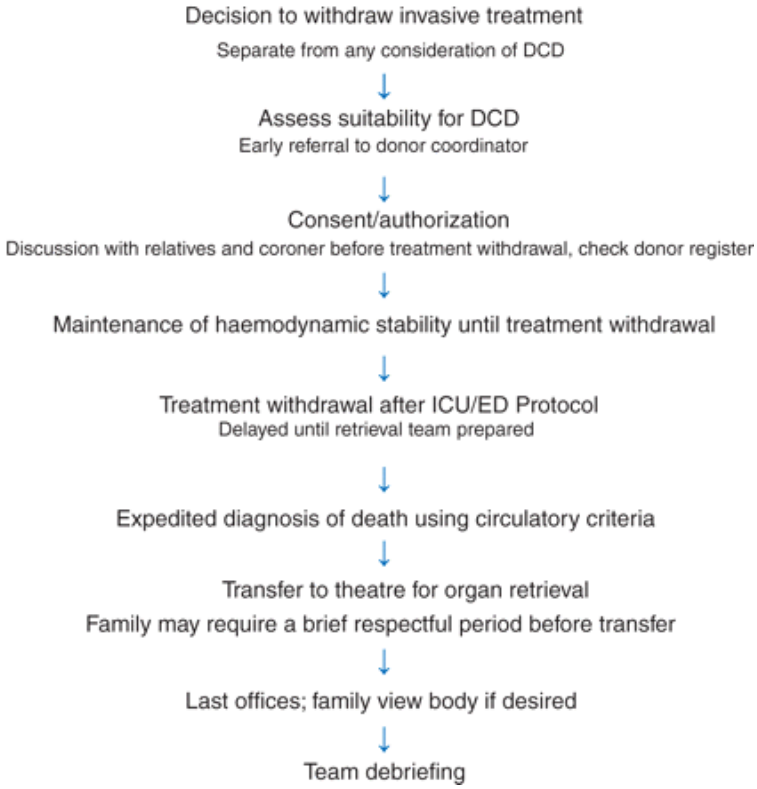


Figure 2-13 The clinical pathway for controlled DCD.
Adapted from Organ and Tissue Donation after Death, for Transplantation. Guidelines for Ethical Practice for Health Professionals 2007 Australian Government, National Health and Medical Research Council http://www.nhmrc.gov.au/_files_nhmrc/file/publications/synopses/e75.pdf

Warm ischaemic time in DCD donation begins at the onset of asystolic arrest. It comprises of an agonal phase commencing either from the withdrawal of life support or more conventionally when the systolic blood pressure drops to below 50mmHg until the cessation of circulation (Iyer *et al*. 2016). The donor is then transferred to the operating theatre whereby the aorta and IVC are immediately cannulated on laparotomy with cold perfusion initiated. Organ hypoperfusion and ischaemia may occur long before the onset of asystole, thereby prolonging the true functional warm ischaemic time (Watson and Dark 2012). Functional warm ischaemic time has the same variable start point ends with the infusion of cardioplegia in the donor. This process brings about profound hypoxia/hypoxemia with vasoconstriction and a catecholamine storm which may cause right ventricular dysfunction (Iyer *et al*. 2016). Once life-sustaining treatment has been withdrawn a stand-down time for the retrieval team of two hours from the time of withdrawal of treatment to death is common although protocols may vary slightly (AoRMC 2016).

Up to 2008, DCD donor organs retrieved included kidneys, pancreases, livers, and lungs. There was an increased incidence of acute tubular necrosis and delay in graft function in kidneys, necessitating post-transplant dialysis in up to 50% of the patients (Watson and Dark 2012). There was a higher incidence of primary non-function, anastomotic and intrahepatic biliary strictures and re-transplantations in livers transplanted from DCD donors with poorer overall survival. However, the survival of these patients was still higher than patients on the waiting list (Merion *et al*. 2006). DCD donor pancreases had a higher incidence of graft thrombosis (Johnson *et al*. 2014).

Lungs from DCD donors showed equivalent function from standard DBD donors. The lungs are inflated during DCD organ donation and thus a unique tolerance of the absence of a circulation(Dark 2008). Another reason for this may be the absence of the mentioned 'catecholamine storm'.

DCD heart transplantation was first attempted in animal models. Gundry et al conducted an anoxic arrest model using juvenile baboons to mimic the ICU setting of withdrawal of treatment. After a period of asystolic (varying from 15-31 minutes, the hearts were implanted in an orthotopic position with encouraging haemodynamic parameters. Pathological studies revealed no fibrosis or ischaemic damage in all subjects (Gundry *et al*. 1995). In 2008, the paediatric heart transplant team in Denver reported a series of 3 successful DCD heart transplantations. They performed this by administering pre-withdrawal heparinisation and insertion of femoral cannulae. An observation period of 3 minutes was used for the first donor prior to the commencement of organ retrieval. The patient was cooled using the administration of perfusion fluid via the femoral cannulae and topical slush after the sternotomy was performed. The observation time was shortened to 1.25 minutes on the recommendation of the Ethics committee after the first recipient required mechanical circulatory support post-operatively by means of ECMO. While the other two patients recovered well (Boucek *et al*. 2008). Although successful, this format of donation was only feasible for short ischaemic times.

To develop a strategy that was feasible for the safe use of DCD hearts, three issues were identified. First, a method to attenuate the effects of warm ischaemia had to be developed to ensure DCD hearts did not require recipient

and donor colocation as with the Denver paediatric experience or Christiaan Barnard's first operation (Dhital *et al*. 2017). Pharmacological intervention in the patient prior to the declaration of death is prohibited, so pre-conditioning of the heart in this period was not permissible. This prevented any mitigation of the effects of warm ischaemic, particularly ischaemic-reperfusion injury. Thus, the following option is to develop a post-conditioning 'cocktail' preferably with the cardioprotective solution. Some animal models have shown benefit in normokalaemic solutions after cold storage (Rudd and Dobson 2011). Other studies have shown benefit but adding an array of post-conditioning agents to standard cardioplegic solutions during the administration of cardioplegia. This includes sodium-hydrogen inhibitor cariporide (HOE 642) (Scheule *et al*. 2003), MCI-186, a free-radical scavenger and antioxidant by means of lipid peroxidation (Kotani *et al*. 2007), p38 mitogen-activated protein kinase (MAPK) inhibitor (Koike *et al*. 2004), erythropoietin, glyceryl trinitrate and zoniporide (Cs) (Iyer *et al*. 2014a). The second obstacle to DCD hearts is donor organ preservation, and the third obstacle was to evaluate the function of the heart prior to implantation (post-warm-ischaemic insult). Cold storage would expose the heart to two separate bouts of ischaemic reperfusion injury. Ex-vivo perfusion of the heart had already been introduced by Barnard's team in 1984 (Wicomb *et al*. 1984). They devised a portable hypothermic perfusion system and trialed it in 4 patients. Perhaps ahead of its time, its outcomes which were similar to cold storage preservation did not support the routine use of ex-vivo perfusion. A group in Australia tested the anoxic arrest animal model on greyhounds using cold storage and normothermic ex-vivo perfusion (Repse *et al*. 2010). They concluded that a strategy of pre-reperfusion cardioplegia, followed by continuous warm blood perfusion, is superior to cold storage. This was reproducible in other studies showing continuous perfusion replenished myocardial energy stores, reduced the impact of ischaemic reperfusion injury and improved cardiac recovery in animal models(White *et al*. 2013)and unused human hearts ((Iyer *et al*. 2014b; Rosenfeldt *et al*. 2014). The use of ex-vivo perfusion devices also ensured the heart could be assessed prior to implantation. To facilitate this, the Organ Care System^{tm} (TransMedics Inc, Andover, MA, USA) was used. As described in 2.3.4.4, it was intended for use in DBD hearts and via its non-inferiority trial PROCEED II (Ardehali *et al*. 2015).

In 2015, the heart transplant team at St Vincent's Hospital in Australia presented their data on the first series of successful DCD heart transplantations using normothermic ex vivo perfusion (Dhital *et al*. 2015). Australian law currently does not permit extracorporeal support to restart the circulation in the donor whose very death was declared on the basis of the cessation of circulation in the absence of certifiable brain death (Dhital *et al*. 2017). They, therefore, employed a technique called direct procurement and perfusion (DPP). After the end of the observation period, the patient was taken into the operation theatre and intubated. A venous cannula was placed in the atrium to drain 1.5L of donor blood into a pre-heparinised bag for priming of the OCS machine. The retrieval process from here onwards follows the cold phase as described in 2.3.4.2. In addition to St Thomas's cardioplegia, erythropoietin and glyceryl trinitrate were also delivered to the aortic root. The heart was placed on the OCS rig as described in 2.3.4.4. Serially samples of lactate concentrations of the perfusate were measured using a point of care analyser (iSTAT analyser (Abbott; Princeton, NJ, USA) with lactate concentration of <5 mmol/L in the perfusate combined with myocardial lactate extraction (coronary inflow lactate>coronary effluent lactate) was considered evidence of myocardial viability (Dhital *et al*. 2015). The implantation of the heart will be covered in 2.5.

Another method of retrieval was developed by the team at Papworth Hospital coined normothermic regional perfusion (NRP). After declaration of death and median sternotomy, a 30,000-unit heparin intracardiac injection was administered. They then clamped off the branches of the aortic arch (brachiocephalic artery, left common carotid and left subclavian), thereby excluding cerebral circulation as per the guidance of AoRMC (AoRMC 2016). The ascending aorta and right atrium were cannulated and connected to a makeshift ECMO circuit consisting of a centrifugal pump and an oxygenator. NRP was commenced to maintain a mean arterial pressure of 50mmHg with a flow of 5L/min at a temperature of ≥ 35°C (Messer *et al*. 2016). This in effect restored circulation to the cardiothoracic and abdominal organs for transplant while excluding the limbs, pelvis, head, and neck. This allowed them to functionally assess the heart using a PAC and TOE. Once satisfactory, 500mls of St Thomas's cardioplegia was administered and the heart was placed on the OCS rig as described in 2.3.4.4.

The rationale for NRP over DPP was based on the biochemical findings at the time of retrieval. Following circulatory death, the donor blood becomes hyperkalaemic, hyperglycaemic, hypoxic, hypercarbic and acidotic with circulating inflammatory markers and catecholamines (Messer and Large 2016). This environment may result in poor function of the heart. When transferred to the OCS rig, the heart is reliant on the right ventricle (RV) pumping perfusate through an oxygenator. In RV failure, this will result in ongoing accumulating hypoxia resulting in ischaemic damage or failure.

In a matched cohort study (NRP vs DPP), despite differences in donation withdrawal ischemic time, functional warm ischemic time, OCS perfusion time and implant duration time (all shorter for the NRP cohort) no differences were noted in patient outcomes post-transplant(Messer *et al*. 2017).

2.5 The Implantation

Preoperative preparation is of paramount importance for the implanting surgeon. More patients are presenting with LVADs, previous sternotomies, complex congenital surgeries; all of which necessitate careful and diligent dissection. Cannulation strategies, communication with the retrieval team and correction of anticoagulation should all be planned accordingly. In patients with multiple sternotomies, femoral vessels should be exposed in case of injury to the heart on re-sternotomy.

The current aim is to limit the total ischaemic time to <4 hours especially when marginal hearts are utilised. The recipient coordinator serves as the liaison in a similar way the SNOD serves as the donor coordinator. Factors to note in particular include the estimated time for inserting monitoring lines and PAC, dissection of the recipient prior to cross-clamp application on the donor, the estimated transport time while communicating with the family of the recipient.

2.5.1 Surgical techniques

Shumway and Lower first introduced the biatrial anastomosis technique of heart implantation, based on Cass and Brock’s animal experimentations as described in Chapter 1. This was adopted worldwide as the ‘standard’ technique due to its

reproducibility. Several studies, however, have shown the lack of a physiological geometry between donor and recipient atrium resulting in atrial dilatation. A sequela of this includes arrhythmias and secondary atrioventricular valvular incompetence, especially in the tricuspid region (Schnoor *et al*. 2007). Yacoub and Dreyfus (Yacoub *et al*. 1990; Dreyfus *et al*. 1991) clinically used a technique known as total orthotopic heart transplantation based on the descriptions of Webb and Neely (Webb *et al*. 1959). This involved complete excision of the recipient atria and transplantation of the complete atria and ventricles with separate bicaval and pulmonary vein anastomosis. This method, however, was associated with longer operating times due to the 6 anastomoses needed and bleeding from posterior segments of the pulmonary veins. It was also prone to anastomotic stenosis in the pulmonary veins (Morgan and Edwards 2005).

The bicaval was first described in 1989 by Yacoub and Banner and later Sievers in 1991(Yacoub and Banner 1989; Sievers *et al*. 1991). This was the first approach to bicaval anastomosis with end-to-end anastomoses both cavae. Proponents of this method argue there is a lesser incidence of tricuspid regurgitation and maintained the geometry of the right to preserve its contractility and sinus node function. These advantages provided potentially conferred better haemodynamics. However, overall survival was similar to the standard method in all studies to date (Schnoor *et al*. 2007; Czer *et al*. 2011; Fiorelli *et al*. 2011; Dell'Aquila *et al*. 2012). The bicaval technique also does not alleviate the conduction issues associated with left atrial to atrial anastomosis and may potentially have a prolonged ischaemic time with a risk of developing stenosis in either cavae. (Morgan and Edwards 2005).

2.6 The Recipient Cardiectomy

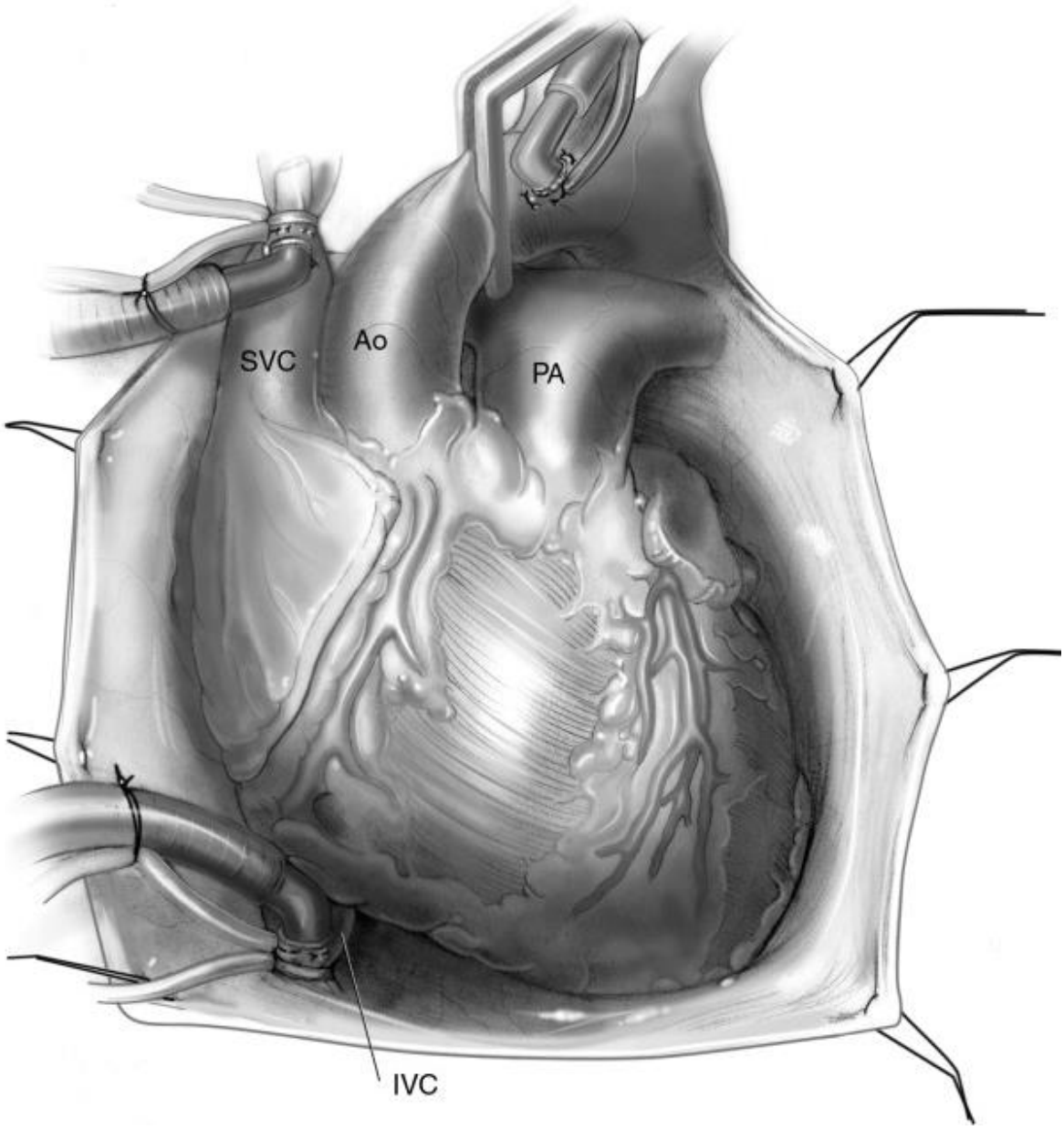


Figure 2-14 Bicaval cannulation of the recipient heart with snares in both cavae in preparation for cardiectomy
With permission from 'Orthotopic Heart Transplantation. Operative Techniques in Thoracic and Cardiovascular Surgery',2010, 15, 138-146. (John and Liao 2010)

A median sternotomy and pericardiotomy are performed to expose both cavae, aorta and pulmonary artery. The pericardium is hitched. Aortic cannulation should be in the distal ascending aorta with bicaval venous cannulation.

Cardiopulmonary bypass is instituted once the Activated Clotting Time (ACT) is at permissive. The aortic cross-clamp is applied and the caval snares fastened. The aorta and pulmonary artery (PA) should be separated so that the interatrial sulcus is clearly appreciated. The aorta and PA are divided distal to their

semilunar valves. The SVC is transected at the superior entry (cavoatrial junction). The right atrium is transected through the coronary sinus ostium and extended laterally through the floor of the fossa ovalis, thereby leaving a large cuff of IVC (John and Liao 2010). The left atrial cuff is incised through the roof of the left atrium to leave behind a generous cuff with all 4 pulmonary vein orifices visible. Ideally, the cardiectomy should be performed just before the arrival of the donor heart to reduce ischaemic time. Meticulous haemostasis should be performed on the view of Figure 2-15 as access to this region becomes difficult once the donor heart is anastomosed.

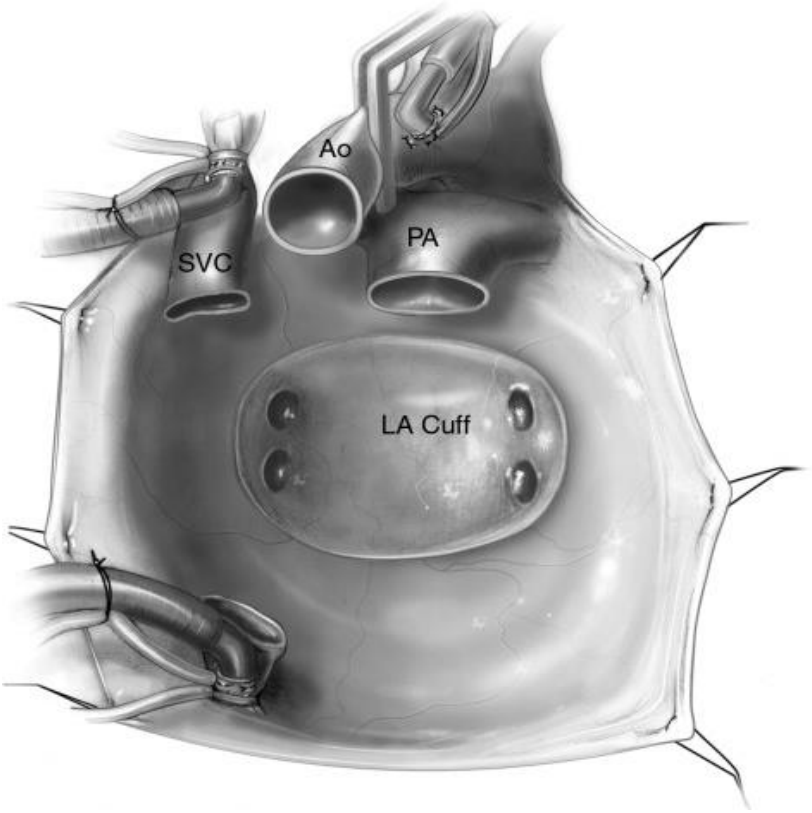


Figure 2-15 View of the structures after cardiectomy
With permission from 'Orthotopic Heart Transplantation. Operative Techniques in Thoracic and Cardiovascular Surgery',2010, 15, 138-146. (John and Liao 2010)

2.7 Implantation

The donor heart is removed from cold storage/the OCS rig (following administration of cardioplegia) and inspected. The donor aorta and donor PA should be separated. The left atrium is divided to create a cuff. This is done by splaying open each of the 4 pulmonary veins and carefully trimming back excess tissue. The donor heart is finally checked for a patent foramen ovale which should be repaired prior to implantation.

The left atrial anastomosis is performed by using a long non-absorbable monofilament suture (e.g. 3-0 Prolene -model DS5526, 135cm). This is usually done starting at the left superior pulmonary vein to the left atrial cuff (close to the left atrial appendage). For comfort, this can be done with the heart held at the sternal edge before it is lowered into the pericardial space(John and Liao 2010). The posterior suture line should be completed prior to the anterior suture line both using the everting suture technique to avoid thrombus formation. The two suture lines are left untied to allow introduction of an LV vent for de-airing.

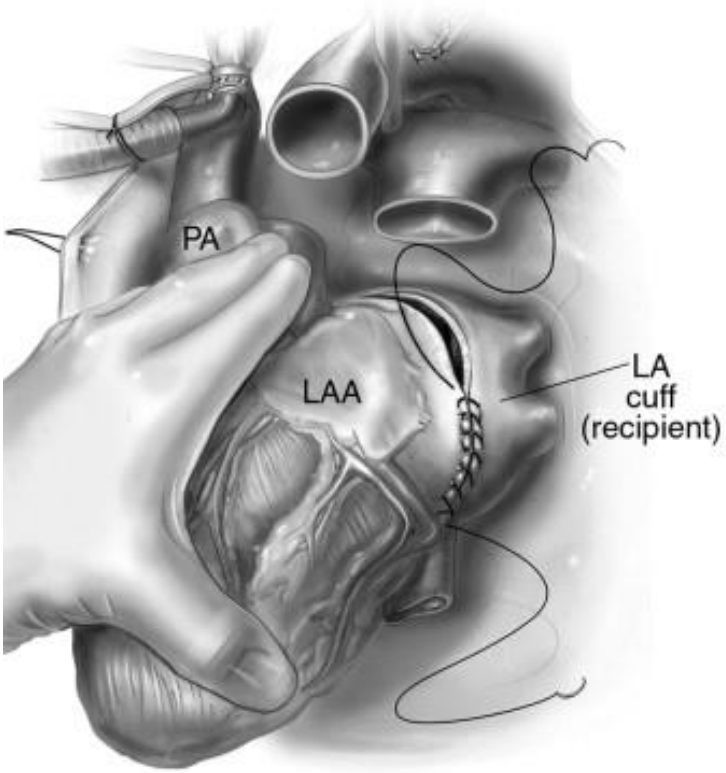


Figure 2-16 Everting sutures in the left atrium with assistant retracting PA to allow completion of the anterior suture line
With permission from 'Orthotopic Heart Transplantation. Operative Techniques in Thoracic and Cardiovascular Surgery',2010, 15, 138-146. (John and Liao 2010)

2.7.1 Biatrial Anastomosis

For the biatrial technique, the right atrial anastomosis is started from the septum and continued laterally using a long non-absorbable monofilament suture ((3-0 Prolene -model DS5526, 135cm) as demonstrated below.

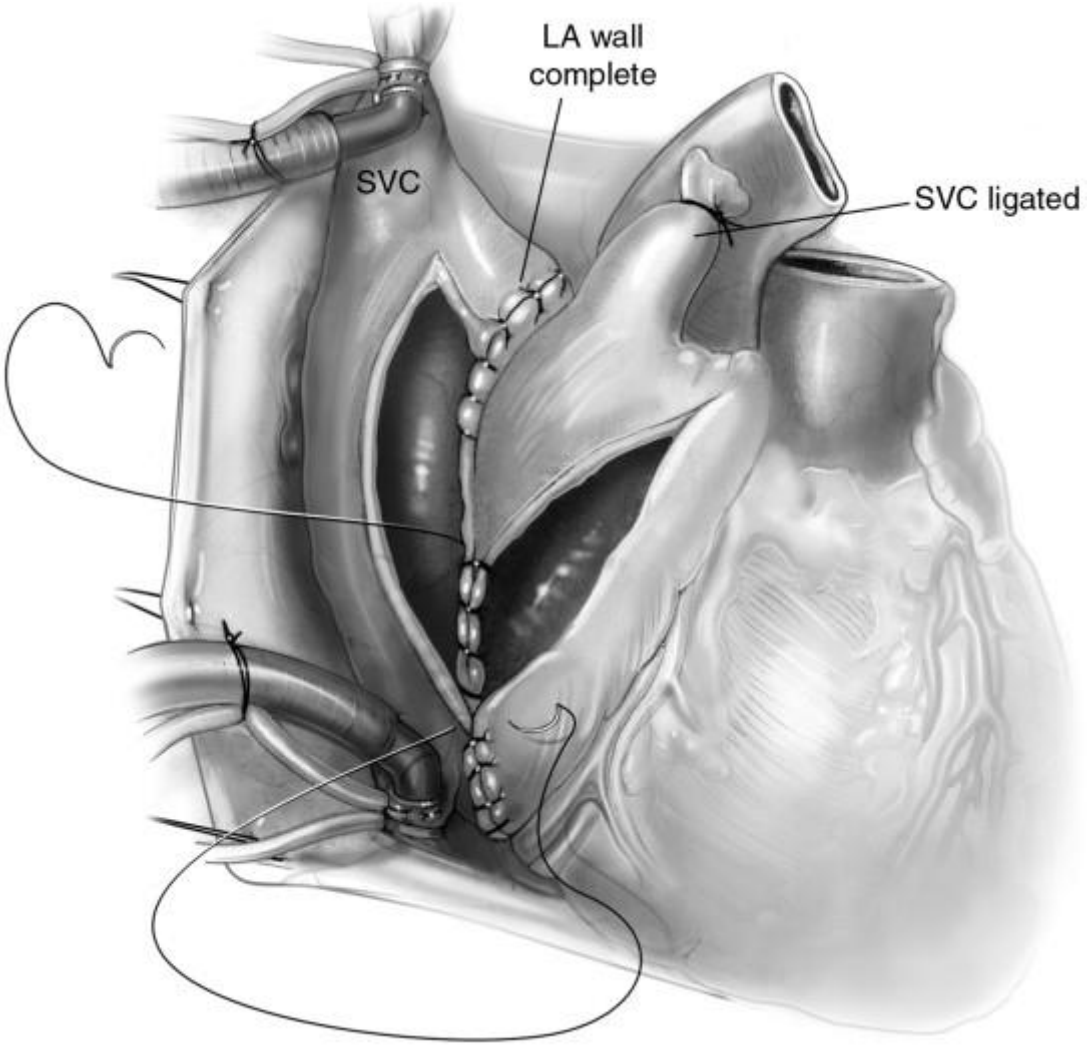


Figure 2-17 Right atrial anastomosis (medial to lateral)
With permission from 'Orthotopic Heart Transplantation. Operative Techniques in Thoracic and Cardiovascular Surgery',2010, 15, 138-146. (John and Liao 2010)

2.7.2 Bicaval Anastomosis

The IVC anastomosis is performed using 3-0 Prolene (or equivalent) with 4-0 Prolene for the SVC anastomosis. Care should be taken to avoid kinking of the SVC or malalignment. This can be avoided by using the donor right atrial appendage as a marker to orientate oneself.

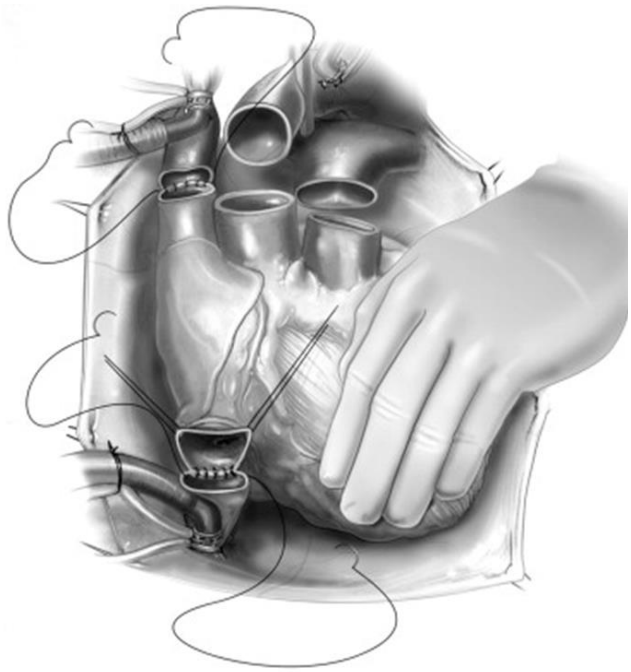


Figure 2-18 IVC and SVC anastomosis (posterior suture lines completed)
With permission from 'Orthotopic Heart Transplantation. Operative Techniques in Thoracic and Cardiovascular Surgery',2010, 15, 138-146. (John and Liao 2010)

The final steps of both techniques are PA and aortic closure. The PA is usually trimmed to prevent kinking. Both are closed using continuous sutures by completing the posterior suture line and then anterior respectively.

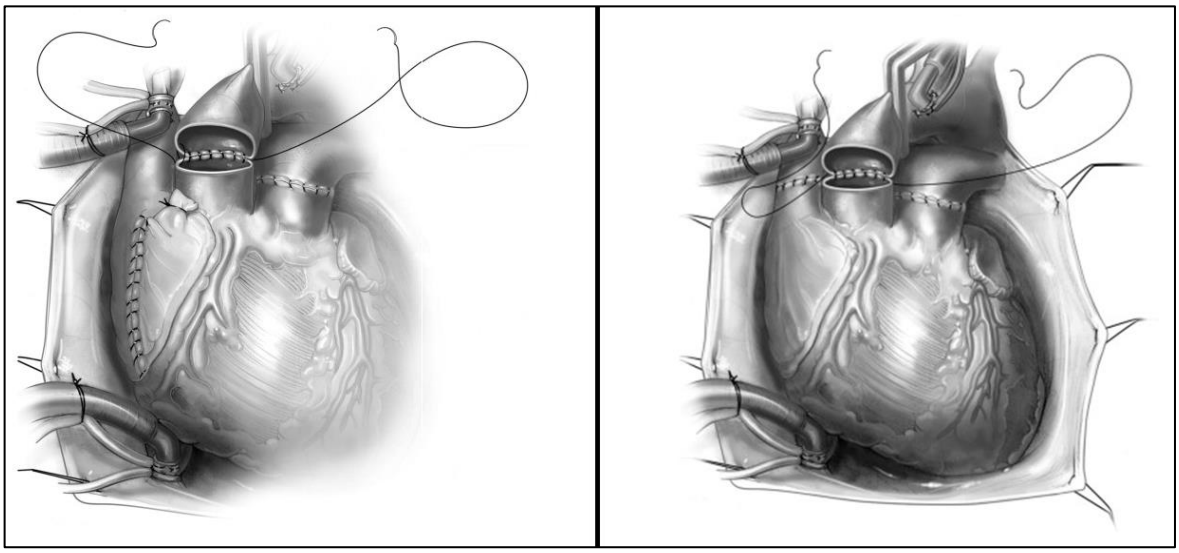


Figure 2-19 Aortic anastomosis in biatrial (left) and bicaval (right) techniques (posterior suture line complete)
With permission from 'Orthotopic Heart Transplantation. Operative Techniques in Thoracic and Cardiovascular Surgery',2010, 15, 138-146. (John and Liao 2010)

2.7.3 Post-operative period

Intravenous steroids (Methylprednisolone) are administered prior to removal of the aortic cross-clamp. The patient is usually also placed in a Trendelenburg position and de-airing is commenced. Once the aortic cross-clamp is removed, suction is maintained via the aortic root and/or LV vent cannula. The patient is kept on bypass during this period of reperfusion and haemostasis is once again confirmed. During this reperfusion time, inotropic support is often required. In addition, RV support using pulmonary vasodilators have become increasingly popular. This includes nitric oxide, inhaled prostaglandins, and even sildenafil. A TOE can be used to assess contractility and valvular function, but also to assist in de-airing. Pacing wires and mediastinal drains are placed. The patient is then weaned off bypass. It is usually at this point that Primary Graft Dysfunction is noted or suspected. Sometimes an intra-aortic balloon pump is placed if there are signs of poor contractility in an adequately filled heart. This may even require escalation to mechanical circulatory support usually in the form of ECMO.

Variations to the implant anastomosis are not uncommon. In order to minimise ischaemic times, some centres elect to perform the left atrial anastomosis followed by aortic anastomosis to facilitated earlier release of the cross-clamp

and reperfusion of the heart, followed by either SVC (bicaval technique) or right atrial (biatrial technique) and pulmonary artery anastomosis.

2.8 Organ Shortage

Despite the addition of DCD hearts to the longstanding DBD donor cohort, deceased human organ donation rates do not currently meet the demand for transplantation. Attempts to improve this discrepancy have led to changes in legislation such as the 'Opt-out' system for organ donation in Wales which came into effect on 1 December 2015. The new initiative, under the Human Transplantation (Wales) Act, assumes that everybody approves the use of their organs after death unless they choose to opt-out. An agreement with the next-of-kin, however, must still be sought. Scotland is expected to follow this direction in the near future. However, the 'opt-out' scheme has not resulted in a significant increase in the number of organ donations from Wales. (Hawkes 2017).

	DBD		**DCD**	
Quarter	England	Wales	England	Wales
Jan - Mar 16	67.8	83.3	63.9	46.2
Apr - Jun 16	65.7	75.0	59.9	52.9
Jul - Sep 16	62.0	78.6	57.7	50.0
Oct - Dec 16	70.8	75.0	58.8	54.5
Jan - Mar 17	71.3	81.3	59.0	66.7

Table 2-2 Percentage deceased donors from England vs Wales since the implementation of the 'Opt-out' legislation.
Source: NHSBT Annual Report (2016/2017)

A potential reason for the lack of a discernible difference is due to the already rising number of potential donors prior to the implementation of the legislation. Given the high numbers, the number of possible donors left who are deemed eligible are too few. Donor fluctuations also suggest that inferring that the act has failed may be premature. Despite not reaching statistical significance, the standardised test statistic shows an upward trend towards increasing the number of donors as demonstrated in Figure 2-20 for DBD and Figure 2-21 for DCD. The

upward swing in both quarterly test statistic towards the higher consent rate in the Welsh cohort vs the English cohort may be a better determinant of the effectiveness of the current legislation. As noted in Table 2-2, there has been a steady rise in DCD rates in Wales which is a possible sequela of this change. A public survey noted that most Americans were willing to serve as organ donors on death but the current system of 'opt-in' does not reflect this (Caplan 2014). Thus far, countries like France, Austria, Belgium, and Spain, have legislated versions of presumed consent with a consequent positive impact on their DBD rates (Byk 2009; Neades 2009).

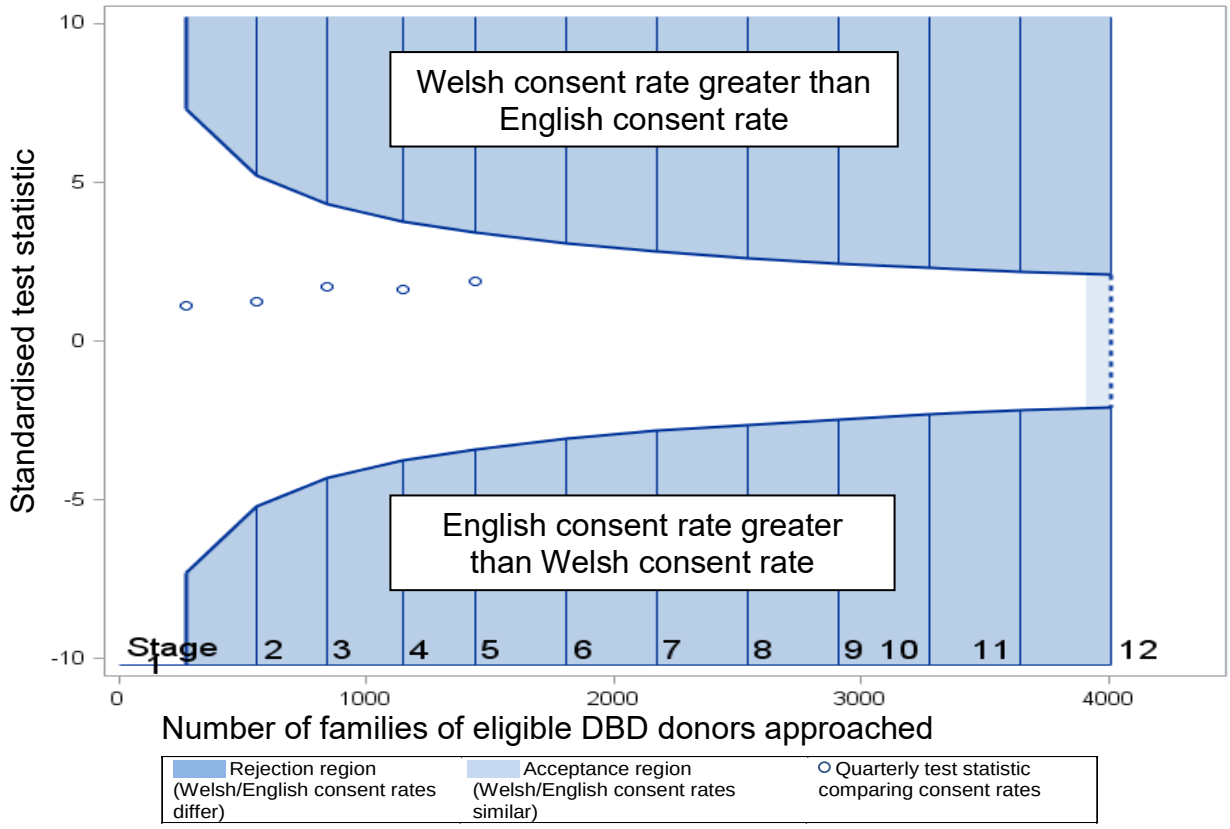


Figure 2-20 Graphical representation of Standardised Test Statistic of Donor Numbers in Wales and England for DBD Donations.
Source: NHSBT annual reports 2016/2017

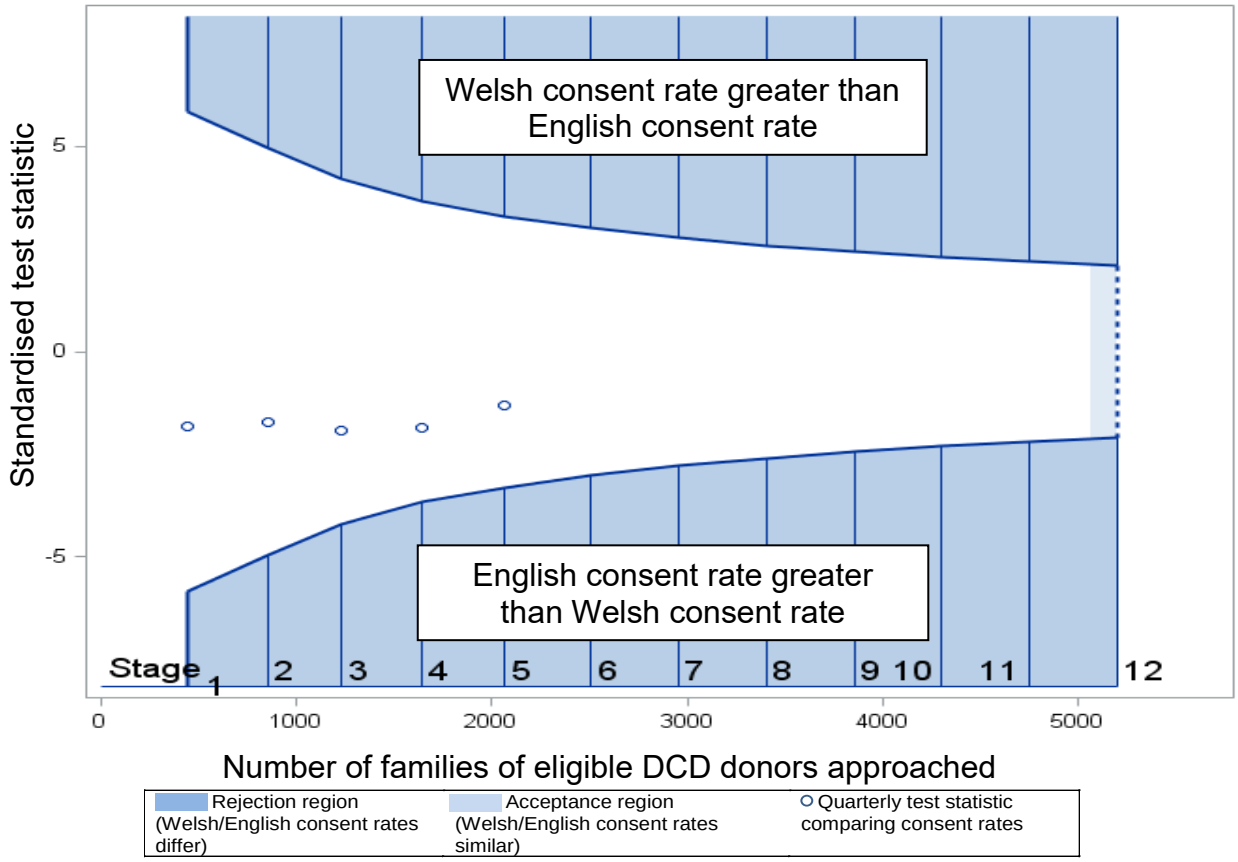


Figure 2-21 Graphical representation of Standardised Test Statistic of Donor Numbers in Wales and England for DCD Donations
Source: NHSBT annual reports 2016/2017

2.8.1 Marginal/Extended Criteria Donor Usage

Donor organ shortage, especially for hearts and increasing waiting list mortalities, has resulted in marginal donor hearts being used for higher risk recipients and critically ill patients. We review the development of two recipient lists as a way to provide cardiac transplantation as an option for recipients who would be otherwise ineligible and determine its impact on expanding the donor pool (Patel and Kobashigawa 2004). Although many studies have demonstrated good long-term outcomes with marginal donor heart usage, some have shown increased early mortality (Laks *et al*. 2003; B. Lima *et al*. 2006; Samsky *et al*. 2013; Taghavi *et al*. 2013; Bombardini *et al*. 2014; Cheng *et al*. 2016).

The marginal donor usually has one or more of the following features. estimated ischemia time longer than 4 hours, LVEF less than 50%, previous donor cardiac arrest, LV Hypertrophy(LVH) with an interventricular septum in diastole of more than 13 mm, history of alcohol/drug abuse, presence of palpable coronary artery disease without coronary angiography, diabetes, donor age>50 years,

cerebrovascular accident/stroke as the cause of death, history of hypertension, high inotrope requirement (dopamine>10 mcg/kg/min) during donor management, elevated cardiac troponin, and left ventricular regional wall motion abnormalities (Khush *et al*. 2013; García Sáez *et al*. 2014).

The use of marginal hearts with the OCS as demonstrated by Harefield Hospital has been associated markedly improved short-term outcomes and transplant activity by allowing the use of organs previously not considered suitable for transplantation (García Sáez *et al*. 2014). A UNOS database analysis demonstrated recipients of marginal allografts that were discharged later from hospital with no significant difference in overall survival (Khush *et al*. 2013). Other studies addressing the differences in outcomes by using diabetic donor hearts showed conflicting results. Analysis of the Eurotransplant registry revealed donor diabetes was not associated with increased recipient mortality. This study was however criticised for only having 41 diabetic donors suggesting a potential selection bias and was too small for subgroup analysis(Smits *et al*. 2012). Interrogation of the Cardiac Transplant Research Database noted similar findings as the Eurotransplant study but highlighted that in a subgroup of male donors (n=85), worse outcomes were associated with diabetes(Stehlik *et al*. 2010b). Analysis of the UNOS database failed to demonstrate significant interactions between diabetic donors and donor age, recipient gender, recipient age, or ischemic time even for diabetic donor hearts that were transplanted into diabetic recipients (Taghavi *et al*. 2013).

The use of marginal organs is currently justified. However, with advances in long-term mechanical circulatory support devices, especially LVADs, this issue may be revisited. In 2008, a study comparing HeartMate XVE Left Ventricular Assist Device (LVAD) (Thoratec Corporation, Pleasanton, CA) vs extended criteria cardiac transplantation (ECCT) was performed. They noted patients with the LVAD were more unstable, with a greater need for inotropes or mechanical support. Despite this, perioperative and 1-year mortality was similar for the two groups but better 3-year survival in the ECCT group (Daneshmand *et al*. 2010). Recently, the same group published a similar study comparing outcomes of extended criteria cardiac transplantation (ECCT) vs continuous flow destination therapy left ventricular assist device (CF DT-LVAD) (HeartMate II, Thoratec

Corp., Pleasanton, California) (Daneshmand *et al*. 2015). After matching the groups, they noted an improved renal function in the CF DT-LVAD cohort but with increased hospital readmission rates.

Currently, Long term LVADs serve as a potential alternative to OHTx. The rates of LVAD implantation over the two decades have increased exponentially and surpassing the heart transplantation rates for the first time in 2009. In January 2010, the HeartMate II LVAD was approved for destination therapy with devices in development expected to follow suit. With the advancements in technology and improving safety profile of devices, the next generation of devices may well present a new dilemma for surgeons and physicians alike especially when it comes to accepting marginal organs and may even surpass the reference standard of heart transplantation. Currently, the index admission costs of VAD implantation is more than double OHTx. This was primarily driven by procurement costs and length of stay. However, the cost of OHTx surpasses the cost of VAD therapy post-discharge (Marasco *et al*. 2016).

Patient satisfaction scores are higher in a post-transplant cohort vs LVAD (Grady *et al*. 2003). A similar outcome with OHTx patients demonstrating higher activity levels and better QoL than LVAD (HeartWare, HeartWare International Inc., Framingham, Massachusetts) patients at 1-year follow-up (Jakovljevic *et al*. 2014). A survey in Sweden showed that 75% of Swedes were willing to accept marginal donors but 83% felt it was pivotal they received information about the expected functional life of the organ. This suggests that marginal organs are not accepted unconditionally (Lundin and Idvall 2003).

2.8.2 Xenotransplantation

Another aspect of increasing organs available for transplant is xenotransplantation. Xenotransplantation is the interspecies transplantation of cells, tissues, and organs, or ex vivo interspecies exchange between cells, tissues, and organs is a frequently suggested alternative to allograft shortage(Anderson 2006). The early days of xenotransplantation are discussed in Chapter 1.

Non-human primates (NHP) are genetically the most similar animal to humans. However, issues raised regarding the risk of cross-species transmission of infection to humans, cost and difficulties in breeding, organ size disparities and other impracticalities, as well as ethical issues have largely excluded them from further consideration (Ekser and Cooper 2010). Currently, pigs are the most commonly studied animal for xenotransplantation as there is considerable experience with techniques of transgenesis in pigs that allow insertion of new genes, ease of breeding, size, and cost (Cooper *et al*. 2002).

Xenotransplantation fell out of favour as xenograft survival times remained modest despite advances in immunosuppressive therapy. Over the past decade, however, there has been a remarkable improvement in survival of xenografts. Several studies have shown that heterotopic heart transplantation into NHP with improved survival (Mohiuddin *et al*. 2012; Muhammad M. Mohiuddin *et al*. 2014; M. M. Mohiuddin *et al*. 2014). This was primarily achieved by 'knocking out' certain genes that are immunogenic to humans. Human transgenes, such as complement regulatory proteins (human complement regulatory protein) and human thromboregulatory protein were then expressed on the donor pig cells (Satyananda *et al*. 2013). One such major advancement was the deletion of gene α 1,3-galactosyltransferase in pigs. Primate antibodies directed against Galactose-α1,3-Galactose (Gal) epitopes on the vascular endothelium of pig organs play a major role in hyperacute and acute humoral xenograft rejection (Kuwaki *et al*. 2005).

The next was the development of targeted immunosuppression instead of generalised immunosuppression. Prior to 1998 most studies used conventional therapy of a biological agent (e.g., antithymocyte globulin) and/or pharmacologic (e.g., cyclophosphamide, cyclosporine, tacrolimus, and corticosteroids). Acute humoral xenograft dysfunction (AHXD) was the primary cause of graft failure. Most experiments in this period had to be abandoned due to infection (Satyananda *et al*. 2013). AHXD is poorly understood but is thought to be a T-cell mediated phenomenon (Ekser and Cooper 2010).

Using genetic engineering, initial efforts were made to increase the expression of immunosuppressive agents endogenously produced by pig cells. This included expressing CTLA4-Ig (Abatacept, Belatacept), which reduced the recipient's T-

cell response(Najafian and Sayegh 2000; Koshika *et al*. 2011). This, however, renders the host immune-incompetent and susceptible to infections (Salliot *et al*. 2009).

Research is now geared towards blockade of T-cell and B-cell mediated pathways such as anti-CD20 monoclonal antibodies and anti-CD40 monoclonal antibodies used by Mohiuddin and colleagues in their experiments. To date, the combination of genetically engineered pigs with a knockout of α-Gal, expression of human CD46 and thrombomodulin alongside co-stimulation blockade and B-cell depletion using the mentioned monoclonal agents have achieved more than 1-year immunogenic survival in primates with heterotopically transplanted hearts (Muhammad M. Mohiuddin *et al*. 2014). Orthotopically implanted cardiac xenografts should be the next step in determining feasibility.

Xenotransplantation has several ethical implications. Safety and cross-transmission from the donor animal need to be considered especially with the concomitant use of monoclonal antibodies and aggressive immunosuppression. Epidemiologists currently recommend an international registry of xenotransplant recipients with associated lifetime surveillance as a precaution (Anderson 2006). This may be expanded to surveillance of family members and close friends which is ethically controversial as it violates individual privacy. Although the Declaration of Helsinki and Nuremberg trials dictate that participation in studies is voluntary, mandatory clinical monitoring may be needed in this group which poses an ethical conundrum (Anderson 2006).

The cost of xenografts also needs to be considered prior to the integration of a xenotransplantation programme. Although transplants are arguably the most expensive of all medical procedures, organ shortages and relatively low frequency make it less than 0.5% of the national budget in the USA (Anderson 2006). The introduction of xenotransplantation will quadruple this budget. It may even add to the organ shortage problem as it may only serve as a bridge to allotransplantation (Anderson 2006).

> "Xenotransplantation is the future of transplantation, and always will be."-Norman Shumway (Cooper 2012)

3 ISHLT Primary Graft Dysfunction incidence, risk factors, and outcomes: a UK National Study

3.1 Abstract

Background

Heart transplantation (HTx) remains the most effective long-term treatment for advanced heart failure. Primary graft dysfunction (PGD) continues to be a potentially life-threatening early complication. In 2014, a consensus statement released by ISHLT established diagnostic criteria for PGD. We studied the incidence of PGD across the UK.

Methods

We analysed the medical records of all adult patients who underwent heart transplantation between October 2012-October 2015 in the 6 UK heart transplant centres Pre-operative donor and recipient characteristics, intraoperative details and post-transplant complications were compared between the PGD and non-PGD groups using the ISHLT definition. Multivariable analysis was performed using logistic regression.

Results

The incidence of ISHLT PGD was 36%. Thirty-day all-cause mortality in those with and without PGD was 31(19%) vs 13(4.5%) (p=0.0001). Donor, recipient and operative factors associated with PGD were: recipient diabetes mellitus (p=0.031), recipient pre-operative BIVAD(p<0.001) and preoperative ECMO (p=0.023), female donor to male recipient gender mismatch(p=0.007) older donor age (p=0.010) and intracerebral haemorrhage/thrombosis in donor (p=0.023). Intra-operatively, implant time (p=0.017) and bypass time(p<0.001) were significantly longer in the PGD cohort. Perioperatively, patients with PGD received more blood products (p<0.001). Risk factors identified by multivariable logistic regression were donor age (p=0.014), implant time (p=0.038), female: male mismatch (p=0.033), recipient diabetes (p=0.051) and pre-operative VAD/ECMO support (p=0.012),

Conclusion

This is the first national study to examine the incidence and significance of PGD after heart transplantation using the ISHLT definition. PGD remains a frequent early complication of heart transplantation and is associated with increased mortality.

3.2 Background

Heart transplantation remains the most successful long-term treatment for advanced chronic heart failure. Survival after cardiac transplantation has improved but primary allograft dysfunction (PGD) remains a significant problem and the predominant cause of early mortality during the first month (Taylor *et al*. 2009; Cosio Carmena *et al*. 2013). In a previous UK study, the incidence of PGD was 32% using a study-specific definition comprising of severely impaired systolic function affecting one or both ventricles accompanied by hypotension, low cardiac output, and high filling pressures occurring in the first 72 hours (in the absence of hyperacute rejection and technical surgical factors, such as cardiac tamponade) (Dronavalli *et al*. 2015).

However, comparative studies of the incidence and outcome of PGD have been hampered by the lack of an agreed definition until, in 2014, an international consensus statement was developed under the auspices of the International Society of Heart and Lung Transplantation (ISHLT).

The consensus classified graft dysfunction as primary graft dysfunction (PGD) or secondary graft dysfunction which had a discernible cause such as hyper-acute rejection, pulmonary hypertension, or surgical complications. PGD must be diagnosed within 24 hours of completion of surgery. PGD is divided into PGD-left ventricle and PGD-right ventricle. PGD-left ventricle is categorized into mild, moderate, or severe grades depending on the level of cardiac function and the extent of inotrope and mechanical support required. Risk factors for PGD include donor, recipient, and surgical procedural factors (J. Kobashigawa *et al*. 2014).

In this study, we aimed to ascertain the incidence of PGD using the ISHLT criteria and examine pre-operative donor and recipient characteristics as well as procedural risk factors for PGD in a study of an unselected national population of adult heart transplants.

3.3 Methods

All first-time orthotopic heart transplants in adults from donors after brainstem death (DBD) were included in this study.

From October 2012-October 2015, 450 adult heart transplants that met our inclusion criteria were performed in the United Kingdom. Data were collected prospectively at the time of the heart transplant and incorporated into the UK Transplant database hosted by NHSBT. Data were retrospectively validated from case records for each of these patients and additional information necessary for the study was extracted from the clinical records. Patients with combined organ transplants were excluded from this study. Donor procurement was performed by the National Organ Retrieval Service (NORS) with all but one centre using 1 litre of cold St Thomas's solution followed by cold stage packed with surrounding ice during transportation. One centre utilized the OCS (TransMedics Inc) and used Custodiol solution cardioplegia at the beginning and end of the OCS run. A Pulmonary Artery Catheter was inserted after the transplantation. If this was not possible, primary graft dysfunction was diagnosed using echocardiographic parameters as per Kobashigawa et al (J. Kobashigawa *et al*. 2014). Induction and maintenance immunosuppression was as per local hospital protocols. Primary Graft Dysfunction was defined using the 2014 ISHLT Consensus (J. Kobashigawa *et al*. 2014). The use of postoperative mechanical support was determined by individual surgeons.

3.4 Statistical Analysis

Continuous variables were described by mean and standard deviation or by median and interquartile range as appropriate. Categorical variables were expressed as number and proportion. Baseline characteristics were compared between PGD and non-PGD groups using Student's t-test and Mann Whitney-U test as appropriate and chi-square test or Fisher's exact test for categorical variables. Variables with significance of $p<0.1$ in the unadjusted analysis were initially introduced as candidate variables in a multivariable logistic regression model for the probability of PGD and removed by stepwise backward elimination. We also included variables that have been shown to be predictive in

other studies as outlined by the ISHLT consensus statement(J. Kobashigawa *et al*. 2014). Variables were retained in the model if they reduced the model deviance significantly ($p<0.05$). This was done using a complete case dataset to ensure appropriate comparison of nested models. A further subgroup analysis was performed on just those with PGD using the same methodology to compare variables that predict the different severities of PGD as defined. The analysis was conducted in Minitab 17 Statistical Software (2010). Minitab, Inc.

3.5 Results

450 adults received heart transplants between 1 October 2012- 1 October 2015. The mean age was 46.3±13.5 years. 348 (77.3%) of the recipients were males. During this period there were 10 Donation after Circulatory Death (DCD) transplants and these were excluded from the study. There were also 3 patients who were re-transplanted. Their second transplants were excluded from this study. Pre-operative, operative and post-operative details of the PGD and non-PGD cohorts are shown in Table 3-1. The overall incidence of Primary Graft Dysfunction was 36.2% (163 patients). There were 7 (1.6%) cases of Secondary Graft Dysfunction. These were graft failure secondary to bleeding, hyperacute rejection and elevated pulmonary pressures as defined by Kobashigawa (J. Kobashigawa *et al*. 2014). The phenotype and severity of PGD are shown in Figure 3-1.

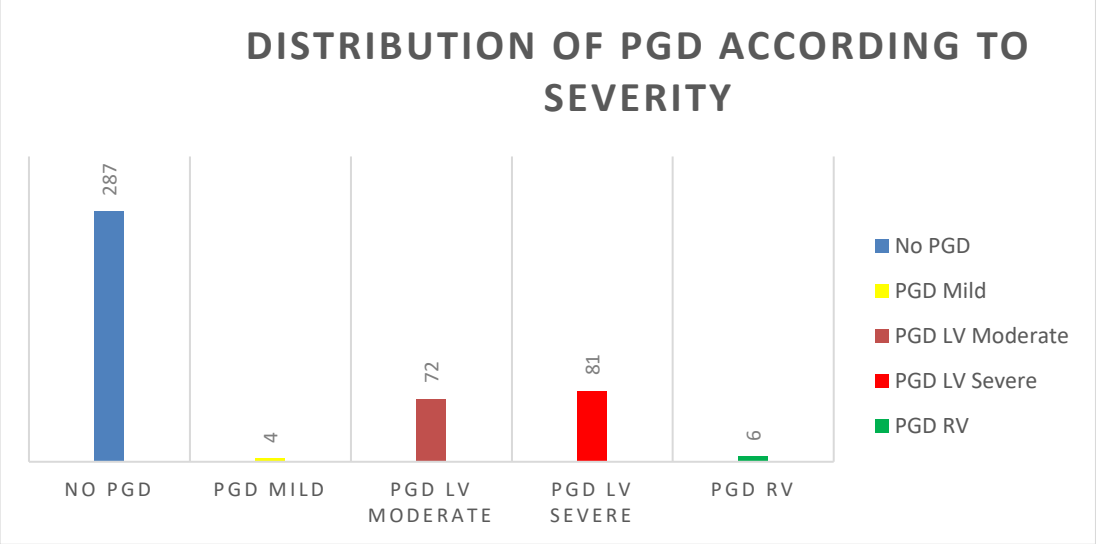


Figure 3-1: Distribution of PGD according to type and severity

Table 3-1 Pre-operative characteristics of recipients.

Recipient Factors	PGD (n=163)	Non-PGD (n=287)	P- value
Male: Female ratio	127:36	221:66	0.824
Age (years)	47.1±14.1	46.1±13.8	0.449
BMI (Kg/m^2)	25.68±3.96	25.34±3.98	0.388
Recipient Creatinine (μmol/L)	98.00 (48)	99.00 (46)	0.217
Recipient Diabetes Mellitus	19 (11.7%)	17 (5.9%)	**0.031**
Recipient Re-sternotomy	33 (20.2%)	47 (16.4%)	0.302
Pre-operative Inotropes	82 (50.3%)	171(59.6%)	0.056
Pre-operative ECMO	5 (3.1%)	1 (0.3%)	**0.023**
Pre-operative IABP	15 (9.2%)	17 (5.9%)	0.193
Pre-operative LVAD	25(15.4%)	35(12.2%)	0.345
Pre-operative BiVAD	20(12.3%)	9(3.1%)	**<0.001**
Pre-operative RVAD	3(1.8%)	20(7.0%)	**0.018**
Pre-operative antiarrhythmics (Amiodarone)	58 (35.6%)	111(38.7%)	0.514
Recipient Aetiology			
Ischaemic Cardiomyopathy	38 (23.3%)	62 (21.6%)	0.464
Dilated Cardiomyopathy	87 (53.3%)	160 (55.7%)	
Congenital Heart Disease	13 (8.0%)	26 (9.1%)	
HOCM	9 (5.5%)	15 (5.2%)	
Restrictive Cardiomyopathy	5 (3.1%)	8 (2.8%)	
Other	11 (6.7%)	7 (2.7%)	

We identified donor, recipient and operative risk factors for PGD. Preoperative factors that were significantly associated with PGD in the unadjusted analysis were recipient diabetes mellitus and female donor-to-male recipient gender mismatch as shown in Table 3-1.

There was no significant difference between the donor-recipient height and weight mismatch but the estimated LV mass showed more downsizing of donor-to-recipient in the PGD cohort as shown in Table 3-2.

Table 3-2 Pre-operative characteristics of donors

Donor Factors	PGD (n=163)	Non-PGD (n=287)	p- value
Donor Cause of death			
Intracerebral haemorrhage/Thrombosis	107 (65.6%)	157 (54.7%)	**0.023**
Hypoxic brain injury	21(12.9%)	48 (16.7%)	0.277
Road Traffic Accident (RTA)	23 (14.1%)	51(17.8%)	0.314
Meningitis	4 (2.5%)	11 (3.8%)	0.434
Brain Tumour	3 (1.8%)	8 (2.8%)	0.216
Other	5 (3.1%)	10 (3.5%)	(0.967
Gender Mismatch	52 (31.9%)	59 (20.6%)	**0.007**
Height Mismatch (%)	-0.55 (6.8)	-1.16 (6.8)	0.166
Weight mismatch (%)	-0.44 (27.8)	-3.90 (33.8)	0.464
Estimated LV mass mismatch (%)	2.76 (25.5)	-1.90 (25.3)	**0.020**
Donor Age	41.6±12.2	38.5±12.4	**0.010**
Donor LVEF (%)	57.77±9.36	58.88±7.41	0.279
Donor Smoker	74	140	0.489

Mismatch calculated as [(Measure ($_{recipient}$) − Measure($_{donor}$)/Measure($_{recipient}$)] X 100

Intra-operatively, implant time and bypass time were significantly longer in the PGD cohort.

Table 3-3 Post-operative details of heart transplant recipients

Operative Details	PGD (n=163)	Non-PGD (n=287)	P- value
Perfusion Solution			
St Thomas	139 (85.3%)	233 (81.2%)	0.378
Custodiol	24 (14.7%)	51 (17.8%)	
*Cold Ischaemic Time (mins)	103(66)	99(62)	0.392
Explant Time (mins)	17 (9)	18 (10)	0.513
Implant Time (mins)	56(24)	52(24)	**0.017**
Warm Ischaemic Time (mins)	72 (28)	70 (27)	**0.045**
Total Ischaemic Time (mins)	179 (86)	171(71)	0.426
Bypass Time (mins)	206(113)	162 (68)	**<0.001**
Post-operative details			
Right Atrial Pressure (mmHg) ϒ	13.01±4.37	11.98±3.97	**0.016**
PA Mean(mmHg) ϒ	22.39±6.02	22.43±5.95	0.958
PA Systolic(mmHg) ϒ	31.75±9.52	32.08±9.23	0.789
PCWP (mmHg) ϒ	12.83±4.92	13.53±5.76	0.355
Transpulmonary Gradient (mmHg)	8.000 (9)	9.000 (8)	0.593
Cardiac Index ϒ	2.5654 (2.4)	3.1074 (1.59)	**0.005**
MAP (mmHg) ϒ	73.1±15.2	80.9± 16.9	**<0.001**
Inotrope Score ϒ	14.533(14.56)	9.985(10.43)	**<0.001**
Blood Products Transfused (units)	9 (11)	5 (6)	**<0.001**
RBCs(units)	4(7)	2(3)	**<0.001**
FFP (units	2.000 (2.8)	2.000 (4)	**0.032**
Platelets(units)	2.0000 (2)	1.0000 (2)	**<0.001**

***Excluding patients on OCS**

ϒ**Part of ISHLT 2014 severity definition**

Patients with PGD had increased transfusion of blood products Table 3-3. 30-day mortality for patients with primary graft dysfunction was 31(19%) vs 13(4.5%) ($p<0.001$). The 6-month mortality for patients with PGD was 52 (31.9%) vs 18 (6.3%) ($p<0.001$). Comparing the PGD groups, there was a significantly higher 30-day mortality in the severe PGD-LV group vs moderate PGD-LV group 27(30%) vs 4(5%) respectively, $p<0.001$).

The total extracorporeal time for the OCS subset was significantly longer than after cold storage (309.4±88.4 minutes vs 100.3±45.8 minutes; $p<0.001$. However, the incidence of PGD was similar to the non-OCS cases (30.3% vs 37.2%, respectively) ($p=0.279$). In a subgroup analysis of the OCS cases, extracorporeal time was significantly longer in the PGD group (344.9±95 minutes vs 294.8±81 minutes; $p=0.048$)

The following variables were considered for multivariable analysis of the probability of PGD in which 21 (5%) patients were excluded due to missing data.

> Continuous Variables: Recipient age, donor age, explant time, implant time
>
> Categorical Variables: Recipient diabetes, recipient pre-operative inotropes, recipient pre-operative VAD/ECMO support, female donor: male recipient mismatch, donor smoking history, OCS usage, recipient aetiology, donor cause of death and recipient pre-operative IABP usage.

Bypass time and total intraoperative blood transfusion were excluded from this analysis. OCS use was not included because it occurred in a small surgeon-selected subset. The final model is shown in Table 3-4.

Table 3-4 Results of multivariable analysis for risk factors for PGD

Factors	Odds Ratio	95% Confidence Intervals	p-value
Donor age (years)	1.02	(1.0043, 1.0383)	**0.014**
Implant time (mins)	1.01	(1.0005, 1.0195)	**0.038**
Female: male mismatch	1.74	(1.0464, 2.9086)	**0.033**
Recipient diabetes	2.04	(0.9993, 4.1720)	**0.051**
Pre-operative VAD/ECMO support	1.79	(1.1371, 2.8295)	**0.012**

In donors, the likelihood of PGD increased by 20% for each decade increment in donor age. A female donor: male recipient combination was 1.7 times more likely to develop PGD.

Recipients requiring preoperative mechanical circulatory support also conferred almost a two-fold increase in the likelihood of PGD. Diabetic recipients were more than twice likelier to develop PGD.

There was also a 1% increase for each minute increment during implantation of the heart.

As an illustrative example, the absolute risk of developing PGD in an average donor (40-year old) to an average recipient (non-diabetic, no preoperative MCS, implant time = 54 minutes, without female donor to male recipient gender mismatch) was 28.7%. This absolute risk increased to 45.1% if there was recipient diabetes or 41.9% if there was preoperative MCS. A female donor-to-male recipient increased the absolute risk to 41.2%.

The absolute PGD risk of advancing donor age in an average recipient is computed in Figure 3-2.

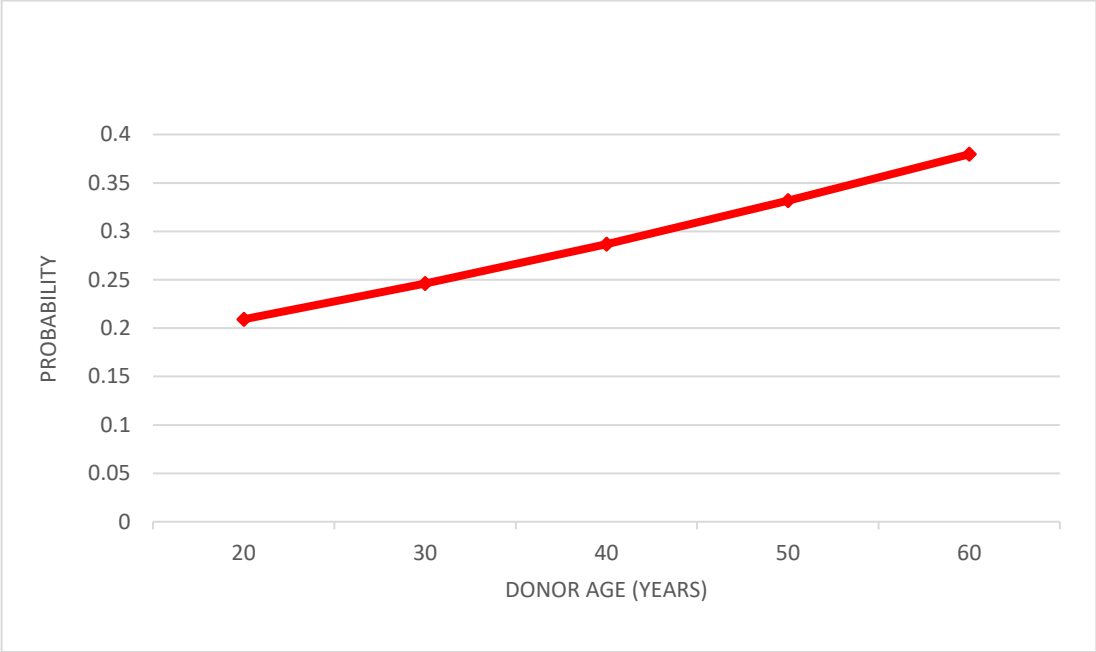


Figure 3-2 Probability of PGD with advancing donor age

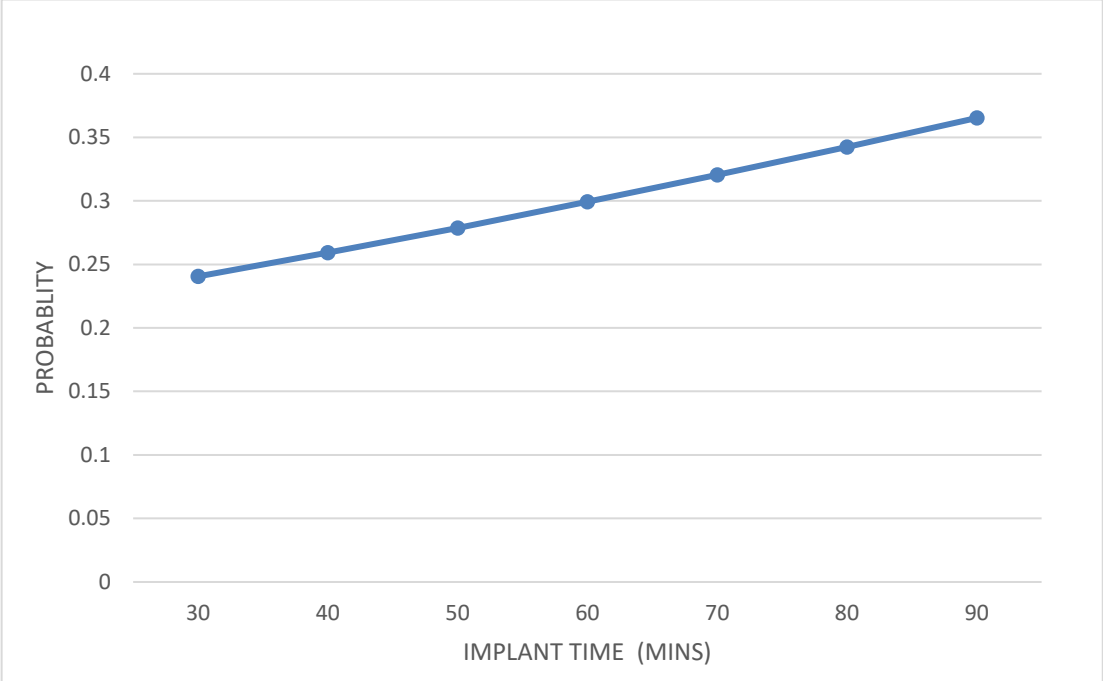


Figure 3-3 Probability of PGD with increasing Implant Time

Figure 3-3 shows the effect of advancing implant time (mins) in a 40-year old donor to an average recipient, who wasn't on any MCS support.

A further subgroup logistic regression analysis was performed to identify risk factors for severe PGD vs mild/moderate PGD on the 163 patients who experienced some degree of PGD.

The variables included for analysis were

Continuous Variables: Recipient age, donor age, explant time, implant time

Categorical Variables: Recipient diabetes, recipient pre-operative inotropes, recipient pre-operative VAD/ECMO support, female donor: male recipient mismatch, donor smoking history, OCS usage, recipient aetiology, recipient re-sternotomy donor cause of death and recipient pre-operative IABP usage

This subgroup analysis revealed implant time, female donor: male recipient gender mismatch and recipient re-sternotomy to be independent risk factors for severe PGD as opposed to mild or moderate PGD as seen in Table 3-5.

Table 3-5 Results of multivariable analysis for risk factors for severe PGD

Factors	Odds Ratio	95% Confidence Intervals	p- value
Implant time(mins)	1.02	(1.0003, 1.0342)	**0.037**
Female: male mismatch	2.43	(1.0966, 5.3722)	**0.026**
Recipient Resternotomy	3.21	(1.3215, 7.8084	**0.008**

3.6 Discussion

This study is the first national study of PGD in an unselected population of adult heart transplants using the ISHLT consensus definition. The main findings were, first, a high overall incidence of PGD and, second, a significant increase in perioperative mortality in the PGD group. Third, the risk factor analysis identifies not only donor and recipient factors but potentially modifiable procedural risk factors such as surgical implant time and use of blood products. Finally, the use of the OCS allowed an extension of the extracorporeal time for the donor heart with a similar incidence of PGD. Nevertheless, increasing

extracorporeal time in the OCS group was associated with an increase in PGD indicating that any protection afforded by OCS was relative, not absolute.

3.6.1 Incidence of PGD

There was a relatively high incidence of PGD (36.2%) in this cohort. This finding is similar to that reported by Dronavalli et al which reported an incidence of about 32% (Dronavalli *et al*. 2015). The changing patient demographics with the increasing use of pre-transplant mechanical circulatory support and increased utilization of marginal donors could be a contributory factor as donor age and preoperative MCS usage were independent risk factors for PGD(Shekar *et al*. 2016). Dronavalli et al also mentioned the lack of echocardiographic criteria which reduced the sensitivity of diagnosing PGD in the previous study. There were more severe PGD-LV patients (18%) and moderate PGD-LV (16%) than mild PGD-LV (1%) and PGD-RV (1%). These findings were similar findings noted in a single centre series by Sabatino et al (Sabatino *et al*. 2017a). The majority of their patients were classified as severe PGD (65%) followed by moderate (12%) and mild (0%; $p < 0.01$). The low rates of mild PGD-LV could be as a result of earlier intervention by physicians and surgeons by increasing the inotropic treatment in response to a low cardiac output state to the point where the inotrope score will meet the ISHLT definition of moderate PGD-LV. The clinical significance of the mild PGD-LV group is uncertain as there was no 30-day mortality in this group.

3.6.2 PGD-related Mortality

The 30-day mortality in our cohort was lower than the previous study (19% vs 37%) and in other studies (Isaac; Brian Lima *et al*. 2006; Segovia *et al*. 2011). The lack of a standardized definition previously also potentially resulted in more conservative definitions of PGD which was the need for instituting MCS. This could also explain the improved mortality figures due to the inclusion of inotrope dependence as part of the definition. The improved 30-day survival could also be a result of improvements in the recognition and treatment of PGD. Short-term PGD related mortality rates in our cohort were also similar to those described by Squiers et al from a high volume centre in the United States

(Squiers *et al*. 2017b). They had a 30-day mortality rate of 25% in the moderate/ severe PGD group. Sabatino et al also reported similar mortality rates in their cohort (37% in-hospital mortality)(Sabatino *et al*. 2017a). However, the mortality rate at 6-months remains high in the PGD cohort (31.9% vs 6.3%). There is a paucity of data regarding longer-term outcomes following PGD. Kim et al retrospectively reviewed a single centre cohort of patients and noted that moderate and severe PGD-LV patients had worse long-term outcomes (Kim *et al*. 2015). Given the large proportion of moderate and severe PGD-LV patients in our cohort, further studies may be needed to evaluate longer-term outcomes of PGD survivors vs non-PGD patients.

3.6.3 Risk Factors

The increased incidence of PGD reported is multifactorial. It highlights several vascular risk factors that may shed light on the aetiology of PGD. Increasing donor age and recipient diabetes were both independent risk factors in our cohort and have identified in previous studies prior to the ISHLT definition(Segovia *et al*. 2011).

3.6.3.1 Donor Age

Donor age was a significant risk factor for both PGD and severe PGD in the subgroup analysis. This finding was also noted by Russo by interrogating the UNOS database(M. J. Russo *et al*. 2007). They concluded that the effect of ischemic time on survival after heart transplantation is dependent on donor age, with a greater tolerance for prolonged ischemic times among grafts from younger donors.

3.6.3.2 Ischaemic Time

Ischemic time was subdivided into warm and cold ischemic time in our cohort (Banner *et al*. 2008). Warm ischemic time was defined as the explant time + the implant time. The implant time was found to be a strong predictor of primary graft dysfunction. Marasco et al (Marasco *et al*. 2012) retrospectively reviewed 206 patients over a period of around 10 years (June 2001-November 2010). Their definition of warm ischemic time included the implant time. They found that

poorer survival with a warm ischemia time (WIT) of >80 minutes having a compared to WIT group of <60 minutes. Donor age was once again an independent predictor of outcome in this cohort.

3.6.3.3 Recipient Diabetes Mellitus

The role of recipient diabetes as a predictor of primary graft dysfunction was evident in our study as it was in the RADIAL study. The UK prospective Diabetes Study trial established a link between microvascular complications and glycaemic control('Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group' 1998). In recipients with diabetes, there may be a combination of direct glucose-mediated endothelial damage, oxidative stress from superoxide overproduction and production of advanced glycation end-products, which may result in changes in endothelial permeability, excessive vascular protein deposition and altered blood flow (Brownlee 2001). A recent metanalysis, diabetes mellitus was an independent predictor of 1-year mortality post-heart transplant (Foroutan *et al.* 2017). They attributed this to the summative increased hazard for comorbidities of diabetes at the time of transplant which was also noted by Russo et al (Russo *et al.* 2006). In a subgroup analysis, diabetic recipients with well-controlled diabetes had similar survival to non-diabetic patients. Interrogation of the UNOS database by Taghavi et al(Taghavi *et al.* 2013) revealed that of 20,348 patients undergoing orthotopic heart transplantation, 496 (2.4%) received hearts from diabetic donors. The diabetic donors were likelier to be females and older. The recipients of diabetic hearts were also older. However, on multivariable analysis of subgroups, neither insulin-dependent diabetes (1.173; 95% CI, 0.884-1.444; *P* = 0.268) nor duration of diabetes for more than 5 years (HR, 1.239; 95% CI, 0.914-1.016; *P* =0.167) were risk factors once the groups had been matched. A similar finding was noted by Smits in a European cohort(Smits *et al.* 2012).

3.6.3.4 Gender Mismatch

The odds ratio for severe PGD was double that of mild/moderate PGD in female donor – male recipient gender mismatched patients in our study. It has also been identified as a risk in several previous studies. Jalowiec et al conducted a study

on early outcomes after heart transplantation in gender mismatched patients (Jalowiec *et al*. 2012). 74/347 patients received a heart from the opposite gender. They concluded that gender-mismatched heart transplant recipients had more complications due to rejection and higher resource utilization due to more re-hospitalization during the first post-operative year as compared to gender-matched recipients. Stehlik et al published similar findings with female donor: male recipients having a higher risk of post-transplant death (Stehlik *et al*. 2010b). Some have postulated the relative differences between the size (body surface area) or weight mismatch between female donor and male recipient, citing a smaller female donor heart being unable to sustain the demands of a larger male patient although there was no significant size mismatch (>20%) noted in our cohort (Young *et al*. 1994; Weiss *et al*. 2009).

3.6.3.5 Recipient resternotomy

Recipient re-sternotomy was identified as a risk factor for developing severe PGD in our subgroup analysis. Patients with previous sternotomies develop adhesions that complicate the surgical dissection thereby prolonging the explantation period and bypass time. They are also at an increased risk of infections (Kansara *et al*. 2014b). This may further exaggerate the inflammatory response explaining the need for increased support post-operatively. Analysis of the UNOS database revealed an increased risk of all-cause mortality in patients with re-sternotomies (Kansara *et al*. 2014b).

3.6.3.6 OCS

It is widely believed that an important factor in the pathogenesis of PGD is acute ischemia-reperfusion injury. The donor heart is exposed to variable blood pressures, hypothermic storage, warm ischemia and finally reperfusion. The role of the OCS in reducing the impact of this has not been studied. A multivariable analysis has not been done here owing to the relatively small number of OCS transplants during the study period (n=66). However, in the unadjusted analysis, the length of time on the OCS machine was a strong predictor of PGD. One hypothesis for this phenomenon is the lack of metabolic and excretory functions within the OCS circuit to sustain the metabolically active heart within the machine. The mean extracorporeal time of hearts on the OCS was significantly

longer than cold storage with similar PGD rates. Garcia-Saez et al reported improved short-term outcomes from the use of the OCS in extended criteria donors (García Sáez *et al*. 2014). The OCS may have a role in improving the logistical limitations of organ procurement. The ex-vivo perfusion of the heart allows evaluation of extended criteria allografts prior to implantation. It also reduces functional ischemia by means of continuous oxygenation and perfusion which may be important in higher-risk recipients who are on MCS. Nevertheless, a randomized study of a larger cohort of donors is needed to establish any benefit of the OCS in reducing PGD.

3.6.3.7 Size mismatch

The height and weight profiles of donors and recipients in our cohort were not significantly different in both groups. This could be due to careful donor selection and matching process to ensure accurate sizing of the cardiac allograft for the recipient. Height mismatch and weight mismatch were negligible in our cohort. However, a composite of the two measurements to calculate the estimated LV mass showed a higher proportion of downsizing in the PGD cohort. We used the following equation which has been published and validated in the literature (Bluemke *et al*. 2008).

$$Predicted\ Left\ ventricular\ mass(g) = \alpha * Height^{0.54}(m) * Weight^{0.61}(kg)$$

$$where\ \alpha\ =\ 6.82\ for\ women\ and\ 8.25\ for\ men$$

However, this was not a significant finding on multivariable analysis. This could be due to the co-efficient weightage which may reflect the potential downsizing in a female donor to male recipient gender mismatch using this equation. The equation is also limited as there is no correlation with other confounders of LV mass such as ethnicity, history of cardiovascular disease and valvular heart disease. Size mismatching has been noted in other studies (Russo *et al*. 2010; D'Alessandro *et al*. 2011a; Sabatino *et al*. 2017a; Squiers *et al*. 2017b). Transplanted hearts are denervated and thus rely on increased stroke volume to augment workload(Robert M. Reed *et al*. 2014). Consistent increments of stroke volume result in increasing filling pressure. Smaller hearts are also prone to tachycardia to meet the demands of the previously larger sized heart which is

mediated by catecholamine release (Ferretti *et al*. 2002; Mettauer *et al*. 2005). Tachycardia may worsen episodes of myocardial ischaemia and significantly increases the production of oxygen free radicals by increased metabolic demand(Critchley *et al*. 2013). These results in immune infiltration and activation, potentially causing acute or chronic rejection.

Consequently, undersized hearts are shown to undergo pathological cardiac hypertrophy, which may cause fibrosis (Mather *et al*. 1995; Bernardo *et al*. 2010). Fibrosis of myocardium and conduction fibres are likely to increase the risk of arrhythmias which may be misconstrued as rejection(Thajudeen *et al*. 2012).

3.6.3.8 Bypass time and blood transfusion

Patients with PGD in our cohort had a significantly longer bypass time. We considered that this may have been due to the need to institute further treatment by means of insertion of IABP or institution of mechanical circulatory support. However, prolonged bypass time in itself is an independent predictor of morbidity and mortality in general cardiac surgery (Salis *et al*. 2008; Ellenberger *et al*. 2017).

The mechanism of injury from CPB and ischaemic-reperfusion of the myocardium is similar; both producing a systemic inflammatory response syndrome (SIRS). They result in a hyperdynamic circulatory state due to the vasoplegia reducing vascular resistance, platelet and coagulation factor dysfunction, inflammatory pathway activation triggered by leucocytes and endothelial cells and finally cytokine release and formation of oxygen free radicals (Anselmi *et al*. 2004). Prolonged cardiopulmonary bypass also increases the transfusion requirement(Al-Sarraf *et al*. 2011). Our PGD cohort had higher blood transfusion requirements compared to the non-PGD cohort. This could once again be a response to the vasoplegic state caused by the SIRS effect from either prolonged bypass time or PGD itself. Blood transfusion in general cardiac surgery is associated with both infection and ischaemic postoperative morbidity, increased hospital stays, increased early and late mortality, and increased hospital costs(Koch *et al*. 2006; Murphy *et al*. 2007). In animal models, stored red blood cells have

implicated in causing organ hypoxia(d'Almeida *et al*. 2000). Blood transfusion also increases pulmonary vascular resistance thereby affecting right ventricular ejection, without improving systemic or regional oxygen utilization(Fernandes *et al*. 2001).

Given these findings, blood transfusion and cardiopulmonary bypass time may both contribute to the worsening of the ischaemic injury caused by PGD.

3.6.4 Treatment of PGD

Treatment of PGD is primarily supportive. As the definition of PGD is based on the treatment modality, mild and moderate PGD-LV is primarily inotropic support. Moderate PGD-LV is also treated with implantation of IABP. Escalation from this usually requires ECMO. Most cases of severe PGD-LV involve failure to wean from bypass, necessitating the institution of ECMO or short term VAD support. PGD-RV is initially treated with inotropic support including agents such as milrinone to promote pulmonary vasodilation. An RVAD is cited if right heart failure persists(J. Kobashigawa *et al*. 2014). Due to the shortage of organs and the increasing waiting list, re-transplantation is rarely done (3 in this study period).

3.7 Limitations

This was a retrospective analysis of prospectively collated national data. This study design is advantageous because the risk factors were recorded before the occurrence of the outcome (PGD). This is important because it allows the temporal sequence of risk factors and outcomes to be assessed. Selection bias was also minimized by including all adults with heart-only transplants during the study period. However, as an observational study, only association and not causation can be inferred from the results. Other unrecorded factors may have affected the outcome(Sedgwick 2014).

As the data collected were from different hospitals, variations in practice were unaccounted for. This included post-operative immunosuppression regimes, choice of inotropes, myocardial preservation methods and MCS experience with some centres having a greater proportion of patients on LVADs. We relied on

both PAC measurements and Echocardiography for defining PGD in patients without devices where possible. Some patients did not have PCWP readings and then we were reliant on echocardiographic criteria and vice versa.

3.7.1 Limitations in PGD definition (ISHLT 2014)

The ISHLT consensus definition relies on the use of mechanical circulatory support to define the more severe forms of PGD.

It also underestimates the true number of PGD-RV as VA-ECMO institution is the commonly used MCS strategy for any low cardiac output state (RV, LV or biventricular). There is a significant overlap between the phenotypical appearance of post-operative right ventricular stunning which occurs post-CPB and PGD-RV. The reliance on an interventional strategy in itself causes an inherent overestimation of the true incidence of PGD. For example, in high-risk cases, a surgeon may opt to prophylactically insert an intra-aortic balloon pump as a precaution which would classify this as moderate PGD-LV. The use of MCS was decided by individual surgeons, therefore, is a potential weakness of the consensus definition. However, the national multicentre nature of this study is likely to have mitigated this problem.

We performed an exploratory analysis of transplants performed on the OCS device but were unable to perform a multivariable analysis because of the limited number of cases and events.

3.8 Conclusion

PGD remains a significant risk factor for early mortality in heart transplant recipients. The standardized definition allows early diagnosis and recognition of this condition. There are several donor, recipient and procedural risk factors that may be contributory to the pathogenesis of PGD that should be considered for predicting outcomes. Further studies are warranted to establish the long-term outcomes of PGD using the current definition.

4 PREDICTA -A model to predict Primary Graft Dysfunction after adult heart transplantation in the United Kingdom

4.1 Abstract

Background

The rates of PGD across Europe are higher than in North America possibly due to the increasing use of extended criteria donors because of organ shortage. However, there is no scoring system currently available in the literature for assessing PGD risk. Our aim was to derive a novel scoring system based on prospective data collected nationally in the UK over a 4-year period. We compared this scoring system to a previously validated (RADIAL) score in a contemporary cohort of patients.

Methods

Medical records of all adult patients who underwent heart transplantation (HTx) between 1 October 2012- 30 September 2016 in the 6 UK heart transplant centres were analysed. Pre-operative donor and recipient characteristics, intraoperative details, and post-transplant complications were compared between the PGD and non-PGD groups using the ISHLT definition. Multivariable logistic regression was used to build the predictive model. An Area Under Receiver Operating Characteristics (ROC) curve was used to test the novel scoring system (PREDICTA) versus the RADIAL score.

Results

613 heart transplants were included in the study. There were 233 patients who had PGD. The variables analysed by multivariate modelling included in the model were recipient diabetes mellitus, pre-operative mechanical circulatory support (ventricular assist devices (VAD)/extracorporeal membrane oxygenation (ECMO)), implant time, donor age, and bypass time >180 Minutes. The C-statistic of the PREDICTA score was 0.704 vs 0.547 for the RADIAL score indicating an acceptable discriminatory value.

Conclusion

The PREDICTA Score is a novel scoring tool with improved ability to predict the development of PGD compared to the RADIAL score in a contemporary cohort of patients. It may help identify patients who are at risk of PGD and therefore allow risk stratification and resource planning for management and therapeutic interventions. Further multicentre studies are needed to investigate its application in the prevention and early management of PGD.

4.2 Introduction

The incidence of Primary Graft Dysfunction (PGD) in Western Europe is around 30% (S. Avtaar Singh *et al*. 2018a). This is due to several factors such as increasing donor and recipient age, increased pulmonary vascular resistance in recipients, donor and recipient co-morbidities and prolonged ischaemic time (Jon Kobashigawa *et al*. 2014; Nicoara *et al*. 2018). PGD remains an important cause of morbidity and mortality following heart transplantation. Improvements in immunosuppression and surgical techniques have resulted in good long-term survival post-transplant; however, the rate of PGD has remained unchanged in the past decade (Nicoara *et al*. 2018). To date, there have been no predictive models for PGD in using the current definition. A previous centre specific definition was used to create a 6-point RADIAL score by Segovia and colleagues which considers donor and recipient factors, namely **R**ight atrial pressure ≥ 10 mm Hg, recipient **A**ge ≥ 60 years, **D**iabetes mellitus, **I**notrope dependence, donor **A**ge ≥ 30 years, **L**ength of ischemic time ≥ 240 minutes(Segovia *et al*. 2011; Singh *et al*. 2019)

Given the relatively high incidence of PGD across Western Europe, it is imperative that a new predictive model is sought to assist in decision-making and resource allocation for heart transplantation. This is an area of increasing significance with increasing patients on the waiting list with a finite donor pool primarily consisting of donors after brainstem death (DBD). Recently, ex-vivo normothermic perfusion (EVNP) and hearts from donors after circulatory death (DCD) has been used to expand the donor pool. Advancements in mechanical circulatory support, especially implantable Left Ventricular Assist Devices (LVADs) have also changed recipient demographics. However, the association between these procedures and PGD has not been clearly established. Most studies in the literature are single-centre studies with the inherent weakness of applicability to wider practice. We, therefore, conducted a multicentre, national study to establish trends and independent risk factors for PGD after heart transplantation. Several risk factors have been identified in previous studies which include donor factors, recipient factors, and procedural factors. Our aim was to derive a multivariable model to identify and predict PGD. This would allow resource provision in high-risk cases to allow early intervention and

management of these patients. We then explored the performance of a previously validated PGD scoring system, the RADIAL score as a comparison using our validation cohort. Our aim was to develop a predictive risk score for ISHLT-defined PGD that would be applicable at present with the abovementioned developments.

4.3 Methods

4.3.1 Patient population

All consecutive adult patients who underwent first-time orthotopic heart transplants from 1 October 2012 – 30 September 2016 from 6 heart transplant centres in the United Kingdom were included in our study (n=613). Data were collected prospectively at the time of the heart transplant and incorporated into the UK Transplant database hosted by NHSBT. Data were retrospectively validated from case records for each of these patients and additional information necessary for the study was extracted from the clinical records. Patients with combined organ transplants (n=23) were excluded.

4.3.2 Donor Organ Procurement

4.3.2.1 DBD Donation

Donor procurement was performed by the National Organ Retrieval Service (NORS) with all but one centre using cold St Thomas's solution followed by static cold storage packing during transportation. One centre utilized the Organ Care System^{tm} (OCS), an EVNP device (TransMedics Inc) and used Custodiol solution cardioplegia at the beginning and end of the OCS run. Further details are explained in chapter 3.

4.3.2.2 DCD Donation

DCD donations were done by direct procurement or normothermic regional perfusion. During the duration of the study, only 2 centres performed DCD heart transplants. All DCD hearts were placed on the OCS with one centre using Custodiol solution cardioplegia and the other using St Thomas' Solution. Further details are explained in chapter 3.

4.3.3 Post-operative haemodynamic measurements

PGD was diagnosed using echocardiographic parameters or invasive cardiac monitoring parameters as per the ISHLT definition(Jon Kobashigawa *et al*. 2014). Induction and maintenance immunosuppression was as per local hospital protocols. The use of postoperative mechanical support was determined by individual surgeons.

4.3.4 Primary Graft Dysfunction

Primary Graft Dysfunction was defined by the 2014 ISHLT Consensus(Jon Kobashigawa *et al*. 2014). PGD was diagnosed within 24 hours after the completion of transplantation. The severity of left-sided PGD (PGD-LV) was determined by the inotrope score, placement of a new intra-aortic balloon pump or institution of mechanical circulatory support as detailed by the consensus statement. Echocardiographic findings of Left Ventricular Ejection Fraction (LVEF) of <40% could also be used for determination of mild/moderate PGD in the absence of pulmonary pressure and cardiac monitoring measurements. Right-sided PGD (PGD-RV) was determined by a right VAD implantation or elevated right atrial pressure in the absence of elevated pulmonary pressures. Further details are elaborated in chapter 2.

4.3.5 Statistical Analysis

Continuous variables were described by mean and standard deviation. Categorical variables were expressed as the actual number and proportion. Baseline characteristics were compared between PGD and non-PGD groups using Student's t-test and Mann Whitney-U test as appropriate and chi-square test or Fisher's exact test for categorical variables. Survival data were analysed using the Kaplan–Meier method and survival curves were compared using the log-rank test. Surviving patients were censored at their last known follow-up. $p<0.05$ was considered statistically significant.

4.3.5.1 Derivation Cohort

A number generator was used to randomly select 75% of the cohort for the purpose of model derivation (n=460). Variables with significance of $p<0.1$ in the unadjusted analysis above were initially introduced as candidate variables in a multivariable logistic regression model for the probability of PGD and removed by stepwise backward elimination. Variables were retained in the model if they reduced the model deviance significantly ($p<0.1$). This was done using a complete case dataset to ensure appropriate comparison of nested models. The goodness of fit of the model to the observed event rates (PGD) was evaluated by calculating the Hosmer–Lemeshow statistic. All statistical analysis was undertaken using SPSS v.18.0 (IBM Corp., Armonk, NY, USA).

4.3.5.2 Validation cohort

The remainder of patients (n=153) were used for validation of the model. The ability of the model to identify patients with PGD was evaluated using the C-statistic, equivalent to the area under a receiver-operating characteristic (AUROC) curve for dichotomous outcomes.

4.4 Results

4.4.1 Demographic data

The demographic details of these patients are listed below in Table 4-1. The incidence of PGD was 38%. Patients with PGD had a poorer survival post-transplant with higher 30-day (18.9% vs 3.9%, $p<0.001$) and 1-year mortality rates (32.6% vs 6.6%, $p<0.001$). Figure 4-1 depicts the 5-year survival of both cohorts. The p-value for the log-rank test for the Kaplan-Meier curve depicting survival of the two groups of patients was <0.001.

Details	PGD (n=233)	No PGD (n=380)	p-value
Age (years)	46.5±13.4	46.2±13.8	0.78
Recipient height (cm)	172.5±8.5	173.2±9.2	0.35
Recipient Weight (kg)	76.3±14.4	76.3±14.6	0.99
Cardiac Index (L/min)	2.22±1.4	3.14±1.2	**<0.001**
MAP (mmHg) (L/min/m^2)	71.1±13.8	79.1±15.7	**<0.001**
Inotrope Score	18.4±11.7	12.4±8.5	**<0.001**
Total Ischaemic time(mins)	165.7±60.7	161.0±62.5	0.36
Cold Ischaemic Time(mins)	101.36±42.7	99.7±47.8	0.6
Time on OCS (mins)	221.6±155.7	204.7±142.0	0.52
Number of DBD OCS (%)	32(13.8)	49(12.9)	0.77
Number of DCD (%)	7 (3)	15(3.9)	0.54
Explant Time(mins)	19.8±10.1	19.6±11.0	0.83
Warm Ischaemic Time (mins)	63.5±20.5	57.5±22.2	**0.001**
Bypass Time(mins)	218.2±93.1	174.3±66.3	**<0.001**
Height Mismatch (%)	1.3±5.0	1.3±5.2	0.99
Weight Mismatch (%)	5.6±23.4	7.0±24.6	0.099
Total Units of Blood transfused	10.7±12.1	7.7±30.7	0.096
Donor Age (years)	41.1±12.6	38.1±12.1	**0.003**
Recipient Re-sternotomy (%)	59(25.3)	80(21.0)	0.13
Recipient Diabetes (%)	40(17.2)	22(5.8)	**<0.001**
Pre-operative Inotropes (%)	120(51.5)	215(56.6)	0.22
Donor Smoker (%)	119(51.1)	190(50.0)	0.43
Pre-operative Recipient ECMO (%)	6(2.6)	1(0.3)	**0.015**
Pre-operative Recipient VAD			
LVAD (%)	38(16.3)	45(11.8)	0.94
RVAD (%)	3(1.3)	9 (2.4)	0.35
BIVAD (%)	29(12.4)	27(7.1)	**0.026**
Donor Male: Recipient Female (%)	24(10.3)	32(8.4)	0.43
Donor Female: Recipient Male (%)	45(19.5)	49(13.0)	0.11

Table 4-1 Demographic details of all patients undergoing heart transplantation in the United Kingdom (01/10/2012-30/9/2016)

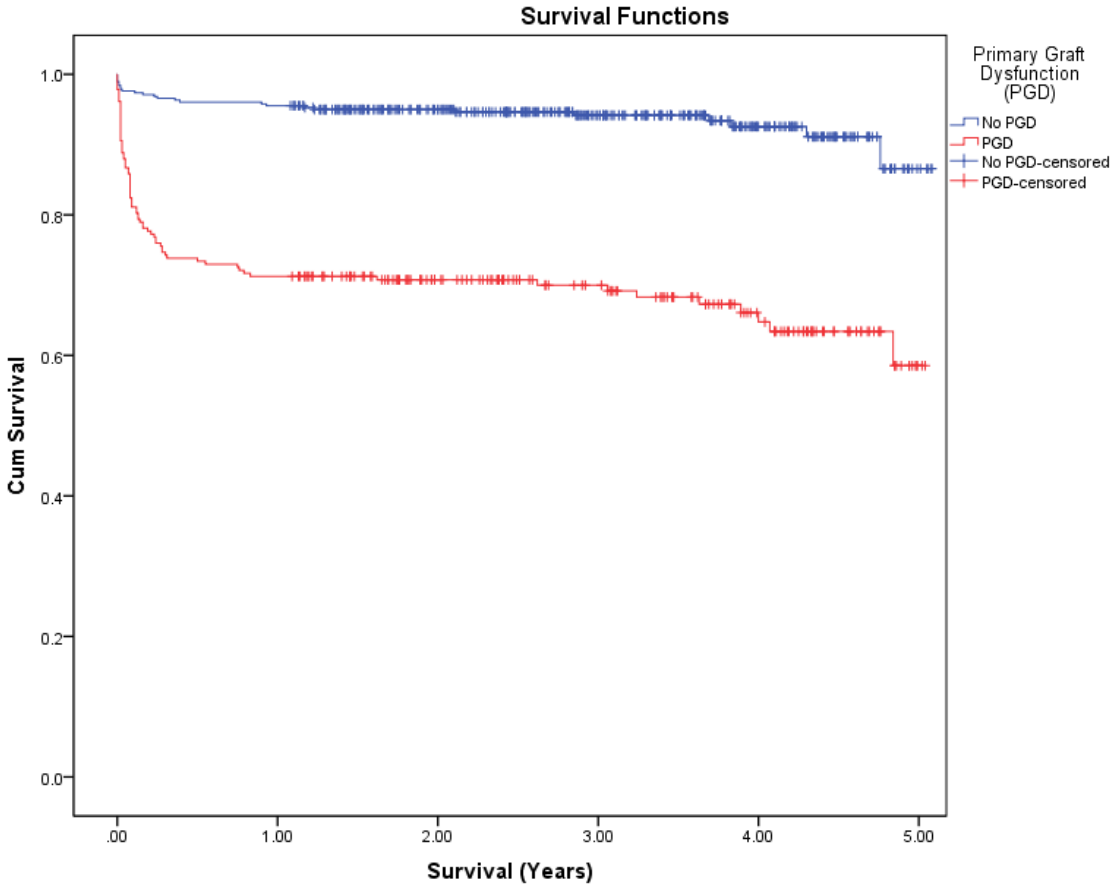


Figure 4-1 Kaplan-Meier curves depicting the survival of PGD and non-PGD patients. (Log-rank= p<0.001)

4.4.2 Cohort comparisons

To ensure the applicability of data, demographic data of both cohorts were compared. The demographic data of both cohorts are shown in Table 4-2, depicting no statistically significant differences between the derivation and validation cohort of patients.

Details	Derivation Cohort (n=460)	Validation Cohort (n=153)	p-value
Age (years)	46.6±13.4	45.3±14.4	0.304
Recipient height (cm)	172.6±9.3	173.9±7.9	0.352
Recipient Weight (kg)	76.7±14.1	75.2±14.2	0.274
Cardiac Output(L/min)	5.1±2.4	5.3±2.7	0.526
Cardiac Index (L/min)	2.96±1.2	3.00±1.46	0.238
MAP (mmHg) (L/min/m^2)	71.1±13.8	79.1±15.7	0.763
Inotrope Score	14.7±10.8	14.3±8.5	0.663
Total Ischaemic time(mins)	163.7±63.7	163.0±57.3	0.931
**Time on OCS (mins)	262.3±122.1	246.9±97.2	0.663
Explant Time(mins)	19.8±9.8	19.7±12.4	0.973
Implant Time(mins)	55.5±21.1	57.5±20.6	0.306
Bypass Time(mins)	185.1±82.9	192.7±86.7	0.342
Donor Height (cm)	174.6±9.0	175.1±8.6	0.533
Donor Weight (kg)	79.3±14.9	79.2±13.7	0.941
Donor Age (years)	39.6±12.7	38.3±11.9	0.272
Donor Smoker (%)	233(50.7)	76(49.7)	0.834
DCD (%)	20(4.3)	5(3.3)	0.559
M:F ratio	336:124	122:31	0.099
Recipient Diabetes Mellitus (%)	46(10.0)	16(10.5)	0.871
Recipient Re-sternotomy (%)	99(21.5)	40(26.1)	0.237
Pre-operative ECMO (%)	6(1.3)	1(0.7)	0.687
Pre-operative VAD (%)	106(23.0)	45(29.4)	0.113
Gender Mismatch (%)	114(24.8)	42(27.5)	0.512

Table 4-2 Demographic details of the derivation and validation cohorts of patients.
**** Only DCD and EVNP donations**

The incidence of PGD in the derivation cohort was 38.3%(n=176) and 37.5%(n=57) in the validation cohort.

There was no statistically significant difference between the total ischaemic time (for hearts procured using cold storage) for the derivation cohort(n=374) and the validation cohort(n=133) (163.7±63.7 mins vs 163.0±57.3 minutes, p=0.93). No differences were noted between the time on OCS (for hearts procured using EVNP) for the derivation cohort(n=86) and the validation cohort(n=20), (262.3±122.1 mins vs 246.9±97.2 mins, p=0.66).

4.4.2.1 Derivation Cohort

The demographic details of the derivation cohort are listed below.

Recipient Variables	PGD (n=176)	No PGD (n=284)	P- value
Male: Female ratio	125:51	211:73	0.44
Age (years)	47.1±13.5	46.3±13.3	0.54
Recipient Height (cm)	172.0±8.8	173.0±9.5	0.27
Recipient Weight (kg)	76.8±14.0	76.6±14.7	0.93
Recipient BMI (kg/m^2)	25.9±3.9	25.5±3.9	0.33
Recipient Creatinine (μmol/L)	105.7±45.7	106.7±38.1	0.38
Recipient Re-sternotomy (%)	42(23.9)	57(20.1)	0.34
Recipient Diabetes (%)	27(15.3)	19(6.7)	**0.003**
Recipient pre-operative Inotropes (%)	90(51.1)	171(60.2)	0.056
Pre-operative ECMO (%)	5(2.8)	1(0.4)	**0.033**
Pre-operative IABP (%)	15(8.5)	17(6.0)	0.25
Pre-operative LVAD (%)	26(14.8)	32(11.3)	0.27
Pre-operative BiVAD (%)	21(11.9)	16(5.6)	**0.016**
Pre-operative RVAD (%)	3(1.7)	8(2.8)	0.45
Pre-operative amiodarone usage	63(35.8)	116(40.8)	0.28
Recipient Aetiology			
Ischaemic Cardiomyopathy (%)	40(22.7)	54(19.0)	0.34
Dilated Cardiomyopathy (%)	95(53.9)	147(51.8)	
Congenital Heart Disease (%)	18(10.2)	28(9.9)	
Other (%)	23(13.1)	55(19.4)	

Table 4-3 Recipient variables between PGD and non-PGD patients in the derivation cohort
Continuous data are shown as mean ± SD with categorical data shown as an absolute number and (percentage). Recipient aetiology shown in grey. MI: Body Mass Index, ECMO: Extracorporeal Membranous Oxygenation, LVAD: Left Ventricular Assist Device, BiVAD: Biventricular Ventricular Assist Device, RVAD: Right Ventricular Assist Device, IABP: Intra-Aortic Balloon Pump

Donor Factors	PGD (n=176)	No PGD (n=284)	P- value
Donor Height (cm)	174.9±9.1	174.4±9.2	0.59
Donor Weight (kg)	80.1±15.4	79.0±13.6	0.45
Estimated Donor LV Mass (g)	148.6±26.9	149.9±28.1	0.64
Gender Mismatch (%)	26.1	23.9	0.60
Height Mismatch (%)	2.0±7.6	1.5±8.0	0.54
Weight mismatch (%)	8.0±30.9	5.6±28.2	0.41
Estimated LV mass mismatch (%)	3.81±22.9	4.13±22.8	0.81
Donor Age	41.6±12.6	38.4±12.6	**0.007**
Donor LVEF (%)	57.7±10.3	58.9±7.8	0.3
Donor Smoker (%)	88(50.0)	147(51.7)	0.722
Donor Cause of death			
Intracerebral haemorrhage/Thrombosis (%)	106(60.4)	164(57.8)	
Hypoxic brain injury (%)	12(6.7)	27(9.5)	
Road Traffic Accident (RTA) (%)	22(12.7)	47(16.6	
Meningitis (%)	4(2.2)	12(4.3)	
Other (%)	32(17.9)	34(11.8)	0.31
DCD (%)	6(30)	14(70)	
DBD (%)	170(38.6)	270(61.4)	0.44

Table 4-4 Donor variables between PGD and non-PGD patients in the derivative cohort
Continuous data are shown as mean ± SD with categorical data shown as an absolute number and (percentage). Donor cause of death shown in grey. LV: Left Ventricle, LVEF: Left Ventricular Ejection Fraction, DCD: Donation after Circulatory Death, DBD: Donation after Brainstem Death

Operative Details	PGD (n=176)	Non-PGD (n=284)	P- value
Perfusion Solution			
St Thomas (%)	146(83.0)	242(85.2)	
Custodiol (%)	30(17.0)	42(14.8)	0.52
EVNP (%)	33(18.7)	54(19.0)	
Cold Storage (%)	143(81.3)	230(81.0)	0.94
*Cold Ischaemic Time (mins)	102.5±44.1	99.6±48.6	0.33
**Time on OCS	221.8±155.8	232.2±136.9	0.72
Explant Time (mins)	20.0±10.7	20.5±10.5	0.60
Implant Time (mins)	59.6±21.1	53.0±20.7	**0.001**
Total Ischaemic Time (mins)	166.9±63.7	160.5±62.9	0.11
Bypass Time (mins)	196.3±77.3	187.9±76.2	0.095
Post-operative details			
Right Atrial Pressure (mmHg) ϒ	13.8±4.4	11.7±4.1	<**0.001**
PA Mean(mmHg) ϒ	22.0±6.0	22.2±5.3	0.93
Cardiac Index ϒ	2.2±1.3	3.1±1.1	<**0.001**
MAP (mmHg) ϒ	71.5±13.0	78.7±15.8	<**0.001**
Inotrope Score ϒ	18.9±12.4	12.3±8.8	<**0.001**
Blood Products Transfused (units)	8.6±11.3	9.0±34.7	0.078

Table 4-5 Perioperative and postoperative variables between PGD and non-PGD patients in the derivative cohort

Continuous data are shown as mean ± SD with categorical data shown as an absolute number and (percentage). OCS donors denoted with **. EVNP: Ex-vivo Normothermic Perfusion, PA: Pulmonary Artery, MAP: Mean Arterial Pressure

*Non-OCS donors

** OCS donors

ϒDenotes measures used in the current ISHLT PGD definition

From the unadjusted analysis, variables with p<0.1 were included in the multivariable analysis. Continuous data were stratified into categorical variables with reference categories. Five variables were identified as significant predictors of PGD on multivariable analysis. These include 1 donor variable (donor age), 2 recipient variables (recipient diabetes mellitus and pre-operative recipient MCS), and 2 procedural variables (implant time and bypass time).

Variable	Odds Ratio	95% Confidence Intervals	P-value
Recipient Diabetes Mellitus	3.04	(1.49, 6.21)	0.002
Pre-operative MCS	2.73	(1.35, 5.55)	0.009
Implant time			0.021
≤45 Minutes	Reference Category		
46-60 Minutes	1.80	(1.11, 2.93)	
61-90 Minutes	1.96	(1.22, 3.15)	
>90 Minutes	2.15	(1.01, 4.60)	
Donor Age			0.025
<21 years	Reference Category		
21-40 years	1.44	(0.72, 2.85)	
41-50 years	1.81	(0.89, 3.67)	
>50 years	2.60	(1.26, 5.37)	
Bypass Time >180 minutes	2.53	(1.75, 3.66)	0.000

Table 4-6 Multivariable analysis of risk factors for PGD from the derivation cohort
Binary variables in grey, non-binary variables in white. Odds ratios depicted with 95% Confidence intervals. MCS: Mechanical Circulatory Support

An additive score was formulated using the odds ratios (rounded) of binary variables with an ordinal scoring system for the non-binary variables with respect to the odds ratio. The scoring system was entitled **PREDICTA** (**Pre**operative mechanical circulatory support in the recipient, **D**iabetes mellitus in the recipient, **C**ardiopulmonary bypass time>180 minutes, implant **T**ime, donor **A**ge) score with the breakdown of its derivatives listed below in Table 4-7.

Variable	Points
Pre-operative Mechanical Circulatory Support	3
Recipient Diabetes Mellitus	3
Cardiopulmonary Bypass Time >180 minutes	2
Implant Time	
≤45 Minutes	0
46-60 Minutes	1
61-90 Minutes	2
>90 Minutes	3
Donor Age	
<21 years	0
21-40 years	1
41-50 years	2
>50 years	3
Total	__/14

Table 4-7 The PREDICTA score points allocation
For binary variables, points are allocated as 0 or values depicted in the following boxes. For continuous variables, points are allocated based on the values they lie in.

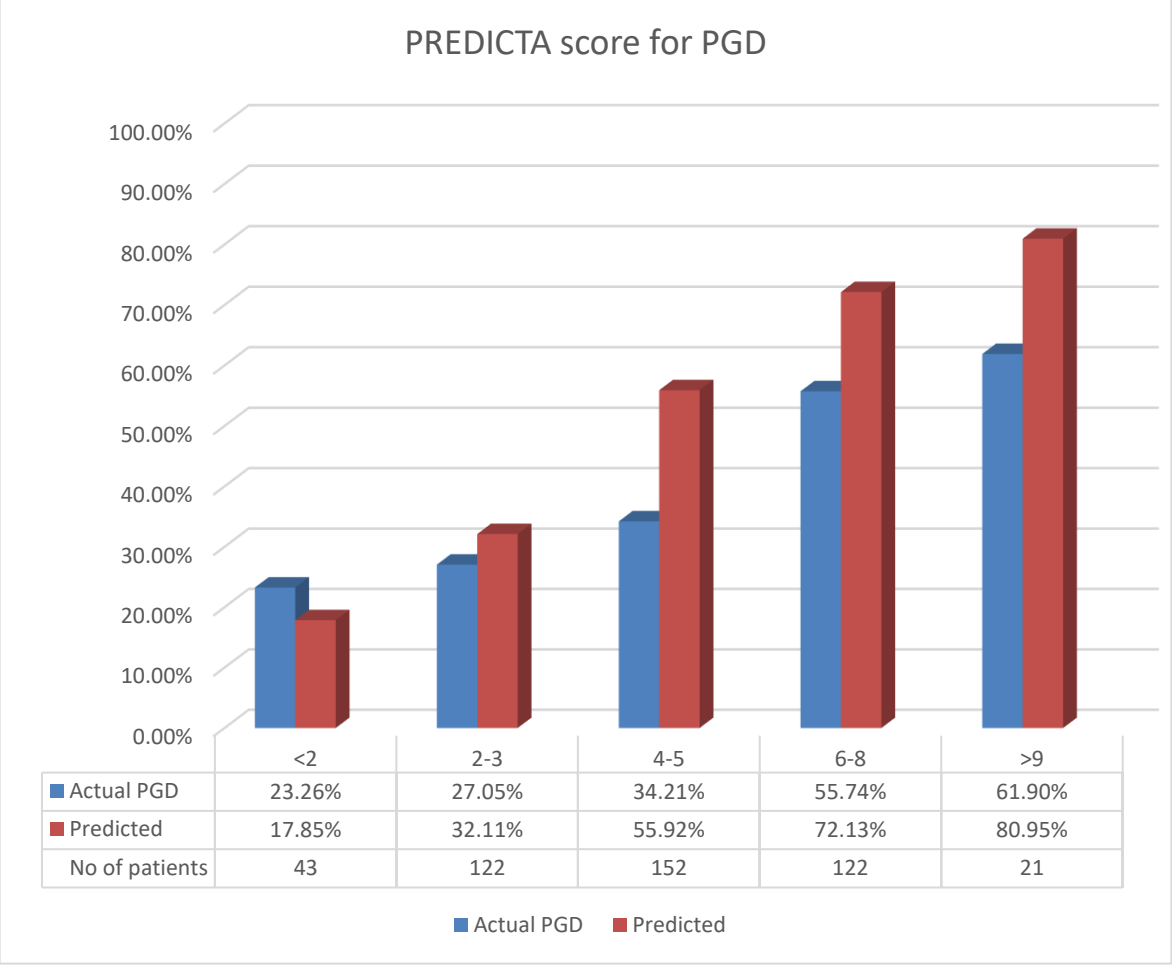


Figure 4-2 PREDICTA score for predicting PGD post-heart transplantation.

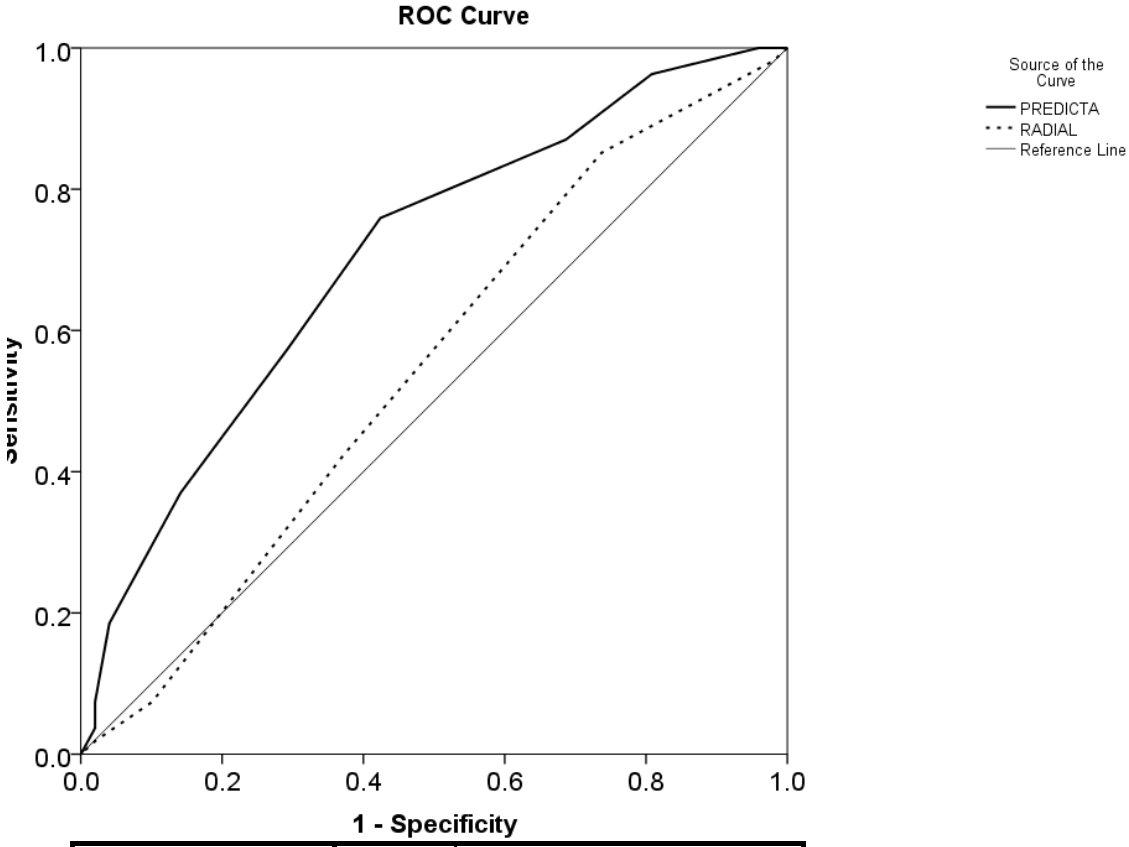
The PREDICTA score was calculated by using the values as listed in Table 4-7. Rates of actual and predicted PGD were calculated for patients were calculated based on the number of risk factors present in the multivariable model. The PGD rate increased significantly as the scores increased

4.4.2.2 Validation cohort

A PREDICTA score of <3 indicated a low risk for PGD, and a score of >9 coincided with a high risk of PGD (>60%). A score of 4-8 indicated a moderate risk for PGD with the risk of PGD crossing the 50% mark at 4-5.

We used the validation cohort to compare the predictive value of the PREDICTA score vs the RADIAL score, a validated published PGD predictive score. Area under Receiver Operating Characteristics curves was used to compare the observed and expected rate of moderate/severe PGD in this cohort (PREDICTA Score >4). The AUROC curves are depicted in Figure 4-3.

The C-statistic of the PREDICTA score was 0.704 vs 0.547 for the RADIAL score indicating a good predictive value.



Test Result Variable(s)	Area	Asymptotic 95% Confidence Interval	
		Lower Bound	Upper Bound
PREDICTA	0.704	0.619	0.790
RADIAL	0.547	0.453	0.640

Figure 4-3 AUROC curves depicting the predictive value of the PREDICTA score vs RADIAL score in the Validation cohort.

4.5 Discussion

The incidence of PGD in the UK from October 2012-October 2016 was 38% as defined by the ISHLT consensus statement. The risk factors identified from the derivation cohort included recipient diabetes mellitus, prolonged cardiopulmonary bypass time, increasing donor age, pre-operative mechanical circulatory support usage and prolonged implant time. The 30-day and 1-year mortality were significantly higher in the PGD cohort as shown in Figure 4-1. The rate of PGD in our study was also higher when compared to recent single centre studies reported in the literature ranging from 10-31% (Seguchi *et al*. 2016; Sabatino *et al*. 2017b; Squiers *et al*. 2017a; Nicoara *et al*. 2018; Pozzi *et al*. 2018; Sasha Still *et al*. 2018). Older studies prior to the consensus statement have shown a PGD range of between 2.5-24% with varying centre specific definitions of PGD (Jon Kobashigawa *et al*. 2014). Our previous multicentre study showed an incidence of 36% with little variation over the 3 years (S.S. Avtaar Singh *et al*. 2018). We strictly adhered to the ISHLT guidelines thereby preventing under-estimation of the true PGD rate by using both LVEF and/or inotrope score definitions with corresponding cardiac monitoring studies in all of our patients which may have led to the significantly higher number.

A variety of donor, recipient and procedural factors have been identified in the literature to be associated with PGD. However, given the variability in definitions and the different periods analysed, there was significant heterogeneity noted in risk factors. Some of the risk factors that have been suggested include donor age (Sabatino *et al*. 2017b), pre-operative mechanical support, length of ischaemic time (Sabatino *et al*. 2017b) and recipient diabetes mellitus (Sabatino *et al*. 2017b); all of which were noted in our study. Other risk factors such as recipient age (D'Alessandro *et al*. 2011a), pre-operative recipient amiodarone therapy (Wright *et al*. 2017), recipient inotropic support (Segovia *et al*. 2011), donor inotropic support (D'Alessandro *et al*. 2011a), donor-to-recipient size mismatching (Gong *et al*. 2018), and donor aetiology of death (D'Alessandro *et al*. 2011a), did not possess predictive value in our study.

Recipient age was not noted to be significant in more recent studies, potentially due to improving medical and device therapy. Recipient amiodarone therapy was

not noted to be an increased risk factor for PGD in our study and other previous studies (Macdonald *et al*. 1991; Chelimsky-Fallick *et al*. 1992; Rivinius *et al*. 2016; Cooper *et al*. 2017). Amiodarone therapy may reflect the pro-arrhythmogenic state of unwell patients and therefore be a surrogate for the critical state of these patients. Analysis of the ISHLT registry highlighted increased mortality in recipients with previous amiodarone therapy; however, recipient age was a major confounder with more older patients receiving amiodarone (Cooper *et al*. 2017). Pre-operative inotropic support in both the donor and recipient were not risk factors for PGD in our study. This could possibly reflect the increasing use of VADs in recipients with escalating inotropic requirements in the current era and better donor management strategies including the use of vasopressin as an inotropic sparing agent (McKeown *et al*. 2012). The universal improvement in donor management could also explain the lack of difference in donor aetiology of death as a risk factor for PGD.

We emulated the methodology for LV mass prediction to study the effect of donor-recipient mass mismatch as a potential cause for PGD as suggested by Gong et al (Gong *et al*. 2018). However, there was no significant difference in the predicted mass mismatch between the two groups, with no donor under-sizing >30%.

Prolonged bypass time was noted to be a risk factor for PGD post-transplant. Although the aetiology of PGD is multifactorial, the unifying pathophysiology is the occurrence of ischaemic reperfusion injury (IRI) (Alam *et al*. 2015). There are a variety of neutrophil-mediated post-ischaemic inflammatory responses that propagate this condition, alongside the formation of free radicals that result in a cascading series of insults resulting in the inability of the implanted graft to meet the circulatory requirements of the recipient. Efforts to minimise the effects of IRI include minimising ischaemic time and bypass time has been used to good effect in general cardiac surgery (Beyersdorf 2009). Although reperfusion occurs while the heart is on the cardiopulmonary bypass circuit, the adequacy of reperfusion especially to the ventricles is uncertain (Roshanali *et al*. 2008). Prolonged bypass time also causes vasoplegia with reduced vascular resistance with platelet and coagulation factor dysfunction, further contributing to IRI (Anselmi *et al*. 2004).

The RADIAL score was the only validated scoring system for prediction of PGD. Segovia and colleagues validated it in a Spanish cohort of heart transplant patients using a centre specific definition of PGD (Segovia *et al*. 2011). It consists of 6 risk factors derived from a multivariable analysis of 621 heart transplants between 1984 and 2006 with a PGD incidence of 9%. From this study, they noted that an increased right atrial pressure ≥ 10 mm Hg, recipient age ≥ 60 years, recipient diabetes mellitus, recipient inotrope dependence, donor age ≥ 30 years, and length of ischemic time ≥ 240 minutes to be significant risk factors. We did not find the RADIAL score to be predictive of PGD in our cohort as demonstrated by Figure 4-1. This similar finding was noted by Alina et al (Nicoara *et al*. 2018). They attributed this to the different periods in which the heart transplantations had occurred. Certainly, there were increasing numbers of re-sternotomies with an increasing number of patients on both short-term and long-term mechanical assist devices compared to those in the studies by both Carmena(Cosio Carmena *et al*. 2013) and Segovia(Segovia *et al*. 2011). The donors in our cohort of patients were older as well, in keeping with the general trend noted worldwide and especially in Europe with an increased number of donors which would be considered extended criteria in previous eras forming a substantial proportion of donors today (L. H. Lund *et al*. 2017). Total ischaemic time has been described as a predictor of mortality by Banner et al (Banner *et al*. 2008). However, when looking at it in greater detail, the inclusion of total ischaemic time (summation of warm ischaemic time/implant time and cold ischaemic time) resulted in a reduced odds ratio when compared to warm ischaemic time alone. Similar findings were noted by Marasco's group (Marasco *et al*. 2012). Warm ischaemic time also proved detrimental in kidney transplantation (Tennankore *et al*. 2016). In addition, the introduction of DCD and EVNP has also reduced total ischaemic times and negated the use of static cold storage.

We used a random number generator to ensure there were equal numbers of patients in the validation and derivation cohort with DCD and EVNP which were more prevalent in the later years of the study. This is the first scoring system derived from multiple centres to include patients who have undergone transplants using DCD and EVNP hearts. It is, therefore, a more accurate

representation of the cohort of patients undergoing heart transplantations in the current era.

We report a 30-day mortality of 18.9% (n=44) in the PGD cohort, majority (88.7%) of whom required MCS and therefore were classed as severe PGD. The in-hospital mortality, however, was 22.7%. A recent study by Sabatino (Sabatino *et al*. 2017b) reported a higher in-hospital mortality of 12% for moderate PGD and 68% for severe PGD. Nicoara and colleagues (Nicoara *et al*. 2018) reported an in-hospital mortality of 23% in the PGD cohort while Squiers et al (Squiers *et al*. 2017a) reported an in-hospital mortality of around 25%. These figures are indicative of the nature of the condition which has high post-operative mortality and morbidity. Identification of risk factors using scoring systems like the PREDICTA score or RADIAL score may, therefore, assist in resource allocation and planning.

4.6 Limitation

There are several limitations to our study. The multicentre nature of the study introduces several different peri-transplant protocols, especially in post-operative management. The choice of inotropes and escalation of therapy is determined by centre specific experience and clinician familiarity. The retrospective nature of the study may also introduce uncontrolled biases that may have influenced decision-making at the time of transplantation. The score was tested in a UK cohort of patients and may require external validation to ascertain feasibility and suitability in other centres.

I was unable to collect accurate cumulative dosages of amiodarone therapy. I was, however, able to ascertain if a recipient had previously received amiodarone. The relatively small sample size is also a limiting factor in this study. However, to date, this is the largest multicentre PGD study in the literature.

4.7 Conclusion

This is the first comprehensive national validated model for PGD after heart transplantation using the ISHLT definition. It identifies the donor, recipient and

procedural risk factors for PGD. The PREDICTA score is able to accurately predict PGD and is superior to the RADIAL score when used in recent cohorts of patients. It may help identify patients who are at risk of PGD and therefore allow risk stratification and resource planning for management and therapeutic interventions. Further multicentre studies are needed to determine the applicability of the PREDICTA score in other centres.

5 The Glasgow Experience of extended myocardial protection: A novel method of implantation to reduce primary graft dysfunction after heart transplantation

5.1 Abstract

Background

With the increasing demand for organs with a limited supply of donors, novel techniques such as ex-vivo normothermic perfusion have garnered increasing interest. We present a series of patients who underwent heart transplantation at our unit using a novel implantation technique to reduce PGD.

Methods

All recipients at our centre received inhaled nitric oxide during induction. On arrival to theatre, the donor heart is removed from cold static storage and placed in an ice slush basin. A small aortic cross-clamp is applied distal to the donor ascending aorta. An antegrade infusion of 600mls of cold blood cardioplegia followed by cold oxygenated blood (4-6^{o}C) is infused to achieve a mean aortic root pressure of 60-70 mmHg employing a constant pressure-variable CPB flow pump with an in-situ leucocyte depleting filter. This continuous antegrade perfusion is maintained throughout the left atrium and Aortic anastomosis with a left ventricular vent in situ. Upon completion of the aortic anastomosis, a warm cardioplegia hotshot is infused into the aortic root followed by removal of the recipient aortic cross-clamp.

Systemic perfusion is initiated with continued aortic root and LV venting. The remaining anastomoses are carried out in the usual fashion sequentially.

We compared our experience with this method with a contemporary national UK cohort (2015-2016) of patients (Control Group). We performed multivariable logistic regression comparing the Glasgow Experience to the control group PGD as the outcome measure. Confounders adjusted for include donor age, recipient diabetes mellitus, urgent listing status, bypass time and total ischaemic time.

Results

140 (72.1 %) patients were male. 36(18.6%) of the patients had ischaemic cardiomyopathy. The odds ratio of PGD in the control group was 2.99 (95% CI 1.02- 8.75) when compared to the Glasgow Experience.

Conclusion

This novel approach is associated with significant reductions in PGD rates with a trend towards improved 1-year survival. Larger studies are needed to show differences after further adjustment for known confounders of PGD. We believe this novel technique is safe, cost-effective and reproducible.

5.2 Introduction

The high rates of PGD across Europe have resulted in a renewed interest in perfecting myocardial protection techniques to increase the yield of organs retrieved. With the increasing demand for organs from a limited supply of donors, novel techniques such as the use of ex-vivo normothermic perfusion have also been introduced although the cost of the equipment limits its widespread usage. Despite this, the incidence of PGD remains unchanged(S.S. Avtaar Singh *et al*. 2018). Improving myocardial protection may play a role in reducing the incidence of PGD and improving early mortality rates.

Wheeldon and co-workers noted that up to 55% of the surveyed transplant centres used some form of reperfusion during heart transplantation (Wheeldon *et al*. 1992). This includes intermittent cold blood or oxygenated crystalloid cardioplegia during implantation of the heart followed by the administration of 'hot shots' as described by Buckberg (Buckberg 1989).

We present a cohort of patients who underwent heart transplantation at our unit using a novel implantation technique aimed to reduce PGD. We used a national cohort of patients (UK-wide) who received heart transplants within this period as controls. Our co-primary outcome measures were the incidence of PGD and all-cause mortality at 1 year.

5.3 Objectives

The Glasgow method of implantation was first introduced following a review by CTAG triggered after the unit was identified as an outlier. We identified the geographical limitations of the unit (being furthest north with the largest zonal allocation but the smallest population) as a risk factor and implemented several proven techniques to reduce warm ischaemic time to improve outcomes. We audited our results and compared it with the national average.

We utilised the enhanced recovery technique (ERAS) of employing a summation of marginal gains to improve outcomes. This serves as a proof of concept prior to

application for an animal model study to identify biochemical improvements to supplement the clinical outcomes.

5.4 Method

5.4.1 Operative technique

All recipients at our centre receive inhaled nitric oxide at 20ppm during induction of anaesthesia. On arrival to theatre, the donor heart is removed from cold static storage and placed in an ice slush basin.

An aortic cross-clamp is applied onto the donor ascending aorta. An aortic root cannula (model 23009, DLP™ (11 Fr (9ga) (13.3cm) Aortic Root Cannula, Medtronic Inc., Minneapolis, MN) is inserted and secured in the ascending aorta, close to the aortic root anteriorly.

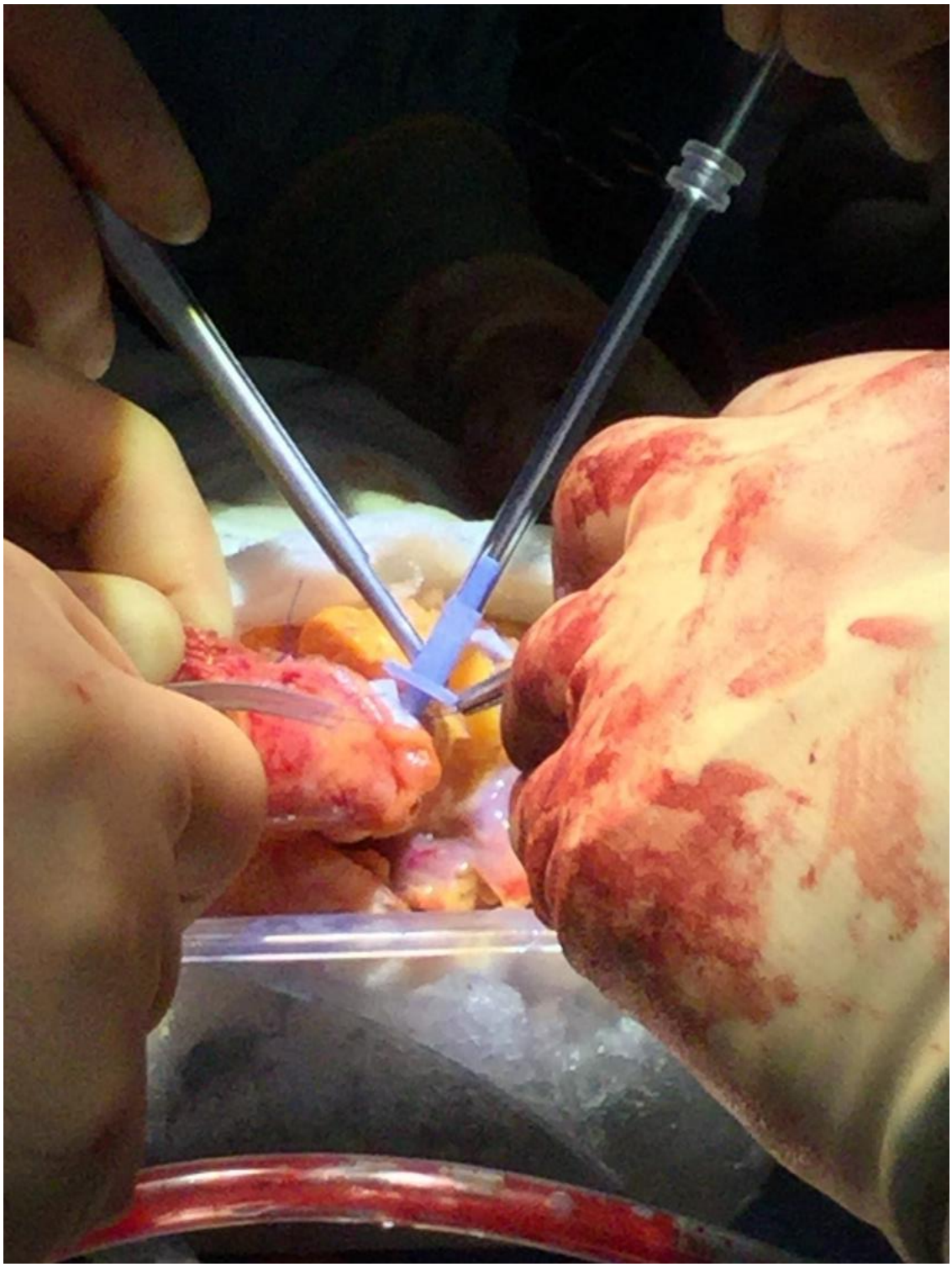


Figure 5-1 Insertion of DLP cannula in the aortic root of donor heart

An antegrade infusion of adenosine (12mg) followed by 700mls solution of blood cardioplegia and St Thomas's solution (4:1), at 4ºC followed by cold oxygenated blood (4-6ºC) is infused to achieve a mean aortic root pressure of 60-70 mmHg with flows of 200-300 ml/min employing a constant pressure-variable CPB flow

pump through an in-situ leucocyte depleting filter (Pall LeukoGuard LG Arterial Filter (Pall Biomedical, Portsmouth, UK).

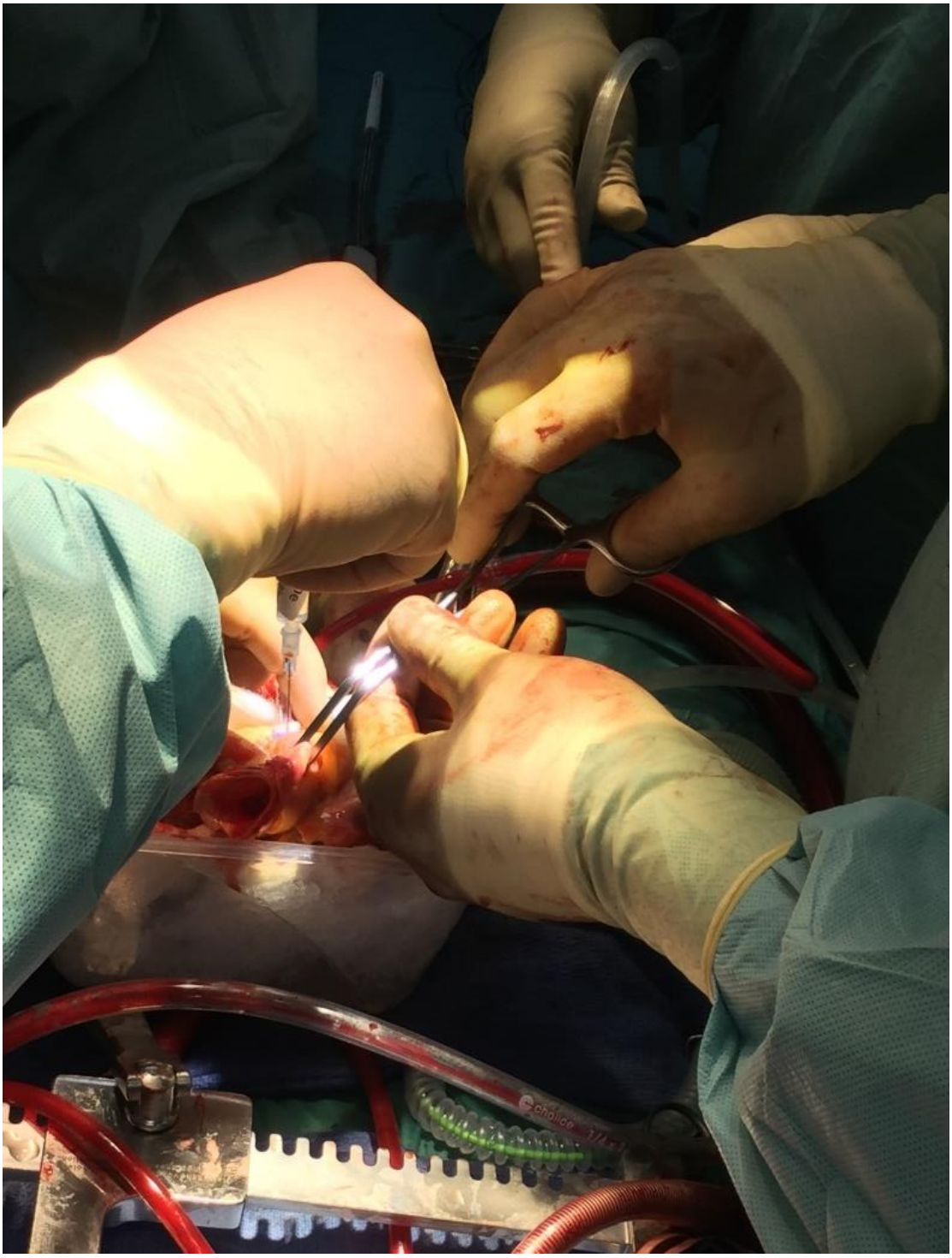


Figure 5-2 Administration of Adenosine to the aortic root (donor heart)

This continuous antegrade perfusion is maintained throughout the left atrium and aortic anastomosis with a left ventricular vent in situ.

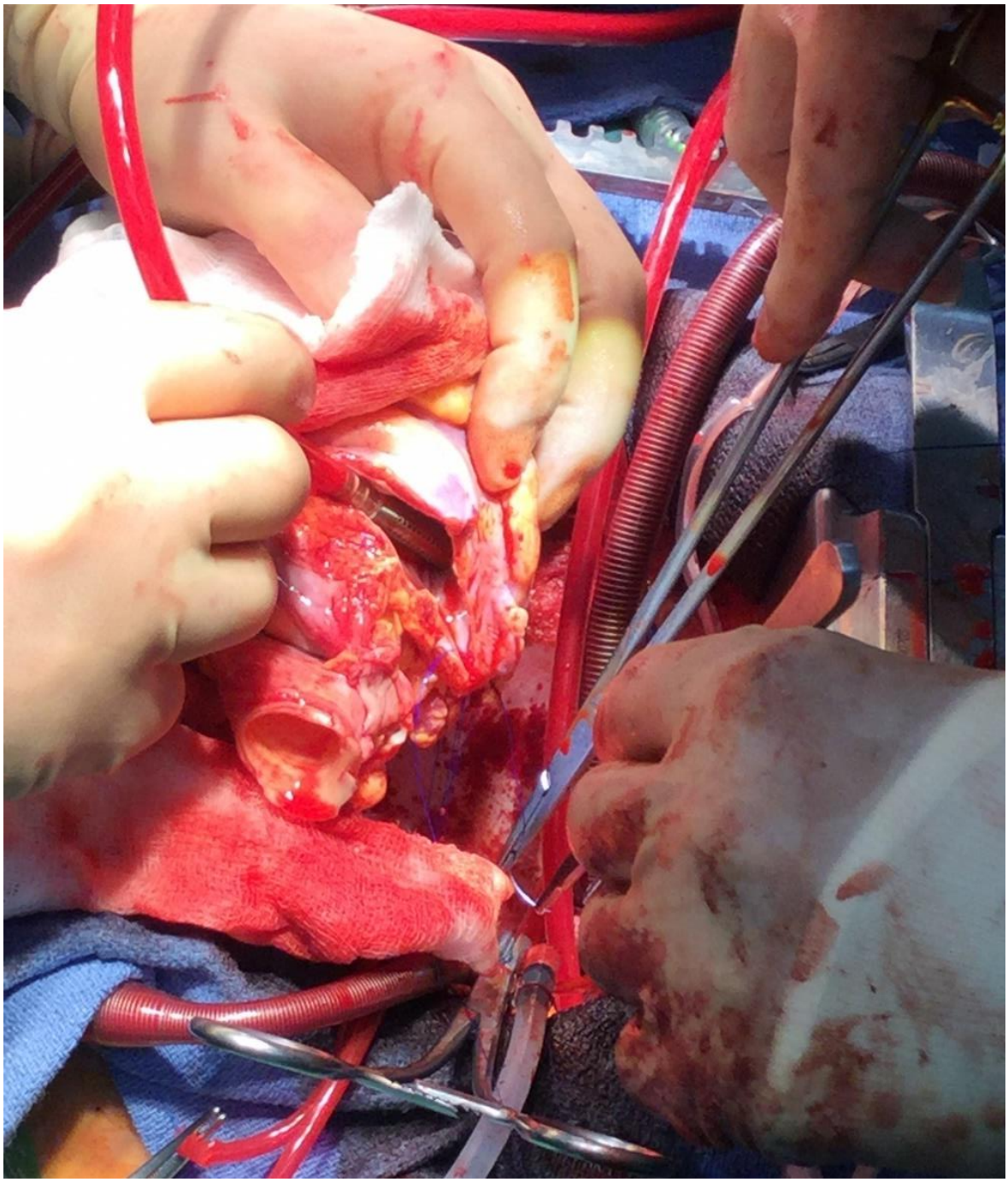


Figure 5-3 LA anastomosis with a vent in situ

Upon completion of the aortic anastomosis, the Y-limb of the DLP cannula is then connected to a de-airing channel for de-airing of the ascending aorta and aortic root followed by gradual rewarming of infused blood before removal of the recipient aortic cross-clamp.

Systemic perfusion is initiated with continued aortic root and LV venting. The remaining anastomoses are carried out in the usual fashion sequentially with

pulmonary artery, inferior vena cava and superior vena cava with normothermic systemic perfusion and ventricular pacing.

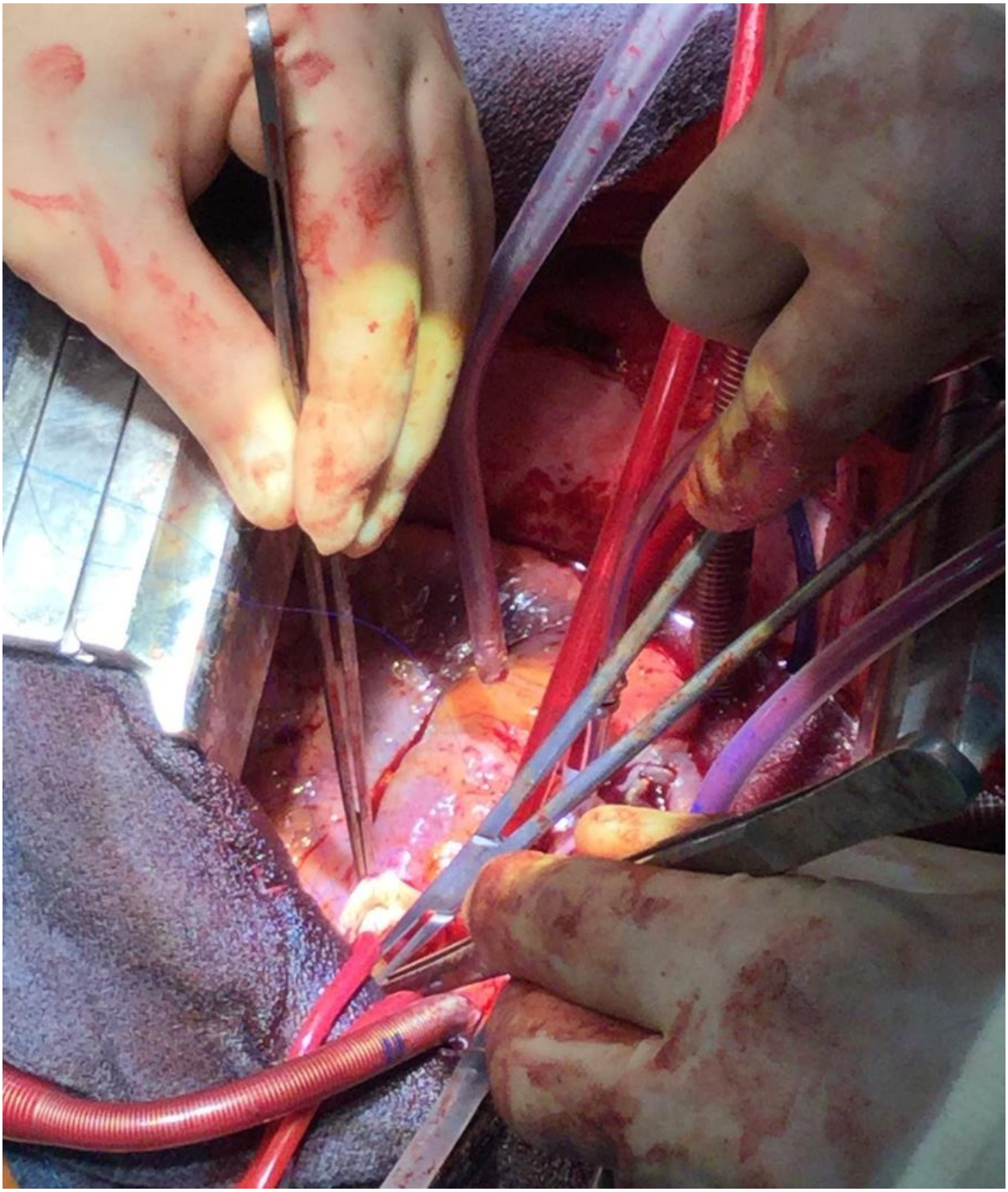


Figure 5-4 Pulmonary artery anastomosis (Aortic Cross-Clamp released)

5.4.2 Statistical Methodology

We compared our experience with this method with the national UK cohort (2015-2016) of patients (Control Group). Transplanted hearts procured using

normothermic ex-vivo perfusion (TransMedics Organ Care System (OCS) Andover, MA, USA) were excluded from the study. Continuous variables were described by mean and standard deviation. Categorical variables were expressed as a percentage. Baseline characteristics were compared between the intervention and control groups using Student's t-test and Mann Whitney U test as appropriate and chi-square test or Fisher's exact test for categorical variables. Variables with significance of $p<0.1$ in the unadjusted analysis were initially introduced as candidate variables in a multivariable logistic regression model for the probability of PGD and removed by stepwise backward elimination. Other variables of interest that have been shown to contribute to PGD were also included in the multivariable analysis. Variables were retained in the model if they reduced the model deviance significantly ($p<0.05$). Analysis was conducted in Minitab 17 Statistical Software (2010), Minitab, Inc.

5.5 Results

A total of 194 patients were studied; 28 patients were in the Glasgow group and 166 in the control group. The mean age of the recipients was 47.5±13.7 years and the donors were 38.2±12.1 years.

The incidence of PGD was 39.2% (n=76) with 14.9%(n=29) of patients having severe PGD requiring institution of advanced mechanical circulatory support within 24 hours of transplantation. The demographic details of the patients in the 2 groups are as follows.

Table 5-1 Pre-operative characteristics of recipients

Details	Glasgow (n=28)	Control (n=166)	p-value
Male: Female ratio	21:7	119:47	0.456
Age (years)	48.6±11.6	46.8±13.8	0.581
BMI (Kg/m^2)	25.3±3.6	25.7±3.8	0.583
Creatinine (µmol/L)	93.3±28.9	104.1±37.7	0.147
Diabetes Mellitus (%)	0	15.2	**0.026**
Urgent listing status (INTERMACS 1-3)	85.7	59.6	**0.005**
Pre-operative LT LVAD (%)	10.7	9.9	0.990
Recipient Re-sternotomy (%)	35.7	23.5	0.169
Recipient Aetiology			
Ischaemic Cardiomyopathy	21.4	18.0	0.426
Dilated Cardiomyopathy	67.9	55.4	
Congenital Heart Disease	0	7.8	
HOCM/ Restrictive Cardiomyopathy	7.1	12.0	
Other	3.6	6.6	

Donor Factors	Glasgow (n=28)	Control (n=166)	p- value
Donor Cause of death			
Intracerebral haemorrhage (%)	67.8	53.6	
Hypoxic brain injury (%)	17.9	26.0	
Road Traffic Accident (%)	3.6	9.7	
Meningitis (%)	3.6	9.0.	
Intracerebral malignancy (%)	7.1	1.8	0.198
Donor Gender (M: F)	18:10	117:49	0.510
Donor Age	36.5±11.4	38.5±12.2	0.409
Donor BMI (kg/m^2)	27.1±4.9	25.8±4.5	0.135
Donor LVEF (%)	60.7±6.1	58.2±9.3	0.267
Donor Smoker (%)	45.4	56.0	0.349
Height Mismatch (%)	1.2±8.0	1.2±8.0	0.659
Weight mismatch (%)	10.7±17.7	5.7±25.2	0.389
Estimated LV mass mismatch (%) *	-7.5±23.0	-7.6±30.5	0.997
Donor: Recipient Gender Mismatch (%)	25.0	25.0	0.973

Table 5-2 Pre-operative characteristics of donors
Mismatch calculated as [(Measure ($_{recipient}$) − Measure($_{donor}$)/Measure($_{recipient}$)] X 100

$$Predicted\ Left\ ventricular\ mass(g) = \alpha * Height^{0.54}(m) * Weight^{0.61}(kg)$$

$$where\ \alpha\ =\ 6.82\ for\ women\ and\ 8.25\ for\ men$$

LV Mismatch calculated by

$$\frac{(\boldsymbol{pHM^{recipient} - pHM^{donor}})}{\boldsymbol{pHM^{recipient}}} * \mathbf{100}$$

(R. M. Reed *et al.* 2014)

There were more diabetic recipients in the control group and a higher incidence of pre-operative urgent listed patients in the Glasgow group. All other donor and recipient demographic parameters were comparable across the groups.

Details	Glasgow (n=28)	Control (n=166)	P-value
Total Ischaemic time (min)	154.3±52.1	170.0±46.4	0.143
Cold Ischaemic time (min)	116.9±48.2	100.8±46.4	0.093
Explant Time(min)	20.6±9.9	18.9±12.3	0.502
Implant time (min)	50.3±20.3	63.9±17.5	**0.020**
Bypass Time (min)	217.6±64.2	189.8±87.4	0.11
Inotrope Score (units)	14.6±7.9	14.5±7.9	0.987
Post-operative Cardiac Index	2.8±0.8	2.8±1.1	0.975
Post-operative Right Atrial Pressure (mmHg)	11.2±3.2	12.9±4.8	**0.023**
Post-Operative Mean Arterial Pressure (mmHg)	72.2±9.8	73.8±13.8	0.491
Post-Operative Pulmonary Capillary Wedge Pressure (mmHg)	10.4±5.2	16.0±6.4	**0.004**
Post-Operative Mean Pulmonary Arterial Pressure (mmHg)	18.5±6.0	23.2±5.7	**0.002**
Post-operative ECMO (%)	14.3	15.1	0.590
Post-operative newly inserted IABP (%)	17.8	22.9	0.552
30-day Mortality (%)	0	9.6	0.088
1-year Survival (%)	96.4	83.7	0.059
Post-operative PGD (%)	21.4	42.2	**0.038**
Post-operative PGD-RV (%)	0	3.6	0.387

Table 5-3 Post-operative outcomes of both cohorts

Post-operative outcomes showed similar total ischaemic times for both groups with similar rates of MCS and IABP institution rates. The cold ischaemic time was longer in the Glasgow group as part of the operative technique although this did not reach statistical significance (p=0.093). Bypass times were also longer in the Glasgow cohort (p=0.013).

The Glasgow Experience patients had a lower pulmonary capillary wedge pressure and mean Pulmonary Arterial Pressure compared to the control group with an overall reduction in post-operative PGD rates. The mortality at 1 year was not significantly different between the groups.

We did not include the PCWP, mPAP, and CVP in the multivariable analysis as they were part of the diagnostic criteria of PGD. Parameters included in the multivariable analysis to assess independent predictors of PGD included bypass time, donor age, recipient diabetes status, urgent listing status alongside grouping (Glasgow vs Control). The results of the multivariable analysis are presented in Table 5-4

Risk factor	β coefficient	OR (95% CI)	p-value
Donor Age	0.035	1.036(1.008, 1.065)	0.010
Bypass Time	0.011	1.01 (1.005, 1.017)	<0.001
Grouping (Control)	1.102	2.99(1.02, 8.75)	0.033
Diabetes Mellitus	2.00	6.29 (2.19, 18.04)	0.001

Table 5-4 Independent predictors of PGD from multivariable logistic regression

The odds ratio of PGD in the control group was 2.99 (95% CI (1.02, 8.75)) when compared to the Glasgow Experience.

5.6 Discussion

5.6.1 Functional warm ischaemia time

This novel technique utilizes a minimisation in functional warm ischaemic time by antegrade perfusion of the donor graft using cold blood cardioplegia alongside topical cooling. Cardioplegia negates the electromechanical energy consumption associated with myocyte contraction thereby reducing myocardial oxygen demand. In addition, the topical cooling reduces enzymatic reactions which in turn reduces cellular metabolism (Banner *et al*. 2008). Several studies have shown similar findings with prolonged warm ischaemia linked with an increased incidence of PGD. Avtaar Singh and colleagues highlighted the role of prolonged warm ischaemia time as an independent predictor of PGD(S.S. Avtaar Singh *et al*. 2018). Marasco's group noted that warm ischaemic time in excess of 80 minutes was associated with reduced survival when compared to a warm ischaemic time of fewer than 60 minutes(Marasco *et al*. 2012). Both the studies also noted donor age to be a significant independent predictor of PGD and survival as noted in our cohort. Conversely, prolonged cold ischaemic time was not associated with PGD in our cohort. These findings were also noted by the UCLA group in which cold ischaemic times of > 300 minutes were not associated with adverse outcomes (Mitropoulos *et al*. 2005). This could be due to attenuation of ischaemic reperfusion injury (IRI) which is thought to be the pathophysiological basis of PGD. Registry data from ISHLT is difficult to interpret given the overlapping results of warm and cold ischaemic time, commonly presented as a total ischaemic time (Lars H. Lund *et al*. 2017b). Other solid organ transplantation studies have also shown a direct correlation between increased warm ischaemic time and IRI(Zhai *et al*. 2013; Tennankore *et al*. 2016). Ischaemia promotes the expression of proinflammatory factors and bioactive agents such as leucocyte adhesion molecules, cytokines, endothelin, thromboxane A2 while repressing 'protective' factors like constitutive nitric oxide (NO) synthase, thrombomodulin, and prostacyclin (Eltzschig and Collard 2004).

The use of continuous antegrade oxygenated cold blood perfusion ensures universal cooling of the heart. The oxygen delivery is impaired at hypothermia as the dissociation curve of haemoglobin is displaced toward the left, and oxygen delivered to the tissues is mainly transported in the dissolved form. However, as opposed to cold crystalloid, oxygenated blood has a buffer capacity of the imidazole nucleus of the haemoglobin molecule (Bachet *et al*. 1999). Cold blood cardioplegia usage also resulted in lower post-operative cardiac enzyme levels when compared to cold crystalloid cardioplegia in general cardiac procedures (Braathen and Tønnessen 2010).

5.6.2 Ischaemic reperfusion injury

The length of ischaemia has a direct effect on cell dysfunction leading to cell injury or death, with reperfusion being the ideal treatment option. Reperfusion restores oxygen delivery to facilitate aerobic ATP generation while flushing out H^+ accumulation from anaerobic states. Jennings initially described an accelerated state of necrosis on reperfusion in 1960, coining the term reperfusion injury (Jennings *et al*. 1960). It arises due to rapid generation of reactive oxygen species, increased intracellular calcium due to attenuated ATP-dependent exchangers, the opening of Mitochondrial Permeable Transition Pores (MPTP) which dissipates mitochondrial membrane potential, and endothelial dysfunction accompanied by activation of inflammatory pathways leading to a vicious cycle of increasing tissue injury (Yellon and Hausenloy 2007).

5.6.3 Inhaled Nitric oxide (NO)

We hence utilized targeted therapeutic strategies to attenuate IRI. Inhaled NO may play a role as a preconditioning factor alongside a pulmonary vascular dilator. NO has antioxidant properties not related to alterations in neutrophil migration or adhesion but by reduction by NO of superoxide anion-mediated tissue toxicity which may account for much of the protective effect of NO during IRI (Phillips *et al*. 2009). It also acts as an oxygen radical scavenger (Massoudy *et al*. 1995). It attenuates the effects of reperfusion by competitively binding to cytochrome-c oxidase. This prevents abrupt resumption of the electron transport chain during reperfusion with oxygen-rich blood which would result in the

generation of oxygen radicals (Jones and Bolli 2006). Its role in reducing RV afterload is well established in the literature (Lindberg *et al*. 1994; Fullerton *et al*. 1996) as is its role as a coronary vasodilator (Quyyumi *et al*. 1995). The thin-walled RV is more compliant thus accommodates right-sided venous return well but struggles against acute increases in afterload, resulting in dilation and impaired contractility (Hurford and Zapol 1988; Vonk Noordegraaf *et al*. 2017). Reducing the afterload may, therefore, assist the rewarming RV contraction and prevent dilation. The coronary vasodilatory effect may also allow greater reperfusion and controlled rewarming of the donor graft on release of the aortic cross-clamp.

5.6.4 Leukocyte depleting filter

We use a leukocyte depleting filter (LDF) in all cases to prevent leukocyte-mediated IRI. Leukocyte activation results in chemotaxis, leukocyte-endothelial cell adhesion and transmigration. Activated leucocytes release toxic oxygen radicals, proteases and elastases, resulting in increased microvascular permeability, oedema, thrombosis, and parenchymal cell death while activating a positive feedback loop resulting in increased transmigration(Carden and Granger 2000). The role of LDF in reducing myocardial reperfusion injury in general cardiac surgery is well understood with reductions in biochemical markers and post-operative inotropic requirements without any difference in clinical outcomes (Han *et al*. 2013). In heart transplants, it has been shown to reduce creatinine phosphokinase-MB and thromboxane B2 post-reperfusion (Pearl *et al*. 1992). Another trial showed similar results with reduced markers of reperfusion injury, easier wean off cardiopulmonary bypass and lower need for inotropic support post-operatively (Dvorak *et al*. 2006).

5.6.5 Ischaemic Pre-conditioning

Ischaemic preconditioning has been shown to improve ventricular function and reduce myocardial neutrophil accumulation and apoptosis in experimental models (Kloner and Jennings 2001). It is associated with an increase in extracellular adenosine production with experimental studies highlighting the role of A_1, A_{2a} and A_3 ADO receptor involvement in endogenous cardioprotective

responses (Auchampach *et al.* 1997; Linden 2001). The administration of adenosine to the donor graft during perfusion permits the preconditioning effect enhances coronary vasodilation while slowing the sinoatrial nodal pacemaker rate, delaying atrioventricular nodal impulse conduction and reducing atrial contractility; all of which may contribute to ensuring the heart is arrested while cardioplegia is administered after removal from cold storage. In heart valve replacement operations, it has been shown to reduce cTnI, IL-6 and IL-8 release, resulting in less myocardium injury in ultrastructure after surgery(Liu *et al.* 2009).

5.7 Limitations

The study has some limitations. Due to the multicentre nature of the control group, regional variations between patient management strategies such as inotropic preference and choice of immunosuppression cannot be accounted for. Some standardized criteria are established by the Cardiothoracic Advisory Group (CTAG) and the National Health Service Blood and Transfusion to keep the variations to a minimum. The current experience at our centre with the nascent method is relatively new, hence the smaller numbers in the Glasgow cohort. We were unable to collect biomarkers to assess the biochemical changes postulated by this method.

Another major limitation is the number of patients with diabetes in the control group. As identified in Chapter 3, diabetes is an independent predictor of PGD. Despite covariate adjustment, the true impact of diabetes mellitus on outcomes remains unknown. Other methods that could have been used such as propensity score stratification, propensity score matching and propensity score inverse probability weighting all have their limitations in smaller cohorts, without accounting for confounding and is less precise(Elze *et al.* 2017). Ongoing studies or animal model studies may highlight the impact of diabetes mellitus towards outcomes using this method.

5.8 Conclusion

This novel approach is associated with significant reductions in PGD rates with a trend towards improved 1-year survival. Larger studies are needed to show differences after further adjustment for known confounders of PGD. We believe this novel technique is safe, cost-effective and reproducible.

6 Mechanical circulatory support for refractory cardiogenic shock post-acute myocardial infarction – A decade of lessons

6.1 Abstract

Background

There are 0.9 catheterization labs per 100,000 inhabitants in Scotland for percutaneous coronary intervention (PCI) for acute myocardial infarction (AMI), which are much less accessible to patients in remote and rural areas. An uncommon but sinister sequela following AMI is cardiogenic shock (CS) that could be refractory to inotropic support. CS complicates 5-15% of AMIs occurring in ST-segment Elevation Myocardial Infarctions (STEMIs). Outcomes of CS are poor with mortalities of up to 90% reported in the literature in the absence of experienced care (9). We report our experience as the tertiary referral centre in Scotland for MCS and heart transplantation over 8 years.

Methods

A retrospective review of prospectively collected data was undertaken on all patients registered to the MCS service. The database was interrogated for patient demographics, type of mechanical circulatory support and duration of MCS support, PCI-outcomes and survival to 30-days. Time-To-Event analysis was performed using patient survival as the primary outcome measure.

Results

Twenty-three patients (16M:7F) were included. The median age of the patients as 50 years (45-56 years). VA-ECMO was the initial MCS of choice in 17(73.9%) patients with BIVAD for 4(17.4%) patients and LVAD for 2(8.7%) patients. 30-day mortality was 21.8% in this cohort, however, survival to discharge was 52.2%.

Eleven (47.8%) patients recovered without the need for any further support, however, only 9 (81.8%) patients in this subgroup survived to discharge. Three (13%) patients received a durable LVAD. In this subgroup, one patient was transplanted whereas two patients died due to complications while on support.

The median length of in-hospital MCS support was 4 days. The median in-hospital stay was 27 days.

Long-term follow up of up to 8 years demonstrates a high mortality beyond 30-days up to the first 6-months post MCS support.

Conclusion

MCS usage in these patients carries a high mortality in the early post-implantation period. However, there is a significant benefit to patients who survive the initial bridging period to recovery or destination therapy

6.2 Introduction

In the preceding decades, Scotland has drastically reduced the mortality from coronary heart disease (72% reduction in 2009 compared to 1950)(Lewsey *et al*. 2015). Despite this, post-MI mortality remains among the highest in Western Europe(Lewsey *et al*. 2015), branding Scotland as the 'sick man of Europe' (McCartney *et al*. 2012). The inequalities in Scottish morbidity and mortality have resulted in an overall increase in health inequalities across the United Kingdom(Hanlon *et al*. 2005). Ischaemic heart disease is associated with a higher level of disability-adjusted life years (DALY) than any other condition in Scotland, mirroring not just the UK, but also DALY in the Global Burden of Disease Survey('Global, regional, and national disability-adjusted life-years (DALYs) for 315 diseases and injuries and healthy life expectancy (HALE), 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015' 2016).

There are 0.9 catheterization labs per 100,000 inhabitants in Scotland for percutaneous coronary intervention (PCI) for acute myocardial infarction (AMI)(Hagen *et al*. 2015), which are much less accessible to patients in remote and rural areas. An uncommon but sinister sequela following AMI is cardiogenic shock (CS) that could be refractory to inotropic support. CS complicates 5-15% of AMIs occurring in ST-segment Elevation Myocardial Infarctions (STEMIs)(Babaev *et al*. 2005; Goldberg *et al*. 2009; Aissaoui *et al*. 2012). Outcomes of CS are poor with mortalities of up to 90% reported in the literature in the absence of experienced care(Reynolds and Hochman 2008).

Initial management of CS consists of identifying incidental complications e.g. acute left ventricular rupture or mitral regurgitation, assessing haemodynamics, and optimising the reperfusion in the culprit coronary artery. Clinical trials of therapeutic interventions have not led to changes in practice. The results of the Intra-Aortic Balloon Pump in Cardiogenic shock II (IABP-SHOCK II) trial highlighted the lack of survival benefit from the routine use of IABP therapy for this condition(Thiele *et al*. 2012). The only available option for patients with refractory, life-threatening illness would be the institution of mechanical circulatory support (MCS), involving either Extracorporeal Membranous Oxygenation (ECMO) or Ventricular Assist Devices (VADs). MCS can potentially

improve survival, however, the evidence is lacking. EURO-SHOCK (ID754946-2), which is a clinical trial funded by the EU-Horizons 2020 7th Framework programme, will address this gap. EURO-SHOCK is a multicentre, randomised, controlled trial of management involving ECMO vs. standard care without ECMO in patients with cardiogenic shock post-MI. Given the current gap in knowledge, we studied the outcomes following the use of MCS for treatment of cardiogenic shock post-AMI in Scotland during an 8-year period.

6.3 Methodology

6.3.1 Patients

All patients who were referred to the MCS service in the Golden Jubilee National Hospital from January 2009 - August 2017 following primary PCI-treated ST-segment elevation MI (STEMI) with refractory cardiogenic shock were included in this study.

A retrospective review of prospectively collected data was undertaken on all patients registered to the MCS service. The database was interrogated for patient demographics, type of mechanical circulatory support (Veno-arterial Extracorporeal Membranous Oxygenation/Ventricular Assist Device) and duration of MCS support, PCI-outcomes and survival to 30-days. Time-To-Event analysis was performed using patient survival as the primary outcome measure. Kaplan-Meier curves were used to graphically display data of 30-day survival. Students t-tests and Mann-Whitney U tests were used to analyse data for 30-day survival for continuous data with Fisher's exact test used for categorical data. The study was registered with the Clinical Governance and Audit Department at the Golden Jubilee National Hospital with a data protection registration number Z7996020

6.4 Results

Twenty-three patients (16M:7F) were included. The median age of the patients as 50 years (45-56 years). VA-ECMO was the initial MCS of choice in 17(73.9%) patients with BIVAD for 4(17.4%) patients and LVAD for 2(8.7%) patients. 30-day mortality was 21.8% in this cohort, however, survival to discharge was 52.2%.

Eleven (47.8%) patients recovered without the need for any further support, however, only 9 (81.8%) patients in this subgroup survived to discharge. Three (13%) patients received a durable LVAD. In this subgroup, one patient was transplanted whereas two patients died due to complications while on support (VAD thrombus, Disseminated Intravascular Coagulation).

The median length of in-hospital MCS support was 4 days (4-43 days). The median in-hospital stay was 27 days (9-41 days). The 30-day mortality data of survivors vs. non-survivors are as follows.

Details	Total (n=23)	Survivors (n=18)	Non-Survivor (n=5)	p-value
Age (years)	50 (11)	50 (9.3)	56 (16)	0.289
Male gender (%)	65	72	60	0.599
BMI (kg/m^2)	28.2±3.3	28.7±2.7	27.2±4.1	0.337
Hypertension (%)	13 (3/23)	6 (1/18)	40 (3/5)	0.021
Smoker (%)	35 (8/23)	38 (7/18)	20 (1/5)	0.621
Diabetes Mellitus (%)	4 (1/23)	0	20 (1/5)	0.217
Blood Group A (%)	48 (11/23)	44 (8/18)	60 (3/5)	0.640

Table 6-1 Preoperative demographics of survivors and non-survivors
The first column highlights the total cohort with survivors and non-survivors highlighted in the succeeding columns. Continuous variables are expressed as median (Interquartile Range) while categorical variables are depicted as percentages (numerator= total affected/ denominator (sample size))

Details	Total (n=23)	Survivors (n=18)	Non-Survivor (n=5)	p-value
Post PCI MAP mmHg	47.9±8.1	48.1±8.7	47.0±5.4	0.755
Creatinine µmol/L	200.7±109.2	198.4±87.9	201±120	0.951
PCI - MCS initiation time (hours)	7 (18.5)	8 (19.5)	4 (2)	0.370
CPR in Cath Lab % (n)	48 (11/23)	39 (7/18)	80 (4/5)	0.155
IABP in Cath Lab % (n)	91 (21/23)	94 (17/18)	80 (4/5)	0.395
Bilirubin mg/dL	11.5 (11)	11 (11)	16 (10)	0.551
AST u/L	463 (457.5)	383 (396.5)	825 (1298)	0.052
ALT u/L	174 (234)	164 (201.5)	258 (487)	0.126
HsTnI ng/L	18057(11241)	18057(12422)	20211(12708)	0.559
Pulmonary oedema at presentation % (n)	78 (18/23)	72(13/18)	100 (5/5)	0.545
Culprit Vessel				
Isolated LAD % (n)	39 (9/23)	39 (7/18)	40 (2/5)	0.999
Isolated RCA % (n)	26 (6/23)	33 (6/18)	0	0.272
Isolated LCx % (n)	4 (1/23)	0 (0/18)	20 (1/5)	0.217
Isolated LMS% (n)	9 (2/23)	11 (2/18)	0	0.999
>1 vessel involvement % (n)	22 (5/23)	17 (3/18)	40 (2/5)	0.291

Table 6-2 PCI demographics of survivors' vs non-survivors
The first column highlights the total cohort with survivors and non-survivors highlighted in the succeeding columns. Continuous variables are expressed as median (Interquartile Range) while categorical variables are depicted as percentages (numerator= total affected/ denominator (sample size))

Details	Total (n=23)	Survivors (n=18)	Non-Survivor (n=5)	p-value
ECMO (%)	74 (17/23)	72 (13/18)	80 (4/5)	0.999
VAD (%)	26 (6/23)	28 (5/18)	20 (1/5)	0.999
Post MCS Lactate (mmol/L)	6.64±3.64	6.07±3.22	8.60±5.03	0.339
PaO_2/FiO_2	0.402±0.135	0.394±0.133	0.444±0.169	0.675
Post MCS MAP (mmHg)	64.83±6.76	64.44±7.59	66.20±3.90	0.494
Inotrope Score	25.0±18.3	18.1±10.2	50.0±22.1	0.035
Platelet (x 10^3 units/ u/L)	211.4±81.2	216.9±87.1	176.2±61.6	0.267
CRRT post-MCS	48(11/23)	61(11/18)	0(0/5)	0.037
Sequential Organ Failure Assessment Score (SOFA)	8.00±2.35	8.22±2.51	7.20±1.64	0.307

Table 6-3 Postoperative details of the patients
The first column highlights the total cohort with survivors and non-survivors highlighted in the succeeding columns. Continuous variables are expressed as Mean±SD while categorical variables are depicted as percentages (numerator= total affected/ denominator (sample size))

Complications	Total (n=23)	Survivors (n=18)	Non-Survivor (n=5)	p-value
Pump Thrombus % (n)	8 (2/23)	6 (1/18)	20(1/5)	0.395
Bleeding % (n)	13 (3/23)	11 (2/18)	20(1/5)	0.539
ICH % (n)	13 (3/23)	11 (2/18)	20(1/5)	0.539
TIA/Stroke % (n)	13 (3/23)	17 (3/18)	0(0/5)	0.999
Distal Limb Amputation % (n)	8 (2/23)	11 (2/18)	0(0/5)	0.999
Ischaemic colitis % (n)	4 (1/23)	0(0/18)	20(1/5)	0.999
Malignant Arrhythmia % (n)	8 (2/23)	11(2/18)	0(0/5)	0.999
Aspiration pneumonia	4 (1/23)	0(0/18)	20(1/5)	0.250

Table 6-4 Post-operative complications of survivors vs non-survivors
The first column highlights the total cohort with survivors and non-survivors highlighted in the succeeding columns. Variables are depicted as percentages (numerator= total affected/ denominator (sample size))

6.4.1 Removal of MCS

Death post-removal of the MCS device was caused by malignant arrhythmia (n=2).

6.4.2 Post 30-day survival

Three (13%) of patients underwent heart transplantation and are well at up to 6 years post-operatively.

Patients who were successfully weaned had a mean ejection fraction of 35.6±10.2% and received ongoing heart failure medical therapy.

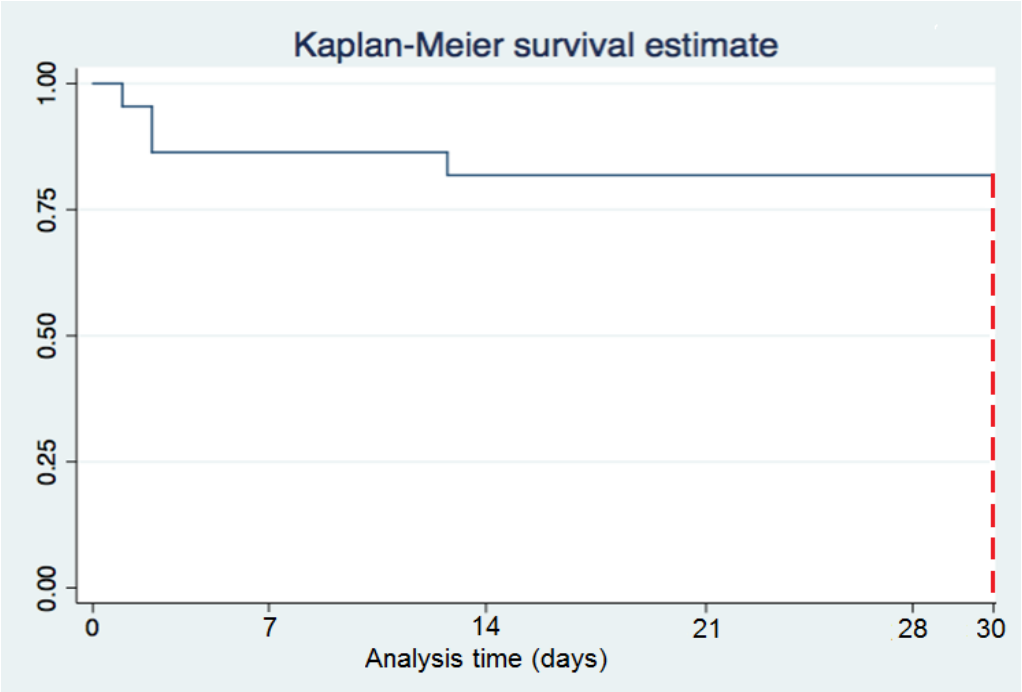


Figure 6-1 Kaplan Meier curve showing 30-day survival

Long-term follow up of up to 8 years is depicted in Figure 6-2. The curve demonstrates a high mortality beyond 30-days up to the first 6-months post MCS support.

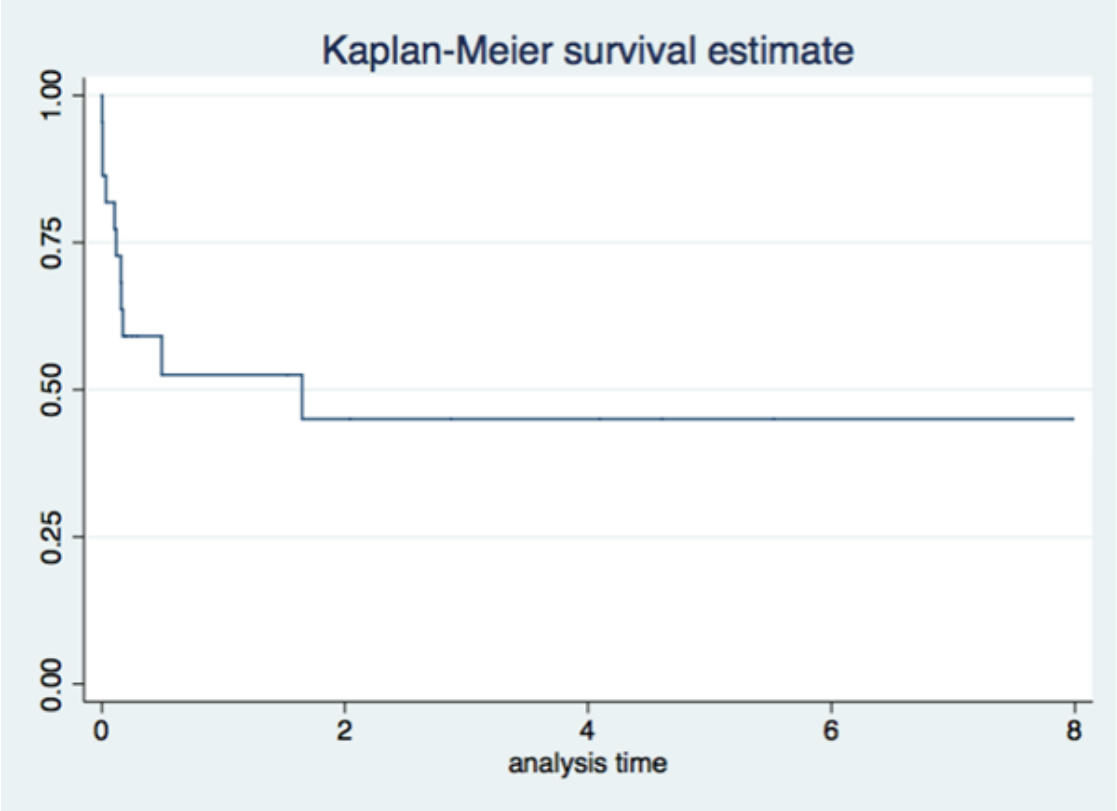


Figure 6-2 Kaplan Meier Curve showing outcomes at up to 8 years follow up

6.5 Discussion

For the first time, we have documented MCS therapy and related outcomes in a contemporary Scottish population of patients with AMI complicated by CS. More than 79.2%of patients survived to 30-days. This result compares favourably to other studies investigating outcomes of patients receiving MCS therapy in AMI/CS. In the ENCOURAGE study, approximately half of the cohort survived to 30-days (Muller *et al*. 2016). One other North American study reported a 30-day mortality rate of 41%(Truby *et al*. 2015). Most other publications report a 30-day survival rate of 23-76% survival rate in this specific patient cohort(Hendry *et al*. 1999; Kar *et al*. 2011; Tang *et al*. 2013)

Among the survivors, 16.7% subsequently underwent heart transplantation.

There are challenges to comparisons of outcomes in post-AMI-CS patients between studies, not least because of the heterogeneity in patient populations and practice. comparing outcomes of existing studies, however, is complicated by the variability of the cohorts as CS comprises a wide spectrum of clinical and haemodynamic instability. There is substantial heterogeneity with presentations of the patients with several factors being predictors of poor outcomes in larger studies. A literature review revealed older age (Zeymer *et al*. 2004; Babaev *et al*. 2005), signs of end-organ hypoperfusion(Sleeper *et al*. 2010), involvement of the LAD artery(Zeymer *et al*. 2004; Klein *et al*. 2005; Sleeper *et al*. 2010), severity of disease (triple vessel disease)(Zeymer *et al*. 2004) and renal failure (identified by elevated creatinine)(Zeymer *et al*. 2004; Klein *et al*. 2005). Our cohort was limited in size. Nonetheless, our findings indicate 30-day mortality results are similar to or potentially better than prior cohort studies.

We concentrated on the presenting pathology (AMI with CS) and not the device (VAD vs ECMO) as we felt most patients would receive a strategy that was either escalated or de-escalated based on recovery. Patients who were improving, for example, were stepped down from ECMO to a VAD (short term or long term). ECMO was the treatment of choice in most patients as in the acute phase, almost all the patients presented with acute pulmonary oedema.

Almost half (47.8%) of the patients had their support successfully weaned from ECMO and/or VAD without any further support device or transplantation. Myocardial recovery has been reported in previous publications(Combes *et al*. 2008; Brechot *et al*. 2013; Abrams *et al*. 2014). Veno-arterial ECMO (VA-ECMO) is readily available and can be rapidly instituted percutaneously negating the need for operating theatre resources. Some limitations to ECMO have been reported in the literature. This includes inadequate left ventricular decompression as emptying depends on the native ejection function of the ventricle. Decreasing the flow rate on the ECMO circuit also reduces afterload alongside using inotropes such as dobutamine to improve contractility and decrease ejection. This may result in pulmonary hypertension, oedema and bleeding(Pagani *et al*. 1999). The interaction between the tubing surfaces causes activation of monocytes and the release of interleukins 1 and 6(Pennington *et al*. 1985). Some of the decompression can be attenuated by IABP insertion. It is associated with a

smaller left ventricular dimension and a lower pulmonary artery pressure by restoring pulsatility and decreasing left ventricular afterload(Petroni *et al*. 2014). IABP may also reduce the mean of cerebral blood flow during myocardial stunning, and increases the mean flow during cardiac recovery(Risnes *et al*. 2006). Activation of clotting cascades is the predominant reason for bleeding complications. Frequent echocardiograms are done at our unit to ensure there is adequate decompression of the right and left ventricles. Another deleterious effect of VA ECMO is the neurological morbidity. Brain death has been reported in up to 21% in adults treated in ECMO centres. Up to 50% of patients have evidence of cerebral injury(Risnes *et al*. 2006). In our cohort, 26.1% of patients had evidence of a cerebral injury. The same deleterious effects of ECMO are also noted in VADs (about 20%)(Backes *et al*. 2012).

Myocardial ischaemia is commonly the preceding event in CS(Reynolds and Hochman 2008; Thiele *et al*. 2010). It impairs myocardial contractility which in turn reduces stroke volume. An impeded cardiac index causes tissue hypoperfusion, which includes coronary hypoperfusion causing worsening myocardial ischaemia, resulting in a vicious cycle. Serum lactate, creatinine, and AST are used as surrogates of organ hypoperfusion in our study. Initial compensatory vasoconstriction arises from catecholamine release to increase blood pressure but systemic inflammatory response syndrome (SIRS) mediated pathological release of vasodilatory agents results in a net reduction in cardiac index. This acts in conjunction with the reduction in left ventricular function as a result of myocardial stunning from the primary insult. There is a small window of reversibility afforded during myocardial stunning by reperfusion which is facilitated by early reperfusion(Kajimoto *et al*. 2013). Capillary leakage from SIRS causes tissue oedema and a reduction in circulating volume.

Decision making for MCS is also an important part of the discussion. Traditional ethical principles are not straightforward when applied to ECMO patients as it is often seen as the ceiling of therapy available. A survey of self-reported physicians with vast experience in VA-ECMO revealed the majority of physicians felt physicians should have the right to discontinue management over the family's objection(Meltzer *et al*. 2016). MCS is a costly intervention thereby complicating the decision-making process with finite resources available for

clinicians in the National Health Service (NHS). In our unit, a multidisciplinary team is consulted to ensure an informed decision that takes into account all facets of care prior to initiating MCS support.

6.6 Limitations

The data presented represents the first reported series of patients in Scotland with AMI complicated by CS treated with MCS. However, as it is a retrospective study with a small cohort of patients, the reproducibility of the results may vary and may not capture the European or British population as a whole. There is a selection bias in the sample as only patients who were deemed potentially salvageable were included in the study, which may comparisons with other studies difficult.

6.7 Conclusion

MCS usage in these patients carries a high mortality in the early post-implantation period. However, there is a significant benefit to patients who survive the initial bridging period to recovery or destination therapy. Further prospective studies are needed to identify predictors of long term survival.

7 The Post-Operative Glasgow Transplant Score (GTS™)

7.1 Abstract

Background

Heart transplantation is still the only definitive treatment for advanced heart failure refractory to medical management. Patients often require inputs from a multitude of disciplines due to the significant physical and physiological insults incurred which include mechanical circulatory support, inotropic usage, nutritional deficits, critical care weakness, and immunosuppression. There is a paucity of scoring systems available that incorporate the multimodal treatment that these patients undergo. We, therefore, devise the Glasgow Transplant Score(GTS) using a modified Delphi method.

Methods

We tested to model on a single centre retrospective cohort study to evaluate the GTS in a clinical setting. We compared the GTS to the other available scoring tools; CASUS, SOFA, and Euroscore. All patients who underwent heart transplants at the Golden Jubilee National Hospital, Clydebank, the National Heart Transplant Unit of Scotland between May 2012-September 2016 were included in the study. Data on the pre-operative condition, intraoperative parameters, and postoperative course retrospectively analysed. The postoperative scores were calculated by using the most abnormal value for each element of care at the 5th post-operative day (POD5).

The primary outcome for the study was mortality which was defined as death within 30 days after surgery. The secondary outcome of the study was Primary Graft Dysfunction (PGD). The accuracy of outcome prediction by the GTS, CASUS, SOFA, and Euroscore systems and the comparisons between the four scoring systems for predicting ability was assessed with area under the receiver operating characteristic (AUROC) curves.

Results

56 patients were included in the study. There was a 14.2% 30-day mortality in this cohort. The GTS score fared well in terms of predicting mortality, PGD and ICU stay (AUC 0.855,0.881,0.885 respectively).

Conclusion

The Pilot study illustrates the GTS is a good scoring tool for predicting outcomes post-heart transplantation. Ongoing prospective studies are needed to further validate this score in a multicentre setting.

7.2 Introduction

Heart transplantation is still the only definitive therapy for end-stage heart failure. Patients undergoing transplants require tailored management in their surgery, intensive aftercare and organ support, physiotherapy and cardiology input. Although there have been several scores available for cardiac surgery patients, to date there is none incorporates all the facets of care mentioned.

Preoperative scoring systems such as the European System for Cardiac Operative Risk Evaluation (EUROSCORE) are widely used in cardiac surgery although but is not applicable in a transplant setting as it was primarily intended for the general cardiac setting(Nashef *et al*. 1999). It is also a pre-operative scoring tool which does not consider intra-operative or anaesthetic complication which may differ significantly from the initial predicted risk. Other scoring systems like the Sequential Organ Failure Assessment (SOFA) provides a broadly applicable value that allows for the calculation of both the number and the severity of organ dysfunction in six organ systems (respiratory, coagulation, liver, cardiovascular, renal, and neurologic)(Jones *et al*. 2009). The Cardiac Surgery Score (CASUS) was first introduced in 2005 to provide a predictive scoring system for cardiac surgical patients in the Intensive Care Unit (ICU) setting(Hekmat *et al*. 2005). It takes into account the acute pathophysiology of the post-cardiopulmonary bypass setting has shown to be effective at predicting outcomes post-cardiac surgery and has been validated in large cohorts (Khosro Hekmat *et al*. 2010). This scoring system provides a day-to-day update on the patients' physiological status to allow assessment of trends to tailor management. The CASUS score, however, fails to incorporate the functional state of the patient with outcomes solely focused on surgical and intensive care parameters.

We, therefore, devised the post-operative Glasgow Transplant Score (GTS^{tm}), a multidisciplinary scoring system that is represented as a polygon to allow a quantitative and qualitative approach in guiding care. The polygon allows a quick visual appreciation of the 'score' to assess trends and highlight areas of additional input needed.

7.3 Methodology

We employed a modified Delphi method to specify variables for consideration in the Glasgow Transplant Score as detailed below. Clinical governance approval was provided by the Golden Jubilee National Hospital and an audit number was obtained.

7.3.1 Panel Selection

There were initially 10 experts contacted to participate in the modified Delphi process. Experts were chosen based on their experience in each of the abovementioned fields. The panel consisted of intensivists, cardiac surgeons, physiotherapists, dietitians, heart failure cardiologists and clinical psychologists with experience in heart transplantations. Each panel expert identified potential factors that were relevant to outcomes post-transplantation prior to the literature review.

7.3.2 Systematic review of the literature

A systematic review of the literature was performed to identify best practice evidence for parameters of interest to be included in the score using MEDLINE from 1946 to April 2017 was searched for English-language literature. The search strategy combined headings and keywords for “heart transplantation” and “primary graft dysfunction” or “management” or “treatment”. A core group was formed by a cardiac surgeon, intensivist and research fellow. The members of the core group screened the literature review to retain necessary titles and discard irrelevant studies. Reference lists from selected studies were also screened to potentially highlight additional papers. The second screening was performed independently by each member of the core group prior to the final selection process.

7.3.3 Email Voting and Vetting

The initial draft containing all the parameters of interest from the initial selection process was circulated to all the members of the panel accompanied by descriptions of each variable. Experts then selected whether to include or exclude each parameter. They were also given the opportunity to justify their

decisions in the comment section as well as suggest parameters of interest that may have been left out during the literature review process. A cut off value of 80% agreement was needed to include/exclude a parameter in the study based on work by Eubank(Eubank *et al*. 2016). At the conclusion of round 1, 30 parameters were selected (5 Cardiac surgery, 5 Cardiology, 5 Intensive Care, 5 Physiotherapy, 5 Dietetics, and 5 Psychology)

7.3.4 Face-to-face discussion

In round 2, a group meeting (face-to-face) was arranged. Panelists discussed and voted on each parameter and decided on whether to retain or reject each parameter, with an 80% agreement for either. The final Post-Transplant GTS consisted of 9 parameters.

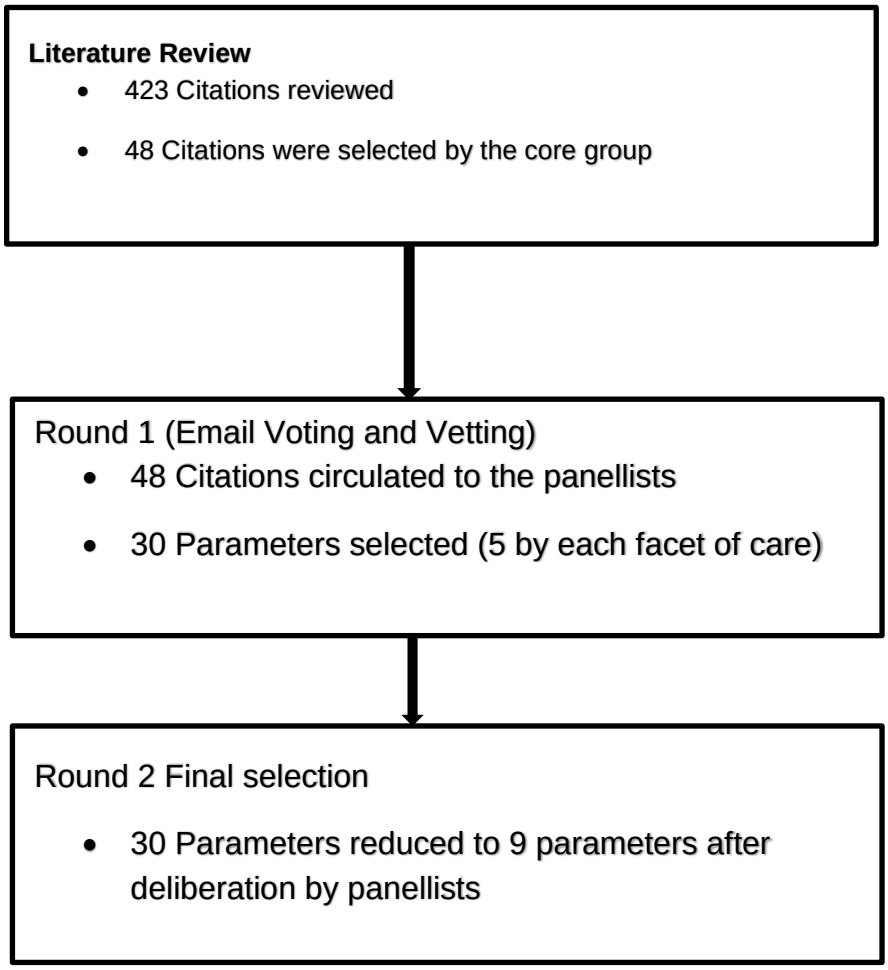


Figure 7-1 Modified Delphi Process of Selection of Parameters for Inclusion
Final Set of Parameters

Measurable elements of care for each sub-specialty of the multidisciplinary team for post-operative phases of the patients undergoing transplants that were

chosen are highlighted below. A 5-point scale was appointed to each of the measurable elements to allow vector plots for the polygon.

The elements are as follows.

7.4 Elements of the Post-op GTS™ and Summary of Deliberations

Parameter	0	1	2	3	4	5
LVEF(%)	<25% (severe impairment)	25-35 (moderate/severe impairment)	35-45 (moderate impairment)	45-55 (mild Impairment)	-	> 55 (good)
Inotrope Score	>30	21 - 30	11 - 20	6 -10	<5	No inotropes
Serum Creatinine	RRT	↑ SCr >3 x baseline	↑ SCr 2-3 x baseline	↑ SCr ≥ 26.4µmol/l or 1.5-2 x baseline	↑ SCr ≤ 26.4µmol/l	Normal U&E
Bilirubin	>150	100-150	75-100	50-75	25-50	<25
AST	>300	200-300	150-200	100-150	50-100	<50
Lactate	>12	8.1 – 12.0	6.1 – 8.0	4.1 – 6.0	2.1 – 4.0	< 2.1
MCS (post-op)	Yes - ECMO	Yes - VAD	IABP	-	-	No
Grip Strength	Not able to assess	<10%	11-25%	26-50%	51-75%	>75%
Mobility	Unable to assess	Moving limbs to command	Able to sit at edge of bed with or without assistance	Able to sit in chair with/without assistance OR able to do a chair to stand test (<10 for males, <9 for females)	Chair to stand test Male= 10≤M<14 Female= 9≤F<12	Chair to stand test Male ≥14, Female ≥12

Table 7-1. Post-op GTS™ elements of care

7.4.1.1 LVEF (%)

The first parameter selected was Left Ventricular Ejection Fraction (LVEF). Ejection fraction is one of the strongest predictors of mortality in patients with left ventricular systolic dysfunction(Cintron *et al*. 1993; Hughes *et al*. 1993; Pouleur *et al*. 1993). In several landmark studies, the Department of Veterans Affairs Cooperative Vasodilator-Heart Failure Trials (V-HeFT VA Cooperative Studies Group) and The Studies of Left Ventricular Dysfunction (SOLVD) investigators, the relationship between LVEF and mortality was established. Cut-offs for percentages of LVEF for the scale were set as per the European Society of Cardiology and American Society of Echocardiography guidelines(Lang *et al*. 2005).

7.4.1.2 Inotrope score

The recent ISHLT consensus statement for stratifying Primary Graft Dysfunction(PGD) severity(J. Kobashigawa *et al*. 2014) used cutoffs for inotrope scores as defined by Wernovsky in determining the severity of PGD (mild <10, moderate >10) (Wernovsky *et al*. 1995a). Increasing use of inotropes was indicative of increasing support required as well as the vasoplegic status of the patient. Subsequent studies revealed high inotropic scores were associated with prolonged ICU stay, duration of mechanical ventilation and time to negative fluid balance(Gaies *et al*. 2010). Shahin and colleagues evaluated the relationship of inotrope use to morbidity and mortality in a cohort of consecutive patients undergoing cardiac surgery(Shahin *et al*. 2011). They concluded that inotrope exposure was associated with increased hospital mortality and renal dysfunction in cardiac surgery patients.

7.4.1.3 Serum Creatinine

Deviation from baseline serum creatinine was selected based on the Acute Kidney Injury Network criteria for Acute Kidney Injury(AKI) (Mehta *et al*. 2007). A study in Edinburgh revealed how AKIN scores (compared to RIFLE (Risk/Injury/Failure/Loss/End-stage)) were more sensitive at picking up AKIs (12.4% vs 6.5%)(Duthie *et al*. 2014). The AKIN score however also includes urine volumes which we have omitted from our study as this may be artificially influenced by renal replacement therapy and administration of diuretics.

7.4.1.4 Bilirubin & Aspartate aminotransferase (AST)

Bilirubin levels may be elevated post-transplant due to increased pressure in from a hypofunctioning right ventricle or hepatocyte necrosis and inflammation from decreased perfusion. A similar phenomenon is noted with AST levels as well. Both of these markers, therefore, serve as indirect representations of right ventricular function post-transplant.

Sabzi and colleagues showed that AST was the most sensitive test for postoperative evaluation of hepatic function in hypothermic and normothermic cardiopulmonary bypass (Sabzi and Faraji 2015). AST is a liver enzyme that is often elevated in response to declining right heart function. It is also an

indication of decreased liver perfusion resulting in hepatocyte necrosis(Anker *et al*. 2003). A study by Vakilian (Vakilian *et al*. 2015) highlighted that a pre-operatively elevated AST was predictive of increased post-operative inotrope use Vakilian et al., 2015).

Bilirubin has also been used in several other studies as a predictive marker of increasing end-organ hypoperfusion and liver congestion. The CASUS score is one such example(K. Hekmat *et al*. 2010). A raised bilirubin in combination with mechanical circulatory support is also linked with poorer outcomes. The mechanism for this could be due to increased haemolysis as well as possible reduced perfusion.

Overall, these two liver function tests correlate well with increasing cardiopulmonary bypass time and overall graft function.

7.4.1.5 Lactate

Scalea et al found that up to 80% of critically ill patients who have normal blood pressure and have adequate urine output may remain in a state of compensated shock(Scalea *et al*. 1994). Measures of oxygen extraction variables and gastric intramucosal pH have been explored as viable alternatives but did not distinguish survivors from non-survivors over time. The two most commonly used markers in assessing the resuscitation of critically ill patients remain base deficit and lactate(Joynt *et al*. 1997).

In cardiac surgery, tissue perfusion is at risk during the perioperative period with the association of low blood flow with metabolic acidosis and accumulation of lactate perioperatively has been well established.

With the improvements in cardiopulmonary bypass and overall hemodynamic management, severe peri- and postoperative hypoperfusion has become rare however several lines of evidence suggest that episodes of less severe hypoperfusion and borderline tissue oxygenation are relatively common, although generally well tolerated. Measurement of blood lactate levels is widely used to assess the adequacy of tissue perfusion(Takala *et al*. 1996).

Hyperlactatemia can occur even in the absence of tissue hypoperfusion(Raper *et al*. 1997). Intraoperative catecholamine administration intraoperatively can lead to increased lactate levels owing to their action on oxidative glucose metabolism(Stainsby *et al*. 1987).

Hyperlactataemia has a bimodal distribution in the perioperative period. An early increase in lactate levels, arising intraoperatively or soon after intensive care unit admission is highly suggestive of tissue ischaemia and is associated with a prolonged intensive care unit stay, a prolonged requirement for respiratory and cardiovascular support and increased postoperative mortality. Late-onset hyperlactataemia occurs 4 to 24 hours after completion of surgery and is typically associated with preserved cardiac output and oxygen delivery but has a longer duration of ventilation and intensive care unit length of stay than those with normolactataemia(O'Connor and Fraser 2012).

Hajjar and colleagues revealed that patients in whom complications developed had higher lactate levels immediately after ICU admission, 6 hours and 12 hours after admission(Hajjar *et al*. 2013).

This also identified patients with worse outcomes including a higher rate of 30-day mortality after cardiac surgery. Also, a lactate level exceeding 3 mmol/L at 6 hours after surgery is independently associated with a 3.3 times risk of a major complication after cardiac surgery, including death. Another study revealed an association between higher lactate levels at ICU admission and complications that included longer duration of mechanical ventilation and length of ICU stay(Maillet *et al*. 2003).

Polonen's group showed that normalizing lactate concentrations, as a therapeutic goal is associated with decreased morbidity and hospital length of stay in patients undergoing cardiac surgery(Polonen *et al*. 2000).

7.4.1.6 Mechanical Circulatory Support (MCS)

PGD is the leading cause of early mortality following orthotopic heart transplantation. However, a widely approved definition for PGD was not available, albeit the clinical characteristics of hypotension despite adequate

filling pressures and the absence of hyperacute rejection and tamponade were used as a guide(J. Kobashigawa *et al*. 2014). The ISHLT consensus statement (2014) produced a definition of PGD alongside grading systems for severity. This included the use of Intra-Aortic Balloon Pumps (IABPs) and Ventricular Assist Devices (VADs)/Extracorporeal Membranous Oxygenation (ECMO) as predictors of outcome. The use of any MCS device is classified as a severe PGD. ECMO is a recognized treatment for PGD. In a case series of 366 consecutive heart transplants, post-operative ECMO institution in the recipient occurred in 40 cases of cardiopulmonary failure. The recipients included 35 males and 5 females with an overall median age of 42.3 years. More than 70% of the patients were successfully weaned with an overall survival exceeding 50%. Although ECMO provided temporary MCS rescuing some recipients with post-transplant cardiopulmonary failure, no patient receiving ECMO support for >4 days survived. (Chou *et al*. 2010)

For VADS, several annual reports from the International Society for Heart and Lung Transplantation registry reported increased early post-transplant mortality in patients supported with VADs(Taylor *et al*. 2006; Trulock *et al*. 2007).

The implantation of IABPs is used for a variety of reasons. However, in advanced heart failure, it denotes moderate primary graft dysfunction. It is used to stabilize patients in end-stage heart failure, is safe, well-tolerated, and bridging acutely decompensated patients to transplantation, Complications are few and manageable. Following IABP and HTx, short- and long-term survival, biochemical and invasive and non-invasive haemodynamic outcomes were similar to those in electively transplanted patients(Gjesdal *et al*. 2009).

7.4.1.7 Grip Strength

Grip strength is a way of quantifying the amount of static force that a hand can squeeze around a dynamometer. It is associated with increased mortality in a host of chronic conditions as a marker of general nutrition. Poor handgrip strength is highly prevalent among Heart failure patients as a result of the derangement of muscle structure and metabolism, contributing to exercise intolerance, frailty, and mortality. The Columbia group noted that in patients with advanced HF before VAD implantation (2.3 ± 4.9 days pre-VAD) handgrip

strength correlated with serum albumin levels. They also found that patients with a handgrip strength <25% of body weight had an increased risk of mortality, increased postoperative complications, and lower survival after VAD implantation(Chung *et al*. 2014).

Grip strength is also commonly used as a gauge to frailty. Frailty is common among patients with HF. One study concluded that frailty is a strong and independent predictor of ED visits and hospitalizations and should be incorporated into the clinical evaluation of patients with HF(McNallan *et al*. 2013).

7.4.1.8 Mobility

One tool that has been extensively validated and compared favourably with others is the Elderly Mobility Scale (EMS). It evaluates an individual's mobility via seven functional activities including bed mobility, transfer, and reactions to perturbations. We based the bed mobility, mobility and physical transfer aspect of our physiotherapy polygon based on some of the common assessors used in this scale. This included the independence of mobility in bed, transfers and personal care(Smith 1994). Other similar tools that we adapted from includes the Berg Balance Score(Berg *et al*. 1995). Both these tests showed good inter-operator reliability with a high rate of reproducibility(Chiu *et al*. 2003).

A sit to stand test was employed as another marker for frailty. The primary focus of this test is lower limb strength. The use of the sit to stand test has been validated in other cohorts. One such example is Millor et al (2013) whose study concluded that parameters such as velocity peaks, impulse, and orientation range are able to differentiate between adults and older populations with different frailty levels during the 30-second sit to stand test(Millor *et al*. 2013). It has also been employed by the Centre for Disease Control (CDC) with relevant cut-offs that have been employed in this score. (CDC 2017).

7.5 Polygon Formation

To allow visual representation of the data, a 9 Point radial plot (Polygon) was created using Microsoft Excel 2013. Values on each spoke of the polygon

corresponded to the numerical value of the score above. Each of the lines was connected to represent a performance polygon for each patient. The higher the score as determined by Table 7-1, the further the radiation of the polygon from the centre. The use of polygons to display the score was adapted from the Chelsea Critical Care Physical Assessment Tool(Corner *et al*. 2013).

7.6 Pilot Study

We conducted a single centre retrospective cohort study to evaluate the GTS in a clinical setting. We compared the GTS to the other available scoring tools; CASUS, SOFA, and Euroscore. All patients who underwent heart transplants at the Golden Jubilee National Hospital, Clydebank, the National Heart Transplant Unit of Scotland between May 2012-September 2016 were included in the study.

7.6.1 Patients

Our sample comprised of all adult patients who underwent heart transplants during this period. Data on the pre-operative condition, intraoperative parameters, and postoperative course retrospectively analysed. The postoperative scores were calculated by using the most abnormal value for each element of care at the 5th post-operative day (POD5). No data was missing.

The primary outcome for the study was mortality which was defined as death within 30 days after surgery. The secondary outcome of the study was Primary Graft Dysfunction.

7.6.2 Statistical analysis

Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) Version 22 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.). The level of statistical significance was set at 5%. A Kolmogorov-Smirnov test was used to indicate the normality of the quantitative variables prior to performing Students ‘T’ Tests for continuous data. Categorical data were analysed using a Chi-Squared Test. Non-Parametric data were analysed using the Mann-Whitney U test. Continuous data were presented using Mean values ± Standard deviation. The accuracy of outcome prediction by the GTS, CASUS, SOFA, and Euroscore systems and the

comparisons between the four scoring systems for predicting ability was assessed with area under the receiver operating characteristic (AUROC) curves.

7.7 Results

56 patients were included in the study. There was a 14.2% 30-day mortality in this cohort. Patient demographics, intraoperative and post-operative outcomes are demonstrated below

Recipient Variable	Survivors (n=48)	Non-Survivors (n=8)	P-value
Age (years)	46.1±12.9	46.1±12.5	0.998
Male sex (%)	72.9	75.0	0.902
Body Mass Index	25.4±3.5	27.3±3.9	0.220
Non-ischaemic Cardiomyopathy (%)	79.2	62.5	0.301

Table 7-2 Preoperative Demographic data of both groups of patients

Intraoperative	Survivors (n=48)	Non-Survivors (n=8)	P-value
Cardiopulmonary bypass time (mins)	222.3±75.7	329.0±105.1	**0.024**
Total Ischaemic Time (mins)	179.3±52.2	180.8±36.7	0.924
Cold Ischaemic Time (mins)	136.6±50.3	128.5±40.8	0.625
Donor Age (years)	41.8±11.1	41.0±12.1	0.865

Table 7-3 Intraoperative details of both groups of patients

Post-operative	Survivors (n=48)	Non-Survivors (n=8)	P-value
Hours of mechanical ventilation	110.4±164.2	135.0±97.4	0.565
Inotrope Score	5.7±7.2	21.2±13.3	**0.035**
Renal Replacement Therapy (%)	6.3	50	**0.001**
ECMO (%)	31.3	75.0	**0.018**
IABP (%)	56.3	62.5	0.741
Primary Graft Dysfunction (%)	54.2	100	**0.014**
Post-operative Ventilation Time(hours)	128.5±40.8	136.6±50.3	0.565
GTS score	30.6±6.9	16.9±10.1	**0.006**
CASUS score	7.9±6.2	20.1±3.0	**<0.001**
SOFA score	6.4±3.4	15.9±2.8	**<0.001**
Euroscore	22.0±14.1	13.8±7.8	**0.029**

Table 7-4 Postoperative outcomes of both groups of patients

The accuracy of outcome prediction by the scoring systems for predicting ability was assessed with area under the receiver operating characteristic (AUROC) curves. The outcomes of interest were 30-day mortality, Primary Graft Dysfunction and ICU length of stay>14 days in survivors.

7.7.1 GTS™

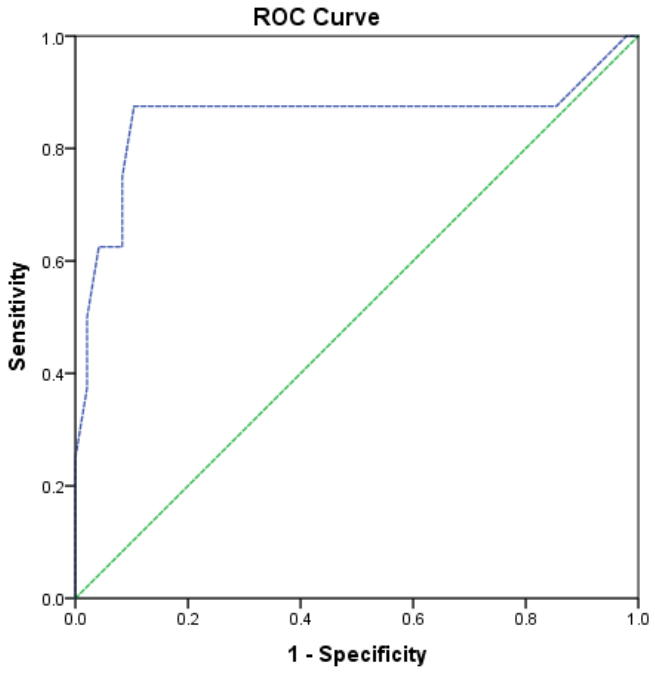


Figure 7-2 ROC Curve showing GTS prediction and mortality

Area under the curve for GTS^{tm} and mortality is 0.855

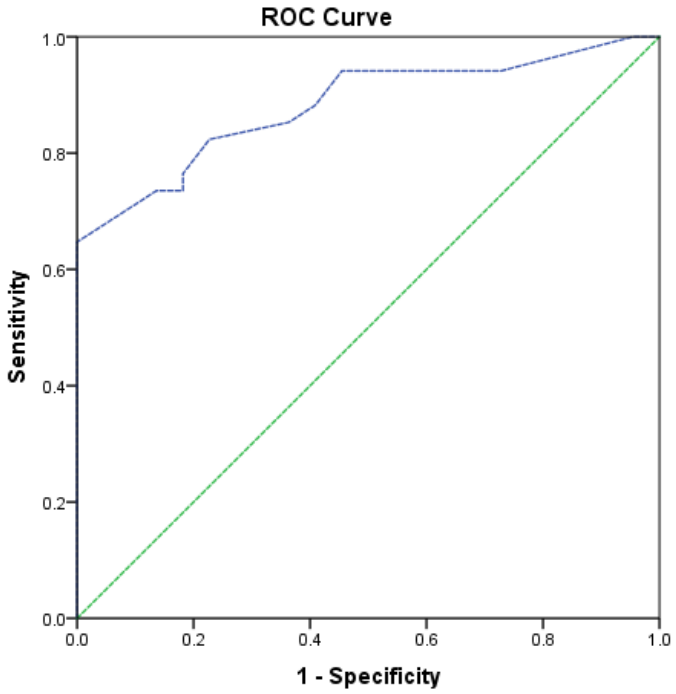


Figure 7-3 ROC Curve showing GTS prediction and PGD

Area under the curve for GTS[tm] and PGD is 0.881

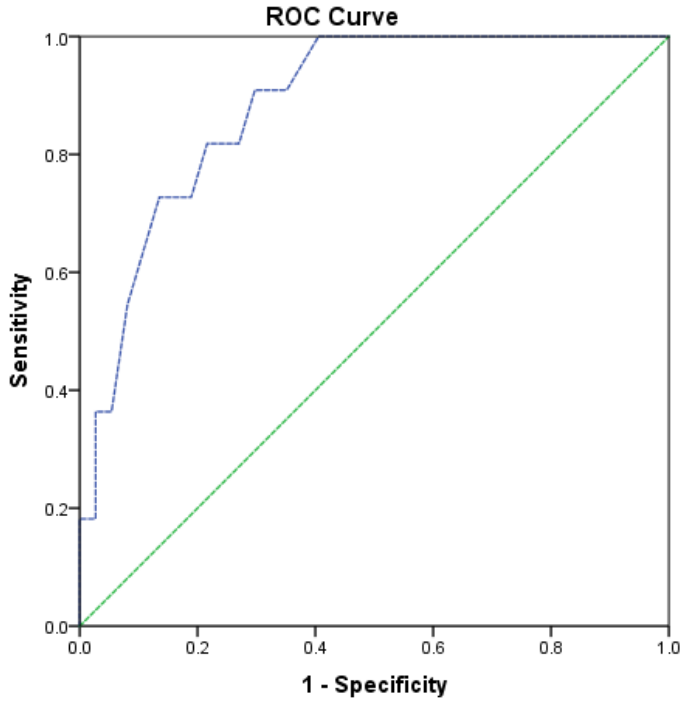


Figure 7-4 ROC Curve showing GTS prediction and prolonged ICU stay

Area under the curve for GTS[tm] and prolonged ICU stay is 0.885

7.7.2 SOFA & CASUS

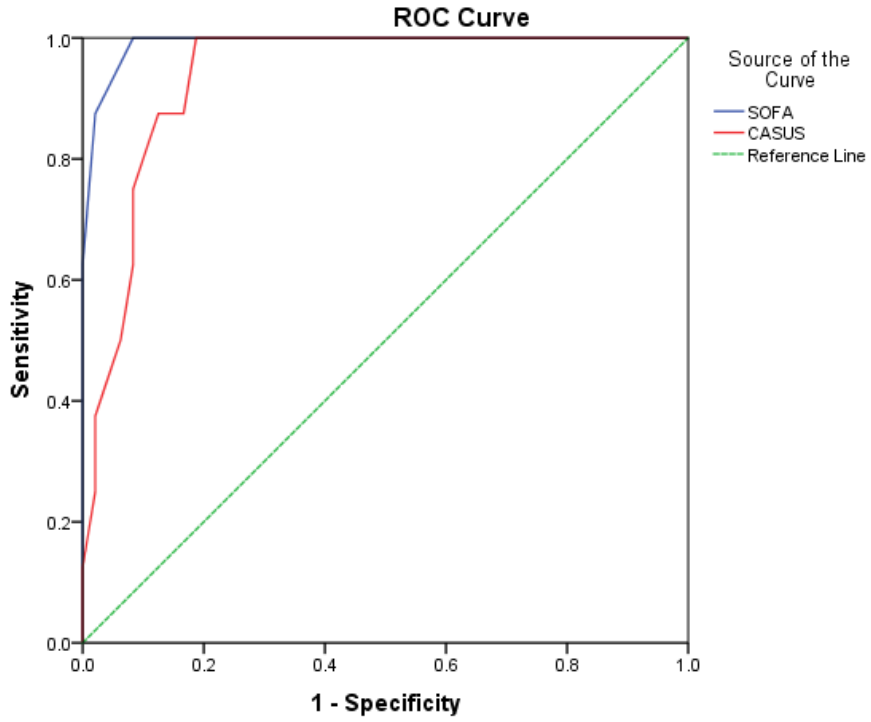


Figure 7-5 ROC Curve showing SOFA and CASUS prediction and Mortality

Area under the curve for SOFA is 0.991, while the area under the curve for CASUS is 0.936.

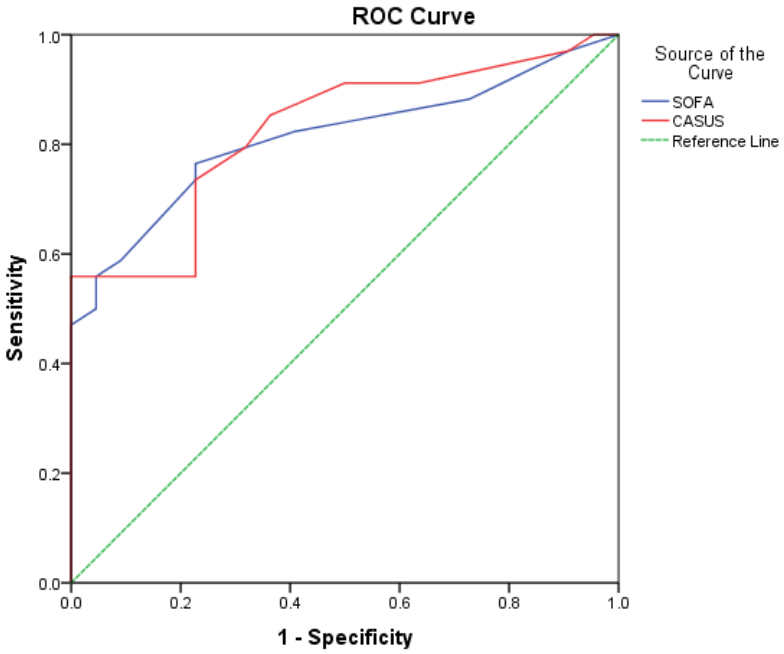


Figure 7-6 ROC Curve showing SOFA and CASUS prediction and PGD

Area under the curve for SOFA is 0.812, while the area under the curve for CASUS is 0.826.

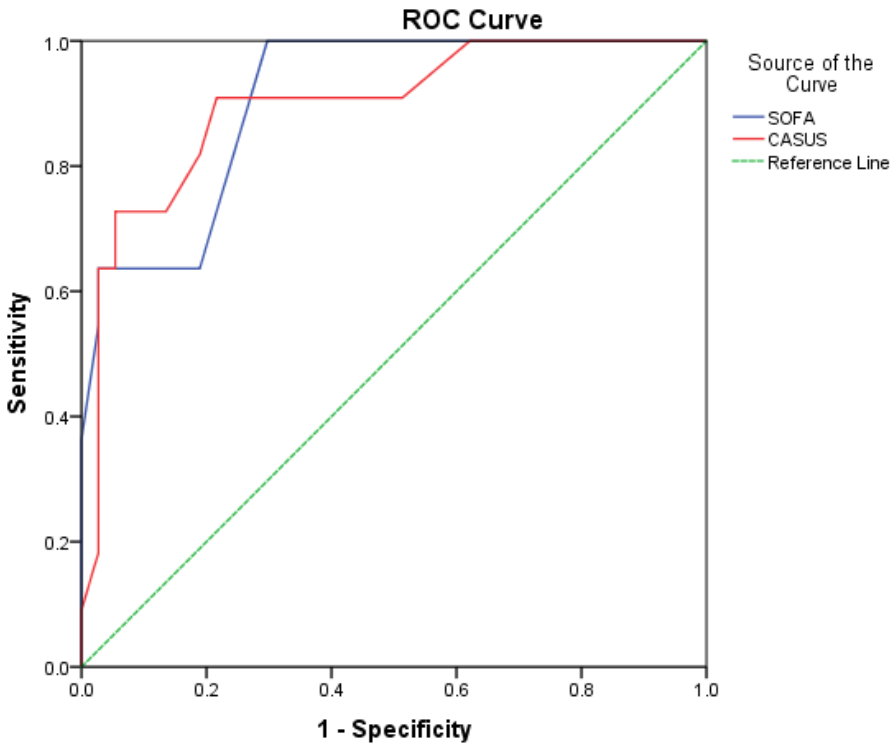


Figure 7-7 ROC Curve showing SOFA and CASUS prediction and prolonged ICU stay

Area under the curve for SOFA is 0.907, while the area under the curve for CASUS is 0.897.

7.7.3 Euroscore

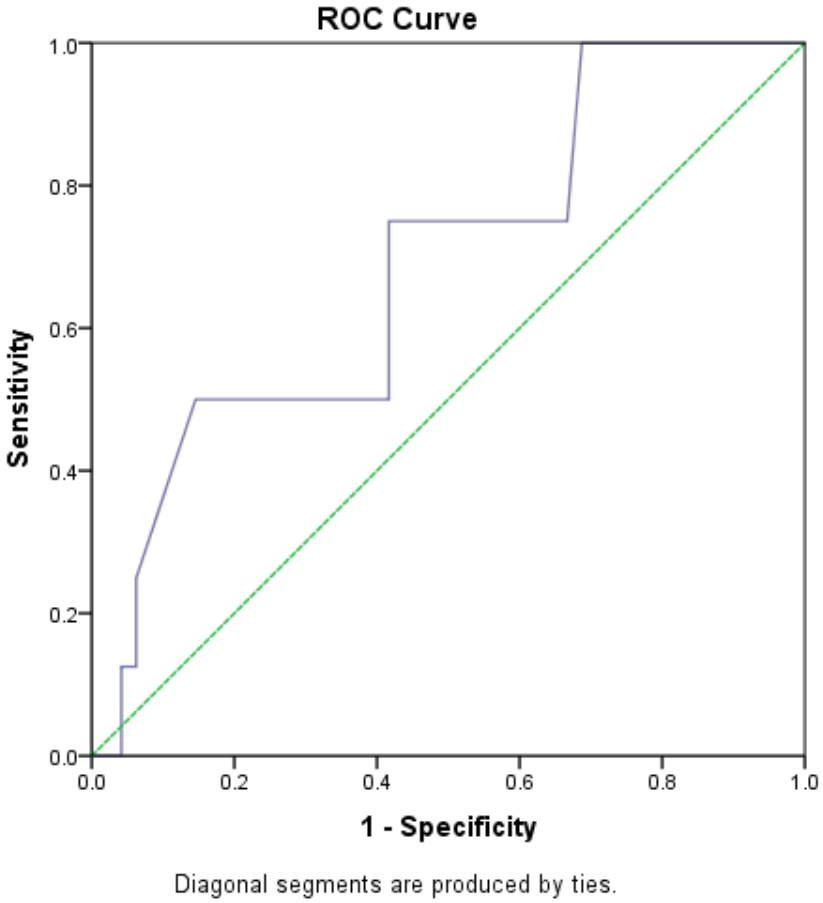


Figure 7-8 ROC Curve showing Euroscore prediction and mortality

Area under the curve for Euroscore is 0.688

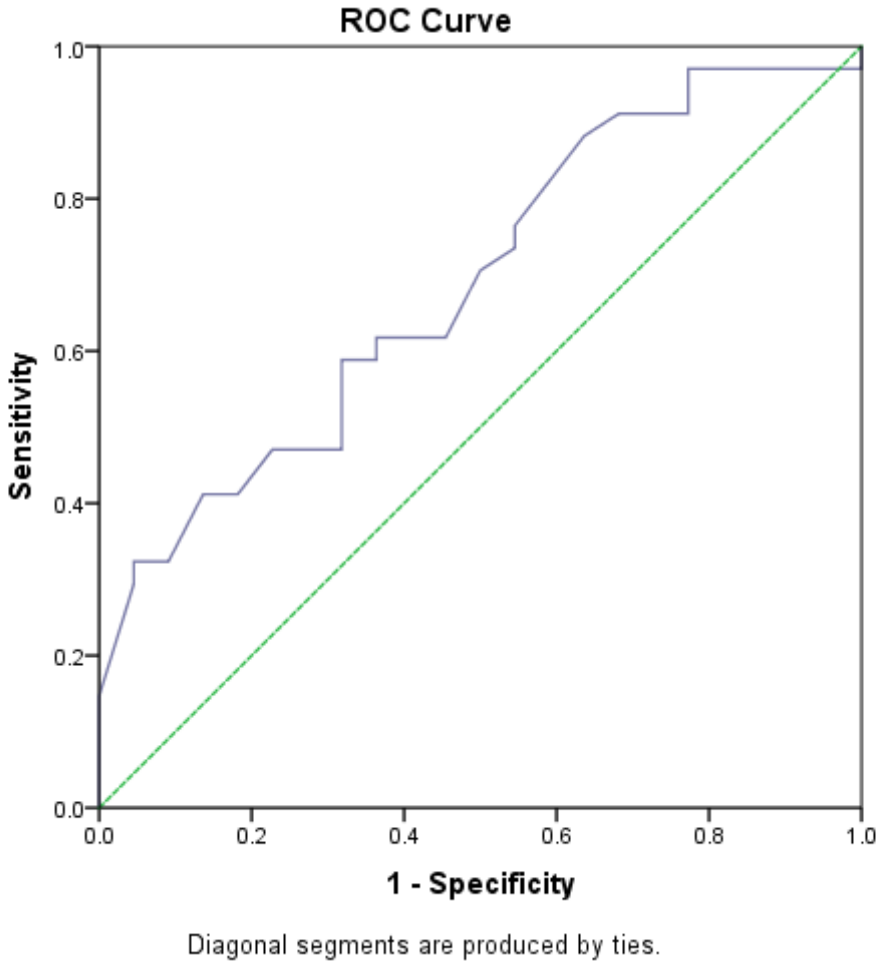


Figure 7-9 ROC Curve showing Euroscore prediction and PGD

Area under the curve for Euroscore is 0.688

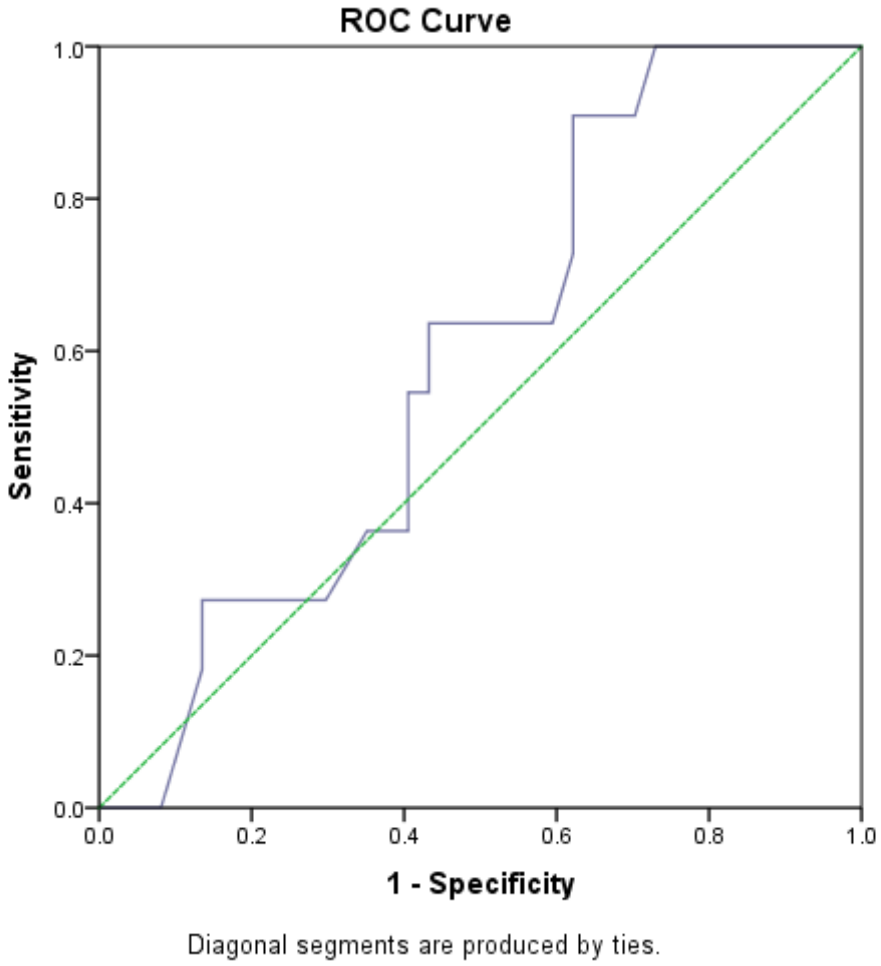


Figure 7-10 ROC Curve showing Euroscore prediction and prolonged ICU stay

Area under the curve for Euroscore is 0.592

7.7.4 Qualitative analysis using performance polygons

A composite polygon showing mean results of all patients (Survivors Vs Non-Survivors) is depicted in Figure 7-11 whereas a composite polygon showing outcomes of patients with and without PGD is depicted in Figure 7-12.

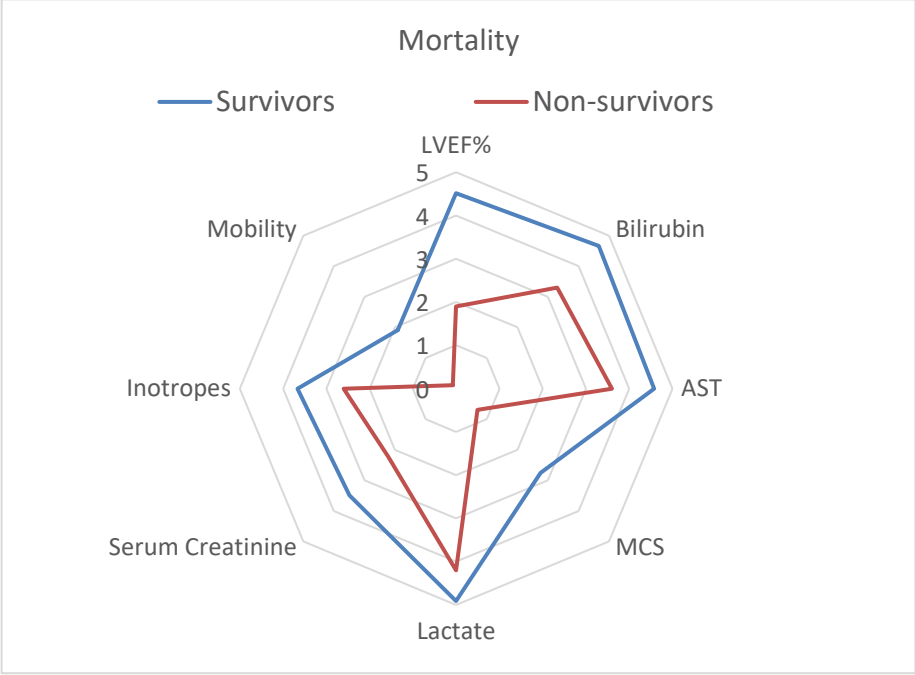


Figure 7-11 Polygons depicting GTS of survivors vs non-survivors (Grip strength omitted due to incomplete datasets).

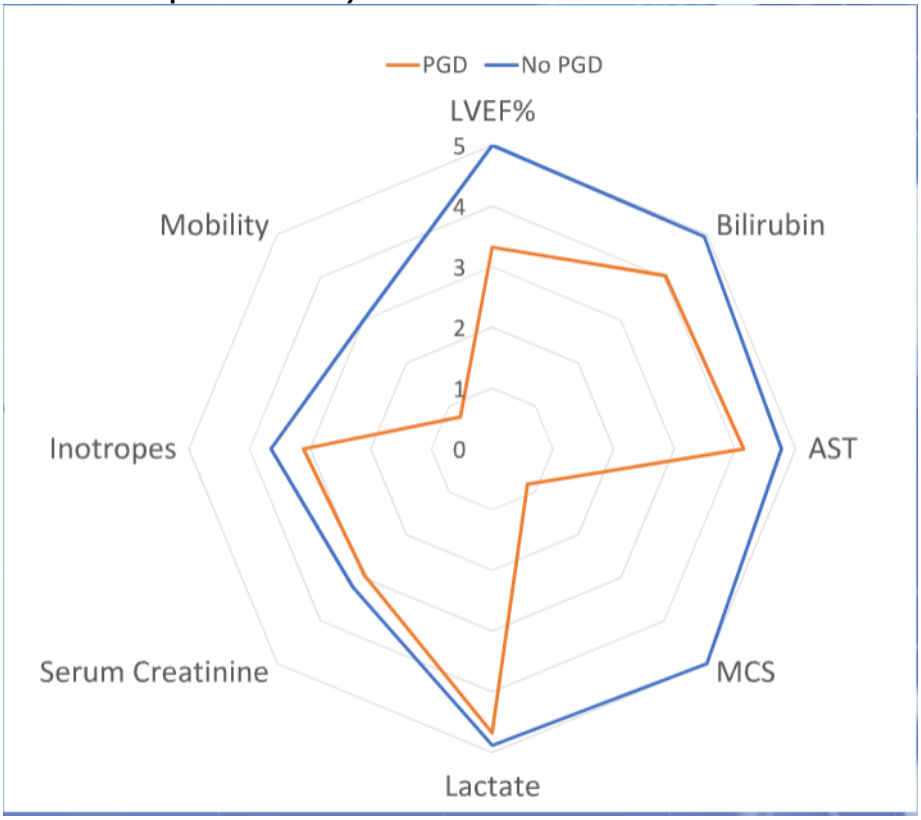


Figure 7-12 Polygons depicting GTS of patients with PGD and No PGD (Grip strength omitted due to incomplete datasets).

7.8 Discussion

The DELPHI method was originally designed to apply expert opinion to a selection of questionnaires interspersed with controlled opinion feedback(Dalkey and Helmer 1963). Although initially used for military strategic planning, it is

now utilised in the healthcare setting to determine consensus for a pre-defined problem. One such example is the consensus statement for the management of medical conditions such as Barrett's Oesophagus (Bennett *et al*. 2012), renal cell carcinoma (Wood *et al*. 2013) and rotator cuff tears(Eubank *et al*. 2016). It is a technique that incorporates individual judgements and combining them to address an incomplete state of knowledge(Powell 2003). We utilised this method to incorporate elements of frailty into practice. The GTS incorporates biochemical, clinical and functional assessments of the patient thereby providing a more holistic scoring system that can be used to facilitate multi-disciplinary meeting discussions.

A key strength of the Delphi method is that it provides a summation of judgements which in theory is more accurate than that of individuals(Rowe *et al*. 1991). Informal consensus discussions without the Delphi methodology may be influenced by more 'powerful' individuals, which may, therefore, overlook the other facets of care in decision-making(Murphy *et al*. 1998). This may also be influenced by personality traits and seniority(Rowe *et al*. 1991).The first part of the Delphi method, in which panelists anonymously select parameters allows objectivity to the outcome, thereby promoting the sharing of responsibility. This has been shown to reassure participants(Lindeman 1975).

One of the criticisms of the Delphi method includes the assumption that panelists contribute equally and are not duly influenced or persuaded to conform rather than express true agreement. This may, therefore, mirror other informal consensus agreements that allow the abovementioned biases(Goodman 1987). Panelists are assumed to provide objective and neutral solutions or responses. Lay persons were not included in our Delphi methodology. This was to minimise discrepancies arising due to cognitive bias or emotions(Hussler *et al*. 2011).

A variation from the 'true' Delphi method that we employed was the face-to-face discussion. We felt this may deprive panelists of critiquing and seeking clarification and deliberation which we felt would drive the selection process(Walker and Selfe 1996). The final process in our methodology also allowed the generation of alternatives and applicability of the scoring system in a real-world setting(Ali 2005).

A major strength of this study is the incorporation of the whole multidisciplinary team to mimic a real-life setting. The scalar representation of each variable allows a uniform depiction of the patient's clinical condition with experts in each field able to interpret the results of other fields and vice versa. This also allows the quantification of frailty measures alongside biochemical and clinical parameters for each patient.

Another major highlight of the GTS is the qualitative depiction of the dataset in the polygons. This allows easy interpretation and appraisal of the clinical condition of a patient while highlighting areas of increased need of support. Performance polygons are a simple but powerful way to represent data over multiple domains(Cook *et al*. 2012). They can also be used as a comparison between patients or at different time points to enhance their value as a potential driver of change and quality improvement(Cook *et al*. 2012). This also permits a continuous assessment by assessing the change of shape of the polygons to show improvement or worsening of parameters from the end of the bedside. This visual depiction also serves as a guide for patients and relatives to monitor progress within the hospital setting as they provide a visual representation of data that is easily understood by observers. The use of polygons in medicine also allows the merging of fundamentally unconnected data that have similar vectors (move in the same direction).

The quantitative score of the GTS has similar AUCs as the other ICU post-operative scoring systems for ICU stay and mortality. However, the GTS also has good predictability for Primary Graft Dysfunction which is an important recognised complication of heart transplantation. The Euroscore performed poorly compared to the other scoring systems. However, it should be noted that it is primarily a pre-operative risk assessment tool designed for general cardiac surgery and thus may accurately predict outcomes post-heart transplantation. SOFA and CASUS showed good predictability of mortality as it highlights the common pathway of tissue hypoperfusion and end-organ dysfunction.

7.9 Limitations

7.9.1 Outcomes

The GTS fared well when compared to the Euroscore but did not perform as well with CASUS and SOFA. There are several reasons to explain this. There were limited numbers of patients in the study. In addition, CASUS and SOFA which are intensive care centered measures are more sensitive at identifying the acutely unwell patients within the intensive care setting as opposed to the GTS which works on trending improvements to identify progress. The utility of the score is therefore aimed at different outcomes. While GTS, which assesses frailty may identify patients at risk of poor outcomes, CASUS and SOFA are useful for identifying more objective markers of poor outcomes. The utility of frailty assessment in the post-operative setting is limited, however, its role in measuring ongoing progress may be of benefit especially to the multimodality treatments offered by the MDT.

7.9.2 Data

The consensus statements were not wholly supported by level 1 studies. Most of the literature on heart transplantation and primary graft dysfunction is based on observational studies and analysis of large databases like UNOS or ISHLT. Where possible, data was sourced from well-designed randomised controlled trials. In order to ensure ubiquitous applicability of the scoring system, we opted to include routine measurements in clinical practice such as AST and lactate while omitting more obscure and costly tests that are only available at certain centres such as SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily A-like protein 1 (SMARCAL-1)(Aharinejad *et al*. 2009). Consistent level 2 and 3 studies have been used numerous times to provide strong recommendations and assuming level 1 studies that are underpowered or poorly conducted as being superior to level 2 studies should be done with caution(Burns *et al*. 2011).

7.9.3 Polygons

The polygon formation also assumes equal weightage of all the parameters within the GTS. An ordinal scale of 0-5 was formed with 5 being the most

favourable outcome. The weightage of the values and escalation from one category to the next is assumed to be a linear progression. This is a major assumption as there may be a large number of patients who may fall within a category of the scale (e.g. 3). The Glasgow Coma Scale as introduced by Teasdale and Jennett was also initially criticised for lacking weightage. This mathematical imprecision has a bearing also on clinical accuracy and precision. For instance, in the present structure of the scale, the same sum score could be produced by totally different clinical states. The was also overall motor dominance at both the lower and higher ends of the scale(Bhatty and Kapoor 1993). A large scale prospective study is currently being developed for the GTS to provide weightage to the scales to allow a more uniform comparison. The initial iteration of the GTS is primarily a proof of concept in which the polygons can be used to display a patient's condition, and evolution of the polygon over time to highlight areas of increased input required. Once weightage has been established, it may then be possible to calculate the area of the polygon for quantitative analysis. A known limitation with any polygons is the requirement for large databases of robust data to generate meaningful, reliable polygons. However, this holds true for any other data representation method(Cook *et al.* 2012).

7.9.4 Unadjusted confounders

Another limitation of the GTS is the potential confounding effects of the variables. A patient on ECMO/IABP would be limited on the mobility scale or a patient with a low ejection fraction may require increased inotropes, potentially need MCS support and therefore not be able to mobilise. This also holds true for most other scoring systems such as CASUS or SOFA whereby one organ failure may lead to ongoing organ failure as tissue hypoperfusion is the common pathophysiological pathway. We, however, believe that the trend of the scores, as opposed to a score in isolation, will, therefore, highlight improvements and be of greater utility. We envisage the polygons to be available in a digital format by the patient's bedside with continuous input, thereby evolving to highlight improvement or worsening of the clinical and physiological conditioning of the patient.

7.10 Conclusion

Post-GTS is a novel scoring tool that can be used to guide MDT decision making in the post-operative period for cardiac transplant patients. More data is needed to provide weightage and further enhance its predictive ability.

8 Conclusions

The objectives achieved with this thesis are as follows

8.1.1 The incidence of PGD in the UK (Chapter 3)

The first aim of the thesis was to ascertain the true incidence of PGD in the UK. To date, there was no accurate incidence reporting due to the lack of a unifying definition. Dronavalli and colleagues (Dronavalli *et al*. 2015) used a definition that was similar to the ISHLT consensus statement. This thesis, however, is based on a contemporaneous cohort of patients which highlights changing demographics of the donors, recipients, the introduction of ex-vivo normothermic perfusion devices and the start of the Donation after Circulatory Death era worldwide and in the UK (Chapter 2). To date, this is the largest national study worldwide to identify the true incidence of PGD in the UK. As part of the changes made and ongoing data collection initiatives led by my work and integrated into NHSBT's data collection, PGD rates are now reported prospectively which allows ongoing monitoring and incidence reporting.

8.1.2 To identify risk factors for PGD according to ISHLT 2014 consensus statement

The lack of a consensus statement prior to 2014 made identification and comparison of PGD difficult. The findings of these were included in chapter 3. We created a multivariable logistic regression model to identify risk factors within our cohort of patients. We were also able to highlight the role of warm ischaemic time as opposed to total ischaemic time as a risk factor which has not been noted in studies derived from the United Network for Organ Sharing (UNOS) database due to limitations of data collection. From the risk factors noted, we provided potential pathophysiological mechanisms to highlight the role of ischaemic reperfusion injury with accumulation of succinate as the common pathway based on previous studies done on other transplanted organs (Section 1.12.2.4). Future studies should incorporate ameliorating the risk factors identified to reduce the risk of PGD. Ongoing work is underway with CTAG commencing a trial to identify the role of different cardioplegic solutions in myocardial protection (St Thomas's solution vs Custodiol^{tm}).

8.1.3 A scoring system

Another aim was to create a ubiquitous, easy to use, reproducible scoring system to allow benchmarking of PGD rates using observed vs expected analysis as a statistical quality control assessment. We derived the PREDICTA score (Chapter 4) based on a contemporary cohort of patients with good predictability. This would allow continuous monitoring of outcomes to identify outliers using the VLAD plot. This serves to improve outcomes by improving measures to manage PGD such as resource allocation (MCS, theatre space, ICU staffing) and subconsciously via the Hawthorne effect of altering by increasing vigilance. This tool could potentially serve as a governance tool for NHSBT to improve clinical effectiveness by auditing outcomes and ease the implementation of cost-effective novel technologies within a public healthcare system. Future studies should concentrate on the search for a biomarker to improve the precision of the PREDICTA score. To date, the ideal biomarker has not been identified but further studies along the ischaemic reperfusion pathway may yield measurable by-products for quick point-of-care testing in the near future.

8.1.4 Cold antegrade perfusion

The Glasgow method of implantation described in Chapter 5 has improved short-term post-transplant survival. The retrospective nature of the study, however, has several confounders that should be addressed. This should be performed via a proof of concept study using animal models (e.g. Juvenile Landrace Pigs) to ascertain if the clinical improvement noted by this method is shown at a biochemical or cellular level. The use of antegrade cardioplegia has multiple advantages from a surgical perspective as detailed in Chapter 5. This could then extend to a low fidelity model of continuous cold perfusion during transportation (vs the ex-vivo normothermic perfusion models). In addition, the role of extracorporeal removal of cytokines using devices such as the CE-marked CytoSorb whole blood adsorber needs to be explored in addition to the leukocyte depleting filter. I plan to undertake training in animal model handling to co-supervise the next Ph.D. candidate with regards to implementing the abovementioned techniques.

8.1.5 Post-MCS-MI

Outcomes post-MCS-MI have improved with improved referral pathways and early initiation of therapy. This study has also led to the creation of an online referral form to assist decision-making prior to initiation of MCS, which places a significant burden on the NHS. Our unit has been included in the EURO-SHOCK trial of evaluating early MCS initiation in patients with cardiogenic shock. Recruitment began in October 2019 and we await the outcomes of this trial to identify patients who would benefit from this. This would invariably increase the number of candidates for long-term VAD/heart transplantation in the near future.

8.1.6 Frailty assessment for transplantation

A major limitation of this thesis is the lack of frailty assessment biomarkers and tools. Whilst frailty is common among heart failure patients, the abstract nature of it often prevents an accurate diagnosis. We, therefore, aim to conduct an observational study on frailty that is currently awaiting ethical approval. This study would include hand-grip strength testing, baseline cognitive assessments, baseline nutritional assessments, and deprivation index to identify the biopsychosocial model of the heart failure patient and evaluate outcomes following heart transplantation. The study was well-received at the CTAG clinical trials meeting in August 2018 and we are aiming to recruit candidates by the end of 2020.

9 Personal Reflection

I was informed by a colleague at a conference that a Ph.D. is a journey and not a destination. This has held through for a novice researcher in me. I recall the interview process for the appointment whereby I was informed that my research portfolio was ‘light’. In the process of completing this thesis, I was fortunate enough to have met pioneers such as Sir Terence English, Dr. Jon Kobashigawa, and Professor John Dark, all of whom have significantly contributed to the field of cardiothoracic organ transplantation. I was invited to chair a session with Dr. Kobashigawa at ISHLT in 2018, 2019 and again in 2020. Professor Al-Attar poignantly recalled how I barely knew what primary graft dysfunction was at the start of my thesis, and now am rubbing shoulders with the ‘experts’.

Throughout this thesis, we had to accommodate changes within the transplantation setting. The advent of OCS usage and DCD implied a change in the definition of ischaemic time. The lack of nationally collected data on frailty meant that we had to use a modified Delphi method to create the GTS and trial it locally. Improved understanding of risk factors for PGD allowed us to implement suitable changes to the standardise out transplantation process locally using the ‘Glasgow Method’. We also noticed an increasing number of patients with STEMI’s with cardiogenic shock referred to our tertiary centre for mechanical circulatory support, which prompted the study in chapter 6.

If I had a chance to start over, I would study the clustering of PGD, to identify if PGD in one organ from a donor is linked to poor function in other organs retrieved from the same donor. I would also link this with PGD in lungs to identify an association. The role of DCD vs DBD should also be further explored to ascertain the role of brainstem death for PGD.

Part of my work has resulted in prospective collection of data for PGD analysis for each centre within the UK using a programmed excel sheet to identify patients in the mild and moderate category without needing circulatory support by means of IABP or advanced MCS as to date, little is known about the significance of mild or moderate PGD without IABP and outcomes.

My experience throughout the past few years has also improved my confidence in public speaking and enhancing my appreciation for critical appraisal of research presentations and publications as I have been invited to review multiple articles with PGD as the subject by peer-reviewed journals.

I, therefore, wish to thank the University of Glasgow for providing me with the support to undertake this thesis. I am currently applying for a National Training Number in Cardiothoracic surgery and hope this serves a good platform for ongoing research in the near future.

10 Appendix

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10.2 Data collection sheet for National PGD study

Patient Number	Age	ODT Recipient ID	ODT Donor ID	D.O.B.	Hospital	Transplant Date	Recepient height (cm	Recipient weight (kg)	Gender	Recipient Aetiology	LVEF (post transplant	LVEF<40%	RA Pressure (1st 24 hours)	TPG	PA mean	PA Systolic	PCWP	Cardiac Outpu	BSA	Cardiac Index	MAP

Figure 10-1 Data Collection Sheet 1

Patient Number	Age	Dopamine (µg/kg/min)	Dobutamine (µg/kg/min)	Milrinone (µg/kg/min)	Adrenaline (µg/kg/min)	Noradrenaline (µg/kg/min)	Inotrope Score	Pre-op Inotropes	VAD	ECMO	Pre-op IABP	Post-op IABP	VAD	ECMO	PGD	Primary Graft YES	Recipient Diabetes Mellit	Recipient Resternot	Recipient Creatinine

Figure 10-2 Data Collection Sheet 2

Patient Number	Age	Donor Age	Donor LVEF%	Sex mismatch?	Donor Height	Donor Weight	Donation after Circulatory Death?	Height Mismatch (cms)	Weight mismatch (kg)	Donor Smoker	Aetiology of death	30 day mortality	6 month mortality	1 year mortality	RIP date	Total Blood	RBC	FFP	Platelet

Figure 10-3 Data Collection Sheet 3

Patient Number	Age	Total Ischaemic time	Cold Ischaemic time	OCS	Time on OCS	Explant	Warm Ischaemic time	Implant Time	Bypass time	Perfusion fluid	Isoprenaline (mcg/kg/hr)	Enoximone (mcg/kg/hr)	Vasopressin (unit/kg/min)	Intraoperative issues	Additional Comments

Figure 10-4 Data Collection Sheet 4

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