The use of biventricular assist devices in end stage chronic heart failure

Sajad Shehab B Med Sci (Hons)

This thesis is presented in fulfilment of the Degree of Doctor of Philosophy

University of Technology Sydney

February 2018

CERTIFICATE OF ORIGINAL AUTHORSHIP

I certify that the work in this thesis has not previously been submitted for a degree nor has it been submitted as part of requirements for a degree except as fully acknowledged within the text.

I also certify that the thesis has been written by me. Any help that I have received in my research work and the preparation of the thesis itself has been acknowledged. In addition, I certify that all information sources and literature used are indicated in the thesis.

This research is supported by an Australian Government Research Training Program Scholarship.

Signature of Student:

Name: Sajad Shehab

Date:

ACKNOWLEDGEMENTS

This thesis would not have been possible without the enormous support and guidance of my supervisors and peers that I have had the privilege to work with. I would like to express my most sincere gratitude to Prof Christopher Hayward, who has guided me throughout this entire PhD. Thank you for your continuous support, encouragement and unwavering mentorship. Your knowledge, experience, expertise and work ethic has inspired me strive to become a doctor of similar caliber. Your enthusiasm, persistence and constructive comments endorsed a sustained version of my thesis all year. Although no amount of words can express the appreciation I have for your efforts, I would still like to say thank you for everything. Of the many things I have gained during these last four years, your friendship is the one I will value the most.

I would also like to express my most heartfelt appreciation for Prof Phillip Newton, who always supported, encouraged and motivated me throughout any hardships I may have experienced. Thank you for your availability, feedback and contribution, for without it I would not be here. You have been a pillar of strength these last four years. Much of the success of my PhD is due to the many skills I have learnt from you during my Honours year. I look forward to honing my skills further and potentially collaborating in the near future.

I would also like to extend my appreciation to Dean Patricia Davidson for it was her who inspired me to pursue this PhD. Her positive and supportive attitude has lifted much of the weight associated with a PhD. Her constant contribution to my manuscripts has been invaluable. Most importantly, thank you for never doubting me and for all your feedback on the thesis.

I would also like to thank Desiree Robson for all her support during my time at St. Vincent's Hospital. Your assistance in the collection of tissue samples has been invaluable. Thank you for welcoming me with such kindness. With you, I always had a friend around the hospital and I will forever cherish you for it.

I would also like to thank Dr Kavitha Muthiah for all her guidance during my first year of PhD. It was an absolute pleasure to work alongside you. Your positive attitude and gentle spirit is a welcome reminder of what doctors should be like. Thank you for all your help, but most of all, thank you for you friendship.

I would also like to thank Dr David Humphreys, the senior research scientist, for all his support, mentorship and guidance in the labs. Thank you for taking the time to teach me various laboratory skills required to complete this thesis. Your contributions, expertise and insight have been invaluable. Working in the lab has been an absolute pleasure and I am sure your teaching will serve me well in my future endeavours.

I would like to thank the staff at St. Vincent's hospital (nurses, clinicians and surgeons). In particular I would like to thank Elyn and the rest of the transplant co-ordinators for all their support with the tissue collection. I would also like to acknowledge all the help from Luija during after hour collections.

A big thank you also to the incredible staff at the Faculty of Health, in particular, I would like to thank A/Prof Sally Inglis for all her support throughout my young academic career. I would also like to thank my wife for her encouragement, support and belief in me. Thank you for always reviewing my work and providing constructive feedback. Last but not least, I would like to thank my family who have supported me these last four years. Thank you for being so understanding and patient with me.

FUNDING SOURCES

The following funding sources are thankfully acknowledged:

- Australian Postgraduate Award Scholarship, University of Technology Sydney
- Health Services and Practice Research Student Development Award, University of Technology Sydney

ANTHOLOGY OF PUBLICATIONS AND PRESENTATIONS ASSOCIATED WITH THIS THESIS

PEER-REVIEWED PUBLICATIONS RELATED TO THIS THESIS

1. **Shehab, S.**, Newton, PJ., Allida, SM., Jansz, PC., & Hayward, CS. (2015) Biventricular mechanical support devices- clinical perspectives. Expert Review of Medical Devices. **(Impact factor 1.784)**
2. **Shehab, S.**, Macdonald, PS., Keogh, AM., Kotlyar, E., Jabbour, A., Robson, D., Newton, PJ., Rao, S., Wang, L., Allida, SM., Connellan, M,, Granger, E., Dhital, K., Spratt, P., Janssz, PC., & Hayward, CS. (2015) Chronic biventricular HVAD support- Case series of right atrial and right ventricular implantation outcomes. Journal of Heart and Lung Transplantation. **(Impact factor 7.509)**
3. **Shehab, S.**, Allida, SM., Robson, D., Newton, PJ., Davidson, PM., Jansz, PC., & Hayward, CS. (In press) Right ventricular failure post LVAD implantation corrected with biventricular support: an in-vitro model. American Society of Artificial Internal Organs. **(Impact factor 2.291)**

CONFERENCE PRESENTATIONS RELATED TO THIS THESIS

1. **Shehab, S.**, Allida, SM., Newton, PJ., Davidson, PM., Macdonald, PS., Jansz, PC., & Hayward, CS. (2016) Right ventricular failure post LVAD implantation corrected with biventricular support: An in-vitro model. Poster Presentation at International Society of Heart and Lung Transplant, 27-30th April, 2016. Washington DC, United States of America
2. **Shehab, S.**, Vickers, DJ., Jain, NS., Newton, PJ., Davidson, PM., Jansz, PC., Macdonald, PS., & Hayward, CS. (2015) In-vitro assessment of the HeartWare HVAD in a biventricular configuration. Poster Presentation at the Cardiac Society of Australia and New Zealand, 11-14th August, 2015. Melbourne, Australia
3. **Shehab, S.**, Macdonald, PS., Keogh, AM., Kotlyar, E., Jabbour, A., Robson, D., Newton, PJ., Rao, S., Wang, L., Allida, SM., Connellan, M,, Granger, E., Dhital, K., Spratt, P., Janssz, PC., & Hayward, CS. (2015) Long-term biventricular HeartWare ventricular assist device support- Case series of right atrial and right ventricular implantation outcomes. Oral presentation at the International Society of Heart and Lung Transplant, 18th April, 2015. Nice, France

AWARDS AND PRIZES RELATED TO THIS THESIS:

2015-2016	UTS HSP Research Student Development Award

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND ACRONYMS USED IN THIS THESIS

Abbreviation	Full term
AHA	American Heart Association
AoP	Aortic pressure
AR	Aortic regurgitation
ASAIO	American Society of Artificial Internal Organs
BMI	Body mass index
BiVAD	Biventricular assist device
BiVF	Biventricular failure
BP	Blood pressure
BTB	Bridge to bridge
BTR	Bridge to recovery
BTT	Bridge to transplant
CDAS	Continuous Data Acquisition System
cfBiVAD	Continuous flow biventricular assist device
cfLVAD	Continuous flow left ventricular assist device
cfTAH	Continuous flow total artificial heart
cfVAD	Continuous flow ventricular assist device
CHF	Chronic heart failure
CO	Cardiac output
CVP	Central venous pressure
DCM	Dilated cardiomyopathy
ECMO	Extracorporeal membrane oxygenation
FDA	Food and Drug Administration
HR	Heart rate
HVAD	HeartWare Ventricular Assist Device
IABP	Intra-aortic balloon pump
ICU	Intensive care unit
INTERMACS	Interagency Registry for Mechanically Assisted Circulatory Support
IQR	Interquartile range
IVAD	Intracorporeal ventricular assist device
LA	Left atrium
LAP	Left atrial pressure
LDH	Lactate dehydrogenase

LoS	Length of stay
LVAD	Left ventricular assist device
LV	Left ventricle
LVP	Left ventricular pressure
MAP	Mean arterial pressure
MCL	Mock circulatory loop
MCSD	Mechanical Circulatory Support Device
MPAP	Mean pulmonary arterial pressure
MR	Mitral regurgitation
MVAD	Miniaturized ventricular assist device
NYHA	New York Heart Association
PA	Pulmonary artery
PAP	Pulmonary artery pressure
PVAD	Paracorporeal ventricular assist device
PVC	Poly-vinyl
PVR	Pulmonary vascular resistance
RAP	Right atrial pressure
RNA	Ribonucleic acid
RV	Right ventricle
RVAD	Right ventricular assist device
RVF	Right ventricular failure
RVP	Right ventricular pressure
SD	Standard deviation
SOFA	Sequential Organ Failure Assessment
SPSS	Statistical Software Package for the Social Sciences
SVR	Systemic vascular resistance
TAH	Total Artificial Heart
TET	Transcutaneous energy transfer
TR	Tricuspid regurgitation
UK	United Kingdom
USA	United States of America
VAD	Ventricular Assist Device
VA-ECLS	Veno-arterial extracorporeal life support
VPA-ECLS	Veno-pulmonary arterial extracorporeal life support

ABSTRACT

Patients with severe biventricular failure are often supported with early generation paracorporeal biventricular assist devices (BiVAD). Compared to durable continuous flow left ventricular assist devices (LVAD), these pulsatile BiVAD systems are decades behind in terms of both design and performance. Therefore the aim of this thesis was to assess the use of two continuous flow LVADs (HeartWare HVAD) for biventricular support. Various aspects of this novel BiVAD system were tested. Pump performance and haemodynamic characteristics were tested using an in-vitro model of the human cardiovascular system, clinical short and long term outcomes were retrospectively reviewed in 14 patients (10 over the course of this thesis), and laboratory assessment was undertaken to evaluate the consequences of BiVAD support on the patients cardiac parameters, particularly on the genetic variations of cardiomyocytes in 7 paired samples (implant vs. explant). Our in-vitro simulations revealed that dual LVAD therapy (BiVAD with two LVADs) was an acceptable form of biventricular support. Interestingly, from a haemodynamic viewpoint, post-LVAD induced right ventricular failure was successfully reversed with delayed RVAD support. In addition, our experiments also revealed successful BiVAD support despite the presence of mitral or tricuspid regurgitation. Our clinical investigations depicted acceptable 1 year survival and high transplantation rates. It also demonstrated an innovative methodology of implanting LVAD in both the right ventricle and right atrium for right ventricular support. The laboratory findings resulted in the development of sound methodology and application of investigatory techniques. However, no differences were found between the up/down regulation of genetic markers pre- and post BiVAD support. Further research in the area is warranted. In conclusion, the use of dual LVAD therapy is an acceptable means of providing durable BiVAD support in patients unsuitable for isolated LVAD therapy.