

# Extracorporeal Normothermic Pancreas Perfusion

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A Study of Normothermic Hemo-Perfusion of the Porcine Pancreas and Kidney

**Operative description with illustrations**

# Abstract

Pancreas and islet transplantation are important treatment options for insulin dependent diabetes. However, one of the main challenges in pancreas and islet transplantation lies in organ (pancreas) preservation. Ischaemic injury post-retrieval causes significant damage the organ function and reduction in islet yield. It was hypothesised that extracorporeal normothermic perfusion of the pancreas would improve graft function post transplantation and pancreatic islet isolation when compared to traditional methods of organ preservation.

The aims and objectives of the project included:

- Conducting a systematic review of the literature in extracorporeal machine perfusion of the pancreas
- Establishing an extracorporeal normothermic perfusion model of the porcine pancreas
- Comparing the addition of kidney to the circuit of extracorporeal pancreas perfusion model

A thorough systematic review of the available literature concluded the potential benefits of machine perfusion in pancreas preservation. Important insight into the experimental setup, perfusion parameters and vital outcome measures was also attained.

A model of normothermic hemo-perfusion of the porcine pancreas with and without addition of the kidney as a dialysis organ was subsequently established. The organs were perfused for 120 minutes with stable perfusion parameters but sub-optimal acid-base environment. Addition of the kidney did not result in significant improvement of the acid-base environment.

# Acknowledgement

I would like to acknowledge the immense support and guidance provided by my supervisors Professor Guy Maddern and Mr Markus Trochsler during my candidature. In addition, I would also like to thank Dr Santosh Olakkengil (Transplant Surgeon, Royal Adelaide Hospital) for his help in the organ retrieval operations, Mr Peter Frantzis (Head of Perfusion, Royal Adelaide Hospital) for his technical input and Dr John Finnie (Senior Veterinary Pathologist, SA Pathology) for histopathological analysis of specimens.

# Contextual Statement

Pancreas or islet cell transplant is the only curative treatment for insulin dependent diabetes mellitus. Traditionally associated with major morbidity and mortality, recent improvements in immunomodulation therapy, graft preservation and surgical techniques have made transplant increasingly popular. However, organ preservation remain a major hurdle to expanding the donor pool and improve graft function.

Machine perfusion as a preservation method has been attempted decades ago with little success and rapidly fell out of favour due to static cold storage, which is simple and costs less. However, with increasing organ demand and improving technology in pump and monitoring equipment, machine perfusion is gaining attention once again.

Machine perfusion is well established in other organs (heart, lung and kidney) but remain relatively novel in the pancreas. In order to establish a model of extracorporeal normothermic perfusion of the pancreas, a thorough literature review was crucial to obtain insight into previous attempts, perfusion parameters, outcome measures and encountered complications.

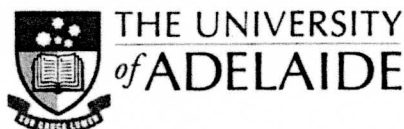
The systematic review titled “Extracorporeal Machine Perfusion of the Pancreas: Technical Aspects and Its Clinical Implications – A Systematic Review of Experimental Models” forms the first part of this thesis. It was published in *Transplantation Reviews* on 19<sup>th</sup> June 2015.

Subsequently, work began on establishing the model of extracorporeal normothermic perfusion of the pancreas and investigating the role of addition of the kidney as a dialysis unit. The process of establishing the model is detailed in the manuscript “A Study of Normothermic Hemo-Perfusion of the Porcine Pancreas and Kidney” which forms the other part of the thesis. The study was accepted for publication in *Artificial Organs* on 21<sup>st</sup> March 2016. Attached in the thesis is the acceptance letter and author proof of the accepted article, expected to appear in the July 2017 edition of the journal.

Based on the examiners’ and supervisor’s reports received on 6 June 2016, grammatical and syntax errors were corrected. An additional segment was also added to the thesis, titled “Operative description and illustrations” to further expand the operative details of organ retrieval as suggested.

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# Certification of Thesis for Examination

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Please note that the generic term "thesis" is used to describe the submission for the degrees named on this form.

### To be Completed by Principal Supervisor

(Please tick the appropriate box)

Student Name	Kean Guan Kuan
Name of Principal Supervisor	Guy Maddern
School/Discipline	Medicine/ Surgery
Program	Masters of Philosophy (Surgery)
E-mail address (for notification of examination outcome)	The student's University e-mail address will be used unless a preferred e-mail address is provided below.  kuankeanguan@gmail.com

Master of Philosophy/Master of Clinical Science students, please indicate your stream:

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I have seen and read the final draft of the above candidate's thesis and, in accordance with the requirement of the Research Student Handbook "Appendix "Responsibilities", certify that:

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Example - A Master of Philosophy by mixed research and coursework, or a combined PhD/Master of Psychology

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Principal Supervisor's name

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P.A. COWLED

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Date

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In accordance with the Research Student Handbook "Certification of Thesis for Examination" and "Appendix 2 Responsibilities of the Supervisors 5.6", supervisors are required to comment on the content and drafts of the thesis and, at the time of submission, recommend that the thesis, prima facie, is worthy of examination both in terms of its content and its presentation relative to the Academic Program Rules for the degree.

In compliance with this requirement, supervisors are required to certify in writing that they have read their student's completed thesis and are satisfied with the content and technical presentation and that the thesis, therefore, is worthy of examination. Technical presentation may include appropriate footnoting, referencing, arrangement of chapters, presentation of charts and figures, appropriate notation, absence of obvious grammatical and typographical errors, etc. The Research Education and Development Committee takes the view that the thesis belongs to the student who ultimately has responsibility for the intellectual content. Note, however, that submission of a thesis which is poorly presented or not of the standard required for the degree will not be permitted. Where a supervisor deems this to be the case, he or she must recommend that the thesis is not acceptable for examination in its current form and prepare a statement outlining the reasons why this is the case. See also Dispute Resolution below.

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The attached certification must be submitted when a student submits his/her thesis. The certification must be completed and signed by the Head of School or Discipline /Postgraduate Coordinator and the Principal supervisor. The Principal supervisor, in consultation with the other supervisors, shall sign the certification on behalf of all the supervisors.

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A student who has lapsed in candidature, for not more than twelve months, may subsequently submit the completed thesis for examination provided that the thesis has not departed from the field of study being pursued before the candidature expired and provided that the School or Discipline concerned is satisfied that the thesis is, prima facie, worthy of examination both in terms of its content and its technical presentation.

By certifying/endorsing that the thesis is worthy of examination the Principal Supervisor and School/Discipline, in the case of a lapsed candidature, are also certifying/endorsing that the completed thesis has not departed from the field of study which was being pursued prior to the candidature lapse date.

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### Dispute Resolution

In the event of a dispute, for example when a student does not agree with the supervisor's adverse recommendation about the readiness of the thesis for examination, it is expected that the dispute will be dealt with at the local level by the Head of School/Discipline or Postgraduate Coordinator in the first instance. If the dispute cannot be resolved at the local level, the matter shall be referred to the Dean of Graduate Studies, either by the Discipline or the student concerned. All relevant documents must be forwarded to the Dean at the same time. The Dean will deal with the matter in consultation with the Convener of the appropriate Faculty Higher Degrees Committee and the Head of School or Discipline/Postgraduate Coordinator concerned, if required.

If the Dean's decision overrides that of the School or Discipline, the matter shall then be referred to the Research Education and Development Committee for final resolution. Depending on the circumstances surrounding each case, the Committee will determine whether or not examiners should be informed of the dispute and what information should be disclosed to examiners. At all times, the independence of examiners must be preserved.

It is the responsibility of the student to ensure that the certification is appropriately completed, signed and submitted, together with three printed and one digital copies of the thesis, to the Adelaide Graduate Centre.

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### Further Information

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# Thesis Declaration

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree. I give consent to this copy of my thesis when deposited in the University Library, being made available for loan and photocopying, subject to the provisions of the Copyright Act 1968. The author acknowledges that copyright of published works contained within this thesis resides with the copyright holder(s) of those works. I also give permission for the digital version of my thesis to be made available on the web, via the University's digital research repository, the Library Search and also through web search engines, unless permission has been granted by the University to restrict access for a period of time.

Yours sincerely,

Dr Kean Guan Kuan

Student ID: 1660895

Program: Masters of Philosophy (Surgery)