CLINICAL ANALYSIS OF LIVER FUNCTION

Development of a Novel Method for the Detection of Portosystemic Shunts

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Abstract

A portosystemic shunt (PSS) is defined as a congenital or acquired abnormal blood vessel that redirects blood around the liver without being filtered through hepatic parenchyma. PSS are thought to contribute to the distribution of isolated secondary metastases beyond the liver in 1.7 - 7.2% of all colorectal cancer patients without cirrhosis of the liver. No standardised clinical test for PSS yet exists and subsequently, the majority of PSS cases are detected incidentally through radiological means. To better identify PSS, a simple standardised clinical test for its detection is needed. The aim of this thesis was to develop a cost effective, non-invasive technique that can detect and measure PSS in a healthy liver model.

Methods

An artificial 8mm diameter PSS was created between the portal vein and the inferior vena in a pig model with a catheter inserted in the confluence of the hepatic veins for sample collection. A spectrum of compounds including indocyanine green (ICG), ^{13}C-methacetin, sorbitol and lignocaine, were injected into the portal system. To analyse the pharmacokinetic nature of the shunt and liver, Evans blue dye and ^{14}C-sucrose were also administered. ICG was measured via a LiMON® spectrometer attached to the pig's snout, while levels of the other indicators were measured by serial blood and breath sample collection over a 40 minute period. The process was repeated with the PSS clamped as the control.

Results

Of the administered compounds, only ICG had the potential to clearly identify and quantify the shunt due to the rapid serial sampling via the LiMON®. Further simulations using ICG demonstrated that the shunted fraction can be calculated using the transit times, including mean residence time, lag time and pharmacokinetic modelling.

Conclusion

Although this study has not yet provided a concise method for PSS detection available for immediate clinical use, it does provide a large foundation for further exploration into a quantitative technique. A future PSS test would allow an added risk assessment for secondary cancer, and consequently individual cancer therapy may be better targeted for individual patient care.

Thesis Declaration

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Preface

This thesis is the first stage toward portosystemic shunt (PSS) detection. Chapter 1 explores the range of PSS diagnosed in patients without liver disease and the associated method that was used for diagnosis, while also underlying the values for a need of a standardised clinical test. Chapter 2 replicates PSS by describing a surgical method to mimic a large PSS within a swine model. With an artificial PSS developed, chapter 3 describes the different practical dynamic techniques that may be plausible for PSS detection, with some viable techniques to be explored further. Chapter 4 studies the techniques chosen from chapter 3 in the PSS swine model and determines which technique is best suited for PSS identification and quantification. Chapter 5 reviews how the best technique from chapter 4 can quantify the shunt and what possible limits the shunt itself has with this technique. Finally, chapter 6 summarises this technique with a future outlook as to what PSS detection implications would have a clinical setting. This chapter also outlines the limitations and complications with the previous methods and what steps were used to overcome these problems. References and additional material can be found in chapters 7 and 8.

Acknowledgements

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Table of Contents

List of Tables, Figures and Equations

CHAPTER 1 Introduction

CHAPTER 2 Development of a Portosystemic Shunt in a Swine Model

CHAPTER 5 Determining Portosystemic Shunt Fractions

List of Abbreviations

Abbreviation	Definition
^{13}C-	[13]Carbon labelled
^{14}C-	[14]Carbon labelled
1-qQ	Difference of flow rate fraction
^{3}H-	3Hydrogen labelled
AUC	Area under curve
CF_4	Tetrafluromethane
CO^2	Carbon dioxide
CT	Computed tomography
CTA	Computer tomography angiography
CTC	Circulating tumour cells
CYP1A2	Cytochrome 1A2
D1	Drug administration site into the portal vein with the shunt closed (normal control).
D2	Drug administration site into the portal vein above the open shunt flowing into the liver only (control).
D3	Drug administration site directly into the start of the shunt.
D4	Drug administration site into the portal vein below the shunt.

E_{ICG}	Extraction of Indocyanine green
$E_{sorbitol}$	Extraction of sorbitol
f(t)	Inverse Gaussian distribution function
GLUTs	Glucose transporter
ICG	Indocyanine green dye
R15	Plasma disappearance rate at 15 minutes
IRMS	Isotope-ratio mass spectrometry
IVC	Inferior vena cava
MATEs	Mammalian multidrug and toxic compound extrusion
MEGX	Monoethylglycinexylidide
MRA	Magnetic resonance angiography
MRI	Magnetic resonance image
MRT	Mean residence time
MTT	Mean transit time
N2O	Nitrogen oxide
NTCP	Sodium-dependent taurocholate co-transporting protein
OATPs	Organic anion transporting polypeptides
OATs	Organic anion transporter

OCTs	Polyspecific organic cation transporters
Ost α and β	Organic solute or steroid transporter alpha and beta
PSS	Portosystemic shunt
PTFE	Polytetrafluroethylene
PV	Portal vein
Q	Flow rate
QC	Quality control
qQ	Fraction of flow
R^2	Correlation coefficient
RD	Relative dispersion
SD	Standard deviation
TIPS	Transjugular intrahepatic portosystemic shunt
TNM	Tumour node metastases staging system
TQEH	The Queen Elizabeth Hospital
TTD	Transit time
UV	Ultraviolet
VOC	Volatile organic compound

Publications, Presentations and Competitions

Publications, papers submitted for publication and conference presentations pertaining to results relating to the thesis are listed below. Abstracts, manuscripts and presentations can be found in Chapter 8: Appendices.

Published Abstracts and Conference Presentations

Matthews, T., Li , P., Hamilton, M., Trochsler, M., Butler, R., Roberts, M., and Maddern, G. J., *Clinical analysis of liver function: Can portosystemic shunts be measured?* , in *The Australiasian Surgical Research Society Meeting*. 2010, ANZ Journal of Surgery: Adelaide, South Australia. p. 11. (Appendix C)

Matthews, T., Li , P., Hamilton, M., Trochsler, M., Butler, R., Roberts, M., and Maddern, G., *Clinical analysis of liver function: Can portosystemic shunts be measured?*, in *The Australasian Surgical Research Society Meeting*. 2011, ANZ Journal of Surgery: Adelaide, South Australia. p. 8. (Appendix D)

Conference Presentations

Matthews, T., Li , P., Hamilton, M., Trochsler, M., Butler, R., Roberts, M., and Maddern, G. J., *Clinical analysis of liver function: Can portosystemic shunts be measured?* , in *The Queen Elizabeth Hospital Research Day*. 2011, The Hospital Research Foundation: Woodville South, South Australia. (Appendix E)

Matthews, T., Li , P., Hamilton, M., Trochsler, M., Butler, R., Roberts, M., and Maddern, G. J., *A novel non-invasive technique for the detection of portosystemic shunts*, in *The Queen Elizabeth Hospital Research Day*. 2012, The Hospital Research Foundation: Woodville South, South Australia. (Appendix F)

Competitions

Matthews, T. *Find that Shunt!* Three minute thesis competition. 2012. University of Adelaide, South Australia. (Appendix G)

Submitted Manuscripts

Matthews T, Trochsler M, Maddern G. Review of Incidentally diagnosed congenital and acquired portosystemic shunts in patients without cirrhotic liver disease: *a need for a standardised clinical test.* Submitted to British Journal of Surgery (Appendix H)

Matthews T, Trochsler M, Hamilton M, Maddern G. Creation of a portocaval shunt in pigs, with a method to estimating shunt fractions. Submitted to Journal of Surgical Research (Appendix I)

Matthews T, Barry S, Zacharakis B, Maddern G. Detrimental effect of isoflurane in gas chromatography. Submitted to Journal of Breath Research (Appendix J)

Matthews T, Kuchel T, Maddern G. Safe and inexpensive method for breath sampling and a technique for continuous intravenous anaesthesia in pigs. Submitted to Journal of Breath Research (Appendix K)

Matthews T, Weiss M, Li P, Trochsler M, Hamilton M, Roberts M, Maddern G. Portosystemic shunt fraction determination by pharmacokinetic modelling. Intended for publication (Appendix L)