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

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.

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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

The author acknowledges the involvement of those who assisted with this study. Mr Mark Hamilton, Dr Nadia Blest and Dr Joe Dawson assisted in the surgical predication of a PSS. Dr Peng Li assisted in sample collection and analysis. Professor Simon Barry, Ms Betty Zacharakis and Ms Esther Burt assisted in breath sample analysis. Dr Timothy Kuchel and Mr Matthew Smith assisted in animal anaesthesia. Professor Guy Maddern supervised the entirety of this study. A special acknowledgment to Mr Markus Trochsler, who assisted in all aspects of this study.
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<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{13}$C-</td>
<td>[13]Carbon labelled</td>
</tr>
<tr>
<td>$^{14}$C-</td>
<td>[14]Carbon labelled</td>
</tr>
<tr>
<td>1-qQ</td>
<td>Difference of flow rate fraction</td>
</tr>
<tr>
<td>$^{3}$H-</td>
<td>3Hydrogen labelled</td>
</tr>
<tr>
<td>AUC</td>
<td>Area under curve</td>
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<tr>
<td>CF$_{4}$</td>
<td>Tetrafluromethane</td>
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<tr>
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<td>CTA</td>
<td>Computer tomography angiography</td>
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<tr>
<td>CTC</td>
<td>Circulating tumour cells</td>
</tr>
<tr>
<td>CYP1A2</td>
<td>Cytochrome 1A2</td>
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<tr>
<td>D1</td>
<td>Drug administration site into the portal vein with the shunt closed (normal control).</td>
</tr>
<tr>
<td>D2</td>
<td>Drug administration site into the portal vein above the open shunt flowing into the liver only (control).</td>
</tr>
<tr>
<td>D3</td>
<td>Drug administration site directly into the start of the shunt.</td>
</tr>
<tr>
<td>D4</td>
<td>Drug administration site into the portal vein below the shunt.</td>
</tr>
<tr>
<td>Symbol</td>
<td>Description</td>
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<tr>
<td>--------</td>
<td>-------------</td>
</tr>
<tr>
<td>$E_{\text{ICG}}$</td>
<td>Extraction of Indocyanine green</td>
</tr>
<tr>
<td>$E_{\text{sorbitol}}$</td>
<td>Extraction of sorbitol</td>
</tr>
<tr>
<td>$f(t)$</td>
<td>Inverse Gaussian distribution function</td>
</tr>
<tr>
<td>GLUTs</td>
<td>Glucose transporter</td>
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<td>ICG</td>
<td>Indocyanine green dye</td>
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<tr>
<td>R15</td>
<td>Plasma disappearance rate at 15 minutes</td>
</tr>
<tr>
<td>IRMS</td>
<td>Isotope-ratio mass spectrometry</td>
</tr>
<tr>
<td>IVC</td>
<td>Inferior vena cava</td>
</tr>
<tr>
<td>MATEs</td>
<td>Mammalian multidrug and toxic compound extrusion</td>
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<td>MEGX</td>
<td>Monoethylglycinexylidide</td>
</tr>
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<td>MRA</td>
<td>Magnetic resonance angiography</td>
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<td>MRT</td>
<td>Mean residence time</td>
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<td>N2O</td>
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<td>NTCP</td>
<td>Sodium-dependent taurocholate co-transporting protein</td>
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<td>OCTs</td>
<td>Polyspecific organic cation transporters</td>
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<td>Ost α and β</td>
<td>Organic solute or steroid transporter alpha and beta</td>
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<td>PSS</td>
<td>Portosystemic shunt</td>
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<td>PTFE</td>
<td>Polytetrafluoroethylene</td>
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<td>PV</td>
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<tr>
<td>$R^2$</td>
<td>Correlation coefficient</td>
</tr>
<tr>
<td>RD</td>
<td>Relative dispersion</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>TIPS</td>
<td>Transjugular intrahepatic portosystemic shunt</td>
</tr>
<tr>
<td>TNM</td>
<td>Tumour node metastases staging system</td>
</tr>
<tr>
<td>TQEH</td>
<td>The Queen Elizabeth Hospital</td>
</tr>
<tr>
<td>TTD</td>
<td>Transit time</td>
</tr>
<tr>
<td>UV</td>
<td>Ultraviolet</td>
</tr>
<tr>
<td>VOC</td>
<td>Volatile organic compound</td>
</tr>
</tbody>
</table>
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


Conference Presentations


Competitions

Submitted Manuscripts


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, 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)