MODELLING AND SIMULATION OF HEPATIC ISCHAEMIA-REFERFUSION INJURY, - MECHANICS OF FLOW REINSTATEMENT ON MICROCIRCULATION AFTER TRANSPLANTATION

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BACKGROUND

Liver transplantation is the surgical replacement of a diseased liver with a healthy liver due to end-stage liver disease, caused by a number of diseases such as viral, cirrhosis and biliary giving rise *inter-alia* to reduced liver function, fatigue and jaundice. Further, liver cirrhosis is a major global cause of morbidity and mortality.

The effect of removal transport and transplantation occurs over the course of a number of hours. During this time, the liver deteriorates and its ability to function normally after transplantation is influenced by this process. Additionally, liver sectioning prior to detachment necessitates a number of procedures that limit full blood and bile flow through the organ and this must be balanced to reduce hepato-cellular damage.

Previous research [1-3] has indicated that heat shock preconditioning encourages the release of heat shock proteins and warm ischaemia-reperfusion injury in many organs as shown in Figures 1 and 2.

EXPERIMENTAL AND COMPUTATIONAL PROGRAMME

In the course of a combined experimental and computational programme to study the effect and resolution of hepatic ischaemia-reperfusion injury, elementary modelling of mechanical events has been undertaken to provide the platform for assessment of this complex organ.

In this case the model has been adapted from a cell growth/behaviour program specially developed for soft tissue and having particular relevance to the vascular system, its cell types and morphologies, [4].

This adaptation is the subject of this paper that describes the evaluations and methodologies necessary to consider the mechanical responses that occur in a freshly reperfused liver and in particular the possibility of micro circulatory perfusion failure. (The authors acknowledge other factors that cause ischaemia-reperfusion injury).

Careful analysis of the results is yielding surprising facts that may help to establish revised transport/delivery systems to better accommodate the length of transplant operations. Further, any improvement in the post-operative micro-circulation of the liver will increase the blood perfusion in the liver and enhance the phagocytosic capability of Kupffer cells.

Currently, mathematical models seek to solve using the stirred tank models for diffusion and mass transport with an additional Michaelis-Menton kinetic model where relevant. These have limitations, and they have been replaced in this case by the use of a numerical analysis, (finite volume method), of the initial and boundary conditions and the mass transport through the capillary system. In this case it was determined that the model could yield appropriate indications for tissue metabolism based on the availability of nutrient and oxygen at the interface of the cells. The model has been used as a basis for further data collection to enable additional validation.

The model is able to mimic the flow impulse on reconnection and the stress derivations necessary to overcome any endothelial adhesion. The model incorporates heat transfer equations to permit assessment at different temperatures allowing for the warming and heating cycles through pre-operative procedures. Work on this aspect is ongoing but believed to be beneficial in the assessment of the effect of heat shock protein availability, as mentioned above.

Sensitivity analysis is being conducted on the data which will yield focal centres for future work. Cross-linked solutions may therefore be derived easily due to the incorporation of heat transfer, flow rates, and stress strain analysis with metabolic and oxygen/nutrient uptake in one complete model.

THE FINITE VOLUME METHOD

The Finite Volume Method was originally developed as a special finite-difference formulation, [5]. The numerical algorithm comprises formal integration of the governing equations over all the (finite) control volumes of the solution domain. Discretisation involves the substitution of a variety of finite-difference-type approximations for the terms in the integrated equation representing flow processes such as convection, diffusion and sources. This converts the integral equations into a system of algebraic equations. Solution of the algebraic equations utilises a fully implicit time step scheme and an iterative solver using a standard Tri-Diagonal Matrix Algorithm, (TDMA). The TDMA iterative scheme enabled satisfaction of non-linearities prior to incrementing for subsequent time steps. The model was tested for convergence by assessing the change over the whole domain whilst maintaining correct solution to discrete equations relevant for each volume. The reference grid was a rectangular grid of Cartesian co-ordinates and required simulation to an accuracy of 0.01%.

1 Seifalian AM, Mallett SV, Rolles K, Davidson BR., 1997, The hepatic microcirculation during human liver transplantation. Br J Surg 84:1391-1395.

2 Seifalian AM, Piasecki C, Agarwal A, Davidson BR., 1999, The effect of graded steatosis on flow in the hepatic parenchymal microcirculation. Transplantation 68:780-784.

3 Koti, R S. Yang, W Dashwood MR. Davidson,BR. and Seifalian A M., 2001, The Effect of Ischemic Preconditioning on Hepatic Microcirculation and Function in a Rat Model of Ischemia Reperfusion Injury, Proceedings of the British Society of Gastroenterology Annual Meeting, March 2001, UK. [Gut 2001; 48 (Suppl I): A23]

4 Kirk, C.S., Horrocks, M., Mileham, A.R., & Chaudhuri, J.B., 2002, *Modelling and Simulation of Vascular Tissue Engineering using the Finite Volume Method,* Proceedings of microCAD2002, (H), International Computer Science Conference, University of Miskolc

5 Kirk, C.S., Tisza M., Balogh, A., and Mileham, A.R., 1999, *Comparison of Numerical Methods; The Finite Element Method and the Finite Volume Method,* Plenary Session, International Regional DAAAM-CEEPUS Workshop on Intelligent Machines and Technologies in the 21st Century, University of Miskolc, Hungary, 27 May 1999

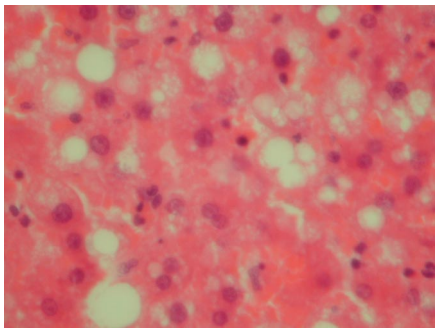

Figure 1: Ischaemic preconditioning

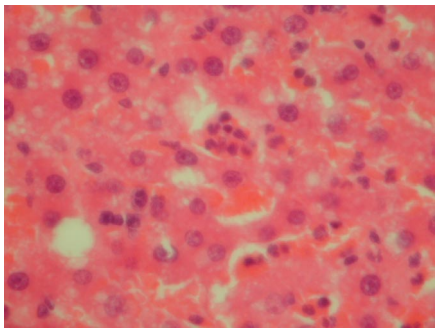

Figure 2: Ischaemic reperfusion