COMPUTATIONAL MODEL FOR IMPROVING OXYGEN TRANSPORT WITHIN BIOARTIFICIAL LIVER DEVICES

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Purpose of Study: In vivo, the transport of nutrients through the interior regions of the liver is aided by sinusoidal networks. These networks serve as transport channels for convective flow, and make it possible for diffusive nutrient transport through the cellular space and extra cellular matrix (ECM) to occur more efficiently. In the case of bioartificial liver devices (BALs), the diffusive transport of substances from the nutrient supply source to the cells serves as a key design limitation. This is particularly true for the nutrient oxygen (O_2) since the major parenchymal cell of the liver, hepatocytes, require specific 0_2 concentration levels to maintain proper viability and function. As a result, improving O_2 transport within three dimensional BAL designs is still an important engineering challenge.

Methods. In our previous work, enhancement of O_2 transport within a BAL configuration was achieved by creating a network of O_2 transport microchannels within the ECM. The enhanced configuration doubled the O_2 transport distance and significantly improved hepatocyte viability and function results over the control. One strength of this enhancement technique was that it can be adapted to any BAL configuration that incorporates a gel ECM. Because of the variety of BAL designs in existence, empirically evaluating how our O_2 enhancement technique improves each of them would be prohibitive in terms of time and capital. As a first line approach, we have developed and tested a predictive model for evaluating O_2 transport as a function of time and the BAL's geometry, components (e.g., cell density), and boundary conditions.

Results. The results demonstrate that the model's predictions of O_2 transport compare well with experimental results for hollow fiber and flat plate BAL configurations. The model is then extended to a hypothetical system of encapsulated cell aggregates to predict the relationship between the aggregate diameter that can be safely supported and surface convection conditions.

IN VIVO BIOSTABILITY STUDY ON A POLYARYLETHERKETONE BIOMATERIAL

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This work was undertaken in order to investigate the long-term biostability of PEEK-OPTIMA® biomaterial in vivo. Developed specifically for the implant market, this material is a high strength thermoplastic polymer, which can be sterilised by all conventional methods including gamma radiation. Devices are made by injection moulding and/or machining from extruded stock. PEEK-OPTIMA polymer is already being used to manufacture implants in Europe and the US.

Six PEEK-OPTIMA polymer samples, in the form of 10mm long, 3mm diameter rods (sterilised and conditioned to simulate 10-year real time ageing) machined from injection moulded plaques were implanted into the paravertabral muscles of each of 3 rabbits (total of 18 implanted pieces) for a period of one year. Excised samples were either fixed for histopathological examination or sterilised for chemical analysis.

Chemical analysis of the excised material was by gas chromatography using headspace and solvent extraction methods to examine volatile and medium volatile substances. Medium volatile substances were identified using GC with mass spectrometric coupling. Infrared spectroscopy and gel permeation chromatography (GPC) methods were used to investigate any changes in the composition and molecular weight of the polymer occurring as a result of the long-term in vivo implantation.

The response to the implanted material in all sites was of minimal, mild or moderate fibrosis degree. There were no muscle degradations, no necroses, no marked inflammatory responses or any other significant changes (no negative response to the implant). Analysis shows no evidence of any change in polymer molecular composition or molecular weight, occurring as a result of implantation. The results of these tests strongly support the use of this material for long-term implantation.

BOVINE PERICARDIUM (BP): EFFECT OF LYOPHILIZATION ON MECHANICAL PROPERTIES, SHRINKAGE TEMPERATURE AND CYTOTOXICITY

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A) PURPOSE: Lyophilization of BP in patches or manufactured valves may possibly provide improved storage, sterilization, biocompatibility and handling. This paper describes the appraisal of some consequences of lyophilization on BP.

B) METHODS: To study effect on mechanical properties and shrinkage temperatures (ST) five groups of BP, 50 samples each, were evaluated. Groups were: fresh BP (p), BP lyophilized and rehydrated (p-l), BP treated with glutaraldehyde/formaldehyde (GA/FA) (p-g), BP treated with GA/FA, lyophilized and rehydrated (p-g-l), and fresh BP lyophilized, rehydrated, treated with GA/FA (p-l-g). We have measured ultimate tensile strength (UTS), elasticity module (EM) (ASTM D638 norms), and ST. We compared cytotoxicity (CT) of groups (p-g) and (p-g-l) following ISO10993 Standards. Results are shown below:

C) SUMMARIZED RESULTS:

SHRINKAGE AND MECHANICAL PROPERTIES

Group		UTS (kgf/mm²)	EM (kgf/mm²)	ST (°C)
1	p	1.75±0.68	5.05±1.93	72.93±7.32
2	p-l	1.96±0.89	4.35±1.91	74.64±8.46
3	p-g	2.84±1.32	7.58±3.05	86.08±6.67
4	p-g-l	3.25±1.47	6.18±3.13	87.56±3.17
5	p-l-g	3.02±1.15	6.81±2.40	88.23±3.21

Statistically non-significant: 1 x 2, and 3 x 4 x 5 ($p<0.05$)

CYTOTOXICITY: (Colonies count expressed in % of negative control)

Extract concentration (%)	p-g colonies	p-g-l colonies
100	0	0
50	0	36.54±6.56
25	0	82.91±6.03
12.5	0	93.59±4.58
6.25	24.15±2.52	98.93±9.01

D) CONCLUSIONS: Bovine pericardium can be lyophilized before and after FA/GA treatment without changing its UTS, EM and ST. Lyophilization decreases cytotoxicity after GA/FA treatment.

A NOVEL HEMOGLOBIN—ADENOSINE—GLUTATHIONE BASED RED CELL SUBSTITUTE: ITS EFFECTS ON HUMAN BRAIN CAPILLARY ENDOTHELIAL CELLS

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With the current problems in blood availability and safety, the potential role of red cell substitutes has become critical. Current products under testing, however, have met with limited success. The problems revolve around blood vessel constriction and the pro-oxidant and pro-inflammatory properties of hemoglobin (Hb). Toward a resolution of these problems, we have developed a novel Hb modification procedure to formulate a more effective and non-toxic product. This red cell substitute is composed of purified Hb, crosslinked intramolecularly with *o*-ATP and intermolecularly with *o*-adenosine, and conjugated with reduced glutathione (GSH). In a recent study, we investigated the direct neurotoxic potential of our red cell substitute using cultures of human brain neurons and astrocytes [*ASAIO J* 46(2)231(2000)]. While the obtained data demonstrated a lack of neurotoxicity, this research failed to answer a question about the possible indirect neurotoxic effect of this product via the activation of the brain capillary endothelial cells (EC). Therefore, this study compared the effects of our novel red cell substitute and those of unmodified (U) Hb, using plasma as a control, on human normal and GSH depleted brain capillary EC. Confluent normal and GSH depleted EC grown on 0.4 μm porous cell culture devices, coverslips and cell culture plates, were incubated overnight with 0.4 mM Hb solutions or plasma. After treatment, cells grown on porous devices were tested for permeability by determining the diffusion rate of ^{125}I-albumin across the monolayer. EC grown on coverslips were evaluated for early and advanced apoptosis using Annexin V-FITC and propidium iodide fluorescence probes, respectively, and for expression of the adhesion molecule ICAM-1. The pro-oxidant effect of Hbs on EC grown in cell culture plates was examined by measurement of intracellular GSH, conjugated dienes, TBAR-S and 8-isoprostane. Results indicate that the UHb increased EC permeability and shrinkage, initiates oxidative stress, apoptosis and inflammatory responses. These effects are aggravated in GSH depleted cells ($p<0.01$). Contrarily, our red cell substitute did not appear to induce apoptosis and oxidative stress nor to increase inflammatory reactions of normal and GSH depleted EC. The diffusion rate of ^{125}I-albumin was similar to that of the control in both tested groups. The effect of this red cell substitute can be linked with the type of modification procedure that lowers Hb pro-oxidant potential and the anti-inflammatory and cytoprotective properties of adenosine.

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