A PHYSIOLOGICALLY-BASED CARDIOVASCULAR MODEL FOR DESCRIBING THE CAPILLARY LEAK ASSOCIATED WITH CARDIOPULMONARY BYPASS.

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Abstract: A compartmental model was modified to describe macro-movement of fluid between the capillaries and the interstitial space according to the Starling Equation.

$$J_v = K_f[(P_c - P_i) - \sigma(\pi_c - \pi_i)] \qquad (1)$$

Where σ, the reflection coefficient in Eq.1 is a measure of the permeability of the capillaries to the proteins responsible for generating the oncotic pressure. This involved continuously updating the oncotic pressures with regard to the flows in and out of each compartment. It was therefore possible to model the effects of administering fluids with different oncotic pressures on filtration.
Clinical HR, MAP, CO, fluid balance and change in circulating volume from nominal data in the time period following CPB were used to identify the best-fit contractility, systemic vascular resistance and reflection coefficient parameters in the model over the same period using a least-squares fitting method.

Introduction

Starling's hypothesis states that the fluid movement due to filtration across a capillary wall is dependent on the balance between the hydrostatic pressure gradient and the oncotic pressure gradient across the capillary [1]. During and after Cardio-pulmonary bypass (CPB) however, this balance is disrupted and there may be a net 'capillary leak' into the interstitial compartment. Capillary leak is one of the symptoms associated with sepsis, which affects a significant proportion of CPB patients. Sepsis is also characterised by increased heart rate and cardiac output, as well as persistent hypotension and hypoperfusion [2].

There are several published circulatory models of various levels of complexity, with the ability to simulate different conditions. However, only a few of these deal with specifically with capillary leak in a physiological sense. The objective here was to develop a physiologically based model, capable of simulating the key haemodynamic variables used by medical staff during and after CPB.

Model development combined ideas and equations from two previous models by Randall [3] and Xie *et al* [4]. Randall's model is a lumped parameter, steady flow model representing commonly measured haemodynamic parameters (see Figure 1). It uses simple elements to describe parts of the circulation. Capacitors represent the veins and arteries, a steady flow pump represents the left and right ventricles and variable resistors represent the systemic and pulmonary vascular resistance. Subscript 'p' denotes pulmonary, 's' systemic, 'a' arterial and 'v' venous. CO_l and CO_r are the left and right cardiac outputs respectively, described by a non-linear function '*f*'.

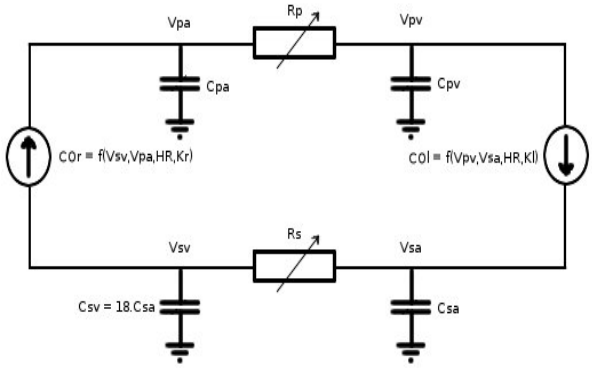

Figure 1: The electrical analogue circuit of the circulatory model where frequency, voltage current and charge are analogues of heart rate, blood pressure, flow rate and volume respectively.

Xie and coworkers [4] developed a compartmental microcirculation model, which describes the transport and distribution of fluid and

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plasma proteins according to physiologically-based, mathematical equations (Figure 2).

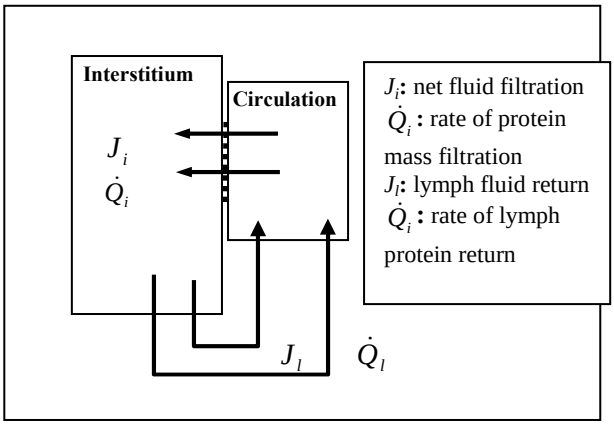

Figure 2: A Schematic of the fluid and protein exchange model by Xie et al [4].

The new model has an additional circulatory compartment, the capillaries, to act as the site of exchange between the circulation and the interstitium (Figure 3). The capillary pressure in this new compartment takes the place of the 'circulation' pressure in Xie's model. Each compartment has a continuously updated oncotic pressure. It was assumed that all capillary leak took place in the systemic circulation. All compartments were assumed to be well mixed, i.e., all properties were considered uniform throughout each compartment. As in Xie's model, at steady state, the transcapillary exchange rate of protein is equal to its removal rate via the lymph.

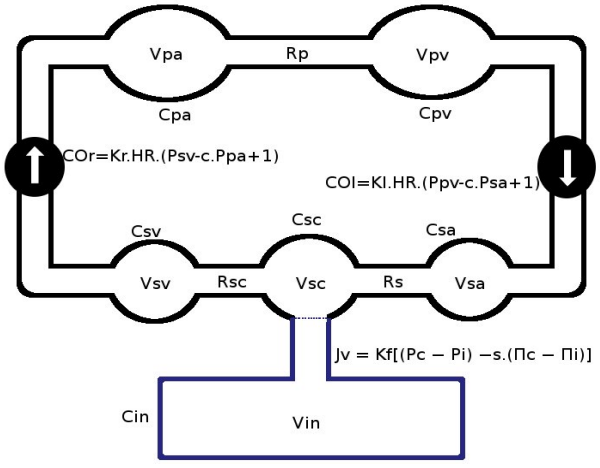

Figure 3: A Schematic diagram of the modified cardiovascular model

Simulations

Grocott and Mythen [5] state that during sepsis induced capillary leak, **σ** decreases in the Starling equation, due to damage to the capillary endothelial structure through the inflammatory process. In the simulation depicted in Figure 4, **σ** was reduced by 50%. This caused a net fluid shift from the circulation to the interstitium of 0.5L. This also caused a drop in CO from 6.2 to 4.2 L/min and MAP fell from 95 to 61 mmHg, which meets the criterion for shock.

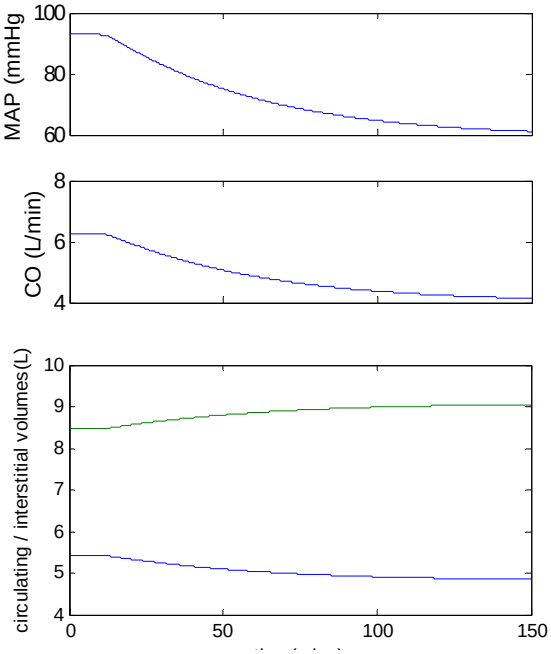

Figure 4: A Simulation run showing progression of capillary leak. Interstitial volume is the higher line on the bottom graph. Circulating volume is below.

To simulate the management of this condition, two iso-oncotic fluid boluses of 250ml were added to the venous compartment, to mimic aggressive fluid therapy. Figure 5 shows that most of the added fluid is lost to the interstitial compartment within an hour. However, when the system reaches steady state, the CO and MAP are higher than in the untreated case.

The difference is clear when hyper-oncotic fluid is used (Figure 6). In this case, two boluses of fluid with double the normal plasma oncotic pressure were added. An hour after the end of the infusion, the majority of the added fluid had been retained.

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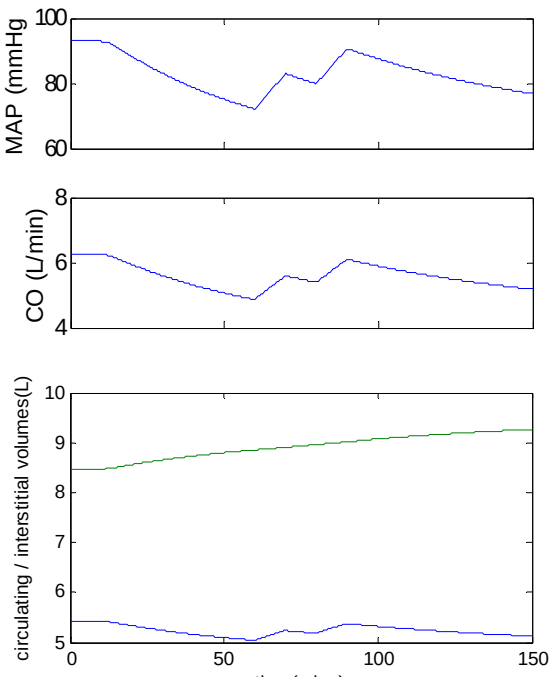

Figure 5: A Simulation run showing capillary leak treated with iso-oncotic fluid.

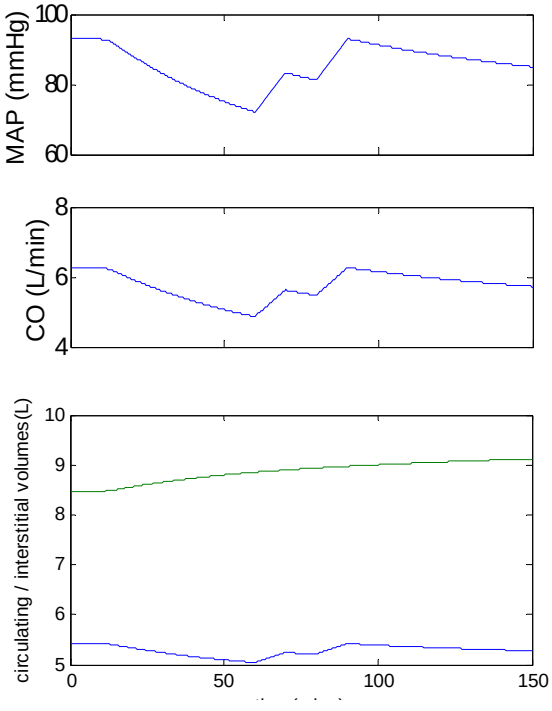

Figure 6: A Simulation run showing capillary leak treated with hyper-oncotic fluid.

Data Fitting

The model's suitability for describing real-life situations was tested by fitting model parameters to clinical data trends. Hamada *et al* [6] have published aggregated data of patients before and after CPB who have suffered capillary leak. This included HR, MAP, CO, fluid balance and change in circulating volume from nominal for 24 hours after the end of surgery. Such data was considered to contain enough information to fit various parameters of the model to the data trends using a least-squares fitting technique.

It was assumed that all variations in haemodynamic parameters were caused by changes in systemic resistance (Rs), contractility (Kl/Kr) and the reflection coefficient (**σ**). The systemic vascular resistance and the contractility will also have been affected by the reflex effects to hypotension and surgical insult. The post-CPB contractility will also be affected by the type of heart surgery. For this reason it was most interesting to estimate **σ** as it was a relatively independent parameter, mostly changing due to sepsis.

Results

The normalised reflection coefficient estimate increased from 1.60 ± 0.15 to 4.45 ± 0.40 in the time period following CPB (see Figure 7). The nominal value being 4.95 [4].

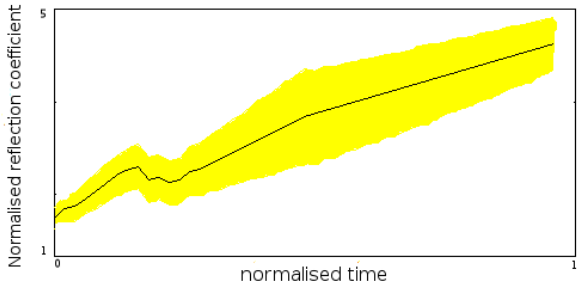

Figure 7: Normalised reflection coefficient estimate ± the variance, against time after CPB .

It is worth noting that it took more than 24 hours for these patients to restore their capillary permeability. It is believed that the dip in the reflection coefficient estimate is a feature of the data set used.

Conclusions

This modelling method is suitable for developing a comprehensive model of the circulation in situations involving volumic flux such as CPB and septic shock.

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With this model structure and appropriate data, it is possible to obtain an estimate of the reflection coefficient after CPB. Additionally, it is possible to model the effects of administering fluids with different oncotic pressures. Future work will consider exploiting this model not only to predict patients' physiological behaviour under routinely encountered scenarios, but also to design automatic control strategies relating to drug and fluid therapies.

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