Closed Loop Circulatory Model with Microcirculatory Local Vasoactive Response

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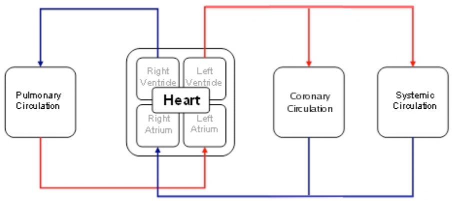
AIM

- Incorporate local arteriolar regulatory mechanics into a closed loop cardiovascular model

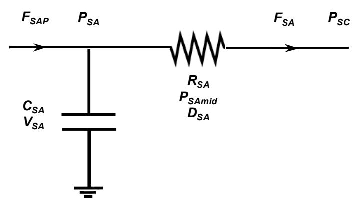
INTRODUCTION

- Preliminary step in the development of a model to predict cardiovascular response to hemorrhagic injury.
- Our model is a simplified version of Lu et al.[1] model and is comprised of four components shown to the right
- A different approach to the arteriole compartment formulation is used in order to incorporate arteriolar regulatory mechanics into the systemic circulation component



METHODS - Arteriole Compartment Formulation

- Each compartment is described with the flow analog of an RC circuit. For the arteriolar compartment:



where the variables are: axial flow, *F*, intraluminal pressure, *P*, resistance to flow, *R*, total vessel compliance, *C*, and total blood volume, *V*. Indices: SA systemic arterioles, SAP systemic arteries and SC systemic capillaries

- Arterioles adjust diameter in response to pressure and axial flow resulting in a variable resistance to flow and variable total vessel compliance.
- The closed set of equations defining the arteriolar state at a given time *t*, F_{SAP} and P_{SC} and an initialized P_{SA} are:

$$D_{SA} = f\left(P_{SAmid}, P_{SC}, D_{SA}\right)$$
$$R_{SA} = \frac{128\mu L_{SA}}{N_{SA}\pi D_{SA}^4}$$
$$V_{SA} = \left(\pi D_{SA}^2/4\right)L_{SA}N_{SA}$$
$$F_{SA} = \left(P_{SA} - P_{SC}\right)R_{SA}$$
$$C_{SA} = g\left(P_{SAmid}, P_{SC}, D_{SA}\right)$$
$$\frac{\partial P_{SA}}{\partial t} = \frac{F_{SAP} - F_{SA}}{C_{SA}}$$

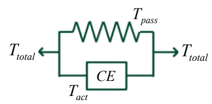
where parameters are: viscosity of blood, μ, effective length of the arterioles, L_{SA}, and total number of arterioles N_{SA}.

- *f* is an implicit function defining D_{SA} and *g* is a non-linear function defining C_{SA}.
- N_{SA} and L_{SA} are specified to match the initial arteriolar volume and resistance parameters of previous models by Neal et al[2,3].

METHODS - Arteriolar Vessel Formulation

- Arteriole vessel is modeled as a nonlinear passive spring in parallel with a vascular smooth muscle (VSM) contractile element (CE)[4].
- The total tension in the vessel wall depends on the VSM activation, *A*, according to:

$$T_{total} = T_{pass} + \mathrm{A}\,T_{act}^{\max}$$



- The length-tension relationship for the passive element is:

$$T_{pass}\left(D_{SA}\right) = C_{p1}\exp\left[C_{p2}\left(D_{SA}/D_{p100} - 1\right)\right]$$

- The maximally active component of tension is described as:

$$T_{act}^{\max}\left(D_{SA}\right) = C_{a1}\exp\left[-\left(\frac{D_{SA}/D_{p100} - C_{a2}}{C_{a3}}\right)^2\right]$$

- The activation is assumed to be a function of total vessel wall tension and shear stress and is given by:

$$\mathrm{A}\left(P_{SAmid}, P_{SC}, D_{SA}\right) = \frac{1}{1 + \exp\left[-C_{myo}T_{total} + C_{shear}\tau_{wall} + C_{tone}\right]}$$

where T_{total} is a function of P_{SAmid} and D_{SA} given by the Law of Laplace, and τ_{wall} is a function of P_{SAmid}, P_{SC} and D_{SA}.

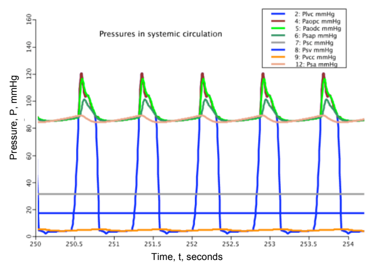
- Arteriolar vessel parameters (C_{p1}, C_{p2}, …, C_{shear}) are determined from best fit to experimental results by Sun et al.[5].

COMPUTATIONAL METHODS

- Expressions for *f* and *g* are developed from arteriolar vessel formulation.
- D_{SA} as a function of P_{SAmid} curves vary minimally with P_{SC} so a P_{SC} of 30 mmHg is specified, and an explicit approximation of D_{SA} as a function of P_{SA} is developed.
- JSim, a Java-based simulation environment, publicly available for multiple platforms at http://nsr.bioeng.washington.edu/. is used to solve the system of ODEs.
- The closed loop circulatory model is run both with and without a locally vasoactive arteriolar compartment.
- Model parameters are based on values specified in previous simulations run by Neal et al.[2,3].
- Both models[3,6] and complete documentation can be found on the Physiome Project model repository, http://www.physiome.org/

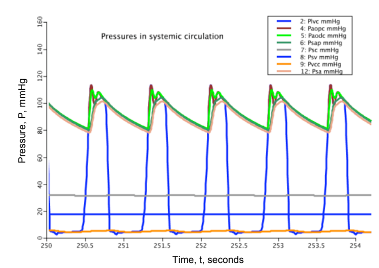
RESULTS

With Locally Vasoactive Arterioles



- Small variation in pressure per beat in the arterioles
- Pressure at arteriole entrance slightly higher than in arteries in systole
- Higher peak pressure in aorta and lower in arteries and arterioles than model without locally vasoactive arterioles

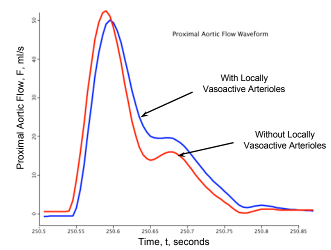
Without Locally Vasoactive Arterioles



- Large variation in pressure per beat in the arterioles
- Pressure at arteriole entrance remains smaller than arteries throughout entire pressure pulse
- Lower peak pressure in aorta and higher in arteries and arterioles than in model with locally vasoactive arterioles

Flowrate Waveform in Proximal Aorta

- Lower peak flowrate in aorta with vasoactive arterioles
- Slight negative flowrate in systole with locally vasoactive arterioles
- Overall flowrate nearly identical in both models
- Total blood volume at stable model solution 60 ml lower in model with locally vasoactive arterioles



DISCUSSION

- With locally vasoactive arterioles a 10% dilation in vessel diameter occurs as compared to the equivalent vessel diameter in the static parameter model.
- This compliance in the locally vasoactive arterioles is positive at low pressures and becomes negative at higher pressures.
- Without local vasoactive arterioles the compliance is very small (rigid vessel) and acts in a purely passive sense (C_{SA}>0).
- With vasoactive arterioles the compliance is two orders of magnitude larger and opposite in sign.
- Lower resistance due to arteriolar dilation in the vasoactive model results in less work by the heart for nearly the same cardiac output.
- Since vascular smooth muscle activation develops over time, the instantaneous reaction of vessel diameter to pressure and flow is not physiologically accurate.
- Specified parameters in all compartments but the arteriolar compartment in both models are identical.
- Model parameters have been specified without a vasoactive response and may need to be adjusted when vasoactivity is included.

CONCLUSIONS AND FUTURE WORK

- Addition of locally vasoactive arterioles significantly affect the modeled cardiac response.
- Local arteriolar responses to pressure and flow must be accounted for when modeling cardiac response to injury.
- Future models including local arteriolar and baroreceptor response and selectable injuries will be validated with previously obtained experimental data.
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