Influence of local auto-regulation mechanisms on flow during the muscle pump effect: a modeling approach

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INFLUENCE OF LOCAL AUTO-REGULATION MECHANISMS ON FLOW DURING THE MUSCLE PUMP EFFECT: A MODELING APPROACH

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SUMMARY

The muscle pump effect increases venous return during muscle contraction and perfusion during muscle relaxation. To investigate the additional contribution of different local auto-regulation mechanisms, a 1D pulse wave propagation model representing the calf vasculature is combined with a local auto-regulation model, which accounts for the metabolic, myogenic and endothelial regulation mechanisms. A simulated muscle contraction results in an increased arterial flow, as observed in literature. However, the expected decrease in baseline flow in the upright position is smaller than observed *in vivo*. In future research, other physiological mechanisms, such as the baroreflex, will be included.

Key words: *muscle pump effect, arterial and venous 1D pulse wave propagation, local auto-regulation*

1 INTRODUCTION

Post-flight orthostatic intolerance is observed in astronauts, which means that they are unable to compensate for the footward blood volume shift in upright position. This can result in critical events as syncope. An important mechanism compensating for this fluid shift in healthy subjects under normal conditions is the muscle pump effect, which is known to increase venous return under muscle contraction (Figure 1A,B). During muscle relaxation, muscle perfusion is known to increase due to an increased perfusion pressure, as the distal venous pressure temporarily decreases due to the closure of proximal venous valves. Besides the direct effect of the muscle pump, local auto-regulation of the peripheral bed is also believed to be involved in regulating flow during and after muscle contraction. Local vasodilation is regulated by three different, but interacting, mechanisms:

- metabolic: vasodilation occurs on increasing metabolic demand.
- myogenic: increasing arteriolar wall tension results in vasoconstriction.
- endothelial: increasing wall shear stress results in vasodilation.

In this study, we aim to investigate the importance of the different regulation mechanisms during the muscle pump effect in the supine and upright position while examining the flow response. The *in vivo* flow response to a muscle contraction [1] [2] in the supine and upright position is given in Figure 1C. It is hypothesized that the increase in flow shortly after the muscle contraction is mainly caused by the metabolic mechanism, since metabolism increases during the muscle contraction. Due to the hydrostatic pressure in upright position, the myogenic response is believed to protect the peripheral bed against too high pressures by vasoconstriction and thereby decrease the baseline flow.

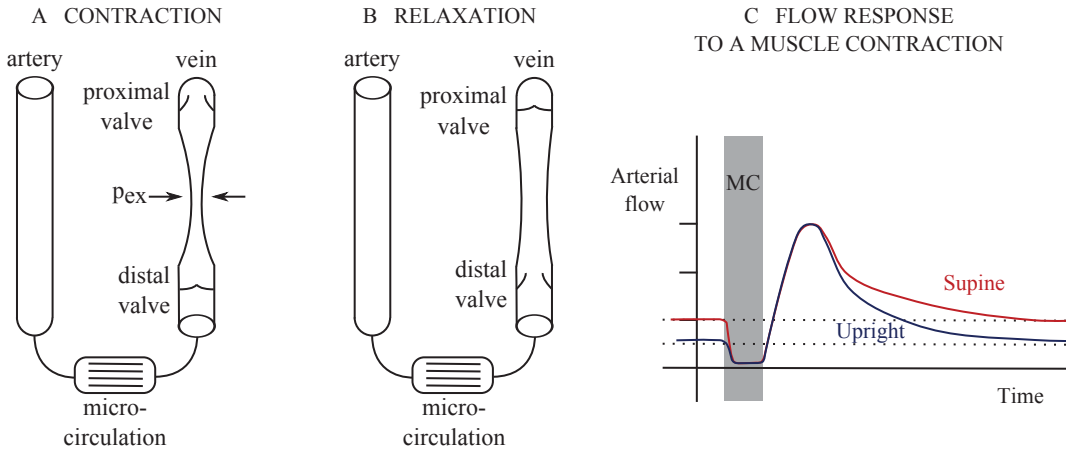

Figure 1: Schematic representation of the muscle pump effect during the contraction (A) and relaxation (B) phase. During the contraction, the embedded vein collapses increasing venous return. During the relaxation, the vein is refilled from artery. (C) The response of arterial flow on muscle contraction, MC, in supine and upright position. (A) and (B) adapted from Keijsers et al [3].

2 METHODS

The main model consists of 1D arteries and veins and a 0D micro-circulation (Figure 2A). It is based on our previous work [3], where the role of venous valves, hydrostatic pressure and superficial veins has been described under a calf muscle contraction. The regulation model (Figure 2B) is adapted from Spronck et al [4], where cerebral auto-regulation and neurovascular coupling are modeled based on metabolic, myogenic, endothelial and neurogenic mechanisms. The latter is not included in the current study, as it is a result of neurovascular coupling.

2.1 1D Arteries and Veins and 0D Valves

The large arteries and veins are split into elements for which the 1D equations of mass and momentum balance including the gravity term hold [3]. Additionally, the arterial constitutive behavior is modeled with a linear pressure, area relation, whereas the venous constitutive law is able to capture collapse for low transmural pressures (Figure 2C) [3]. Furthermore, a muscle contraction is simulated by an increase in extravascular pressure p_{ex} for the venous elements (Figure 2B). Finally, valves are included in the veins as 0D elements, and open on a positive pressure difference and close on negative flow [3].

2.2 Local Auto-Regulation

The 1D artery and vein are coupled using two windkessel elements representing the arterial and venous part of the micro-circulation. Local auto-regulation is included while adapting arterial resistance R_{a} and compliance C_{a} based on the arteriolar radius r_{a}, which is derived from Laplace's law

$$p_{\text{a}} r_{\text{a}} - p_{\text{ex}}(r_{\text{a}} + h_{\text{a}}) = T_{\text{e}} + T_{\text{v}} + T_{\text{m}} = T_{\text{a}}, \tag{1}$$

where h_{a} is the arteriolar wall thickness, p_{a} and p_{ex} are the arteriolar intra- and extravascular pressure respectively, and T_{e}, T_{v} and T_{m} are the elastic, viscous and muscular arteriolar tension respectively. Muscular tension is related to the regulation state and therefore depends on the myogenic, metabolic and endothelial mechanism. Myogenic activation A_{myo} is based on the total arteriolar tension T_{a}

$$A_{\text{myo}} = \frac{T_{\text{a}} - T_{\text{myo,0}}}{T_{\text{myo,s}}}, \tag{2}$$

where $T_{\text{myo,0}}$ is the tension at baseline pressure and $T_{\text{myo,s}}$ is a normalisation tension. The metabolic activation A_{meta} is based on the CO_2 concentration in the tissue $C_{\text{t,CO}_2}$ via

$$A_{\text{meta}} = \frac{C_{\text{t,CO}_2} - C_{\text{t,CO}_2,0}}{C_{\text{t,CO}_2,\text{s}}} \qquad \text{where} \qquad \frac{dC_{\text{t,CO}_2}}{dt} = \frac{1}{V}\left(M_{\text{CO}_2} - q_{\text{a}}\left(C_{\text{v,CO}_2} - C_{\text{a,CO}_2}\right)\right), \tag{3}$$

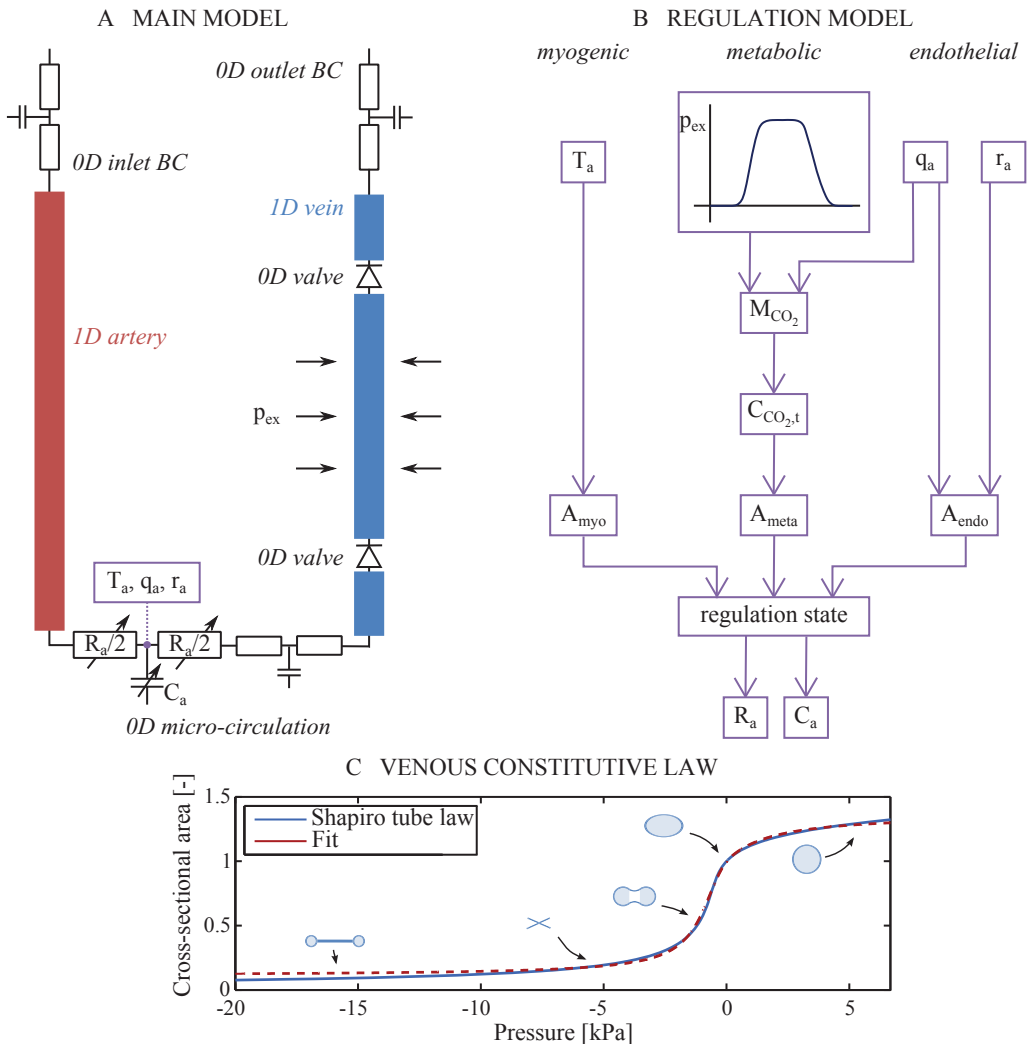

Figure 2: Schematic overview of the model: (A) main model, (B) regulation mechanisms with the myogenic, metabolic and endothelial mechanism and (C) Venous constitutive law according to Shapiro's tube law [5] (-) and a fit by Keijsers et al [3]. (A) and (C) adapted from Keijsers et al [3].

where $C_{\mathrm{t,CO_2,0}}$ is the baseline CO_2 tissue concentration and $C_{\mathrm{t,CO_2,s}}$ is a normalisation concentration. Furthermore, $M_{\mathrm{CO_2}}$ is metabolic rate, q_{a} is the arteriolar flow and $C_{\mathrm{v,CO_2}}$ and $C_{\mathrm{a,CO_2}}$ are the venous and arterial CO_2 concentration respectively. The endothelial activation A_{endo} scales with wall shear stress:

$$A_{\mathrm{endo}} = K_{\mathrm{endo}} \frac{q_{\mathrm{a}}}{r_{\mathrm{a}}^3} - 1, \tag{4}$$

where K_{endo} is a constant chosen, such that $A_{\mathrm{endo}} = 0$ at baseline. All model parameters are either taken from Spronck et al [4] or adapted to muscle tissue based on literature.

3 RESULTS

The responses of the different regulation mechanisms and the arterial flow to a muscle contraction are depicted in Figure 3B and C together with the time course of the extravascular pressure (Figure 3A). The strong metabolic response (dashed) after the muscle contraction is accompanied by an increase in arterial flow for both the supine and upright position (green and dark blue respectively) when compared to the non-regulated simulations (red and light blue). The myogenic response (dotted line) is only slightly increased in the upright position (dark blue) compared to the supine position (green) and almost no difference in baseline flow is observed.

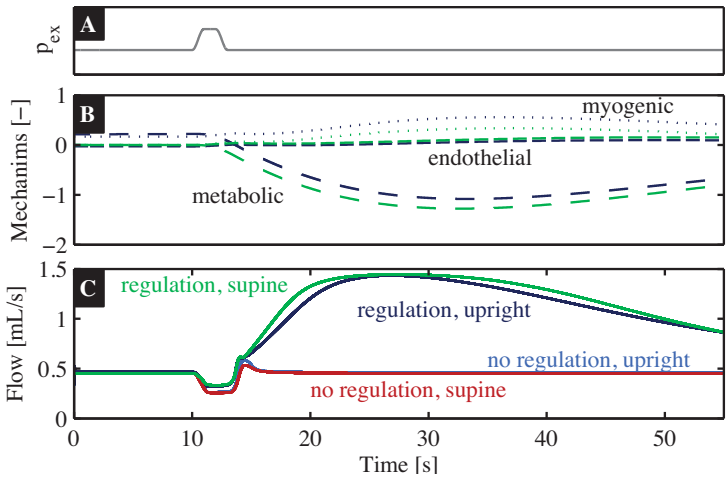

Figure 3: Response to a muscle contraction: (A) course of extravascular pressure, (B) metabolic, myogenic and endothelial response, and (C) arterial flow for supine and upright position, with and without regulation.

4 DISCUSSION AND CONCLUSION

The current study combined a 1D pulse wave propagation model of the arteries and the veins with a local auto-regulation model to examine the influence of different regulation mechanisms during the muscle pump effect. The increase in flow observed after a muscle contraction is similar to the flow increase observed by Leguy et al [1] and Nådland et al [2] and likely results from the strong metabolic vasodilation. However, the expected decrease in baseline flow in upright position is smaller than observed *in vivo* (Figure 1C). This might be a result of the fact that the myogenic response is only slightly increased in the upright position. We hypothesize that other phenomena, such as the baroreflex, also play an important role in vasoconstriction under orthostatic stress [6] and might be the missing mechanism in the current model. In future research, the model will be extended with a baroreflex model to capture the correct decrease in baseline flow.

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A FICTIVE HEALTHY POPULATION TO ASSESS PHYSIOLOGICAL INDEXES

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SUMMARY

Many physiological indexes and methods have been suggested in order to better understand the physiology of arterial hemodynamics (e.g. foot-to-foot pulse wave velocity, augmentation index, central blood pressure estimation). Because these tools are most often computed from hemodynamic measurements, their validation is time-consuming and biased by measurement errors. We present a new methodology to assess theoretically these computed tools. We create a database of healthy fictive subjects using a numerical 1D-0D model of the arterial hemodynamics, which parameters are varied to cover a physiological healthy range. The generated set of simulations encloses a wide selection of possible cases that could be encountered in a clinical study.

Key words: *fictive database, 1D-0D model, population modelling*

1 INTRODUCTION

Arterial blood flow modelling has become nowadays a very efficient tool to better understand the cardiovascular physiology. Different scales of models are being developed, from three-dimensional (3D) models of sections of arteries to lumped zero-dimensional (0D) models of the heart, arterial and venous network. Compared to 0D and 3D models, one-dimensional (1D) models offer a good balance between accuracy, rapidity and availability of data. When coupled with lumped parameters of the peripheral circulation, 1D-0D models have proven very efficient to model pulse wave propagation in healthy [7, 4] and pathological arteries [10, 8].

Thanks to the collaboration between clinicians and biomedical engineers, computed methods and physiological indexes derived from the pulse wave analysis start to be used in clinical practice. Among those, the pulse wave velocity (PWV) and the augmentation index are used as surrogate measure of arterial stiffness, and have been shown to be marker of cardiovascular risks [3, 6]. In addition, the estimation of the central blood pressure from peripheral pressure pulses has become possible thanks to generalised transfer function based methods [5].

Before being used in the clinics though, these new tools need to go through a long validation stage, as they are being tested on cohorts of patients. Assessing the efficiency of a method is indeed a difficult process as physiological measurements are subjected to experimental errors, are not always available at all sites of interest, and most importantly, the estimated index can rarely be compared to its "true" value.

While most of numerical 1D-0D model studies focus on patient-specific applications, trying to reproduce a single set of parameters and a unique hemodynamic state [7, 2], our current work presents a *"population-specific"* approach. We generate a database of fictive subjects presenting a diversity of hemodynamic, structural and geometric characteristics. Because those characteristics are known at every point of the numerical arterial tree, our new methodology can be used to assess theoretically the efficiency of computed physiological indexes and methods.