MINIMAL CARDIOVASCULAR SYSTEM MODEL INCLUDING A PHYSIOLOGICAL DESCRIPTION OF PROGRESSIVE MITRAL VALVE ORIFICE DYNAMICS FOR STUDYING VALVE DYSFUNCTION

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SUMMARY
This research presents a new closed-loop cardiovascular system model including a description of the progressive opening and closing dynamic of the mitral valve. Furthermore, this model includes a mathematical description of the left atrium. This new CVS model enables the study of valve dysfunction in the appropriate clinical context of the overall cardiac and circulatory hemodynamics.

INTRODUCTION
The minimal cardiovascular system (CVS) model described in this study was first developed and optimized [1] to assist clinicians in diagnosing cardiovascular and circulatory dysfunction and (then) selecting reliable and appropriate therapeutic responses. This model is based on the "pressure-volume" (PV) lumped element approach. It divides the cardiovascular system in several chambers described by their own PV relationship [1,4]. This method requires a limited number of parameters, allowing for easy and rapid simulations and for patient specific identification of disease state [5,7].
In this research, this closed-loop CVS model is coupled with a model describing the progressive aperture dynamics of the mitral valve during the cardiac cycle. Thus, a model of the left atrium and its dynamics are also required for an accurate physiological context. The goal is to better take into account the valve dynamics during the entire cardiac cycle and their impact on circulatory dynamics. Clinically, understanding this impact and the ability to identify it would lead to new diagnostic capabilities for valvular dysfunction.

METHODS
Existing CVS model
The initial, fundamental CVS model used consists of 6 elastic chambers (left and right ventricles, vena cava, aorta, pulmonary artery and veins). It accounts for ventricular interaction by means of the septum displacement. The overall model structure is shown in Figure 1. This model was first described by Smith et al [1] and has been validated *in silico* and in several animal model studies [3,5-7].

Atrial model
To describe the mitral valve more accurately, a new elastic compartment modeling the left atrium must be added. For this atrium model, the atrial septum is assumed to be rigid.

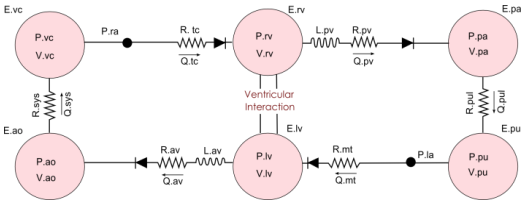

Figure 1 : Schematic overview of the six chamber CVS model

Hence, the atria are uncoupled and have no direct mechanical influence on each other or the ventricles. The atrial free walls are characterized by a time-varying elastance similarly to what is used for the ventricles [4]:

$$e_{la} = A_a \exp(-(1/2)(t-C_a/B_a))$$

Where $A_a=0.9$, $B_a=0.018s$ and $C_a=0.065s$.

Mitral valve model
The normal motion of the mitral valve during a cardiac cycle has been analyzed by Saito et al. [8]. The qualitative normal mitral aperture evolution during the diastole is given in Figure 2. It describes the two peaks, corresponding to the E-wave and A-wave, or, respectively, to the passive filling of the ventricle and the subsequent active ventricular filling due to the atrial contraction.

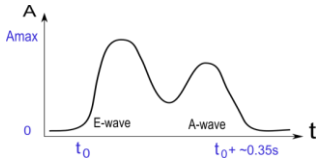

Figure 2 : Effective mitral aperture (A) evolution during the filling phase (diastole), shown schematically

Mitral valve opening and closing can be modeled by a forced harmonic oscillator [9], coupled to the CVS model to simulate cardiac hemodynamics with valve dysfunction.
The intrinsic dynamics of the valve aperture may thus be modeled by a second-order linear differential equation taking into account the mass of the valve cusps, the elasticity of the tissue, and the damping experienced by the valve cusps. Equally, this simplified modeling approach minimizes model complexity. The forcing term is assumed to be only due to the pressure difference between upstream and downstream cavities, the atrium and ventricle in this case, which are both active cardiac chambers. The differential equation defining the mitral valve aperture area (A) is written:

$$(1/\omega^2)(d^2A/dt^2)+2D(dA/dt)+A=(A_{max}-A)K_s(P_{la}-P_{lv})$$

Where A is the mitral aperture area, A_{max} the mitral maximal aperture area, D the mitral damping coefficient, □ the mitral natural frequency, P_{la} the pressure in the left atrium, P_{lv} the pressure in the left ventricle and K_s the gain coefficient for static pressure.

The modified CVS model includes the left atrium and the mitral valve as described previously.

RESULTS AND DISCUSSION

Simulation of the new model allows us to plot the pressure-volume (PV) loops for both ventricles. Left ventricle PV loops are shown in Figure 3. On top of this, we can also plot the pressure volume loop of the left atrium and find similar results to those obtained in previous studies [10].

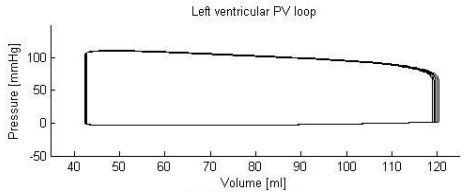

Figure 3 : Pressure-volume loop of the left ventricle

Figure 4 shows the simulated transmitral flow with both the E- and the A-waves, as expected physiologically, are similar to Figure 2, as desired. Hence, the model realistically describes mitral valve opening and closing in the context of this validated full circulatory cardiovascular system model.

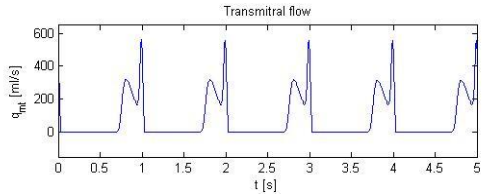

Figure 4 : Transmitral flow evolution

While these results show strong physiological correlation to independently measured data, the second order model used to model the mitral valve aperture dynamics is not very physiologically relevant. Specifically, the terms in the equation do not relate directly to the observed anatomical structure and function of the valve. Hence, the model itself, while capturing the effective dynamics can provide no insight into specific disease impact or damage that results in valve dysfunction, even though it can model that dysfunction.

A more anatomically accurate model could be used with clinical data to identify more physiologically relevant parameters. In such a case, the identified values, being physiologically relevant to the existing anatomical structure, could provide significant added diagnostic value to a clinical end-user. Equally, valvular dysfunctions might then be directly associated with defects in anatomical structures providing insight into their clinical causes and treatment.

This modeling remains a part of ongoing work. However, this report clearly shows that a model capable of capturing these valve dynamics can provide a useful addition to a clinically validated overall cardiovascular system model.

CONCLUSIONS

This work describes a new CVS model that accounts for progressive opening and closing of the mitral valve to enable the study of valve dysfunction on overall hemodynamics. Simulations show physiologically expected hemodynamic behaviour for healthy valves, and provide initial validation for its further use to monitor, diagnose and control valvular pathologies. The model itself remains to be independently validated using clinical or animal trial test data. However, these results justify such clinical tests and can be used to govern their design and implementation.

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