MODEL ANALYSIS OF RESPIRATORY MODULATION OF HEART HAEMODYNAMICS

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Abstract: Volume and pressure fluctuations in all heart chambers are the main modulators of cardiac and vascular haemodynamics under both normal and pathological conditions. These variables are significantly influenced by respiration, which elicits control on all cardiovascular phenomena generated by interdependent mechanical and neural mechanisms, such as beat-to-beat fluctuations of heart rate and arterial blood pressure. Mechanical coupling between the ventricles has been observed to be amongst the factors responsable for these changes. In the present study phenomenological analysis of cardiorespiratory interaction is performed by developing a computational model of the mechanics of the intact heart, which explicitly accounts for the direct (across the septum) and indirect (through the pericardium) interaction between ventricles. The model heart is incorporated in a lumped parameter model of systemic and pulmonary circulations, describing respiration as external modulation of intrathoracic pressure. Simulations under different intrathoracic pressure values as well as continuous modulation of the latter show that the effects of respiration on pressure and volume waveforms are greatly enhanced by ventricular interdependence. Further, ventricular interdependence generates a marked increase in the active contractility, especially in the right ventricle. The inclusion of the ventriculare interdependence significantly affects the structural response of the model to respiration and highlights the crucial role of the latter in influencing cardiovascular events.

Introduction

Interactions between the cardiac and pulmonary systems under physiological as well as pathological conditions have been seen to play a key role in the genesis and course of cardiovascular disease. Hence, the clinician's need to deepen the understanding of the nature of mechanical cardiorespiratory interactions has motivated extensive research, and several physiological maneuvers -such as Mueller and Valsalva- have been broadly investigated in the attempt to identify the underlying mechanisms which govern their outcome [1]. However, in spite of extensive and somewhat concerted efforts, there is still noticeable ambiguity and controversy about several aspects. In particular, the role played by the pericardium (which is believed to be significant especially during acute distension of the heart) as well as by direct trans-septal interventricular interaction in the cardiac haemodynamic events following these maneuvers is poorly understood. Moreover, respiration elicits oscillatory modulation of heart rate and arterial blood pressure through interdependent mechanical and neural pathways of closed-loop nature, thereby affecting dynamic response of short-term cardiovascular control significantly [2]. Currently, the functional state of baroreceptors (both aortic and pulmonary) is assessed mainly through spectral analysis of cardiopulmonary signals [3].

The separate influence of single mechanical or neural effects on these signals is not understood, and changes in atrial and ventricular haemodynamics are a crucial factor in mediating the cardiac-pulmonary interdependence. Aim of the study is to investigate and characterize respiratory modulation of cardiac volumes and pressures in order to clarify the nature of cardiovascular phenomena stimulated by changes in intrathoracic pressure.

Materials and Methods

Respiration influences cardiac haemodynamics through variations in the intrathoracic pressure (P_t), tramsmitted across the compliant pericardium to the free walls of left ventricle (LV) and right ventricle(RV). Mutual ventricular interaction, which is caused by the constraining effects of the pericardium (*indirect interaction*) as well as by the common septal wall between the two ventricles (*direct interaction*) significantly affects cardiac pressures, volumes and flows of the four cardiac chambers [4,5]. Moreover, the mutual indirect interaction trough the pericardium between atria and ventricles is documented [6]. Hence, in order to study the haemodynamic effects of respiration, a model of the whole heart describing explicitly the mechanical direct and indirect interactions between the four cardiac chambers is mandatory.

A previously developed model of the entire circulatory system [7,8] was improved in order to account for all aspects which are relevant to this study.

Heart model: the mechanical model which is adopted for the two ventricles separately accounts for the elastic properties of septum and ventricular free walls, as well as the different transmural pressures of the various wall segments. The model is based on the concept of "compliance of a open membrane" introduced in [9] which is largely employed in the

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literature to analyze the mechanical behaviour of the heart [10]. The electric analog of the mechanical heart model is shown in Figure 1. Each wall is described by a two-phase elastance: a non-linear diastolic passive elastance and a time-varying systolic active elastance. A linear pressure-volume curve is assumed for the pericardium. The atria are described as passive. The timing and strength of contraction of ventricular muscle are controlled by specifying the state of activation as a given function of time. At the present time, we supply the same activation function for both ventricles assuming that all parts of the cardiac chambers contract simultaneously and that contraction of both ventricles is synchronous. Dependence of the systolic interval (T_s) on the heart rate (HR) is also accounted for assuming the relationship $T_s = 0.16 + 12/HR$ and, on the basis of experimental observation of normalized ventricular activation function, we assume that the ventricles fully relax from the maximum activation in a time equal to 30% of the time necessary to reach the maximum activation [11,12]. On this basis, the following functional pressure-volume relationship was assumed for each ventricle:

$$P_v(t) = P_{pass}(t) + P_{act}(t) + K_{vs} P_{cv}(t) + K_{vp} P_p(t) \quad (1)$$

$$P_{act}(t) = E_{max} (V_v(t) - V_0) A_N(t,HR,T_s) \quad (2)$$

where t = time; P_v = ventricular pressure; P_{pass}= end-diastolic pressure-volume relationship;P_{act} = actively developed pressure; P_{cv} = contralateral ventricular pressure; P_p = pericardial pressure; V_v = ventricular volume; V_0 = volume intercept value of the end-systolic pressure-volume relationship with the volume axis; K_{vs} = interventricular coupling coefficient (through the septum); K_{vp} = coupling coefficient of each ventricle to pericardium (through the free wall); E_{max} = maximum value of elastance corresponding to the value of the slope of the ventricular end-systolic pressure-volume relationship. $A_N(t,HR,T_s)$ = normalized activation function, HR = heart rate; T_s = systolic interval. According to [14] the following relationships between the coupling coefficients and the ventricular compliances are assumed:

$$K_{vs} = C_s/(C_{vf} + C_s) \quad (3)$$

$$K_{vp} = C_{vf}/(C_{vf} + C_s) \quad (4)$$

where C_{vf}, C_s and C_p represent the ventricular free wall compliance (right or left), the septum compliance and pericardial compliance, respectively. Values of the parameters describing the interaction were derived by suitably modifying experimental data obtained from animals in rest conditions and to fit human haemodynamics. The same values of the coupling coefficients were assumed to model both systolic and diastolic ventricular interaction.
Respiration is simulated by intrathoracic pressure (P_t) variations.

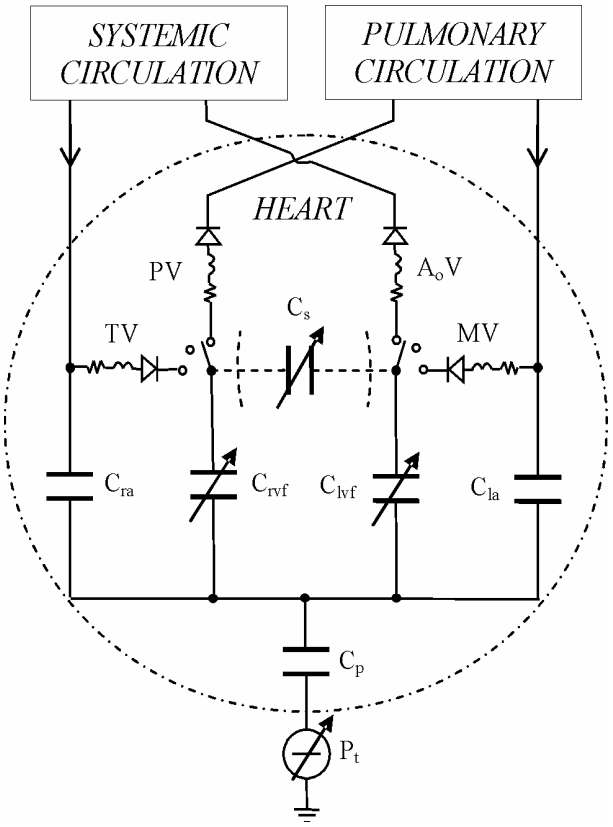

Figure 1: Analog electric of the mechanical heart model. C_{ra}, C_{la} = right , left atrial compliances; C_{rvf}, C_{lvf} = right, left ventricular free wall compliances; C_s = septum compliance; C_p = pericardium compliance; MV, A_oV, TV,PV = mitral, aortic, tricuspid and pulmonary valves; P_t = intrathoracic pressure.

Model structure is designed to allow investigation of factors affecting cardiovascular response to different hemodynamic stress, either in presence or in absence of interdependence, either separately and in combination.
Model validation was performed by computer simulation, using the lumped parameter models of the systemic and pulmonary circulations previously developed [7,8], which attain the physiological ventricular afterloads in normal, resting humans in terms of input vascular impedance spectra. Physiological values of the cardiac and vascular haemodynamic variables were obtained across a wide range of cardiac output.

Results and Discussion

Several experimental studies [13-18] have shown that ventricular interaction influences cardiac haemodynamics by enhancing the ejection of both ventricles. This effect is much more evident in the right ventricle, where a significant contribution to the systolic ventricular pressure is caused by the left ventricle, acting across the septum. E_{max}, i.e. the slope

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of the end-systolic pressure-volume relation, is the index currently assumed to represent the intrinsic pressure-generating properties of the ventricular chamber. We therefore begin by examining how the interaction influences the contractile strength of the right and left ventricles, comparing the effective value of E_{max}, in presence or absence of interaction. All simulations were performed maintaining a constant heart rate of 70 min^{-1}. The variation in E_{max} was calculated in every case by simulating haemodynamic states with varying cardiac stroke volume, generated by modulating systemic venous pressure. The effect of intrathoracic pressure was investigated by varying the mean value of the intrathoracic pressure $\pm$ 4 mmHg around the reference value of -4 mmHg.

As shown in Figure 2 (A vs. C and B vs. D), ventricular interaction is seen to increase E_{max} by about 10% in the LV and by about 60% in the RV, in agreement with reported experimental results. The leftward shift in the operating point of the system resulting from including ventricular interaction reflects a greater contractile efficacy which is consistent with an increase in E_{max}. Also, the decrease in end-diastolic volume is consistent with a greater pressure exerted by the contralateral ventricle across the septum, preventing increased filling. Moreover, the mechanical interaction can explain the response of the left (decrement) and right (increment) ventricular stroke volume following the onset of the inspiration. Without interdependence ventricular volumes change after a delay of one to two heartbeats and left ventricular volume decrement is small.

As far as ventricular afterloads are concerned, simulations show that interaction cause a decrement of the mean aortic pressure as well as an increment of the mean pulmonary pressure. This behaviour was consistently observed while varying P_t beween 0 mmHg and –8 mmHg (dashed vs. dotted. vs. solid lines) as well as different heart rate values (data not shown).

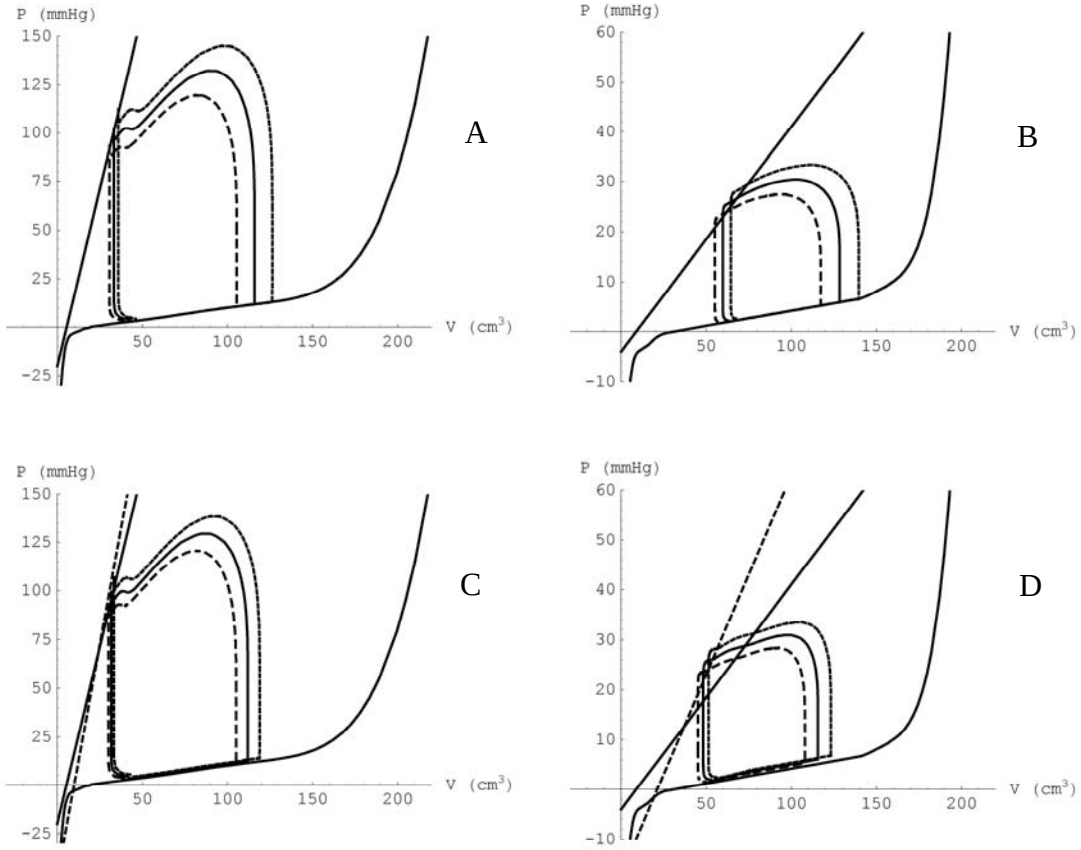

Figure 2: Model-generated steady-state left ventricle (A,C) and right ventricle (B,D) Pressure-Volume loops, obtained by varying Pt (intrathoracic pressure) from –4 mmHg (solid lines), to –8 mmHg (dotted lines) to 0 mmHg (dashed lines), in absence (A, B) and presence (C, D) of ventricular interaction through the septum and pericardium. Plots are superimposed to passive and active P-V relationships employed in the calculations. In the bottom pane (C, D), the variation in E_{max} resulting from allowing ventricular interaction is visualised as a dashed straight line.

Figure 3 shows the effect of simulating normal breathing as a continuous sinusoidal variation in Pt between 0 mmHg and –8 mmHg. The results are in qualitative agreement with those shown in Figure 2, where a significant alteration of both E_{max} and the position of the system's operating point can be observed as a result of ventricular interaction (A-B). In addition, the haemodynamic effects of respiration on RV (D-F) are much more marked than on the LV (C-E).

Conclusions

- Mechanical interaction between heart chambers is mandatory to explain the initial response of ventricular volume changes and the decrement of the left ventricular volume following the onset of inspiration. Without interdependence, ventricular volumes change after a delay of one to two heartbeats and left ventricular volume decrement is small.

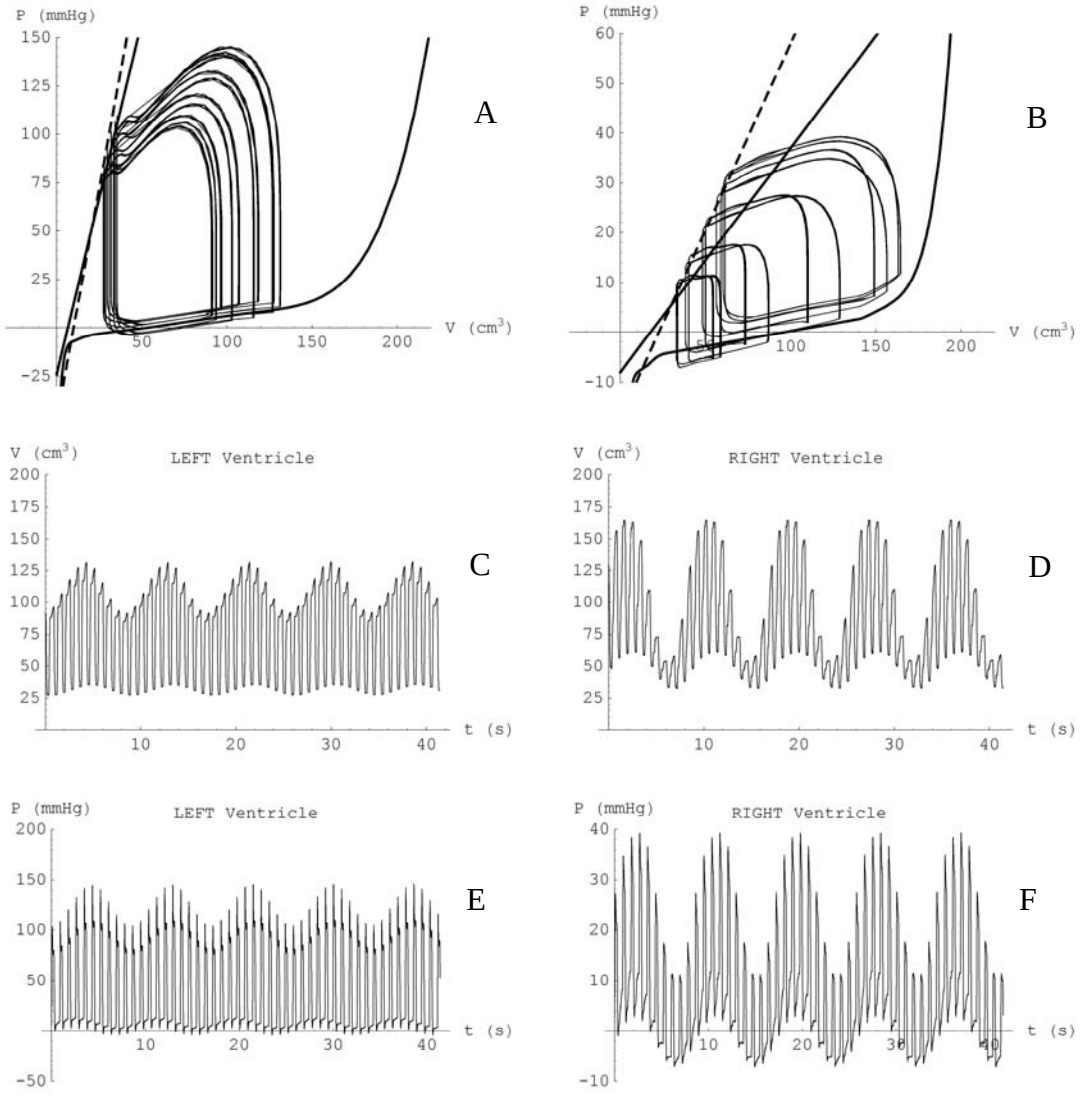

Figure 3: **A, B:** Model generated state LV (A) and RV (B) Pressure-Volume loops, obtained by varying Pt (intrathoracic pressure) between 0 mmHg and –8 mmHg sinusoidally (7 cycles/min) in presence of ventricular interaction through the septum. Plots are superimposed to passive and active P-V relationships employed in the calculations, and the variation in E_{max} resulting from allowing ventricular interaction is visualised as a dashed straight line. **C, D:** Model generated volume waveforms for LV (C) and RV (D). **E, F:** Model generated pressure waveforms for LV (E) and RV (F).

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- From present data, the relative timing of cardiac cycle and respiration phases appears to significantly affect the cardiac time intervals and volumes, influencing not only the entity, but also the direction of change. Further investigation is necessary in order to completely characterise the mechanisms underlying this aspect of cardiorespiratory interaction.
- Interaction plays a significant role in determining the extent of respiratory modulation of ventricular volumes, where the model heart displays a greater tolerance to intrathoracic pressure changes when ventricular interdependence is incorporated.
- Atrial and ventricular volumes as well as their fluctuations in time play an important role in the short-term control of circulation and maintenance of physiological homeostasis, and they have been shown to be significantly affected by their mutual interdependence.

Since cardiovascular response to stress is bound to cause acute changes in cardiac chamber volumes as well as in their time evolution, for model analysis to afford accurate description and/or prediction of beating heart behaviour it is strictly necessary to account for mutual chamber interaction explicitely.

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