MATHEMATICAL MODEL ANALYSIS OF HEART-ARTERIAL INTERACTION IN HYPERTENSION

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Abstract

We studied heart-arterial interaction in hypertension-induced left ventricular hypertrophy (LVH) using a LV time-varying elastance model coupled to a 4-element lumped parameter model of the systemic arterial system. After assessing cardiac and arterial model parameters for normotensive control subjects, we applied arterial changes as observed in hypertensive patients with LVH (resistance +40% ; compliance –25%) and assumed (i) no cardiac adaptation; (ii) LVH normalizes systolic wall stress (σ_s); (iii) LVH normalizes σ_s and venous filling pressure (P_v) increases such that end-diastolic wall stress (σ_d) is normalized as well. Human in vivo data show that in hypertensives with LVH, systolic and diastolic blood pressure increase by about 40% while cardiac output is constant and wall thickness increases by 30-55%. In both (i) and (ii), blood pressure increased by only 10% while cardiac output dropped by 20%. In (ii), LV wall thickness increased by only 10%. In contrast, the predictions of (iii) were in qualitative and quantitative agreement with in-vivo human data. We conclude that besides an increase in LV mass and wall thickness, normalizing σ_s, cardiac adaptations further consist of an increase in P_v, normalizing σ_d and preserving cardiac output in the presence of an impaired diastolic function.

Introduction

The complex interaction of the heart and the arterial system is most obvious in conditions of sustained pressure overload, such as systemic hypertension. The generally accepted concept is that, as a response to chronic pressure overload, the left ventricle (LV) hypertrophies to compensate for increased systolic wall stress by increasing its wall thickness; i.e., wall stress is maintained at normal values [1]. The increase in pump function then allows for the generation of a normal cardiac output against higher loads [2]. However, this straightforward adaptive pattern is not always observed in experimental animal studies with induced chronic pressure overload. Alternative hypotheses of LV systolic and/or end-diastolic wall stress normalization have been put forwward [3-6].

In this paper, we use a mathematical model [7] to study heart-arterial interaction in conditions of chronic pressure overload, i.e., essential hypertension, where total peripheral resistance is increased and total arterial compliance decreased compared to normotensive controls (9, 30). Implementing these arterial changes, left ventricular pressure-volume loops and aortic pressure and flow waves are calculated according to three heart-arterial interaction scenarios: (i) there are no cardiac changes in response to the increased load; (ii) peak systolic wall stress is normalized via an increase in LV wall thickness; (iii) peak systolic wall stress is normalized through an increase in LV wall thickness, and LV end-diastolic pressure is allowed to change such as to normalize end-diastolic wall stress.

Materials and methods

The heart-arterial model

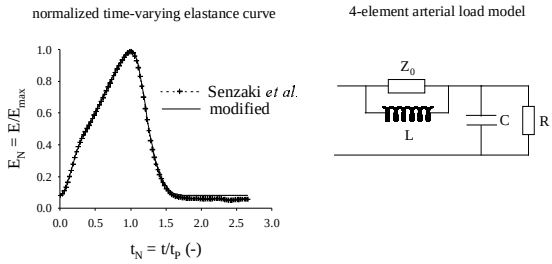

Figure 1. Original and modified normalized time-varying elastance curve time [12] and arterial 4-element lumped parameter model.

The heart–arterial model consists of a time-varying elastance model E(t) [8] coupled to a 4-element lumped parameter windkessel model representing the arterial load [9]. Making use of a normalized formulation of ventricular elastance, E(t) can be fully described by 3 parameters: maximal (E_{max}) and minimal (E_{min}) elastance and the time to reach peak elastance (t_P). Other heart related parameters are heart period (T), venous filling pressure P_v, and V_d, the intercept

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Abstract

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of the end-systolic pressure-volume relation with the volume axis. In diastole, the heart fills through the mitral valve which is, in the open position, modeled as a linear resistance (0.001 mmHg/(ml/s)). The arterial model is a 4-element lumped parameter windkessel model [9], consisting of total peripheral resistance (R), total arterial compliance (C), total blood inertance (L) and the characteristic impedance of the aorta (Z_0) (Figure 1). Further details on the model, programmed in Matlab 5.2 (The Mathworks, Inc), and the validation are found elsewhere [7].

Simulation of chronic LV pressure overload

Model parameters for the normotensive subject

Control values for total peripheral resistance (R) and total arterial compliance (C) are taken as 1.1 mmHg/(ml/s) and 1.1 ml/mmHg [2], respectively. Characteristic impedance Z_0 = 0.033 mmHg/(ml/s) [10], and total arterial inertance L is set to 0.005 mmHg/(ml/s) [9]. Heart period is taken 0.86 s (70 beats/min), and t_P = 0.32 s. E_{max} is 1.5 mmHg/ml, P_v is set to 5 mmHg, V_d = 15 ml giving E_{min} = 0.031 mmHg/ml

Model parameters for the hypertensive subject

Arterial changes in hypertension are modeled as a 25% decrease in arterial compliance (0.82 ml/mmHg) and a 40% increase in total peripheral resistance (1.54 mmHg/(ml/s)) (9, 30). Z_0 varies proportional to $1/\sqrt{C}$ and increases by 15% to 0.038 mmHg/(ml/s).

Cardiac adaptation scenarios

Three heart-arterial coupling scenarios are performed: (i) cardiac parameters do not vary; (ii) peak systolic wall stress (σ_s) is normalized via an increase in LV wall thickness; (iii) σ_s is normalized through an increase in LV wall thickness, and Pv is allowed to change such as to normalize end-diastolic wall stress (σ_d). Systolic and diastolic (σ_d) wall stress are calculated using the Laplace formula for a thick-walled sphere [11]. Wall thickness for the control condition is taken 1.6 cm yielding σ_s and σ_d 11.7 and 0.6 kPa, respectively. These values are used as the level to which stress is normalized in hypertension. As the LV pressure-volume relations in systole and diastole are proportional to wall thickness, derived parameters E_{max} and E_{min} are proportional to wall thickness as well.

Results

When cardiac parameters are kept constant (scenario (i)), the arterial changes in hypertension lead to an increase in systolic (from 124 to 143 mmHg) and diastolic blood pressure (from 76 to 90 mmHg) (Figure 2). Stroke volume is predicted to decrease by 18% (from 80 to 65 ml), peak flow is reduced as well as the duration of LV ejection (Figure 2, panels A-B). As preload is unchanged, end-diastolic volume

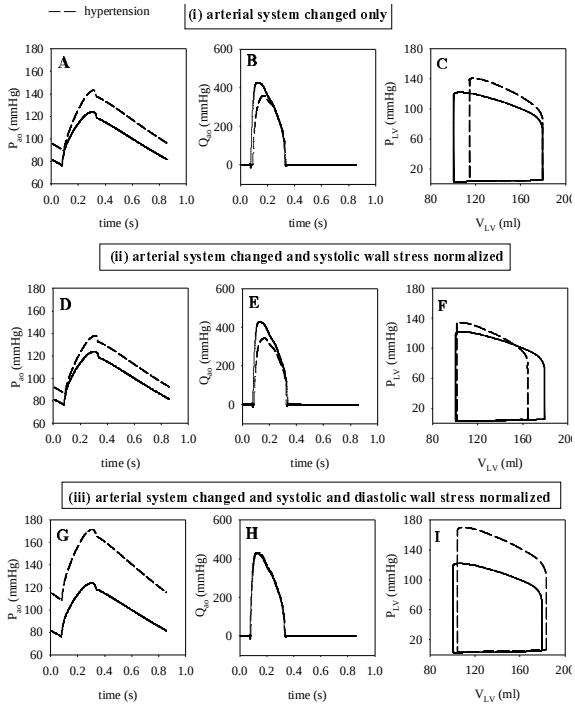

Figure 2. Simulated aortic pressure (panels A,D,G flow (panels B,E,H) and LV pressure-volume loo (C,F,I) for the three scenarios.

is constant while end-systolic LV volume is increased (Figure 2, panel C).

The results for scenario (ii), where left ventricular wall thickness is increased to normalize σ_s, are shown in figure 2 panels D, E and F. Aortic systolic and diastolic pressures are about 5 mmHg lower than in scenario (i) and stroke volume is further depressed (63 ml), mainly due to the lower end-diastolic volumes (E_{min} increases and filling pressure remains the same). To normalize systolic wall stress, wall thickness (and accordingly E_{max} and E_{min}) has increased by 10%.

Panels G through I in figure 2 show aortic pressure and flow and LV pressure-volume relations when σ_s is normalized by an increase in wall thickness, and when σ_d is normalized via an increase in preload (Pv), i.e., scenario (iii). Both diastolic (108 mmHg) and systolic (172 mmHg) blood pressure have increased by about 40%, while stroke volume and cardiac output are preserved (-0.4%). Wall thickness has increased by 34%, and P_v has risen from 5.0 mmHg to 6.9 mmHg (+38%).

The effects of the different heart-interaction scenarios on systolic and diastolic blood pressure and on cardiac output are summarized in Figure 3, where a comparison with data [12] measured in normotensive controls (n=125) and in hypertensives with compensated concentric hypertrophy (n=13) is shown.

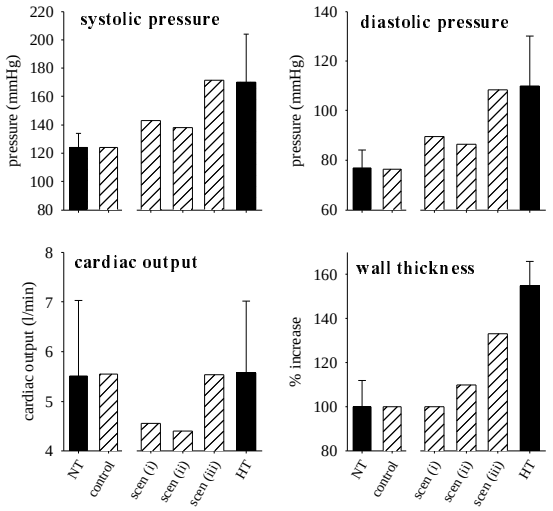

Figure 3. Comparison of model simulations (hatched bars) with in vivo measured (solid bars; mean values + standard deviation) data (data from [2]). Simulations are control and the 3 cardiac adaptation scenarios.

Discussion

In the present study, we used a theoretical model to study the interaction between the left ventricle and the systemic circulation in conditions of chronic pressure overload as observed in hypertensive patients with compensated concentric hypertrophy. We assumed arterial compliance 25% lower and peripheral resistance 40% higher in hypertensives than in normotensive controls [13], and predicted blood pressure, cardiac output, left ventricular filling pressure and wall thickness according to three cardiac adaptation scenarios. The scenario where left ventricular hypertrophy normalizes peak systolic wall stress and preload increases to normalize end-diastolic wall stress, presented results most in line with data in literature. The increase in systolic and diastolic blood pressure and the preservation of cardiac output is in qualitative and quantitative agreement with in vivo measurements (Fig. 3), and the 33% increase in wall thickness approximates that (30-55%) observed in patients with essential hypertension [13].

We used a relatively simple model, consisting of a LV time-varying elastance model coupled to an arterial lumped parameter model, to simulate hemodynamics in the intact human. It has been shown earlier that similar models generate pressure, flow and pressure-volume curves that are in good agreement with data measured in the isolated canine [14] or cat [15] heart, pumping into an artificial load or in the intact sheep [16] and human [7].

Left ventricular wall stress normalization in compensated hypertrophy is used as a mechanism to explain left ventricular hypertrophy in the presence of an increased load [1]. An increased load results in higher systolic blood pressure and, following Laplace's law, to an increased wall stress. To reduce wall stress back to normal levels, we increased LV wall thickness, keeping LV internal diameter (at maximal systolic pressure) constant (concentric hypertrophy). The resulting increase in mass thus reflects a larger number of sarcomeres in parallel in the same number of myocytes. Neglecting possible intrinsic contractility changes due to altered calcium handling in hypertrophy [4, 17, 18], active contractile properties of the left ventricle (E_{max}) thus vary in proportion to the increase in LV mass. On the other hand, the greater wall thickness will influence the passive diastolic pressure-volume relation (E_{min}) as higher pressures are needed to fill the stiffer ventricle. We thus assumed that E_{min} changes in proportion to E_{max}, and this assumption is supported by human studies reporting parallel changes in E_{max} and E_{min} [19].

In the scenario where peak systolic LV wall stress was normalized to compensate for the increased afterload, blood pressure and wall thickness increased by only 10%. The main effect was a reduction in cardiac output due to the stiffer ventricle in diastole, while LV filling pressure remained at the same level. End-diastolic wall stress thus decreased, as end-diastolic pressure was constant, end-diastolic chamber dimensions reduced and wall thickness increased. Therefore, LV wall stress normalization alone can not account for the hemodynamic observations in hypertensives with LV hypertrophy.

Normalization of systolic wall stress is not always observed in experiments on chronic pressure overloaded hearts. In dogs with an aortic constriction, Sasayama et al. reported normalized end-diastolic wall stress after 18 days of chronic pressure overload [5] but no normalized systolic wall stress. In dogs with reno-vascular hypertension, end-diastolic but not end-systolic wall stress appears normalized [4] while in dogs with perinephritic hypertension, it has been reported that both end-diastolic and end-systolic wall stress are normalized [3, 6].

When we allowed venous filling pressure to rise to normalize end-diastolic wall stress while still normalizing systolic wall stress, the hemodynamic data better matched the in vivo observations, with a marked elevation of systolic and diastolic pressure. For unaltered left ventricular dimensions, wall thickness and Pv are both increased by about 40%. This increase in wall thickness is within the range reported in hypertensive patients with concentric hypertrophy [2]. Also, stroke volume and cardiac output are preserved, as reported [2, 13]. An increased venous filling pressure in the presence of an increased arterial load was observed earlier in animals in reno-vascular [4] and perinephrinic [3, 6] hypertension. In humans, elevated filling pressures have been reported in LV hypertrophy patients [17, 20]. Pulmonary venous pressure is often

increased in patients with acute left ventricular dysfunction. In a theoretical model study [21], Burkhoff and Tyberg have shown that the increase in P_v is hardly due to the left ventricular dysfunction itself; they hypothesize that the changes in P_v are dictated by sympathetic control on venous capacity. The mechanism of a reduced venous capacity, yielding higher filling pressures to compensate for the impaired diastolic filling in the hypertrophied heart, is also supported by Safar and London [22].

This study, being a mathematical model study, inherently has some limitations. We assumed linear end-diastolic and end-systolic pressure-volume relationships. We also modeled the arterial tree as a linear windkessel model, neglecting nonlinear pressure dependent arterial properties. Further, we modeled an increase in contractility in hypertrophy by an increase in left ventricular wall thickness, also affecting passive diastolic properties and thus neglecting changes of intrinsic contractile myocyte properties.

In conclusion, concentric LV hypertrophy can be explained as a cardiac adaptation pattern to an increased afterload, in which peak systolic wall stress is normalized by increasing LV wall thickness, while an increased preload filling pressure compensates for the impaired diastolic filling and normalizes end-diastolic wall stress. The proposed mechanisms may explain some of the ambiguity in literature. It should be realized however that left ventricular hypertrophy occurs only in about 10% of all hypertensive patients, and that the model still cannot explain why some patients develop hypertrophy, or how and why in some hearts hypertrophy is only an intermediate step towards heart failure.

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