Description of Cardiac Hemodynamics Using a Physical Model: Pressure-Volume Diagrams and the Effect of AV Delay

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Summary

A newly-developed computer model of the cardiovascular system facilitates the analysis of various mechanisms of the cardiac and nervous regulation, as well as the study of their influence on hemodynamics by means of the resulting pressure-volume diagrams (PV diagrams). Knowledge of these interconnections supports the understanding of electrophysiologic processes and the diagnosis and therapy of pathologic changes in the cardiovascular system. The model clearly reproduces the pressure-volume relationships in the heart chambers identified during clinical observations, including the typical effects of the Frank-Starling mechanism. The resulting PV diagrams illustrate the influence of changed pre- and afterloads and thus, reflect the autoregulatory change of the myocardial contraction force. If PV diagrams are generated for different heart rates or contractility levels, characteristic mechanisms of the system can be deduced from the dynamics of the end-diastolic and end-systolic pressures and volumes, which in each case are reflecting the known physiologic conditions. The effects of changed atrioventricular conduction times can also be reproduced and understood. The value for an optimal atrioventricular delay (leading to a maximum stroke volume) decreases with increasing heart rate due to the interaction of various diastolic and systolic effects.

Key Words

Hemodynamics, Frank-Starling mechanism, AV delay optimization, modeling

Introduction

In the field of biophysics, especially in the study of the cardiovascular system, theoretical study models are of crucial importance. In many cases it is impossible to perform experimental research on the physiologic mechanisms due to a lack of technical prerequisites, or the necessity of invasive interventions that would endanger the human subject. Moreover, a detailed understanding of the dynamics within the cardiovascular system is of immeasurable value in the development and optimization of diagnostic and therapeutic methods. A literature review of numerous published models of the cardiovascular system shows that none of the existing models are capable of meeting the demands for a comprehensive tool that can be used in a wide range of applicable fields [1-17].

In the context of a dissertation, an expanded model for the cardiovascular system has been developed that is capable of qualitatively and quantitatively reproducing system characteristics recognized in the medical literature, and furthermore, answers concrete questions from the practice of electrophysiology [18]. In developing this model, physiologic processes at the cellular mechanism level (e.g., electromechanic coupling) were included, as well as the dynamics of the cardiac action, the hemodynamics of the vessel system, and the cardiovascular control via nervous regulation processes. All aspects of the cardiac and vascular hemodynamic systems (pressure, volume, blood-flow) were recognized in such a way that their values corresponded to empirically obtained data [19,20]. As part of the model validation, physiologic mechanisms, such as the Frank-Starling mechanism (autoregulation of the myocardial contraction force) and the effects of a time difference between atrial and ventricular contraction were reproduced.

To understand various aspects of cardiovascular regulation, especially cardiac hemodynamics, the analysis of

left-ventricular pressure-volume (PV) diagrams is an important tool. The interaction of cardiac chronotropy and inotropy, myocardial autoregulation (Frank-Sterling mechanism), and the principle function of the baroreceptor reflex can be studied using PV diagrams. These basic properties of the cardiovascular system, as well as the hemodynamic effect of varying the AV conduction time, are presented and discussed in this article using results generated from a computer model.

The Route of Cardiac Pressures and Volumes Used in the Model

The combination of models derived from different fields and the addition of numerous new features necessitated a completely new definition of the initial values and the parameter values for the model. As much as possible the values were taken from literature sources [19,20]; in part the values were optimized so that physiologic pressure and volume responses were achieved. As part of the validation model the pressures and volumes in the four heart chambers were graphed under normal resting conditions. The calculation was performed with a standard parameter set, i.e., for a cardiovascular system without pathologic changes and under resting conditions. Figure 1 shows the respective results of the model. The results reflect typical characteristics of cardiac hemodynamics: a fourfold systolic pressure in the left ventricle compared to the right ventricle; the lower pressure level of the atria; the approximately identical volumes of the left and right ventricles and atria; and the effect of atrial contractions on ventricular volumes. The effects of the valve plane motion can also be seen in the volume curves (note the spontaneous increase in atrial volume after the end of ventricular systole).

Frank-Starling Mechanism

One of the basic characteristics of the cardiovascular system is the Frank-Starling mechanism, i.e., the autonomous adaptation of the heart due to changing load conditions. This model of electromechanic coupling accounts for the dependency of the actively generated wall tension on the momentary dilatation of the myofibrils and the speed with which it occurs. The hemodynamic responses to changes in the cardiac pre- or afterload were examined with the help of our model.

Adaptation to Acute Volume Load (Preload)

An increased venous blood flow into the heart leads to a greater end-diastolic ventricular volume. The actively generated rise in wall tension is due to the more pronounced length and dilatation of the myofibrils, which triggers a stronger contractionwith a resultant increase in stroke volume (SV). Thus, the heart is able to cope with this autoregulatory increase in diastolic filling by ejecting a larger SV, without changing the heart rate (HR) and without external (e.g., vascular) influences [19].

The study model determined to what degree reactions to a change in the ventricular preload could be reproduced. Preload modification was achieved by a gradual

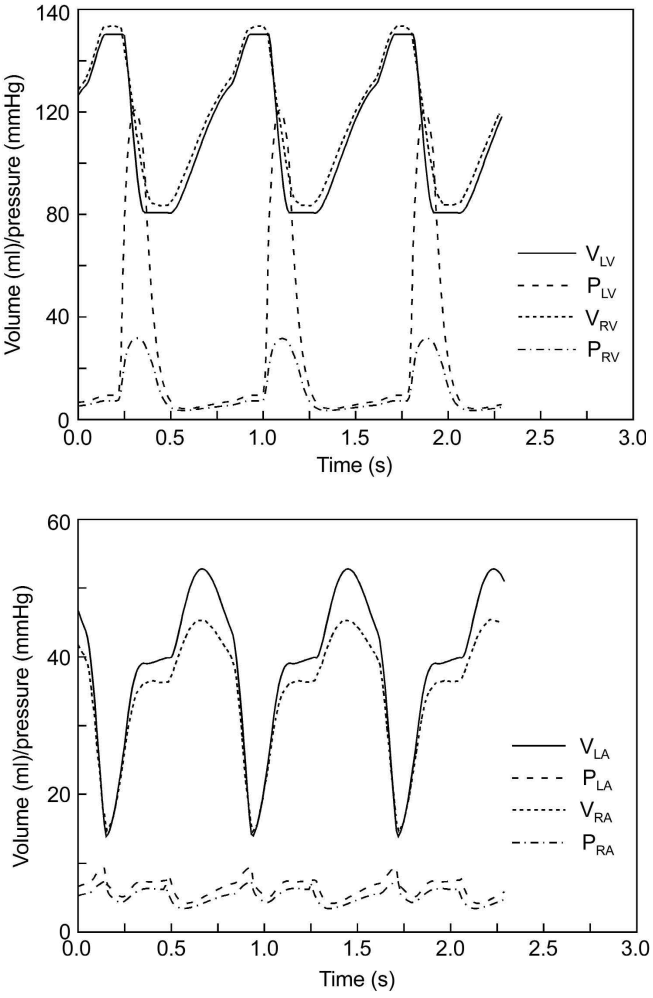

Figure 1. Pressures (P) and volumes (V) of the heart for validating the model. Above = left and right ventricle (LV, RV), below = left and right atrium (LA, RA).

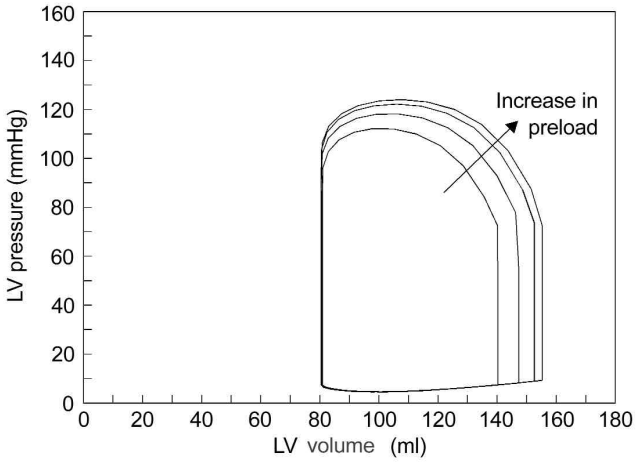

Figure 2. Left-ventricular PV diagrams when varying the left-ventricular preload.

variation in the venous compliance. Since this was not a simulation in an isolated heart, a complete separation of the pre- and afterload effects was not possible. However, changing the compliance primarily constitutes a change in preload. Figure 2 shows simulated PV diagrams for four different preload levels. The PV diagrams show that an increased volume load dilates the myocardial fibers and leads to a higher active systolic pressure in the left ventricle. Consequently, the SV rises as expected. In an important deviation from descriptions of the effect in the isolated heart, the end-systolic volume does not increase in the model of the complete cardiovascular system. This effect can be explained by two mechanisms. First, after a few cardiac cycles a new equilibrium is established in the closed cardiovascular system, following the emptying or filling of the blood reservoirs in the veins due to compliance changes. Secondly, the baroreceptor reflex counteracts the resultant change in blood pressure by varying the contractility, and thus, at least partially compensates for the effects of the changed preload. To permit an even better analysis of the mechanisms of myocardial autoregulation, the baroreceptor reflex was deactivated in a further simulation by providing the input (at the baroreceptor) with a constant blood pressure signal. Figure 3 displays the effects of the change in preload with a deactivated baroreceptor reflex. The SVs clearly differ for the different preload levels. Variations in the systolic peak pressure are also more pronounced when the baroreceptor reflex is deactivated. This also results in a slight variation in the end-systolic volume.

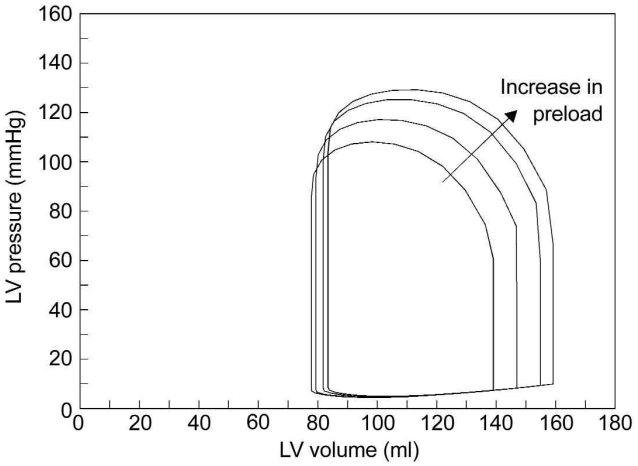

Figure 3. Left-ventricular PV diagrams when varying the left-ventricular preload; baroreceptor reflex deactivated.

Adaptation to Acute Pressure Changes (Afterload)

Cardiac activity gradually adapts to a rising flow resistance in the vascular system. Due to the greater aortic pressure, the increase in afterload first causes a reduction of the SV, and subsequently, an increase in the end-diastolic volume, given an unchanged inflow. This change enables the heart to develop a higher pressure as a consequence of the greater predilatation of its muscle fibers. The work range of the left ventricle is thus shifted towards greater volumes until the original SV has been reestablished under the higher pressure [19].

In the simulation, the variation of the afterload was achieved by a gradual change in the flow resistance of the systemic periphery. The results in Figure 4 show that the model also reproduced the physiologic autoregulatory mechanisms during this examination. In each case the operating point of the ventricle is set so that a largely constant SV with different values for the end-diastolic and end-systolic volumes is achieved. In this case another simulation using a deactivated baroreceptor reflex was again calculated to highlight the effect. The respective PV diagrams (Figure 5) clearly show the shift in the PV diagrams; the width of which (i.e., SV) remains unchanged along the volume axis with a simultaneous adaptation of the systolic pressure level.

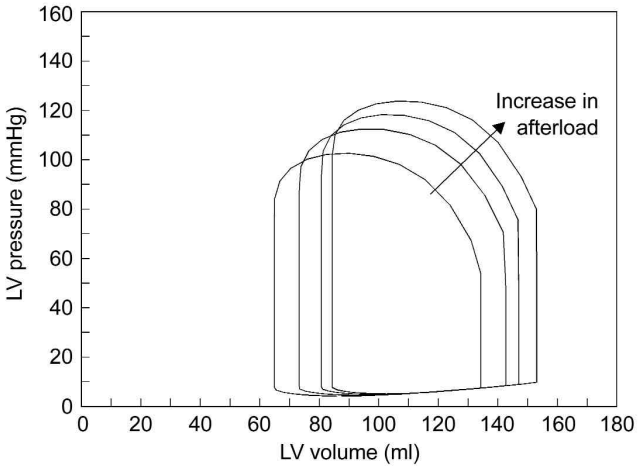

Figure 4. Left-ventricular PV diagrams when varying the left-ventricular afterload.

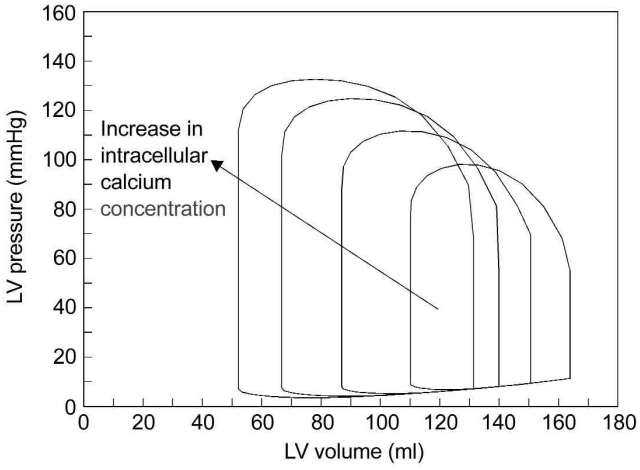

Figure 6. Left-ventricular PV diagrams when varying the intracellular calcium concentration

Inotropic and Chronotropic Changes

Changes in the contractility and the HR strongly influence cardiac mechanics, which is expressed in the changed PV diagrams. The inotropic regulation, i.e., the load-dependent change in inotropy, offers another possibility – aside from the described autoregulatory processes – to adjust the cardiac output (CO) to changing hemodynamic conditions independent of the rate. The model accomplished the coupling of the baroreceptor output signal with the model of the electromechanic coupling through a linear progression of the intracellular calcium concentration. The PV diagrams calculated with the model for different scaling factors of the intracellular calcium concentration (Figure 6) reflect the significantly increasing left-ventricular systolic pressure with increasing intracellular calcium concentration. Furthermore, a higher intracellular calcium concentration also results in a greater SV. The effect of a decreasing volume level in the left ventricle with increasing contractility requires some thought. Due to the increased ejection, the left ventricle is emptied more thoroughly and thus, a decrease in diastolic volume is resulting. After a few heartbeats, this effect is compensated by means of an increased venous backflow. However, it is possible that the vessels will store a greater amount of blood due to the higher pressure level in the vascular system, so that only a partial compensation of the reduced ventricular volume takes place. Thus, an equilibrium with decreased end-diastolic and end-systolic volumes results from a rise in contractility. Therefore, an increase in contractility is indirectly connected to a reduced preload and an increased afterload. These mechanisms partially counteract the improved CO. In the isolated heart with constant pre- and afterload, the effect of inotropic regulation on the resulting ejection fraction is therefore greater than in the closed cardiovascular system.

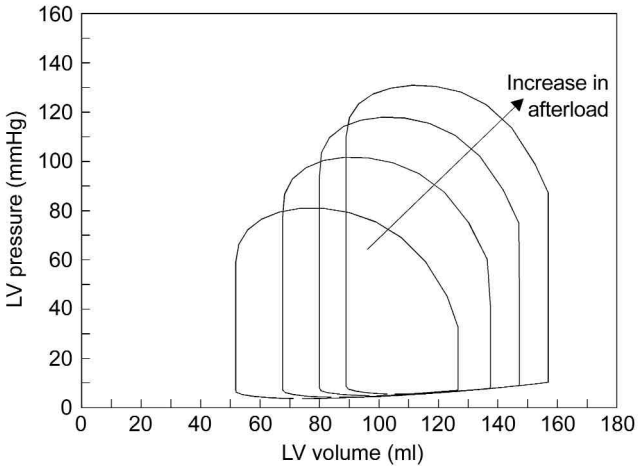

Figure 5. Left-ventricular PV diagrams when varying the left-ventricular afterload; baroreceptor reflex deactivated.

Of major importance in the cardiovascular system is the influence of a changed HR on cardiac mechanics. An externally programmed change in the HR that has

not been initiated by the closed control system causes a number of reaction mechanisms in the autoregulatory, hemodynamic, and neurohumoral systems. In our model, a constant offset was added to the respective current HR, which was gradually varied, resulting in HRs in the range from 50 to 100 beats/min. Figure 7 shows PV diagrams for different HRs with the deactivated baroreceptor reflex, in order to provide a detailed analysis of the effects of the hemodynamic mechanisms.

The PV diagrams reflect the following behavior:

- the ejection fraction is the greatest for the lowest HR and continuously decreases up to the highest HR;
- the end-systolic volume continuously increases with an increasing HR;
- the end-diastolic volume is constant at low and medium HRs and slightly decreases at higher HRs;
- the systolic peak pressure has a maximum at medium HRs and decreases when lowering as well as when increasing the HR.

In order to understand the observed dependencies, the various cardiac and vascular mechanisms must be discussed: The percentage of diastole within a cardiac cycle decreases with increasing HRs. At low and medium HRs the time period for diastolic filling is long enough to allow a rather complete pre-filling of the left ventricle through continuous inflow and the atrial contraction. The end-diastolic volume is constant in this range. If the HR continues to rise, the cardiac cycle starts before the main phase of the diastolic filling is completed. This interruption of the filling phase leads to a reduced end-diastolic volume and a reduced preload. As a result of a higher HR, a higher pressure builds up in the vascular system on average, especially in the arterial vascular system. The raised aortic pressure acts as increased afterload on the left ventricle. As has been previously discussed, this increase in afterload leads to a higher systolic peak pressure and to greater values for the end-systolic volume. The maximum systolic pressure first increases with a rising HR; however, it then decreases at high rates because of the increasingly dominant effect of the decreasing preload (see Figure 7).

All together an increase in HR has a counterproductive effect on the ejection fraction and the SV. A solitary increase in HR by a defined factor will thus only cause an increase in CO by a smaller factor. A slightly different situation results if the baroreceptor reflex is also considered (Figure 8). The activated baroreceptor reflex counteracts the aortic pressure (which is too low at low HRs and too high at high HRs) mainly by changing the myocardial contractility and also through the vasomotor response. Inotropic regulation increases or decreases the maximum systolic pressure (compared to the results from Figure 7) in such a way that the influence of an increasing afterload on the systolic pressure is largely compensated for. Furthermore, the vasomotor response partially neutralizes the pre- and afterload effects. In addition, this leads to an increase in the volume level at low HRs and a slight decrease at high HRs.

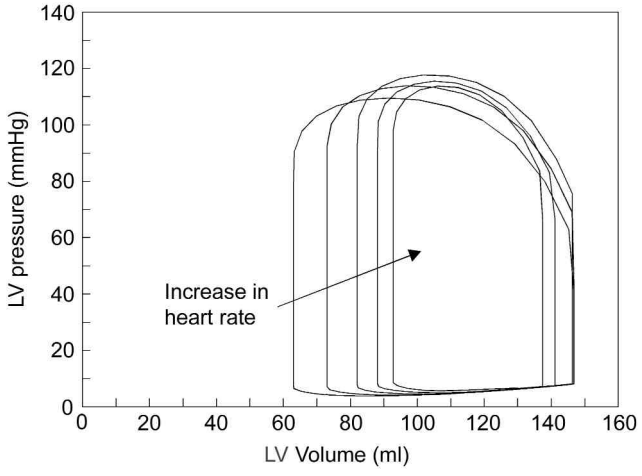

Figure 7. Left-ventricular PV diagrams when varying the heart rate, baroreceptor deactivated.

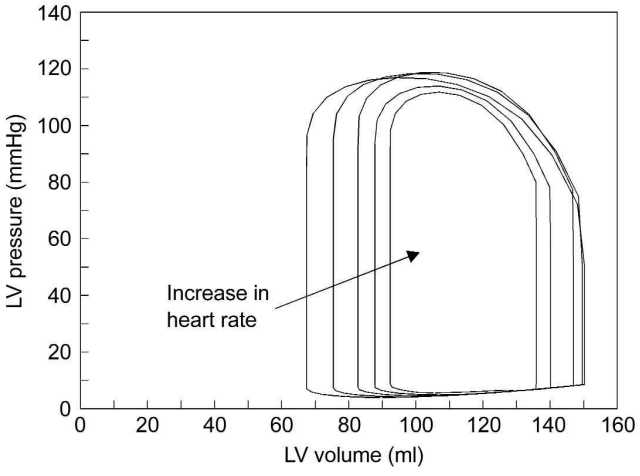

Figure 8. Left-ventricular PV diagrams when varying the heart rate; baroreceptor active.

Atrioventricular Conduction Time

Besides chronotropic and inotropic regulation, dromotropy, i.e., the situation-dependent variation of the atrioventricular (AV) conduction time (AV delay), also plays an important role in adapting the cardiac activity to the respective demand. Too short as well as too long AV delays have an unfavorable effect on hemodynamics. The value for the optimal AV delay or the optimal AV-delay range differs from individual to individual and depends in particular on the HR. The optimization variable for the AV delay is primarily the SV; in this way the optimal effect of the contraction can be achieved without "adaptation losses." Only secondarily, a change of the AV delay can have a relieving function on the myocardium, especially in case of pathologic myocardial changes. The diagram in Figure 9a shows the dependency of the SV on the programmed AV delay at different HRs. For a better understanding of the mechanisms, Figure 9b shows the dependency of the end-diastolic left-ventricular volume on the AV delay and HR. The optimal AV delay (at which the SV is the greatest) is rate-dependent; in our model it is about 200 ms for low HRs and falls to about 140 ms for higher HRs. Furthermore, it is noteworthy that the influence of the AV delay on the SV is clearly less pronounced at low HRs than at high HRs. In particular, long AV delays have hardly any effect on the SV at low HRs, while long AV delays have clear hemodynamic consequences at high HRs. The variation of the SV due to changes of the AV delay is at an overall low level in the model with a range of ±10%. This is due to the fact that the effects of the mechanical flow (based on the change in the coordination of the contraction and the resulting flow obstructions and turbulences) are not considered in the simplified sphere model. Nevertheless, in general, the observed effects reflect the mechanisms observed in clinical practice very well. The significance of the AV delay for the hemodynamics becomes clear in clinical studies. Comparing different pacemaker therapy forms, they partially consider the advantage of an optimal AV delay to be of greater hemodynamic relevance than the disadvantage of having to use right-ventricular pacing for this [21].

The analysis of the end-diastolic volume (Figure 9b) illustrates the underlying mechanisms for the observed dependency of the SV on the AV delay and the HR. Two questions are of critical importance:

- Is the AV delay long enough to attain a sufficient pre-filling of the ventricle by means of the atrial contraction?
- Is the ventricular-atrial (VA) delay long enough to attain a sufficient diastolic filling of the heart?

It can be observed that the first effect occurs almost identically at all HRs, while the effect of the diastolic filling can be seen especially at high HRs, at which the VA delay is already significantly shortened anyway. The additional dependency of the end-diastolic volume on the HR has its basis in the changing pre- and afterload effects, which have already been discussed in this paper (see Figure 8).

The importance of an optimal AV delay for the hemodynamics, especially at high HRs, is confirmed by the results. For instance, very short AV delays (< 100 ms)

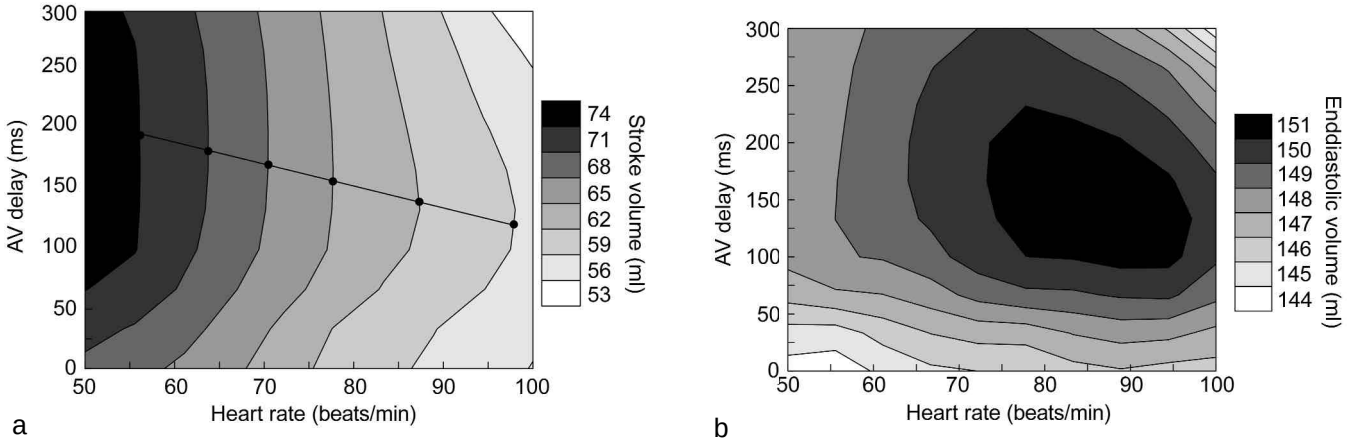

Figure 9. a) Stroke volume is dependent on the AV delay and heart rate. The line highlights the course of the optimal AV delay at changing heart rates. b) End-diastolic volume of the left ventricle is dependent on the AV delay and heart rate.

with a forced contraction by a suboptimally programmed cardiac pacemaker, are hemodynamically unfavorable in all HR ranges.

Conclusion

An understanding of cardiovascular processes and their effect on cardiac hemodynamics is essential for a far-reaching analysis of clinical results in the development and testing of new diagnostic and therapeutic methods. With the aid of a recently developed numerical model, we are able to visualize and analyze the underlying mechanisms of cardiac hemodynamics, such as pressure-volume relationships in the ventricles and the effects of modified AV conduction times. Based on new insights and due to the targeted application of the module, we are able to address concrete questions pertaining to the diagnosis of pathologically altered characteristics of the cardiovascular system. In this manner, we can obtain clarification in the preliminary stages of a study regarding the extent to which newly developed diagnostic or therapeutic methods are expected to exhibit sufficient sensitivity and specificity before animal experiments and invasive clinical examinations are performed.

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