A mechanical modeling of cardiac pressure–volume loops

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SUMMARY. We present a reduced–order heart model aimed to introduce a novel point of view in the interpretation of the pressure–volume loops. The novelty of the approach is based on the definition of active contraction as opposed to that of active stress. The consequences of such assumption are discussed with reference to a specific pressure-volume loop characteristic of a normal human patient.

1 INTRODUCTION

The heart is a specialised muscle that contracts regularly and pumps blood to the body and the lungs. The center of the pumping function are the ventricles; due to the higher pressures involved, the left ventricle (LV) is especially studied. The pace of the pumping action is triggered by the diffusion of the so-called *activation potential* through the heart tissue. The effectiveness of the pumping action may be evaluated through the analysis of different parameters: the stroke volume, the ejection fraction, the end–systolic pressure–volume relationship, and many others. All of them are well represented in the *pressure–volume loop*, the so-called PV loop, which, in the end, represents a synthesis of the mechanical activity of the heart [1], [2], [3]. Ventricular chamber pressures and volumes are strictly related to the contractile capacities of the heart due to the muscular structure of the cardiac tissue. A qualitative and quantitative bridge between the function of the heart as a whole and the microscopic dynamic characterizing muscle contraction would be desirable but it is considered still unrealized [4].

Here, we present and discuss a reduced–order heart model aimed to introduce a novel point of view in the interpretation of the pressure–volume loops. The key point is the notion of active contraction as opposed to that of active stress (see [5]). We assume that the contraction experienced by the walls of the left ventricle under stimulus is described at the macroscopic scale by a change in the length of the muscular fibres, a change that we call active deformation.

The actual length of the fibres, in turn, depends on the amount of stress they sustain. So, we associate with each element of the contractile chamber two different states: the contracted and the visible one. The typical pressure–volume pair of the cardiac PV loop lives at the visible layer and the volume change is measured with respect to a slack volume through a deformation that we call *the visible deformation*. Nevertheless, there is a hidden layer characterized by an active deformation which measures macroscopically the contraction of the slack volume into a volume which is still unstressed (that is, corresponding to zero pressure). The key issue is the distinction between the two basic components of the visible deformation: the active strain of the left chamber, due to the activation of cardiac muscles, describing the global contraction of the ventricle; the passive strain, due to the elastic structure of the tissue, measuring the difference between the unstressed, contracted volume and the visible volume.

The simplest geometric approximation of the left ventricle is the spherical surface of constant wall thickness: it allows to write a handy relation between the pressure p inside the chamber and the mean tension σ generated in the LV tissue. Moreover, we assume that the fibres are tightly embedded in the tissue and do not account for any tissue anisotropy: both the passive and the active response of the tissue are assumed to be completely isotropic. Nevertheless, the large deformations of the ventricle make mandatory to set the modeling within the context of non–linear elasticity. As the PV loop attains to the mechanics of the heart, the electrophysiology of the tissue does not enter the model (see [6] for an electromechanical model of the heart based on the notion of active contraction).

In the end, we use a specific sample extracted by [7] to better illustrate and discuss our point of view. In [7], with reference to a normal human patient, the pairs pressure–volume are measured and the PV loop shown in figure 4 is developed. From there and with reference to our reduced–order heart model, a discussion on the main characteristics of the PV loop is engaged.

2 THE PRESSURE-VOLUME LOOPS

Of the four chambers that comprise the whole heart, the left ventricle accomplishes the major mechanical work, while undergoing large deformations and intense stress states. On a simplistic level, the ventricle is an ellipsoidal chamber, whose walls are composed of muscle fibres. It is the *contraction* originated in the muscles that translates into pressure and/or volume changes of the chamber. The LV cycle may be schematized as the sequence of four steps: filling–the *diastolic* phase; isovolumetric contraction; ejection–the *systolic* phase; isovolumetric relaxation.

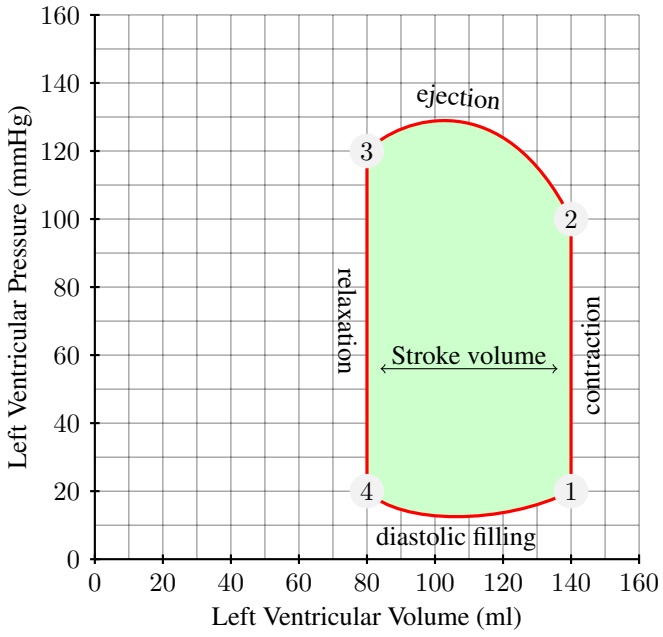

Figure 1: Phases of the cardiac cycle of a normal human patient. 1) Mitral valve closes; isovolumetric contraction. 2) Aortic valve opens; ejection. 3) Aortic valve closes; relaxation. 4) Mitral valve opens, filling. The green area represents the stroke work.

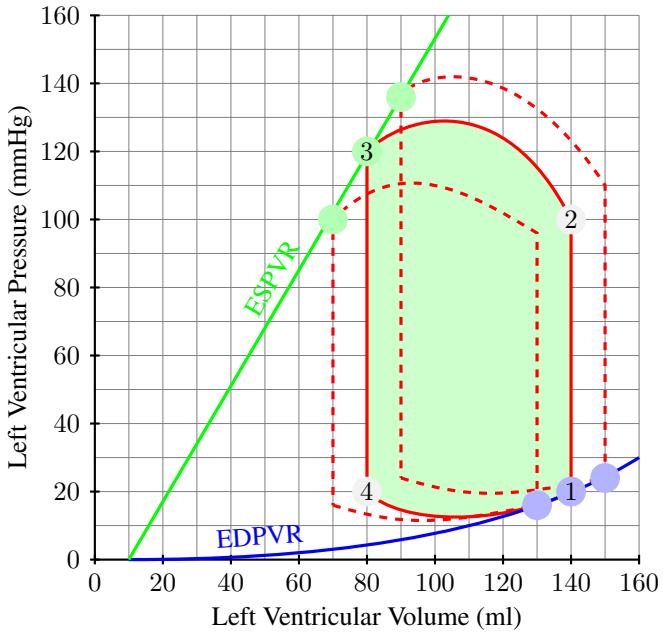

Figure 2: EDPVR and ESPVR represent the pressure-volume relationship for a complete relaxed state, and a highly activated state, respectively. Changes in EDP make point 1 move along the EDPVR; changes in ESP move point 3 along ESPVR.

During the cycle, both pressure and volume vary in time, and a quite useful determinant of the cardiac performance is the plot representing the pressure-volume relationship in the LV during the entire cycle, that is, the PV loop; some of the many clues contained in the plot (see Fig. 1) are briefly summarized in the following. Point 1 defines the end of the diastolic phase and is characterized by the end–diastolic volume (EDV) and pressure (EDP); at this point the mitral valve closes and cardiac muscle starts to *contract* in order to increase the blood pressure. At point 2 the systolic phase begins: the aortic valve opens and blood is ejected outside the LV; muscles keep on contracting in order to further the ejection, while volume decreases to a minimum. Point 3 defines the end of the systolic phase, and is characterized by the end–systolic volume (ESV) and pressure (ESP); starting from here, LV undergoes an isovolumic *relaxation* until point 4, where mitral valve opens and filling begins. During the filling phase, muscle keep on relaxing in order to accomodate a large increase in blood volume, while maintaining the pressure at a quite low level. Filling is completed at point 1. The difference between maximum and minimum volume is called stroke volume (SV): $SV := EDV - ESV$. Two important curves are usually represented in a PV diagram: the end–diastolic pressure–volume relationship (EDPVR) and the end–systolic pressure–volume relationship (ESPVR): these curves characterize the *passive* mechanical response of the ventricle in two quite different states: the relaxed state, and the contracted one, respectively (see Fig. 2). Let us consider point 1: muscles are in their most relaxed state (the slack state), and any pressure variation will cause a volume change along the EDPVR, *provided muscles stay inactive*. Thus, the EDPVR provides a lower boundary for the pressure at which the mitral valve closes, and the position of point 1

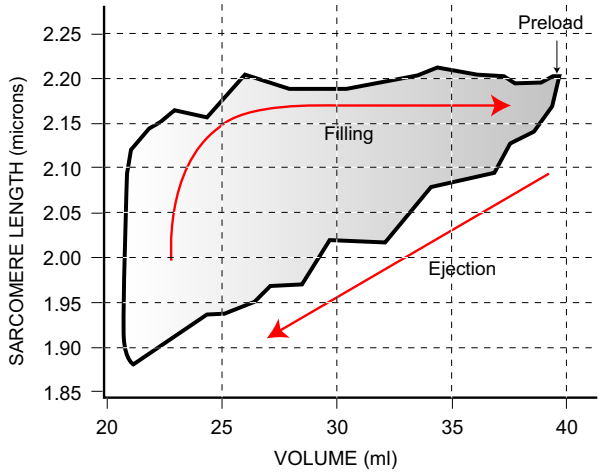

Figure 3: Sarcomere length as function of volume (Elaboration from [8]).

depends on the end-diastolic filling pressure. Physiologically, the EDPVR changes as the heart grows during childhood; most other changes accompany pathologic situations (hypertrophy, infarct, dilated cardiomyopathy).

Let us now consider point 3: muscles are in a highly activated state, and LV behaves as a much stiffer chamber; any pressure variation will cause a volume change along the ESPVR, *provided muscles maintain the same level of activation*. Thus, the ESPVR provides an upper boundary for the pressure at which the aortic valve close, and the position of point 3 depends on the end-systolic ejection pressure or volume.

The interactions between the LV and the *preload*, the inflow conditions determined by the venus system, and the *afterload*, the outflow conditions determined by the arterial system, strongly influence the arterial blood pressure and the cardiac output, which in turn constitute two key factors for the assessment of the overall cardiovascular performance. Thus, a change in preload or in afterload conditions may markedly alter the PV loop, and results in a shift of point 1 or point 3 along the EDPVR or the ESPVR, respectively, as Fig. 2 shows.

A meaningful measure of the preload would probably be the sarcomeres length at end diastole; due to the intrinsic difficulties related to this measurement, EDP is the most common index of preload. Afterload is in general related to the arterial system, but also pathologic conditions, as a leaky mitral valve, or a stenotic aortic valve, could be accounted for.

To any point in the PV loop there corresponds a specific level of muscular activation, and thus, a specific average sarcomere length. A quantitative sampling of sarcomere lengths versus the volume is depicted in figure 3: at the preload condition sarcomeres are slightly stretched but still not activated and passive elasticity predominates; isovolumic contraction and ejection are the consequences of an increasing muscle activation, and thus, an increasing sarcomere shortening; during isovolumic relaxation and subsequent filling, sarcomere elongates, and eventually recover their initial length.

3 VENTRICULAR PRESSURE–VOLUME RELATIONSHIPS

The behavior of individual cardiac muscle cells has been extensively studied ([9], [10]) but the integration of the muscle dynamics into a model able to produce the global behavior of the beating

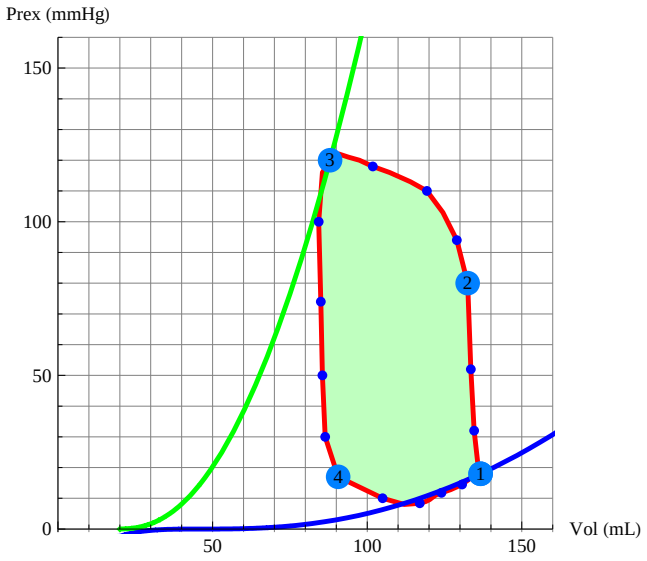

Figure 4: A typical PV loop of a normal human patient, as measured in [7], with our ESPVR and EDPVR curves superimposed, as equation (3.7) dictates; the large blue dots correspond to the same four key points shown in figure 1.

heart has not fully developed yet ([4], [8]). Here, we present a macroscopic model of the left ventricle embodying the notion of muscle contraction: it is a zero dimensional model, simple enough to enlighten the key ideas at the bases of the modeling; nevertheless, it is able to capture the important features of the pump function of the heart which are collected in the PV loop, and it is rigorously extendible to the full fledged non-linear 3D elasticity theory. We characterize the pump function of the left ventricle through a macroscopic model based on a two–layer kinematics. The volume V measured in a typical cardiac loop lives at the visible layer; the deformation ε measures the strain of V with respect to a reference volume, here assumed to be the slack volume V_s. Then, there is a hidden layer describing the contracted volume V_c, meant to be a coarse modelling of the muscle contraction; the active deformation ε_c measures the contraction of V_c with respect to V_s. It is worth saying that V_c is assumed stress free, that is, it models the muscular contraction prior to the loading (that is, in correspondence to zero pressure). The key issue is the distinction between the two basic components of ε: the active strain ε_c of the left chamber, due to the activation of cardiac muscles, describing the global contraction of the ventricle; the passive strain φ, due to the elastic structure of the tissue, measuring the difference between the unstressed, contracted volume V_c, and the visible volume V; thus, we have

$$\varepsilon = \varphi\, \varepsilon_c \tag{3.1}$$

In the following, before turning to complex mathematical models for interrelating ventricular chamber pressure and volume to a suitable measure of contraction, we deal with a simple model of the ventricle camera which is rich enough to enlightening our ideas. The simplest geometric approximation of the left ventricle is the spherical surface of constant wall thickness h, insofar it allows to write a handy relation between the pressure p inside the chamber and the mean tension σ generated

in the LV tissue in the form

$$p = 2\,\frac{\sigma}{r}\,, \quad \sigma = \sigma_m\, h\,, \tag{3.2}$$

with σ_m the mean value of the hoop stress on the wall thickness [1]. The balance of a spherical membrane of radius r is satisfied if equation (3.2) holds. As it is well known, the radius r of the surface is related to the volume V by

$$V \mapsto r = \hat{r}(V) = (\frac{3}{4}\frac{V}{\pi})^{1/3}\,, \tag{3.3}$$

so, it is easy to re–write the balance equation (3.2) in terms of pressure and volume instead of pressure and radius. We introduce the notion of ground volume V_c corresponding to the pair (p, V): it is defined as the pressure–free volume of the spherical surface which has the volume V under the pressure p. It is worth noting that, due to the balance equation (3.2), the pressure–free volume is a stress–free volume, too; nevertheless, it is not contraction–free. We assume that at the ground volume V_c corresponding to the pair $(p,\, V)$ muscles have a level of activation measured by ε_c which influences the stiffness of the chamber at that state. Precisely, denoted as V_s the volume associated to the slack state[1], we set

$$\varepsilon_c = (\frac{V_c}{V_s})^{1/3}\,. \tag{3.4}$$

With reference to a PV cardiac cycle, we assume that the end–diastolic state be the slack state of the chamber and measure contraction from there: $V_s = V_{ED}$. Moreover, the volume V is attained from V_c through an elastic deformation φ. In the following, we often refer to r_c and r_s as to the radii corresponding to the ground contracted volumes V_c and to the slack volume V_s, respectively. Of course, $r_c = \hat{r}(V_c)$ and $r_s = \hat{r}(V_s)$; moreover, $\varepsilon_c = r_c/r_s$. As in the preparatory example, the elastic strain of the chamber is measured through the Kirchhoff–Saint Venant strain measure λ defined as

$$\lambda = \frac{1}{2}((\frac{r}{r_c})^2 - 1)\,. \tag{3.5}$$

Hence, the elastic strain λ is zero at the ground volumes ($r = r_c$) which are mechanically relaxed even if places of active distortion (contraction). Moreover, we still write

$$\sigma = Y\varphi^3 = Y(\frac{1}{2}((\frac{r}{r_c})^2 - 1))^3\,, \quad r_c = \varepsilon_c\, r_s\,, \tag{3.6}$$

for the tension developed into the chamber whose slack radius is r_s with Y the elastic membrane stiffness of the chamber. Equations (3.2), (3.5), and $(3.6)_1$ turn out a basic equation relating the pressure p and the volume V of a spherical surface characterized by the slack radius r_c and by the elastic modulus Y:

$$p = 2\,\frac{Y}{r}(\frac{1}{2}((\frac{r}{r_s}\varepsilon_c^{-1})^2 - 1))^3\,, \quad r = \hat{r}(V)\,. \tag{3.7}$$

For a fixed Y, equations (3.7) give a pressure–volume relationship depending on the contraction ε_c. As first, we can determine, for any Y, the contraction measure $\varepsilon_c = r_c/r_s$ corresponding to a specific pair $(p,\, V)$; then, to any characteristic value of ε_c it corresponds a specific pressure–volume relationship which may be represented as a curve in the $p - V$ plane. Specifically, when $\varepsilon_c = 1$, we find the EDPVR curve; when ε_c attains its maximum value, we find the ESPVR curve. In between, we find pressure–volume curves representing a transition from the EDPVR to the ESPVR.

[1] If one does exist.

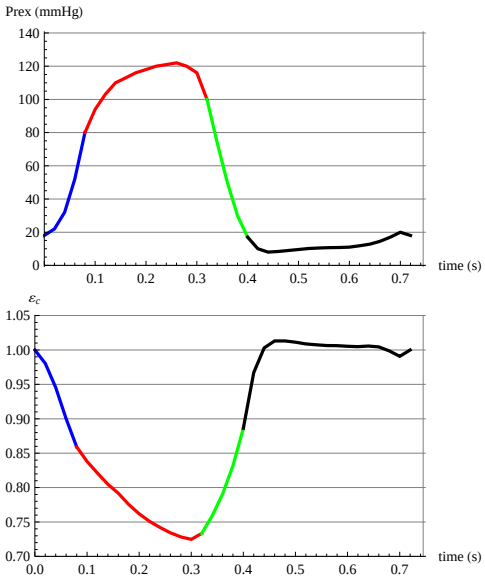

Figure 5: A typical pressure cycle VS time (top, measured from [7]) and the corresponding contraction (bottom) as given by equation (3.7).

Moreover, the assumption that the muscle stiffness Y does not change during contraction is just a simplifying hypothesis which, however, does not alter the capacity of the model. So, let us get on with a specific sample extracted by [7]. There, with reference to a normal human patient, the pairs pressure–volume are measured and the PV loop shown in figure 4 is generated. Precisely, points from 1 to 2 describe the isovolumic contraction; points from 2 to 3 describe the ejection phase; points from 3 to 4 describe the isovolumic relaxation; and points from 4 to 1 describe the filling phase. For a better comprehension, in figure 5, top, we represent with different colours the time course of the pressure corresponding to the four characteristic phases of the cardiac cycle: blue for isovolumic contraction, red for ejection, green for isovolumic relaxation, and black for ventricular filling.

We assume that the points labelled 1 and 3 correspond to the end–diastolic and the end–systolic pressure–volume pairs, respectively. Following our idea, we recovered the contraction measures associated to every $(p,\, V)$ state in the loop. Figure 5, bottom, shows the time course of the contraction cycle as it turns out from equations (3.7) for a fixed value of the elastic stiffness of the chamber.

As figure 5 shows, the end–diastolic state corresponds to $\varepsilon_c = 1$ and the end–systolic state to $\varepsilon_c = 0.72$. In correspondence of these values, equations (3.7) gives the EDPVR and ESPVR curves which are represented in figure 4 (blu and green solid line, respectively) as superimposed on the PV loop.

Moreover, the transition from EDPVR to ESPVR may be derived through a generalization to any point during the cardiac cycle of the procedure used to extract the EDPVR and the ESPVR relationships from equation (3.7). Figure 6, left, shows the contraction–volume loop corresponding to the PV loop we are examining; it is worth saying that our model captures the experimental loop shown in figure 3. Of course, all our results depend strongly from the elastic modulus Y here set to a

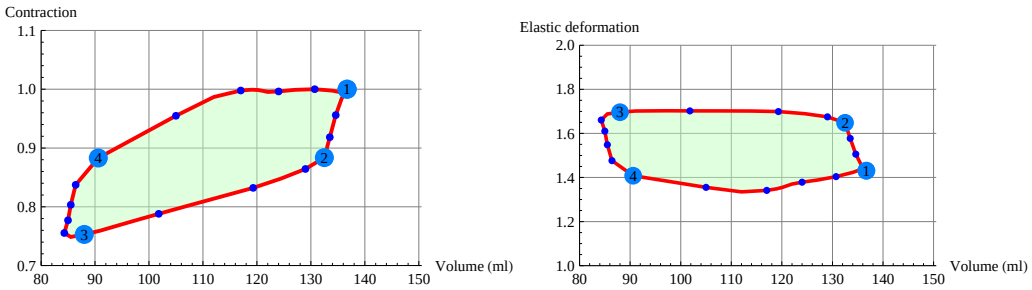

Figure 6: Contraction (left) and elastic deformation (right) along the cardiac cycle as function of volume.

fixed value. In the end, it is worth noting the trend of the elastic deformation associated to the cardiac loop shown in figure 6, right. As expected, the elastic deformation increases when pressure increases and decreases when pressure decreases, along the isovolumic contraction and relaxation, respectively (it is worth remind that along the latter phases, it is the visible volume of the left chamber to be constant). Along the intermediate states (ejection and filling) the elastic deformation is substantially constant.

4 CONCLUSIONS AND FUTURE DIRECTIONS

A novel point of view is introduced in the modeling of the activable nature of cardiac tissue defining the muscle contraction as an active deformation of the tissue. Here, with reference to a simple heart model, a mechanical interpretation of cardiac PV loops is proposed based on the notion of active deformation.

In our opinion, the simplicity of the model helps to enlighten the basic characteristics of the PV loop and, as will be shown in future works, to discuss typical heart dysfunctions detectable through the PV loop. Nevertheless, a less simple heart modeling would be more fit to account for the complex material structure of the walls of the left chamber as well as for the interaction between the mechanics and the electrophysiology of the cardiac tissue. In these directions, further work must be done following the lines already identified in [6], [11], [12].

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