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Criteria for Study of Heart Failure derived from ESPVR*

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Abstract— **In this study, the end-systolic pressure-volume relation (ESPVR) is used to derive new criteria that can help understand the problem of heart failure with normal or preserved ejection fraction (HFpEF). It is shown that the ejection fraction (EF) is just one index of several indexes that can be derived from the parameters describing the ESPVR and related areas under ESPVR.**

I. Introduction

Heart failure with normal or preserved ejection (HFpEF) [1-3] refers to systolic contraction of the left ventricle in cases of patients with symptoms of heart failure (HF) when the ejection fraction (EF) is greater than 50%. It is estimated that half of the patients presenting with symptoms of HF have preserved EF [2]. Most of the HFpEF studies have focused on two themes: 1) the change in the geometry of the left ventricle during the ejection phase such as long axis shortening or twisting and/or 2) the study EF [4-7]. It was first reported by Dumesnil et al. [8-10] that patients with aortic stenosis can have decreases in longitudinal shortening and wall thickening of the left ventricle, while the EF remains within normal limits because of the influence of intrinsic myocardial factors and/or left ventricular geometry. Several studies have since then been published to explain the influence of both intrinsic myocardial factors and ventricular geometry on EF [11, 12]. It is clear that HF is a complex process influenced by the interaction of several factors like the metabolism of the myocardium, ventricular suction and filling, preload and afterload relaxation. In this study we look at the problem of HF from one angle to see how the parameters describing the end-systolic pressure-volume relation (ESPVR) and related areas under the ESPVR can be used to assess the condition of the heart.

ESPVR is the relation between pressure and volume in the left or right ventricle when the myocardium reaches its maximum state of activation. There have been several studies on the ESPVR [13-17], for a review see [13]. Most of these studies have focused on the use of the maximum slope E_{max} and the volume axis intercept V_{om} of the ESPVR in order to study the state of the myocardium. In a series of studies on the ESPVR published by one of the authors, special attention was given to the introduction of the active force of the myocardium (also called isovolumic pressure P_{iso} by physiologists) in the mathematical formalism describing the pressure-volume relation (PVR) and the ESPVR in the ventricles [18-23]. In this study we show how the EF is influenced not only by ventricle geometry, but also by myocardium forces and the systolic contraction energy as derived from the areas under the ESPVR. Applications to experimental data are also presented. Although the formalism developed can be applied to the four chambers of the heart, we restrict our applications to experimental data for the left ventricle.

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II. Mathematical Formalism

A. PVR

As in previous publications [18-23], the left ventricle is represented as a thick-walled cylinder contracting symmetrically (see Fig. 1). A radial active force D_r (force per unit volume of the myocardium) is developed by the myocardium during the contraction phase. The active pressure on the inner surface of the myocardium (endocardium) is given by $\int_a^b D_r\, dr = P_{iso}$, where a = inner radius of the myocardium, b = outer radius of the myocardium. We neglect inertia and viscous forces since they are relatively small. The equilibrium of forces on the endocardium can then be expressed in the form

$$P_{iso} - P = E\,(V_{ed} - V) \tag{1}$$

where P is the left ventricular pressure, V is the corresponding left ventricular volume, V_{ed} is the end-diastolic volume (the largest volume when dV/dt = 0). The right-hand side of (1) is the pressure on the endocardium resulting from the elastic deformation of the myocardium. When the elastance E reaches its maximum value E_{max} near end-systole (maximum state of activation of the myocardium), we can write (1) as follows

$$P_{isom} - P_m = E_{max}\,(V_{ed} - V_m) \tag{2}$$

In (2) P_{isom}, P_m and V_m are the corresponding values of P_{iso}, P and V, with $V_m \approx V_{es}$ the end-systolic volume when dV/dt = 0.

B. ESPVR

Equations (1) and (2) are represented graphically in a simplified way in Fig. 2. The ESPVR is a relation between P_m and V_m such that when the myocardium reaches its maximum state of activation represented by P_{isom}, it is represented by the line d_3V_{om} with slope E_{max}, mid-point d_5 and volume axis intercept V_{om}. The line with slope E and volume axis intercept V_o in Fig. 2 is an intermediate position. During a normal ejecting contraction the PVR is represented by the rectangle $V_{ed}d_2d_1V_m$. Equ. (1) can be split into the following form

$$P = E\,(V - V_o) \tag{3}$$

$$P_{iso} = E\,(V_{ed} - V_o) \tag{4}$$

and (2) can be split into the form

$$P_m = E_{max} (V_m - V_{om}) \quad (5)$$

$$P_{isom} = E_{max} (V_{ed} - V_{om}) \quad (6)$$

These equations represent ways to represent the equations of the two lines with slope E and E_{max} respectively in Fig.2.

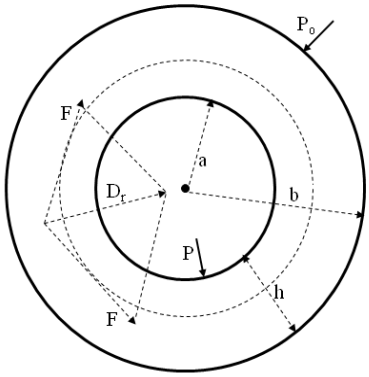

Figure 1: Left ventricle represented by the cross-section of a thick-walled cylinder, D_r = active radial force/unit volume of the myocardium, P = left ventricular pressure, P_o = outer pressure (assumed zero) on the myocardium, a = inner radius, b = outer radius, h = b – a = thickness of the myocardium.

The relative position of the points d_1 and d_5 on the ESPVR (line d_3V_{om}) gives important information on the state of the myocardium. This relative position can be described by the ratio E_{max}/e_{am} (maximum ventricular elastance/maximum arterial elastance) and its relation to the stroke volume $SV \approx V_{ed} - V_m$ (see Fig. 2). We can distinguish the following cases:

a) Normal physiological state of the heart, with d_1 below d_5 on the line d_3V_{om}. In this case we have $SV > (V_{ed} - V_{om})/2$, with $E_{max}/e_{am} \approx 2$ and $P_{isom}/P_m \approx 3$. This case corresponds also to maximum efficiency for oxygen consumption by the myocardium.

b) Mildly depressed state of the heart, with d_1 and d_5 coinciding. In this case we have $SV \approx (V_{ed} - V_{om})/2$, with $E_{max}/e_{am} \approx 1$ and $P_{isom}/P_m \approx 2$. The stroke work SW reaches its maximum value SW_{max}.

c) Severely depressed state of the heart, with d_1 above d_5 on the line d_3V_{om}. In this case we have $SV < (V_{ed} - V_{om})/2$, with $E_{max}/e_{am} < 1$ and $P_{isom}/P_m < 2$.

Notice from Fig. 2 that in cases (b) and (c) an increase in pressure P_m causes a decrease of the stroke work SW, resulting in cardiac insufficiency.

Experimental verification of these results can be found in the work of Burkhoff et al. [14] and Brimouille et al. [15] for experiments on dogs, and Asanoi et al. [16] for results on humans.

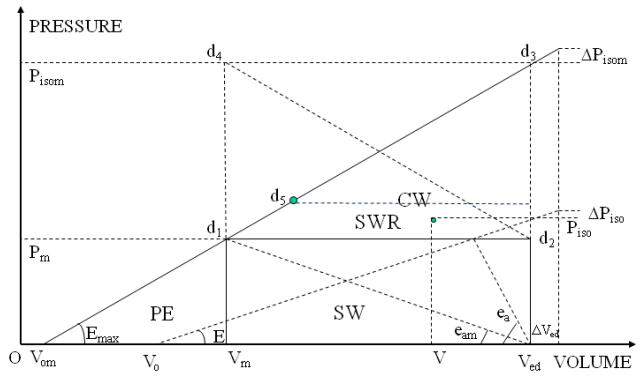

Figure 2: Drawing showing the PVR in the left ventricle, $V_{ed}d_2d_1V_m$ represents the pressure-volume loop in a normal ejecting contraction. The ESPVR is represented by the line d_3V_{om} with midpoint d_5 and slope E_{max}, the line with slope E corresponds to an intermediate position. The left ventricular pressure P_m is assumed constant during the ejection phase. The changes ΔP_{iso} and ΔP_{isom} correspond to ΔV_{ed} according to the Frank-Starling mechanism.

The previous result can be expressed in terms of the areas under the ESPVR, which are sensitive indexes that reflect the state of the myocardium [18-23]. One can distinguish the following areas under the ESPVR:

a) SW = stroke work area $V_{ed}d_2d_1V_m$ in Fig. 2, energy delivered to the systemic circulation. It reaches its maximum value SW_{max} when point d_1 and d_5 coincide.

b) PE = triangular area $d_1V_mV_{om}$ in Fig. 2, potential energy apparently related to the internal metabolism of the myocardium.

c) CW = triangular area $d_3d_2d_1$ in Fig. 2, energy apparently absorbed by the passive medium of the myocardium.

d) SWR = stroke work reserve, $SWR = SW_{max} - SW$, it is the reserve energy that can be delivered to the systemic circulation when there is an increase in afterload represented by an increase in P_m.

We have SW + PE + CW = TW the total area under ESPVR, relation between TW and oxygen consumption is discussed in [23]. We have also the following relations for the stroke volume:

$$SV/(V_{ed} - V_{om}) = (P_{isom} - P_m)/P_{isom} \quad (7)$$

$$CW = (P_{isom} - P_m)\, SV/2 \quad (8)$$

$$TW = P_{isom} (V_{ed} - V_{om})/2 \quad (9)$$

Equations (7) to (9) can be combined to give the following expression for the stroke volume:

$$SV = (CW/TW)^{1/2} (V_{ed} - V_{om}) \quad (10)$$

which shows how SV (and $EF = SV/V_{ed}$) is influenced by the areas CW and TW under the ESPVR, as well as the intercept V_{om} of the ESPVR with the volume axis (see Fig. 2). When $CW/TW = 1/4$ (d_1 and d_5 coincide in Fig. 2), we get from (10) $SV = (V_{ed} - V_{om})/2$. One can also notice that we have [18, 19]:

$$E_{max}/e_{am} = 2*CW/SW \quad (11)$$

which implies that SV in (10) can be expressed in terms of E_{max}/e_{am}. We have also the following relations between the areas under the ESPVR [18,19]:

$$PE*CW = SW^2/4 \quad (12)$$

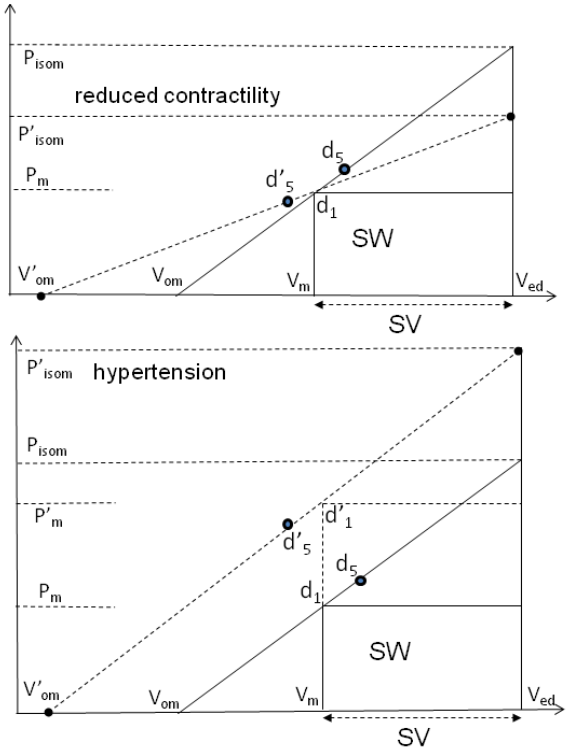

Figure 3: One normal and two abnormal cases of left ventricular contraction with the same EF. Normal physiological case with d_1 below midpoint d_5 (solid line); abnormal case of reduced contractility with d_1 above midpoint d'5 (dotted line, top); abnormal case of hypertension with d'_1 above midpoint d'_5 (dotted line, bottom). Notice that the three cases have the same EF = SV/V_{ed}. Definitions are as in Fig. 2.

Figure 3 shows cases of a normal ESPVR with d_1 below d_5 (solid line), and two cases of reduced contractility of myocardium and hypertension with d_1 above d_5 on the ESPVR (dotted lines), the three cases have the same EF = SV/V_{ed}. For simplicity the drawing in Fig. 3 does not show the variation in V_{ed} in cases of cardiomyopathies (and consequently the influence of the end-diastolic pressure-volume relation on HFpEF), as well as the variation in E_{max} in cases of hypertension. It is known also that in cases of cardiomyopathies the ESPVR (and consequently V_{om}) has a tendency to shift to the right.

III. Experimental Applications

Experimental verification of (10) is shown in Fig. 4 (left side), the vertical and horizontal lines indicate the values $SV/(V_{ed} - V_{om}) = 0.5$ and $CW/TW = 1/4$ that correspond to the critical case when points d_1 and d_5 on the ESPVR (line d_3V_{om} in Fig. 2) coincide. This is the critical case indicating transition from normal to depressed state of the heart (mildly depressed state of the heart).

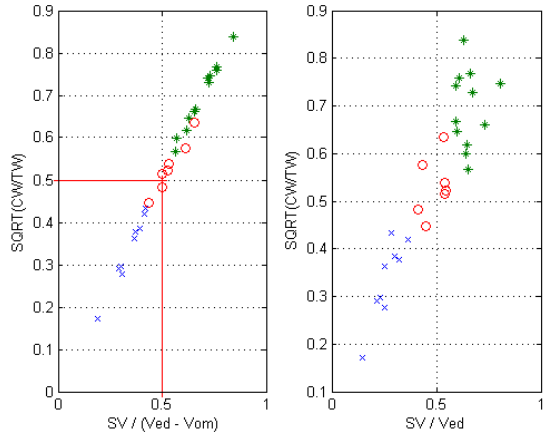

Figure 4: Verification of (10) (left side), and similar relation with the EF = SV/V_{ed} (right side). Experimental data from Asanoi et al [16]. Data correspond to three clinical groups: (a) EF >= 60% '*'; (b) 40% < EF < 59% 'o'; (c) EF < 40% 'x'.

On the right side of Fig. 4 is the corresponding relation with EF = SV/V_{ed}, notice that cases considered as preserved with EF ≈ 0.5 appear as critical with $SV/(V_{ed} - V_{om}) \approx 0.5$ on the left side as discussed in relation to Fig. 2. On the left side of Fig. 5, we see a verification of (10) and (11), where the vertical and

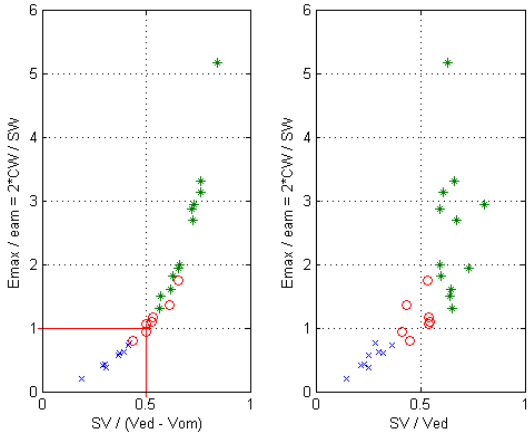

Figure 5: Relation between E_{max}/e_{am} and $SV/(V_{ed} - V_{om})$ (left side), and similar relation with EF = SV/V_{ed} (right side). Experimental data from Asanoi et al [16]. Data correspond to three clinical groups: (a) EF >= 60% '*'; (b) 40% < EF < 59% 'o'; (c) EF < 40% 'x'.

horizontal lines indicate the values $SV/(V_{ed} - V_{om}) = 0.5$ and $E_{max}/ e_{am} = 1$ that correspond to the critical case when points d_1 and d_5 coincide in Fig. 2. On the right side of Fig. 5, is the corresponding relation with EF = SV/V_{ed}. Notice that cases considered as preserved with EF ≈ 0.5 appear as critical with $SV/(V_{ed} - V_{om}) \approx 0.5$ on the left side. If we designate the effective ejection fraction EFe = $SV/(V_{ed} - V_{om})$, then we have the relation

$$E_{max}/e_{am} = EFe / (1 - EFe) \quad (13)$$

which is the equation of the curve on the left side of Fig. 5. The ratio SWR/SW = (stroke work reserve) / (stroke work) is calculated and displayed in Fig 6. From Fig. 2, we see that SWR = 0 for the critical case $SV/(V_{ed} - V_{om}) = 0.5$ and $E_{max}/e_{am} = 1$ (mildly depressed state of the heart). We also see that when SWR < 0, $SV/(V_{ed} - V_{om}) < 0.5$ (depressed state of the heart), and when SWR > 0, $SV/(V_{ed} - V_{om}) > 0.5$ (normal state of the heart). On the right side of Fig. 6 one can again see that cases with preserved EF ≈ 0.5 appear as critical when considered on the left side of Fig. 6.

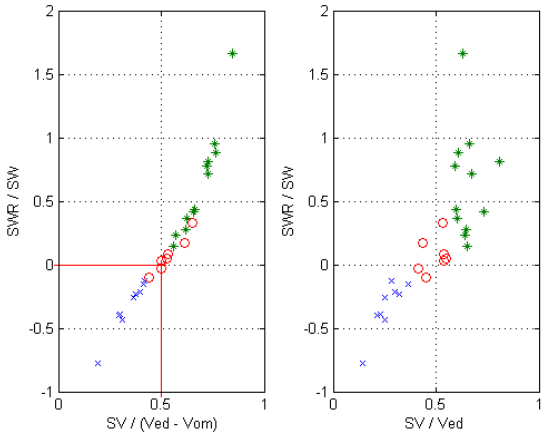

Figure 6: Relation between SWR/SW and $SV/(V_{ed} - V_{om})$ (left side), and similar relation with EF = SV/V_{ed} (right side). Experimental data from Asanoi et al [16]. Data correspond to three clinical groups: (a) EF >= 60% '*'; (b) 40% < EF < 59% 'o'; (c) EF < 40% 'x'.

It should be clear that the difficulty in using the ESPVR to evaluate HFpEF comes from the difficulty of measuring E_{max} and V_{om} in a non-invasive way [17].

IV. Conclusion

We have shown in this study that the ejection fraction (EF) is just one index from a rich collection of indexes that can be derived from ESPVR analysis. Contributions from different clinical groups are necessary in order to see how good these indexes are in the assessment of HFpEF.

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