

## Special Issue on “Heart Failure- An Issue on Heart Failure Clinics”

# Basic Relations between Ejection Fraction and ESPVR

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Received: September 23, 2014; Accepted: October 17, 2014; Published: October 20, 2014

## Abstract

Heart Failure with normal or Preserved Ejection Fraction (HFpEF) is a subject that has received particular attention in the medical literature. In this study we show how the Ejection Fraction (EF) can be expressed as function of parameters describing the End-Systolic Pressure-Volume Relation (ESPVR), and the areas under the ESPVR, with new insight in some aspects of ventricular contraction. It is shown also that the Ejection Fraction (EF) is just one index of several indexes that can be derived from the parameters describing the ESPVR in order to assess the performance of the ventricles. Bivariate (or multivariate) analysis of indexes gives better segregation between cardiac cardiomyopathies. The ordinates of the ESPVR (units of pressure), and the areas under the ESPVR (units of energy) are sensitive parameters that reflect the state of the myocardium. Possible application of these results to the study of HFpEF is explained.

**Keywords:** End-Systolic pressure-volume relation; Ejection fraction; Cardiomyopathies; Ventricular contraction; Myocardium

## Introduction

It has been observed for some time that left (or right) ventricles presenting signs of cardiomyopathies can have normal Ejection Fraction (EF). It was first reported by Dumesnil et al. [1,2] 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 been published to explain the influence of intrinsic myocardial factors and ventricular geometry on EF, as well as other factors like the structure of the tissues of the myocardium, metabolism, ventricular suction and filling, preload and after load [3-6]. A related problem is the problem of heart failure with normal or preserved ejection (HFpEF), it is estimated that half of the patients presenting symptoms of heart failure HF have preserved EF, defined as EF greater than 50% [7-9]. In this study we look at the way the EF is determined by parameters describing the End-Systolic Pressure-Volume Relation (ESPVR), these parameters include the ordinates of the ESPVR (units of pressure) and the areas under the ESPVR (units of energy). It is shown that new indexes derived from the ESPVR can also be used in assessing the ventricular contraction.

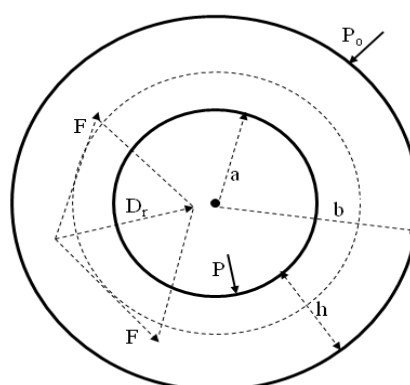
The ESPVR is the relation between the ventricular pressure  $P_m$  and volume  $V_m$  in the left (or right) ventricle when the myocardium reaches its maximum state of activation indicated by the elastance  $E_{max}$  (slope of the ESPVR). There have been several studies on the ESPVR [10-16] and its clinical applications, for a review see [11,16]. In a series of studies on the ESPVR published by the author, 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 [17-23]. In this study we review some basic relations that were derived to describe the ESPVR, as well as various relations to express the Stroke Volume (SV) (and consequently the  $EF = SV/V_{ed}$ ) in terms of the parameters

describing the ESPVR and the areas under the ESPVR. We then show some new applications of these relations to clinical data published in the literature that give further evidence of the consistency of the mathematical formalism used. It is also shown that the EF is just one index of several new indexes derived from the ESPVR that can be used to assess the ventricular function. We finally indicate how the results obtained can open the way to new directions of research that can lead to new insight in the study of HFpEF.

## Mathematical Formalism & Applications

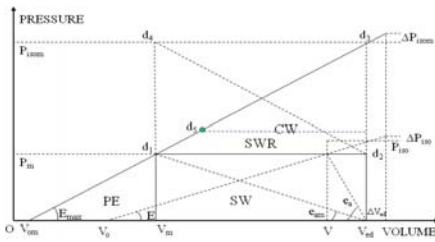
### Some basic relations

This section introduces some basic mathematical relations that are needed to describe the PVR in the ventricles. The left ventricle is represented as a thick-walled cylinder contracting symmetrically, as in previous publications [17-23]. A radial active force  $D_r$  (force per unit volume of the myocardium) is developed by the myocardium during the contraction phase (Figure 1). The active pressure on the



**Figure 1:** Cross-section of a thick-walled cylinder representing the left ventricle.

P: Left Ventricular Pressure;  $P_o$ : Outer Pressure (assumed zero),  $D_r$ : Active Radial Force/unit volume of the Myocardium; a: Inner Radius; b: Outer Radius,  $h = b - a$ : Thickness of the Myocardium.



**Figure 2:** PVR in the left ventricle represented by the loop  $V_{ed}d_2d_1V_m$  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  $\Delta P_{iso}$  and  $\Delta P_{isom}$  correspond to changes  $\Delta V_{ed}$  according to the Frank-Starling mechanism. The areas PE, SW, CW and SWR are defined in text.  $TW = PE + SW + CW$  is the total area under the ESPVR.

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. In a quasi-static approximation, we neglect inertia and viscous forces since they are relatively small. The equilibrium of forces on the surface of 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, the corresponding left ventricular volume is  $V$ , and  $V_{ed}$  is the end-diastolic volume (the largest volume, when  $dV/dt = 0$ ). The right-hand side of Eq. (1) represents the pressure on the endocardium resulting from the elastic deformation of the myocardium from  $V_{ed}$  to  $V$ . When the elastance coefficient  $E$  reaches its maximum value  $E_{max}$  near end-systole (maximum state of activation of the myocardium), we can write Eq. (1) as follows

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

In Eq. (2)  $P_{isom}$ ,  $P_m$  and  $V_m$  are the corresponding values of  $P_{iso}$ ,  $P$  and  $V$  when  $E_{max}$  is reached, with  $V_m \approx V_{es}$  the end-systolic volume (when  $dV/dt = 0$ ). For simplicity we shall assume that the ventricular pressure  $P = P_m$  is constant during the ejection phase.

Equations (1) and (2) are represented graphically in a simplified way in Figure 2. The ESPVR is the relation between  $P_m$  and  $V_m$  when the myocardium reaches its maximum state of activation represented by  $P_{isom}$ , it is represented by the line  $d_3V_{om}$  with slope  $E_{max}$ , midpoint  $d_5$  and volume axis intercept  $V_{om}$ . The line with slope  $E$  and volume axis intercept  $V_o$  in Figure 2 is an intermediate position. One can look at Eq. (1) in two ways:

a)  $P$  and  $V$  are varied by keeping  $P_{iso}$  constant as if a balloon is inflated against a constant  $P_{iso}$ , we get an approximate linear relation shown in Figure 2, with slope  $E$  and intercept  $V_o$ . Similarly when  $P_m$  and  $V_m$  are varied against a constant  $P_{isom}$  in Eq. (2), we get an approximate linear relation represented in Figure 2 by the line  $d_3V_{om}$  with slope  $E_{max}$  (ESPVR).

b) When  $P_{iso}$ ,  $P$ ,  $V$ ,  $E$  are varied simultaneously in Eq. (1) as in a normal ejecting contraction, we get the PVR represented in a simplified way by the rectangle  $V_{ed}d_2d_1V_m$  in Figure 2.

Equations (1) and (2) can be split into two equations

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

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

and

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

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

These relations indicate that there are three ways to represent the equation of the line with slope  $E$  (Eqs. (1), (3), (4)), as well as the equation of the line with slope  $E_{max}$  (Eqs. (2), (5), (6)) (see Figure 2).

**The state of the myocardium**

Important information on the state of the myocardium can be obtained from the study of the relative position of the point  $d_1$  (corresponding to  $P_m$ ) with respect to the mid-point  $d_5$  on the ESPVR (line  $d_3V_{om}$  in Figure 2). 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 Figure 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 [22].

b) Mildly depressed state of the heart, with  $d_1$  and  $d_5$  nearly coinciding. In this case we have  $SV \approx (V_{ed} - V_{om})/2$ , with  $E_{max}/e_{am} \approx 1$  and  $P_{isom}/P_m \approx 2$ . Notice from Figure 2 that when  $d_1$  moves on the line  $d_3V_{om}$ ,  $SW$  reaches its maximum value  $SW_x$  when  $d_1$  coincides with the mid-point  $d_5$ .

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  $P_{isom}/P_m < 2$ .

In cases (b) and (c) an increase in pressure  $P_m$  causes a decrease in the stroke work  $SW$ , resulting in cardiac insufficiency.

Experimental verification of these results can be found in the works of Burkhoff et al. [12] (left ventricle) and Brimouille et al. [13] (right ventricle) for experiments on dogs, and in Asanoi et al. [15] for results on humans (left ventricle).

In the following new indexes derived from the ESPVR are used to classify the state of the myocardium as just described. It is also shown how  $SV$  and  $EF$  can be related to the indexes derived, and finally how the results obtained can be extended to the study of HFpEF. Experimental applications are based on clinical data taken from Borow et al [14] and from Asanoi et al [15]. In Borow et al [14] values of  $E_{max}$  and  $V_{om}$  are given for patients in control state and after injection of dobutamine. We have used the data of the first six groups in Table 1 of Borow et al [14], where also the dimensions of the left ventricle and the measurement of ESP (called  $P_m$  in our notation) are given. In Asanoi et al [15] values of  $E_{max}$  and  $V_{om}$  are given for three clinical groups of patients with  $EF \geq 60\%$ ,  $40\% \leq EF < 59\%$ , and  $EF \leq 39\%$ . We have also taken from Table 1 of Asanoi et al [15] the dimensions of the left ventricle and the values of ESP (called  $P_m$  in our notation). Notice that the dimensions of the variables used is immaterial if we use dimensionless ratios like  $E_{max}/e_{am}$ .

**Areas under the ESPVR**

Within the approximation used in this study, the areas under the

ESPVR can be expressed as follows:

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

$$SW = P_m * SV \tag{7}$$

b) CW = triangular area  $d_3d_2d_1$  in Figure 2, energy apparently absorbed by the passive medium of the myocardium:

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

c) PE = triangular area  $d_1V_mV_{om}$  in Figure 2, potential energy apparently related to the internal metabolism of the myocardium:

$$PE = P_m * (V_m - V_{om}) / 2 \tag{9}$$

d) SWR = stroke work reserve, it is the reserve energy that can be delivered to the systemic circulation when there is an increase in afterload demand represented by an increase in  $P_m$ :

$$SWR = SW_x - SW \tag{10}$$

e) TW = SW + PE + CW the total area under ESPVR:

$$TW = P_{isom} * (V_{ed} - V_{om}) / 2 \tag{11}$$

Relation between TW and oxygen consumption was discussed in [22].

From these relations, one can derive the following relations for the stroke work (see [19,20]):

$$E_{max} / e_{am} = 2 * CW / SW \tag{12}$$

$$SW / TW = 2 * (E_{max} / e_{am}) / (1 + E_{max} / e_{am})^2 \tag{13}$$

$$SW / PE = E_{max} / e_{am} \tag{14}$$

from which we can derive

$$SW^2 / 4 = PE * CW \tag{15}$$

These relations show the interrelation between SW with the areas under the ESPVR and the ratio  $E_{max} / e_{am}$ . In particular Eq. (15) shows the balance of energy between SW, PE, and CW, that determines the value of SW.

These relations are illustrated in Figs 3 to 6. Experimental data taken from Borow et al [14] are used in Figure 3. The property that  $E_{max} / e_{am} \rightarrow 1$  when  $SV / (V_{ed} - V_{om}) \rightarrow 0.5$  is verified (point  $d_1$  and  $d_5$  coincident in Figure 2), the right hand side shows the corresponding relation between  $E_{max} / e_{am}$  and the EF which represents an approximation of the correct relation on the left hand side. Figure 4 represents the same relations for experimental data taken from Asanoi et al [15] for three clinical groups differentiated by their EF. From Figure 5 (left) we note that  $SWR / SW \approx 0$  for  $E_{max} / e_{am} \approx 1$  as previously discussed (point  $d_1$  and  $d_5$  coincident in Figure 2) and from Figure 5 (right) we note that  $SW / TW \approx 0.5$  for  $E_{max} / e_{am} \approx 1$  ( $SW_x$  is half the total area TW). From Figure 6 (left) we note that  $SWR / SW \approx 0$  for  $SV / (V_{ed} - V_{om}) \approx 0.5$ , and Figure 6 (right) shows the corresponding relation between  $SWR / SW$  and  $SV / V_{ed}$ . From Figure 5 (left) we notice that  $SWR / SW > 0.1$  for  $E_{max} / e_{am} > 2$  corresponds to only normal EF, a similar observation can also be made from Figure 6 with  $SWR / SW > 0.1$  for  $SV / (V_{ed} - V_{om}) > 0.65$ . One can notice that the segregation of clinical groups in Figure 6 (left) is different from that shown in Figure 6 (right).

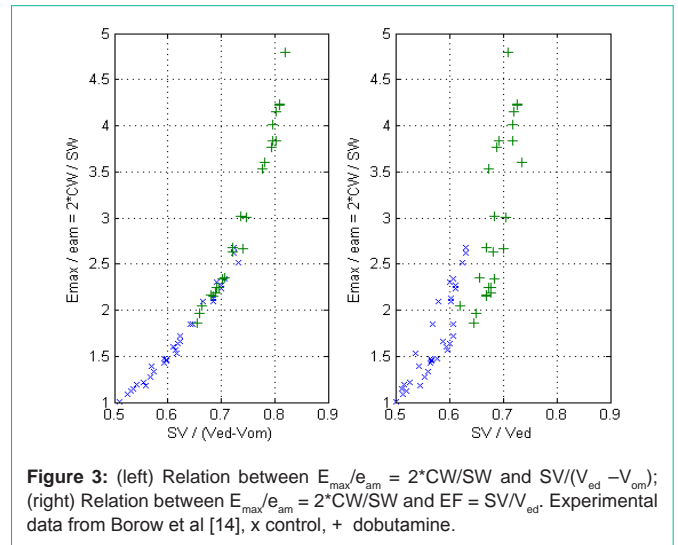


Figure 3: (left) Relation between  $E_{max} / e_{am} = 2 * CW / SW$  and  $SV / (V_{ed} - V_{om})$ ; (right) Relation between  $E_{max} / e_{am} = 2 * CW / SW$  and  $EF = SV / V_{ed}$ . Experimental data from Borow et al [14], x control, + dobutamine.

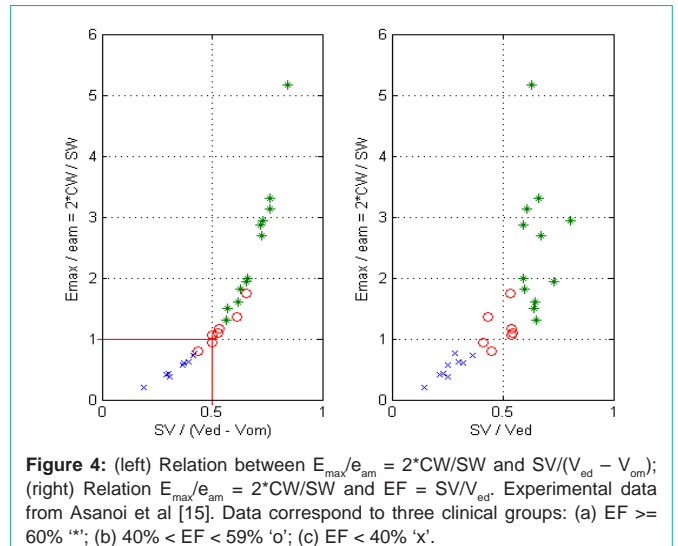


Figure 4: (left) Relation between  $E_{max} / e_{am} = 2 * CW / SW$  and  $SV / (V_{ed} - V_{om})$ ; (right) Relation  $E_{max} / e_{am} = 2 * CW / SW$  and  $EF = SV / V_{ed}$ . Experimental data from Asanoi et al [15]. Data correspond to three clinical groups: (a)  $EF \geq 60\%$  '\*'; (b)  $40\% < EF < 59\%$  'o'; (c)  $EF < 40\%$  'x'.

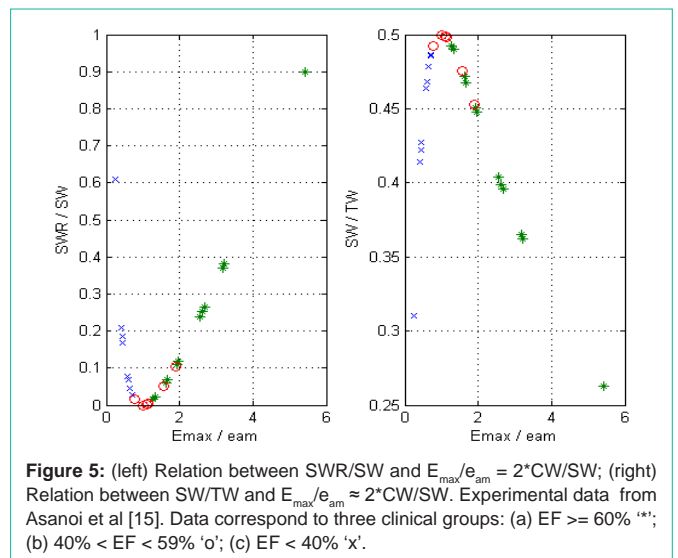
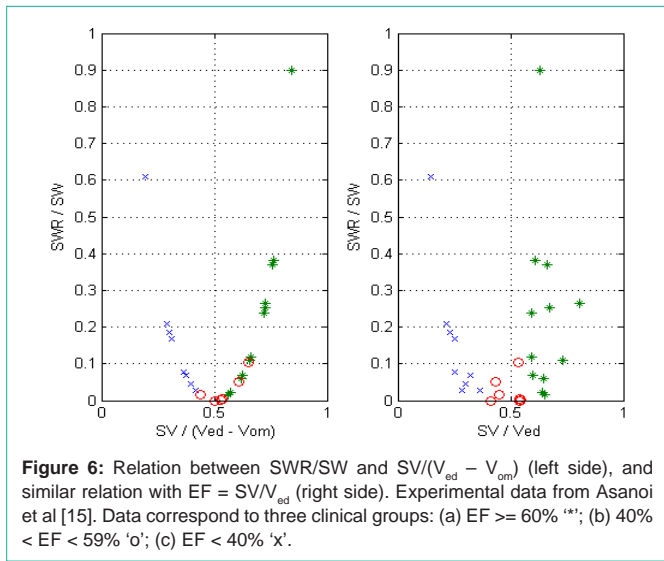


Figure 5: (left) Relation between  $SWR / SW$  and  $E_{max} / e_{am} = 2 * CW / SW$ ; (right) Relation between  $SW / TW$  and  $E_{max} / e_{am} = 2 * CW / SW$ . Experimental data from Asanoi et al [15]. Data correspond to three clinical groups: (a)  $EF \geq 60\%$  '\*'; (b)  $40\% < EF < 59\%$  'o'; (c)  $EF < 40\%$  'x'.

**Stroke volume SV and ejection fraction EF**

One can also derive the following relations (see Figure 2):



$$SV/(V_{ed} - V_{om}) = (P_{isom} - P_m)/P_{isom} \tag{16a}$$

from which we can derive the following expression for SV:

$$SV = (CW/TW)^{1/2} * (V_{ed} - V_{om}) \tag{16b}$$

It shows how SV (and consequently  $EF = SV/V_{ed}$ ) 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. We also have

$$SV = (E_{max}/e_{am}) * (V_m - V_{om}) \tag{16c}$$

which is similar to the equation for SV derived in [24]. From Eq. (16c) one can also derive

$$SV = [E_{max}/(e_{am} + E_{max})] * (V_{ed} - V_{om}) \tag{16d}$$

Equations (16a) to (16d) show how the stroke volume SV (and the  $EF = SV/V_{ed}$ ) is determined by interacting parameters describing the ESPVR. When  $CW/TW = 1/4$  ( $d_1$  and  $d_5$  coincide in Figure 2) we get from Eq. (16b)  $SV = (V_{ed} - V_{om})/2$ , which corresponds to  $E_{max}/e_{am} = 1$ .

Eq. (16d) is illustrated with the experimental results shown in Figure 7, notice that  $SV/(V_{ed} - V_{om}) \rightarrow 0.5$  when  $E_{max}/(e_{am} + E_{max}) \rightarrow 0.5$ , corresponding to  $E_{max}/e_{am} = 1$  ( $d_1$  and  $d_5$  coincident in Figure 2). Similarly Eq. (16b) is illustrated with the experimental results shown in Figure 8, in this case we have  $CW/TW \approx 1/4$  when  $SV/(V_{ed} - V_{om}) \approx 0.5$ .

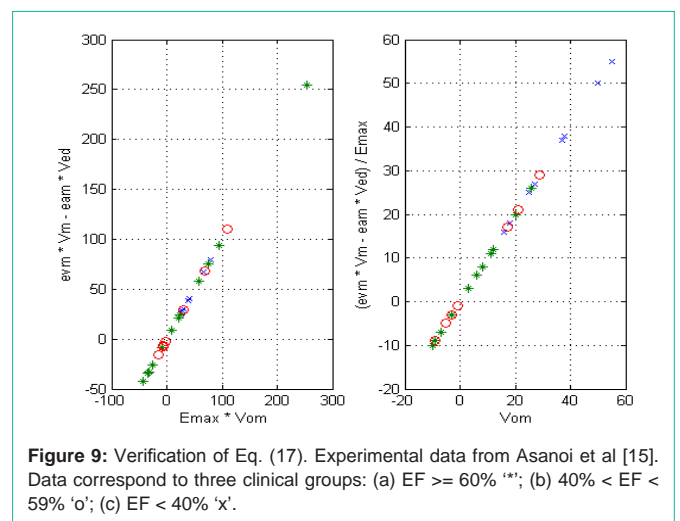
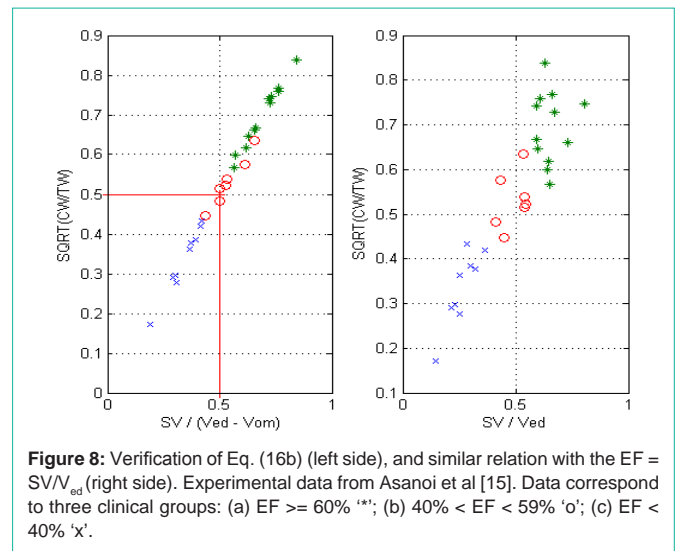
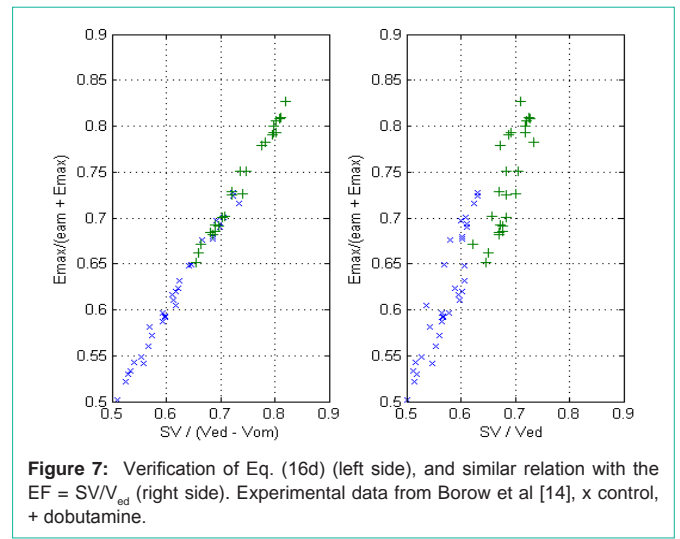
One can finally derive the following relation between the parameters of the ESPVR:

$$E_{max} * V_{om} = e_{vm} * V_m - e_{am} * V_{ed} \tag{17}$$

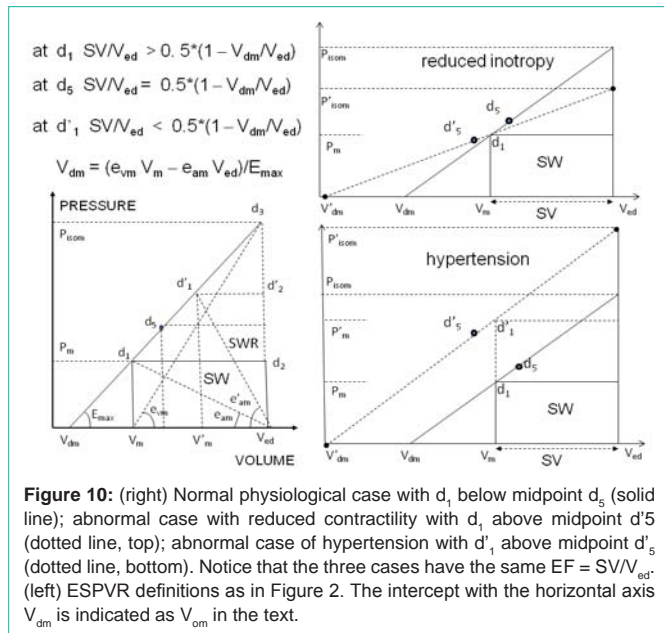
where  $e_{vm} = P_{isom}/SV$ . The relation between the parameters of the ESPVR given by Eq. (17) is illustrated in Figure 9.

**Application to the HFpEF**

We shall briefly show how the preceding results can be extended to the study of HFpEF, which approach is illustrated by the simplified drawing of Figure 10. The right side of Figure 10 (top) shows a case of normal ventricular contraction with  $d_1$  below the mid-point  $d_5$  on the ESPVR (solid line), and a case of depressed state of the myocardium



due to reduced contractility with  $d_1$  above the mid-point  $d_5$  on the ESPVR (dotted line, top), in both cases the  $EF = SV/V_{ed}$  is the same and the detection of the anomaly can be done by using another indexes as shown from Figure 3 to 8. like  $E_{max}/e_{am}$  (Figure 10, left)



or  $SV/(V_{ed} - V_{om})$  or  $(P_{isom} - P_m)/P_m$  or the areas under the ESPVR. Similar observation can be said for the case of hypertension in Fig. 10 (right, bottom) where the normal and hypertensive cases have the same  $EF = SV/V_{ed}$ , the anomaly has to be detected by using other indexes as mentioned. Note that in real situations both  $V_{ed}$  and  $V_m$  change [25], with the ratio  $(V_{ed} - V_m) / V_{ed} \approx k$  nearly constant, which means that  $V_m \approx (1 - k)V_{ed}$ .

In cases of cardiomyopathies the ESPVR (and consequently  $V_{ed}$ ,  $V_m$  and  $V_{om}$ ) have a tendency to shift to the right, Figure 10 is a simplified representation of a complex process.

### Discussion

Previous approaches to the study of the ESPVR [10,11,16] have focused on the part of this relation represented by the area  $PVA = PE + SW$  in Figure 2. An important contribution of the mathematical formalism used in this study is introduction of the active pressure  $P_{iso}$  in the mathematical formalism describing the ESPVR and the appearance of a new area  $d_1 d_2 d_3$  (or CW) in Figure 2. The interrelation between the areas CW, SW and PE (having the units of energy) is an important aspect of the study of ventricular contraction. Only a few applications have been discussed in this study, they illustrate the rich collection of information that can be derived from the mathematical formalism used.

The results presented show that two-dimensional (bivariate) analysis of data is superior to univariate analysis. For instance in Figure 5 & 6, segregation of data with respect to the EF (right side) does not mean segregation with respect to other indexes. We have three clinical groups appearing around  $SV/(V_{ed} - V_{om}) \approx 0.5$  and  $E_{max}/e_{am} \approx 1$  that can be considered as critical values. How to obtain a combination of two indexes that can simultaneously segregate between different clinical cases still needs some study. In [23] we have indicated that dividing each clinical group by its standard deviation can achieve possible segregation; however this creates a problem of classification, given a new piece of data how to choose the standard deviation to classify it.

Future studies include the extension of the results of this study to the case of non-linear ESPVR, some preliminary results are given in [23]. Also the possibility of non-invasive implementation of these results by approximating the end-systolic ventricular pressure  $P_m$  with the peak carotid pressure or the peak blood pressure needs to be considered. Finally the extension of these results to cases of HFpEF as indicated in Figure 10 is a subject that deserves further attention.

### Conclusion

This study has presented some relations that give new insight in the mechanics of ventricular contraction. We have shown how the Ejection Fraction (EF) is related to several parameters related to the ESPVR. Also a rich collection of indexes useful in clinical applications can be derived from the ESPVR. Bivariate (or multivariate) approach appears to be superior to univariate approach for the purpose of segregation and classification of clinical data, and can lead to interesting new results in the study of HFpEF.

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