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Review Article

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Ejection Fraction and Espvr: A Study in the Mechanics of Left Ventricular Contraction

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Abstract

The end-systolic pressure-volume relation (ESPVR) is the relation between pressure P_m and volume V_m in the heart left ventricle when the myocardium reaches its maximum state of activation during contraction near end-systole. Relations between the ejection fraction (EF), parameters describing the ESPVR and the areas under the ESPVR are derived in this study for a linear model of the ESPVR. An important feature of the model is the inclusion of the active pressure generated by the myocardium during an ejecting contraction (also called isovolumic pressure P_{iso}) in the mathematical expression of the linear ESPVR. Criteria that can help in understanding the problem of heart failure with normal or preserved ejection fraction (HFpEF) are discussed. Applications to clinical data published in the literature are presented, the applications show the consistency of the mathematical formalism used. When ratios of pressures are used, the calculation can be carried out with clinical data measured in a non-invasive way (the ratio of pressures can be calculated). This study shows that the EF is just one index of several indexes that can be derived from the ESPVR for the assessment of the ventricular function, and that using bivariate (or multivariate) analysis of data is superior to univariate analysis for the purpose of classification and segregation between different clinical groups.

Keywords: Ventricular Function, Cardiac Mechanics, Contractility of the Myocardium, Pump Function of the Heart, Heart Failure with Preserved Ejection Fraction, HFpEF, End-Systolic Pressure-Volume Relation, ESPVR, Efficiency of Left Ventricle, Mathematical Physiology.

Introduction

The relation between pressure P_m and volume V_m in the heart left ventricle when the mycocardium reaches its maximum state of activation during the contraction phase near end-systole is known as the end-systolic pressure-volume relation (ESPVR). In this study we assume that $V_m \approx V_{es}$ the left ventricular volume at end-systole (defined as the smallest left ventricular volume V, when the time derivative $dV/dt = 0$), P_m is the corresponding left ventricular pressure. Discussion of the properties of the linear ESPVR can be found in several publications [1-18], a review can be found in [5, 6]. Two important new features of the linear model of the ESPVR described in this study are the introduction of the active pressure generated on the inner surface of the myocardium (endocardium) (also called isovolumic pressure P_{iso} by physiologists) in the mathematical formalism describing the ESPVR, and the inclusion of the total area under the ESPVR in the study of its properties [8-18]. The linear model of the ESPVR discussed in this study is a simplifued version of the mathematical formalism for a non-linear model of the ESPVR based on the theory of large elastic deformation of the myocardium. For small variations in P_m and V_m within the physiological range, the linear model is an accepted approximation to the non-linear model. Preliminary results by using the non-linear model of the ESPVR have been published [16-18]. Because those results are at a preliminary stage, this study is confined to the linear model of the ESPVR.

The ejection fraction (EF) is defined as $EF = SV/V_{ed}$, where V_{ed} is the left-ventricular volume at end-diastole (defined as the largest ventricular volume V, when the time derivative $dV/dt = 0$), the stroke volume $SV = V_{ed} - V_m$ since we have assumed $V_m \approx V_{es}$. The EF is widely used in the clinical practice because it can be calculated from non-invasive measurements. One should be careful in using EF that different methods of measurement can give different results [19]. For instance in one observed case, a measurement of $EF = 0.67$ by M-mode echocardiography was measured *0.54* by radionuclide angiography, the reason is damage in the aortic valve causing regurgitation. The EF is also sensitive to preload, afterload and ventriculo-arterial coupling, and consequently cannot be considered as an independent measure of the contractility of the myocardium. As observed by Dumesnil et al. the EF is influenced by intrinsic myocardial properties as well as by the geometry of the left ventricle, and that cases of aortic stenosis may have reduced longitudinal shortening whereas the EF appears normal [20-23]. The effect of intrinsic properties of the myocardium on its contraction is discussed in [24, 25]. The importance of the longitudinal axis dynamics in prognostic and diagnostic applications has been stressed by several authors, facilitated by the introduction of new techniques of measurement like Doppler tissue imaging or speckle tracking

echocardiography [20-23, 26-29]. Particular attention was given to paradoxical low flow/low gradient aortic stenosis with preserved left ventricular *EF* according to the assumed definition *EF > 0.5* [30-35]. It is now recognized that an early detection of signs of heart failure with preserved ejection fraction (HFpEF) or with normal ejection fraction (HFnEF) is an important clinical problem that may allow a better treatment of the underlying causes, delay may lead to complications with poor prognosis [36-39]. Descriptive terms like HFnEF, HFpEF, HFmrEF (mid-range *41% <= EF <=* 50%), HFrEF (reduced *EF <=* 40%) are approximate and arbitrary cut-off values for classification of cases of HF that have overlapping but also dictinct characteristics (another definition of HFpEF is suggested in this study and explained in the discussion section at the end). Attention has also been given recently to pathophysiological mechanisms in HF studies [40-42]. The *EF* remains an important index used in the assessment of the ventricular function and it continues to be used in conjunction with other indexes in clinical applications. Experimental curves between percentage occurrences of HF and *EF* have been reported, they indicate that values of *EF* between 60%-65% are associated with the lowest mortality as discussed in what follows [43-46].

In this study the mathematical expression of the linear ESPVR is first introduced. Then relations between *EF*, the parameters describing the ESPVR and the areas under the ESPVR are derived and discussed, they give new insight into the mechanics of ventricular contraction. Applications to experimental and clinical data published in the literature shows the consistency of the mathematical formalism used [8-13, 47-56]. The mathematical formalism to be discussed in what follows can be applied to the four chambers of the heart, this study is limited to applications to the left ventricle [57-59].

Mathematical Formalism

The following variables are shown in Figure 1 and Figure 2.

V = left ventricular volume.
V_{ed} = left ventriculat volume at end-diastole (when $dV/dt = 0$).
V_{es} = left ventricular volume at end-systole (when $dV/dt = 0$).
V_m = left ventricular volume when the myocardium reaches its maximum state of activation near end-systole (it is assumed that $V_m \approx V_{es}$ in the calculation).
SV = stroke volume = $V_{ed} - V_{es} \approx V_{ed} - V_m$.
P = left ventricular pressure.
P_{ed} = left ventricular filling pressure during diastole
P_{es} = left ventricular pressure at end-systole (when $dV/dt = 0$).
P_m = left ventricular pressure when the myocardium reaches its maximum state of activation near end-systole ($P_m \approx$. (*max. ventricular pressure*)/1.2).
P_{isoL} = maximum active pressure of the myocardium (max. isovolumic pressure in the linear model of the ESPVR).
P_o = outer pressure acting on the epicardium (assumed zero).
V_o = intercept of the linear ESPVR with the horizontal volume-axis.
V_{oL} = intercept of the linear ESPVR with the horizontal volume-axis.
E = left ventricular elastance, slope of the linear ESPVR.
E_{mL} = left ventricular elastance, slope of the linear ESPVR when the myocardium reaches its maximum state of activation near end-systole.
e_{am} = arterial elastance when the myocardium reaches its maximum state of activation near end-systole.

e_{vL} = elastance related to P_{isoL} as shown in Figure 2, $e_{vL} = e_{am} + E_{mL}$.

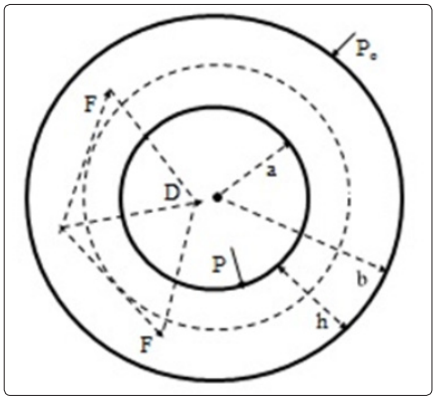
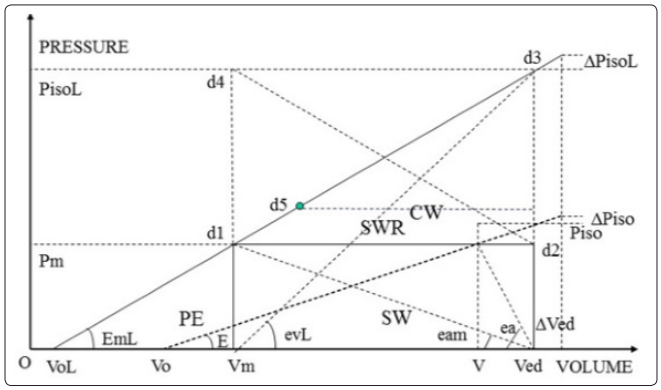


Figure 1: Cross-section of a thick-walled cylinder representing the left ventricle, D = active radial force/unit volume of the myocardium, P = left ventricular pressure, Po = outer pressure (assumed zero) on the epicardium, a = inner radius, b = outer radius, h = b – a = thickness of the myocardium. F = projection on the cross-section of the force generated by the myocardial fiber



SW = stroke work area $V_{ed}d_2d_1V_m$, SW_{mx} is reached when point d_1 coincides with mid-point d_5; CW = contraction work area $d_1d_2d_3$; PE = potential energy area $V_md_1V_{oL}$; $SWR = SW_{mx} - SW$ = stroke work reserve; E_{mL} = slope of the linear ESPVR, e_{am} = corresponding arterial elastance, e_{vL} = slope related to P_{isoL}. The changes ΔP_{iso} and ΔP_{isoL} correspond to the change ΔV_{ed} in the end-diastolic volume according to the Frank-Starling mechanism.

Figure 2: Simplified drawing showing the PVR in the left ventricle, it is represented by the loop $V_{ed}d_2d_1V_m$ in a normal ejecting contraction. The linear ESPVR is represented by the segment d_3V_{oL} with midpoint d_5. P_{isoL} is the peak radial active pressure generated by the myocardium on its inner surface (peak isovolumic pressure). It is assumed that $V_m \approx V_{es}$ (end-systolic volume when $dV/dt = 0$).

The left ventricle is represented as a thick-walled cylinder contracting symmetrically. A cross-section of the cylinder is shown in Figure 1 with the forces acting on it. During the contraction phase, a radial active force D per unit volume of the myocardium is generated. As a result an active pressure $\int_a^b D\,dr \approx P_{iso}$ is developed on the inner surface of the myocardium (endocadium), a = inner radius, b = outer radius, $h = b - a$ = thickness of the myocardium. When inertia and viscous forces are neglected, P_{iso} is the same pressure that would be produced in a non-ejecting isovolumic contraction of the myocardium. The outer pressure P_o shown in Figure 1 is neglected in the calculation. In a quasi-static approximation for the contraction of the myocardium (inertia and viscous forces neglected),

the equilibrium of pressures on the inner surface of the myocardium gives the following pressure-volume relation (PVR):

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

where P is the left ventricular pressure, V is the left ventricular volume, V_{ed} is the end-diastolic volume (largest value of the V, reached when the time derivative $dV/dt = 0$), $E(t)$ is a time-varying elastance coefficient. Near end-systole when the myocardium reaches its máximum state of activation, Eq. (1) can be written in the form

$$P_{isoL} - P_m = E_{mL}\,(V_{ed} - V_m) \quad (2)$$

It is assumed that $V_m \approx V_{es}$ (V_{es} is the minimum value of V at end-systole, when the time derivative $dV/dt = 0$), P_{isoL}, P_m and E_{mL} correspond to the values defined in Eq. (1), but taken when the myocardium reaches its maximum state of activation. The subscript L is used in order to indicate that the linear model of the ESPVR is used, as shown in Figure 2. For simplicity, the left ventricular pressure P_m is assumed constant during the ejection phase as shown in Figure 2. When $P_m \rightarrow 0$ along the ESPVR, we have $V_m \rightarrow V_{oL}$ and Eq. (2) becomes:

$$P_{isoL} = E_{mL}\,(V_{ed} - V_{oL}) \quad (3)$$

The intercept of the linear ESPVR with the horizontal volume-axis in Figure 2 is indicated by V_{oL}. From Eqs. (2) and (3) we can derive the relation:

$$P_m = E_{mL}\,(V_m - V_{oL}) \quad (4)$$

Note that one can look at Eq. (2) in two different ways:

1) P_{isoL} is held constant and P_m and V_m are varied near end-systole as if a balloon is inflated against a constant P_{isoL}, one gets in a linear approximation a relationship like the line d_3V_{oL} in Figure 2.
2) P_{isoL} is allowed to vary with P and V as in a normal ejecting contraction, one gets the P-V loop represented in a simplified way as $V_{ed}d_2d_1V_m$ in Figure 2. P_{isoL} varies from d_2 to d_4 in Figure 2 in a normal ejecting contraction.
It is clear from Figure 2 that when $P_m \rightarrow P_{isoL}$, $d_1 \rightarrow d_3$ along the line d_3V_{oL}, and $V_m \rightarrow V_{ed}$. The arterial elastance e_{am} is defined as follows

$$P_m = e_{am}\,(V_{ed} - V_m) \quad (5)$$

In a similar way, we can define the elastance e_{vL} shown in Figure 2 as follows

$$P_{isoL} = e_{vL}\,(V_{ed} - V_m) \quad (6)$$

From the preceding equations it is easy to derive the following relations between various slopes appearing in Figure 2

$$E_{mL}\,V_{oL} = e_{vL}\,V_m - e_{am}\,V_{ed} \quad (7)$$

$$e_{vL} = e_{am} + E_{mL} \quad (8)$$

Areas Under the Linear ESPVR

The areas under the linear ESPVR are shown in Figure 2.
SW = stroke work delivered to the systemic circulation ≈ area $V_{ed}d_2d_1V_m$.

SW_{mx} = maximum stroke work, corresponding to midpoint d_5.

CW = area $d_1d_2d_3$, apparent contraction work absorbed by the passive medium of the myocardium.

PE = area $V_md_1V_{oL}$, potential energy apparently related to the internal metabolism of the myocardium.
SWR = stroke work reserve = $SW_{mx} - SW$.

The areas under the ESPVR are shown in Figure 2, they have units of energy and are sensitive indexes of the state of the myocardium. The area SW is the stroke work delivered to the systemic circulation:

$$SW \approx P_m\,(V_{ed} - V_m) \quad (9)$$

SW is maximum and equal to SW_{mx} when d_1 coincides with the midpoint d_5 of the segment d_3V_{oL}. An increase in P_m that causes d_1 to move above d_5 on the ESPVR will also cause a decrease in SW, which results in cardiac insufficiency. The triangular area PE is apparently related to the internal metabolism of the myocardium.

$$PE = (1/2)\,P_m\,(V_m - V_{oL}) = (1/2)\,(e_{am}/E_{mL})\,SW \quad (10)$$

The triangular area CW is apparenly related to the energy absorded by the passive medium of the myocardium

$$CW = (1/2)\,(P_{isoL} - P_m)\,(V_{ed} - V_m) = (1/2)\,(E_{mL}/e_{am})\,SW \quad (11)$$

Note that physiologists do not agree on the exact physiological meaning of PE and CW. One can easily derive the relation

$$PE*CW = (1/4)\,SW^2 \quad (12)$$

The total area under the linear ESPVR is given by

$$TW = PE + CW + SW = (1/2)\,P_{isoL}\,(V_{ed} - V_{oL}) \quad (13)$$

The ventriculo-arterial coupling is expressed as the ratio of slopes

$$E_{mL}/e_{am} = (V_{ed} - V_m)/(V_m - V_{oL}) = (P_{isoL} - P_m)/P_m \quad (14)$$

Which can also be expressed in terms of the areas by using Eqs. (10) and (11)

$$E_{mL}/e_{am} = 2*CW/SW = (1/2)*SW/PE \quad (15)$$

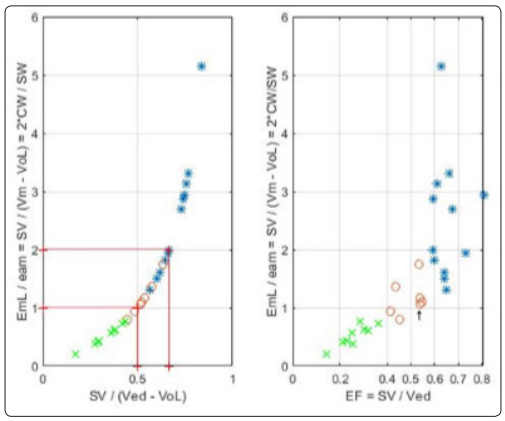


Figure 3: Relation between $SV/(V_{ed} - V_{oL}) = (P_{isoL} - P_m)/P_{isoL}$ *and* $E_{mL}/e_{am} = (P_{isoL} - P_m)/P_m$ (left side). When V_{oL} is neglected, one gets a relation between $EF = SV/V_{ed}$ and E_{mL}/e_{am} (right side). The arrow points to possible cases of HFpEF, pEF is arbitrarily defined as $EF > 0.5$. Data from Asanoi et al correspond to three clinical groups: (a) EF >= 60% '*'; (b) 40% <= EF <= 59% 'o'; (c) EF <= 39% 'x' [3].

From Eq. (14) one can see how the ratio of pressures can be calculated in a non-invasive way if V_{oL} can be estimated. Figure 3 shows the relation between E_{mL}/e_{am} and $SV/(V_{ed} - V_{oL}) = (P_{isoL} - P_m)/P_{isoL}$ (left side), and a similar relation with $EF = SV/V_{ed}$ when V_{oL} is neglected (right side). The data are taken from Asanoi et al [3], they are divided in three clinical groups according to the *EF: EF >= 60% (*); 40% <= EF <= 59% (o); EF <= 39% (x)* [3]. Note the case $E_{mL}/e_{am} \approx 2$ that corresponds to $SV/(V_{ed} - V_{oL}) \approx 2/3$ as can be calculated from triangular relations in Figure 2 (normal state of the heart), and the case $E_{mL}/e_{am} \approx 1$ that corresponds to $SV/(V_{ed} - V_{oL}) \approx 0.5$ (critical state with maximum stroke work at midpoint d_5 in Figure 2). In Figure 3 one can see that cases with $EF > 0.5$ (right side, indicated 'o' and with a vertical arrow) that can be considered as preserved according to the current definition appear as critical with $E_{mL}/e_{am} \approx 1$ and $SV/(V_{ed} - V_{oL}) \approx 0.5$ (Figure 3, left side), corresponding to midpoint d_5 on the ESPVR in Figure 2. These cases correspond to possible cases of HFpEF as currently defined with $EF > 0.5$ (another definition of HFpEF is given in what follows).

Stroke Volume

The stroke volume $SV = V_{ed} - V_m$ is evidently related to the ejection fraction $EF = SV/V_{ed}$, to the stoke work $SW \approx P_m\, SV$, to the arterial elastance $e_{am} = P_m/SV$, and to the elastance $e_{vL} = P_{isoL}/SV$ that is related to e_{am} by the relations shown in Eqs. (7) and (8). From Eqs (10), (11) and (14), (15) one can derive the following relations for the stroke volume in terms of the areas under the linear ESPVR

$$SV = (CW/TW)^{1/2}\,(V_{ed} - V_{oL}) \qquad (16)$$

$$SV = (CW/PE)^{1/2}\,(V_m - V_{oL}) \qquad (17)$$

These two formulas for SV can also be written in the form

$$SV = [(P_{isoL} - P_m)/P_{isoL}]\,(V_{ed} - V_{oL}) = [E_{mL}/e_{am})/(1 + E_{mL}/e_{am})]\,(V_{ed} - V_{oL}) \qquad (18)$$

$$SV = [(P_{isoL} - P_m)/P_m]\,(V_m - V_{oL}) = (E_{mL}/e_{am})\,(V_m - V_{oL}) \qquad (19)$$

Figure 4 shows the limitation of the stroke volume SV and consequently of the ejection fraction $EF = SV/V_{ed}$ in defining uniquely the state of the myocardium. The same normal ejection fraction $EF = SV/V_{ed}$ (point d_1 below the midpoint d_5 of the ESPVR) can also correspond to abnormal clinical cases like hypertension (lower graphics) (point d'_1 above midpoint d'_5) or reduced contractility of the myocardium (upper graphics) (point d_1 above midpoint d'_5). The *EF* however remains a useful index that can be calculated in a non-invasive way and can be used in conjunction with other indexes (bivariate or multivariate analysis) in a preliminary assesment of the ventricular function. These other indexes are suggested by Eqs. (16) to (19) obtained by using parameters like E_{mL} and V_{oL} of the ESPVR or the areas under the ESPVR, relation between *EF* and $E_{mL}/e_{am} = SV/(V_m - V_{oL})$ has already been indicated in Figure 3.

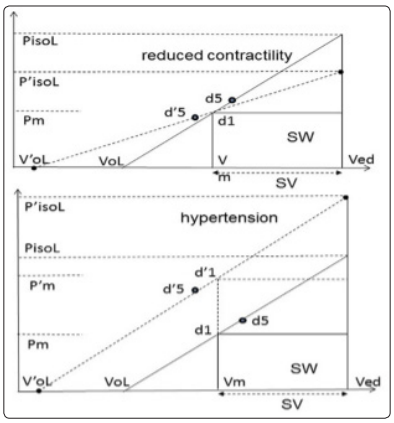


Figure 4: Simplified graphics showing three different clinical cases with the same $EF = SV/V_{ed}$. Normal case with d_1 corresponding to P_m below midpoint d_5 on the ESPVR (solid line). Hypertension with d'_1 corresponding to P'_m above midpoint d'_5 on the ESPVR (dotted curve, lower graphics). Reduced contractility, with d_1 corresponding to P_m above midpoint d'_5 on the ESPVR (dotted curve, upper graphics).

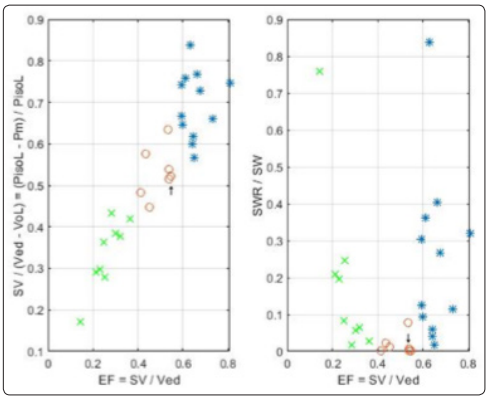


Figure 5: Relations between the ejection fraction $EF = SV/V_{ed}$ and $SV/(V_{ed} - V_{oL})$ (left side), and between *EF* and *SWR*/*SW* (right side). The arrows point to possible cases of HFpEF, pEF is arbitrarily chosen as $EF > 0.5$. Data from Asanoi et al [3] correspond to three clinical groups: (a) EF >= 60% '*'; (b) 40% <= EF <= 59% 'o'; (c) EF <= 39% 'x'. It is important not to confuse $SV/(V_{ed} - V_{oL}) = 0.5$ corresponding to the midpoint d_5 on the linear ESPVR, and the value $EF > 0.5$ arbitrarily chosen as the beginning of the range used to define pEF.

Figure 5 shows that some cases with $EF > 0.5$ (indicated by an arrow), which are arbitrarily defined as preserved according to the current practice, appear as critical with $SV/(V_{ed} - V_{oL}) \approx 0.5$ and $SWR/SW \approx 0$ corresponding to midpoint d_5 on the linear ESPVR in Figure 2. Important not to confuse $SV/(V_{ed} - V_{oL}) = 0.5$ that corresponds to the midpoint d_5 on the ESPVR in Figure 2, and $EF = SV/V_{ed} > 0.5$ which is an arbitrarily chosen value of EF used to define the beginning of the range for preserved ejection fraction (pEF), another definition of HFpEF is suggested in what follows in the discussion section at the end.

Maximum Stroke Work

When point d_1 with coordinates (V_m, P_m) moves upwards along the linear ESPVR in Figure 2, the maximum stroke work SW_{mx} is reached when d_1 coincides with the midpoint d_5 of the segment d_3V_{oL}. The maximum of SW is obtained when $d(SW)/dV_m = 0$. By differentiating Eq. (9) with respect to V_m and equating to zero we get

$$d(SW)/dV_m = (V_{ed} - V_m)\, dP_m/dV_m - P_m = 0 \qquad (20)$$

From Eq. (4) the derivative $dP_m/dV_m = E_{mL}$ for a linear ESPVR, and we get by using Eq. (4)

$$V_m = (V_{ed} + V_{oL})/2 \qquad (21)$$

when SW reaches its maximum value SW_{mx} in a linear approximation of the ESPVR, Eq. (21) indicates that V_m will correspond to the middle point of the horizontal segment $V_{ed}V_{oL}$ in Figure 2, with $E_{mL}/e_{am} = 1$ and $SV/(V_{ed} - V_{oL}) = 0.5$ (in this case point d_1 in Figure 2 will coincide with the midpoint d_5 of the segment d_3V_{oL}). By substituting Eq. (21) in Eq. (9) we get

$$SW_{mx} = P_{isoL}\,(V_{ed} - V_{oL})\,/\,4 \qquad (22)$$

When point d_1 coincides with midpoint d_5 in Figure 2 or is above midpoint d_5, an increase in load demand reflected by an increase in the left ventricular pressure P_m will cause a decrease of the stroke work SW, causing cardiac insufficiency and possible heart failure. When point d_1 is below the midpoint d_5 on the linear ESPVR as in Figure 2, the difference $SWR = SW_{mx} - SW > 0$ can be defined as the *stroke work reserve*, it is the amount of energy that can be supplied to the systemic circulation as a result of an increase in load demand corresponding to an increase in the ventricular pressure P_m. From Figures (3), (5) and (6) one can see that the critical value $SWR = 0$ (point d_1 coincides with midpoint d_5 in Figure 2) corresponds to $E_{mL}/e_{am} = 1$, ventricular volume $V_{mid} = (V_{ed} + V_{oL})/2$ and ejection fraction $EF_{mid} = [V_{ed} - 0.5*(V_{ed} + V_{oL})]/V_{ed} = 0.5*(V_{ed} - V_{oL})/V_{ed}$. It is seen that $EF_{mid} < 0.5$ when V_{oL} is positive, $EF_{mid} > 0.5$ when V_{oL} is negative, $EF_{mid} = 0.5$ when $V_{oL} = 0$ and that EF decreases as V_m increases and d_1 moves upwards on the ESPVR in Figure 2 or Figure 7. We can summarize these results as follows in order to understand an important feature of the mechanics of ventricular contraction:

$V_{oL} > 0$;
$V_m \approx 0.35*V_{ed} \rightarrow EF = SV/V_{ed} \approx 0.65$;
(normal point d_1 in Figure 2 or Figure 7, below midpoint d_5).

$V_m = 0.5*V_{ed} \rightarrow EF = 0.5$;
(point d_2 in Figure 7 below d_5, upper graphics).

$V_{mid} = (V_{ed} + V_{oL})/2 > 0.5*V_{ed}$;
(midpoint d_5 in Figure 7, upper graphics).

$EF_{mid} = 0.5*(V_{ed} - V_{oL})/V_{ed} < 0.5$;
(EF of midpoint d_5 in Figure 7, upper graphics).

$V_{oL} < 0$;
$V_m \rightarrow 0.35*V_{ed} \rightarrow EF = SV/V_{ed} \rightarrow 0.65$;
(normal point d_1 in Figure 2 or Figure 7, below midpoint d_5).

$V_m = 0.5*V_{ed} \rightarrow EF = 0.5$;
(point d_2 in Figure 7 above d_5, lower graphics).

$V_{mid} = 0.5*(V_{ed} - |V_{oL}|) < 0.5*V_{ed}$;
(midpoint d_5 in Figure 7, lower graphics).

$EF_{mid} = 0.5*(V_{ed} + |V_{oL}|)/V_{ed} > 0.5$;
(*EF* of midpoint d5 in Figure 7, lower graphics).

$V_{oL} = 0$;
$V_{mid} = 0.5*V_{ed} \rightarrow EF_{mid} = 0.5$,
(point d_2 and midpoint d_5 coincide).

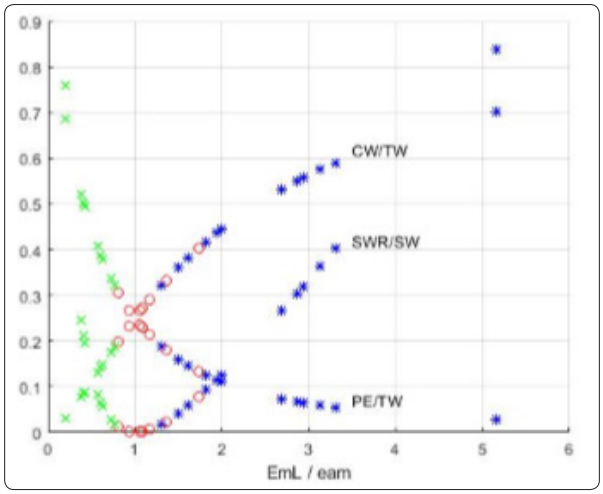


Figure 6: Relation between *CW/TW, PE/TW, SWR/SW* and E_{mL}/e_{am}. The critical value $SWR = SW_{mx} - SW = 0$ corresponds to $E_{mL}/e_{am} = 1$ and $CW/TW = PE/TW \approx 0.25$. The value $E_{mL}/e_{am} \approx 2$ corresponds to $SWR/SW \approx 0.125$, $PE/TW \approx 1/9$, $CW/TW \approx 4/9$. Clinical data from Asanoi et al correspond to three clinical groups: (a) EF >= 60% '*'; (b) 40% <= EF <= 59% 'o'; (c) EF <= 39% 'x' [3].

In Figure 7 (lower graphics) a point like d_2 with abscissa V_m and $EF > 0.5$ will appear higher than the midpoint d_5 on the linear ESPVR, we have in this case $V_{mid} < V_m$ *and* $EF_{mid} > EF > 0.5$. We have here an example of HFpEF by using the arbitrary definition of pEF as $EF > 0.5$.

We can distinguish three states of the left ventricle depending of the position of a point d_1 with coordinates (V_m, P_m) with respect to the midpoint d_5 with coordinates $(V_{mid}, P_{isoL}/2)$ on the linear ESPVR:

a) Normal physiological state of the left ventricle, with d_1 lying below the midpoint d_5 of the segment d_3V_{oL} in Figure 2 or Figure 7, around optimal values $E_{mL}/e_{am} \approx 2$, $P_{isoL}/P_m \approx 3$ and $SV/(V_{ed} - V_{oL}) \approx 2/3$. An increase in the ventricular pressure will result in an increase of the stroke work SW corresponding to normal operation of the left ventricle, as long as d_1 remains lower than the midpoint d_5 on the linear ESPVR.

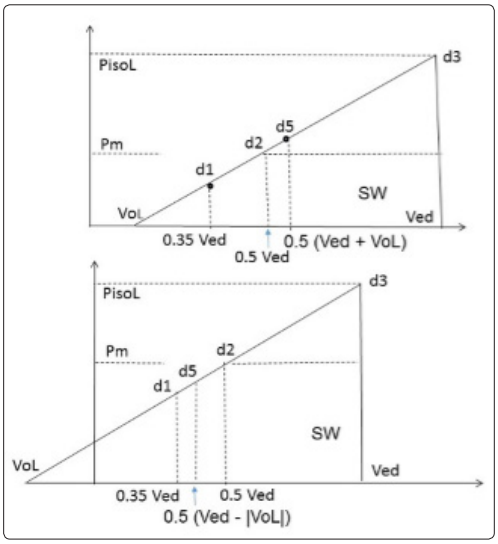


Figure 7: Simplified graphics showing three values of the ventricular volume V_m for $V_{oL} > 0$ (upper graphics), and for $V_{oL} < 0$ (lower graphics). Linear approximation of the ESPVR is represented by the segment d_3V_{oL} with midpoint d_5. Point d_2 corresponds to $V_m = 0.5*V_{ed}$ and $EF = 0.5$. In lower graphics, HFpEF (arbitrarily defined as $EF > 0.5$) corresponds to the region between d_2 and d_5 (at d_5, $V_{mid} = 0.5*(V_{ed} - |V_{oL}|)$ and $EF_{mid} = 0.5*(V_{ed} + |V_{oL}|)/V_{ed}$). This region corresponds to possible cases of low flow ($V_{ed} - V_m$), low gradient ($P_{isoL} - P_m$) with pEF arbitrarily defined as $EF > 0.5$. Note the relative position of point d_2 with respect to the midpoint d_5 in the two graphics as explained in the text. The stroke work *SW* is maximum at midpoint d_5

b) Mildly depressed state of the left ventricle, in this case point d_1 in Figure 2 or in Figure 7 is slightly below the midpoint d_5 of the segment d_3V_{oL} ($V_m < V_{mid}$ *and* $EF > EF_{mid}$), but will move above d_5 as the ventricular pressure P_m increases ($V_m >= V_{mid}$ and $EF <= EF_{mid}$). This will result in a decrease of the stroke work *SW* as P_m increases, which will cause cardiac insufficieny. This case corresponds to possible HFpEF according to the new definition in the discussion section at the end. When point d_1 coincides with midpoint d_5, we have $SWR \approx 0$, $E_{mL}/e_{am} \approx 1$, $P_{isoL}/P_m \approx 2$.

c) Severely depressed state of the heart, with d_1 in Figure 2 or in Figure 7 lying above midpoint d_5 of the segment d_3V_{oL}. In this case, an increase in P_m results in a strong decrease of the stroke work *SW*, which causes cardiac insufficieny. We have in this case $E_{mL}/e_{am} < 1$, $P_{isoL}/P_m < 2$, $V_m > V_{mid}$ *and* $EF < EF_{mid}$.

By using the arbitrary definition of pEF as $EF > 0.5$, the aforementioned cases (b) and (c) present possible examples of heart failure with preserved $EF_{mid} >= EF >= 0.5$, defined in this study as cases where an increase in ventricular pressure P_m corresponds to a decrease of stroke work *SW*, causing cardiac insufficieny (this does not exclude other definitions). The region between midpoint d_5 and d_2 on the segment d_3V_{oL} in Figure 7 (lower graphics) corresponds also to possible cases of low flow ($V_{ed} - V_m$), low gradient ($P_{isoL} - P_m$) with pEF assumed as $EF > 0.5$. The preceding discussion shows the importance of the position of point d_1 with coordinates (V_m,P_m) with respect to midpoint d_5 with coordinates (V_{mid}, $P_{isoL}/2$) on the linear ESPVR d_3V_{oL} in order to understand the mechanics of left ventricular contraction.

Experimental verification that $E_{mL}/e_{am} \approx 2$ corresponds to a normal state of the left ventricle, and that $E_{mL}/e_{am} \approx 1$ corresponds to $SW \approx SW_{mx}$ can be found in the work of Burkhoff et al for the left ventricle (experiments on dogs), in the work of Asanoi et al. for clinical data for the left ventricle obtained on patients, Brimioulle et al. have extended these results to the right ventricle (experiments on dogs) [2, 3, 58]. Further experimental validation is shown in Figures 8 to 10 based on clinical data obtained on twelve patients that were published by Mehmel et al [61]. Figure 8 (left side) shows cases of $EF - EF_{mid} > 0$ for values of $V_m - V_{mid} < 0$ (d_1 below midpoint d_5 on the ESPVR in Figure 2), and $EF <= EF_{mid}$ for values of $V_m >= V_{mid}$ (d_1 above or coincident with midpoint d_5 on the ESPVR in Figure 2). The ejection fraction *EF* gradually decreases as d_1 moves upwards along the linear ESPVR in Figure 2 and as V_m increases.

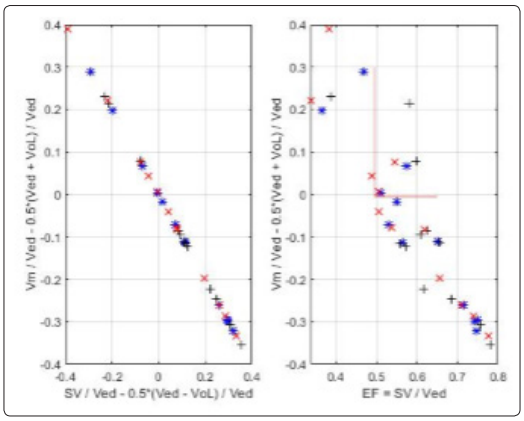


Figure 8: Relation between $(V_m - V_{mid})/V_{ed}$ and $EF - EF_{mid}$ (left side). Note how data with $V_m - V_{mid} >= 0$ and $EF - EF_{mid} <= 0$ (d_1 higher or coincident with midpoint d_5 on the ESPVR in Figure 2) appear on the right side with $EF > 0.5$ corresponding to possible cases of HFpEF as arbitrarily defined. Data from Mehmel et al [61]. Control '*', after oral isosorbide nitrate '+', after infusion of methoxamine 'x.'

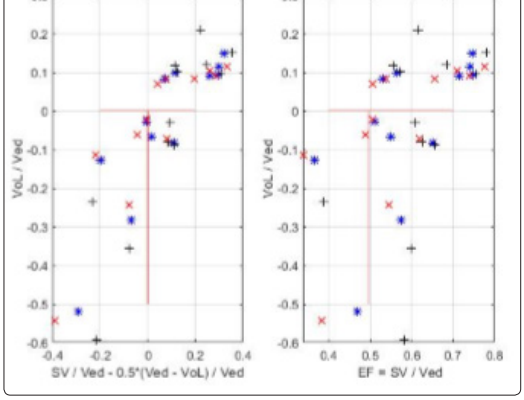


Figure 9: Cases of $V_{oL} <= 0$ and $EF - EF_{mid} <= 0$ (d_1 above or coincident with midpoint d_5 on the ESPVR in Figure 2) (left side) appear on the right side with $EF > 0.5$ corresponding to possible cases of HFpEF as arbitrarily defined. Data from Mehmel et al. [61]. Control '*', after oral isosorbide nitrate '+', after infusion of methoxamine 'x'.

For $V_m >= V_{mid}$ one can see the corresponding data on the right side of Figure 8 indicating possible cases of HFpEF by using the arbitrary definition $EF > 0.5$. This is further illustrated in Figure

9 that shows negative values of V_{oL} and $EF - EF_{mid} <= 0$ on the left side (d_1 above or coincident with midpoint d_5 on the linear ESPVR in Figure 2) that appear with $EF > 0.5$ on the right side of Figure 9, corresponding to the usual arbitrary definition of HFpEF. Finally results in Figure 10 show cases of low flow ($V_{ed} - V_m$), low gradient ($P_{isoL} - P_m$) (left side, lower left corner) that appear on the right side as possible cases of HFpEF ($E_{mL}/e_{am} <= 1$ and $EF > 0.5$). A discussion on the definition of HFpEF is given at the end.

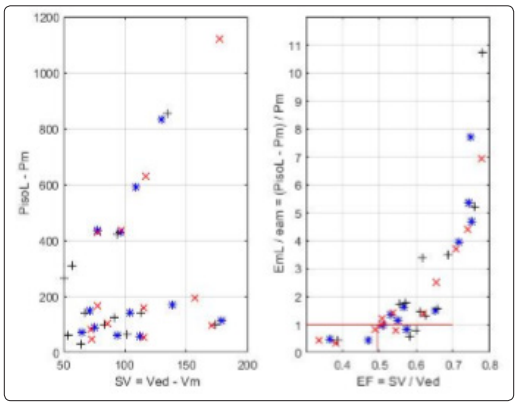


Figure 10: Cases of low flow ($V_{ed} - V_m$), low gradient ($P_{isoL} - P_m$) (lower corner, left side) appear as heart failure ($E_{mL}/e_{am} <= 1$) with preserved ejection fraction ($EF > 0.5$) (right side). Data from Mehmel et al. [61]. Control '*', after oral isosorbide nitrate '+', after infusion of methoxamine 'x'.

Maximum Efficiency

Under normal working condition, the left ventricle seems to work in a way to maximize the ratio of the energy delivered to the load with respect to the total energy absorbed by the myocardium in a cardiac cycle. Most studies assume that the oxygen (O_2) consumption in the myocardium is proportional to the area $PVA = PE + SW$ under the linear ESPVR [4,6,60,64]. In this study the O_2 consumption is assumed to be proportional to the total triangular area $TW = PE + SW + CW$ under the linear ESPVR as explained in [49]. It is also assumed that the left ventricle will distribute energy in an efficient way among the physiological processes corresponding to the respective areas *SW, CW* and *PE* shown in Figure 2, in a way to optimize the efficiency η that can be written in the form

$$\eta = (k_1\, CW + k_2\, SW + k_3\, PE)/TW \qquad (23)$$

How the coefficients k_1, k_2 and k_3 can be simultaneously estimated in a way to reflect the efficient performance of the left ventricle and the complex adaptation of the left ventricle to change in load condition or in inotropic condition is not an easy matter, some hints are given in the Appendix. Figure 11 shows three ways to estimate the efficiency of the left ventricle, as the ratio of $(PE + 2*SW)/TW$ with a maximum around $E_{mL}/e_{am} \approx 0.5$ (d_1 above midpoint d_5 on the ESPVR in Figure 2), or as the ratio SW/TW with a maximum around $E_{mL}/e_{am} \approx 1$ (d_1 coincident with midpoint d_5 on the ESPVR in Figure 2), or as the ratio $(2*SW + CW)/TW$ with maximum around $E_{mL}/e_{am} \approx 2$ (normal case with d_1 below d_5 on the ESPVR in Figure 2). The way the left ventricle will adapt to give efficient performance corresponding to E_{mL}/e_{am} equal to 0.5, 1 or 2 needs further investigation. From the results of Figure 11 one can simply note that in cases with reduced $EF <= 0.39$ (x), the areas *PE* and *SW* dominate with max. of the curve around $E_{mL}/e_{am} \approx 0.5$ (left graphics); in normal cases of *EF* (*) the areas *CW* and *SW* dominate with max. of the curve around $E_{mL}/e_{am} \approx 2$ (right graphics); and the area *SW* dominate with max. of the curve around $E_{mL}/e_{am} \approx 1$ (o) for $40\% <= EF <= 59\%$ (middle graphics). De Tombe et al. have determined experimentally a value of maximum left ventricular efficiency for $e_{am}/E_{mL} \approx 0.638$ (Note that $E_{mL}/e_{am} \approx 2$ corresponds to $e_{am}/E_{mL} \approx 0.5$) [62].

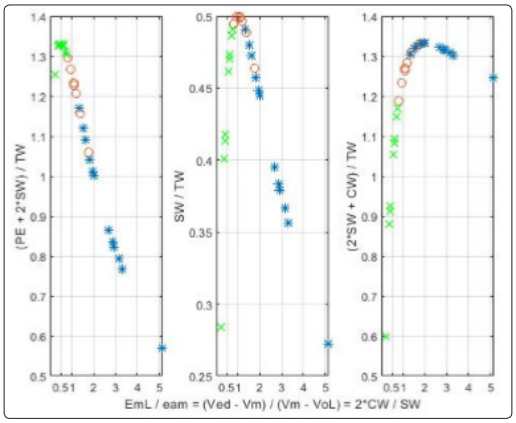


Figure 11: Relation between $(PE + 2*SW) / TW$ and E_{mL}/e_{am} with a maximum at $E_{mL}/e_{am} = 0.5$ (left). Relation between SW/TW and E_{mL}/e_{am} with a maximum at $E_{mL}/e_{am} = 1$ (centre). Relation between $(2*SW + CW)/TW$ and E_{mL}/e_{am} with a maximum at $E_{mL}/e_{am} = 2$ (right). Data from Asanoi et al correspond to three clinical groups: (a) EF >= 60% '*'; (b) 40% <= EF <= 59% 'o'; (c) EF <= 39% 'x' [3].

Percentage Occurrence of Heart Failure

Data in Figure 12 (left) are taken from da Mota, they show a relation between percentage occurrence of heart failure (HF) and left ventricular ejection fraction LVEF in percentage (a different symbol is used than *EF* to stress that LVEF is expressed in percentage) [45]. A least square fit was calculated by using these experimental data, as shown by the solid curve shown in Figure 12 (left). This solid curve was used to interpolate any value of *EF* in order to get the corresponding percentage occurrence of HF.

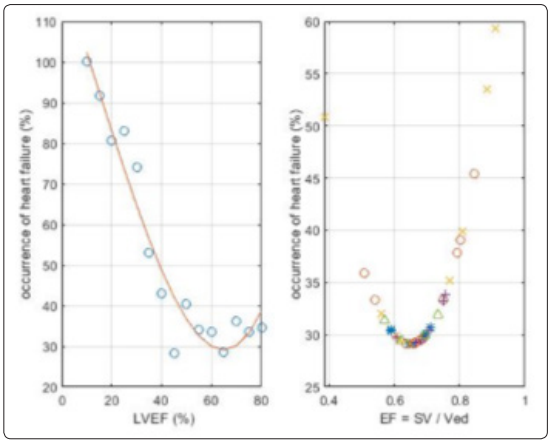


Figure 12: (Left) Relation between percentage occurrence of HF and left ventricular ejection fraction LVEF calculated in percentage, experimental data in round circles from da Mota; solid curve is calculated by using least square fit [45]. (Right) Relation between percentage occurrence of HF and ejection fraction *EF* calculated by interpolation by using the left side curve. Data from Dumesnil et al. for five groups of clinical data: normal *, aortic stenosis o, aortic valvular regurgitation +, mitral regurgitation ^, miscellaneous cardiomyopathies x [20-22].

The result is shown in Figure 12 (right) with data taken from Dumesnil et al. for five groups of clinical cases [20-22]. Note that the normal group indicated with '*' appears near the bottom of the curve around $EF \approx 0.65$. Relations between EF and other indexes like the ventriculo-arterial coupling E_{mL}/e_{am} or $SV/(V_{ed} - V_{oL})$ that can be derived from Eqs. (16) – (19) can also be used to derive new relations with the percentage occurrence of HF as shown in Figure 13. Note that the normal group '*' appears around the minimum of the two curves in Figure 13, corresponding to $E_{mL}/e_{am} \approx 1.9$ and $SV/(V_{ed} - V_{oL}) \approx 2/3$ as indicated previously in relation to Figure 3. This result is further confirmed by the results of Figure 14, in which the ordinates in Figure 13 for each of the five clinical groups are divided by the respective standard deviation of the data in each group. The normal group appears at the top of Figure 14 because the standard deviation STD of the normal group is the smallest. These results show the consistency of the mathematical formalism used. The procedure used in Figure 14 for the two-dimensional display of data by dividing each group by its respective STD offers an interesting way of segregation between different clinical groups. It creates a problem of classification, given a new piece of data how to place it in one of the five (or more) groups involved? This problem can be solved by calculation of the mean and standard deviation of each group, and making use of statistical discriminant analysis of data. One can note that bivariate analysis and display of data is superior to univariate analysis for the purpose of classification and segregation. It has already been reported that using two indexes instead of one like EF can give better assesment of the ventricular function [63].

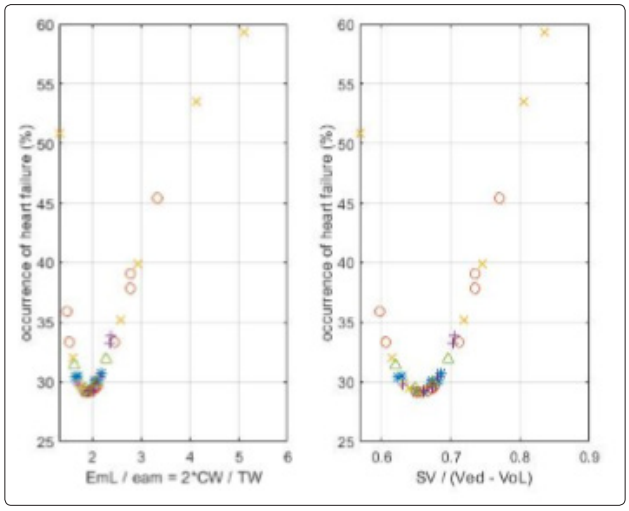


Figure 13: (Left) Relation between percentage of occurrence of HF and the ventriculo-arterial coupling E_{mL}/e_{am}. Note the minimum of the curve around the normal group for $E_{mL}/e_{am} \approx 1.9$. (Right) Relation between percentage of occurrence of HF and $SV/(V_{ed} - V_{oL})$. Note the mimimum of the curve around the normal group for $SV/(V_{ed} - V_{oL}) \approx 2/3$. Data from Dumesnil et al. for five groups of clinical data: normal *, aortic stenosis o, aortic valvular regurgitation +, mitral regurgitation ^, miscellaneous cardiomyopathies x [20-22].

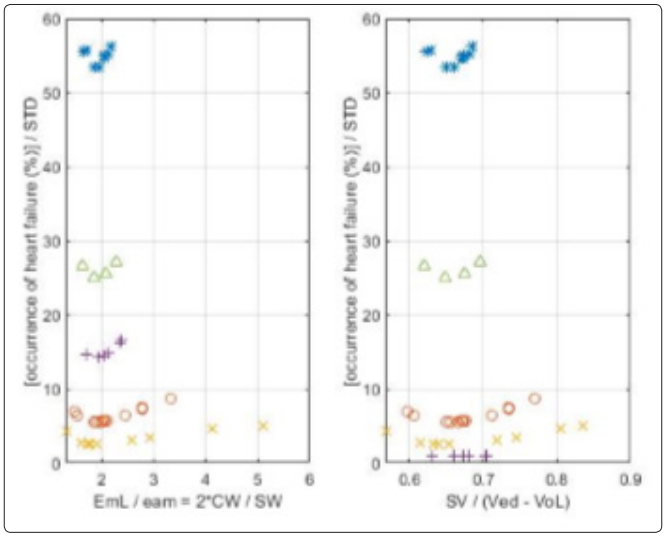


Figure 14: (Left) Relation between [percentage of occurrence of HF]/STD and the ventriculo-arterial coupling E_{mL}/e_{am}. Note the minimum of the curves around $E_{mL}/e_{am} \approx 1.9$. (Right) Relation between [percentage of occurrence of HF]/STD and $SV/(V_{ed} - V_{oL})$. Note the mimimum of the curves around $SV/(V_{ed} - V_{oL}) \approx 2/3$. STD is a symbol representing the respective standard deviation of each group. Data from Dumesnil et al. for five groups of clinical data: normal *, aortic stenosis o, aortic valvular regurgitation +, mitral regurgitation ^, miscellaneous cardiomyopathies x [20-22].

Discussion

The results presented in this study show relations between the ejection fraction EF and the parameters V_{oL}, E_{mL} and P_{isoL} describing the linear ESPVR, as well as possible clinical applications of these relations. The introduction of the maximum active pressure of the myocardium (also called peak isovolumic pressure P_{isoL}) in the mathematical formalism describing the linear model of the ESPVR has allowed the use of the total area $TW = PE + SW + CW$ in the study of the energetics of cardiac contraction (instead of the usual trend of using only the area $PVA = PE + SW$ as in [4, 6, 60, 64]). The results of Figure 11 suggests that the study of the distribution of TW between the three areas PE, SW, CW under the ESPVR is a relevant factor for the understanding of the mechanics of cardiac contraction, whatever the physiological meaning of the areas PE and CW.

For simplicity in this study we have assumed that P_m is constant during the ejection phase, and that $V_m \approx V_{es}$ the end-systolic ventricular volume. Applications to a variety of clinical and experimental data published in the literature and presented in this study show the consistency of the mathematical formalism used. The simplicity of the linear model should not hide the fact that the starting point of the mathematical derivation is based on the theory of large elastic deformation of the myocardium [47,48]. The linear model used in this study is a limiting case of a non-linear model of the ESPVR when the variations in V_m and P_m are relatively small and within the physiological range. Some preliminary results of the non-linear model of the ESPVR have been published, they need further studies for reliable application [16-18, 47, 48, 51].

The ejection fraction *EF* of the left ventricle is one of several indexes that are related to the stroke volume $SV = V_{ed} - V_m$. Equations (16) – (19) show some of the complex relations that exist between *SV,* and consequently $EF = SV/V_{ed}$, and the parameters describing the ESPVR. In this study it was assumed that the parameters V_{oL}, E_{mL} and P_{isoL} describing the linear ESPVR are constant when the point d_1 in Figure 2 with coordinates (V_m, P_m) moves along the linear ESPVR. What actually happens is a complex mechanism that allows V_{oL}, E_{mL} or P_{isoL} to vary in a way to allow the left ventricle to adapt to variation in load condition or inotropic changes in the myocardium, for instance by maintaining a stroke work reserve $SWR = SW_{mx} - SW > 0$ (with point d_1 on the ESPVR remaining below the midpoint d_5 of the segment d_3V_{oL}), as explained in this study and in [8]. When this mechanism of adaptation fails then one can expect symptoms of heart failure, defined in this study as a reduction in stroke work *SW* when an increase in load demand occurs that correspond to an increase in the ventricular pressure P_m. This definition of heart failure is not unique, heart failure can be caused by other cardiac pathologies.

Two ways for the classification of the state of the left ventricle are indicated. One way is the ralation between percentage occurrence of heart failure and *EF* that can be extended to other indexes related to the *EF* as illustrated in Figs 12-14, these results show how useful the *EF* can be. The second way is a careful study of the position of the point d_1 with coordidates (V_m, P_m) on the linear ESPVR with respect to the midpoint d_5 with coordinates ($V_{mid} = 0.5\,(V_{ed} + V_{oL})$, $P_{isoL}/2$). As previously mentioned, the stroke work *SW* is maximum and equal to SW_{mx} when point d_1 coincides with midpoint d_5 in Figure 2. When d_1 is coincident or above the midpoint d_5 on the ESPVR in Figure 2, an increase in P_m causes a decrease in the stroke work *SW* causing cardiac insufficiency. It has already been observed that there is a difficulty in defining HFpEF in terms of $EF > 0.5$ as explained in [65], and as discussed in this study in relation to Figure 7. A possible alternative definition of HFpEF is to refer to cases with d_1 slightly below d_5 on the ESPVR ($V_m < V_{mid}$, $EF > EF_{mid}$) , but with d_1 moving above d_5 as a result of an increase in P_m ($V_m >= V_{mid}$, $EF <= EF_{mid}$). Cases with $V_m >= V_{mid}$ and $EF <= EF_{mid} = (V_{ed} - V_{mid})/V_{ed} = 0.5*(V_{ed} - V_{oL})/V_{ed}$ correspond to cardiac insufficiency, agreeing with $EF <= 0.5$ only when V_{oL} is zero.

Diastolic heart failure is linked to the Frank-Starling mechanism. As shown in Figure 2, normally an increase in the end-diastolic volume V_{ed} by ΔV_{ed} is accompanied by an increase in the active pressure of the myocardium P_{isoL} by ΔP_{isoL}. A good contractility of the myocardium is reflected in the way P_{isoL}, E_{mL} and/or V_{oL} adapt to load condition in a way to maintain normal values for the ventriculo-arterial coupling E_{mL}/e_{am}. If an increase in load condition, as reflected by an increase in the ventricular pressure P_m, is not matched by adequate changes in V_m, V_{ed} and/or P_{isoL}, the pressure gradient $P_{isoL} - P_m$ and/or the stroke volume $SV \approx V_{ed} - V_m$ may decrease when an increase is expected. As noted by Kitzman et al., congestive heart failure can occur in patients with preserved indexes of left ventricular systolic function, even in the absence of coronary and valvular heart disease, and that the patients' ability to augment stroke volume *SV* by means of the Frank-Starling mechanism can be limited by abnormalities in the left ventricular diastolic function [66]. The ability of the ESPVR to adapt to the Frank-Starling mechanism is reflected on *SV* and P_{isoL} by the relations given in Eqs (16) - (19).

The filling pressure P_{ed} during the diastolic phase is small compared to P_{isoL} or P_m and it is assumed zero in this study. The error in the calculation of the gradient $P_{isoL} - P_m = (P_{isoL} - P_{ed}) - (P_m - P_{ed})$. cancels. The error in the calculation of the ratio $(P_{isoL} - P_{ed})/(P_m - P_{ed}) = (P_{isoL}/P_m)*[(1 - P_{ed}/P_{isoL})/(1 - P_{ed}/P_m)] \approx (P_{isoL}/P_m)*[1 + P_{ed}*(P_{isoL} - P_m)/(P_{isoL}*P_m)]$ is small for relatively small P_{ed}. The quantity $P_{ed}*(P_{isoL} - P_m)/(P_{isoL}*P_m)$ is usually much smaller than unity and can be neglected. Note that the linear model of the ESPVR gives a slight overestimate of P_{isoL}.

Several topics have not been discussed in this study. For instance the influence of the geometry of the left ventricle on *EF* has been discussed by Dumesnil et al., possible influence of the geometry of the left ventricle on the ESPVR needs further consideration [20-22]. How coronary, valvular heart diseases or other cardiomyopathies affect the ESPVR is another subject that deserves attention [67-69]. The calculation of the parameters V_{oL} and E_{mL} of the linear model of the ESPVR in a non-invasive way for reliable clinical applications is also a topic of high priority [5,70]. Finally the reader may wish to compare the present study with Otto Frank's original work on the pressure-volume relation in the left venbtricle as presented in a recent study [71].

Conclusion

Results presented in this study indicate that *EF* does not determine uniquely the state of the myocardium, bivariate (or multivariate) analysis of data appears a better way to assess the ventricular function as is evident from the figures presented in this study. New indexes derived from the ESPVR have been introduced, they do not replace, but complement and clarify the application of the *EF* in the study of cardiac mechanics. No one index can be used for classification or segregation between all cases of ventricular malfunction, some indexes are better than others depending on the clinical cases considered. An experimental relation between percentage occurrence of heart failure and *EF* has been used to derive similar relations with indexes derived from the ESPVR, it is an example of a useful use of the *EF*. Definitions of heart failure, HFpEF and diastolic heart failure in terms of the formalism used in this study have been introduced that need further evaluation. Extending the results of this study to a non-linear model of the ESPVR is an important topic for future research work.

Appendix

In this appendix the method of calculating the optimal efficiency given by Eq. (23) is explained. By using Eqs (9) and (13) we have

$$SW/TW = 2*(P_m/P_{isoL})\,(V_{ed} - V_m)/(V_{ed} - V_{oL})$$

$$SW/TW = 2*(e_{am}/E_{mL})\,[(V_{ed} - V_m)/(V_{ed} - V_{oL})]^2 \qquad \text{(A1)}$$

By using Eq. (14) and by writing $u = E_{mL}/e_{am}$, we get

$$SW/TW = 2*u/(1 + u)^2 \qquad \text{(A2)}$$

By using Eqs (10) and (11) we have

$$CW/TW = u^2/(1 + u)^2 \qquad \text{(A3)}$$

$$PE/TW = 1/(1 + u)^2 \qquad \text{(A4)}$$

If we write

$$\eta = (k_1*CW + k_2*SW)/TW \quad \text{(A5)}$$

then we have

$$\eta = (k_1*u^2 + 2*k_2*u)/(1 + u)^2 \quad \text{(A6)}$$

The maximum of the efficiency η is obtained by calculating $d\eta/du = 0$, we get

$$u = E_{mL}/e_{am} = k_2/(k_2 - k_1) \quad \text{(A7)}$$

For $k_1/k_2 = 2/3$, one gets $u = E_{mL}/e_{am} = (V_{ed} - V_m)/(V_m - V_{oL}) = 3$.
For $k_1/k_2 = 0.5$, one gets $u = E_{mL}/e_{am} = (V_{ed} - V_m)/(V_m - V_{oL}) = 2$.
for $k_1/k_2 = 1/3$, one gets $u = E_{mL}/e_{am} = (V_{ed} - V_m)/(V_m - V_{oL}) = 1.5$.
For $k_1 = 0$, one gets $u = E_{mL}/e_{am} = 1$ and $V_{ed} - V_m = V_m - V_{oL}$ (point d_1 coincident with midpoint d_5 in Figure 2).
The case $k_1/k_2 = 0.5$ is shown in Figure 11 (right), the case $k_1 = 0$ is shown in Figure 11 (middle). Similarly the optimization of $\eta = (k_3*PE + k_2*SW)/TW$ gives the result of Figure 11 (left).

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