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The Pythagorean theorem reveals the inherent companion of cardiac ejection fraction☆

Peter L.M. Kerkhof [a,*], Jean Paul Mérillon [b], Byung Won Yoo [c], Richard A. Peace [d], Gareth Parry [e], Guy R. Heyndrickx [f], Tatiana Kuznetsova [g], Lilian J. Meijboom [a], Ralf W. Sprengers [a], Han Ki Park [h], Neal Handly [i]

[a] Amsterdam Cardiovascular Sciences, Dept. Radiology and Nuclear Medicine, VU University Medical Center, Amsterdam, the Netherlands
[b] Dept. Médecine Nucleaire, Hôpital FOCH, 92150 Suresnes, France
[c] Dept. Clinical Pharmacology, Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea
[d] Dept. Nuclear Medicine, Royal Victoria Infirmary, The Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK
[e] Dept. Cardiopulmonary Transplantation, Freeman Hospital, The Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK
[f] Cardiovascular Center, Onze-Lieve-Vrouw Clinic, Aalst, Belgium
[g] Dept. Cardiovascular Sciences, University of Leuven, Leuven, Belgium
[h] Division of Cardiovascular Surgery, Dept. Thoracic and Cardiovascular Surgery, Severance Cardiovascular Hospital, Yonsei University Health System, Seoul, Republic of Korea
[i] Dept. Emergency Medicine, Drexel University College of Medicine, Philadelphia, PA, USA

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ABSTRACT

Background: Quantification of ventricular performance requires a comprehensive metric which is manageable for patient care and clinical trials. Ejection fraction (EF) has been embraced as an attractive candidate. However, being a dimensionless ratio, EF has serious limitations.
Methods: We aim to identify what information is not recognized when limiting the volume-related analysis by exclusively relying on EF. This investigation applies the volume domain concept, relating end-systolic volume (ESV) to end-diastolic volume (EDV). This approach allows graphical identification of the information not covered by EF. Implications for atria, left ventricle (LV) and right ventricle (RV) are investigated in healthy individuals, and cardiac patient groups using various imaging modalities.
Results: The Pythagorean theorem indicates that the hypotenuse which relates any {EDV, ESV} combination to EF corresponds with the information not covered by the single metric EF. The impact of the recovered EF companion (EFC) is illustrated in healthy adults ($N = 410$, LV 2D echocardiography), heart transplant patients ($N = 101$, LV CT), individuals with heart failure ($N = 197$, biplane angiocardiography), for the RV with corrected Fallot ($N = 124$, MRI), diameters for left atrium ($N = 49$, MRI) and area for right atrium ($N = 51$, MRI). For any limited EF range we find a spectrum of EFC values, showing that the two metrics contain (partly) independent information, and emphasizing that the sole use of EF only partially conveys the full information available.
Conclusions: The EFC is a neglected companion, containing information which is additive to EF. Analysis based on ESV and EDV is preferred over the use of EF.

1. Introduction

The quantification of ventricular performance in research and clinical practice has steadily relied on ejection fraction (EF), with few alternative candidates [1]. A recent study explored the relative contribution of the constituent components in various patient populations, and unequivocally established that end-systolic volume (ESV) is the primary determinant of EF [2]. The other component, being end-diastolic volume (EDV), exhibits significantly ($P < 0{\cdot}0001$) less association with EF. The present study further investigates the fundamentals of the popular metric EF, and aims to clarify the strengths and limitations of its routine use. In particular we seek to identify the partner component which complements the partial information embodied by EF, given the fact that this metric consists of the ratio of two volume measurements,

Abbreviations: AP, anterior-posterior; BSA, body surface area; CT, computed tomography; EDV (i), end-diastolic volume (index); EF, ejection fraction; EFC(i), ejection fraction companion (index); ESV(i), end-systolic volume (index); FAC, fractional area change; FACC, fractional area change companion; FS, shortening fraction; FSC, shortening fraction companion; HF, heart failure; LA, left atrium; LV, left ventricle; MRI, magnetic resonance imaging; MV, myocardial volume; RA, right atrium; RF, residual fraction; RV, right ventricle; SPECT, single photon emission computed tomography; SV(i), stroke volume (index); VRG, volume regulation graph.

☆ Statement: All 11 authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

* Corresponding author at: Amsterdam Cardiovascular Sciences, Dept. Radiology & Nuclear Medicine, VU University Medical Center, De Boelelaan 1118, 1081 HZ Amsterdam, Netherlands.
E-mail address: plm.kerkhof@VUmc.nl (P.L.M. Kerkhof).

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namely ESV and EDV. Indeed, looking at EF alone, as is current practice, is insufficient to an as yet unestablished degree.

Analysis is based on a paradigm coined the volume regulation graph (VRG) which describes the working point concept [3, 4]. Quantification of ventricular performance requires a carefully selected indicator which is sound and clinically easy to implement. The metric EF has been around for half a century, but a solid basis for its universal acceptance is virtually absent [1]. Therefore, a robust analysis of the components of EF, the evaluation of the scope of applicability, a delineation of limitations, and the formulation of an alternative for EF are due.

Our starting point is the VRG where each combination of coordinates denoted as {EDV, ESV} refers to the individual working point for the subject studied (Fig. 1) [1–4]. Volume data may be indexed (i) for body surface area (BSA), yielding {EDVi, ESVi}. Obviously, all meaningful working points are confined to the lower right-angled triangle, since ESVi cannot exceed EDVi. Each point can also be fully characterized by the combination of the angle (phi) and the length of the line segment connecting the origin with the working point under consideration (Supplement Fig. S1). This procedure allows graphical visualization of the trajectory of EF in the volume domain (Fig. 1). To clarify we employ a nontraditional but more insightful way to formulate the mathematical interdependence:

$$EF = 1 - (ESVi/EDVi) \quad (1)$$

The interpretation of EF can best be realized in the VRG domain, where the connection between a collection of ESV(i) and EDV(i) data points is expressed as a linear relationship $ESV(i) = \alpha + \beta\, EDV(i)$, with intercept α and slope β [1–3].

The slope of segment **c1** (Fig. 1) is the tangent of phi and equals residual fraction (RF) for the working point P2, being defined as {ESVi/EDVi} [1, 4]. Remarkably, RF was the original expression in vogue, before the term EF was launched, as reviewed elsewhere [1].

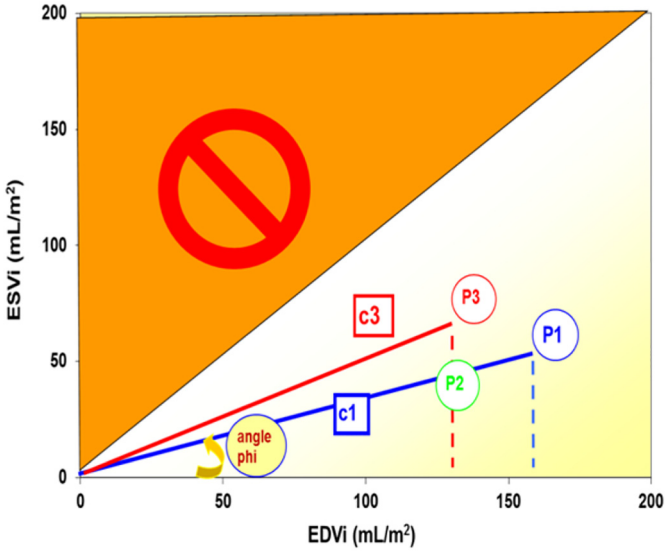


Fig. 1. Volume regulation graph where the working point (P) concept is shown in the volume domain. End-systolic volume (ESV) is related to end-diastolic volume (EDV), with suffix i referring to body surface area indexation. Each point Pj (such as P1, P2, P3) is defined by the prevailing coordinate pair {EDVi, ESVi} and can only be realized within the lower right-angled triangular area. The upper orange colored triangular area has no (patho)physiologically relevant working points, since ESVi must be smaller than EDVi, or equal in the case of an isovolumic beat. Point P1 is fully characterized by the angle phi and the length of the blue line segment (c1). Similarly, point P2 is defined by the same angle but a smaller line segment, and a lower value for EDVi (see broken red line). Taking the same value for EDVi as in P2, we may consider another working point P3, which is associated with an angle larger than phi, and slightly increased C3 compared to C2 which corresponds with P2.

Clearly, EF equals (1-RF). All points (e.g. P1 and P2) on a line (here **c1**) with the same angle (phi) carry identical values for EF. However, EF cannot be used to interpret the working point unless a second piece of information is explicitly known, e.g. ESV, EDV or stroke volume (SV) [4]. If it is desired to not include any of these traditional variables, then the hypotenuse emerges as an easily recognized EF companion (EFC) candidate. For mathematical derivation and calculation of the hypotenuse EFC, see Supplement Fig. S1.

Critical remarks concerning the exclusive use of EF have been voiced as early as 1965, actually barely after its launch, as reviewed elsewhere [5]. Recently, further cautious comments have accumulated [6–8]. However, a precise delineation of the limitations of EF or a solid proof of its inadequacy has not been presented thus far. Therefore our aim is to define what piece of information remains hidden when considering the ratio on which EF is based.

2. Methods

2.1. Description of patients

This retrospective investigation concerns healthy individuals and various patient groups:

1) A representative group of 155 patients (age range 23–86 years, 65 females) with various types of heart disease. Also, 197 patients (67 women) with heart failure (HF), and multiple data series on a single heart transplant patient were analyzed. Data on LV volume were collected between 2000 and 2009 at the Cardiovascular Center in Aalst, Belgium, as described in detail before [5]. Briefly, biplane ventriculograms are recorded using a radiographic contrast agent. All clinical data were primarily obtained for routine diagnostic and treatment purposes, without any additional procedure related to the present analysis. All patients gave permission to use their data in anonymized investigations by signing a consent form. This study was exempt from institutional review by the Onze-Lieve-Vrouw Clinic Review Board.
2) A cohort of 410 healthy volunteers (15–80 years, 215 women) investigated by employing 2D echocardiography, as described elsewhere [9]. The local Institutional Review Board approved the study protocol. All subjects provided informed consent in writing.
3) In 124 post Fallot repair patients (age range 6–47 years, 50 females) undergoing RV status evaluation. Volumes were determined by 1·5 T gated MRI. Also, LV data were available for 121 individuals (49 women). The Institutional Review Board approved the retrospective study, with details published before [10].
4) LV volumes in 101 heart transplant patients (age 4–67 years, 33 females) were obtained by CT and images processed on a Siemens Syngo Via workstation. Approval by the Research Ethics Committee was not indicated for the present retrospective study which is considered service evaluation.
5) For 367 individuals (age 40–86 years, 195 females) with near-normal LV function or subclinical heart disease. This group was evaluated by gated myocardial perfusion Single Photon Emission Computed Tomography (SPECT) in a study between 2001 and 2004, approved by the local Institutional Review Board, and described elsewhere [11]. Participants had normal perfusion images, normal regional wall motion, and absence of ECG abnormalities at rest, as well as during stress testing.
6) Data on left atrial (LA, $N = 49$) and right atrial (RA, $N = 51$) dimensions in cardiac patients (age 25 to 83 years) were evaluated by cardiac MRI, performed with a 1·5 T Siemens Avanto scanner using front and back surface coils. Longitudinal (AP) and transverse atrial diameters and areas were measured in the 4 chambers view, parallel and perpendicular to the atrial septum. We calculated fractional shortening (FS) and fractional area change (FAC) [12, 13].

In most groups the values for ESV, EDV, and companions are normalized to BSA (expressed as m^2).

2.2. Graphical analysis in the volume domain

The working point concept for the volume domain has been explained before [4]. Briefly, the position of point P (Fig. 1) is reflected by the coordinates {EDVi,ESVi}. The prevailing value of EF can be visualized in the VRG [3–5], as further explained in the Supplement. This exercise adds information to the metric EF, and in fact demonstrates that the EFC (or indexed EFCi when BSA is applied) is the inseparable partner of EF.

3. Results

Fig. 2A illustrates the clinical relevance of describing the working point in the VRG representation by considering LV volume data obtained during seven follow-up measurement sessions in a single heart transplant patient over >8 years. Fig. 2B shows the same data,

now in the equivalent EF-EFCi representation (as explained in Fig. S1, supplement). This diagram exhibits a similar pattern as time progresses, and indicates that just before the terminal phase the EF increased (suggesting some clinical improvement based on the traditional interpretation of EF), while EFCi continued to rise. Fig. 2A documents that the VRG description can be applied to an individual, showing the characteristics of the successive working points as time progresses. Clearly, there is a one-to-one translation from the {EDVi,ESVi} based VRG paradigm to the {EFCi,EF} domain (Fig. 2B).

In order to understand the impact of the hypotenuse EFC(i), it is useful to compare small EF intervals with the corresponding distribution of EFC(i) data points. As a means to visualize how EFC(i) relates to EF in each group studied, we consider narrow bands of EF, as exemplified in Fig. 3A. As explained in Fig. S2 (Supplement), we can select a wedge-shaped area referring to any chosen interval for EF. In case of HF patients, such a region is termed *mid-range EF* if the value is between 40 and 50% [1, 7]. We will adopt this choice for volume data, and create for pertinent data sets multiple EF bins each spanning 10%, but limited to 5% if referring to diameter or area as in our LA and RA studies.

The HF group has been stratified for phenotype (i.e. reduced, mid-range, and preserved EF), as well as for sex. Fig. 3A illustrates the scatter for EF versus EFCi. The purple bar refers to the mid-range region, corresponding with the purple wedge in Fig. S2. Conversion of this data into the proposed EF-based bins is presented in Fig. 3B, emphasizing the wide spread of EFCi for each bin with a relatively small EF range.

The healthy cohort regarding the LV is shown (Fig. S3, Supplement), with subdivisions for males and females. Average EF is higher ($P = 0{\cdot}0026$), and EFCi is smaller ($P < 0{\cdot}0001$) in women when compared with men.

Findings for the RV in post Fallot repair patients are presented in Fig. S4 (Supplement), and yield similar results in terms of a wide spread

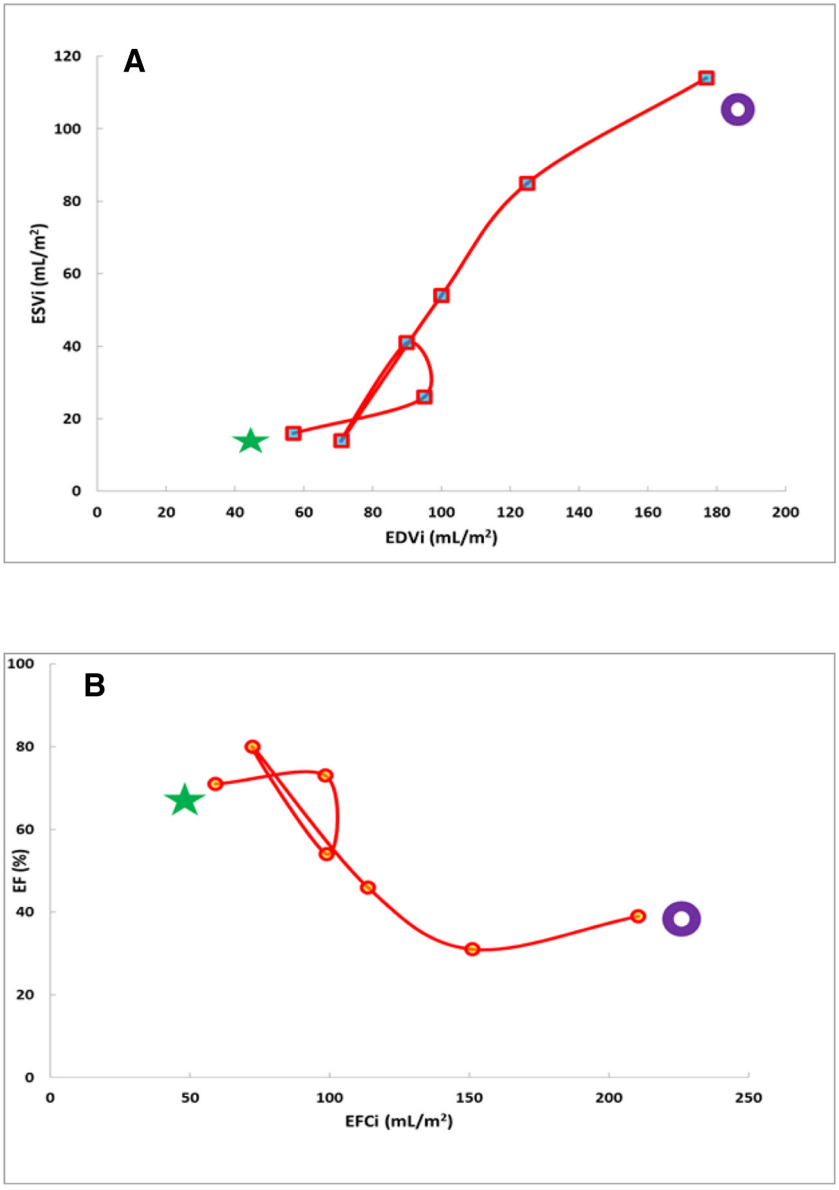


Fig. 2. A. Volumetric data points for a heart transplant patient during follow-up. End-systolic volume (ESVi) versus end-diastolic volume (EDVi), here demonstrated for successive measurements. The first data set collected within this series is marked by the green star, and the last by the purple ring. Curve refers to the time path. The period analyzed spans 3090 days, with variable intervals for data collection. B. Trajectory of ejection fraction (EF) and its companion (EFCi) for the same patient. The data points represented by ESVi versus EDVi (Cartesian coordinates, shown in A) can be translated into an equivalent diagram showing the connection between EF and the EF companion index (EFCi, in polar coordinates). The first data set collected is again marked by the star, and the last by the ring, while the curve refers to the time path.

of EFCi for each EF bin. Results for the LV are shown in Fig. S5. Nonparametric Spearman rank correlation (rho = −0.117, $P = 0.244$) indicates that an association between EF and EFC is absent in heart transplant patients (Fig. S6), making it doubtful to evaluate LV function purely based on EF. In the transplant patients we found that the average EFC value for the male recipients is significantly higher ($P < 0{\cdot}0001$) than for the females, while there is no difference for EF. In a population ($N = 367$) with various types of mild heart diseases we observe in a SPECT study a wide range for both EF and EFC (Fig. S7, Supplement). At any fixed level of EF a relatively wide scatter of EFC is seen, proving that EF alone does not provide unique information, as theoretically explained in Fig. 1. Similar findings as observed for LV and RV can be demonstrated for the LA diameter and RA areas (Figs. S8 and S9).

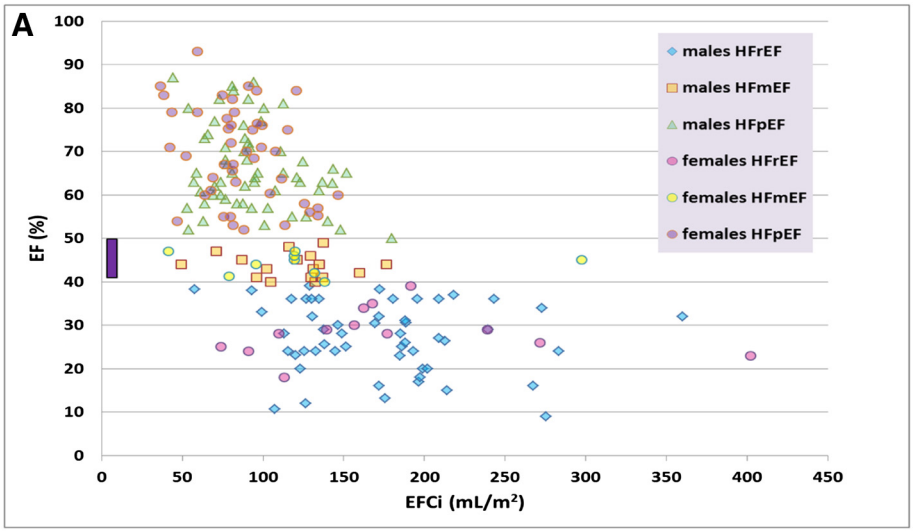
The single heart study illustrates the time-related volume changes following transplantation. The Fig. 2A and B document a small increase in EF between the last two measurements in a series, but a clear decrease in performance (with increasing LV size) on the VRG representation.

4. Discussion

4.1. What is ejection fraction?

The EF is a dimensionless ratio. This fact implies that the number (often displayed as a percentage) attached to EF per se cannot tell us anything about the order of magnitude of ESV and EDV, being the two constituting components [2]. However, as a ratio the EF can help to reduce non-random (systematic) measurement errors of volume inherent in the imaging technique [14].

This study demonstrates that EF emerges as an incomplete metric. The observation that the exclusive use of a ratio like EF provides an inadequate description has *passim* been touched in the recent literature. For example, it was shown that interpretation of strain data should



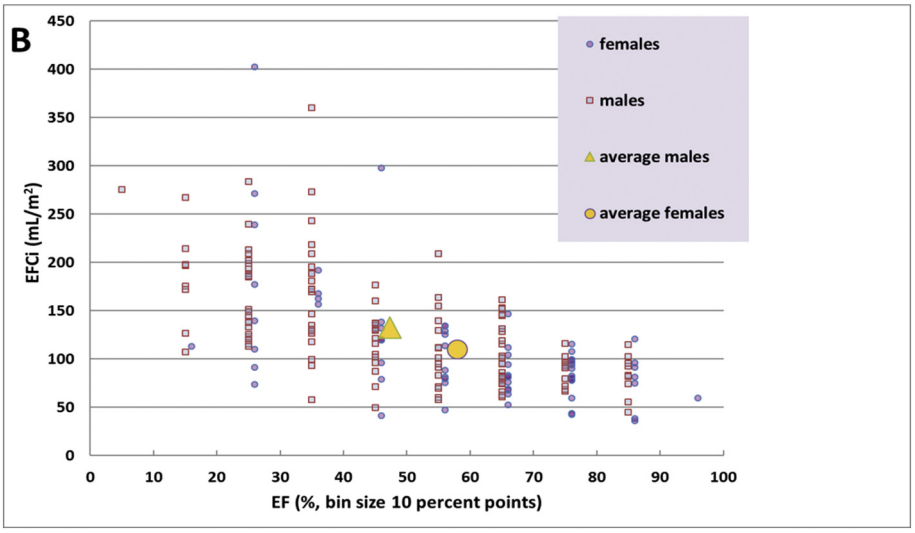


Fig. 3. A. Ejection fraction (EF) and companion index (EFCi), stratified for sex and heart failure phenotype. The distribution of EF and EFCi for 197 heart failure (HF) patients with phenotype (r = reduced, m = mid-range, and p = preserved EF). The purple bar refers to the mid-range with 40 < EF < 50%, as indicated by the purple wedge in Fig. S2 in supplement. Conversely, for each EFCi segment there is wide spread of EF data points, implying that only the combination of EF and EFCi provides accurate information on the individual patient. B. EF bins and companions in the same HF patients, according to sex. The spread of the companion (EFCi) for various EF bins each with a size of 10%. Men and women ($N = 67$) are shown separately, with P(for EF) = 0·0005 and P(for EFCi) = 0·008 for the difference between their average values.

consider EDVi [15]. We pinpoint a problem inherent to the use of metrics such as EF, FS, FAC, and other ratios commonly applied in cardiology, e.g. the ventriculo-arterial coupling index [1, 5]. Unfortunately, the scope of this pitfall is hard to assess, as the findings depend on the values for ESV(i) and EDV(i) in each individual. Any attempt to include a statistical analysis would be rather meaningless, and based on the specific population considered, in the past often being selected by the plagued EF metric.

4.2. Do we need a new metric?

The index EFC (and likewise FSC and FACC) is not new. The companion exists since the time the primary component (EF, FS or FAC) was introduced. Unfortunately, the corresponding companions never received attention. It is important to appreciate that EFC is not an alternative for EF, but an inherent partner which reflects available information not contained within EF. Similar to the starting point of determining both ESV and EDV (Fig. 2A), it is required to consider the combination of EF and EFC (Fig. 2B).

4.3. Two equivalent representations each based on two variables

The data pair {EDV,ESV} uniquely defines an operating state of a cardiac compartment [4], and can be located on a Cartesian coordinate system. However, in clinical practice the single metric EF is often employed to describe systolic function. Insight into the meaning and value of EF can be obtained by transforming the coordinates to the polar system, where EFC is the implicit partner metric (Supplement Fig. S1). Thus, the four components are mathematically related, implying that any two can be derived from the two remaining components, e.g. knowing EF and EFC, we can calculate EDV and ESV. However, EF alone does not permit reconstruction of EFC, ESV and EDV.

4.4. How does EF incorporate alterations of physiologic variables?

Alterations of preload, afterload, contractility and heart rate all impact on ESV or EDV, and occasionally even on their combination. As a consequence it is clear that EF may also be modified. However, the precise effect on the lumped metric EF is difficult to predict and interpret, because EF depends on the ratio of two variables which can be individually affected. Note that in addition EFC depends on (similar factors which influence) ESV and EDV. Therefore the physiologic changes mentioned above also impact on EFC. In conclusion, EF and EFC result from mathematical manipulation (involving a ratio, sum of squared numbers and their square root) of physiologically relevant basic variables (i.h.c. ESV and EDV). The derived pair of metrics is difficult to interpret in clinical practice. The only relief is the observation that EF is mainly determined by ESV [2], while EFC is mostly based on EDV as explained in the present study (Supplement eq. S1). These remarkable connections purely result from the fact that ESV cannot be larger than EDV, while EDV features in the denominator of the ratio [16].

4.5. Impact of the range for ESVi and EDVi

This investigation demonstrates that the popular metric EF which is routinely employed to assess ventricular systolic function should not be used in isolation, but instead interpreted against the background of the inherent companion indicated here as the EFC(i). Identification and calculation of EFC are outlined in detail (supplement Fig. S1). The interdependence between EF and EFC(i) is modulated by the particular characteristics of the study population. Clearly, the EFC(i) will converge to a value of {EDV(i) $\sqrt{2}$} for large ESV(i) implying small EF values (eq. S1, supplement). Therefore, a dilated heart chamber leads to a situation where the individual contributions of ESV(i) and EDV(i) are less outspoken for EF and the companion. Even when the EFC is simply reflected by the corresponding EDV(i), then it is still questionable if the combined use of EF and EFC (being ~ EDV(i) $\sqrt{2}$) has truly advantages over the more straightforward consideration of the basic components ESV(i) and EDV(i).

4.6. Determinants of EF and EFC

In practice, EF can be reformulated as a function of ESV(i), using a few population based constants [1–5]. In contrast, the EFC depends on ESV(i) and (mostly on) EDV(i) (eq. S1, supplement). The actual value of EFC(i) is determined by the balance between the squares of ESV (i) and EDV(i), which depends on the particular clinical characteristics of the individual (Fig. 2B) or population (Figs. S3–S9, see supplement) studied. Due to the documented nonlinear nature of their relationship [1–5], ESV(i) is a more sensitive indicator of remodeling compared to EF. In all cases there is ample room for EDV(i) to be closely connected with EFC(i) which acts as a partner to EF.

4.7. To what extent is EF related to EFC?

It is obvious that EF and EFC(i) are dissociated while considering any small ESV(i) range, as when looking only at healthy individuals, or when studying a relatively narrow spectrum of similar cardiac disease states. This theoretically derived insight regarding nearly constancy for the healthy individuals has been demonstrated in Fig. S3, and heart transplant recipients (Fig. S6). In contrast, when ESV(i) spans a wide range, as when describing a variety of cardiac patients, then the abovementioned balance between ESV(i) and EDV(i) plays a clear role in all its appearances. Indeed, in disease states the range for EF, EDV(i) and ESV(i) is much wider, also implying a broader trajectory for EFC(i), and likely resulting in a significant (non)linear inverse relationship between EF and EFC(i).

4.8. Effect of BSA and myocardial volume on EFC

Remarkably, in analysis of the EFCi this flanking metric contains details on BSA, whereas EF (by definition) is invariant for indexation e.g. based on BSA or myocardial volume (MV) or mass. If we had not chosen to index volumes for BSA, then the figures found for the EFC would be somewhat different, but its clinical implications similar. Effects of BSA on the VRG are minimal, apart from identical scaling factors influencing the coordinates and axes. Alternatively, EFC can be normalized to MV, which procedure is meaningful in cases of hypertrophy [1].

4.9. Sex-specific aspects

Since ventricular volumes in females are significantly smaller than in males, even after indexation for BSA, we analyzed the data in a sex-specific manner [2, 17]. This observation has consequences for EF and EFC(i), including equivalent metrics such as FS, FAC and their companions. Generally, lower average values for ESV(i) in women are associated with higher values for EF [2], and lower EFC(i) because each of the contributing components (namely ESV and EDV) is smaller in EFC. This rule of thumb should be considered when interpreting volumetric measurements and derived indexes in men versus women. An example based on the average values presented in Fig. S3 goes as follows:

Males ($N = 195$): average ESVi = 22.5 mL/m^2; average EDVi = 59.3 mL/m^2; average EF = 61.9%; average EFCi = 63.5 mL/m^2

Females ($N = 215$): average ESVi = 17.7 mL/m^2; average EDVi = 48.7 mL/m^2; average EF = 63.7%; average EFCi = 51.9 mL/m^2. Thus, average EF is higher ($P = 0{\cdot}0026$) for women, while their EFCi is smaller ($P < 0{\cdot}0001$).

4.10. Practical implications following data collection

The calculation of both EF and EFC is based on the combined measurement of ESV and EDV. The VRG concept is needed to define a working point [4]. The working point permits description in terms of

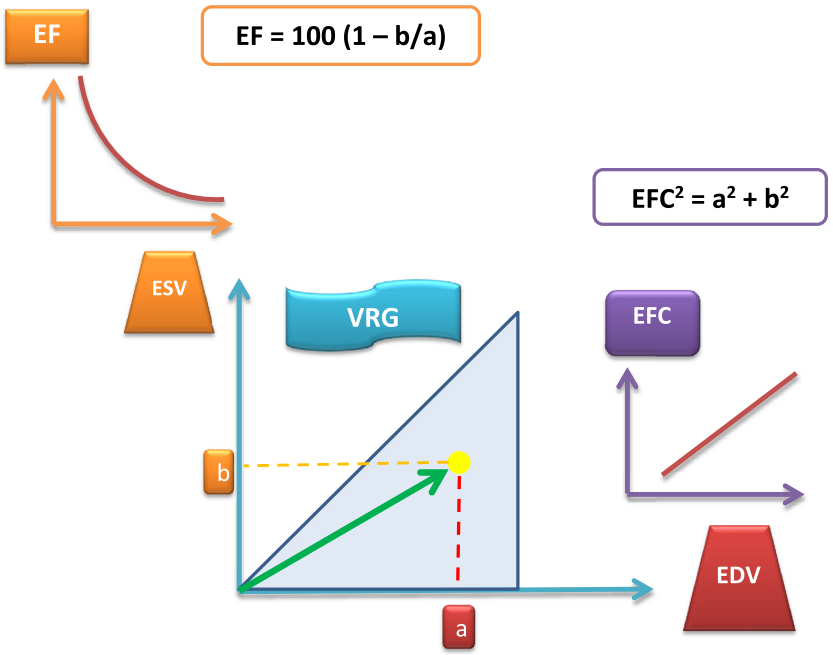


Fig. 4. Schematic overview illustrating that EFC flanks EF. The basic components end-systolic volume (ESV) and end-diastolic volume (EDV) form the ingredients of ejection fraction (EF) and its companion (EFC), being the hypotenuse of the triangle formed by a and b. All four components can be identified in the central diagram which is the volume regulation graph (VRG), as explained in Fig. 2. The yellow point in the VRG diagram represents a typical working point, characterized by the Cartesian coordinates {a,b}. The turquoise line with arrow head pointing to the yellow point shows the polar coordinates (i.e. angle and length) corresponding with {EF,EFC}. The ESV is the major determinant of EF (illustrated in the left upper diagram), reflecting systolic events. The EDV is the dominant component for EFC (as shown in the diagram to the right), mostly referring to diastolic aspects. The VRG representation clarifies that EF and EFC form inseparable partners. Generally, EF decreases when ESV increases, while EFC becomes larger when EDV is greater. Note that ESV serves as ordinate for the VRG, and as abscissa for the EF versus ESV diagram.

Cartesian coordinates {EDV,ESV} as well as polar coordinates {EF,EFC}. These two systems are equivalent, as can be understood from the VRG presentation, and summarized in Fig. 4. Therefore, both metrics can and should always be estimated to permit a more complete interpretation of the data available. The procedure needed to generate the value of EFC can easily be implemented in current imaging tools. However, we still prefer an analysis in the volume domain [1, 2], with focus on ESV and EDV, rather than on derived, more elaborated and less intuitive metrics such as EF and EFC.

4.11. Scope of the problem

Various classification systems (including HF phenotypes) [1, 5] are based on EF, and related misconceptions need repair. The loss of information associated with the use of ratios pertains not only to EF or FAC and FS as discussed, but actually extends to many other dimensionless ratio-based metrics used in cardiology [18].

5. Conclusions

The primary message of this study is that derived metrics such as EF, FS and FAC offer an incomplete picture of the information that is actually available. By taking the ratio of two volume, diameter or area determinations, some valuable information is lost. However, the missing piece can easily be recovered, and is identified as the size of the hypotenuse in the VRG, no matter if we consider volumes, diameters or areas. The value of the companion is dominated by EDVi (simply because EDVi > ESVi), and thus somewhat counterbalances the more influential role played by ESVi in the actual value of EF. Indeed, in earlier work we demonstrated that EF is significantly more strongly determined by ESVi than by EDVi [2]. Therefore, it is important to also analyze the well-defined metric that partners with EF, FS or FAC.

The findings can be summarized in a scheme (Fig. 4): Ventricular and atrial behavior in the volume domain can be described by two approaches:

1. Combination of ESVi (referring to end-systolic elastance) and EDVi (pointing to Starling mechanism), as in the central portion of Fig. 4 showing the VRG and working point concept. [4]
2. Combination of EF (being dominated by ESVi) and EFCi (mostly reflecting EDVi), as illustrated in the two pertinent peripheral graphs.

Alternative 2 is a more complicated way of expressing the rather straightforward option 1. This view “explains” the traditional interest in both EF (as a systolic function index) and the attention given to Starling's law. However, we do not advance the use of the combination of EFC(i) and EF as descriptors for ventricular function, since ESV(i) and EDV(i) are more fundamental and intuitive (Fig. 2A).

Conflict of interest statement

The authors report no relationships that could be construed as a conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.06.074.

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