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

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A B S T R A C T

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.

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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].

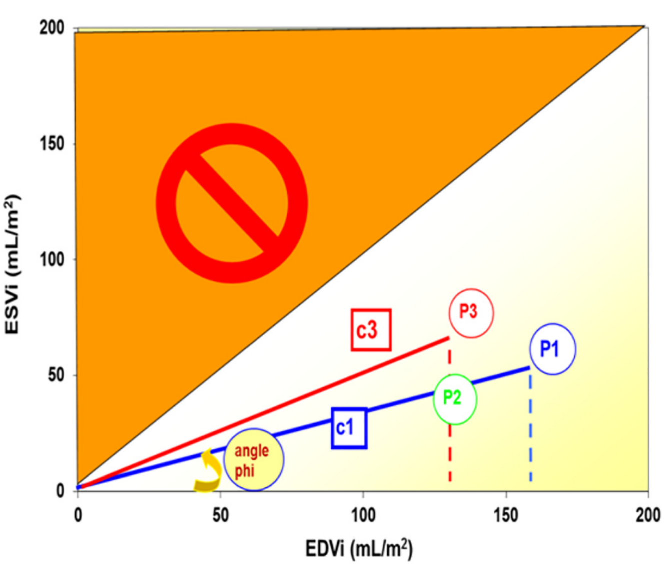

Fig. 1. Volume regulation graph where the working point (P) concept is shown in the volume domain. End-systolic volume (ESV) is related to end-diastolic volume (EDV), with suffix i referring to body surface area indexation. Each point Pj (such as P1, P2, P3) is defined by the prevailing coordinate pair {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. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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,

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