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Ejection fraction as related to basic components in the left and right ventricular volume domains☆

Peter L.M. Kerkhof [a,*], Peter M. van de Ven [b], Byungwon Yoo [c], Richard A. Peace [d], Guy R. Heyndrickx [e], Neal Handly [f]

[a] Amsterdam Cardiovascular Sciences, VU University Medical Center, Amsterdam, The Netherlands
[b] Department Epidemiology and Biostatistics, VU University Medical Center, Amsterdam, The Netherlands
[c] Department Clinical Pharmacology, Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea
[d] Nuclear Medicine Dept., Royal Victoria Infirmary, The Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK
[e] Cardiovascular Center, Onze-Lieve-Vrouw Clinic, Aalst, Belgium
[f] Department Emergency Medicine, Drexel University College of Medicine, Philadelphia, PA, USA

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ABSTRACT

Background: Ejection fraction (EF) is commonly applied as a clinically relevant metric to assess ventricular function. The numerical value of EF depends on the interplay between end-systolic volume (ESV) and end-diastolic volume (EDV). Remarkably, the relative impact of the two constitutive components on EF received little attention.
Methods: Three patient groups not using beta-blockers were analyzed for a robust investigation into the relative contribution of ESV and EDV when assessing EF: cardiac patients (N = 155) with left ventricular (LV) data obtained by biplane ventriculography, near-normals (N = 276) by gated SPECT investigation, and an MRI-based post Fallot repair study including right ventricular (RV) data (N = 124), besides LV. We compared various routes to evaluate EF via linear and several types of nonlinear regression with ESV as independent variable. Advanced statistics was applied to evaluate sex-specific differences.
Results: In all cases ESV emerges as the dominant component of EF, with less ($P < 0.0001$) impact of EDV. The relationship for EF versus ESV is nonlinear ($P < 0.0001$), and similar for both sexes. A linear approach may be inadequate and generate erroneous statistical outcomes when comparing subgroups of patients.
Conclusions: Values for EF primarily depend on ESV, both for LV and RV. This relationship is essentially nonlinear, and similar for both sexes. A logarithmic approximation is convenient and often acceptable. However, application of linear regression for EF vs ESV may lead to incorrect conclusions, particularly when comparing males and females.

1. Introduction

Traditionally, the cardiac performance index ejection fraction (EF) has been widely applied to assess the severity of cardiac disease [1–3]. Typically, a low value of EF corresponds with serious cardiac problems and a poor prognosis, although this may not apply to all types of heart failure (HF) [4]. The majority of clinical trials concentrate on EF as a central metric, yet without systematic attention to the relative role of the constituent components. EF is essentially composed of the ratio of two ventricular volume determinations. Calculation of EF is carried out by taking "one" minus the ratio of two volume determinations, namely end-diastolic volume (EDV), and end-systolic volume (ESV). Thus:

$$EF = 1 - (ESV/EDV) \quad (1)$$

This procedure yields a dimensionless number, usually expressed as a percentage (theoretically ranging from 0 to 100%), and applies to both left ventricle (LV) and right ventricle (RV). Clearly, EF depends on the "balance" between ESV and EDV, and this notion is explored in the present study. The calculation of EF is attractive from a practical point of view, but unfortunately entails shortcomings [3–4]. Note that many {ESV, EDV} combinations can generate identical outcomes for any particular value selected for EF [3].

The few publications available on the subject document an inverse nonlinear relationship between EF and ESV in cardiac patients [5–6]. A

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

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single paper interpreted the linearized slope difference of the regression lines as a sensitive ($P < 0.001$) indicator when comparing survival in two patient groups [7]. In fact, various strategies have been explored to relate EF to ESV. Initially, a linear trajectory was described while excluding the asymptotic region in the lower EF range [5]. It was shown that the correlation for EF vs ESVi (i.e. indexed (i) for body size) regarding patients ($N = 113$) using beta-blockers (BB) is significantly ($P < 0.02$) lower than in controls ($N = 49$). Subsequently, an analytical expression was derived, showing an inverse nonlinear relationship [3,6]. However, further progress was hampered by the fact that no statistical tool was available to compare the analytically derived nonlinear regression lines. Without any attempt for justification of a particular choice regarding the regression model, most studies persisted in using the linear approach for the full clinically relevant spectrum [7–11]. Three major shortcomings of the linear approximation refer to the fact that (i) the theoretical point where EF reaches 100% for small ESVi values is not respected; (ii) the asymptotic range at lower EF values is not adequately incorporated; (iii) thus far the intrinsic nonlinearity of the intermediate range is insufficiently acknowledged. The present paper copes with all these issues, and in addition describes the statistical tools required to compare these robust nonlinear regression curves.

A few investigators recognized the nonlinear nature and looked at logit (EF) vs log (ESVi) [12], an exponential fit [13], or EF vs $\log_{10}$ (ESVi) [14]. Some isolated studies have related EF to ESVi for the RV [15] but mostly in association with the tetralogy of Fallot [16] and applying Spearman ranked correlation [17]. None of these studies compared various regression models, nor gave attention to possible interaction with medication reportedly prescribed to a portion of their study group. The latter aspect may be clinically relevant, in view of documented differences associated with the use of BB [5].

This study is the first to present a statistical tool to compare robust nonlinear regression curves for EF vs ESVi. Applying the newly developed strategy to patient groups not using BB allows us to explore and compare various routes to evaluate EF in dependence upon ESV and EDV. In line with current guidelines we will also pay attention to sex-specific aspects during analysis of the patient data [18].

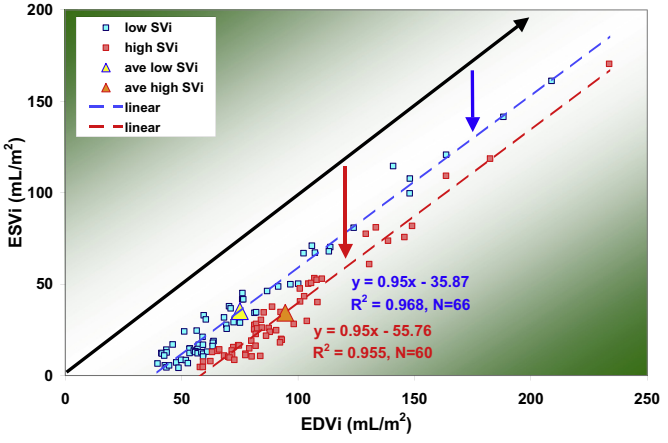

Fig. 1. Volume regulation graph, showing relationship between end-systolic volume index (ESVi) and end-diastolic volume index (EDVi) for two ranges (25–50, and 50–75 mL/m^2, respectively) of stroke volume index (SVi) in the angiographically evaluated group. The black line is the identity line. Therefore, the blue and red lines with arrow head reflect average SVi for each group. Triangles refer to average values for ESVi and EDVi in each group.

2. Methods

The elements ESV and EDV which contribute to EF can be related [2,3,6] to each other:

$$ESV = \alpha + \beta\ EDV \tag{2}$$

and graphically represented (Fig.1) in the volume regulation graph (VRG).

In the past we derived an analytical expression by combining Eqs. (1) and (2):

$$EF = 1 + \gamma\ \{ESV/(\delta - ESV)\} \tag{3}$$

with $\gamma = \beta / R^2$ and $\delta = \alpha - EDV_{ave}\ (1 - R^2)\ \beta / R^2$ where R^2 is the variance in ESV explained by the regression model in Eq. (2), while EDV_{ave} is the average value of EDV for the population under consideration [3,6]. In the present study we compare various routes to evaluate EF relative to ESV:

i) by obtaining γ and δ from α, β, R^2 via linear regression of ESV on EDV (cf. Eq. (2)), and then using the formula given by Eq. (3);
ii) by directly estimating the unknown parameters γ and δ in Eq. (3), while using an iterative mathematical method for nonlinear regression (see Supplement).
iii) using linear, second order polynomial, and logarithmic analysis.

This retrospective investigation concerns three patient groups not using BB:

1) patients ($N = 155$) with various types of heart disease as encountered in a representative major cardiology center. Data on LV volume were collected between 2000 and 2009 at the Cardiovascular Center in Aalst, Belgium, as described in detail before [3]. 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) individuals ($N = 276$) with near-normal LV function or subclinical heart disease. This group was evaluated by gated myocardial perfusion SPECT in a study between 2001 and 2004, approved by the local Institutional Review Board, and described elsewhere [14]. Participants had normal perfusion images, normal regional wall motion, and absence of ECG abnormalities at rest, as well as during stress testing.
3) post Fallot repair patients ($N = 124$) undergoing RV status evaluation. Volumes were determined by 1.5 T gated MRI. Also, LV data were available for 121 of these children. The institutional Review Board approved the retrospective study, with details published before [9].

In all patient groups the values for ESV and EDV are normalized to body surface area (BSA, expressed as m^2) to yield corresponding indexed (i) values (ESVi and EDVi, respectively). Similarly we obtained stroke volume index (SVi) and cardiac output index (COi).

Data are analyzed using IBM SPSS version 22 (IBM Corporation, Armonk NY), and Stata version 12 (StataCorp, College Station TX). Values are presented as average (ave) values with standard deviation (SD), or 95% confidence interval (CI). It must be noted that the direct nonlinear regression (DNR) analysis using Stata follows an independent approach because comparable (primed) γ' and δ' are calculated by DNR on the basis of an iterative procedure (Supplement), and not estimated by substituting α and β from Eq. (2). Values for γ' and δ', plus their CI's are presented. Comparison of means is based on two-sided t-statistics. The Fisher z-transform or the William's test is used to compare R-differences between groups, as appropriate. Differences regarding regression coefficients (i.e. slope and intercept) are based on a comparison of pooled estimates and analysis of variance. Significance is considered at the $P < 0.05$ level.

3. Results

Baseline characteristics for all participating groups are presented in Table 1, with sex-specific comparison in Supplement Tables S3 and S4. The VRG concept is illustrated in Fig. 1 for two subsets with a limited range of SVi in order to illustrate its linearity.

For the angiographically evaluated patient group we found, using linear regression:

$$ESVi = 0.80\ EDVi - 33.6, R^2 = 0.80, N = 155 \tag{4}$$

with $EDVi_{ave.} = 87.6$ mL/m^2. Thus, $\alpha = -33.6$ mL/m^2 and $\beta = 0.80$, resulting in $\gamma = 1.003$ and $\delta = -50.75$ mL/m^2 (Table 1). Following subdivision in males and females, we obtained two regression lines which almost coincide. However, the averages for ESVi and EDVi are different, resulting in significantly different average vales for EF (Supplement Fig. S1A). Similar results were obtained for the other study groups (Supplement Figs S1B and S1C). Supplement Table S1 compares the Pearson