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

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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

☆ Statement: All six 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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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].

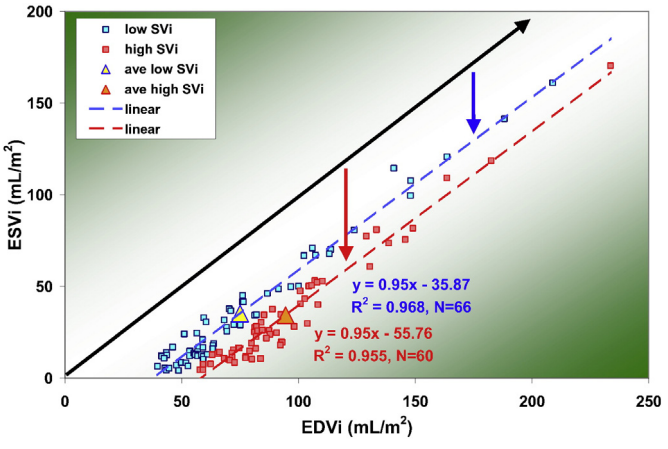


Fig. 1. Volume regulation graph, showing relationship between end-systolic volume index (ESVi) and end-diastolic volume index (EDVi) for two ranges (25–50, and 50–75 mL/m^2, respectively) of stroke volume index (SVi) in the angiographically evaluated group. The black line is the identity line. Therefore, 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

correlation coefficient for EF and each of the two basic constituents (Eq. (1)). From the graphical representation in Figs. S1 it can readily be seen that average EF decreases in a nonlinear fashion when ESVi increases, yielding an asymptotic region for the larger ESVi's as demonstrated in Fig. 2. For all study groups it appears that ESVi is the primary determinant of EF. Consequently, it is relevant to investigate in more detail the precise relationship between EF and ESVi.

Applying Eq. (3), we compared for the three study groups the outcomes with linear, logarithmic and second order polynomial approximations (Fig. 2A, B, C). The outcomes are summarized in Table 1, and indicate that Eq. (3) and logarithmic analysis yield highest correlations, while the two routes are fairly comparable for the range studied. As a next step the regression curves for subgroups were investigated to verify if they are statistically similar or not. We evaluated the sex-specific differences for all study groups (Fig. 2A, B, C), plus additional subgroups based on SVi range (Supplement Table S2), heart failure phenotype (Supplement Table S6), and survival characteristics as mentioned in publications elsewhere (Supplement Table S7). To evaluate a method to identify differences between regression curves for EF versus ESVi in different groups, we divided the angiographically obtained data into subgroups with high and low SVi (Fig. 1), defined as $50 < SVi < 75$ mL/m^2 and $25 < SVi < 50$ mL/m^2, respectively. The traditional linear approach indicates (Fig. S2) that the two slopes are not different ($P = 0.787$), in contrast to the intercept ($P < 0.001$). However, additional findings (Supplement Table S7) suggest that the linear approach may not (always) be correct. In order to more accurately test for differences between curves the *nonlinear* model was extended (Supplement Eq. S3) to include a dummy variable. Supplement Table S7 summarizes findings when comparing regression findings for several subgroups on the basis of the linear and the robust nonlinear DNR approach. Obviously, applicability of a linearized approximation for EF vs ESVi depends on the specific range covered. If the EF-range under consideration is small (as in the Fallot patients), then a simple linear regression may be justified (Supplement Table S5). The same applies to the asymptotic region in the lower range of EF. However, a nonlinear analysis seems mandatory when comparing groups covering a wider EF range.

In an earlier study we analyzed EF versus ESVi in patients with heart failure with preserved EF (denoted as HFpEF), and reduced type (HFrEF), respectively [3]. The slopes of the linearized regression lines were compared and found to differ significantly ($P < 0.0001$). Here we reanalyze those data using the *nonlinear* approach given in Eq. (3) while applying the DNR method. The nonlinear regression coefficients (b1 and b2) are not significantly different (Supplement Table S6). Therefore, we conclude that findings may be incorrect when applying the linear correlation (Fig. 3).

Table 1
Baseline characteristics of all patient groups studied.

	Group I	Group II	Group III (LV)	Group III (RV)
N (F %)	155 (41.9)	276 (49.3)	121 (40.5)	124 (40.3)
age (ave ± SD)	65.2 ± 12.1	63.0 ± 9.5	17.4 ± 7.5	17.3 ± 8.5
EDVi (ave ± SD)	87.6 ± 38.4	52.1 ± 25.8	81.5 ± 21.3	147.1 ± 37.6
ESVi (ave ± SD)	38.8 ± 34.5	26.0 ± 23.5	34.5 ± 14.6	77.0 ± 28.2
EF (%)	63.3 ± 19.3	56.1 ± 14.9	58.5 ± 8.5	48.5 ± 9.2
α (value)	−33.6	−20.3	−10.8	−29.5
β (value)	0.80	0.89	0.55	0.72
R^2 (ESVi vs EDVi)	0.80	0.95	0.71	0.81
γ (value)	1.003	0.9368	0.7746	0.8889
γ'	1.002	0.9137	0.7869	0.8951
δ (value)	−50.75	−22.74	−29.11	−54.34
δ'	−48.12	−21.39	−29.03	−53.54
R^2 (EF-ESVi, Eq. (3))	0.87	0.90	0.64	0.66
R^2 (EF-ESVi, ln)	0.85	0.87	0.64	0.66
R^2_s (EF-ESVi, lin)	0.75	0.77	0.62	0.61
R^2 (EF-ESVi, quad)	0.86	0.89	0.61	0.62
R^2_d (EF vs EDVi)	0.40	0.67	0.12	0.21
P (R_s vs R_d)	<0.0001	<0.0001	<0.0001	<0.0001

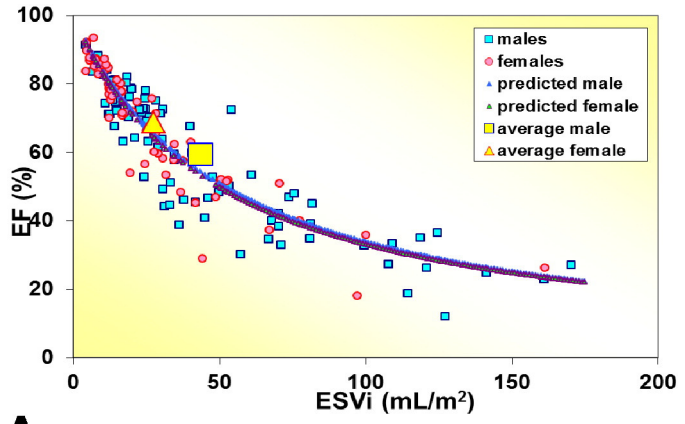
ave = average; ln = natural logarithm; lin = linear; quad = second order polynomial; other abbreviations as in Eq. (3). γ' and δ' calculated with the use of DNR. R^2_d (EF vs EDVi) and R^2_s (EF vs ESVi) are correlation squared for ejection fraction (EF) versus end-diastolic volume index (EDVi), and end-systolic volume index (ESVi),respectively. For male and female (F) subgroups see Supplement Table S1.

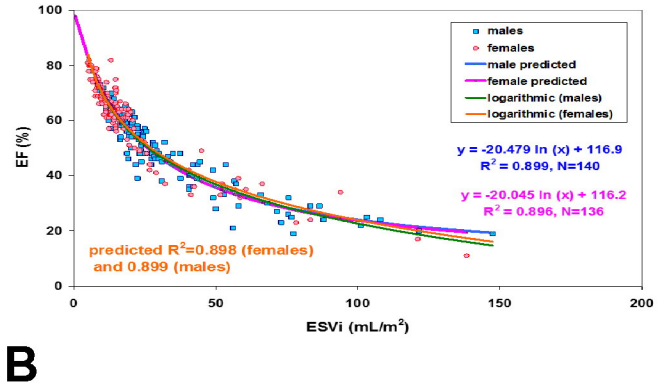
4. Discussion

Application of the novel statistical tool (coined DNR) described in this study has shed a new light on earlier studies [7,8,9,11]. The main findings concern:

1. An insightful and precise description of an inverse nonlinear relationship between EF and ESVi (Eq. (3)), both for LV and RV. Thus, there is a general tendency for the clinically employed metric of EF to decrease if ESVi increases (Fig. 3)
2. The presentation and validation of a robust analytical expression which relates EF primarily to ESVi rather than to EDVi. The simple expression (Eq. (3)) is characterized by a few group-associated and volume-based determinants, namely α, β, and EDV_{ave}. These determinants carry a clear physiologic interpretation related to Starling's law, as shown in the VRG representation (Fig. 1). The VRG may serve as a building block for subsequent derivations, not only for the analytical expression concerning EF-ESVi as formulated here, but also for additional applications such as the estimation of myocardial oxygen consumption, again by using α and β (Eq. (2)) [19].
3. By comparing various regression models, the logarithmic approach is found to offer an acceptable and convenient approximation (Table 1, Supplement Tables S3 and S4).
4. The linear description as often applied in the past may lead to incorrect conclusions whenever regression lines of groups are compared (Supplement Table S7, Fig. 3). Such studies deserve reinterpretation on the basis of the present findings.
5. Average ESVi and EDVi are significantly smaller in adult women for all groups studied, resulting in higher average EF values in females (Supplement Tables S3 and S4). Data points may be fitted to a single curve for both sexes (Figs. 2A, 3), but the distributions of the data points along the curve differ for the two sexes.
6. Obviously, the values for α and β may slightly differ, depending on the population studied and the imaging modality applied [20]. Normalization for BSA is common in cardiac dimension analysis, but body mass, body height, and any suitable allometric relationship may also be considered. In the VRG representation the data on abscissa and ordinate are always equally indexed, regardless of the choice (i.e. BSA or similar), implying that the regression equation is minimally affected by the indexation procedure selected. Obviously, this is not the case for the EF vs ESVi figure, because EF is without dimension and only ESVi is indexed for BSA. Furthermore, the VRG approach allows for stratification, e.g. on the basis of myocardial mass. This aspect requires attention when analyzing specific diagnostic patient groups. However, the general framework outlined here equally applies to all patient groups.
7. However, Eq. (3) applies to all modalities, because the formula is based on a mathematical derivation. Importantly, Eq. (3) adequately covers the full range of EF values, while there is no single portion of the curve that is truly linear (Fig. 2A, B, C).

EF is considered a key metric to assess LV function, but according to recent studies not devoid of important limitations [3,4,21,22]. Since EF directly depends on ESVi and EDVi, it is of paramount importance to delineate their relative roles. In principle, all relevant combinations can be evaluated by bivariate analysis, including SVi, ESVi and EDVi. However, standardized coefficients in multivariate regression analysis are typically not that easy to interpret. If independent variables are correlated (which the large standardized beta for ESVi suggests) it is to some extent arbitrary to which coefficient the part that can be explained by both variables is assigned. Justification that ESVi is more important than EDVi can in fact be better demonstrated using William's test for





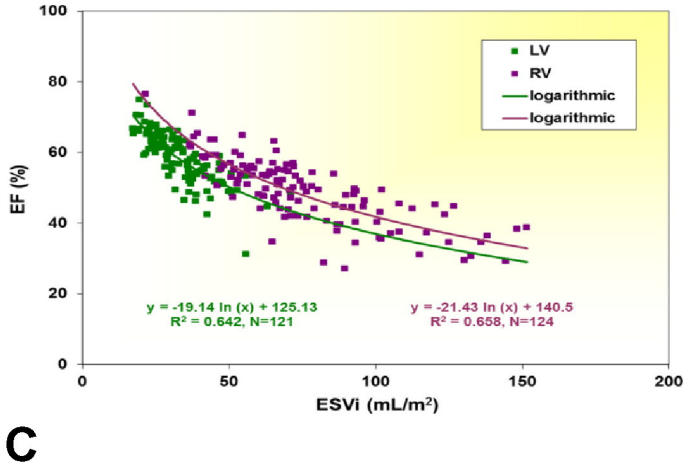


Fig. 2. A. Ejection Fraction (EF) as a function of end-systolic volume index (ESVi) for the patients with LV disease (N = 155). Actual data points for males and females are presented, along with their average values and predicted regression curves based on Eq. (3). B. Ejection Fraction (EF) as a function of end-systolic volume index (ESVi) for the SPECT study. In these cases the predicted and the logarithmic regression equations yield similar results for R^2. Data (N = 276) based on a study by Peace et al. [14]. C. Ejection Fraction (EF) as a function of end-systolic volume index (ESVi), both for the left (LV) and right ventricle (RV) in post Fallot repair patients. A logarithmic (ln) regression curve has been fitted for each group, illustrating that for the full range EF values for the RV are higher at identical values of ESVi.

correlations. The interaction term is also found to be significant implying that the relationship between EF and ESVi depends on the value of EDVi. Statistics document a secondary role for EDVi: ESVi is found to be superior (see William's test), while additionally EDVi is strongly related to ESVi (cf. the VRG), meaning that ESVi already incorporates information that is potentially embodied by EDVi. Indeed, our study (Table S1) demonstrates that ESVi is the dominant factor for EF in comparison to EDVi. We explore and compare various routes to evaluate EF in linear dependence of ESV, as well as being a nonlinear function of ESV using the validated robust formula (Eq. (3)). Besides we employ several other types of nonlinear regression analysis including logarithmic transformation. The ideal description should meet three basic requirements, namely include the theoretical point where EF approaches 100% for the hyperdynamic ventricle, provide adequate coverage of the asymptotic range for larger ESVi values, and a reasonable description of the range between the two extremes. Our approach adequately incorporates the

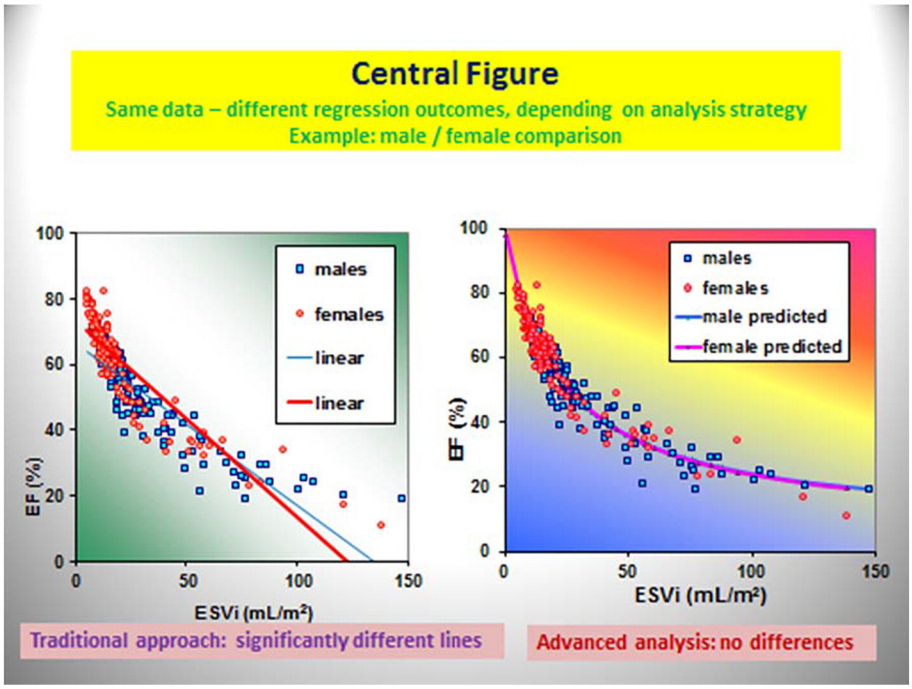


Fig. 3. The relationship between ejection fraction (EF) and end-systolic volume index (ESVi) for the left ventricle has often been described by an inverse linear relationship (left panel). This study shows that a nonlinear approach is more appropriate (right panel), especially when comparing regression curves for various populations, or establishing reference ranges for subgroups. Here we compare females (N = 136) and males (N = 140).

intrinsic nonlinearity of the full intermediate range. Thus, the present paper copes with all three concerns, and in addition offers the statistical DNR tools required to compare the robust nonlinear regression curves.

When considering a sufficiently small range (as e.g. in Fig. 2C) it may be tempting to employ a linear approximation. Remarkably, the logarithmic regression [14] yields a curve which parallels the robust approach (Eq. (3)) in a fair manner with similar correlations (Fig. 2A, B, C). However, when extrapolating the mathematical expression for each individual case we observe difficulties similar as inherent to the log-logit [12] or exponential approach [13]. We conclude that the robust method presented here carries universal and reliable applicability to the question at hand, and permits correct comparison of any two subgroups, for example as based on sex as we have documented. It is important to emphasize that linear descriptions employed for comparison of two groups [7,11] may imply incorrect conclusions, as exemplified in our study (Fig. 3). Our robust DNR method for relating EF to ESVi is based on the VRG concept [3,6]. A VRG type of presentation for the RV is also reported in patients with sepsis, but no connection was made with the expected inverse behavior of the EF versus ESVi relationship [15].

The linear EF-ESV representation has been advanced as a method to predict mortality in myocardial infarction patients [7], because the regression lines were shown to differ significantly for two survival categories. This remarkable finding has been confirmed in neonates with congenital heart disease [3]. However, in both cases the analysis was based on the assumption of a linear approach which may not be universally applicable, as shown here (Supplement Table S7).

Our findings have clear clinical implications and provide fundamental insight into the nature of the metric EF. Interestingly, EF has been endowed with a central role when quantifying LV performance, mostly because of the simplicity of its measurement, in particular by current noninvasive routine clinical work. However, the underlying foundation remained obscure. More recently the end-systolic elastance (Emax) concept has been advanced as an alternative candidate to characterize systolic function of the LV. Interestingly, both metrics clearly depend on ESV which variable therefore may embody pivotal information. Unraveling the precise relationship between EF and ESVi is important, because ESVi constitutes the major determinant of the end-systolic elastance concept [3,6]. Thus, a description of EF in terms of ESVi (Eq. (3)) helps to clarify the connection between the two most popular metrics of cardiac performance, namely EF and the elastance concept.

A simplified linear approach to describe EF versus ESVi is not routinely acceptable, and may provide incorrect results when comparing patient groups (Fig. 3), and in defining reference ranges [14].

Conflicts of interest

None.

Acknowledgments

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ijcard.2017.09.019.

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