Noninvasive assessment of left ventricular and myocardial contractility in middle-aged men and women: disparate evolution above the age of 50?

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Claessens TE, Rietzschel ER, De Buyzere ML, De Bacquier D, De Backer G, Gillebert TC, Verdonck PR, Segers P. Noninvasive assessment of left ventricular and myocardial contractility in middle-aged men and women: disparate evolution above the age of 50? Am J Physiol Heart Circ Physiol 292: H856–H865, 2007. First published October 20, 2006; doi:10.1152/ajpheart.00759.2006.—End-systolic elastance (Ees) is a frequently used index of left ventricular (LV) contractility. However, because of its inherent dependence on LV geometry, Ees cannot be used to compare myocardial contractile state between ventricles with different geometries, which is the case in any cross-sectional study. Various normalization methods for Ees have been proposed in the literature, but a standardized method is still lacking. In this study, we introduced a novel alternative normalization technique and compared it with three previously suggested methods. We tested all normalization methods to assess the age- and sex-related differences in myocardial contractility in a large population sample of 2,184 middle-aged (ages, 35–55 yr) untreated subjects free from overt cardiovascular disease. Ventricular contractility Ees was determined using a previously validated noninvasive single-beat method, based on two-dimensional echocardiographic and brachial blood pressure measurements. Myocardial contractility was estimated as 1) Ees/ed-dia-stolic volume (EDV); 2) Ees/LV mass (LVM); 3) 0.433·Ees·LVM/relative wall thickness (RWT), based on a theoretical LV model; and 4) 0.0941·Ees·LVM0.455·RWT−0.159, a novel semimipirical expression derived in this study. Because of the difference in their underlying assumptions, the various myocardial contractility indexes do not provide consistent information with respect to sex differences. Despite these discrepancies, it was found that myocardial contractility in women appears to be better preserved after the age of 50 yr compared with that in men. The physiological mechanisms behind this potentially clinically important phenomenon at population level require further investigation.

THE END-SYSTOLIC pressure-volume relationship (ESPVR) uniquely represents the end-systolic state of the ventricle irrespective of the mode of contraction. End-systolic elastance (Ees), calculated from the slope of the ESPVR, is considered a relatively preload- and afterload-independent index of left ventricular (LV) contractility, which is often used in basic research wherein it is considered a “gold standard” (27, 29). Its clinical application, however, is somewhat limited due to its invasive nature and the need for considerable changes in loading conditions.

Whereas the concept of Ees is generally applied to assess changes in ventricular contractile state (e.g., due to inotropic stimulations) within a single individual, interpretation of differences in Ees in ventricles with different geometries appears cumbersome (6, 8, 9), since Ees is intrinsically influenced by LV dimensions (1, 8). Indeed, because LV volume can differ widely for various subjects while LV pressure remains constant, it is obvious that the pressure-volume ratio Ees is a function of LV volume. Normalizing or scaling ventricular contractility Ees is thus required to cancel out the effect of geometry and to obtain a useful index of myocardial contractile state, which ideally should reflect the mechanical characteristics of the myocardial fibers. Moreover, the use of such a scaled index would allow assessment of age- and sex-related differences in myocardial contractility. A number of normalization methods have already been proposed in the literature (4, 28), but a generally accepted standard has not been agreed on nor have the existing methods been compared with each other.

The primary aims of this study, conducted in a large population setting (the Asklepios study) of middle-aged untreated subjects free from overt cardiovascular disease, were to 1) calculate ventricular contractility Ees in a noninvasive way, 2) propose a novel population-specific normalization method for Ees, and 3) assess the effects of age and sex on myocardial contractility as determined with the various normalization methods.

METHODS

Subject Population

The population participating in the Asklepios Study consists of 2,524 subjects free from overt cardiovascular disease and between 35 and 55 yr old at the initiation of the study. All echocardiographic and blood pressure measurements were single device and single observer and performed between October 2002 and September 2004 at a single study site in Erpe-Mere/Nieuwerkerken (Belgium). The Ethical Committee of the Ghent University Hospital approved the study protocol. Written informed consent was given by all subjects. To exclude the effect of antihypertensive drugs, we selected 2,184 (1,115 women and 1,069 men) out of the original 2,524 subjects for this analysis. We excluded 340 subjects because 1) 264 patients were drug treated for hypertension and thus excluded from the study, and 2) data about stroke volumes (SVs), timings of onset and cessation of aortic flow, and/or ejection fraction (EF) data were incomplete in 76 additional subjects because of various technical reasons.

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Blood Pressure Measurement

Brachial systolic (P_s) and diastolic blood (P_d) pressures were recorded using bilateral triplicate measurements on a rested subject using a validated oscillometric Omron HEM-907 device (Omron, Matsuwa, Japan). Subjects were blinded to the blood pressure results during measurements. Cuff size was individually chosen based on arm circumference. Blood pressure values of these six readings were averaged, and the mean value was used throughout the whole study, except when there was a persistent discrepancy of more than 20 mmHg between left- and right-sided blood pressures after a second bilateral triplicate measurement. In that case, the mean value from the limb with the highest pressure was taken to represent blood pressure.

Echocardiography

Echocardiographic measurements were performed using a commercially available ultrasound system (Vivid 7, GE Vingmed Ultrasound, Horten, Norway) equipped with a cardiac transducer (M3S 1.7/3.4-MHz matrix transducer). Subjects were examined in the left lateral recumbent position using standard parasternal short- and long-axis and apical views. All measurements were ECG gated and consisted of cineloops of recordings of at least five (up to 30) cardiac cycles during normal breathing. Images and loops were exported in RAW Dicom format to magneto-optical disks and an image server. Measurements were performed off-line in a blinded fashion on a dedicated Compaq Evo W4000 workstation running GE Vingmed Echopac Version 2.0.1 software (GE Vingmed Ultrasound).

Data Analysis

LV geometric parameters. LV geometry is commonly characterized by its resting end-diastolic volume (EDV), LV wall mass (LVM), and relative wall thickness (RWT) (Fig. 1). LV volumes at end diastole were calculated from the two-dimensional parasternal long-axis images using the standard volumetric methods (Teicholz’ formula) (32):

\[
EDV = (7 \cdot LVID^3)/(2.4 + LVID)
\]

where LVID represents the internal LV diameter. End-diastolic LV dimensions were also used to calculate LVM by a validated formula, shown to yield LVM values closely related to necropsy measurements (12):

\[
LVM = 0.8 \cdot (1.04 \cdot ((SWT + LVID + PWT)^3 - LVID^3)) + 0.6
\]

where SWT and PWT equal the septal and posterior wall thickness at end diastole, respectively, RWT was calculated as 2-PWT/LVID.

In each subject, ventricular contractility was estimated as the slope of the ESPVR using the noninvasive single-beat technique, described by Chen et al. (11) and also applied in a recent population-based study by Redfield et al. (25). This algorithm assumes a linear ESPVR and a constant volume intercept (V0) of the ESPVR and was validated against invasive measurements of \( E_{es} \). Briefly, the single-beat elastance is calculated as follows:

\[
E_{es} = (P_d - 0.9 \cdot E_{Ns\text{est}} \cdot P_s)/(SV \cdot E_{Ns\text{est}})
\]

The SV is obtained from the LV outflow tract diameter and the pulsed-wave Doppler signal as previously described (23). \( E_{Ns\text{est}} \) represents the individual noninvasive estimated LV elastance during midisovolumic contraction:

\[
E_{Ns\text{est}} = 0.0275 - 0.165 \cdot EF + 0.3656 \cdot (P_d/P_s) + 0.515 \cdot (E_{Nd\text{avg}})
\]

EF was acquired with the Teicholz’ method. The end-systolic LV pressure (P_es) was estimated as 0.9 P_d. Previous studies have reported high correlations between this estimation and invasively measured P_es in patients of widely varied ages and vascular properties (17). \( E_{Nd\text{avg}} \) is an averaged normalized LV elastance during midisovolumic contraction, approximated by a seven-term polynomial function:

\[
E_{Nd\text{avg}} = \sum_{i=0}^{7} a_i \cdot t_i^3
\]

with the normalized time (\( t_{avg} \)), obtained as preinjection period (\( t_a \)), total systolic period (\( t_s \)). Both \( t_a \) and \( t_s \) were assessed from the continuous-wave Doppler flow measurements as the time delay between the QRS peak and the onset and cessation of aortic flow, respectively. The values of the regression coefficients \( a_i \) have been discussed previously (11).

Normalization of \( E_{es} \) for LV geometry. Linear regression was used to estimate the sensitivity of \( E_{es} \) for geometric parameters EDV and LVM. Since \( E_{es} \) is intrinsically dependent on LV geometry (6, 8, 9, 27, 28), it cannot be applied to estimate and compare myocardial contractility between subjects with different LV geometries. Hence, an appropriate normalization method that converts \( E_{es} \) into an index of myocardial contractility is highly desired to estimate sex- and age-related differences in myocardial contractile state. A number of normalization methods can be found in the literature (4, 28), but a single-accepted standard has not been agreed on (6).

Existing methods to normalize \( E_{es} \), and applied in this work, include 1) normalizing for EDV: \( E_{es}/EDV \), 2) normalizing for LVM: \( E_{es}/LVM \), and 3) elastance index (EI): 0.433 \( E_{es}/LVM/RWT \). EI is an index of myocardial contractility, introduced by Beyar and Sideman (4) and based on a mathematical, but physiologically realistic, thick-walled ellipsoid model of the LV; it incorporates both the passive and active properties of the myocardial fibers, accounts for the anatomical fiber angle distribution throughout the wall, and assumes a radial propagation of the electrical activation front from the endocardium toward the epicardium (3).

In addition to these methods, we developed an alternative, semimetric approach to normalize \( E_{es} \). From our population of healthy middle-aged subjects, we have first selected a subpopulation of “physiological reference” subjects, based on a list of 12 criteria (see Table 1). We subsequently assumed that, in this subpopulation, the spectrum of \( E_{es} \) values is largely explained by the differences in LV geometries rather than by the differences in myocardial contractility. Minimization of variance in \( E_{es} \) using a linear regression model would allow us to propose a formula to determine a geometry-normalized measure of contractility. We specifically opted for obtaining a formula that is similar to Beyar and Sideman’s EI. In Appendix A, it is described how we derived our geometry-adjusted \( E_{es} \) (\( E_{es, adj} \)), which is of the general form:

\[
E_{es, adj} = a \cdot E_{es} \cdot LVM^b \cdot RWT^c
\]

where \( a, b, \) and \( c \) represent the coefficients of a log-converted linear regression model.
Table 1. Criteria for determining the “physiological reference” subpopulation

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP, mmHg</td>
<td>100 &lt; SBP ≤ 140</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>60 &lt; DBP ≤ 90</td>
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<tr>
<td>HR, beats/min</td>
<td>50 ≤ HR ≤ 90</td>
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<tr>
<td>Ejection fraction, %</td>
<td>≥ 60</td>
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<tr>
<td>Systolic tissue Doppler index, mm/s</td>
<td>≥ 70</td>
</tr>
<tr>
<td>Filling pressure index (E/E')</td>
<td>≤ 8</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>&lt; 30</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>&lt; 88</td>
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<tr>
<td>Men</td>
<td>&lt;102</td>
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<tr>
<td>Diabetes Type 2</td>
<td>none</td>
</tr>
<tr>
<td>Atherosclerosis (carotid and/or femoral)</td>
<td>none echographically detected</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>≥ 30</td>
</tr>
<tr>
<td>High-sensitive CRP, mg/l</td>
<td>&lt; 3</td>
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</table>

Carotid and femoral arteries were carefully scanned bilaterally for the presence of plaque (focal protrusion > 50% compared with adjacent sites; absolute thickness > 1.5 mm). Intima-media thickness (IMT) was defined as the distance from the leading edge of the lumen-intima interface to the leading edge of the media- adventitia interface, measured in lateral plane B-mode projection, in end diastole, at the far wall, 1–2 cm before the bifurcations. Atherosclerosis was defined as a carotid or femoral IMT > 0.9 mm and/or the presence of carotid or femoral plaque. SBP and DBP, systolic and diastolic blood pressures, respectively; HR, heart rate; E/E', filling pressure index; BMI, body mass index; CRP, C-reactive protein.

Statistics

Statistics have been performed with commercially available software (SPSS 12.0, SPSS, Chicago, IL). All parameters were screened for deviation from normality. Measures of central tendency are means (SD) (normal distribution) or median and interquartile range. Pearson correlation coefficients were used to quantify the agreement between two variables. The geometry dependence (in terms LVM and EDV) of the various contractility indexes was analyzed by using univariate and multiple linear regression models. Two-way ANOVA was used to detect differences in contractility due to sex and age. When using analysis of covariance, homogeneity of the regression slopes (response variable vs. the potential covariates) was verified by testing for significance of the interaction term between the covariate and the grouping variable. All P values are specified in RESULTS, unless P < 0.001.

RESULTS

Baseline Demographics and Hemodynamics

Table 2 displays baseline demographic and hemodynamic data and geometric parameters for the study population and the selected “reference” subpopulation. In the study population, women had higher resting heart rates and lower brachial blood pressure values. As expected, women had smaller hearts with significantly smaller EDV and lower LVM. No age difference was observed between men and women. EF, a commonly used index of systolic function, was significantly higher in women (see also Fig. 2A).

End-Systolic Elastance (Ees)

Ees was significantly higher in women than in men at all ages (2-way ANOVA, P < 0.001, post hoc t-test, P < 0.001). On average, Ees in men is 2.40 (SD 0.64) versus 2.89 mmHg/ml (SD 0.80) in women (P < 0.001, Table 2). When analyzing the evolution of Ees with age, the curves in Fig. 2B suggest a more or less parallel time course of Ees in men and women until the age of 50 yr. After the age of 50 yr, however, Ees in women continues to rise (P = 0.058 vs. age 46–50 yr), whereas Ees remains constant in men (P = 0.82). Figure 2, C and D, also displays the age and sex dependence of EDV and LVM. EDV and LVM were significantly higher in men than in women at all ages (2-way ANOVA, P < 0.001, post hoc t-test, P < 0.001). LVM was significantly influenced by age in both men and women (ANOVA, both P < 0.001), whereas EDV appeared unaffected by age (ANOVA: women, P = 0.928; and men, P = 0.596).

Differences in LV geometry are likely to be one of the major contributors to the sex-related differences in Ees, with EDV [115.79 (SD 23.71) vs. 92.60 ml (SD 18.26), P < 0.001] and LVM [177.22 (SD 39.53) vs. 121.40 g (SD 29.07), P < 0.001] being higher in men. In men, Ees is significantly influenced by the geometric parameters LVM and EDV (Ees = 3.616 – 0.002LVM – 0.008EDV; P < 0.001; R² = 0.134) with EDV about 2.5 times as important as LVM. In women, on the other hand, Ees was only determined by the geometric parameter EDV (Ees = 4.238 – 0.015EDV; P < 0.001; R² = 0.111); LVM did not enter the model. Figure 3, A and B, shows the relation between Ees and both predictor variables separately. It can be seen that women tend to have smaller EDV and LVM as well as higher Ees compared with those in men.

Because of its geometry dependence, Ees thus requires normalization to study differences across subgroups (such as men and women) with varying geometry.

Normalization Based on the “Physiological Reference” Subpopulation

Two-hundred ninety-four subjects (175 women and 119 men) from the study population (13.5%) fulfilled the criteria to be designated as “physiological reference” subjects. Their baseline characteristics are presented in Table 2. The prevalence of women is somewhat higher in the subpopulation than in the complete population. Based on the principles that are outlined in APPENDIX A, the following formula was obtained, which converts Ees into a geometry-adjusted index of myocardial contractility (Ees,adj):

$$E_{es,adj} = 0.0941 \cdot E_{es} \cdot LVM^{0.455} \cdot RWT^{-0.159}$$

As anticipated, this expression is similar to the EI (EI = 0.433·Ees·LVM·RWT⁻¹) in terms of its functional form.

Comparison of Normalization Techniques

To verify whether our normalization method worked well, linear regression was performed between Ees,adj and the geometry-related predictor variables EDV and LVM in the subpopulation. As anticipated, no statistically significant regression model could be found (Table 3). Note, however, that this was not the case for the three other normalization methods, where significant regression functions were found in the subpopulation. Whether this implies that we overcompensate the effect of geometry using our normalization approach or that it is a manifestation of the inability of the existing methods to compensate for geometry is an open question, since none of the indexes has been validated. Note also that Ees·EDV was even dependent on both EDV and LVM. Nevertheless, the coefficient of variation (CV), an indication of the relative amount of
Hemodynamics

LVM/BSA); RWT, relative wall thickness; PWT, posterior wall thickness; EDV, end-diastolic volume; Ps, brachial SBP; Pd, brachial

Left ventricular geometry

LVM, g 121.40 (SD 29.07) 177.22 (SD 39.53)† 115.46 (SD 8.39) 125.29 (SD 7.36) †
LVMI, g/m² 70.91 (SD 14.35) 89.73 (SD 17.75)† 65.40 (SD 11.58) 82.13 (SD 16.45)†
RWT 0.36 (SD 0.06) 0.39 (SD 0.07)† 0.35 (SD 0.05) 0.37 (SD 0.05)*
PWT, mm 8.12 (SD 1.17) 9.55 (SD 1.30)† 7.70 (SD 0.99) 8.97 (SD 1.10)‡
EDV, ml 92.60 (SD 18.26) 115.79 (SD 23.71)† 88.28 (SD 16.03) 111.43 (SD 20.26)†

Baseline demographics

Age, yr 45.2 [40.6–50.3] 45.7 [40.9–50.4] 42.8 [39.0–47.8] 40.9 [38.2–44.8]‡
Height, cm 163.3 (SD 6.0) 175.8 (SD 65)† 164.5 (SD 5.7) 177.5 (SD 6.4)‡
Weight, kg 65.7 (SD 11.9) 81.2 (SD 12.2)† 60.7 (SD 7.0) 76.7 (SD 8.2)†
BMI, kg/m² 24.61 (SD 4.29) 26.21 (SD 3.59)† 1.66 (SD 0.15) 1.94 (SD 0.12)‡

Values are means (SD) or median [interquartile range] where appropriate; n, number of subjects; BSA, body surface area; LVMI, LV mass index (LVM/BSA); RWT, relative wall thickness; PWT, posterior wall thickness; EDV, end-diastolic volume; Ps, brachial SBP; Pd, brachial DBP; PP, pulse pressure; SV, stroke volume; CO, cardiac output; EF, ejection fraction; Ees, end-systolic elastance. *P < 0.05 and †P < 0.001 men vs. women using a nonparametric Mann-Whitney test.

scatter in the data, is minimal in case of Ees,adj, showing that Ees,adj performed best in reducing the amount of variance (Table 3) in the subpopulation.

Table 4 provides Pearson correlation coefficients between myocardial contractility according to the various normalization methods in the whole study population. Correlation coefficients vary between 0.782 (Ees–EDV vs. Ees–LVM) and 0.943 (EI vs. Ees–EDV). Despite the rather complex mathematical description of our approach, our novel Ees,adj appears to correlate well with the previously reported normalization methods.

**Age- and Sex-Related Differences in Myocardial Contractility**

Figure 4 depicts the age- and sex-related differences in myocardial contractility obtained from the various normalization methods. A common finding is that, similar to Ees, myocardial contractility continues to rise after the age of 50 yr in women, whereas myocardial contractility in men seems to top off at that age. However, there are serious inconsistencies with regard to the absolute values of the calculated indexes and, hence, the relative position of the female and male curves.

All indexes, except for Ees,adj, yield higher values in men than in women, thus reversing the higher values of ventricular contractility (Ees) in women. Nevertheless, for Ees–EDV, the differences were not significant. Both Ees–LVM and EI are higher in men than in women by 13.0% and 7.6%, respectively (2-way ANOVA, P < 0.001). In contrast to the other myocardial contractility indexes, Ees,adj eliminates the systematic sex difference and reveals the apparently different time course of myocardial contractility in men and women, being similar up to the age of 50 yr, where after it becomes significantly higher in women [3.03 (SD 0.85) vs. 2.82 mmHg/ml (SD 0.72), P < 0.005].

**DISCUSSION**

Studies in isolated dog ventricles, performed by Suga (29) and Sugawa et al. (30, 31) in the 1970s, have shown that the slope of the ESPVR, Ees, is a relatively load-independent index of ventricular contractility. Ees has since then known a widespread use for research purposes to detect changes in LV inotropic state in humans (14), dogs (16, 30), and rodents (13).

One has to realize that the concept of Ees was originally applied in acute experiments within a single individual, where it will show an increase as a result of a positive inotropic stimulation. In these circumstances, the increase in the slope of the ESPVR is easily interpreted as a change in ventricular contractility, since only the inotropic state has altered and LV geometry stays unaffected. However, appreciation of differences in Ees becomes much more complicated when evaluating and comparing contractility in cross-sectional studies in which the ventricles have a spectrum of different geometries. Since Ees is highly affected by LV geometry (1, 8), a difference in Ees between two given ventricles does not necessarily indicate a different myocardial contractile state. Scaling or normalization of geometry is thus required to provide information about myocardial contractile state.

Stress-strain relationships, derived from invasively acquired pressure-volume signals, have been used successfully in the past as a virtually load- and geometry-independent measure of contractility (21, 33). In our large population, invasive techniques are obviously not feasible. To the best of our knowledge, normalization of Ees for LV geometry is the only approach that permits one to estimate myocardial contractility noninvasively. Even though the geometry dependence of Ees was already acknowledged in the 1970s, a single accepted standard to convert Ees into a measure of myocardial contrac-
tility (i.e., an intrinsic muscle property) has not yet been defined (6), nor have the existing normalization methods been evaluated and compared in a large population sample of apparently healthy middle-aged subjects. Sagawa (28) mentioned that normalization with respect to LVM, or EDV measured under a standardized resting condition, may provide information regarding myocardial contractility. Normalizing by the volume intercept of the ESPVR (V₀) has also been suggested (22). However, the fact that V₀ may take on negative values renders it practically useless as a scaling factor. From a conceptual point of view, multiplication with EDV could indeed provide an acceptable index of myocardial contractility since \( E_{es}/H_{18528} \) would remain virtually constant. This method, however, can in theory only be applied accurately when \( E_{es} \) is inversely proportional with EDV. Under the assumptions that 1) EF is virtually constant in normal ventricles, 2) the volume intercept of the ESPVR (V₀) equals zero, and 3) \( P_{es} \) remains constant, \( E_{es} \) can be expressed as \( P_{es}/ESV = P_{es}/[EDV \cdot (1 - EF)] = k \cdot EDV^{-1} \) (where ESV is end-systolic volume), which indeed fulfills the criterion. Unfortunately, these assumptions are not entirely fulfilled, introducing scatter and uncertainty in this method of normalization. Other potential limitations of this normalization method include its undesired preload dependence (as it incorporates EDV) (4) and the fact that wall thickness is not directly accounted for.

Normalization by LVM can arguably be considered as a superior method, because LVM is an invariant property of ventricular muscle and is thus not subject to changes in loading conditions (although in clinical echocardiography, EDV and LVM may be related to each other due to the way LVM is measured). Beyar and Sideman (4) stated that this approach works well in ventricles with a normal RWT. However, in particular, when RWT deviates from normal (as in concentric hypertrophy or concentric remodeling), the reliability of this method becomes questionable.

Based on a mathematical model of LV mechanics, Beyar and Sideman (4) introduced the EI (\( EI = E_{es}/H_{18528} \cdot LVM/RWT \)), a measure of myocardial contractility that was shown to be superior to \( E_{es} \cdot EDV \) and \( E_{es} \cdot LVM \) in their numerical experiments, because it accounts for changes in both LVM and RWT. Within a wide range of different values of RWT and LVM, their EI values showed a coefficient of variation [mean (SD)] of no more than 3.5%, in contrast to 25% and 17% in the case of \( E_{es} \cdot EDV \) and \( E_{es} \cdot LVM \), respectively. We believe that by raising the main factors (LVM and RWT) in their index to a certain power, their EI could even be optimized. However, no such attempts were made in their study.

Our normalization method relies on a principle that is somewhat comparable with EI. In a subpopulation of 294 “physiological reference” subjects, selected on the basis of

![Fig. 2. A: ejection fraction (EF), a measure of systolic function, is higher in women than in men (ANOVA, \( P < 0.001 \)). B: end-systolic elastance (\( E_{es} \)) is smaller in men than in women (ANOVA, \( P < 0.001 \)). The curves suggest a more or less parallel time course of \( E_{es} \) until the age of 50 yr. After the age of 50 yr, \( E_{es} \) in women tends to increase, whereas \( E_{es} \) remains constant in men. C and D: end-diastolic volume (EDV) and LVM are lower in women than in men (ANOVA, \( P < 0.001 \)). In men and women, LVM is influenced by age (ANOVA, both \( P < 0.001 \)). Data are shown as means ± SE. *\( P < 0.05 \) men vs. women using a t-test.](http://ajpheart.physiology.org/)
very strict criteria, we have made a critical, but reasonable, assumption, namely, that myocardial contractility is similar (apart from some natural dispersion) in this population sample. In other words, we assumed that there is no relationship between myocardial contractility and a geometric parameter. In this sense, we wish to draw the parallel with experimental work, where control animals would also be sampled from a normal population that would also exhibit a range of myocardial contractility values. Using linear regression on log-converted variables, we were able to define $E_{es,adj}$ to quantify myocardial contractility. Belcher et al. (2) previously applied a similar method in dogs to remove the variance in $E_{es}$ due to the mass of the dog or the LV mass. An important benefit of our method is that it does not require any modeling assumptions regarding passive and active stress-strain relations, activation function, depolarization sequence, or fiber orientation in contrast to the EI. A practical limitation of our method, however, lies in its population-specific character, which may render $E_{es,adj}$ less suitable for making comparisons with other populations and/or species. One must realize that normalization methods based on a regression function can only guarantee reliable values for myocardial contractility when they are used within the range of the studied variables (RWT and LVM). As such, application of our method in species with much larger or smaller ventricular dimensions (such as mice or rats) should be clearly discouraged at the moment so as not to arrive at incorrect conclusions regarding myocardial contractility.

The difference between the multipliers (0.0941 vs. 0.45) of our and Beyar and Sideman’s contractility index, although dramatic, is irrelevant, since both $E_{es,adj}$ and EI represent (differently) scaled indexes. The exponents of RWT ($0.159$) and LVM (0.455) are much lower than in EI, suggesting that $E_{es,adj}$ is far less affected by LV geometry than is EI. This was confirmed by comparing the $R^2$ values obtained from linear regression between contractility indexes and geometry (EDV and LVM): $E_{es,adj} = 2.964 - 0.006\cdot EDV + 0.003\cdot LVM$, $R^2 = 0.022$, $P < 0.001$, whereas EI = 160.243 + 2.162\cdot EDV + 0.371\cdot LVM, $R^2 = 0.245$, $P < 0.001$. The exact reason for this discrepancy between the exponents could not be determined. However, it might be related to the fact that we assumed a

**Table 3.** Linear regression of myocardial contractility indexes versus geometry parameters in the subpopulation

<table>
<thead>
<tr>
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<th>$C_1$</th>
<th>$C_2$</th>
<th>$C_3$</th>
<th>$R^2$</th>
<th>$P$</th>
<th>CV</th>
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</thead>
<tbody>
<tr>
<td>$E_{es}$, mmHg/ml</td>
<td>3.985 (3.650; 4.320)</td>
<td>-0.006 (-0.011; -0.001)</td>
<td>-0.006 (-0.009; -0.003)</td>
<td>0.210</td>
<td>&lt;0.001</td>
<td>25.9</td>
</tr>
<tr>
<td>$E_{es,adj}$, mmHg/ml</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.210</td>
<td>&lt;0.001</td>
<td>25.9</td>
</tr>
<tr>
<td>$E_{es} \cdot$ EDV, mmHg</td>
<td>124.4 (94.0; 154.8)</td>
<td>2.090 (1.605; 2.575)</td>
<td>-0.578 (-0.859; -0.296)</td>
<td>0.234</td>
<td>&lt;0.001</td>
<td>25.1</td>
</tr>
<tr>
<td>$E_{es} \cdot$ LVM, mmHg $\cdot$ g $\cdot$ ml$^{-1}$</td>
<td>142.7 (111.1; 174.3)</td>
<td>-</td>
<td>1.471 (1.236; 1.706)</td>
<td>0.342</td>
<td>&lt;0.001</td>
<td>27.5</td>
</tr>
<tr>
<td>EI, mmHg $\cdot$ g $\cdot$ ml$^{-1}$</td>
<td>127.2 (76.9; 177.6)</td>
<td>2.839 (2.335; 3.344)</td>
<td>-</td>
<td>0.296</td>
<td>&lt;0.001</td>
<td>27.3</td>
</tr>
</tbody>
</table>

Regression coefficients of the regression function: myocardial contractility index $= C_1 + C_2 \cdot$ EDV + $C_3 \cdot$ LVM. Ninety-five percent confidence intervals of the coefficients are shown in parentheses. As expected, geometry-adjusted contractility ($E_{es,adj}$) is a myocardial contractility index that is totally independent of geometry in the subpopulation of “physiological reference” subjects. The coefficient of variation (CV) is minimal for $E_{es,adj}$. EI, elastance index.
constant myocardial contractility, while in reality, even in the subpopulation, a significant relationship between myocardial contractility and geometry can probably not be excluded.

The CV corresponding with our method (22.3%, Table 3) was lower than the CV obtained from any other method. This result is in agreement with the method of Belcher et al. (2), who concluded that adjustment by regression reduces CV more effectively than mere indexing (i.e., multiplication or division by a variable). Note, however, that this finding is only by definition and by no means proves that our method is superior to other ones.

From the discussion above, it should be clear that all normalization methods have their strengths and limitations. Moreover, because these methods all rely on different assumptions, the discrepancies of sex difference are not really surprising. Ultimately, validation of the approaches is mandatory to know which one is the most reliable.

One of the major questions that has been the issue of many investigations is whether basal myocardial contractile state is different for men and women. Do men simply happen to be larger mammals than women, with a bigger ventricle, but with an identical myocardial state?

EF, a geometry-independent but load-dependent index of systolic function, was higher in women than in men in our population [66.88% (SD 7.66) vs. 64.50% (SD 8.26), P < 0.001], confirming the findings in other studies (10, 15, 25). Even though EF is load dependent and therefore not a proper index of contractility, the reported differences in EF between men and women may actually suggest a true sex-specific difference (15).

The higher $E_s$ in women compared with that in men, as was shown in our study, was already observed in an invasive study performed in patients (age, 48–75 yr) undergoing routine cardiac catheterization (15) and in a cross-sectional population study (age ≥ 45 yr) on ventriculo-vascular interaction (25). However, this difference in $E_s$ only offers a limited amount of information from a physiological point of view and does not provide specific mechanical information about the myocardium. Here, a higher $E_s$ in women simply signifies an increased sensitivity of systolic pressure to changes in volume. Using linear regression analysis, Redfield et al. (25) showed that the relation between $E_s$ and age is steeper in women than in men. Although linear regression analysis of our data (women: $E_s = 2.075 + 0.018 \cdot \text{age}$, $P < 0.001$; and men: $E_s = 2.008 + 0.008 \cdot \text{age}$, $P < 0.012$) confirms their findings, only after grouping the continuous variable age into half decades, an

<table>
<thead>
<tr>
<th>$E_s$ · EDV, mmHg</th>
<th>$E_s$ · EDV</th>
<th>$E_s$ · LVM, mmHg·g·ml⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.858</td>
<td></td>
<td>0.834</td>
</tr>
<tr>
<td>0.834</td>
<td>0.782</td>
<td>0.802</td>
</tr>
<tr>
<td>0.782</td>
<td>0.943</td>
<td>0.854</td>
</tr>
</tbody>
</table>

Table 4. Pearson correlation coefficients between geometry-adjusted contractility indexes in the whole study population

Fig. 4. Myocardial contractility indexes geometry-adjusted $E_s$ ($E_{s,adj}$; A), $E_s$-EDV (B), $E_s$-LVM (C), and elastance index (EI; D) as a function of age (in half decades) are shown. There is a noticeable vertical shift in the curves of men and women between the different contractility indexes. $E_{s,adj}$ reveals the apparently different time course of myocardial contractility in men and women, being similar up to the age of 50 yr, where after it becomes significantly higher in women. Data are shown as means ± SE. *P < 0.05 men vs. women using a t-test.
apparently different time course between men and women (which is also reflected in the analysis of myocardial contractility) from the age of 50 yr could be revealed. Note, however, that age in the study of Redfield et al. (25) ranged from 45 to about 95 yr, whereas the examined range in our study is much narrower and limited to the age of 55 yr.

We are convinced that differences between men and women could more objectively be assessed on the basis of direct measurement of myocardial contractility instead of indirect estimation. This is, however, a difficult, and probably virtually impossible task. As such, literature about quantification of myocardial contractility is limited and mostly restricted to papillary muscle studies in rodents. Even then, there are a number of inconsistencies between these studies, partially due to differences in age, animal strains, and measurement methods (20). Over a wide range of muscle lengths and bath concentrations of calcium, Capasso et al. (7) did not detect a significant difference in peak tension between male and female rats. In isotonic measurements, peak shortening was higher in female rats, but maximum velocity of shortening was similar in male and female animals. In another study by Leblanc et al. (19), it was found that papillary muscles of female rats aged 6 mo and older exhibited smaller isometric and isotonic contractions, smaller maximal rates of tension and shortening development and decline velocities during both the onset and relaxation phases, and shorter contractions than in age-matched males.

In our study, analysis of EI and $E_{es}$-LVM suggested that myocardial basal state is mildly higher in men than in women, whereas no statistical difference was seen in terms of $E_{es}$-EDV. The latter observation was confirmed in the study of Redfield et al. (25). Hayward et al. (15), on the other hand, found that $E_{es}$-EDV was higher in men (265.8 ± 12.5 mmHg, mean ± SE) than in women (221.5 ± 9.3 mmHg, mean ± SE). Our novel index, $E_{es, adj}$, suggests that myocardial contractility remains nearly identical in men and women until the age of 50 yr. After the age of 50 yr, a relative decline in myocardial contractility is observed in men. To approach the problem in a slightly different way, we also calculated $E_{es}$ values that were statistically adjusted for the subject’s length and weight using covariance analysis. These data are shown in Fig. 5. Note the remarkable resemblance with $E_{es, adj}$. This approach thus appears to confirm that there are no differences between men and women in contractility when adjusting the measurements for geometric and/or morphological differences between the sexes. It is to be mentioned that, in contrast to $E_{es, adj}$, there was no significant difference between the curves in Fig. 5 at the age of 51–55 yr ($P = 0.264$). All normalized contractility indexes show a time course that is very similar to the nonnormalized, but shifted vertically. This is explained by the fact that the geometric parameters EDV, LVM, and RWT, i.e., the variables that are used to convert $E_{es}$ into a measure of myocardial contractility, are not, or very poorly, related with age ($R^2$ values ranging between 0.021 and 0.045).

A remarkable phenomenon that definitely deserves further investigation is that, regardless of the index that was used, contractility increases consistently in women with age, whereas, in men, it seems to reach a plateau value at the age of 51–55 yr. The sex-specific time course after the age of 50 yr has not been described before and was not related to a possible selection bias due to age differences between men and women (age, 51–55 yr; $P = 0.672$). Therefore, other factors must have come into play. In recent publications, attention was focused on the protective effect of sex hormones (mainly oestrogen) on the heart and vascular system in premenopausal women. However, the impact of menopause and loss of oestrogen remains controversial, and the higher cardiovascular risk in postmenopausal women compared with premenopausal women has not been fully elucidated (5).

However, women do have a specific preponderance for diastolic heart failure, characterised by heart failure symptoms in the presence of a preserved EF, while men more often present with systolic heart failure (decreased EF) (24, 26). In this regard, the relative decrease in $E_{es}$ in men from age 50 yr and onward and the better preservation in women do have a clinical mirror image, although the underlying mechanics are probably more complex and need to be investigated.

### Methodological Considerations

A considerable amount of geometric assumptions and simplifications was required to calculate LV mass, volumes, and pressures and to estimate $E_{es}$ because of the noninvasive nature of our measurement methods. These assumptions are expected to reduce the accuracy of our calculations. However, each of the assumptions were based on correlations that were previously published in validation studies, and it is therefore unlikely that a bias in our results would alter our conclusions. Moreover, it should be realized that the large sample size in this study significantly strengthens our conclusions and that this study simply could not have been completed by using invasive methods.

All of the suggested normalization procedures intrinsically assume that a difference in geometry between two ventricles is accompanied by a proportional difference in volume of contractile units. As a result, potential changes in the volume or mechanical properties of the extracellular matrix, which may vary with age and between sexes, were not accounted for. In this sense, one might wonder whether geometry-normalized indexes of contractility could ever assess fiber contractility as such.

We also wish to point out that the $E_{es}$ values were obtained by using a so-called single-beat method, which is noninva-
sively applicable and does not require changing loading conditions. Although the method has been validated (11) and has recently been applied in a population study on ventriculovascular interaction (25), it remains an estimate of $E_{es}$ with potential limitations, as pointed out by Kjørstad et al. (18) in a validation study.

In our novel method, we assumed that the formula for $E_{es,adj}$, which is derived from the data in the subpopulation, is also applicable in the whole population. Care should be taken since the range of geometric and demographic characteristics in the study population is broader than the subpopulation range. On the other hand, there is no proof that this formula would not be valid for the whole group either.

A last potential limitation is that the $E_{es}$ ultimately should be calculated with different heart stimulation frequencies (due to the force-frequency effect). However, to the best of our knowledge, no methods for accounting for heart rate have been suggested. We moreover speculate that the influence of the minor difference in heart rate between men and women is negligible.

In conclusion, the present study showed that $E_{es}$ as such cannot be used to compare myocardial contractile state between men and women of various ages in a cross-sectional study. Normalization is required to cancel out the effect of geometry. Because of the difference in their underlying assumptions, the various myocardial contractility indexes do not provide consistent information with respect to sex differences. However, regardless of the index that was used, it was found that myocardial contractility appears to be better preserved in women than in men after the age of 50 yr. This finding at the population level could have potentially important clinical implications that require further investigation.

**APPENDIX A**

**Normalization of $E_{es}$ Based on a “Physiological Reference” Subpopulation**

Based on the linear relationship between dependent variable $E_{es}$ and the independent variables LVM and RWT, a geometry-adjusted $E_{es}$ can be determined as $E_{es,adj} = \frac{E_{es}}{d_{es}}$, where $d_{es}$ is the deviation from regression, i.e., $E_{es} - \bar{E}_{es}$, where $\bar{E}_{es}$ is the predicted value. This adjustment removes the variation in $E_{es}$ that is accounted for by the variation in geometry, so that the adjusted values are those to be expected if all $E_{es}$ values were taken at the mean geometry (2). The adjusted $E_{es,adj}$ can then be determined as $E_{es,adj} = \frac{E_{es}}{d_{es}} - (a + b \cdot LVM + c \cdot RWT)$, where $a$, $b$, and $c$ are determined from linear regression.

To obtain a formula that has the same functional form as Beyar and Sideman’s EI, the very same principle is applied to the logarithms of variables $E_{es}$, LVM, and RWT. Log-converted variables are defined as follows:

$$E'_{es} = \log(E_{es})$$
$$RWT' = \log(RWT)$$
$$LVM' = \log(LVM)$$
$$E_{es,adj} = \log(E_{es,adj})$$

Linear regression yields coefficients $a$, $b$, and $c$ as follows:

$$E'_{es} = a + b \cdot LVM' + c \cdot RWT'$$

The adjusted $E'_{es,adj}$ is then found as follows:

$$E_{es,adj} = \text{mean}(E'_{es}) - a + \log(E_{es}) - b \cdot \log(LVM) - c \cdot \log(RWT)$$

$$= \log[10^{\text{mean}(E'_{es})} \cdot E_{es} \cdot LVM^{-b} \cdot RWT^{-c}]$$

$E_{es,adj}$ is thus defined as follows:

$$E_{es,adj} = \text{mean}(E'_{es}) \cdot E_{es} \cdot LVM^{-b} \cdot RWT^{-c}$$

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**REFERENCES**


