Int J Cardiovasc Imaging (2014) 30:1191–1199
DOI 10.1007/s10554-014-0431-y

ORIGINAL PAPER

Gender- and age-related differences in rest and post-stress left ventricular cardiac function determined by gated SPECT

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Received: 12 December 2013 / Accepted: 18 April 2014 / Published online: 26 April 2014

Abstract Gender- and age-related changes of left ventricular (LV) function and dimensions have not been elucidated in a large population by gated SPECT. Thus, the aim of this study was to derive male and female reference limits for left ventricular functional parameters, and determine the effect of age on LV dimensions and systolic function for this imaging modality. 1,639 (53 % males) subjects without cardiovascular disease who underwent cardiac SPECT between January 2002 and June 2012 were included in this study. Mean age at presentation was 61 ± 12 years (range 18–92 years). A significant effect of age ($p = 0.011$) and gender ($p < 0.0001$) on resting LV ejection fraction (LVEF) was observed, with an increase in LVEF with age being more pronounced in women (ΔB-coefficient: −0.088, $p = 0.011$). Overall, mean LVEF was higher in women compared to men (70.3 ± 8.6 % vs. 64.4 ± 7.5 %, $p < 0.0001$). LVEF after pharmacological stress with adenosine was significantly lower than at rest in both women and men (ΔLVEF = 1.1 % in males and ΔLVEF = 1.6 % in females, $p = 0.01$), which was the result of a significant increase in end-systolic volume after stress ($p = 0.0001$). With advancing age an increase in LVEF was observed that was more pronounced in women than in men. These findings indicate that the evaluation of cardiac function and volumes of patients by gated SPECT should consider age- and gender-matched normative values.

Keywords Gated SPECT · Left ventricular ejection fraction · Gender · Age

Introduction

Recently published studies have indicated that there are gender-related differences in cardiac function, and, starting from the observation that women are more likely to present with heart failure with preserved ejection fraction but reduced diastolic compliance, the issue of gender-related variability of cardiac pathologies came into light. Despite a growing awareness of gender-related differences in diagnostic approaches, gender-specific reference values for left ventricular (LV) dimensions and systolic function are lacking and so far, the effect of aging on LV systolic function assessed by ECG-gated SPECT has only been studied in relatively small populations and yielded conflicting results [1–3]. Further, the extent to which age and gender influence measures of LV function and dimensions as estimated by gated SPECT has not been reported in combination.

Since left ventricular ejection fraction (LVEF), as well as end-systolic (ESV) and end-diastolic (EDV) volumes have been considered to be important factors for the diagnosis and management of cardiac events, establishing appropriate reference limits is vital for the assessment of clinical significance of LV functional parameters. Thus, the aim of this study was to develop age- and gender-specific reference values of LV dimensions and systolic function

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Table 1 Characteristics of study population

Parameters	Females	Males	*p*
n (%)	770 (47)	869 (53)	
Age (years, mean ± SD)	62 ± 11	61 ± 12	NS
BMI			
All (kg/m^2, mean ± SD)	25.1 ± 5.0	26.2 ± 4.1	NS
>30 kg/m^2, n (%)	114 (14.8)	134 (15.4)	NS
BSA (m^2, mean ± SD)	1.73 ± 0.18	1.98 ± 0.2	<0.05
Current or former smoker, n (%)	70 (9.1)	102 (11.7)	<0.05
FHx of premature CAD, n (%)	87 (11.3)	58 (6.7)	NS
Dyslipidemia, n(%)	82 (10.6)	82 (9.4)	NS
Dyspnea, n (%)	91 (11.8)	59 (6.7)	<0.01
Chest pain, n (%)	205 (26.6)	164 (18.8)	<0.01
Systolic BP at rest (mmHg, mean ± SD)	133.9 ± 11.2	128.3 ± 14.5	NS
HR at rest (bpm, mean ± SD)	81.4 ± 14.3	74.3 ± 16.2	NS
Agatston calcium score, mean ± SD	133.9 ± 376.3	362.5 ± 624.4	NS
Small heart (ESV < 20 ml), n (%)	346 (48.8)	113 (13)	<0.001

$p < 0.05$ compared to females

BMI body mass index, *BSA* body surface area, *FHx* family history, *BP* blood pressure, *HR* heart rate, *ESV* end-systolic volume

for SPECT myocardial perfusion images for the second through the eighth decade of life. Further, we aimed to determine the relationship between rest LVEF and stress LVEF dependent on age and gender and to identify possible predictors of variability.

Methods

Patients and study protocol

We retrospectively identified 1,639 individuals (53 % males, mean age 61 ± 12 years, range 18–92 years) who fulfilled the following criteria: absence of known structural heart disease, no history of hypertension or ventricular hypertrophy, no diabetes, no high pre-test probability of coronary artery disease (CAD), no ECG abnormalities at rest or during exercise-tolerance testing, no clinical evidence or history of CAD, no cardiac pacemaker, normal stress and rest perfusion images, absence of atrial fibrillation, and no ECG with signs or suspicion of myocardial infarction (MI), left bundle brunch block (LBBB), or pre-excitation. High (>85 %) pre-test probability of CAD was defined by gender, age (men >40 years, women >50 years), and symptom status [4].

Patients underwent clinically indicated cardiac SPECT between January 2002 and June 2012. Patients with incomplete data and studies with technical problems were excluded. The majority of the subjects had at least one of the risk factors for CAD (Table 1). Risk factors in patients were hyperlipidaemia, family history of premature CAD, smoking, and obesity (Table 1). Patients were neither included nor excluded on the basis of visual or quantitative analysis of global LV function from the gated SPECT images. Patients were retrospectively included in the study if they had signed informed consent authorizing their records to be included in our cardiac imaging research registry. The indications for referral were previous positive treadmill test, atypical or typical chest pain, shortness of breath with or without atypical angina, and syncope (Table 1). Clinical data were obtained retrospectively from case notes and patient interviews. Men and women were divided into six age groups: men and women aged ≤40 years, >40 and ≤50 years, >50 and ≤60 years, >60 and ≤70 years, >70 and ≤80 years, and >80 years. The youngest patient included was 18 years old.

Image acquisition

Patients were advised to refrain from theophylline or caffeine containing beverages for at least 12 h before the study. All patients underwent a 1-day pharmacological stress/rest SPECT Myocardial Perfusion Imaging (MPI) protocol according to the guidelines of the European Association of Nuclear Medicine [5] with adenosine (0.14 mg/kg per min over 6 min) followed by injection of 300 MBq (in patients with BMI >28 kg/m^2 400 MBq) and 900 MBq (in patients with BMI >28 kg/m^2 1,200 MBq) of 99mTc-tetrofosmin. After 60 min, the gated acquisition of the stress study was performed. 1 h after the first injection, 900 MBq (1,200 MBq, respectively) of 99mTc-tetrofosmin were injected, and the gated image acquisition of the rest examination started 60 min later. Data acquisition was performed with a dual-head detector hybrid SPECT/CT camera (Millenium VG and Hawkeye; GE Healthcare) or an ultrafast CZT camera (Discovery 530 NMc, GE Healthcare). Acquisitions were gated for 16 frames per R–R cycle with an acceptance

window of 50 %. Mean heart rate (HR) during acquisition was recorded for each scan.

MPI reconstruction and quantitative analysis

Images were viewed on a dedicated workstation (Xeleris; GE Healthcare). LV volumes were calculated from the gated SPECT images using the commercially available software package Myovation for Alcyone (GE Healthcare) and QGS/QPS (Cedars-Sinai Medical Center). Briefly, the algorithm segments the LV, estimates and displays the endo- and epicardial surfaces, and the valve plane for every gating interval, calculates LV-ESV and -EDV, and derives the related LVEF by dividing stroke volume (EDV–ESV) by EDV. In addition, polar maps of perfusion and wall motion were acquired. The results in respect of LVEF, EDV, ESV, and volumes normalised to body surface area (EDVI, ESVI), were calculated and summarised to obtain normal limits. The normal limits for LVEF were determined from the overall population by a 2-standard deviation (SD) threshold.

Statistical analysis

All analyses were performed with SPSS 19.0 for Windows (Chicago, IL, USA). If not otherwise indicated, data are expressed as mean ± standard deviation (SD). LVEF and LV volumes are indicated as model-estimated marginal means (ANOVA) and standard error (SE). Test for homogeneity of variance by Levene's test was performed based on groups classified according to gender and age. Differences in between stratified age groups for both genders were calculated using ANOVA post hoc tests. The Kolmogorow–Smirnow test was used to test for normal distribution. LV volumes and LVEF were normally distributed, and consequently, normal limits were defined as the mean values ±2 SDs for LVEF as representing the 95 % confidence limit of normality. We examined the influence of age (centered at mean value) and gender on resting LVEF, EDV, and ESV by using two-way analysis of covariance (ANCOVA). As a consequence of a significant interaction of age and gender, we further stratified our sample by both gender and age, categorizing age (10-year intervals). Two-way repeated measures ANCOVA was used to assess gender and age effects on post-stress LV parameters. Kruskal–Wallis test and paired-samples *t* test were used for non-parametric and parametric data, respectively, to test for differences between parameters acquired during the scans. Similarly, Spearman or Pearson analysis was applied to assess correlations. To determine whether our findings were independent of confounders, multivariable linear regression was performed (dependent variable LVEF, independent variables EDV, gender and age, covariates body mass index [BMI], mean arterial pressure, heart rate, Agatston calcium score). A value of $p < 0.05$ was considered statistically significant.

Table 2 Data output of multivariable regression analysis and test for interaction amongst independent variables (end-diastolic volume [EDV], gender and age)

	Mean	SE	*p* value	Beta coefficient	VIF
Covariable					
Calcium score	253.02	20.23	NS	−0.062	1.17
Syst BP (mmHg)	131.26	2.7	NS	−0.043	2.14
Heart rate	78.5	1.5	NS	−0.012	1.34
BMI	25.7	0.11	NS	−0.031	2.2
Independent variable					
Rest EDV	77.8	0.61	0.0001	−0.339	1.43
Age	61.4	0.9	0.01	0.91	1.21
Gender	–	–	<0.0001	−0.155	1.43
Interaction					
Age × gender			0.034		
Age × rest EDV			NS		
Gender × rest EDV			NS		

Calcium score, systolic blood pressure (BP), heart rate, and body mass index (BMI) were tested as covariates

SE standard error, *VIF* variance inflation factor

Results

Patient characteristics

A total of 1,639 subjects (869 (53 %) males) with normal SPECT studies were analyzed. Fewer women than men were referred for ECG-gated SPECT. The demographic characteristics of the study population are listed in Table 1. The mean age was 62 ± 11 years for women and 61 ± 12 years for men (p = NS), reflecting the high age of the population. There was no significant difference in demographic characteristics, except for greater tobacco use in men compared with women (9.1 % vs. 11.7 %; $p < 0.05$), women had a higher prevalence of family history of CAD (11.3 % vs. 6.7 %; $p < 0.05$) and were more often symptomatic (chest pain and dyspnoea: 11.8 and 26.6 % vs. 6.7 and 18.8 %, respectively, $p < 0.05$). As expected, more women than men had smaller hearts (defined as ESV <20 ml; 48.8 % in females vs. 13 % in males; $p < 0.001$). Younger patients had a lower BMI and a lower body surface area (BSA; data not shown). Subjects were classified into six age groups: Group 1 consisted of 62 subjects (23 women) aged 18–39 years, group 2 consisted of 200 subjects (93 women) aged 40–49 years, group 3 consisted of 451 subjects (207 women)

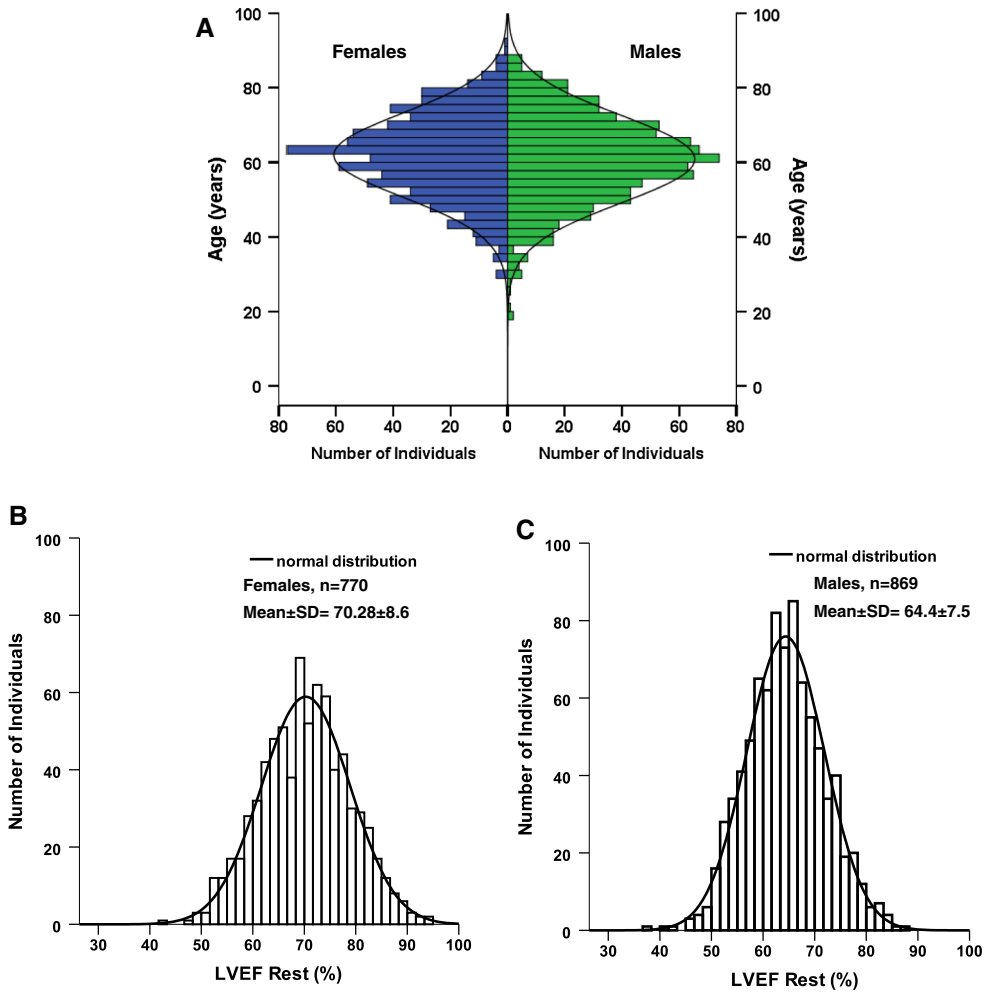

Fig. 1 **a** Histograms of age distribution. **b**, **c** Histogram showing distribution of LVEF for females (**b**) and males (**c**). *LVEF* left ventricular ejection fraction

aged 50–59 years, group 4 consisted of 533 subjects (255 women) aged 60–79 years, group 5 consisted of 304 subjects (154 women) aged 60–79 years and group 6 consisted of 84 subjects (33 women) aged 80–92 years (Table 2; Fig. 1a). Although the majority of patients were referred for the evaluation of chest pain or dyspnoea and many had cardiac risk factors, all had normal exercise capacity corrected for age, no electrocardiographic signs of ischemia, normal results on perfusion scans, and normal wall motion determined by means of quantitated gated SPECT (QGS). Age of the study population was normally distributed (p = NS, Fig. 1b, c).

Left ventricular ejection fraction at rest is increased in women and increases with age

The mean LVEF at rest for women (n = 770) was higher (70.3 ± 8.6 %) than for men (64.4 ± 7.5 %, n = 869; $p < 0.0001$). ANCOVA demonstrated a significant effect of age (centred at mean, $p = 0.011$) and gender ($p < 0.0001$) on resting LVEF, as well as a significant age–gender interaction ($p = 0.03$) indicating that the age influence on LVEF is depending on gender (Table 2). Multivariable linear regression analysis with LVEF being the dependent variable revealed that EDV, age and gender were the only influencing variables [covariates BMI, systolic arterial pressure, heart rate, Agatston calcium score] (Table 2). A significant positive correlation of age and LVEF at rest was observed for both males and females (females: r = 0.21, $p < 0.0001$; males: r = 0.11; $p < 0.001$). When LVEF was stratified by both gender and age, categorizing age in 10 year intervals, LVEF increased by 7 % from 65.4 ± 1.8 % for age 30–40 years to 72.4 ± 0.7 % for age 70–80 years in females and by 4.2 % from 62.3 ± 1.2 % for age 30–40 years to 66.5 ± 0.6 % for age 70–80 years in males ($p = 0.001$, ANOVA, Fig. 2a). Regression lines indicated that age is a stronger predictor of LVEF for females (B-coefficient 0.159) than for males (B-coefficient 0.071; Fig. 2c). Accordingly, a significant difference in slopes was found between regression lines of males and females (ΔB-coefficient: −0.088, $p = 0.011$, Fig. 2c). Both BMI or BSA did not correlate with LVEF in men and women (r = 0.005; $p = 0.9$, and r = 0.002; $p = 0.6$, respectively; data not shown).

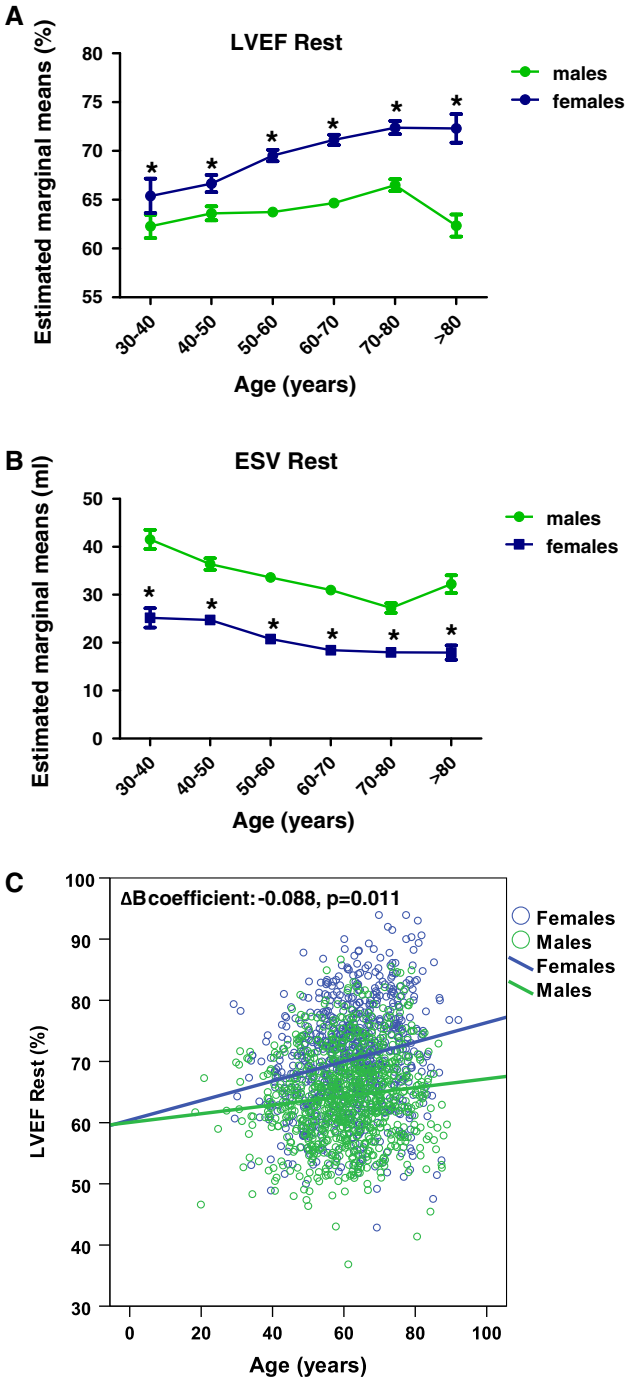

Fig. 2 **a** Comparison of left ventricular ejection fraction (LVEF). Data are presented as estimated marginal mean ± SE. *$p < 0.05$ (male vs. female). **b** Comparison of left ventricular end-systolic volume (ESV). Data are presented as estimated marginal mean ± SE. *$p < 0.05$ (male vs. female). **c** *Regression lines* and *scatter plots* of relationship between LVEF and age in males and females

Left ventricular volume dimensions decrease with age

Women had lower ESV and EDV as compared to men (Table 3; Fig. 2b). ANCOVA demonstrated a significant effect of gender on both resting EDV ($p < 0.0001$) and resting ESV ($p < 0.0001$). Age (centred at mean), however, only had a significant effect on ESV ($p = 0.04$) but not on EDV ($p = 0.2$), indicating that age-dependent changes in ESV might trigger the observed changes in LVEF with increasing age. Neither for ESV nor for EDV an age-gender interaction was observed ($p = 0.1$ and $p = 0.2$, respectively). When ESV at rest was stratified by both gender and age, categorizing age in 10 year intervals, ESV decreased with age in females from 25.3 ± 9.0 ml (<40 years) to 17.9 ± 9.6 ml (>80 years; $p < 0.0001$) and in males from 41.5 ± 12.2 ml (<40 years) to 32.2 ± 13.0 ml (>80 years; $p < 0.0001$) (Fig. 2b; Table 3). Normalizing left ventricular volumes to BSA (data indicated by EDVi and ESVi) did not change the differences seen in non-indexed left ventricular volumes (Table 3). Accordingly, ANCOVA demonstrated a significant effect of gender on both resting EDVI ($p < 0.0001$) and resting ESVI ($p < 0.0001$). Age (centred at mean), only had a significant effect on ESVI ($p = 0.03$) but not on EDVI ($p = 0.067$). When a small heart was defined as ESV <20 ml, the percentage of women and men having a small heart was 48.8 and 13 %, respectively ($p < 0.001$, Table 1). The percentage of female patients with a small heart was higher in the older age groups (17 % for <40-year group, 64 % for >80-year group; $p < 0.05$; Table 3). In multiple regression analysis, gender and age were the only significant variables for LVEF, ESV, and ESVI either post-stress or at rest when using the QGS method based on a forward stepwise regression model.

Comparison of rest and post-stress LVEF, EDV, and ESV

In a subgroup analysis in 914 patients undergoing pharmacological stress with adenosine, the latter caused a decrease in LVEF in both men and women (ΔLVEF = absolute increase in LVEF at post-stress: ΔLVEF = −1.1 % in males and ΔLVEF = −1.6 % in females, $p = 0.01$). A greater decrease in LVEF (ΔLVEF = LVEF stress − LVEF rest) in response to adenosine stress was observed in women >60 years compared to younger women, a phenomenon that was not observed in older men (Fig. 3a). Accordingly, regression analysis suggested that age is a stronger predictor of post-stress LVEF for females (0.064) than for males (−0.005). However, B-coefficients were not significantly different between males and females ($p = 0.28$; Fig. 3c). Multivariate analysis (considering baseline LVEF) revealed a significant age-gender interaction but no significant effect of either age or gender on post-stress LVEF (data not shown). A similar tendency was observed for post-stress ESV (Δstress ESV = ESV after stress − ESV at baseline) without reaching statistical significance (data not shown).

Table 3 Gender-related differences in different age groups in left ventricular ejection fraction (LVEF) and left ventricular volumes

Variable	Age					
	<40	40–50	50–60	60–70	70–80	>80
Males						
n	39	107	244	278	150	51
LVEF rest (%)*	62.3 (1.2)	63.6 (0.7)	63.7 (0.5)	64.7 (0.5)	66.5 (0.6)	62.4 (1.1)
EDV rest (ml)#	109.5 (3.8)	98.9 (2.3)	91.5 (1.5)	85.9 (1.4)	79.5 (1.9)	83.7 (3.5)
ESV rest (ml)*	41.5 (2.0)	36.4 (1.2)	33.6 (0.8)	31.0 (0.7)	27.2 (1.0)	32.2 (1.9)
EDVi rest (ml/m^2)#	55.2 (1.2)	49.3 (1.2)	46.4 (0.83)	43.7 (0.8)	40.8 (1.1)	44.9 (1.9)
ESVi rest (ml/m^2)*	20.9 (1.0)	18.2 (0.6)	17.0 (0.4)	15.7 (0.4)	13.9 (0.5)	17.3 (1.0)
ESV < 20 ml (small heart, %)	0	7.5	9.8	15.1	22	11.8
Females						
n	23	93	207	255	154	33
LVEF rest (%)*	65.4 (1.8)	66.7 (0.9)	69.5 (0.6)	71.1 (0.5)	72.4 (0.7)	72.4 (0.7)
EDV rest (ml)#	71.6 (3.8)	73.3 (1.7)	66.5 (1.2)	62.3 (1.1)	61.9 (1.4)	61.9 (2.8)
ESV rest (ml)*	25.2 (2.1)	24.7 (0.9)	20.8 (0.62)	18.4 (0.56)	18.0 (0.7)	17.9 (1.5)
EDVi rest (ml/m^2)#	43.2 (2.4)	43.6 (1.1)	38.9 (0.8)	35.8 (0.7)	36.6 (0.9)	35.8 (1.8)
ESVi rest (ml/m^2)*	15.3 (1.2)	14.7 (0.5)	12.2 (0.4)	10.6 (0.3)	10.5 (0.4)	10.4 (0.9)
ESV < 20 ml (small heart, %)	17.4	29.0	43.0	55.3	61.0	63.6

EDV end-diastolic volume, *EDVI* EDV adjusted for body surface area, *ESVI* ESV adjusted for body surface area

Values are all given as estimated marginal mean ± SE. * $p < 0.05$ (ANOVA) for effect of age and gender on LV parameter, # $p < 0.05$ (ANOVA) for effect of gender on LV parameter

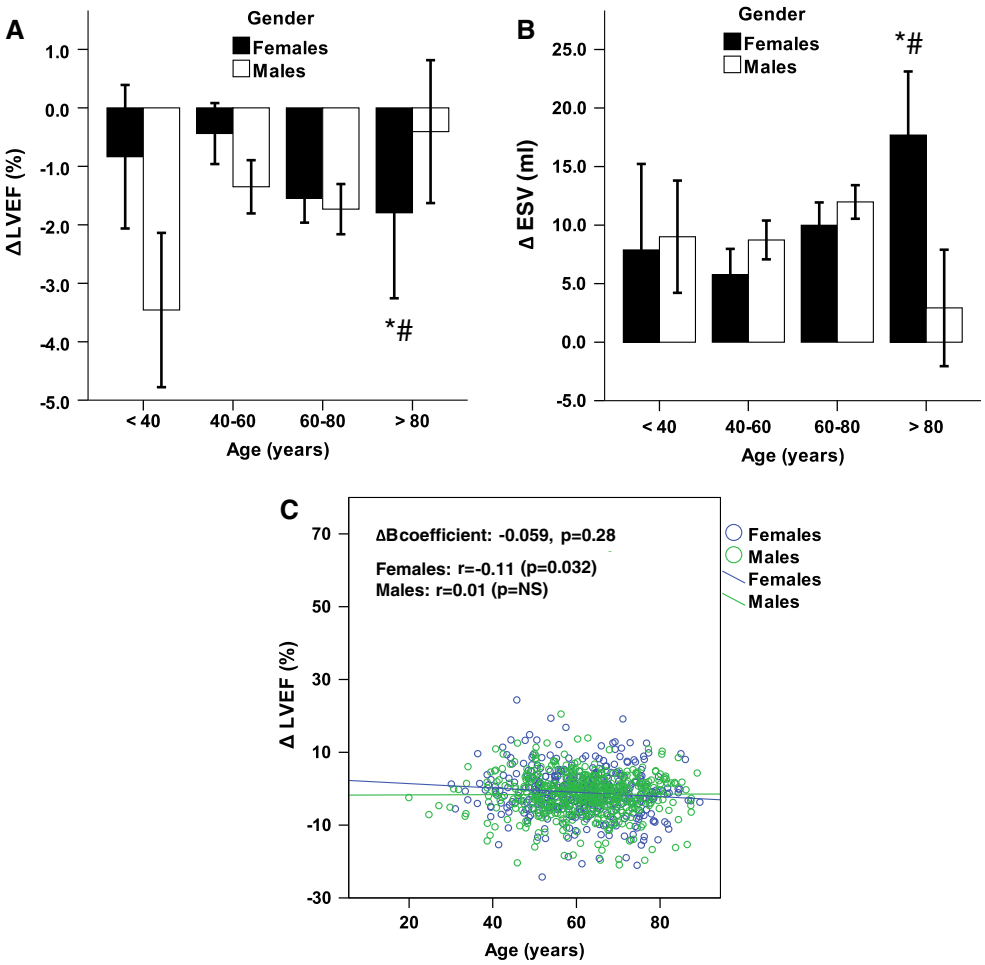

Fig. 3 Gender-specific change in left ventricular ejection fraction (LVEF) and left ventricular end-systolic volumes (ESV) from rest to post-stress **a** Sex differences in post-stress LVEF, ΔLVEF indicates post-stress LVEF—rest LVEF (%). **b** Sex differences in post-stress ESV, ΔESV indicates post-stress ESV—rest ESV (ml). **c** Regression lines and scatter plots of relationship between post-stress LVEF and age in males and females. ΔLVEF indicates post-stress LVEF—rest LVEF (%)

Table 4 Values for left ventricular ejection fraction (LVEF; mean ± 2SD), and lower and upper limits of bootstrap 95 % confidence interval (CI) of the mean based on gender and age

Age	Males					Females				
	LVEF (%)									
	LLN	Mean	ULN	95 % CI		LLN	Mean	ULN	95 % CI	
				Lower	Upper				Lower	Upper
30–40	50.2	62.3	74.4	60.4	64.2	50.0	65.4	80.8	62.0	68.7
40–50	48.6	63.6	78.6	62.1	65.0	52.0	66.7	81.3	65.2	68.1
50–60	49.1	63.7	78.3	62.8	64.7	54.3	69.5	84.7	68.5	70.5
60–70	49.5	64.7	79.9	63.8	65.6	54.1	71.1	88.1	70.1	72.2
70–80	50.5	66.5	82.5	65.2	67.8	53.6	72.4	91.2	70.8	73.9
>80	48.0	62.4	76.7	60.3	64.4	50.9	72.3	93.7	70.0	70.9

ULN upper limit of normal calculated as the mean + 2 SD, *LLN* lower limit of normal calculated as the mean − 2 SD

Reference limits for LVEF

The rest LVEF in our study population demonstrated normal distribution ($p = 0.60$) about a mean of 67.2 % (95 % CI, 66.7–67.6 %), with a range of 37–94 %. Thus, values exceeding 2 SDs of mean values were used to define abnormality at the 95 % confidence limit. Men and women were separated for these analyses, given the marked gender differences in mean LVEF measurements (Table 4). The lower reference limits (LLN = lower limit of normal, defined as mean − 2 SD) and the upper reference limits (ULN = upper limit of normal, defined mean + 2 SD) are shown in Table 3. There was no overlap between the limits of the bootstrap 95 % CI for women and men (69.7–70.9 % for women, 63.9–64.9 % for men) indicating that different normal limits should be used for women and men.

Discussion

In our study, age and LVEF were significantly correlated for both genders, although this association was more pronounced in women than in men. Women had a higher LVEF cut off for normal values (53.1 %) than men (49 %), mainly due to smaller ventricular volumes. In our study cohort, a significant increase in both BSA and BMI with increasing age was noted. However, in multivariable analysis, age and gender were associated with LVEF despite adjustment for BMI. These data suggest that age- and gender-specific LVEF criteria may be necessary in clinical decision-making.

The effect of increasing age or gender on LV end-diastolic dimensions and volumes has been controversially discussed in previous studies. Age-related differences were found in men but not in women in the multi-centre J-ACCESS study in 268 Japanese patients [1]. De Bondt et al. [6] found higher LVEF and lower LV volumes only in women older than 65 years (n = 102), and Rozanski et al. [7] reported that age correlated only weakly with LVEF but not with LV volume (n = 178) [3]. Previous SPECT studies of small cohorts have shown higher LVEF in women than in men [1, 6–10] with some reporting no correlation between LVEF and age in the same population [8], and others finding age-dependent LVEF differences in women but not in men [6] or only with one (QGS) but not with another software package (4D-MSPECT) [2]. These controversial observations may well result from different patient populations, varying age ranges, and the lack of large study populations. To date, normal limits for gated SPECT and QGS software were determined based on the J-ACCESS database that has been compiled since 2001 [1]. However, no age-and gender-related reference values have been published and the normal values for female patients in the J-ACCESS study showed a higher LVEF and lower LV volumes in comparison with non-Japanese studies indicating that normal values may vary among different populations.

Several mechanisms might be involved in the observed increase in LVEF with age: First, an age-related increase in arterial stiffening and a decreased aortic wall compliance may enhance LV afterload, and thereby promote elevated systolic LV stiffening and increase in LV mass [11]. Second, decreased LV end-diastolic dimensions already previously observed with aging [12], require increased global systolic contractility to maintain adequate cardiac output in elderly subjects. In contrast to previous studies, we found age-related changes of LVEF already at age <40 years. As LVEF and LV volumes seem to change continuously with increasing age, minor differences could easily been missed in smaller study populations. These interesting findings suggest that subclinical alterations in LV systolic structure and function display a continuous process occurring during whole life and lacking age limits. Nevertheless, the data in the present study do not allow us to determine with certainty whether the higher stroke volumes with advancing age or in women were secondary to differences in contractile state or loading conditions. Finally, an effect of undiagnosed hypertension cannot be ruled out completely

given the retrospective nature of the study. Technical factors that could lead to differences in quantification of functional parameters include smaller heart size, soft tissue attenuation, higher resting heart rate, smaller body habitus, and circumferences of the chest and waist. Women in general have smaller hearts [13], and when gated SPECT is analysed with QGS software, one of the most important issues is underestimation of LV volumes in small heart patients due to more significant photon scatter, and hence, lower image resolution [14]. Since we found a high correlation between ESV and LVEF, it is likely that the gender difference in LVEF is partially based upon women having smaller hearts. Currently, new methods are being developed for better delineation of small ventricles [15] and future studies will have to address this problematic finding.

It is well described that post-stress LVEF and ESV by gated myocardial perfusion SPECT provide incremental prognostic information over perfusion, in particular, in specific situations such as in patients with previous MI or for better identification of multivessel CAD [16, 17]. To assess effects of age and gender on post-stress cardiovascular function, gated SPECT was performed before and after adenosine stress in a subgroup analysis of our study ($n = 917$ patients). Adenosine stress resulted in a significant decrease in LVEF obtained with gated SPECT in both genders suggesting a remaining dilating and weakening effect of adenosine on LVEF and LV volumes 30 min after administration at the moment of acquisition which is not expected considering its short half-life. How adenosine exerts this effect and whether this effect has any prognostic significance needs to be further elucidated. We further found an impairment of LV contractile reserve in older females after adenosine stress when categorized age groups were compared, a phenomenon that was not observed in men. Interestingly, similar post-exercise changes in cardiac performance have previously been observed in postmenopausal women and in diabetic patients [18–21]. LV diastolic decompensation or sub-endocardial ischemia following pharmacological stress could account for these observations [22], however, determining what factors play a key role in the depression of LV contractile reserve in aged women warrants further investigation.

There are limitations to this study that should be pointed out. This retrospective study selected apparently healthy patients with normal myocardial perfusion imaging for reference limits of LV functional parameters. A large group of randomly selected healthy volunteers would probably be a better study group for establishing normal limits. However, this type of reference population is rarely available in nuclear medicine and we used patients without known cardiovascular disease instead. This approach can be criticized, since subjects referred to myocardial perfusion imaging may have some reasons for the referral which may not be found at the examination, e.g. microvascular disease or non-cardiac disease, indicating that they may not be representative of a healthy reference population. Since patients with diabetes, hypertension and prior revascularization are likely to represent a—less well—part of the reference population, leading to excessively broad normal limits we therefore excluded patients with documented hypertension, diabetes, CAD, MI, heart failure, previous revascularization, cardiomyopathy, valvular heart disease, ECG signs or suspicion of previous MI and LBBB at rest in our study. On the other hand, applying very rigorous exclusion criteria may have led to a reference population that represents a 'too healthy' part of the population. We believe that the inclusion and exclusion criteria in this study represent a reasonable balance in order to have a relevant reference population that reflects the real word for establishing normal limits. Further, our database did not cover information on racial background (the majority of the Swiss population being Caucasian). This limits the use of our results throughout the world. In addition, the ascertainment of a cardiovascular disease free study population to define LVEF reference limits may have been biased by differential reporting of medical illness by women and men, although the exclusion criteria should have reduced this bias. Obviously, values from any individual laboratory will need to be validated by means of specific tracers and acquisition, reconstruction, and analysis protocols. Similarly, the differences in geometry between the standard SPECT camera and the CZT camera used in the present study may have further increased the data variability. It should be emphasized that the present results pertain the 16 frame acquisition protocol, and caution is advised when extrapolating our results to 8-frame acquisitions because of the systematic 2–4 % EF point difference compared with 16-frame acquisition. Finally, we lack a standard reference modality such as CMR for comparison and, since LVEF was assessed with gated SPECT only, our conclusions may not be applicable to assessments by other imaging modalities.

In summary, using QGS, we observed significant changes in both LV chamber volumes and LVEF with increasing age, with gender-specific differences becoming more pronounced with advancing age. Further, our results suggest that ventricular contractile reserve is impaired in elderly women. Although the physiological significance of our results is uncertain and needs further study, these data raise the question of whether gender- and age-specific reference values are needed in clinical decision-making.

Acknowledgments The study was supported by Grants from the Swiss National Science Foundation (PAK, MF) and from the Olten Heart Foundation, Switzerland (CG, BES).

Conflict of interest None.

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