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ORIGINAL PAPER

Age related structural and functional changes in left ventricular performance in healthy subjects: a 2D echocardiographic study

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Abstract
Left ventricular (LV) adaptation to aging is currently poorly understood. We aimed to characterize age related changes in LV structure and function by studying a large group of healthy subjects across a wide age range. Prospectively enrolled healthy volunteers (n = 778, 327 females; age 18 to 100 years, mean age 49.8 ± 18.1 years), were divided into 4 age groups: 18 to 34 years (n = 165); 35 to 49 years (n = 242), 50 to 79 years (n = 334) and ≥ 80 years (n = 40). All subjects underwent clinical examination, as well as comprehensive transthoracic echocardiogram [TTE]. Body mass index, systolic blood pressure (BP), and left atrial volume ($p < 0.0001$) increased with age while diastolic BP ($p < 0.0001$) decreased over time. LV mass/body surface area (BSA) and relative wall thickness increased with age ($p < 0.0001$) coincident with worsening parameters of diastolic function (E/A and E/Em, $p < 0.0001$). The ejection fraction and Sm did not change significantly. Stroke volume, ejection time index, flow rate and stroke work significantly increased with age ($p < 0.01$). The arterial elastance (Ea), a measure of ventricular afterload, and ventricular elastance (Ees), an index of LV systolic stiffness did not change with age nor did their ratio (Ees/Ea) the latter being an expression of ventricular-arterial coupling. Age, gender and LVM were the main independent variables associated with LV systolic function. In conclusion, LV adaptation to aging in a healthy cohort is characterized by concentric LV remodeling, increased contractility and preserved ventricular-arterial coupling.

Keywords Left ventricular function · Aging · Echocardiography

Introduction

Left ventricle (LV) size and function are variably influenced by age, and aging per se is associated with greater cardiovascular disease burden even in the absence of other cardiovascular risk factors. Although aging does not in itself cause heart failure, it lowers the threshold for developing heart failure. In an aging society, heart failure has thus become a typical disease of the elderly with a massive impact on morbidity and mortality. There is also greater loss of muscle mass and associated reduced oxygen uptake of exercising muscles [1]. As a consequence, the aged heart has a reduced ability to respond to increased workload manifesting as reduced cardiovascular reserve. Several published series [2, 3] confirmed the above observations and lead to a general consensus that diastolic function declines with age [4, 5]. Conflicting data however have been reported regarding systolic function [6, 7] over the age continuum. In the present study we aimed to characterize LV adaptation to aging, focusing particularly on systolic function. To this end, we studied a large group of subjects encompassing a wide age range, self-reported in good health and with no overt cardiovascular risk factors (age excluded).

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Methods

Seven hundred and seventy eight healthy subjects aged 18 to 100 years were prospectively recruited from a single center (San Daniele del Friuli, Italy). Subjects were recruited from individuals being assessed for: (i) work eligibility (ii) subjects who were healthy blood donors and (iii) subjects who underwent electrocardiogram for obtaining access to spa facilities [8]. In particular the elderly and very elderly subjects were recruited from members of the university of the third age or relatives and friend referred to us by our staff. They were independent in their activities of daily living and were physically active, being regularly engaged in activities such as gardening and out of any chronic medication. All subjects underwent physical examination, anthropometric measurements, and assessment of lifestyle habits such as dietary and physical activity. They were excluded if they had diabetes mellitus, kidney disease, known pre-existing cardiovascular disease, dyslipidemia (requiring lipid-lowering therapy), history of coronary artery disease or any chronic condition requiring medication [9]. The study population was divided into four groups: group 1–165 subjects aged 18 to 34 years; group 2–242 subjects aged 35 to 49 years, group 3–334 subjects aged 50 to 80 years and group 4–40 subjects aged $\geq$ 80 years.

The study was approved by the local ethics committee and an informed consent was obtained from all participants.

An oscillometric device (Omrom HEM-759-E, Omron Healthcare Co. Ltd., Japan) was used for BP and heart rate (HR) measurement. The BP was taken twice, 10 min apart from the right arm before the echocardiographic exam. Normal BP was defined as a systolic BP (SBP) < 140 mm Hg and a diastolic BP (DBP) < 90 mm Hg). Among subjects older than 80 years, the threshold to define a normal BP was < 150/90 mmHg [10, 11]. Measurements taken before echocardiography were considered for all the haemodynamic parameters.

Body surface area (BSA), calculated using the DuBois formula ($0.20247 \times \text{height}^{0.725} \times \text{weight}^{0.425}$) and $\text{height}^{2.7}$ were used for structural and/or LV function parameters indexation.

Body mass index (BMI) was calculated as the body weight in kilograms divided by the square of height in m^2.

A standardized transthoracic echocardiographic examination under continuous ECG recording was performed (Alfa 10; Aloka Co, Ltd, Tokyo, Japan), according to the American Society of Echocardiography [12]. All studies were reviewed and analyzed offline with an image processing workstation implemented by the software COMPACS (Rev. 10.5.8, Medimatic, Genoa, Italy). Each parameter was assessed in 3 to 5 consecutive cardiac cycles, and the corresponding mean values were recorded.

Linear internal measurements of the LV cavity and its walls were performed in the parasternal long-axis view whenever possible, otherwise two-dimensionally guided M-mode was used from the parasternal short-axis view, with the patient in the left lateral position. LV mass was calculated according to the Penn convention [13]. Relative wall thickness (RWT) was calculated as 2 × posterior wall thickness/LV diameter in diastole using the 2D measures when available otherwise M-mode -based measurements were used. LV ejection fraction (EF) was calculated in the apical 4 and 2-chamber view using the method of discs. Left atrial volume was measured from the apical 4 and 2 chambers view according to the American Society of Echocardiography [12].

Doppler-derived LV diastolic inflow from the apical four-chamber was recorded at the mitral, peak E-wave velocity and A-wave velocity. Pulse tissue Doppler imaging (TDI) was performed in four chamber view at the septal and lateral mitral annular level. Peak myocardial wave velocity during systole (Sm), early diastole (Em), and late diastole (Am) (in centimeters per second) were measured [14]. E/A was the ratio between transmitral E-wave and A-wave, while E/Em was the ratio between transmitral E-wave and early diastole Em on TDI. The LV end-diastolic pressure (LVEDP) was calculated according to the following formula: $11.96 + 0.596 \times \text{E/Em}$ [15].

LV ejection time (LVET) was measured using the continuous wave (CW) Doppler outflow tract signal as the time interval between the beginning and the end of the CW trace of the aorta. LVET index (LVETI) was derived from the sex specific resting regression equations:

$$\text{Male LVETI} = (1.7 \times \text{HR}) + \text{ejection time};$$

$$\text{Female LVETI} = (1.6 \times \text{HR}) + \text{ejection time}.$$

Flow rate (FR) was calculated as SV/LVET [16, 17].

The stroke volume (SV) was derived from

$$\text{SV} = (\text{LVOT}_{\text{area}} \times \text{LVOT VTI}).$$

LVOT was measured in mid-systole at the aortic annulus level. Spectral Doppler LVOT VTI was obtained by the pulse wave Doppler and then SV was corrected by the BSA.

Stroke work (SW), a measure of myocardial work taking into account both blood pressure and shortening capacity, was calculated as

$$\text{SW} = (\text{MAP} + \text{MG})\ \text{SV} \times 0.0136$$

where SV is stroke volume, MAP is mean arterial pressure and MG is the trans-aortic mean gradient measured by CW [18].

Arterial elastance was calculated as $\text{Ea} = (\text{SBP} \times 0.9)/\text{SV}$ where SBP is brachial systolic BP and SV is stroke volume [19].

Ventricular elastance (Ees) was derived from the so called single-beat method developed by Chen et al. [20] by the formula.

$$Ees = \left(DBP - \left(E_{nd(est)} \times SBP \times 0.9\right)\right)/E_{nd(est)} \times SV,$$

where DBP and SBP are diastolic and systolic brachial BP, $E_{nd(est)}$ is the estimated normalized ventricular elastance at the onset of ejection, and SV is Doppler-derived stroke volume. $E_{nd(est)}$ is described by the formula:

$$E_{nd(est)} = 0.0275 - 0.165 \times EF + 0.3656 \times (DBP/SBP \times 0.9) + 0.515 \times E_{nd(avg)},$$

where EF is the basal ejection fraction and $E_{nd(avg)}$ is derived by the following formula:

$$E_{nd(avg)} = 0.35695 - 7.2266 \times tNd + 74.249 \times tNd^2 - 307.39 \times tNd^3 + 684.54 \times tNd^4 - 856.92 \times tNd^5 + 571.95 \times tNd^6 - 159.1 \times tNd^7,$$

where tNd is the ratio of pre-ejection period to total systolic period.

Global afterload or Zva was calculated as.

$$Zva = (SBP + MG)/SVI,$$

where SVI is stroke volume index [21]. This parameter represents the valvular and arterial impedance that opposed the ventricular ejection. This parameter includes the valvular load, the pulsatile and steady components of the arterial load, which are associated with reduced arterial compliance and increased vascular resistance, respectively.

$$SVR = 80(MAP - 5)/CO,$$

where MAP is mean arterial pressure and CO is cardiac output.

Statistical analysis

Data are expressed as mean ± SD. The study population was divided into four groups and differences between groups were tested by ANOVA either unadjusted or adjusted for gender, BMI, and physical activity; then, a post hoc pairwise comparison among groups was carried out. The partial correlation test by the Pearson method was used to assess clinically relevant variables, which were then incorporated into the multivariate model. A regression analysis to test the independent association between age, BMI, gender, mean BP, LVM, RWT, E/A, E/Em, and Zva were performed for LV systolic and diastolic parameters. The variance inflation factor (VIF) was considered for multicollinearity in regression analysis and the value of collinearity statistics was constantly < 5. Statistical significance was set at $p < 0.05$. All statistical analyses were performed using SYSTAT for Windows, release 12.0 (Systat Software Inc, Chicago, IL).

Results

The main characteristics of the study population are reported in Table 1. Women had lower arterial BP and higher HR, smaller LV dimensions and lower LV ejection fractions. Ventricular and arterial stiffness, expressed by Ees and Ea respectively, were significantly higher in women but their ratio did not differ between sexes (Table 1). Age Group related changes are presented in Table 2. Overall, group 4 had lower body weight (group 1 70.3 ± 13.7, group 2 73.7 ± 14.2, group 3 72.8 ± 12.9 and group 4 66.7 ± 10.6 kg, $p < 0.0001$) and height (group 1 173.4 ± 9, group 2 172.2 ± 9.1, group 3 167.8 ± 10.1 and group 4 160.1 ± 9.4 cm, $p < 0.0001$). BMI increased significantly with age (group 1 23.2 ± 3.4, group 2 24.7 ± 3.7, group 3 25.7 ± 3.6 and group 4 26.1 ± 4.4 kg/m^2, $p < 0.0001$). Blood pressure and heart rate increased significantly with age as well (Table 2).

With ageing LV diameter in diastole and end diastolic volume/BSA or end diastolic volume/height$^{2.7}$ did not change significantly. In contrast there was a progressive increase in in left atrial volume either indexed to BSA or height$^{2.7}$, wall thickness, as well as in LV mass and RWT. On the other hand, when LVM was indexed to BSA it decreased significantly across age groups, and an opposite trend was observed when indexed by height$^{2.7}$. Diastolic function worsened with age: the E/A ratio decreased significantly, whereas the E/Em ratio and LVEDP increased along with left atrial volume. The difference among age groups remained statistically significant even after adjustment for gender, BMI and physical activity for all the above mentioned parameters except LVEDP (Table 2).

Ejection fraction did not change with age (Fig. 1a), while age was inversely correlated to Sm (Fig. 1b) and SV/BSA progressively and significantly increased with age (Fig. 1c). FR increased with age but was not statistically significant after adjustment for sex, level of physical activity and BMI (Table 3). All parameters of LV systolic performance were getting better with age parallel to SW, which represents the LV work having taken into account the afterload (Table 2).

The LV-arterial coupling Ees/Ea ratio, Ees (i.e., LV elastance) and Ea (i.e., arterial stiffness that represents the LV afterload) (Fig. 1d) (Table 2) did not change with age.

Arterial impedance and systemic vascular resistances were similar in the various age groups (Table 3).

On multivariable regression analysis, parameters of LV systolic function, age, mean BP, and LVM were the predominant determinants of diastolic function. Age and diastolic

Table 1 General characteristics of the study population, both considered as a whole and in each sex group

Variable	All population N = 778 Mean ± SD	Male N = 451 Mean ± SD	Female N = 327 Mean ± SD	p
Anthropometric/hemodynamic data				
Age (years)	49.8 ± 18.1	48.8 ± 17.5	51.2 ± 18.8	NS
Weight (kg)	72.2 ± 13.5	79 ± 11	62 ± 10	0.0001
Height (cm)	169.9 ± 10.1	176 ± 7	161 ± 7	0.0001
BMI (kg/m^2)	24.9 ± 3.8	25.5 ± 3.4	24.2 ± 4.3	0.0001
BSA (m^2)	1.82 ± 0.2	1.94 ± 0.17	1.66 ± 0.13	0.0001
SBP (mmHg)	127.4 ± 12.2	128.1 ± 11.3	126.4 ± 13.2	0.051
DBP (mmHg)	76.3 ± 9.0	77.0 ± 8.9	75.38 ± 9.2	0.013
PP (mmHg)	51.0 ± 10.4	51 ± 10	50.9 ± 10.9	NS
MAP (mmHg)	93.1 ± 10.2	93.8 ± 9.7	92.1 ± 10.8	0.018
HR (bpm)	69.0 ± 12.3	67.5 ± 12.7	71.0 ± 11.6	0.0001
Echocardiografic data				
Left atrial volume/BSA (ml/m^2)	25.5 ± 9.3	28.1 ± 9.9	22.8 ± 6.9	0.0001
Left atrial volume/height$^{2.7}$ ($ml/m^{2.7}$)	11 ± 4.2	11.4 ± 4.6	11.2 ± 4.0	NS
LVIDD (mm)	50.3 ± 5.0	52.45 ± 4.4	47.4 ± 4.5	0.0001
IVSD (mm)	8.5 ± 1.3	8.8 ± 1.3	8 ± 1.1	0.0001
PWTD (mm)	8.2 ± 1.3	8.6 ± 1.4	7.8 ± 1.1	0.0001
LVM (g)	171 ± 52.9	194.1 ± 50.5	140.3 ± 35.5	0.0001
LVM/BSA (g/m^2)	93.1 ± 25.6	99.9 ± 26.5	84.1 ± 21.3	0.0001
LVM/ height$^{2.7}$ ($g/m^{2.7}$)	40.8 ± 11.7	42.3 ± 11.2	38.7 ± 11.9	NS
RWT	33.9 ± 5.6	33.93 ± 5.7	33.98 ± 5.6	NS
EDV/BSA (ml/m^2)	51.3 ± 12.8	57.3 ± 14.7	47.3 ± 10.2	0.0001
EDV/height$^{2.7}$($ml/m^{2.7}$)	8.7 ± 2.7	9.1 ± 2.8	8.0 ± 2.4	0.007
Diatolic parametes				
E/A	1.5 ± 0.8	1.49 ± 0.7	1.52 ± 0.9	NS
E/Em	6.0 ± 2.0	5.97 ± 2	6.0 ± 2	NS
LVEDP (mmHg)	15.16 ± 1.4	15.52 ± 1.19	15.55 ± 1.22	NS
LV systolic function parameters				
Sm (cm/s)	9.0 ± 1.9	9. ± 1	9 ± 2	NS
EF (%)	63.1 ± 6.6	62.9 ± 6.7	63.2 ± 6.4	NS
SV (ml)	71.8 ± 14.6	76.4 ± 14	65.5 ± 13.3	0.0001
SVI (ml/m^2)	39.6 ± 7.3	39.6 ± 7.4	39.5 ± 7.6	NS
SV/ height$^{2.7}$($ml/m^{2.7}$)	17.4 ± 3.7	16.7 ± 3.1	18.4 ± 3.7	0.0001
CO (L/min)	4.9 ± 1.3	5135 ± 1307	4638 ± 1169	0.0001
LVET (ms)	302.6 ± 36.7	299.3 ± 35	305.5 ± 42.3	NS
LVETI (ms)	417.2 ± 32.6	414.7 ± 30	419.3 ± 39.4	NS
FR (ml/s)	238.5 ± 51.5	258 ± 50.1	214.5 ± 42.2	0.0001
SW gr/min	89.2 ± 22.4	101.7 ± 21.6	86.0 ± 20.6	0.0001
LV arterial-coupling				
Ees mmHg/ml	1.99 ± 0.58	1.8 ± 0.54	2.1 ± 0.6	0.0001
Ea mmHg/ml	1.60 ± 0.32	1.5 ± 0.28	1.77 ± 0.31	0.0001
Ea/Ees	0.87 ± 0.19	0.87 ± 0.20	0.87 ± 0.19	NS
Afterload parameters				
Zva (mmHg/ml m^2)	3.71 ± 0.82	3.41 ± 0.6	3.37 ± 0.6	NS
Systemic vasc res (dyn s/cm^5)	1.63 ± 0.44	1.45 ± 0.3	1.57 ± 0.4	0.0001

BSA body surface area, *LVIDD* left ventricular internal diameter in diastole, *IVSD* interventricular septum in diastole, *PWTD* posterior wall thickness in diastole, *EDV* end diastolic volume, *BSA* body surface area, *LVMI* left ventricular mass index, *RWT* relative wall thickness, *EF* ejection fraction, *LVOT* left ventricular outflow tract, *LVEDP*: LV end-diastolic pressure, *SV* stroke volume, *SVI* stroke volume index, *CO* cardiac output, *LVET* left ventricular ejection time, *LVETI* left ventricular ejection time, *FR* flow rate, *SW* systolic work, *Zva* arterial impedence, *Ese* vntricular elastance, *Ea* arterial elastance

P values refer to differences between sexes

Table 2 Clinical, hemodynamic characteristics and parameters of left ventricular function, according to age group

Age interval (years)	Group 1 N = 165 (18–35)	Group 2 N = 240 (≥ 35–50)	Group 3 N = 333 (≥ 50–80)	Group 4 N = 40 (≥ 80)	p	p Adjusted by sex, physical activity, BMI
Variable	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD		
Age (years)	25.8 ± 5.3	42.1 ± 4.2	62.9 ± 8.5	86.7 ± 5.9	0.0001	–
Gender (M/F)	95/70	144/96	186/147	20/20	0.7	–
Weight (kg)	70.3 ± 13.7	73.7 ± 14.2	72.8 ± 12.9	66.7 ± 10.6	0.002	
Height (cm)	173.4 ± 9	172.2 ± 9.1	167.8 ± 10.1	160.1 ± 9.4	0.0001	0.0001
BMI (kg/m^2)	23.2 ± 3.4	24.7 ± 3.7	25.7 ± 3.6	26.1 ± 4.4	0.0001	–
BSA (m^2)	1.5 ± 0.07	1.7 ± 0.05	1.9 ± 0.08	2.2 ± 0.1	0.0001	–
SBP (mmHg)	122.2 ± 12.1	123.2 ± 12.1	131.3 ± 9.8	140.4 ± 9.1	0.0001	0.0001
DBP (mmHg)	72.9 ± 9.5	76.4 ± 8.8	77.8 ± 8.6	77.9 ± 8.5	0.0001	0.004
MAP (mmHg)	89.3 ± 9.3	91.9 ± 9	95.4 ± 9.5	98.7 ± 7.5	0.0001	0.0001
PP (mmHg)	49.3 ± 9.8	46.9 ± 9.3	53.5 ± 9.6	62.5 ± 9.3	0.0001	0.0001
HR (bpm)	70.9.3 ± 13	68.2 ± 12.7	68.3 ± 11.6	71.6 ± 10.2	0.054	0.013
LV parameters						
Left atrial volume/BSA (ml/m^2)	26.7 ± 9.2	25.3 ± 9.1	24.7 ± 9.3	27.9 ± 10.7	0.07	0.0001*
Left atrial volume/height$^{2.7}$ (ml/m$^{2.7}$)	9.3 ± 3.06	10.1 ± 3.37	12.1 ± 4.33	17.2 ± 5.5	0.0001	0.0001*
LVIDD (mm)	49.7.3 ± 4.7	50.7 ± 4.8	50.5 ± 5.3	49.0 ± 5.9	0.07	0.1
IVSD (mm)	7.9 ± 1.1	8.3 ± 1.2	8.7 ± 1.2	9.4 ± 1.2	0.0001	0.0001
PWTD (mm)	7.8 ± 1.1	8.1 ± 1.2	8.5 ± 1.3	9.1 ± 1.6	0.0001	0.0001
EDV (ml)	98.2 ± 27.3	100.4 ± 57.8	95.7 ± 29.7	90.1 ± 24.7	0.012	0.08
EDV/BSA (ml/m^2)	53.4 ± 11.9	54.1 ± 15.9	52.2 ± 13.6	50.0 ± 11.4	0.2	0.7*
EDV/height$^{2.7}$	8.3 ± 2.46	8.7 ± 2.74	8.6 ± 2.76	9.5 ± 2.67	0.08	0.09*
LVM (g)	153.9 ± 45.3	168.8 ± 53.8	179.0 ± 52.7	188.7 ± 59.7	0.0001	0.0001
LVMI (g/m^2)	99.8 ± 31.0	96.8 ± 31.2	90.9 ± 27.2	85.1 ± 25.9	0.0001	0.0001*
LVMI(g/height$^{2.7}$)	34.6 ± 8.1	38.5 ± 10.26	44.1 ± 11.6	52.5 ± 14.3	0.0001	0.0001*
RWT	32.2 ± 4.7	33.0 ± 5.6	34.9 ± 5.5	38.9 ± 6.7	0.0001	0.0001
Diastolic parameters						
E/A	2.23 ± 0.9	1.65 ± 0.6	1.1 ± 0.4	0.99 ± 1.0	0.0001	0.0001
E/Em	5.3 ± 1.4	5.8 ± 1.6	6.1 ± 2.1	8.8 ± 3.7	0.0001	0.0001
LVEDP (mmHg)	15.1 ± 0.8	15.4 ± 0.9	15.6 ± 1.2	16.5 ± 1.6	0.0001	0.065
LV parameters of systolic function						
Sm (cm/s)	9.5 ± 1.7	9.0 ± 1.7	9.5 ± 1.1	8.0 ± 1.7	0.5	0.6
EF (%)	63.0 ± 6.5	62.7 ± 6.6	63.5 ± 6.5	61.9 ± 7	0.3	0.3
LVET (ms)	296.2 ± 51.7	298.1 ± 33.2	308.6 ± 31.6	310.0 ± 42.3	0.0001	0.0001
LVETI ms	409.2 ± 48.5	412.8 ± 32.8	421.6 ± 25.2	428.0 ± 33.7	0.0001	0.002
FR (ml/s)	230.6 ± 51.6	236.2 ± 48.9	242.5 ± 51.4	251.3 ± 61.6	0.05	0.06
SV (ml)	68.7 ± 14.2	70.8 ± 13.8	74.2 ± 13.4	76.4 ± 15.3	0.0001	0.0001
SVI (ml/m^2)	37.6 ± 6.7	38.3 ± 7.9	40.8 ± 6.9	44.8 ± 7.1	0.0001	0.0001*
SV/height (ml/height$^{2.7}$	15.5 ± 2.8	16.9 ± 3.2	18.5 ± 3.6	21.5 ± 4.3	0.0001	0.0001*
CO (l/min)	4.8 ± 1.3	4.7 ± 1.2	5.0 ± 1.2	5.5 ± 1.3	0.003	0.03
SW (g/m)	87.0 ± 21.4	91.4 ± 22.9	99.8 ± 21.6	107.6 ± 22.1	0.0001	0.0001
LV arterial coupling						
Ees mmHg/ml	2.0 ± 0.59	1.96 ± 0.59	1.94 ± 0.53	2.0 ± 0.86	0.5	0.5
Ea mmHg/ml	1.67 ± 0.32	1.62 ± 0.32	1.64 ± 0.30	1.72 ± 0.37	0.2	0.4
Ea/Ees	0.86 ± 0.2	0.86 ± 0.17	0.88 ± 0.2	0.92 ± 0.21	0.2	0.2
Zva (mmHg/ml m^2)	3.44 ± 0.63	3.41 ± 0.67	3.38 ± 0.54	3.33 ± 0.59	0.3	0.3
Systemic vasc res (dyn s/cm^5)	1.47 ± 0.35	1.52 ± 0.36	1.51 ± 0.33	1.45 ± 0.40	0.4	0.5

LVIDD left ventricular internal diameter in diastole, *IVSD* interventricular septum in diastole, *PWTD* posterior wall thickness in diastole, *EDV* end diastolic volume, *BSA* body surface area, *LVMI* left ventricular mass index, *RWT* relative wall thickness, *EF* ejection fraction, *LVOT* left ventricular outflow tract, *LVEDP* LV end-diastolic pressure, *SV* stroke volume, *SVI* stroke volume index, *CO* cardiac output, *LVET* left ventricular ejection time, *LVETI* left ventricular ejection time, *FR* Flow rate, *SW* systolic work, *Zva* arterial impedance, *ESS* ventricular elastance, *Ea* arterial elastance

*No adjusted by BSA

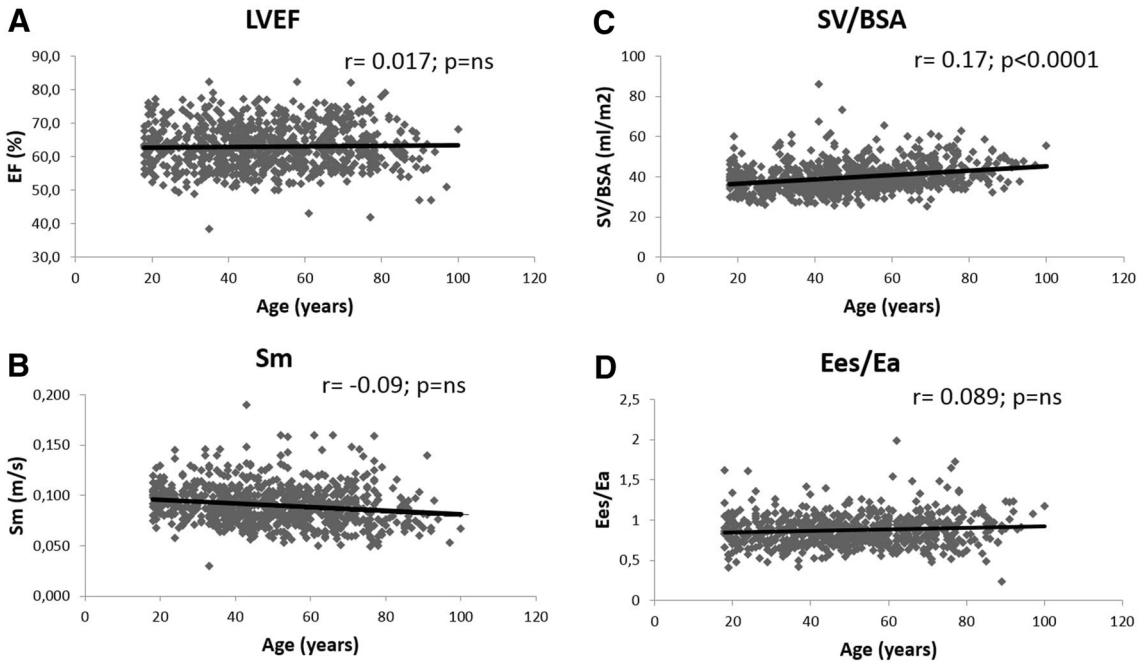

Fig. 1 Correlation analysis between ang and EF (**a**), SV/BSA (**b**), Sm (**c**), Ees/Ea (**d**)

parameters independently determined LVETI, while LVMI and arterial impedance were associated with LVEF. Age, gender and LVM were independently associated with the SV and SW. Age, diastolic function, arterial pressure, LVM and aortic impedance were the parameters independently predictive of LV-arterial coupling (Table 3). Mean BP and BMI were the independent parameters associated with E/A, while age and LV remodeling were associated with E/Em (Table 4).

Discussion

In the present study LV function related to aging was evaluated in a large healthy cohort. We documented the following: (1) with older age, LVM and wall thickness increased along with progressive diastolic impairment marked by higher diastolic filling pressure, and greater left atrial volume; (2) though LVEF did not change across the age continuum. There was an increase in SV, CO, LVET and SW. On the other hand, Sm, an index of longitudinal contractility, was inversely related to age. (3) LV arterial-coupling did not change across the age groups because the vascular stiffness increased in tandem with LV contractility. Moreover, neither Ea nor Ees changed significantly with age (Table 5).

Diastolic function and estimated left ventricular filling pressure

It is well known that aging is associated with an increase in LV mass and an impairment of diastolic function [22, 23]. These findings are confirmed in the present study with an increase in wall thickness and progressive impairment of diastolic function, represented by decreased E/A ratio and increased E/Em, LVEDP, and left atrial volume/BSA with age. Although our results, in terms of LV remodeling, are similar to those observed by Iannelli et al. [23], diastolic function in the present study seems to be less affected by age. Iannelli et al. demonstrated that the average E/Em in the age group 50–69 years was 8 and in subjects 70 years old and older was 8.6 [23]. In the present study, average E/Em was 8.8 in the very elderly, who were on average 13 years older than those studied by Iannelli et al. We observed the same trend for E/A. These differences might be related to the different sample size (298 subjects) and different selected population. They included also a pediatric group of subjects and only 20 subjects were included in the group older than 70 years. Our study not only included a larger number of elderly but the very old were not only healthy but also physically active [24].

Systolic function

The EF, a load dependent parameter of LV systolic function, was similar in the four age groups. However, SW, SV and cardiac output, all indices of LV performance increased

Table 3 Univariate and backward multiple regression analysis for LV systolic parameters

Simple correlation			Backward multiple regression analysis		
	r	p	R2	b	p
LV systolic function parameters-shortening properties					
EF			0.019		NS
Age	0.017	NS		–	–
BMI	0.038	NS		–	–
Gender	0.021	NS		–	–
Mean blood pressure	− 0.018	NS		–	–
LVM I	− 0.061	NS		− 0.125	0.011
RWT	− 0.018	NS		–	–
E/A	0.04	NS		–	–
E/Em	0.03	NS		–	–
Zva aortic impedence	− 0.047	NS		− 0.106	0.038
LVETI			0.05		0.0001
Age	0.169	0.001		0.273	0.0001
BMI	0.03	NS		–	–
Gender	0.104	NS		–	–
Mean blood pressure	− 0.018	NS		–	–
LVMI	− 0.025	NS		–	–
RWT	− 0.037	NS		–	–
E/A	0.02	NS		0.179	0.028
E/Em	0.127	NS		–	–
Zva aortic impedence	− 0.102	NS		–	–
FR			0.260		0.0001
Age	0.098	NS		–	–
BMI	0.249	0.0001		–	–
Gender	− 0.408	0.0001		− 0.263	0.0001
Mean blood pressure	0.173	0.001		–	–
LVM I	0.411	0.0001		0.274	0.0001
RWT	0.127	NS		–	–
E/A	− 0.211	0.0001		− 0.154	0.0001
E/Em	0.008	NS		–	–
Zva aortic impedence	− 0.454	0.0001		–	–
LV systolic performance-pumping properties					
SV			0.260		0.0001
Age	0.172	0.0001		0.242	0.0001
BMI	0.261	0.0001		0.103	0.003
Gender	− 0.368	0.0001		− 0.235	0.0001
Mean blood pressure	0.092	NS		–	–
LVMI	0.418	0.0001		− 0.276	0.0001
RWT	0.113	0.047		–	–
E/A	− 0.104	NS		–	–
E/Em	0.098	NS		–	–
SW			0.298		0.0001
Age	0.283	0.0001		0.255	0.0001
BMI	0.323	0.0001		0.132	0.0001
Gender	− 0.34	0.0001		− 0.220	0.0001
LVM I	0.381	0.0001		0.240	0.0001
RWT	0.161	0.0001		–	–
E/A	− 0.239	0.0001		–	–
E/Em	0.135	0.005		–	–
LV arterial coupling					
Ees			0.39		0.0001
Age	0.023	NS		0.27	0.0001
BMI	− 0.07	NS		–	–
Gender	0.22	0.0001		–	–
Mean blood pressure	0.227	0.0001		0.163	0.0001
LVMI	− 0.297	0.0001		− 0.134	0.002
RWT	0.008	NS		–	–
E/A	0.14	0.008		0.37	0.0001
E/Em	0.013	NS		–	–
Zva aortic impedence	0.47	0.0001		0.693	0.0001
Ea			0.185		0.0001
Age	0.036	NS		− 0.123	0.007
BMI	− 0.143	0.0001		–	–
Gender	0.359	0.0001		0.15	0.0001
LVMI	− 0.360	0.0001		− 0.233	0.0001
RWT	0.008	NS		–	–
E/A	− 0.09	NS		− 0.159	0.0002
E/Em	0.007	NS		–	–
Ees/Ea			0.058		0.0001
Age	0.089	NS		–	–
BMI	0.02	NS		− 0.087	0.044
Gender	0.01	NS		− 0.084	0.052
LVM I	0.044	NS		0.138	0.007
RWT	0.06	NS		–	–
E/A	− 0.20	0.001		− 0.247	0.0001
E/Em	0.028	NS		–	–

For abbreviations see Table 2

with age. In the current literature there is conflicting data regarding how LV systolic performance changes over age. In a study of 105 healthy subjects aged 24 to 84 years, Gerstenblith et al. [25] did not find any significant change in LV fractional shortening and LV dimensions. Ruan et al. [6] selecting systolic isovolumetric acceleration rate as a less load dependent parameter of systolic function, also were unable to identify any significant relationship between age

Table 4 Univariate and backward multiple regression analysis for LV diastolic parameters

Simple correlation			Backward multiple regression analysis		
	r	p	R2	b	p
LV diastolic function					
LVEDP			0.063		0.0001
Age	0.074	0.04		0.343	0.0001
BMI	0.04	NS		–	–
Gender	0.05	NS		–	–
Mean blood pressure	− 0.019	NS		–	–
LVM I	0.079	0.042		0.114	0.023
RWT	0.037	NS		–	–
ZVA aortic impedence	− 0.03	NS		–	–
E/A			0.39		0.0001
Age	0.5	0.0001	− 0.49		0.0001
BMI	− 0.27	0.0001	− 0.107		0.001
Gender	0.05	NS	–		–
Mean blood pressure	− 0.35	0.0001	− 0.170		0.0001
LVM I	0.062	0.08	–		–
RWT	− 0.17	0.0001	–		–
ZVA aortic impedence	− 0.10	0.003	–		–
E/Em			0.099		0.0001
Age	0.28	0.0001	0.277		0.0001
BMI	0.1	0.0027	–		–
Gender	0.05	NS	–		–
Mean blood pressure	− 0.08	0.02	–		–
LVMI	0.05	NS	0.15		0.012
RWT	0.18	0.0001	0.076		0.04
ZVA aortic impedence	− 0.05	NS	–		–

For abbreviations see Table 2

and systolic LV function. In contrast, other Authors found a reduction in SV with age, likely related to reduced diastolic LV volume. These findings however originated from heterogeneous populations including those affected by cardiovascular disease, [26] m hospitalized patients with extravascular disease [27], sedentary subjects [28] or simply small size study groups of healthy elderly subjects [7, 29] where limited inferences can be made. This was not the case for the present study, where LV diastolic volume index did not change significantly with age, while LVM increased due to the increase in wall thickness. These changes combined with similar afterload among the age groups might explain the increase in SV and systolic function in general.

Table 5 Relationship of LV structural and functional parameters in healthy subjects with aging

Parameters	Relation with age
Left atrial volume/body surface area (BSA)	Increase
Left atrial volume/height$^{2.7}$	Increase
Left ventricular mass (LVM)/BSA	Decrease
LVM/ height$^{2.7}$	Increase
Relative wall thickness (RWT)	Increase
E/A	Decrease
E/Em	Increase
Ejection fraction (EF%)	No change
Stroke volume (SV ml)	Increase
Stroke volume index by BSA (SV/BSA ml/m^2)	Increase
Cardiac output (CO L/min)	Increase
Left ventricular ejection time/heart rate (LVET/HR)	Increase
Frame rate (FR ml/s)	No change
Stroke work (SW g/min)	Increase
Ventricular elastance (Ees mmHg/ml)	No change
Arterial elastance (Ea mmHg/ml)	No change
Ea/Ees	No change
Arterial impedance (Zva mmHg/ml m^2)	No change

The LVETI is another simple parameter used to estimate LV systolic function. It is sensitive to inotropic state and preload, and correlates well with SV, LV output and dP/dTmax. It shortens in LV dysfunction [30–32] and combined with preserved systolic function—prolongs in relation to age, hypertension and arterial stiffness among subjects aged > 50 years [33–35]. In the present study, LVETI was positively related to age in a setting of normal LV systolic function and increased afterload. The flow rate, another parameter of systolic function, increased with age parallel to increase in CO, HR and LVET. However, the increment did not reach statistical significance. It could be that the prolonged LVET was necessary to balance the reduced inotropic capacity of the aging heart to maintain the same flow. Currently the upper normal limit for flow rate has been set either to an arbitrary 250 ml/s(36) or to 200 ml/s, based on an in vitro study [37] while, in our cohort of healthy subjects, we found a mean of 238.5 ± 51.5 (ml/s). Doppler Sm wave [38] represents the regional longitudinal contraction and, although the oldest group had lower Sm, the difference was not significant, This is in stark contrast to previously reported data [23] but, Sm might not be representative of the overall LV contractility.

The interaction between the LV and the arterial system, so called ventricular-arterial coupling, is the major determinant of the cardiovascular performance. In humans, the most optimal ventricular-arterial coupling values are between 0.7 and 1 [39–41]. Vascular stiffness increases with age as does

arterial elastance (Ea) and LV end systolic stiffness (ventricular elastance, Ees), so that the relation between arterial and ventricular elastance remains the same. Ea represents total arterial afterload and incorporates mean and pulsatile components, while LV end systolic stiffness is a measure of contractility that is affected by chamber geometry and stiffening and is negatively related to LVM [42]. This parameter seems to be a reliable tool in different pathologies as an expression of global cardiovascular performance [43–46]. Several Authors have reported that the Ea/Ees ratio does not change with age. Chen et al. observed that Ea correlated significantly with age in association with a modest increase in Ees, while Ea/Ees remained unchanged [47]. In another study on centenarians without cardiovascular disease but recruited as inpatients, the Ea/Ees ratio was low (0.4), reflecting a disproportionate increase in Ees related to a pathological LV concentric remodeling (RWT = 0.6) [27]. In the present study, Ees values were similar between groups, including the very elderly subjects combined with increased LV contractility. The progressive increase in concentric LV remodeling, although still maintained within the normal range, most likely preserved LV systolic function through aging, as described for example in hypertensive patients [42, 48]. The Ea/Ees value was always close to the unit, which stays for a mechanical efficiency at the cost of a minimal decrease in stroke volume permitting a smaller loss of mechanical efficiency in case of an increase in afterload.

Ea, aortic impedance and vascular resistance, did not change among age groups. Most likely the in BP was balanced by the parallel increase in SV and/or CO. Moreover, BPs are included in the numerator of the equations while flow (SV and/or CO) are the numerators and both increase with age.

On multiple regression analysis age and diastolic function were independently related to LV systolic performance-shortening parameters. Moreover, LV parameters of systolic performance-pumping were affected by age and LVM. With aging, the LV performance counted on increased LV mass/remodeling as reported in other clinical scenarios [42, 48]. Blood pressure was not independently related to LV systolic adaptation; this is reasonable, taking into account the narrow range of BP values of this population. Conversely, age and mean BP were positively related to Ees while E/A ratio and LVM were negatively related to Ees. Thus, on top of age, increased afterload, impaired diastolic function/LV compliance and increased LVM mass were further determinants of Ees. Gender had an impact on LV function. Female gender was negatively associated with LV performance parameters most likely due to a smaller and less performing heart. Female gender was independently and positively related to Ea (increased impedance and decrease compliance). As reported by our group and others, arterial stiffness increased more rapidly in women than men [8, 49]. Although in the present study we dealt with normal subjects, these findings may contribute to understanding better the predisposition of women to develop congestive heart failure with a preserved EF [50].

The variables considered were independently related to the LV parameters of systolic and diastolic function but in general they could explain (Ees and E/A excluded) only a small or very small proportion of their variability. Probably the week relation between variables is due to the narrow range of these variables in healthy subjects.

The present study has some limitations: (1) we do not provide data based on new technologies and parameters such as LV volumes, LVEF measured by 3D or the spackle tracking analysis for the evaluation of LV systolic function and left atrium, mainly because when the study was started those tools were not available. (2) The group of very elderly subjects without known cardiovascular disease and active in daily life is relatively small, though representative of their rarity in the general population. (3) Moreover, we did not perform the echocardiographic examination under physical or pharmacological stress, therefore how the LV systolic function changes under such conditions with aging, remains to be determined. (4) This is a single center study, so the results might not be applicable to centers with different echocardiographic expertise and/or to other ethnic groups.

Conclusions

In conclusion, we provide here, to the best of our knowledge, the first paper taking into account changes of LV systolic and diastolic parameters in a large group of healthy people representative of all adult ages, including the very elderly. The study shows that LV adaptation to aging is characterized by concentric LV remodeling combined with increased LV systolic function and unchanged Ees, Ea and Ees/Ea. Age related LV performance depends on diastolic function and LV remodeling. However, the "unchanged" ventricular-arterial coupling through aging does not strictly mean cardiovascular reserve adaptability, but rather age-related increased at rest systolic function that can be an expression of increased rest work threshold.

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Compliance with ethical standards

Conflict of interest None of the authors had any personal or financial conflict of interest. All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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