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Determinants of cardiac structure in frail and sarcopenic elderly adults☆,☆☆

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ABSTRACT

Background: Cardiac structure and function change with age. The higher prevalence of left ventricular hypertrophy (LVH) with concentric remodeling is indicative of a typical geometric pattern of aging associated with a higher cardiovascular (CV) risk and diseases. The recent associations found between low left ventricular and skeletal mass in older patients with frailty and sarcopenia have raised great interest in investigating cardiac characteristics and determinants of left ventricular mass (LVM) in this population.
Design: Cross-sectional study.
Methods: We evaluated 100 sarcopenic and physically frail outpatients, 33 men (M), 67 women (F), aged ≥70 years (mean age 79 ± 5) and enrolled in the Parma site of *European multicenter SPRINTT* population.
Results: All male and female participants showed LVH, assessed as indexed LVM to body surface area (LVM/BSA) (M = 128 ± 39 g/m^2; F = 104 ± 26 g/m^2), and were more prone to have concentric geometry, as demonstrated by relative wall thickness value (0.41 in both sexes). After backward regression analysis, including covariates such as age, sex, office or ABPM systolic blood pressure (SBP), heart rate, BSA, use of β blockers, ACE-inhibitors, angiotensin receptor blockers, calcium channel blockers, diuretics, physical activity, hemoglobin level, and Mini Mental State examination - the most powerful determinants of LVM were clinical SBP (β = 1.51 ± 0.31, p = 0.0005), BSA (β = 165.9 ± 41.4, p = 0.0001), while less powerful determinants were 24 h, daily and nightly SBP (p = 0.02, p = 0.002, p = 0.004 respectively).
Conclusions: Older sarcopenic and physically frail patients showed LVH with a tendency towards concentric geometry. The main determinant of LVM was SBP, highlighting the key role that hemodynamic condition plays in determining LVH in this population.

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.☆☆ Some authors of the present work (ST, YL, RC, MC, AC, RB, MDB, FL, EM, FL and MM) are partners of the SPRINTT consortium, which is partly funded by the European Federation of Pharmaceutical Industries and Associations (EFPIA). The present work was funded by a grant from the Innovative Medicines Initiative - Joint Undertaking (IMI-JU 115621).

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1. Introduction

Changes in the cardiovascular (CV) system occur during aging and include left ventricular (LV) remodeling characterized by increased LV mass (LVM), LV hypertrophy (LVH), which is strictly related to the coupling of ventricular and vascular stiffening processes (Lakatta, 2015; Paneni et al., 2017; Houghton et al., 2016).

Data from the Framingham Heart Study demonstrated, many years ago, that LVH further increases the risk of CV morbidity and mortality. LVH is also considered "target organ damage" according to the Hypertension Guidelines (Levy et al., 1990; Williams et al., 2018).

Furthermore, aging is associated, both in males and females, with changes in LV geometry, i.e., concentric remodeling, expressed as LV mass-volume ratio or relative wall thickness (RWT) (Cheng et al., 2009).

The combination of age and concentric LVH results in the highest CV risk for cardiovascular diseases such as systemic hypertension, coronary artery diseases (CAD), heart failure, and stroke (North and Sinclair, 2012; Koren et al., 1991).

The risk of CV diseases (angina, myocardial infarction, heart failure) and CV mortality is also increased by the presence of higher prevalent conditions in older persons, such as sarcopenia and physical frailty (Newman et al., 2001; Gharacholou et al., 2015; Leibowitz et al., 2016; Nadruz et al., 2017; Veronese et al., 2017; Byeon et al., 2015).

Sarcopenia is defined as the loss of skeletal muscle strength and mass (both qualitative and quantitative), while physical frailty is a multidimensional geriatric syndrome characterized by a reduced homeostatic reserve (Cruz-Jentoft et al., 2019; Longobucco et al., 2019).

In a sample of older persons with low muscle mass and physical performance, we recently demonstrated the existence of cardiac muscle axis, by showing that LVM and Appendicular Lean Mass (ALM) were positively and significantly correlated, independently from blood pressure, physical activity, and other potential confounders (Pelà et al., 2021).

These considerations highlight the interest in studying frail and sarcopenic elderly individuals in order to address the cardiac structure and to investigate the factors that more influence LV remodeling. We tested this hypothesis in a population enrolled in the SPRINT-T study and evaluated during clinical activity at Frailty Clinic of University-Hospital of Parma site (Landi et al., 2017; Marzetti et al., 2018).

2. Methods

2.1. Study population

Data are from an ancillary study (CARDIO SPRINTT) of the **S**arcopenia and **P**hysical f**R**ailty **IN** older people: multi-componen**T** **T**reatment strategies (SPRINTT) project, a randomized control trial conducted in frail, sarcopenic older subjects aged 70 years and older, without significant heart disease to demonstrate the effectiveness of a multicomponent (MCI) intervention based on physical activity, nutritional and technological intervention versus a healthy aging lifestyle education (HALE) program for the prevention of mobility disability (Landi et al., 2017; Marzetti et al., 2018). Sarcopenia was estimated by Dual X-ray absorptiometry as ALM values according to the recommendation of the Foundation for the National Institutes of Health (FNIH) as described elsewhere (Pelà et al., 2021; Studenski et al., 2014). Short Physical Performance Battery (SPPB) assessed physical frailty, with a score in the range between 3 and 9 (Longobucco et al., 2019). Participants in the SPRINTT trial needed to have sufficient cognitive abilities measured using Mini Mental State Examination test (MMSE), and those with MMSE $\geq$ 24 were included in the study (Longobucco et al., 2019).

The investigators of the Parma SPRINTT site added, at the time of enrollment of participants, a complete cardiac assessment including clinical evaluation with 12-lead resting Electrocardiogram (ECG) and Conventional and Doppler Tissue Echocardiographic (DTE) examination as part of the ancillary protocol CARDIO-SPRINTT.

This ancillary study was submitted to SPRINTT Scientific Committee and accepted by the Managing Entity and subsequently approved by AVEN Local ethics committee (ID 82/2016/SPER/AOUPR). Written informed consent was obtained from the participants.

One-hundred subjects, from those enrolled in the SPRINTT study in the Frailty Clinic of University-Hospital of Parma site, were selected. Blood pressure (BP) and heart rate (HR) (OMRON 705 IT) were assessed with three consecutive measurements whose data were averaged. Clinical blood pressure was measured by the doctor at the end of the visit to reduce the white coat effect, in a sitting position, in a comfortable environment where only the subject and the doctor were present in the room.

Ambulatory Blood Pressure Monitoring (ABPM) (MEDIGAS Italia S.r.l.) was also performed in about 50% of study population.

Level of physical activity (PA) was assessed by a questionnaire providing detailed information on type, intensity and duration of physical activity in three periods of their life: from 20 to 40 years old, from 40 to 60 years old and in the last year (supplementary Table 1) (Wareham et al., 2002). It was clearly demonstrated that PA declines with aging, whereas the percentage of time spent sedentary increases.

Charlson Comorbidity Index (CCI) was used to assess multimorbidity, the median score of CCI was estimated according to Charlson et al. (1987).

A standard 12-lead ECG was performed: heart rate (HR), PR-interval, QRS-duration, and corrected QT-interval were measured. R/S amplitude in precordial leads (S1 + R5) and Sokolow-Lyon criterion (positive if $\geq$35 mm), prevalence of Q-waves ($\geq$2 mm in depth in $\geq$2 adjacent leads), presence of ST-segment depression, of inverted T-waves (in $\geq$2 adjacent leads, excluding aVR and III), were also assessed.

2.2. Echocardiography

M-mode, two-dimensional, and Doppler ECHO were performed by an ultrasonography-experienced cardiologist (GP), using a commercially available, multi-hertz sector, 2–4 MHz probe-equipped machine (Vivid S5, GE Healthcare, USA). The interventricular septal (SWT) and posterior wall (PWT) thicknesses, systolic (ESD) and diastolic (EDD) diameters, systolic (ESV) and diastolic (EDV) left ventricular (LV) volumes, absolute LVM and indexed to body surface area (LVM/BSA) were calculated as previously described (Pelà et al., 2016). LVH was defined as LVM/BSA of >95 g/m^2 in women and >115 g/m^2 in men. Relative wall thickness (RWT) was calculated as: (SWT + PWT) / EDD, using the 0.42 cut-off to define eccentric ($\leq$0.42) or concentric (>0.42) remodeling (Lang et al., 2005; Lang et al., 2015). Simpson's biplane rule-based end-diastolic (EDV) and systolic (ESV) volumes and ejection fraction (EF) were calculated, while Fractional Shortening (FS) was: [(EDV − ESV) / EDV] × 100. Cardiac output (CO) was derived by the formula: EDV-ESV.

Mitral inflow pattern was analysed from apical 4-chamber view and E and A wave and their ratio were considered as peak flow velocity (pv) and time velocity integral (tvi), to evaluate the conventional diastolic function. From the same projection, DTE analysis was performed at lateral site and postero-septum of mitral annulus to assess myocardial systolic (S) and diastolic (E′, A′) waves of LV. The ratio of early diastolic mitral inflow velocity to early diastolic mitral annulus velocity (E/E′ ratio) was calculated for the estimation of LV filling pressure.

2.3. Statistical analysis

Data are reported as means ± SD, median and interquartile range [Q1–Q3] or numbers and percentage. We compared variables between male and female subjects through Student's *t*-test, Mann-Whitney *U* test or chi-squared test, as appropriate. Univariate analysis was performed to analyse the relationship of LVM and RWT (dependent variables) and age, sex, anthropometric parameters, systolic BP (SBP), heart rate (HR), hemoglobin concentration (Hb), level of PA, beta-blockers or ACE-

inhibitors/angiotensin receptor blockers as well as other structural and functional cardiac parameters.

Parsimonious models obtained by backward selection from initial fully adjusted models were used to identify independent factors of LVM (dependent variable) including parameters such as age, sex, BSA, SBP, HR, level of PA, MMSE score, Hb, beta-blockers, ACE-inhibitors/angiotensin receptor blockers (ARB), calcium channel blockers and diuretics. In the analysis SBP, from time to time, was included both to the clinical, 24 h-ABPM, daily-ABPM and nightly ABPM.

Backward analysis was also performed to analyse the determinants of LV geometry (RWT dependent variable) including as covariates age, sex, BSA, SBP, HR, level of PA, MMSE score, Hb, and pharmacological therapy.

The relationship between LVM and cardiac function, estimated as EF, CO, S and E′ (independent variables), was assessed by a multivariate analysis including as covariates age, sex, BSA, SBP and HR.

A 2-tailed p value<0.05 was considered as statistically significant. SAS 8.2 statistical package was used for all analyses (SAS Institute, Inc., Cary, NC, USA).

3. Results

3.1. Clinical characteristics

Table 1 shows the main characteristics of the study population: 67 were female (F) and 33 male (M) (mean age was 79 ± 5 years). The mean BMI was higher than 27.6 kg/m^2 with one third of the sample obese having BMI value >30 kg/m^2. CCI median score was 0, without significant differences between men and women. The SBP was high-normal (Williams et al., 2018) in both sexes without significant differences. The prevalence of hypertension was 70% in both groups. Twelve percent had coronary artery disease, and 3% had significant cardiac valve disease. No sign of heart failure was detected in any of the patients. Thyroid diseases were reported in 20% and diabetes mellitus in 9% of total sample (Table 1). As expected, levels of Hb were significantly lower in females. Forty-one percent of the participants were on β-blockers, 32% on ACE-inhibitors, 21% on Angiotensin II Receptor Blockers (ARB), 22% on calcium channel blockers and 36% on diuretics. Mean values of ALM, ALM/BMI and SPPB were consistent with the eligibility criteria adopted in SPRINTT for defining a sarcopenic and physically frail population, and M showing significantly high values of ALM and ALM/BMI than F (Table 1).

Electrocardiographic data showed repolarization abnormalities such as ST depression (6%), negative (24%) or flat T wave (34%) and pathological Q (5%) in a minority of elderly population, nobody had ST elevation, 22 subjects (22%) presented sign of LVH. PR, QRS and QTc intervals were in the normal range (data not shown).

Table 1
Characteristics of CARDIO-SPRINTT population (N = 100).

Variable	Total	Female	Male	p value
Age (years)	79 ± 5	79 ± 5	80 ± 5	0.28
Sex (n, %)	100 (100)	67 (67)	33 (33)	–
BMI (kg/m^2)	27.6 ± 5.1	27.5 ± 5.5	28.8 ± 4.3	0.8
BSA (m^2)	1.7 ± 0.2	1.6 ± 0.2	1.9 ± 0.2	<0.001
Height (cm)	159 ± 8	155 ± 6	167 ± 7	<0.001
Weight (kg)	70 ± 15	65 ± 18	79 ± 13	<0.001
HR (bpm)	66 ± 11	67 ± 12	65 ± 6	0.41
SBP (mm Hg)	138 ± 18	138 ± 17	140 ± 20	0.46
DBP (mm Hg)	80 ± 9	80 ± 9	79 ± 9	0.25
Hb (g/dl)	13.3 ± 1.4	13.0 ± 1.1	14.0 ± 1.9	<0.01
Smoking (n, %)	8(8)	4(6)	4(12)	=0.74
Hypertension (n, %)	70 (70)	47 (70)	23 (70)	0.92
CAD (n, %)	12 (12)	3 (4)	9 (27)	0.002
Cardiac valve disease (n, %)	3 (3)	3 (4)	–	–
COPD (n, %)	9 (9)	3 (4)	6 (18)	0.94
Beta-blockers (n, %)	41 (41)	26 (39)	15 (45)	0.64
Ace-inhibitors (n, %)	32 (32)	21 (31)	11 (33)	0.87
ARB (n, %)	21 (21)	14 (21)	7 (21)	0.06
Calcium channel blockers (n, %)	22 (22)	13 (19)	9 (27)	0.37
Diuretics (n, %)	36 (36)	26 (39)	10 (30)	0.41
ALM (kg)	17.2 ± 3.7	15.2 ± 2.1	21.3 ± 3.0	<0.001
ALM/BMI	0.62 ± 0.12	0.56 ± 0.08	0.76 ± 0.07	<0.001
SPPB (score)	7.1 ± 1.2	7.2 ± 0 0.1	6.9 ± 1.6	0.89
MMSE (score)	27.9 ± 1.7	27.9 ± 1.6	28.0 ± 1.8	0.74

Footnotes: data are expressed as mean ± standard deviation, median and interquartile range [Q1-Q3] or number of subjects with corresponding percentage. ALM, appendicular lean mass; ALM/BMI, indexed appendicular lean mass; ARB, angiotensin receptor blocker; BMI, body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; Hb, hemoglobin; HR, heart rate; MMSE, Mini Mental State Examination; SBP, systolic blood pressure; SPPB, short physical performance battery.

3.2. Echocardiographic results

The thicknesses of SWT and PWT and the LV cavity size, as assessed by diameters and volumes, were in the normal range, with M exhibiting greater LV thicknesses and dimensions compared with F (Table 2). Both M and F had sex-based higher mean value of LVM and LVM/BSA compatible with aging and hypertension status with a tendency to a concentric remodeling, as evaluated by RWT, in both groups (Table 2).

By using RWT and sex-based LVM cut-off values to define the distribution in the 4 types of LV remodeling in the Cardiosprintt population (Lang et al., 2005; Lang et al., 2015), 60% of our population had LVH, 26% and 34% with concentric remodeling and eccentric remodeling respectively, 40% had LVM in the normal range, 19% and 21% with

Table 2
Echo-based left ventricular structural and functional data in CARDIO-SPRINTT population (N = 100).

Variable	Total	Female	Male	p value
EDD (mm)	46.6 ± 6.3	45.0 ± 5.4	49.9 ± 6.8	<0.001
ESD (mm)	27.8 ± 6.2	26.2 ± 3.9	30.9 ± 8.5	<0.001
SWT (mm)	9.7 ± 1.5	9.2 ± 1.2	10.6 ± 1.6	<0.001
PW (mm)	9.3 ± 1.5	8.9 ± 1.3	10.0 ± 1.7	<0.001
EDV (ml)	95.1 ± 31.3	87 ± 22	112 ± 40	<0.001
ESV (ml)	29.9 ± 15.9	26 ± 8	38 ± 24	<0.001
LVM (g)	193 ± 67	169 ± 45	241 ± 79	<0.001
LVM/BSA	112 ± 33	104 ± 26	128 ± 39	<0.001
RWT	0.41 ± 0.07	0.41 ± 0.007	0.41 ± 0.06	ns
FS (%)	40 ± 8	42 ± 6	39 ± 10	ns
EF (%)	69 ± 7	70 ± 5	66 ± 10	<0.01
CO (ml)	65 ± 19	61 ± 17	74 ± 21	<0.001
Mitral Epv (cm/s)	59 ± 17	60 ± 17	55 ± 15	ns
Mitral Etvi (cm)	10.5 ± 3.1	10.5 ± 3.0	10.6 ± 3.4	ns
Mitral Apv (cm/s)	82 ± 19	84 ± 20	78 ± 16	ns
Mitral Atvi (cm)	9.4 ± 2.7	9.8 ± 2.8	8.8 ± 2.5	ns
Mitral E/Apv (cm/s)	0.8 ± 0.4	0.8 ± 0.4	0.7 ± 0.2	ns
Mitral E/Atvi (cm)	1.3 ± 0.9	1.2 ± 0.5	1.5 ± 1.5	ns
DTE Spv (cm/s)	8.1 ± 2.0	8.3 ± 1.9	7.8 ± 2.3	ns
DTE Stvi (cm)	1.6 ± 0.4	1.7 ± 0.3	1.5 ± 0.4	ns
DTE E′pv (cm/s)	6.9 ± 2.1	7.1 ± 2.2	6.6 ± 2.0	ns
DTE E′tvi (cm)	0.9 ± 1.1	0.9 ± 0.8	1.0 ± 1.6	ns
DTE A′pv (cm/s)	11.6 ± 2.9	11.3 ± 2.9	12.0 ± 3.0	ns
DTE A′tvi (cm/s)	0.9 ± 0.2	0.9 ± 0.2	1.0 ± 0.2	ns
DTE E′/A′pv	0.7 ± 0.4	0.7 ± 0.4	0.6 ± 0.2	ns
DTE E′/A′tvi	1.0 ± 1.0	1.0 ± 0.9	1.0 ± 1.2	ns
E/E′	9.9 ± 4.2	10.1 ± 4.4	9.5 ± 3.9	ns

Footnotes: data are expressed as mean ± standard deviation. A′, end-diastolic myocardial wave; BSA, body surface area; CO, cardiac output; DTE, doppler tissue echocardiography; E′, proto-diastolic myocardial wave; EDD, end-diastolic diameter; EDV, end-diastolic volume; EF, ejection fraction; ESD, end-systolic diameter; ESV, end-systolic volume; FS, fractional shortening; LVM, left ventricular mass; pv, peak velocity; PW, posterior wall thickness; RWT, relative wall thickness; S, systolic myocardial wave; SWT, septal wall thickness; tvi, time velocity integral. Values from DTE analysis are the mean of septal and lateral walls.

normal and concentric geometry respectively without significant differences in the distribution between sexes (Fig. 1).

LV systolic functions, assessed by EF and FS was normal as well as CO in total population, F showing significantly lower CO and higher EF compared to M (Table 2). Regarding the diastolic function, the mitral inflow pattern, assessed as E/Apv, showed an impaired relaxation, which was confirmed by a reduction of E′ wave but E/E′ excluded an increased LV filling pressure in our cohort without significant differences between male and female (Table 2).

In a group of our population (n = 52 subjects) we could measure ABPM 24 h BP, finding in both sexes that mean values of 24-SBP and daily SBP were at the upper limit of normal range, slightly lower in F than in M (Supplementary Table 2). Despite of reducing BP during the night, 48% of subjects had a non-dipper pattern, presenting a reduction lower than 10% and 17% a reverse dipper with a nightly increase of SBP. Mean values of both absolute and BSA-adjusted LVM and geometry of dipper and non-dipper subjects (including also reverse-dipper) were higher in non-dipper group, even difference between the profiles was not significant (data not shown). HR was slightly higher in F.

The determinants of LVM at univariate analysis are shown in Supplementary Table 3. LVM was positively and significantly correlated with male sex ($p < 0.0001$), height ($p < 0.001$), weight ($p < 0.001$), and BSA ($p < 0.001$), and BMI ($p = 0.05$). No significant correlation was found between LVM and age, SPPB, MMSE, Hb and levels of PA in the three periods of life.

A significant positive relationship was detected between LVM and clinical ($r = 0.24$; $p = 0.01$), night-time SBP ($r = 0.30$; $p < 0.05$) and standard deviation of daily SBP ($r = 0.27$; $p < 0.05$), while no correlation was found with daily and 24 hour SBP. An inverse correlation was found between LVM and clinical HR ($r = -0.16$; $p = 0.05$), but not ABPM-derived HR (Supplementary Table 3).

At univariate analysis, the cardiac function, assessed as EF, FS, S and E′ waves, was negatively correlated with LVM and positively with CO (Supplementary Table 3).

QRS and QTc duration, LVH and ST depression were positively and significantly correlated with LVM (Supplementary Table 3).

In a stepwise regression analysis (backward), including as independent variables age, sex, BSA, HR, use of ACE inhibitors, ARB, beta-blockers, calcium channel blockers, diuretics, levels of PA, MMSE score, Hb and SBP, included from time to time as clinical or 24 h-, daily-, nightly-SBP and standard deviation (SD) of SBP, demonstrated that the powerful determinants of LVM were clinical SPB ($p = 0.0005$) and BSA ($p = 0.0001$), while 24 h, daily and nightly SBP less significantly influenced LVM ($p = 0.02$, $p = 0.002$, $p = 0.004$ respectively) (Table 3, Model 1 to Model 4); 24-hour SD of SBP ($p = 0.04$) correlated with LVM (data not shown). A non-significant inverse correlation was found with HR (Table 3, Model 2 and Model 3). Age, sex, pharmacological therapy (with beta-blockers, ACE-inhibitors, ARB, calcium channel blockers and diuretics), levels of PA, Hb, and MMSE were not related to LVM.

In a multivariate backward analysis, only the significant positive correlation between LVM and CO was confirmed ($p < 0.001$) (data not shown).

The only determinant of RWT, both at univariate and multivariate analysis, was age ($r = 0.25$, $p = 0.0126$ and β 0.0034 + 0.0013, $p =$

Table 3
Factors independently related to Left Ventricular Mass: multiple backward regression analysis.

Backword analysis	Variables	β ± SE	p value	95%CI
Model 1	BSA (m^2)	165.9 ± 41.4	0.0001	[147; 272.5]
	Clinical SBP (mm Hg)	1.15 ± 0.31	0.0005	[0.53; 1.81]
Model 2	BSA (m^2)	156.1 ± 40.0	<0.001	[75.6; 236.6]
	24 h SBP (mm Hg)	2.3 ± 2.5	0.02	[0.6; 9.2]
	HR (bpm)	−1.39 ± 0.8	0.08	[−3.0; 0.2]
Model 3	BSA (m^2)	158.5 ± 40.9	<0.001	[76.2; 240.7]
	Daily SBP (mm Hg)	2.0 ± 0.63	0.002	[0.5; 9.1]
	HR (bpm)	−1.5 ± 0.8	0.06	[−3.1; 0.05]
Model 4	BSA (m^2)	169.4 ± 40.0	<0.001	[88.8; 249.9]
	Nightly SBP (mm Hg)	1.61 ± 0.5	0.004	[0.5; 7.5]

Regression coefficient (β), standard error (SE). The full model included age, heart rate (HR), body surface area (BSA), sex, Mini Mental State Examination, ace-inhibitors, beta-blockers, angiotensin receptor blocker, calcium channel blockers, diuretics, hemoglobin, physical activity intensity in three different periods of life. Systolic blood pressure (SBP) was included as clinical BP (Model 1) or ABPM 24 h BP (Model 2), daily SBP (Model 3) and nightly SBP (Model 4).

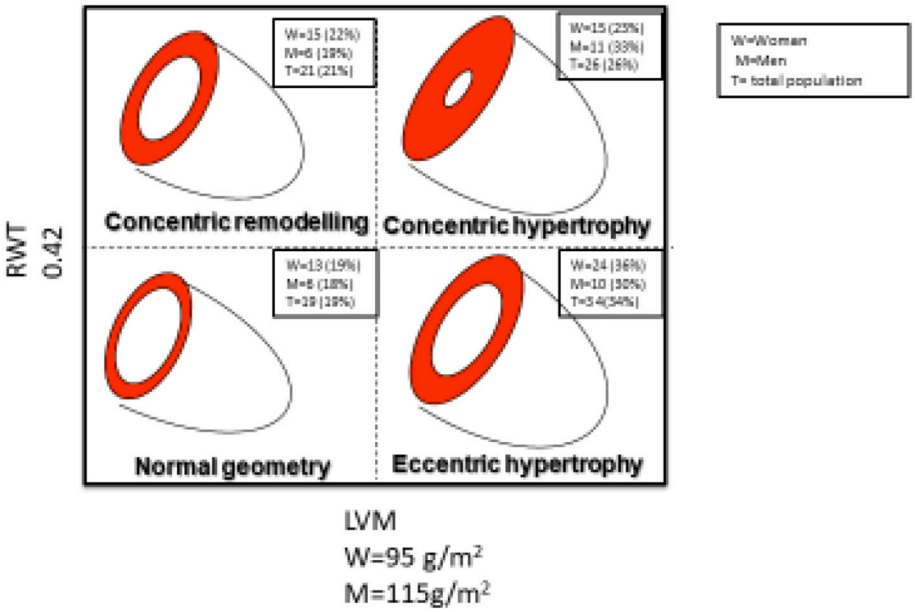

Fig. 1. Distribution of left ventricular remodeling in Cardiosprintt population.

0.010 respectively); sex, BSA, SBP, HR, beta-blockers, ACE-inhibitors and ARB, level of PA, Hb, MMSE did not influence the LV geometry (data not shown).

4. Discussion

The present study demonstrates the presence of LVH in 60% of frail and sarcopenic elderly subjects, with prevalent concentric geometry, as assessed by RWT (Lang et al., 2015).

In this population, the main determinants of LVM were BSA and SBP, while RWT was primarily correlated with age. Sex, pharmacological-treatment, Hb, MMSE, and PA did not correlate with both parameters of LV remodeling.

The determinants of LVM have been rarely investigated in older individuals, population with higher CV risk (Cheng et al., 2009; Toba et al., 2017). To our knowledge, this is also the first study enrolling older patients with both frailty and sarcopenia.

Frailty is associated with higher prevalence of CV diseases and subclinical CV abnormalities, such as higher LVM, lower stroke volume and LV diastolic dysfunction (Newman et al., 2001; Gharacholou et al., 2015; Leibowitz et al., 2016; Nadruz et al., 2017; Veronese et al., 2017; Alonso Salinas et al., 2018; Afilalo et al., 2017).

Similarly, sarcopenia, i.e., low skeletal muscle mass, has been related in young and middle-aged Koreans (Byeon et al., 2015) to a higher CV risk, LV diastolic dysfunction, or LVH. Consistently, in CV disease-free, Attican adults 45+ years old, low skeletal muscle mass was a negative predictor of the 10-year incidence of CV diseases (Tyrovolas et al., 2020).

In the present study, frail and sarcopenic older adults showed LVH in both groups with a tendency to concentric remodeling. This finding is not unexpected given the well-known influence of aging process on structural remodeling of the heart, i.e., LVH, mainly mediated by vascular stiffening processes (Lakatta, 2015; Paneni et al., 2017; Houghton et al., 2016).

However, eccentric and concentric patterns are due not only to age, but also to hemodynamic condition. Changes in LV geometry reflect alteration of LV volume- and pressure-load.

In hypertensive patients, Ganau et al. (1992) demonstrated that each LV remodeling, normal geometry, concentric remodeling, concentric and eccentric remodeling, is related to different hemodynamic profile. Concentric remodeling, in particular, is associated with the highest peripheral resistance.

In healthy individuals, aging results in an increased incidence of LVH, decline of LV diastolic function, left atrial dilation (mirror of LV diastolic dysfunction), with preserved ejection fraction. Cheng et al. (2009), using magnetic resonance imaging, demonstrated that age is associated with a mass-to-volume ratio markedly increased, indicating a concentric remodeling, a significant fall in stroke volume with strain patterns reflecting systolic as well diastolic myocardial dysfunction. These LV adaptations of aging heart reflect both central and peripheral changes: an increased aortic stiffening and consequent increased systolic pressure, a major determinant of LVM, and diastolic dysfunction, closely LVH- related.

LVH develops as an adaptive process that allows the heart to normalize afterload, to maintain LV wall stress and forward output. This compensatory mechanism is confirmed in our population where we found a positive correlation found between LVM and CO.

LVH is, likewise, associated with worse LV systolic and diastolic function, as demonstrated by the negative correlation between LVM and S and E′ waves. These results corroborated the hypothesis that pathological LVH rather than a physiological one, i.e., athlete's heart, is associated with both diastolic and systolic dysfunction (Pelà et al., 2004; Pelà et al., 2001).

The aging process is also associated with changes in the LV geometry - ranging from eccentric, that most observed in the young, adult Caucasian population, to concentric type because of a substantial decline in LV dimensions due to an impaired LV relaxation (Cheng et al., 2009). In essential hypertensive patients, the concentric LVH was related to the highest CV risk (Koren et al., 1991).

Data from 5004 MESA study participants from the ages of 45 to 84 and without overt CV disease, who underwent cardiac magnetic resonance imaging (MRI), show that age is associated with a phenotype of LV remodeling that is characterized by increased LV mass-to-volume ratio (MRI-index of LV geometry as ECHO-RWT). This pattern of LV remodeling, stronger in younger (<65 years) than older (≥65 years) subjects, confers a significant risk for total CV events, thus confirming the prognostic role of concentric geometry (Cheng et al., 2009).

Taken together, these findings suggest that biological aging predisposes to greater CV risk, but, nowadays, the impact of LVH on CV prognosis in elderly people remains elusive.

After categorization of LV remodeling into four groups, based on the sex-specific distribution of LVM and RWT (normal geometry, concentric remodeling, and concentric and eccentric hypertrophy) (Lang et al., 2005; Lang et al., 2015), 24% and 34% among females and 33% and 30% among males had concentric and eccentric LVH, with normal geometry found in only 22% and 15% of females and males, respectively. RWT above 0.42 was detected in 53% of men and in 41% of women.

Recently, Lieb et al. (2014) demonstrated dynamic changes in the LV geometric pattern, including the development of an abnormal geometry with increased risk of CV diseases of Framingham Heart study participants (mean age 51 years, 59% women) with LV geometry at baseline and after 4 years.

Our results demonstrate that LVM positively correlates with sex, height, weight, BSA and BMI, SBP, both at clinical and ABPM evaluation. Age, SPPB score and the levels of PA, at three different ages, do not influence LVM. The lack of association between age and the grading of frailty and LVM is not surprising, as the age window was so narrow in our sample. Unlike other studies, we used SPPB, as proxy of physical frailty and inclusion criterion of the study, rather than Fried criteria which are actually considered the gold standard for detecting frailty (Fried et al., 2001).

The strong correlation between LVM and BSA at multivariate analysis confirms that body size is an important determinant of LVM, even in the elderly population (De Simone et al., 1995; De Simone et al., 1992). It is well-known that, starting from adolescence to adulthood, the influence of body size on LVM variability decreases because of the increasing effects of hemodynamic load conditions on the heart and the physiologic augmentation of SBP (De Simone et al., 1998; De Simone et al., 2001). In the elderly, LVH develops as consequence of artery stiffness (Lakatta, 2015; Paneni et al., 2017; Houghton et al., 2016).

Our data confirm the role of SBP as a main predictor of LVM, such as body size, in a population of frail and sarcopenic elderly subjects. Interestingly, clinical SBP, but not ABPM was the most powerful predictor, of LVM.

Our results are in contrast with previous reports demonstrating that SBP obtained at ABPM is more strongly correlated with LVM and target organ damage than clinical SBP (Fan et al., 2020). The results could be easily explained by the low number of subjects who have undergone ABPM (52 of 100 participants), thus reducing the statistical value of ABPM data as compared to the clinical evaluation of SBP.

Age did not correlate with LVM at either univariate or multivariate analysis, but it was a powerful determinant of RWT, thereby suggesting its role in the progression of LV concentric changes (Cheng et al., 2009; Toba et al., 2017). Concentric geometry, in addition to aging, is strictly related with other specific conditions, such as obesity and metabolic syndrome (Ponce et al., 2018; Lee et al., 2019).

In our population, both groups showed RWT values (0.41) closer to the cut-off point, suggesting a higher probability of a concentric remodeling without gender differences. These results highlight the usefulness of cardiovascular screening, which should include an echocardiographic examination for the assessment of the cardiac structure and function, to estimate CV risk in frail and sarcopenic elderly subjects,

including asymptomatic ones.

The data presented here are part of an ancillary study of SPRINTT, a multicenter study which involved frail and sarcopenic elderly adults, aged 70 years and older, without significant heart disease, offered us the unique opportunity to study this selected population. Regarding the afore-mentioned population, we found an increase in LVM in both M and F, with a tendency towards a concentric geometry (RWT near the cut off value of 0.42 which defines concentric vs eccentric remodeling) (Landi et al., 2017; Marzetti et al., 2018).

We acknowledge as limitations of the study both the limited number of subjects enrolled and the cross-sectional nature of analysis. Moreover, given the strict inclusion criteria and the precisely defined cohort features, the generalization of results to the entire population of older individuals deserves further investigation. Another limitation is the small number of participants who underwent ABPM (52 of 100 participants), and the lack of information on the history of good or poor control of hypertension in this specific group of individuals. We also acknowledge that frail individuals may have substantially lower BP than non-frail older adults and the process of increasing LVM can be attenuated in this group of individuals. All these data, regarding the exposure to uncontrolled blood pressure and frailty status, could have been useful to better address the complex relationship between frailty and cardiovascular aging. Levels of PA did not influence either LVM or RWT. However, whether lifestyle, exercise, can modulate LV geometric changes of aging will be the focus of the perspective part of the study.

Furthermore, instead of the current criteria and gold standard of sarcopenia and physical frailty, we used adapted measurements (Landi et al., 2017; Marzetti et al., 2018).

Despite these limitations, our study has important strengths. The main one is represented by the homogeneous sample of frail and sarcopenic older persons enrolled in the study. What is more, the echocardiographic examinations were performed by a single experienced operator to limit the variability of the calculation of the LVM, a measure usually affected by both the quality of the images and the experience of the operator. Our study both underlines the need for echocardiographic examination to follow sex specific ECHO Guidelines and confirms the low sensitivity of ECG (22% vs 60%) in accurately assessing LVH. Clinical blood pressure was measured by the doctor at the end of the visit by using standardized procedures.

Moreover, to our knowledge, this is the first time a study has investigated the determinants of LVM in a group of frail and sarcopenic older people.

5. Conclusion

Older sarcopenic and physical frail persons showed a higher prevalence of LVH and concentric geometry. The main determinants of LVM were body size expressed as BSA and SBP (mainly office SBP), thus indicating the key role of hemodynamic conditions (afterload) in the development of left ventricular hypertrophy in the elderly.

CRediT authorship contribution statement

Giovanna Pelà, Fulvio Lauretani and Marcello Maggio contributed to the conceptualization and design of the work. Fulvio Lauretani and Sara Tagliaferri: data analysis. Sara Tagliaferri: data presentation. All authors contributed to investigation and data collection. Giovanna Pelà performed all echocardiographic examinations and drafted the original manuscript. Giovanna Pelà, Fulvio Lauretani, Marcello Maggio and Sara Tagliaferri reviewed and edited the draft. All authors critically revised the final manuscript and gave approval.

Declaration of competing interest

No conflicts of interest to declare. Some authors of the present work are partners of the SPRINTT consortium, which is partly funded by the European Federation of Pharmaceutical Industries and Associations (EFPIA). The present work was funded by a grant from the Innovative Medicines Initiative - Joint Undertaking (IMI-JU 115621).

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Appendix A. Supplementary data

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References

Afilalo, J., Lauck, S., Kim, D.H., Lefèvre, T., Piazza, N., Lachapelle, K., Martucci, G., Lamy, A., Labinaz, M., Peterson, M.D., Arora, R.C., Noiseux, N., Rassi, A., Palacios, I. F., Généreux, P., Lindman, B.R., Asgar, A.W., Kim, C.A., Trnkus, A., Morais, J.A., Perrault, L.P., 2017. Frailty in older adults undergoing aortic valve replacement: the FRAILTY-AVR Study. J Am Coll Cardiol. 70 (6), 689–700. https://doi.org/10.1016/j.jacc.2017.06.024.

Alonso Salinas, G.L., Sanmartin, M., Pascual Izco, M., Rincon, L.M., Martin-Acuna, A., Pastor Pueyo, P., Del Val Martín, D., Marco Del Castillo, Á., Recio-Mayoral, A., Martin-Asenjo, R., Garcia-Guerrero, A., Caravaca-Perez, P., Camino Lopez, A., Jimenez-Mena, M., Zamorano, J.L., 2018. The role of frailty in acute coronary syndromes in the elderly. Gerontology 64 (5), 422–429. https://doi.org/10.1159/000488390.

Byeon, C.H., Kang, K.Y., Kang, S.H., Bae, E.J., 2015. Sarcopenia is associated with Framingham risk score in the Korean population: Korean National Health and Nutrition Examination Survey (KNHANES) 2010–2011. J. Geriatr. Cardiol. 12 (4), 366–372. https://doi.org/10.11909/j.issn.1671-5411.2015.04.007.

Charlson, M.E., Pompei, P., Ales, K.L., MacKenzie, C.R., 1987. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J. Chronic Dis. 40 (5), 373–383. https://doi.org/10.1016/0021-9681(87)90171-8.

Cheng, S., Fernandes, V.R., Bluemke, D.A., McClelland, R.L., Kronmal, R.A., Lima, J.A., 2009. Age-related left ventricular remodeling and associated risk for cardiovascular outcomes: the Multi-Ethnic Study of Atherosclerosis. Circ. Cardiovasc. Imaging 2 (3), 191–198. https://doi.org/10.1161/CIRCIMAGING.108.819938.

Cruz-Jentoft, A.J., Bahat, G., Bauer, J., Boirie, Y., Bruyère, O., Cederholm, T., Cooper, C., Landi, F., Rolland, Y., Sayer, A.A., Schneider, S.M., Sieber, C.C., Topinkova, E., Vandewoude, M., Visser, M., Zamboni, M., Writing Group for the European Working Group on Sarcopenia in Older People 2 (EWGSOP2), and the Extended Group for EWGSOP2, 2019. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing 48 (1), 16–31. https://doi.org/10.1093/ageing/afy169.

De Simone, G., Daniels, S.R., Devereux, R.B., Meyer, R.A., Roman, M.J., de Divitiis, O., Alderman, M.H., 1992. Left ventricular mass and body size in normotensive children and adults: assessment of allometric relations and impact of overweight. J. Am. Coll. Cardiol. 20 (5), 1251–1260. https://doi.org/10.1016/0735-1097(92)90385-z.

De Simone, G., Devereux, R.B., Kimball, T.R., Mureddu, G.F., Roman, M.J., Contaldo, F., Daniels, S.R., 1998. Interaction between body size and cardiac workload: influence on left ventricular mass during body growth and adulthood. Hypertension 31 (5), 1077–1082. https://doi.org/10.1161/01.hyp.31.5.1077.

De Simone, G., Pasanisi, F., Contaldo, F., 2001. Link of nonhemodynamic factors to hemodynamic determinants of left ventricular hypertrophy. Hypertension 38 (1), 13–18. https://doi.org/10.1161/01.hyp.38.1.13.

Fan, H., Onakpoya, I.J., Heneghan, C.J., 2020. 24-h ambulatory blood pressure versus clinic blood pressure as predictors of cardiovascular risk: a systematic review and meta-analysis of prospective studies. J. Hypertens. 38 (11), 2084–2094. https://doi.org/10.1097/HJH.0000000000002500.

Fried, L.P., Tangen, C.M., Walston, J., Newman, A.B., Hirsch, C., Gottdiener, J., Seeman, T., Tracy, R., Kop, W.J., Burke, G., McBurnie, M.A., Cardiovascular Health Study Collaborative Research Group, 2001. Frailty in older adults: evidence for a phenotype. J. Gerontol. A Biol. Sci. Med. Sci. 56 (3), M146–M156. https://doi.org/10.1093/gerona/56.3.m146.

Ganau, A., Devereux, R.B., Roman, M.J., de Simone, G., Pickering, T.G., Saba, P.S., Vargiu, P., Simongini, I., Larag, J.H., 1992. Patterns of left ventricular hypertrophy and geometric remodeling in essential hypertension. J. Am. Coll. Cardiol. 19 (7), 1550–1558. https://doi.org/10.1016/0735-1097(92)90617-v.

Gharacholou, S.M., Tashiro, T., Cha, S.S., Scott, C.G., Takahashi, P.Y., Pellikka, P.A., 2015. Echocardiographic indices associated with frailty in adults ≥65 years. Am. J. Cardiol. 116 (10), 1591–1595. https://doi.org/10.1016/j.amjcard.2015.08.023.

Houghton, D., Jones, T.W., Cassidy, S., Siervo, M., MacGowan, G.A., Trenell, M.I., Jakovljevic, D.G., 2016. The effect of age on the relationship between cardiac and vascular function. Mech. Ageing Dev. 153, 1–6. https://doi.org/10.1016/j.mad.2015.11.001.

Koren, M.J., Devereux, R.B., Casale, P.N., Savage, D.D., Laragh, J.H., 1991. Relation of left ventricular mass and geometry to morbidity and mortality in uncomplicated

essential hypertension. Ann. Intern. Med. 114 (5), 345–352. https://doi.org/10.7326/0003-4819-114-5-345.
Lakatta, E.G., 2015. So! What's aging? Is cardiovascular aging a disease? J. Mol. Cell. Cardiol. 83, 1–13. https://doi.org/10.1016/j.yjmcc.2015.04.005.
Landi, F., Cesari, M., Calvani, R., Cherubini, A., Di Bari, M., Bejuit, R., Mshid, J., Andrieu, S., Sinclair, A.J., Sieber, C.C., Vellas, B., Topinkova, E., Strandberg, T., Rodriguez-Manas, L., Lattanzio, F., Pahor, M., Roubenoff, R., Cruz-Jentoft, A.J., Bernabei, R., Marzetti, E., SPRINTT Consortium, 2017. The "Sarcopenia and Physical fRailty IN older people: multi-componenT Treatment strategies" (SPRINTT) randomized controlled trial: design and methods. Aging Clin. Exp. Res. 29 (1), 89–100. https://doi.org/10.1007/s40520-016-0715-2.
Lang, R.M., Bierig, M., Devereux, R.B., Flachskampf, F.A., Foster, E., Pellikka, P.A., Picard, M.H., Roman, M.J., Seward, J., Shanewise, J.S., Solomon, S.D., Spencer, K.T., Sutton, M.S., Stewart, W.J., Chamber Quantification Writing Group, American Society of Echocardiography's Guidelines and Standards Committee, European Association of Echocardiography, 2005. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J. Am. Soc. Echocardiogr. 18 (12), 1440–1463. https://doi.org/10.1016/j.echo.2005.10.005.
Lang, R.M., Badano, L.P., Mor-Avi, V., Afilalo, J., Armstrong, A., Ernande, L., Flachskampf, F.A., Foster, E., Goldstein, S.A., Kuznetsova, T., Lancellotti, P., Muraru, D., Picard, M.H., Rietzschel, E.R., Rudski, L., Spencer, K.T., Tsang, W., Voigt, J.U., 2015. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur. Heart J. Cardiovasc. Imaging 16 (3), 233–270. https://doi.org/10.1093/ehjci/jev014.
Lee, T.C., Jin, Z., Homma, S., Nakanishi, K., Elkind, M., Rundek, T., Tugcu, A., Matsumoto, K., Sacco, R.L., Di Tullio, M.R., 2019. Changes in left ventricular mass and geometry in the older adults: role of body mass and central obesity. J. Am. Soc. Echocardiogr. 32 (10), 1318–1325. https://doi.org/10.1016/j.echo.2019.05.018.
Leibowitz, D., Jacobs, J.M., Gilon, D., Lande-Stessman, I., Ein-Mor, E., Stessman, J., 2016. Cardiac structure and function and frailty in subjects aged 85 and 86 years. Am. J. Cardiol. 118 (5), 760–764. https://doi.org/10.1016/j.amjcard.2016.06.005.
Levy, D., Garrison, R.J., Savage, D.D., Kannel, W.B., Castelli, W.P., 1990. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. N. Engl. J. Med. 322 (22), 1561–1566. https://doi.org/10.1056/NEJM199005313222203.
Lieb, W., Gona, P., Larson, M.G., Aragam, J., Zile, M.R., Cheng, S., Benjamin, E.J., Vasan, R.S., 2014. The natural history of left ventricular geometry in the community: clinical correlates and prognostic significance of change in LV geometric pattern. JACC Cardiovasc. Imaging 7 (9), 870–878. https://doi.org/10.1016/j.jcmg.2014.05.008.
Longobucco, Y., Benedetti, C., Tagliaferri, S., Angileri, V.V., Adorni, E., Pessina, M., Zerbinati, L., Cicala, L., Pelà, G., Giacomini, V., Barbolini, M., Lauretani, F., Maggio, M.G., 2019. Proactive interception and care of Frailty and Multimorbidity in older persons: the experience of the European Innovation Partnership on Active and Healthy Ageing and the response of Parma Local Health Trust and Lab through European Projects. Acta Biomed 90 (2), 364–374. https://doi.org/10.23750/abm.v90i2.8419.
Marzetti, E., Cesari, M., Calvani, R., Msihid, J., Tosato, M., Rodriguez-Mañas, L., Lattanzio, F., Cherubini, A., Bejuit, R., Di Bari, M., Maggio, M., Vellas, B., Dantoine, T., Cruz-Jentoft, A.J., Sieber, C.C., Freiberger, E., Skalska, A., Grodzicki, T., Sinclair, A.J., Topinkova, E., SPRINTT Consortium, 2018. The "Sarcopenia and Physical fRailty IN older people: multi-componenT Treatment strategies" (SPRINTT) randomized controlled trial: case finding, screening and characteristics of eligible participants. Exp. Gerontol. 113, 48–57. https://doi.org/10.1016/j.exger.2018.09.017.
Nadruz Jr., W., Kitzman, D., Windham, B.G., Kucharska-Newton, A., Butler, K., Palta, P., Griswold, M.E., Wagenknecht, L.E., Heiss, G., Solomon, S.D., Skali, H., Shah, A.M., 2017. Cardiovascular dysfunction and frailty among older adults in the community: the ARIC study. J. Gerontol. A Biol. Sci. Med. Sci. 72 (7), 958–964. https://doi.org/10.1093/gerona/glw199.
Newman, A.B., Gottdiener, J.S., Mcburnie, M.A., Hirsch, C.H., Kop, W.J., Tracy, R., Walston, J.D., Fried, L.P., Cardiovascular Health Study Research Group, 2001. Associations of subclinical cardiovascular disease with frailty. The journals of gerontology. J. Gerontol. A Biol. Sci. Med. Sci. 56 (3), M158–M166. https://doi.org/10.1093/gerona/56.3.m158.
North, B.J., Sinclair, D.A., 2012. The intersection between aging and cardiovascular disease. Circ. Res. 110 (8), 1097–1108. https://doi.org/10.1161/CIRCRESAHA.111.246876.
Paneni, F., Diaz Cañestro, C., Libby, P., Lüscher, T.F., Camici, G.G., 2017. The Aging Cardiovascular System: understanding it at the cellular and clinical levels. J. Am. Coll. Cardiol. 69 (15), 1952–1967. https://doi.org/10.1016/j.jacc.2017.01.064.
Pelà, G., Bruschi, G., Cavatorta, A., Manca, C., Cabassi, A., Borghetti, A., 2001. Doppler tissue echocardiography: myocardial wall motion velocities in essential hypertension. Eur. J. Echocardiogr. 2 (2), 108–117. https://doi.org/10.1053/euje.2000.0057.
Pelà, G., Bruschi, G., Montagna, L., Manara, M., Manca, C., 2004. Left and right ventricular adaptation assessed by Doppler tissue echocardiography in athletes. J. Am. Soc. Echocardiogr. 17 (3), 205–211. https://doi.org/10.1016/j.echo.2003.12.004.
Pelà, G., Crocamo, A., Li Calzi, M., Gianfreda, M., Gioia, M.I., Visioli, F., Pattoneri, P., Corradi, D., Goldoni, M., Montanari, A., 2016. Sex-related differences in left ventricular structure in early adolescent non-professional athletes. Eur. J. Prev. Cardiol. 23 (7), 777–784. https://doi.org/10.1177/2047487315608826.
Pelà, G., Tagliaferri, S., Perrino, F., Bussolati, G., Longobucco, Y., Zerbinati, L., Adorni, E., Calvani, R., Cesari, M., Cherubini, A., Bernabei, R., Di Bari, M., Landi, F., Marzetti, E., Lauretani, F., Maggio, M., 2021. Interaction of skeletal and left ventricular mass in older adults with low muscle performance. J. Am. Geriatr. Soc. 69 (1), 148–154. https://doi.org/10.1111/jgs.16812.
Ponce, S., Allison, M.A., Swett, K., Cai, J., Desai, A.A., Hurwitz, B.E., Ni, A., Schneiderman, N., Shah, S.J., Spevack, D.M., Talavera, G.A., Rodriguez, C.J., 2018. The associations between anthropometric measurements and left ventricular structure and function: the Echo-SOL Study. Obes. Sci. Pract. 4 (4), 387–395. https://doi.org/10.1002/osp4.279.
De Simone, G., Devereux, R. B., Daniels, S. R., & Meyer, R. A., 1995. Gender differences in left ventricular growth. Hypertension. 26(6 Pt 1), 979–983. doi:https://doi.org/10.1161/01.hyp.26.6.979.
Studenski, S.A., Peters, K.W., Alley, D.E., Cawthon, P.M., McLean, R.R., Harris, T.B., Ferrucci, L., Guralnik, J.M., Fragala, M.S., Kenny, A.M., Kiel, D.P., Kritchevsky, S.B., Shardell, M.D., Dam, T.T., Vassileva, M.T., 2014. The FNIH sarcopenia project: rationale, study description, conference recommendations, and final estimates. J. Gerontol. A Biol. Sci. Med. Sci. 69 (5), 547–558. https://doi.org/10.1093/gerona/glu010.
Toba, A., Kariya, T., Aoyama, R., Ishiyama, T., Tsuboko, Y., Takeda, K., Fujimoto, H., Shimokado, K., Harada, K., 2017. Impact of age on left ventricular geometry and diastolic function in elderly patients with treated hypertension. Blood Press. 26 (5), 264–271. https://doi.org/10.1080/08037051.2017.1306422.
Tyrovolas, S., Panagiotakos, D., Georgousopoulou, E., Chrysohoou, C., Tousoulis, D., Haro, J.M., Pitsavos, C., 2020. Skeletal muscle mass in relation to 10 year cardiovascular disease incidence among middle aged and older adults: the ATTICA study. J. Epidemiol. Community Health 74 (1), 26–31. https://doi.org/10.1136/jech-2019-212268.
Veronese, N., Cereda, E., Stubbs, B., Solmi, M., Luchini, C., Manzato, E., Sergi, G., Manu, P., Harris, T., Fontana, L., Strandberg, T., Amieva, H., Dumurgier, J., Elbaz, A., Tzourio, C., Eicholzer, M., Rohrmann, S., Moretti, C., D'Ascenzo, F., Quadri, G., Correll, C.U., 2017. Risk of cardiovascular disease morbidity and mortality in frail and pre-frail older adults: results from a meta-analysis and exploratory meta-regression analysis. Ageing Res. Rev. 35, 63–73. https://doi.org/10.1016/j.arr.2017.01.003.
Wareham, N.J., Jakes, R.W., Rennie, K.L., Mitchell, J., Hennings, S., Day, N.E., 2002. Validity and repeatability of the EPIC-Norfolk Physical Activity Questionnaire. Int. J. Epidemiol. 31 (1), 168–174. https://doi.org/10.1093/ije/31.1.168.
Williams, B., Mancia, G., Spiering, W., Agabiti Rosei, E., Azizi, M., Burnier, M., Clement, D., Coca, A., De Simone, G., Dominiczak, A., Kahan, T., Mahfoud, F., Redon, J., Ruilope, L., Zanchetti, A., Kerins, M., Kjeldsen, S., Kreutz, R., Laurent, S., Lip, G., List of authors/Task Force members, 2018. 2018 Practice Guidelines for the management of arterial hypertension of the European Society of Hypertension and the European Society of Cardiology: ESH/ESC Task Force for the Management of Arterial Hypertension. J. Hypertens. 36 (12), 2284–2309. https://doi.org/10.1097/HJH.0000000000001961.