Determinants of cardiac structure in frail and sarcopenic elderly adults

Experimental Gerontology

Determinants of cardiac structure in frail and sarcopenic elderly adults

--Manuscript Draft--

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Abstract:	Background: Cardiac structure and function change with age. The higher prevalence of left ventricular hypertrophy (LVH) with concentric remodelling 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±39g/m 2 ; F=104±26g/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 (b=1.51±0.31, p=0.0005), BSA (b=165.9±41.4, p=0.0001), while less powerful determinants were 24h, 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.
Suggested Reviewers:	Antonello Ganau, Prof. University of Sassari: Universita degli Studi di Sassari antonello.ganau@uniss.it expertise on left ventricular hypertrophy
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Response to Reviewers:	Point-by-point replay to the Editor and Reviewers comments Manuscript Number: EXG-D-21-00154 Title: Determinants of cardiac structure in frail and sarcopenic elderly adults Christiaan Leeuwenburgh Editor Experimental Gerontology I have completed my evaluation of your manuscript. The reviewers recommend reconsideration of your manuscript following minor revision and modification. I invite you to resubmit your manuscript after addressing the comments below. Please resubmit your revised manuscript by Apr 05, 2021. When revising your manuscript, please consider all issues mentioned in the reviewers' comments carefully: please outline every change made in response to their comments and provide suitable rebuttals for any comments not addressed. Please note that your revised submission may need to be re-reviewed. Response: Thank you for the comments. We carefully revised the manuscript according to Reviewers' suggestions. The document titled "EXG-D-21-00154 R1_Track Changes" contains minor changes according to reviewers' suggestions; the one titled "EXG-D-21-00154_R1_Clean" is the final version. Reviewer #1: This distinguished group of researchers investigated cardiac characteristics and determinants of left ventricular mass (LVM) in older patients with sarcopenia. Authors found that older sarcopenic and physically frail patients showed left ventricular hypertrophy (LVH) with a tendency towards concentric geometry. The main determinant of left ventricular mass was systolic blood pressure, highlighting the key

role that hemodynamic condition plays in determining LVH in this population.
The manuscript is interesting, well written, concise. Statistical analysis was rigorously conducted. Data collecting was accurate. References are updated. No major issues.

Response:
Thanks to the Reviewer for your appreciation of our manuscript.
Minor comments:
Authors documented the association between systolic blood pressure and LVH in frail sarcopenic elderly patients.
Seventy percent of study population had hypertension, 12% had CAD and 3% had valve disease. Since a significant association between natriuretic peptides and LV remodeling has been previously described (also in older population) [i.e. PMID: 16874155; PMID: 16951263], are natriuretic peptide data available for adjusting statistical models? If not, it should be briefly discussed for research agenda.

Response:
We thank the reviewer for citing the two important contributions which evaluated, both in adult and older patients, the effects of physical exercise on resting plasma of NT-pro-BNP and left ventricular remodeling after myocardial infarction and moderate left ventricular dysfunction demonstrating a decrease of this hormone and a significant increase in maximal and in sub-maximal exercise parameters and in work efficiency and an improvement of left ventricular filling.
Data from the present manuscript come from CardioSprintt Study, an ancillary study of of the Sarcopenia and Physical fRailty IN older people: multi-componenT Treatment strategies (SPRINT-T) project, a randomized control trial conducted in frail, sarcopenic older subjects aged 70 years and older, 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 (Aging Clin Exp Res. 2017;29(1):89-100. doi:10.1007/s40520-016-0715-2). During the 2-year study we collected blood samples and therefore, based on your suggestion, we could evaluate the changes in BNP induced by the exercise protocol in the prospective study.

A significant interaction between 25(OH)D and hypertension on the risk of LV hypertrophy have been previously reported in a normative aging population from BLSA [PMID: 23061475]. In addition, vitamin D deficiency is associated with increased arterial stiffness per se correlated to LV dysfunction and remodeling. Vitamin d play a key role in sarcopenia management too. Are vitamin D data available for adjusting statistical models? If not, it should be briefly discussed for research agenda.

Response:
Vitamin D levels are available for our subjects but we could not report any laboratory data in the present paper because of the actual embargo regarding the current use of biomarkers in ancillary studies of SPRINTT. This issue will be part of the research agenda in the next future.
After analyzing the current literature on this topic, we observed conflicting data on the relationship between Vitamin D and LVM. Some studies describe a positive relationship between Vitamin D and LV thickness (e.g. Ameri et al., 2013; PMID: 23061475), while others found that low levels of Vitamin D are associated with higher blood pressure and a higher rate of hypertension, which in turn may cause an increase of LVM (e.g. Witham et al., 2014; PMID: 24420547). Thus, controversial opinions are still present and further studies may clarify this specific issue.

Are data on Calcium Channel Blockers available? What about diuretics?

Response:
We apologize for the omission of these data that we added in the text. Twenty-two % of the participants were on Calcium Channel Blockers and 36% on diuretics. We re-performed the multivariate backward regression analysis including Calcium Channel Blockers and diuretics confirming previous results. We modified Tables 1 and 3 (pages 31, 35) and the text (Abstract, page 3; Methods, page 9; Results pages 10, 13).

Dipping/non dipping profile or morning surge phenomenon/values at ABPM predict LVH?

Response:
We thank the Reviewer for giving us the opportunity to better elucidate this specific issue.
We subdivided our population in dipper, non-dipper and reverse dipper finding they were 34.6% (n=18), 25 (48%) and 9 (17%), respectively. To evaluate whether the dipping/non-dipping profile may predict LVM and LVM/BSA, we tested differences between mean values through the analysis of variance (ANOVA) age- and sex-adjusted, finding no significant effect on both dependent variables (to see the following Table). In this analysis, reverse dipper subjects (n=34, 65.4%) were included in the non-dipper group.
However, data on dipping/non-dipping profile were available only for about 50% of subjects, thus not representing the entire population.
We modified the text in Results section (page 12).
Table
Mean±SDp-value
Dipper (n=18)Non-dipper (n=34)
LVM181.9±62.1195.2±65.90.89 (age-, sex- and BSA-adjusted)
LVM/BSA105.7±33.9112.4±32.60.91 (age- and sex-adjusted)
RWT0.38±0.070.41±0.060.08 (age- and sex-adjusted)

Reviewer #2:
The author evaluated a cardiac structure of frail and sarcopenic elderly patients, and concluded that left ventricular hypertrophy and concentric change was seen among them. The author also stated that the main determinant of structural change was systolic blood pressure.
The paper is of interest but some methodological issue and results have to be checked to conclude the paper. The discussion is somewhat confusing and should be revised.

①Abstract line17　clinical SPB →clinical SBP

Response:
We thank the Reviewer for the opportunity to correct the mistake.

②Page6, line3　ALM is an abbreviation, the definition should be shown.

Response:
We added the definition of ALM.

③Page 6
The estimation of sarcopenia; is there information regarding gait speed and grip strength? If so, it should be stated in the method, results, and table.

Response:
Data on performance status, such as gait speed and hand-grip strength, are available for all subjects enrolled in the study. Gait speed was measured as a subtask of Short Physical Performance Battery (SPPB), which was an inclusion criterion (SPPB score ranging from 3 to 9).
As stated in SPRINTT protocol (Landi et al., 2017; Marzetti et al., 2018), sarcopenia was identified according to FNIH criteria, not basing on those by EWGSOP2. In particular, we measured the appendicular lean mass (ALM) through DXA scan.
In this case, we decided to not report the data because the focus of present manuscript includes determinants of LVM and RWT. However, we plan to analyse functional data of our subjects for an additional paper.

④Page 7 Blood pressure (BP) and heart rate (HR) (OMRON 705 IT) were assessed with three consecutive measurement whose data were averaged.
How was the BP measured? In the clinic by doctor, or in the waiting room, or in other examination room? Were the patients alone or medical staffs were present? Please note.

Response:
Clinical blood pressure was measured by the doctor at the end of the visit to reduce the effects of white coat, in a sitting position, in a comfortable environment where only the subject and the doctor were present in the room. This information is now reported in the Methods Section of the Manuscript (page 7).

⑤Page 8 Relative wall thickness (RWT) was calculated as: (SWT+ PWT)/ EDD
Calculation of relative wall thickness (RWT) defined by the European Society of Cardiology (Lang et al. Eur J echocardiography, 2006) is, 2 x PWTd/LVIDd .

Response:
We agree with the Reviewer that Guidelines recommend the formula 2 x PWTd/LVIDd. However, the formula we used is also accepted in the literature (Am J Cardiol 2011;107:321-324; JACC 2003;41:955-960). We believe that the measurement of the interventricular septum is a reliable parameter that can increase the accuracy of the RWT formula (Pelà et al., International Journal of COPD 2016:11 1015–1022; Pelà et al., Scand J Med Sci Sports 2015: 25: 382–389).

⑥Page 10 The prevalence of hypertension was 70% in both groups
Table 1 shows the prevalence of hypertension and also, the use of β-blockers, ACE-inhibitors, and ARB. Please show the prevalence of patients with antihypertensive use. Why wasn't other antihypertensive (Ca blockers, diuretics, α-blockers) presented in the table? The number was small, or no one had them prescribed?

Response:
We included in Table 1 (page 31) and Table 3 (page 35) and in the text (Abstract, page 3; Methods, page 9; Results pages 10, 13) the required data. Twenty-two % of the participants were on Calcium Channel Blockers and 36% on diuretics and none was on α-blockers. All hypertensive patients were treated with antihypertensive therapy.

⑦Page11 60% of our population had LVH, 26% and 34% with concentric remodelling and eccentric remodeling respectively, 40% had LVM in the normal range, 19% and 21% with normal and concentric geometry respectively without significant differences in the distribution between sexes.
It is mentioned in the text that SWT and PWT were in normal range. Why was there a high prevalence of LVH in this research population? If the LVMI was calculated as:
LV mass /BSA =0.8x(1.04((LVIDd+PWTd+SWTd)3-LVIDd3))+0.6/ BSA, the data of LVM and LVMI is somewhat larger in table2. Please confirm this.

Response:
We confirm the data in Table 2. The Devereux formula, for the assessment of LV mass, includes not only the thickness of the septum and posterior wall but also the end-diastolic diameter. We would like to emphasize that both females and males of our population had mean values of LV wall thickness and diameters very close to the sex-related upper range, as reported by ECHO Guidelines (Lang RM et al. 2015; LV end-diastolic dimension, Men: 50.2+4.1mm; Female: 45.0+3.6mm; LV wall thickness, Men: 0.6-1.0mm, Female: 0.6-0.9mm). This justifies the LVM values that we found, which are slightly higher than upper limit.

I also think that it is better and be more clear to present as: concentric hypertrophy is ○%, eccentric hypertrophy is ○%, concentric remodeling is○%,and normal structure is ○%.

Response:
We included this information in Figure 1rev.

⑧Page 11 48% of subjects had a non-dipper pattern.
This is quite a high percentage, and since non-dipper has a great relation with concentric hypertrophy, univariate analysis of non-dipper and LV mass and RWT should be done.

Response:
We subdivided our population in dipper (n=18, 34.6%), non-dipper (N=25, 48%) and reverse dipper (N=9, 17%) subjects. To evaluate whether the dipping/non-dipping profile may predict LVM and LVM/BSA, we tested differences between mean values through the analysis of variance (ANOVA) age- and sex-adjusted, finding no significant effect on both dependent variables (Table below reported). In this analysis, reverse dipper subjects (n=34, 65.4%) were included in the non-dipper group.
However, data on dipping/non-dipping profile were available only for about 50% of subjects, thus not representing the entire population.
We modified the text in Results section (page 12).
Table
Mean±SDp-value
Dipper (n=18)Non-dipper (n=34)
LVM181.9±62.1195.2±65.90.89 (age-, sex- and BSA-adjusted)
LVM/BSA105.7±33.9112.4±32.60.91 (age- and sex-adjusted)
RWT0.38±0.070.41±0.060.08 (age- and sex-adjusted)

⑨Page 12
Univariate and multivariate analyses was performed. As stated previously, antihypertensive use as a whole instead of each antihypertensive (βblockers, ACEI, ARB) is recommended to see the relation with LVMI or RWT. If not, the reason these three medication was chosen need to be stated.

Response:
We thank the reviewer for her/his suggestion. The univariate model did not show any significant relationship between all medications and LVM and RWT. By performing the multivariate backward regression analysis, which included all antihypertensive medications, we found that calcium channel blockers and diuretics were not significant determinants of LVM. We modified the text (Methods, page 9; Results pages 10, 13) and footnotes of Table 3 (page 35) by adding the two classes of medications to other covariates.

⑩ Page14 LVH is likewise, associated with worse LV systolic and diastolic function.
LVH is not always related to systolic dysfunction. In the Framingham study, with ageing, LV mass increased, with decreasing LV diameter and increasing fractional shortening.

Response:
It is well known that Ejection fraction and Fractional shortening are LV pump indexes influenced not only by myocardial contractility but also by heart rate, preload and afterload. One example is the severe low-flow, low –gradient aortic stenosis wit reduced ejection fraction, a pattern of aortic stenosis in which depressed ejection fraction is due to an excess of after-load.
The technique of Doppler Tissue Echocardiography offers more sensitive indexes of myocardial contraction and relaxation and therefore DTE-derived can be used to detect early target-organ damage. Pathological LVH rather than a physiological one, is associated with the development of myocardial fibrosis, as aging heart, that justifies the early deterioration of LV cardiac function. In hypertensive patients we demonstrated a marked reduction of E' and S myocardial waves. In addition we found a negative association between age and E' wave both in hypertensive and normotensive subjects; age was also positively correlated with high values of tissue A' wave in both group (Pelà et al. 2001).

In the next paragraph, the author states the ageing process. Eccentric and concentric pattern are due to not only age, but volume overload or pressure overload is related.

The author should mention the basic difference between eccentric and concentric structural change.

Response:
We agree with the Reviewer that 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. The different LV remodeling of endurance and power athletes, the first characterized by eccentric geometry and the second by concentric geometry are perfect examples. Endurance exercise is a volume overload while power exercise is a pressure overload for increased vascular resistances.
In hypertensive patients, Ganau et al (Patterns of Left Ventricular Hypertrophy and Geometric Remodeling In Essential Hypertension, JACC 1992;19:1550) demonstrated that each LV remodeling, normal geometry, concentric remodeling, concentric and eccentric remodeling, is related to different hemodynamic profile; in particular concentric remodeling 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 (Circulation Cardiovascular Imaging, 2009;2:191), 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 stiffens and consequent increased systolic pressure, a major determinant of LVM, and diastolic dysfunction, closely LVH- related.
All these considerations are now reported in the Discussion Section of the Manuscript (pages 14,15).

⑪Page 15, second paragraph
Please confirm the results as mentioned before.

Response:
We confirm the results.

⑫Page16, line 20 ABMP→ABPM

Response:
Thank to the Reviewer for the opportunity to correct the mistake.

⑬The author found out that, (in journal of geriatric society,2020) ALM and LVM were positively correlated. If sarcopenia and LVH is both a risk for CVD, why is the result inversed? In the discussion part, the author stated that frail and sarcopenia are related to LVH. Please evaluate the findings and state in the discussion.

Response:
Our data are consistent with Keng BMH et coworkers (J Am Geriatr Soc 2019;67:2568-2573) who recently demonstrated, among a study sample of Asian older adults without cardiovascular disease, that sarcopenic participants (n=88 subjects aged 74) had smaller LV cavity size and mass than not sarcopenic ones, suggesting the presence of cardio-sarcopenia syndrome. We confirmed these results in older individuals using a robust technique of DEXA (instead of bioimpedance) to assess body composition. We are aware that high LVM is traditionally viewed as clinically unfavourable phenomenon and LVH in hypertensive pathology is associated with greater CV risk and poorer prognosis. The higher incidence of CV, mainly coronary LVH-related events, is justified by the imbalance between increased consumption and insufficient O2 intake available for increased demand. Conversely, it should be also underlined the potential role of LVH as a secondary compensatory mechanism adopted for increasing cardiac work. Examples in this regard include the physiological LVH of the athlete, i.e., the athlete's heart or pathological LVH occurring with the hypertensive heart or aortic stenosis. While physiological LVH allows an increase in cardiac output during sports performance, the pathological LVH ensures the maintenance of a normal cardiac throw, despite the increased after-load. Pathological

LVH, in contrast to the physiological one, is associated with both diastolic and systolic dysfunction, which can be highlighted not with conventional functional indices, such as ejection fraction and fractional shortening, but with more sophisticated techniques such as DTE and Strain.
We already provided all this information in the Discussion Section of the paper "Interaction of Skeletal and Left Ventricular Mass in Older Adults with Low Muscle Performance September 2020 Journal of the American Geriatrics Society 69(7) DOI: 10.1111/jgs.16812.

⑭Patients with sarcopenia and frailty tend to have lower blood pressure as they get older, and process of increasing LV mass attenuate. And patients with well controlled blood pressure do not necessarily have LVH. I am concerned about the high prevalence of hypertrophy in this population of age and with ABPM level within normal range. Did they have a long hypertension history?
I would like to hear the author's opinion, and it should be mentioned in the discussion.

Response:
We thank the reviewer for this comment. We confirm that the majority (seventy percent) of our frail population had a long history of hypertension with mean values of systolic and diastolic blood pressure values of 138 and 80, respectively. We are aware that the relationship between hypertension and adverse clinical outcomes in older adults differs from adult population. Several cohort studies in older adults show that relatively low BP increases the risk of mortality, worsens physical and cognitive abilities, augments the risk of falls and delirium (Ravindrarajah R, et al. Systolic blood pressure trajectory, frailty, and all-cause mortality >80 years of age: cohort study using electronic health records. Circulation. 2017;135(24):2357-2368. Sabayan B et al. High blood pressure and resilience to physical and cognitive decline in the oldest old: the Leiden 85-plus Study. J Am Geriatr Soc. 2012;60(11):2014-2019. Streit S, et al. Lower blood pressure during antihypertensive treatment is associated with higher all-cause mortality and accelerated cognitive decline in the oldest-old-data from the Leiden 85-plus Study. Age Ageing. 2018;47(4):545–550). Moreover, recent studies show that frail individuals had a substantially lower (and not higher) BP compared with non-frail older adults, posing the accent on the need of personalized management of high BP in older adults. (Blood pressure in relation to frailty in older adults: A population-based study. Anker D, et al. J Clin Hypertens (Greenwich). 2019. PMID: 31661601).
It is plausible that the process of increasing LVM can be attenuated in this group of individuals. However, given the cross-sectional nature of the study, we have no information on the relationship between the exposure to frailty condition and LVM. This information will be easily and prospectively addressed during the 2 year follow-up period. One additional information, missing in our dataset, and useful to address the reviewer comments is whether hypertension was well or poorly controlled during the years preceding the evaluation.
This important point raised by the reviewer is now reported in the Discussion Section of the Manuscript.

⑮Table3
Please show the 95% CI in the table.

Response:
We added 95%CI in Table 3.

Reviewer #3:
As part of the field of researches on the relationship between aging-related sarcopenia and myocardium, Pelà and coworkers studied 100 frail and sarcopenic adults aged 70 years and over, and without significant heart disease, to investigate the determinants of echocardiographic left ventricular (LV) remodeling. LV mass was positively correlated with sex, height, weight, BSA and BMI, and systolic BP, while no association was found between age, grading of frailty and LVM. Relative wall thickness, a measure di LV concentricity, was significantly related to age. The multivariate analysis confirmed the role of clinical SBP and body size as the most powerful predictors of LVM.
The authors concluded that older persons with sarcopenia and physical frailty had high prevalence of LV hypertrophy and concentric geometry. The main determinants of LVM were body surface area and office SBP, highlighting the key role of afterload in

developing LVH in the elderly.

This is a clear and interesting paper, the data are thorough and well discussed. Yet, I am intrigued by some differences with the work of Keng et al. (J Am Geriatr Soc. 2019; 67: 2568-73). These Authors observed that sarcopenic subjects showed decreases in wall thickness and ventricular mass, and speculated that LV mass reduction may represent myocyte losses in tandem with skeletal muscle loss as a systemic manifestation that extends into key organs such as the heart ('Cardio-Sarcopenia' syndrome). I think Pelà et coworkers should briefly comment about these conflicting data, to increase strength and interest of this paper.

Response:
As already reported in the response 13 to Reviewer 2, our data are consistent with Keng BMH et coworkers (J Am Geriatr Soc 2019;67:2568-2573) who recently demonstrated, among a study sample of Asian older adults without cardiovascular disease, that sarcopenic participants (n=88 subjects aged 74) had smaller LV cavity size and mass than not sarcopenic ones, suggesting the presence of cardio-sarcopenia syndrome. We confirmed these results in older individuals using a robust technique of DEXA (instead of bioimpedance) to assess body composition. We are aware that high LVM is traditionally viewed as clinically unfavourable phenomenon and LVH in hypertensive pathology is associated with greater CV risk and poorer prognosis. The higher incidence of CV, mainly coronary LVH-related events, is justified by the imbalance between increased consumption and insufficient O2 intake available for increased demand. Conversely, it should be also underlined the potential role of LVH as a secondary compensatory mechanism adopted for increasing cardiac work. Examples in this regard include the physiological LVH of the athlete, i.e., the athlete's heart or pathological LVH occurring with the hypertensive heart or aortic stenosis. While physiological LVH allows an increase in cardiac output during sports performance, the pathological LVH ensures the maintenance of a normal cardiac throw, despite the increased after-load. Pathological LVH, in contrast to the physiological one, is associated with both diastolic and systolic dysfunction, which can be highlighted not with conventional functional indices, such as EF and FS, but with more sophisticated techniques such as DTE and Strain.
We already provided all this information in the Discussion Section of the paper: Interaction of Skeletal and Left Ventricular Mass in Older Adults with Low Muscle Performance September 2020 Journal of the American Geriatrics Society 69(7) DOI: 10.1111/jgs.16812.

I have a few comments and suggestions:
1)BMI is an important determinant of LVM and should be included in the multivariate regression model with BSA, or without BSA in a separate model. This can be relevant in a sample of overweight subjects.

Response:
In the multiple regression model, BSA was included instead of BMI because LVM is usually indexed by BSA. BSA and BMI are multicollinear ($r=0.6$, $p<0.0001$), thus it would be not appropriate to include both variables in the same model (Figure).
We agree with the reviewer that normalization of LVM for BSA or for other measures of body size, that are body weight dependent, does not represent the real impact of body size when body composition is severely altered, as it happens in obesity. A surrogate of fat-free mass is body height. In obese patients LVM can be indexed for height 2.7 (LVM/h 2.7) (De Simone et al., Hypertension 2001;38:13-18).

Figure 1

	2)Pages 11 and 15: when LV remodeling are categorized into four groups, the specific reference has to be added, since different classification of LV geometry have been proposed (see Mesa Study), including undetermined eccentric hypertrophy and concentric dilated LVH. Response: We added the specific references in the text (pages 11 and 16). 3)Page 11: LVM was positively correlated to male sex Response: We added “male”. 4)Pages 14 and 15: interpretation of hemodynamic mechanisms of concentric and eccentric remodeling is more complex than just a reduction of LV chamber size due to diastolic dysfunction. In fact, eccentric LVH was found in 34% of females and 30% of males, which is a quite usual finding in hypertensive subjects. More classical mechanisms are likely to play a role, such as volume overload in eccentric LVH, and volume underload in concentric remodeling, associated respectively with normal-to-slightly increased and with elevated total peripheral resistance. Response: We thank the reviewer for asking this important point. We already provided this relevant information in the response to number 10 question to Reviewer 2. “It is well known that Ejection fraction and Fractional shortening are LV pump indexes influenced not only by myocardial contractility but also by heart rate, preload and afterload. One example is the severe low-flow, low –gradient aortic stenosis wit reduced ejection fraction, a pattern of aortic stenosis in which depressed ejection fraction is due to an excess of after-load. The technique of Doppler Tissue Echocardiography offers more sensitive indexes of myocardial contraction and relaxation and therefore DTE-derived can be used to detect early target-organ damage. Pathological LVH rather than a physiological one, is associated with the development of myocardial fibrosis, as aging heart, that justifies the early deterioration of LV cardiac function. In hypertensive patients we demonstrated a marked reduction of E’ and S myocardial waves. In addition we found a negative association between age and E’ wave both in hypertensive and normotensive subjects; age was also positively correlated with high values of tissue A’ wave in both group (Pelà et al., 2001). 5)Table 3: the meaning of β should be explained in footnotes, as well its units of measurements; change sex with male sex, and explain in footnotes how sex was coded. Response: We thank the Reviewer for giving us the opportunity to improve Table 3. We made changes to the Table (page 35), according to her/his suggestion. 6)Table 3 Supplement: male sex and coding Response: We thank the Reviewer for giving us the opportunity to improve Table 3 Supplement. We made changes to the Table (page 40), according to her/his suggestion.

April 5th, 2021

Christiaan Leeuwenburgh
Editor in Chief
Experimental Gerontology

Dear Editor,

Thank you for your evaluation of our manuscript EXG-D-21-00154, titled "**Determinants of cardiac structure in frail and sarcopenic elderly adults"** to the *Special Issue "Cardiovascular Disease and Frailty: Beyond Physical Performance and Cognition"* on *Experimental Gerontology Journal*, as an original article.

We carefully revised our paper according to the reviewers' suggestions and we are now submitting a new version for your kind consideration.

We hope you will find this improved version acceptable for publication in the "*Experimental Gerontology***"** and we thank you very much for your kind assistance.

Sincerely,

Giovanna Pelà MD, PhD

Point-by-point replay to the Editor and Reviewers comments

Manuscript Number: EXG-D-21-00154

Title: Determinants of cardiac structure in frail and sarcopenic elderly adults

Christiaan Leeuwenburgh
Editor
Experimental Gerontology

I have completed my evaluation of your manuscript. The reviewers recommend reconsideration of your manuscript following minor revision and modification. I invite you to resubmit your manuscript after addressing the comments below. Please resubmit your revised manuscript by Apr 05, 2021.
When revising your manuscript, please consider all issues mentioned in the reviewers' comments carefully: please outline every change made in response to their comments and provide suitable rebuttals for any comments not addressed. Please note that your revised submission may need to be re-reviewed.

Response:

Thank you for the comments. We carefully revised the manuscript according to Reviewers' suggestions. The document titled "EXG-D-21-00154 R1_Track Changes" contains minor changes according to reviewers' suggestions; the one titled "EXG-D-21-00154_R1_Clean" is the final version.

Reviewer #1:
This distinguished group of researchers investigated cardiac characteristics and determinants of left ventricular mass (LVM) in older patients with sarcopenia. Authors found that older sarcopenic and physically frail patients showed left ventricular hypertrophy (LVH) with a tendency towards concentric geometry. The main determinant of left ventricular mass was systolic blood pressure, highlighting the key role that hemodynamic condition plays in determining LVH in this population.
The manuscript is interesting, well written, concise. Statistical analysis was rigorously conducted. Data collecting was accurate. References are updated. No major issues.

Response:

Thanks to the Reviewer for your appreciation of our manuscript.

Minor comments:
Authors documented the association between systolic blood pressure and LVH in frail sarcopenic elderly patients.
Seventy percent of study population had hypertension, 12% had CAD and 3% had valve disease. Since a significant association between natriuretic peptides and LV remodeling has been previously described (also in older population) [i.e. PMID: 16874155; PMID: 16951263], are natriuretic peptide data available for adjusting statistical models? If not, it should be briefly discussed for research agenda.

Response:

We thank the reviewer for citing the two important contributions which evaluated, both in adult and older patients, the effects of physical exercise on resting plasma of NT-pro-BNP and left ventricular remodeling after myocardial infarction and moderate left ventricular dysfunction demonstrating a

decrease of this hormone and a significant increase in maximal and in sub-maximal exercise parameters and in work efficiency and an improvement of left ventricular filling.
*Data from the present manuscript come from CardioSprintt Study, an ancillary study of of the **S**arcopenia and **P**hysical f**R**ailty **IN** older people: multi-componen**T** **T**reatment strategies (SPRINT-T) project, a randomized control trial conducted in frail, sarcopenic older subjects aged 70 years and older, 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 (Aging Clin Exp Res. 2017;29(1):89-100. doi:10.1007/s40520-016-0715-2). During the 2-year study we collected blood samples and therefore, based on your suggestion, we could evaluate the changes in BNP induced by the exercise protocol in the prospective study.*

A significant interaction between 25(OH)D and hypertension on the risk of LV hypertrophy have been previously reported in a normative aging population from BLSA [PMID: 23061475]. In addition, vitamin D deficiency is associated with increased arterial stiffness per se correlated to LV dysfunction and remodeling. Vitamin d play a key role in sarcopenia management too. Are vitamin D data available for adjusting statistical models? If not, it should be briefly discussed for research agenda.

Response:

Vitamin D levels are available for our subjects but we could not report any laboratory data in the present paper because of the actual embargo regarding the current use of biomarkers in ancillary studies of SPRINTT. This issue will be part of the research agenda in the next future.
After analyzing the current literature on this topic, we observed conflicting data on the relationship between Vitamin D and LVM. Some studies describe a positive relationship between Vitamin D and LV thickness (e.g. Ameri et al., 2013; PMID: 23061475), while others found that low levels of Vitamin D are associated with higher blood pressure and a higher rate of hypertension, which in turn may cause an increase of LVM (e.g. Witham et al., 2014; PMID: 24420547). Thus, controversial opinions are still present and further studies may clarify this specific issue.

Are data on Calcium Channel Blockers available? What about diuretics?

Response:

We apologize for the omission of these data that we added in the text. Twenty-two % of the participants were on Calcium Channel Blockers and 36% on diuretics. We re-performed the multivariate backward regression analysis including Calcium Channel Blockers and diuretics confirming previous results. We modified Tables 1 and 3 (pages 31, 35) and the text (Abstract, page 3; Methods, page 9; Results pages 10, 13).

Dipping/non dipping profile or morning surge phenomenon/values at ABPM predict LVH?

Response:

We thank the Reviewer for giving us the opportunity to better elucidate this specific issue.
We subdivided our population in dipper, non-dipper and reverse dipper finding they were 34.6% (n=18), 25 (48%) and 9 (17%), respectively. To evaluate whether the dipping/non-dipping profile may predict LVM and LVM/BSA, we tested differences between mean values through the analysis of

variance (ANOVA) age- and sex-adjusted, finding no significant effect on both dependent variables (to see the following Table). In this analysis, reverse dipper subjects (n=34, 65.4%) were included in the non-dipper group.
However, data on dipping/non-dipping profile were available only for about 50% of subjects, thus not representing the entire population.
We modified the text in Results section (page 12).

Table

		Mean±SD	***p-value***
	Dipper (n=18)	*Non-dipper (n=34)*	
LVM	*181.9±62.1*	*195.2±65.9*	*0.89 (age-, sex- and BSA-adjusted)*
LVM/BSA	*105.7±33.9*	*112.4±32.6*	*0.91 (age- and sex-adjusted)*
RWT	*0.38±0.07*	*0.41±0.06*	*0.08 (age- and sex-adjusted)*

Reviewer #2:
The author evaluated a cardiac structure of frail and sarcopenic elderly patients, and concluded that left ventricular hypertrophy and concentric change was seen among them. The author also stated that the main determinant of structural change was systolic blood pressure.
The paper is of interest but some methodological issue and results have to be checked to conclude the paper. The discussion is somewhat confusing and should be revised.

① Abstract line17 clinical SPB →clinical SBP

Response:

We thank the Reviewer for the opportunity to correct the mistake.

② Page6, line3 ALM is an abbreviation, the definition should be shown.

Response:

We added the definition of ALM.

③ Page 6
The estimation of sarcopenia; is there information regarding gait speed and grip strength? If so, it should be stated in the method, results, and table.

Response:

Data on performance status, such as gait speed and hand-grip strength, are available for all subjects enrolled in the study. Gait speed was measured as a subtask of Short Physical Performance Battery (SPPB), which was an inclusion criterion (SPPB score ranging from 3 to 9).

As stated in SPRINTT protocol (Landi et al., 2017; Marzetti et al., 2018), sarcopenia was identified according to FNIH criteria, not basing on those by EWGSOP2. In particular, we measured the appendicular lean mass (ALM) through DXA scan.
In this case, we decided to not report the data because the focus of present manuscript includes determinants of LVM and RWT. However, we plan to analyse functional data of our subjects for an additional paper.

④ Page 7 Blood pressure (BP) and heart rate (HR) (OMRON 705 IT) were assessed with three consecutive measurement whose data were averaged.
How was the BP measured? In the clinic by doctor, or in the waiting room, or in other examination room? Were the patients alone or medical staffs were present? Please note.

Response:

Clinical blood pressure was measured by the doctor at the end of the visit to reduce the effects of white coat, in a sitting position, in a comfortable environment where only the subject and the doctor were present in the room. This information is now reported in the Methods Section of the Manuscript (page 7).

⑤ Page 8 Relative wall thickness (RWT) was calculated as: (SWT+ PWT)/ EDD
Calculation of relative wall thickness (RWT) defined by the European Society of Cardiology (Lang et al. Eur J echocardiography, 2006) is, 2 x PWTd/LVIDd .

Response:

We agree with the Reviewer that Guidelines recommend the formula 2 x PWTd/LVIDd. However, the formula we used is also accepted in the literature (Am J Cardiol 2011;107:321-324; JACC 2003;41:955-960). We believe that the measurement of the interventricular septum is a reliable parameter that can increase the accuracy of the RWT formula (Pelà et al., International Journal of COPD 2016:11 1015–1022; Pelà et al., Scand J Med Sci Sports 2015: 25: 382–389).

⑥ Page 10 The prevalence of hypertension was 70% in both groups
Table 1 shows the prevalence of hypertension and also, the use of β-blockers, ACE-inhibitors, and ARB. Please show the prevalence of patients with antihypertensive use. Why wasn't other antihypertensive (Ca blockers, diuretics, α-blockers) presented in the table? The number was small, or no one had them prescribed?

Response:

We included in Table 1 (page 31) and Table 3 (page 35) and in the text (Abstract, page 3; Methods, page 9; Results pages 10, 13) the required data. Twenty-two % of the participants were on Calcium Channel Blockers and 36% on diuretics and none was on α-blockers. All hypertensive patients were treated with antihypertensive therapy.

⑦ Page11 60% of our population had LVH, 26% and 34% with concentric remodelling and eccentric remodeling respectively, 40% had LVM in the normal range, 19% and 21% with normal and concentric geometry respectively without significant differences in the distribution between sexes.
It is mentioned in the text that SWT and PWT were in normal range. Why was there a high prevalence of LVH in this research population? If the LVMI was calculated as:

LV mass /BSA =0.8x(1.04((LVIDd+PWTd+SWTd)3-LVIDd3))+0.6/ BSA, the data of LVM and LVMI is somewhat larger in table2. Please confirm this.

Response:

We confirm the data in Table 2. The Devereux formula, for the assessment of LV mass, includes not only the thickness of the septum and posterior wall but also the end-diastolic diameter. We would like to emphasize that both females and males of our population had mean values of LV wall thickness and diameters very close to the sex-related upper range, as reported by ECHO Guidelines (Lang RM et al. 2015; LV end-diastolic dimension, Men: 50.2±4.1mm; Female: 45.0±3.6mm; LV wall thickness, Men: 0.6-1.0mm, Female: 0.6-0.9mm). This justifies the LVM values that we found, which are slightly higher than upper limit.

I also think that it is better and be more clear to present as: concentric hypertrophy is ○%, eccentric hypertrophy is ○%, concentric remodeling is○%,and normal structure is ○%.

Response:

We included this information in Figure 1rev.

⑧ Page 11 48% of subjects had a non-dipper pattern.
This is quite a high percentage, and since non-dipper has a great relation with concentric hypertrophy, univariate analysis of non-dipper and LV mass and RWT should be done.

Response:

We subdivided our population in dipper (n=18, 34.6%), non-dipper (N=25, 48%) and reverse dipper (N=9, 17%) subjects. To evaluate whether the dipping/non-dipping profile may predict LVM and LVM/BSA, we tested differences between mean values through the analysis of variance (ANOVA) age- and sex-adjusted, finding no significant effect on both dependent variables (Table below reported). In this analysis, reverse dipper subjects (n=34, 65.4%) were included in the non-dipper group. However, data on dipping/non-dipping profile were available only for about 50% of subjects, thus not representing the entire population.
We modified the text in Results section (page 12).

Table

	Mean±SD		***p-value***
	Dipper (n=18)	*Non-dipper (n=34)*	
LVM	*181.9±62.1*	*195.2±65.9*	*0.89 (age-, sex- and BSA-adjusted)*
LVM/BSA	*105.7±33.9*	*112.4±32.6*	*0.91 (age- and sex-adjusted)*
RWT	*0.38±0.07*	*0.41±0.06*	*0.08 (age- and sex-adjusted)*

⑨ Page 12
Univariate and multivariate analyses was performed. As stated previously, antihypertensive use as a whole instead of each antihypertensive (βblockers, ACEI, ARB) is recommended to see the relation with LVMI or RWT. If not, the reason these three medication was chosen need to be stated.

Response:

We thank the reviewer for her/his suggestion. The univariate model did not show any significant relationship between all medications and LVM and RWT. By performing the multivariate backward regression analysis, which included all antihypertensive medications, we found that calcium channel blockers and diuretics were not significant determinants of LVM. We modified the text (Methods, page 9; Results pages 10, 13) and footnotes of Table 3 (page 35) by adding the two classes of medications to other covariates.

⑩ Page14 LVH is likewise, associated with worse LV systolic and diastolic function.
LVH is not always related to systolic dysfunction. In the Framingham study, with ageing, LV mass increased, with decreasing LV diameter and increasing fractional shortening.

Response:

It is well known that Ejection fraction and Fractional shortening are LV pump indexes influenced not only by myocardial contractility but also by heart rate, preload and afterload. One example is the severe low-flow, low –gradient aortic stenosis wit reduced ejection fraction, a pattern of aortic stenosis in which depressed ejection fraction is due to an excess of after-load.
The technique of Doppler Tissue Echocardiography offers more sensitive indexes of myocardial contraction and relaxation and therefore DTE-derived can be used to detect early target-organ damage. Pathological LVH rather than a physiological one, is associated with the development of myocardial fibrosis, as aging heart, that justifies the early deterioration of LV cardiac function. In hypertensive patients we demonstrated a marked reduction of E' and S myocardial waves. In addition we found a negative association between age and E' wave both in hypertensive and normotensive subjects; age was also positively correlated with high values of tissue A' wave in both group (Pelà et al. 2001).

In the next paragraph, the author states the ageing process. Eccentric and concentric pattern are due to not only age, but volume overload or pressure overload is related. The author should mention the basic difference between eccentric and concentric structural change.

Response:

We agree with the Reviewer that 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. The different LV remodeling of endurance and power athletes, the first characterized by eccentric geometry and the second by concentric geometry are perfect examples. Endurance exercise is a volume overload while power exercise is a pressure overload for increased vascular resistances.
In hypertensive patients, Ganau et al (Patterns of Left Ventricular Hypertrophy and Geometric Remodeling In Essential Hypertension, JACC 1992;19:1550) demonstrated that each LV remodeling, normal geometry, concentric remodeling, concentric and eccentric remodeling, is related to different hemodynamic profile; in particular concentric remodeling 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 (Circulation Cardiovascular Imaging, 2009;2:191), 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 stiffens and consequent increased systolic pressure, a major determinant of LVM, and diastolic dysfunction, closely LVH- related.
All these considerations are now reported in the Discussion Section of the Manuscript (pages 14,15).

⑪ Page 15, second paragraph
Please confirm the results as mentioned before.

Response:

We confirm the results.

⑫ Page16, line 20 ABMP→ABPM

Response:

Thank to the Reviewer for the opportunity to correct the mistake.

⑬ The author found out that, (in journal of geriatric society,2020) ALM and LVM were positively correlated. If sarcopenia and LVH is both a risk for CVD, why is the result inversed? In the discussion part, the author stated that frail and sarcopenia are related to LVH. Please evaluate the findings and state in the discussion.

Response:

Our data are consistent with Keng BMH et coworkers (J Am Geriatr Soc 2019;67:2568-2573) who recently demonstrated, among a study sample of Asian older adults without cardiovascular disease, that sarcopenic participants (n=88 subjects aged 74) had smaller LV cavity size and mass than not sarcopenic ones, suggesting the presence of cardio-sarcopenia syndrome. We confirmed these results in older individuals using a robust technique of DEXA (instead of bioimpedance) to assess body composition. We are aware that high LVM is traditionally viewed as clinically unfavourable phenomenon and LVH in hypertensive pathology is associated with greater CV risk and poorer prognosis. The higher incidence of CV, mainly coronary LVH-related events, is justified by the imbalance between increased consumption and insufficient O2 intake available for increased demand. Conversely, it should be also underlined the potential role of LVH as a secondary compensatory mechanism adopted for increasing cardiac work. Examples in this regard include the physiological LVH of the athlete, i.e., the athlete's heart or pathological LVH occurring with the hypertensive heart or aortic stenosis. While physiological LVH allows an increase in cardiac output during sports performance, the pathological LVH ensures the maintenance of a normal cardiac throw, despite the increased after-load. Pathological LVH, in contrast to the physiological one, is associated with both diastolic and systolic dysfunction, which can be highlighted not with conventional functional indices, such as ejection fraction and fractional shortening, but with more sophisticated techniques such as DTE and Strain.
We already provided all this information in the Discussion Section of the paper "Interaction of Skeletal and Left Ventricular Mass in Older Adults with Low Muscle Performance September 2020 Journal of the American Geriatrics Society 69(7) DOI: 10.1111/jgs.16812.

⑭Patients with sarcopenia and frailty tend to have lower blood pressure as they get older, and process of increasing LV mass attenuate. And patients with well controlled blood pressure do not necessarily have

LVH. I am concerned about the high prevalence of hypertrophy in this population of age and with ABPM level within normal range. Did they have a long hypertension history?
I would like to hear the author's opinion, and it should be mentioned in the discussion.

Response:

We thank the reviewer for this comment. We confirm that the majority (seventy percent) of our frail population had a long history of hypertension with mean values of systolic and diastolic blood pressure values of 138 and 80, respectively. We are aware that the relationship between hypertension and adverse clinical outcomes in older adults differs from adult population. Several cohort studies in older adults show that relatively low BP increases the risk of mortality, worsens physical and cognitive abilities, augments the risk of falls and delirium (Ravindrarajah R, et al. Systolic blood pressure trajectory, frailty, and all-cause mortality >80 years of age: cohort study using electronic health records. Circulation. 2017;135(24):2357-2368. Sabayan B et al. High blood pressure and resilience to physical and cognitive decline in the oldest old: the Leiden 85-plus Study. J Am Geriatr Soc. 2012;60(11):2014-2019. Streit S, et al. Lower blood pressure during antihypertensive treatment is associated with higher all-cause mortality and accelerated cognitive decline in the oldest-old-data from the Leiden 85-plus Study. Age Ageing. 2018;47(4):545–550). Moreover, recent studies show that frail individuals had a substantially lower (and not higher) BP compared with non-frail older adults, posing the accent on the need of personalized management of high BP in older adults. (Blood pressure in relation to frailty in older adults: A population-based study. Anker D, et al. J Clin Hypertens (Greenwich). 2019. PMID: 31661601).
It is plausible that the process of increasing LVM can be attenuated in this group of individuals. However, given the cross-sectional nature of the study, we have no information on the relationship between the exposure to frailty condition and LVM. This information will be easily and prospectively addressed during the 2 year follow-up period. One additional information, missing in our dataset, and useful to address the reviewer comments is whether hypertension was well or poorly controlled during the years preceding the evaluation.
This important point raised by the reviewer is now reported in the Discussion Section of the Manuscript.

⑮ Table3
Please show the 95% CI in the table.

Response:

We added 95%CI in Table 3.

Reviewer #3:
As part of the field of researches on the relationship between aging-related sarcopenia and myocardium, Pelà and coworkers studied 100 frail and sarcopenic adults aged 70 years and over, and without significant heart disease, to investigate the determinants of echocardiographic left ventricular (LV) remodeling. LV mass was positively correlated with sex, height, weight, BSA and BMI, and systolic BP, while no association was found between age, grading of frailty and LVM. Relative wall thickness, a measure di LV concentricity, was significantly related to age. The multivariate analysis confirmed the role of clinical SBP and body size as the most powerful predictors of LVM.
The authors concluded that older persons with sarcopenia and physical frailty had high prevalence of LV hypertrophy and concentric geometry. The main determinants of LVM were body surface area and office SBP, highlighting the key role of afterload in developing LVH in the elderly.

This is a clear and interesting paper, the data are thorough and well discussed. Yet, I am intrigued by some differences with the work of Keng et al. (J Am Geriatr Soc. 2019; 67: 2568-73). These Authors observed that sarcopenic subjects showed decreases in wall thickness and ventricular mass, and speculated that LV mass reduction may represent myocyte losses in tandem with skeletal muscle loss as a systemic manifestation that extends into key organs such as the heart ('Cardio-Sarcopenia' syndrome). I think Pelà et coworkers should briefly comment about these conflicting data, to increase strength and interest of this paper.

Response:

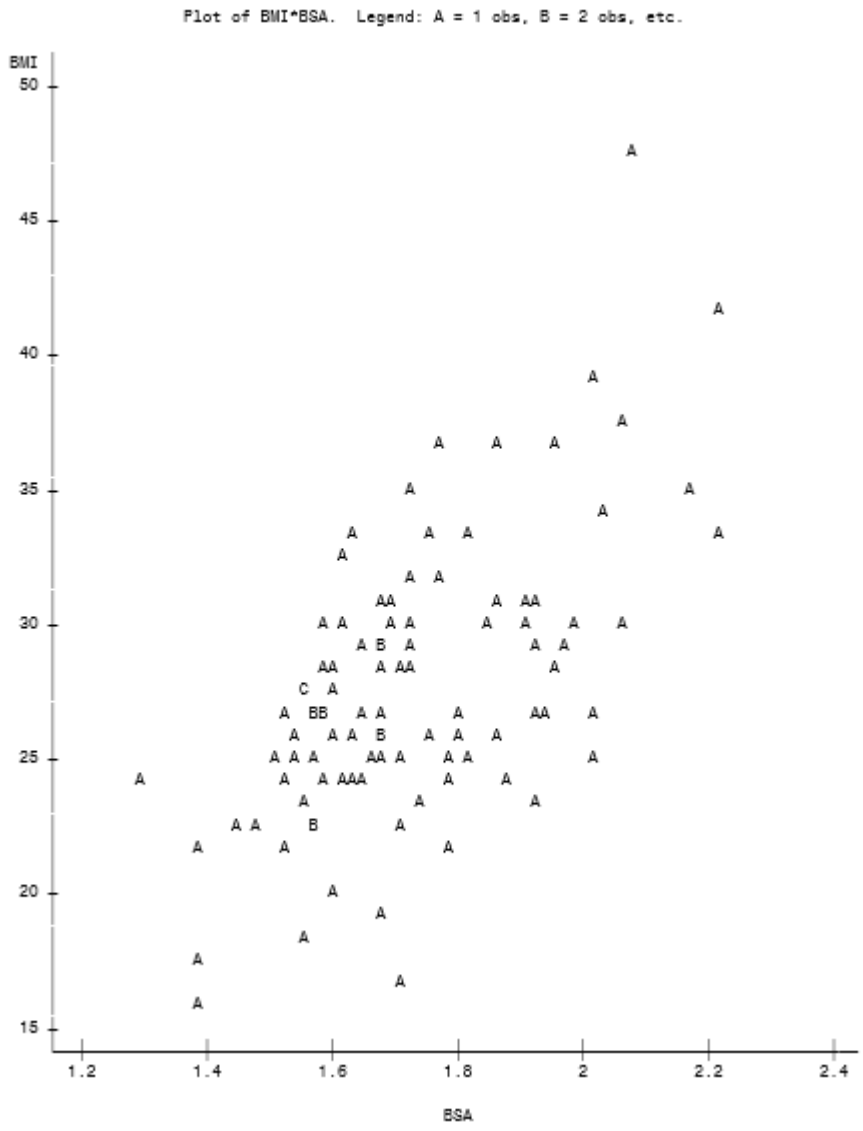
As already reported in the response 13 to Reviewer 2, our data are consistent with Keng BMH et coworkers (J Am Geriatr Soc 2019;67:2568-2573) who recently demonstrated, among a study sample of Asian older adults without cardiovascular disease, that sarcopenic participants (n=88 subjects aged 74) had smaller LV cavity size and mass than not sarcopenic ones, suggesting the presence of cardio-sarcopenia syndrome. We confirmed these results in older individuals using a robust technique of DEXA (instead of bioimpedance) to assess body composition. We are aware that high LVM is traditionally viewed as clinically unfavourable phenomenon and LVH in hypertensive pathology is associated with greater CV risk and poorer prognosis. The higher incidence of CV, mainly coronary LVH-related events, is justified by the imbalance between increased consumption and insufficient O2 intake available for increased demand. Conversely, it should be also underlined the potential role of LVH as a secondary compensatory mechanism adopted for increasing cardiac work. Examples in this regard include the physiological LVH of the athlete, i.e., the athlete's heart or pathological LVH occurring with the hypertensive heart or aortic stenosis. While physiological LVH allows an increase in cardiac output during sports performance, the pathological LVH ensures the maintenance of a normal cardiac throw, despite the increased after-load. Pathological LVH, in contrast to the physiological one, is associated with both diastolic and systolic dysfunction, which can be highlighted not with conventional functional indices, such as EF and FS, but with more sophisticated techniques such as DTE and Strain.
We already provided all this information in the Discussion Section of the paper: Interaction of Skeletal and Left Ventricular Mass in Older Adults with Low Muscle Performance September 2020 Journal of the American Geriatrics Society 69(7) DOI: 10.1111/jgs.16812.

I have a few comments and suggestions:
1) BMI is an important determinant of LVM and should be included in the multivariate regression model with BSA, or without BSA in a separate model. This can be relevant in a sample of overweight subjects.

Response:

In the multiple regression model, BSA was included instead of BMI because LVM is usually indexed by BSA. BSA and BMI are multicollinear (r=0.6, p<0.0001), thus it would be not appropriate to include both variables in the same model (Figure).
We agree with the reviewer that normalization of LVM for BSA or for other measures of body size, that are body weight dependent, does not represent the real impact of body size when body composition is severely altered, as it happens in obesity. A surrogate of fat-free mass is body height. In obese patients LVM can be indexed for height $^{2.7}$ (LVM/h $^{2.7}$) (De Simone et al., Hypertension 2001;38:13-18).

Figure 1



2) Pages 11 and 15: when LV remodeling are categorized into four groups, the specific reference has to be added, since different classification of LV geometry have been proposed (see Mesa Study), including undetermined eccentric hypertrophy and concentric dilated LVH.

Response:

We added the specific references in the text (pages 11 and 16).

3) Page 11: LVM was positively correlated to male sex

Response:

We added "male".

4) Pages 14 and 15: interpretation of hemodynamic mechanisms of concentric and eccentric remodeling is more complex than just a reduction of LV chamber size due to diastolic dysfunction. In fact, eccentric LVH was found in 34% of females and 30% of males, which is a quite usual finding in hypertensive subjects. More classical mechanisms are likely to play a role, such as volume overload in eccentric LVH, and volume underload in concentric remodeling, associated respectively with normal-to-slightly increased and with elevated total peripheral resistance.

Response:

We thank the reviewer for asking this important point. We already provided this relevant information in the response to number 10 question to Reviewer 2.

"It is well known that Ejection fraction and Fractional shortening are LV pump indexes influenced not only by myocardial contractility but also by heart rate, preload and afterload. One example is the severe low-flow, low –gradient aortic stenosis wit reduced ejection fraction, a pattern of aortic stenosis in which depressed ejection fraction is due to an excess of after-load.
The technique of Doppler Tissue Echocardiography offers more sensitive indexes of myocardial contraction and relaxation and therefore DTE-derived can be used to detect early target-organ damage. Pathological LVH rather than a physiological one, is associated with the development of myocardial fibrosis, as aging heart, that justifies the early deterioration of LV cardiac function. In hypertensive patients we demonstrated a marked reduction of E' and S myocardial waves. In addition we found a negative association between age and E' wave both in hypertensive and normotensive subjects; age was also positively correlated with high values of tissue A' wave in both group (Pelà et al., 2001).

5) Table 3: the meaning of β should be explained in footnotes, as well its units of measurements; change sex with male sex, and explain in footnotes how sex was coded.

Response:

We thank the Reviewer for giving us the opportunity to improve Table 3. We made changes to the Table (page 35), according to her/his suggestion.

6) Table 3 Supplement: male sex and coding

Response:

We thank the Reviewer for giving us the opportunity to improve Table 3 Supplement. We made changes to the Table (page 40), according to her/his suggestion.

Manuscript R1 track changes

Determinants of cardiac structure in frail and sarcopenic elderly adults

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All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Declarations of interest: none'.

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Tables: 3

Figures: 1

Supplementary Tables: 3

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Abstract

Background: Cardiac structure and function change with age. The higher prevalence of left ventricular hypertrophy (LVH) with concentric remodelling 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±39g/m^2; F=104±26g/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 24h, 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.

Keywords: Left ventricular geometry; cardiovascular aging; gender differences; sarcopenia; frailty**.**

Highlights:

- Frailty and sarcopenia are cardiovascular risk factors.
- This is the first time a study has investigated the determinants of left ventricular mass in this high-risk population demonstrating the key role of systolic blood pressure.
- These findings could influence clinical care for older persons.

1. Introduction

Changes in the cardiovascular (CV) system occur during aging and include left ventricular (LV) remodelling 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, ageing is associated, both in males and females, with changes in LV geometry, i.e., concentric remodelling, 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 remodelling. 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., 2020; 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 ≥ 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 ageing, 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 (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 ≥ 35mm), prevalence of Q-waves (≥ 2mm in depth in ≥ 2 adjacent leads), presence of ST-segment depression, of inverted T-waves (in ≥ 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 (≤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] x 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, 24h-ABPM, daily-ABPM and nightly ABPM.

Backward analysis was also performed to analyze 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/m² with one third of the sample obese having BMI value >30 Kg/m². 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).

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 remodelling in the Cardiosprintt population (Lang et al., 2005; Lang et al., 2015), 60% of our population had LVH, 26% and 34% with concentric remodelling and eccentric remodelling respectively, 40% had LVM in the normal range, 19% and 21% with normal and concentric geometry respectively without significant differences in the distribution between sexes (Figure 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 24h 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 ($r=0.27$; $p<0.05$), whilst no correlation was found with daily and 24 hours 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 24h-, 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), whilst 24h, 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-hours 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, $p=0.010$ 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 remodelling.

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 5,004 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 and colleagues (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 remodelling) (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.

Disclosures

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).

Author contributions: 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.

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Figure legend

Figure 1. Distribution of left ventricular remodelling in Cardiosprintt population.

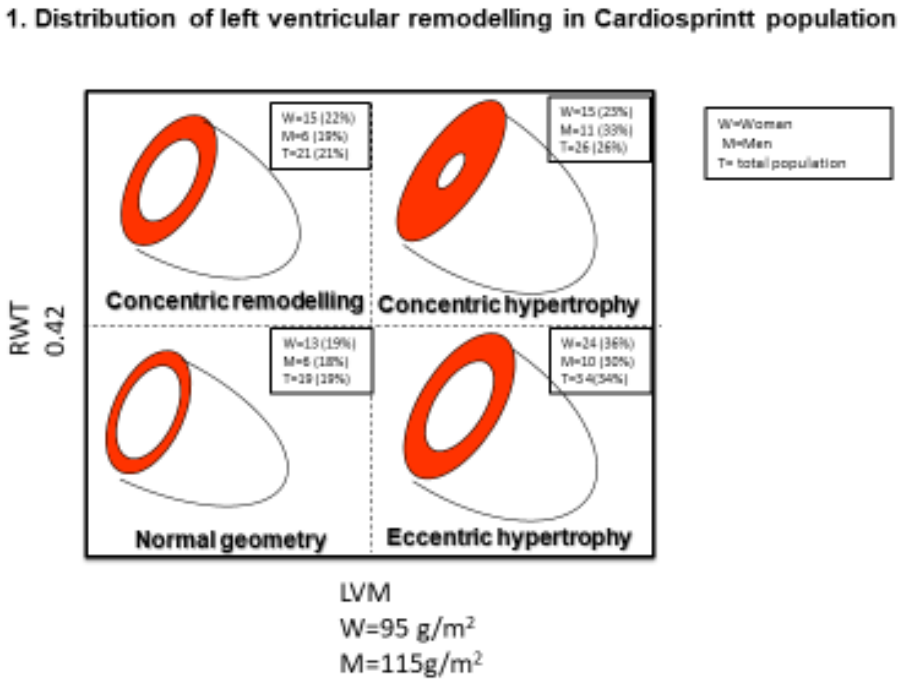

Table 1. Characteristics of CARDIO-SPRINTT population (N=100).

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 (mmHg)	138 ± 18	138 ± 17	140 ± 20	0.46
DBP (mmHg)	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 .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.

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/sec)	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/sec)	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/sec)	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/sec)	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/sec)	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/sec)	11.6 ± 2.9	11.3 ± 2.9	12.0 ± 3.0	ns
DTE A'tvi (cm/sec)	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.

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 (mmHg)	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]
	24h SBP (mmHg)	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 (mmHg	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 (mmHg)	1.61 ± 0.5	0.004	[0.5; 7.5]

Footnotes: 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 24h BP (Model 2), daily SBP (Model 3) and nightly SBP (Model 4).

Supplementary Table 1.

Physical activity intensity in different periods of life.

PA	%
PA from 20 to 40 years old	
Level 1	11
Level 2	36
Level 3	32
Level 4	5
Level 5	13
Level 6	2
PA from 40 to 60 years old	
Level 1	13
Level 2	47
Level 3	27
Level 4	4
Level 5	7
Level 6	1
PA in the last year	
Level 1	59
Level 2	34
Level 3	6
Level 4	-
Level 5	-

Supplementary Table 2.

Ambulatory blood pressure monitoring (ABPM) 24 hours data of 52 patients.

Parameters ABPM	*Tot*	*(n 52)*	*Men*	*(n 18)*	*Women*	*(n34)*	*p*
***SBP 24h** (mmHg)*	*128.62*	*±12.59*	*130.82*	*±15.91*	*128.02*	*±10.48*	*0.35*
***DBP 24h** (mmHg)*	*68.52*	*±6.37*	*70.29*	*±7.95*	*67.73*	*±5.42*	*0.64*
***MAP 24h** (mmHg)*	*88.42*	*±7.19*	*90.41*	*±9.46*	*87.64*	*±5.67*	*0.23*
***HR 24h** (bpm)*	*69.34*	*±9.04*	*66.76*	*±7.39*	*70.26*	*±9.52*	*0.73*
***Daily SBP** (mmHg)*	*131.42*	*±12.41*	*132.94*	*±15.13*	*131.14*	*±10.85*	*0.24*
***Daily DBP** (mmHg)*	*71.32*	*±6.52*	*72.82*	*±8.11*	*70.64*	*±5.66*	*0.25*
***Daily MAP** (mmHg)*	*90.83*	*±8.59*	*92.22*	*±9.40*	*90.08*	*±8.18*	*0.74*
***Daily HR** (bpm)*	*73.18*	*±11.92*	*69.52*	*±7.81*	*73.05*	*±9.60*	*0.23*
***Nightly SBP** (mmHg)*	*123.21*	*±14.87*	*127.06*	*±19.43*	*121.97*	*±11.98*	*0.77*
***Nightly DBP** (mmHg)*	*62.88*	*±7.08*	*65.64*	*±8.38*	*61.61*	*±6.12*	*0.34*
***Nightly MAP** (mmHg)*	*82.90*	*±8.52*	*85.33*	*±11.12*	*81.62*	*±6.57*	*0.66*
***Nightly HR** (bpm)*	*64.26*	*±9.62*	*62.17*	*±8.28*	*64.97*	*±10.14*	*0.22*
SD SBP 24 h	*16.15*	*±3.18*	*16.88*	*±3.74*	*16.24*	*±2.89*	*0.74*
SD DBP 24h	*11.02*	*±2.31*	*10.44*	*±2.15*	*11.32*	*±2.36*	*0.23*
SD daily SBP	*16.10*	*±3.36*	*16.11*	*±4.25*	*16.09*	*±2.84*	*0.77*
SD daily DBP	*10.81*	*±2.55*	*10.22*	*±2.39*	*11.12*	*±2.61*	*0.34*
SD nightly SBP	*13.00*	*±4.09*	*12.22*	*±4.02*	*13.41*	*±4.13*	*0.67*
SD nightly DBP	*8.40*	*±2.83*	*7.83*	*±2.60*	*8.71*	*±2.94*	*0.34*

ABPM: ambulatory blood pressure monitoring, SD: standard deviation, DBP: diastolic blood pressure, HR: heart rate, MAP: mean arterial pressure, SBP: systolic blood pressure.

Supplementary Table 3. Factors significantly related to LVM in the whole population.

Variable category	Variable	Pearson's r value	p value
Clinical variables	Sex	0.51	<0.0001
	Height	0.43	<0.001
	Weight	0.42	<0.001
	BMI	0.19	0.05
	BSA	0.52	<0.001
	Clinical SBP	0.24	0.01
	HR	-0.16	0.05
Echo variables	FS	-0.33	<0.001
	CO	0.54	<0.0001
	EF	-0.59	<0.0001
	S pv	-0.35	<0.001
	S tvi	-0.28	<0.01
	E' pv	-0.20	<0.05
	A' pv	-0.19	<0.05
ECG variables	QRS	0.27	<0.01
	LVH	0.30	<0.01
	QTc	0.29	<0.01
	Under ST	0.43	<0.01
Blood pressure variables	Nightly SBP	0.30	<0.05

	Daily SD SBP	0.27	<0.05

Footnotes: A', end-diastolic myocardial wave; BMI, body mass index; BSA, body surface area; CO, cardiac output; E', proto-diastolic myocardial wave; EF, ejection fraction; FS, fractional shortening; HR, heart rate; LVH, ECG-based left ventricular hypertrophy; LVM, left ventricular mass; pv, peak velocity; QRS, QRS duration; QTc, corrected QT-interval; S, systolic myocardial wave; SD, standard deviation of BP data; SBP, systolic blood pressure; tvi, time velocity integral. Sex was coded as it follows: male=1, female=2.