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FULL RESEARCH PAPER
Imaging

Left ventricular volume as a predictor of exercise capacity and functional independence in individuals with normal ejection fraction

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Aims Low cardiorespiratory fitness (CRF) is associated with functional disability, heart failure, and mortality. Left ventricular (LV) end-diastolic volume (LVEDV) has been linked with CRF, but its utility as a diagnostic marker of low CRF has not been tested.

Methods and results This multi-centre international cohort examined the relationship between LV size on echocardiography and CRF [peak oxygen uptake (peak VO_2) from cardiopulmonary exercise testing] in individuals with LV ejection fraction ≥50%. Absolute and body surface area–indexed LVEDV (LVEDVi) were tested as predictors of low CRF and functional disability (peak VO_2 <1100 mL/min or <18 mL/kg/min) and compared against candidate measures of cardiac structure and function. A total of 2876 individuals (309 endurance athletes, 251 healthy non-athletes, 1969 individuals with unexplained dyspnoea, and 347 individuals with heart failure with preserved ejection fraction) were included. For the entire cohort, LVEDV had the strongest univariable association with peak VO_2 [$R^2 = 0.45$, standardized (std) $\beta = 0.67$, $P < 0.001$] and remained the strongest independent predictor of peak VO_2 after adjusting for age, sex, and body mass index (std $\beta = 0.30$, $P < 0.001$). Left ventricular end-diastolic volume was better in identifying low CRF than most established echocardiographic measures [LVEDV area under the receiver operating characteristic curve (AUC) 0.72; LVEDVi AUC 0.71], but equivalent to the E/e′ ratio. The probability of achieving a peak VO_2 below the functional independence threshold was highest for smaller ventricular volumes, with LVEDV and LVEDVi of 88 mL and 57 mL/m^2 providing the optimal cut-points, respectively.

Conclusion Small resting ventricular size is associated with a higher probability of low CRF and functional disability. Left ventricular size is the strongest independent echocardiographic predictor of CRF across the health–disease continuum.

Lay summary Our study aimed to examine the relationship between resting echocardiographic measures of left ventricular (LV) size and cardiorespiratory fitness in individuals with normal LV ejection fraction (≥50%) across the health-disease continuum.

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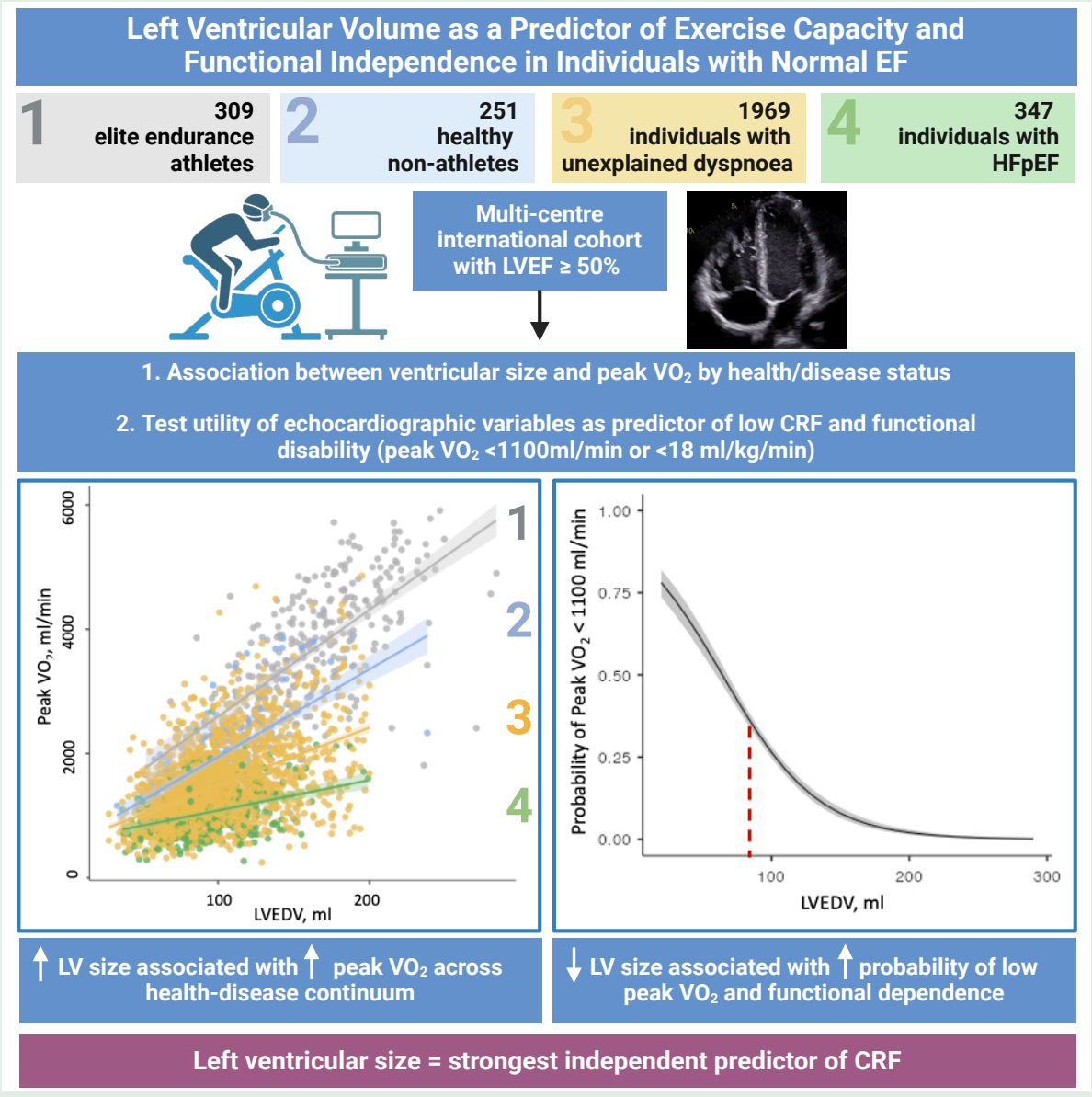
- Small heart chamber size is associated with lower fitness, increased likelihood of functional disability, and may be a cause of breathlessness.
- Regular exercise is likely important in preventing the development of small heart size and low fitness.

Graphical Abstract



Keywords Cardiorespiratory fitness • Left ventricle • Functional status • Echocardiography

Introduction

Cardiorespiratory fitness (CRF) is a robust independent predictor of morbidity and all-cause and cardiovascular disease mortality.[1] Furthermore, low CRF can lead to a loss of functional independence in older age, with every 1 mL/kg/min decline in peak oxygen uptake (peak VO_2) increasing the risk of dependency by 14%.[2] Peak VO_2 declines with ageing secondary to a decline in both maximal oxygen delivery and extraction.[3] Various prior reports have identified physiological thresholds of peak VO_2 required to maintain full and independent living in older age[2,4–6] with lifelong habitual physical activity slowing and adherence to a sedentary lifestyle accelerating declines in peak VO_2 and subsequent disability.[7,8] Indeed, the classic 'Dallas bedrest study' demonstrated that 3 weeks of bed rest leads to a marked reduction in peak VO_2 equivalent to 40 years of ageing[9] and a concomitant decrease in cardiac size similar to the regression of the 'athlete's heart' seen with deconditioning.[9–11] These studies suggest a strong connection among CRF, ventricular size, and physical activity through dynamic cardiac

remodelling and raise the possibility of the use of exercise to modify this relationship. Recently, low CRF and physical inactivity have been linked to smaller ventricular size through reduced cardiac reserve in healthy volunteers, women with breast cancer, and heart failure with preserved ejection fraction (HFpEF).[12–16] This 'small heart' phenotype (previously termed 'the walnut heart') fits Braunwald's textbook definition of heart failure as it is unable to augment stroke volume (SV) and cardiac output during exercise enough to meet the body's metabolic demands of exercise since its ejection fraction at rest is already maximized.[17,18] Recognizing and understanding this clinical phenotype is vital as these individuals are at risk of the health consequences associated with low CRF[1,2] and are also likely to be troubled by dyspnoea on exertion with no traditional explanation.

This study aimed to examine the relationship between resting echocardiographic measures of ventricular size and peak VO_2 in individuals with normal left ventricular ejection fraction (LVEF ≥ 50%) across the health–disease continuum. To extend a theoretical concept to a useful clinical tool, we sought to identify a cut-point of left ventricular (LV) size that may distinguish between a CRF threshold indicative of functional independence and functional disability.

Methods

Study design and population

This international observational study involved participants from medical facilities in Australia (Baker Heart and Diabetes Institute, Melbourne) and Belgium (Jessa Hospital, Hasselt) encompassing the entire CRF spectrum, ranging from patients with exertional dyspnoea to competitive athletes. These included the following: (i) patients with New York Heart Association functional Class II or III symptoms referred to a dedicated dyspnoea clinic assessment who underwent exercise echocardiography with simultaneous cardiopulmonary exercise testing, some of which subsequently met criteria for HFpEF, (ii) ostensibly healthy subjects with no symptoms of heart disease or breathlessness, and (iii) endurance athletes [enrolled participants were current or former endurance-trained athletes (currently or previously competing in endurance sports at national or international level for at least 2 years), and these sports included, but were not limited to, rowing, cycling, and triathlon]. The study protocols have been described in detail elsewhere.[19,20] All participants underwent testing between April 2016 and September 2023. Participants were included in the current analysis if they were >16 years of age and were excluded if they had reduced LVEF <50% or primary or secondary valvular disease graded more than mild severity at rest. Ethical approval was granted by the Human Research Ethics Committees at participating sites.

Clinical information and anthropometry

Clinical information was collected by lifestyle questionnaire or chart review. Resting systolic blood pressure and diastolic blood pressure were measured, and height and body mass were collected to calculate body surface area (BSA) and body mass index (BMI). Participants were classified as having HFpEF based on a HFA-PEFF score ≥5[21] or H_2FPEF score ≥6.[22] Blood samples for N-terminal pro-B-type natriuretic peptide (NT-proBNP) were collected in patients in the cohort referred through the dedicated dyspnoea clinic.

Transthoracic echocardiography

Comprehensive transthoracic echocardiography was performed at rest while the participant was lying in a 45° position on a semi-supine tilt table ergometer for exercise echocardiography or performed in the supine position. Acquisition of resting 2D, Doppler, and tissue Doppler images occurred according to current guidelines[23,24] with LV end-diastolic volume (LVEDV) calculated using the biplane method of discs summation technique and indexed to BSA (LVEDVi).

Cardiopulmonary exercise testing

Cardiopulmonary exercise testing was performed on a cycle ergometer using electrocardiogram, blood pressure, and an expired gas analysis. Participants completed a peak exercise test to quantify measures of CRF on a semi-supine bicycle as part of a simultaneous echocardiography protocol as previously described[25] (patients with New York Heart Association functional Class II or III symptoms referred to a dedicated dyspnoea clinic assessment) or on an upright cycle ergometer (elite endurance athletes and ostensibly healthy non-athlete cohort). An individualized ramp protocol was used with a progressive increase in power output by 5–25 W/min determined by participant age, weight, and physical activity level. Peak VO_2 was defined as a 30 s rolling average of the six highest 5 s oxygen consumption values. Maximum exercise testing was defined as a respiratory exchange ratio >1.05 and/or maximal heart rate >90% predicted and/or maximal perceived exertion. The percentage of predicted exercise capacity (VO_2pred%) was utilized to assess an individual's exercise capacity compared with that predicted based on age, sex, and anthropometry and was derived using the Wasserman/Hansen equation.[26] A peak VO_2 of <18 mL/kg/min or an absolute peak VO_2 <1100 mL/min were considered thresholds for functional disability based on previous studies that assessed task-related metabolic requirements.[4–6]

Statistical analyses

Continuous variables were described using means ± standard deviation or medians [inter-quartile range (IQR)] according to normal distribution status. Categorical variables were expressed as frequencies and percentages. Univariable linear regression was used to assess associations between measures of CRF (absolute peak VO_2 and indexed to body weight) and ventricular chamber size (LVEDV and LVEDVi) by health status and sex. Multivariable linear regression adjusted for age, sex, and BMI was used to analyse the association between LVEDV and absolute peak VO_2, in addition to other commonly utilized echocardiographic measures [left atrial end-systolic volume indexed to BSA (LAVi), LVEF, maximal tricuspid valve velocity at rest (TR Vmax), BSA-indexed LV mass (LVMi), and mitral valve septal E/e′].

To assess the utility of these variables in delineating individuals with low peak VO_2 (using the functional disability threshold definition of <18 mL/kg/min and/or <1100 mL/min) and individuals with higher peak VO_2 (≥18 mL/kg/min and/or ≥1100 mL/min), non-parametric receiver operating characteristic (ROC) curves and area under the ROC curve (AUC) were used. The DeLong test was used to compare AUCs for each measure. The Youden index (J) was used to assess the maximum potential effectiveness of LVEDV and LVEDVi in differentiating participants with lower and higher peak VO_2 (absolute and body weight indexed, respectively), and the cut-point that achieves this maximum was identified. Binomial logistic regression was used to model the predicted probability of peak VO_2 <18 mL/kg/min and peak VO_2 <1100 mL/min based on LV chamber size.

Statistical analyses were performed using STATA v17.0 (STATACorp, College Station, TX, USA), Jamovi v2.4.8 (open-source statistical software, Sydney, Australia), and MedCalc Statistical Software v22.021 (MedCalc Software Ltd, Ostend, Belgium). Statistical significance was accepted at a two-sided $\alpha = 0.05$.

Results

Study cohort

The study included 2876 participants (309 elite endurance athletes, 251 ostensibly healthy non-athletes, 1969 unexplained dyspnoea patients, and 347 HFpEF patients; Supplementary material online, *Figure S1*). The baseline characteristics are summarized in *Table 1*. The median age was 64 years (49% female). The baseline echocardiographic profile and CPET results separated by health/disease status are presented in

Table 1 Baseline characteristics by health/disease status

Characteristics	All participants (*N* = 2876)	Endurance athletes (*N* = 309)	Healthy non-athletes (*N* = 251)	Unexplained dyspnoea (*N* = 1969)	HFpEF (*N* = 347)
Age, years	64 (20.3)	45 (22–60)	54 (45–65)	64 (55–72)	75 (69–79)
Female	1405 (48.9%)	74 (23.9)	151 (60.2)	980 (49.8)	200 (57.6)
BMI, kg/m^2	25.9 (6.0)	23.5 (21.8–25.4)	26.9 (23.7–30.4)	26.0 (23.4–29.3)	27.5 (24.2–31.3)
Current or previous AF	437 (15.2%)	63 (20.4)	1 (0.4)	137 (7.0)	236 (68.0)
Hypertension	1175 (40.9%)	28 (9.1)	72 (28.7)	796 (40.4)	279 (80.4)
Diabetes	372 (12.6%)	2 (0.6)	62 (24.7)	241 (12.2)	67 (17.9)
Hx IHD	320 (11.1%)	13 (4.2)	5 (2.0)	227 (11.5)	75 (21.6)
Smoking history					
Current	125 (4.35%)	2 (0.6)	9 (3.6)	91 (4.6)	23 (6.9)
Ex-smoker	444 (15.4%)	36 (11.7)	56 (22.3)	320 (16.3)	32 (9.2)
Rate-lowering medication	971 (33.7%)	9 (2.9)	7 (2.8)	674 (34.2)	281 (81.0)
ACE/ARB	660 (22.9%)	30 (9.7)	58 (23.1)	435 (22.1)	137 (39.5)
Statin	832 (28.9%)	23(7.4)	62 (24.7)	589 (29.9)	158 (45.5)
NT-proBNP, pg/mL	—	—	—	99 (50–190)	420 (254–830)

Values are median (IQR) or *n* (%).
BMI, body mass index; AF, atrial fibrillation; Hx IHD, history of current/previous ischaemic heart disease; ACE/ARB, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker; rate-lowering medication, beta blocker or calcium channel blocker use.

Supplementary material online, *Table S1*. The baseline characteristics, echocardiographic, and CPET results separated by sex are shown in Supplementary material online, *Tables S2 and S3*. The median LVEF for each health/disease subgroup was between 58 and 61% (see Supplementary material online, *Table S1*). For elite athletes, the median LVEDV and LVEDVi were 159.3 mL (IQR 132.5–186.8 mL) and 83.0 mL/m^2 (IQR 69.0–94.0 mL/m^2), respectively. In comparison, the median LVEDV and LVEDVi were 88.0 mL (IQR 72–113.5 mL) and 47.4 mL/m^2 (38.8–57.6 mL/m^2), respectively for participants with HFpEF. The median absolute peak VO_2 achieved ranged from 980 to 3675 mL/min and indexed to weight ranged from 13.1 to 48.4 mL/kg/min depending on health/disease status.

Association between ventricular size and cardiorespiratory fitness

Figure 1 and Supplementary material online, *Table S4* demonstrate the relationship between absolute LVEDV and peak VO_2 by health/disease category. Elite endurance athletes showed the strongest association between LVEDV and peak VO_2 [$R^2 = 0.47$, standardized (std) $\beta = 0.68$, $P < 0.0001$] with weaker associations and lesser degrees of peak VO_2 variability explained by LVEDV with declining health status. The association between ventricular size and CRF for different indexing methods and by sex is illustrated in *Figure 2A and B* and Supplementary material online, *Table S5*. In females, the relationship between LVEDV and LVEDVi with peak VO_2 was weaker than in males. On multivariable analysis, LVEDV, LAVi, and E/e′ septal remained predictors of peak VO_2 for both sexes (see Supplementary material online, *Table S5*).

Table 2 demonstrates the associations among peak VO_2, clinical variables, and echocardiographic measures for the entire cohort. The most robust relationship among all variables was seen with LVEDV. There was a moderate positive association between LVEDV and peak VO_2 (std $\beta = 0.67$, $P < 0.001$), with only a weak relationship between peak VO_2 and LVEF (std $\beta = -0.16$, $P < 0.001$). Left ventricular end-diastolic volume explained 45% of the variability in peak VO_2 (*Table 2*). Multivariable analysis with adjustment for age, sex, and BMI showed that LVEDV, LAVi, and septal E/e′ remained independent predictors of peak VO_2 ($P < 0.001$). Of these independent predictors, LVEDV was strongest (std $\beta = 0.30$, $P < 0.001$) with weaker contributions for LAVi and E/e′ (std $\beta = 0.18$, $P < 0.001$ and std $\beta = -0.13$, $P < 0.001$, respectively).

On multivariable analysis by health/disease status, LVEDV remained an independent predictor of peak VO_2 for all cohorts except in participants with HFpEF (see Supplementary material online, *Table S4*). Body surface area–indexed LV mass was an independent positive predictor of CRF for elite athletes, and E/e′ septal was a weak but significant predictor among all subpopulations.

Utility of echocardiographic measures to predict cardiorespiratory fitness

Figure 3 and Supplementary material online, *Figures S2 and S3* demonstrate how well echocardiographic measures of resting cardiac structure and function can differentiate between higher and lower CRF. Two different methods were used to define the CRF required for functional independence: an absolute peak VO_2 ≥1100 mL/min (*Figure 3A*; Supplementary material online, *Figure S2*) and indexed peak VO_2 ≥18 mL/kg/min (*Figure 3B*; Supplementary material online, *Figure S3*). Left ventricular size showed to be a strong predictor of CRF status for both peak VO_2 ≥1100 mL/min and peak VO_2 ≥18 mL/kg/min [LVEDV AUC 0.73, 95% confidence interval (CI) 0.71–0.75; LVEDVi AUC 0.71, 95% CI 0.69–0.73, respectively] and was equivalent to E/e′ ratio. Additional measures of cardiac structure and function, including LVEF, had significantly lower predictive abilities.

Cut-point for ventricular size predictive of higher cardiorespiratory fitness and functional independence

The predicted probabilities of achieving peak VO_2 <1100 mL/min and <18 mL/kg/min for the continuous measures of LVEDV and LVEDVi are

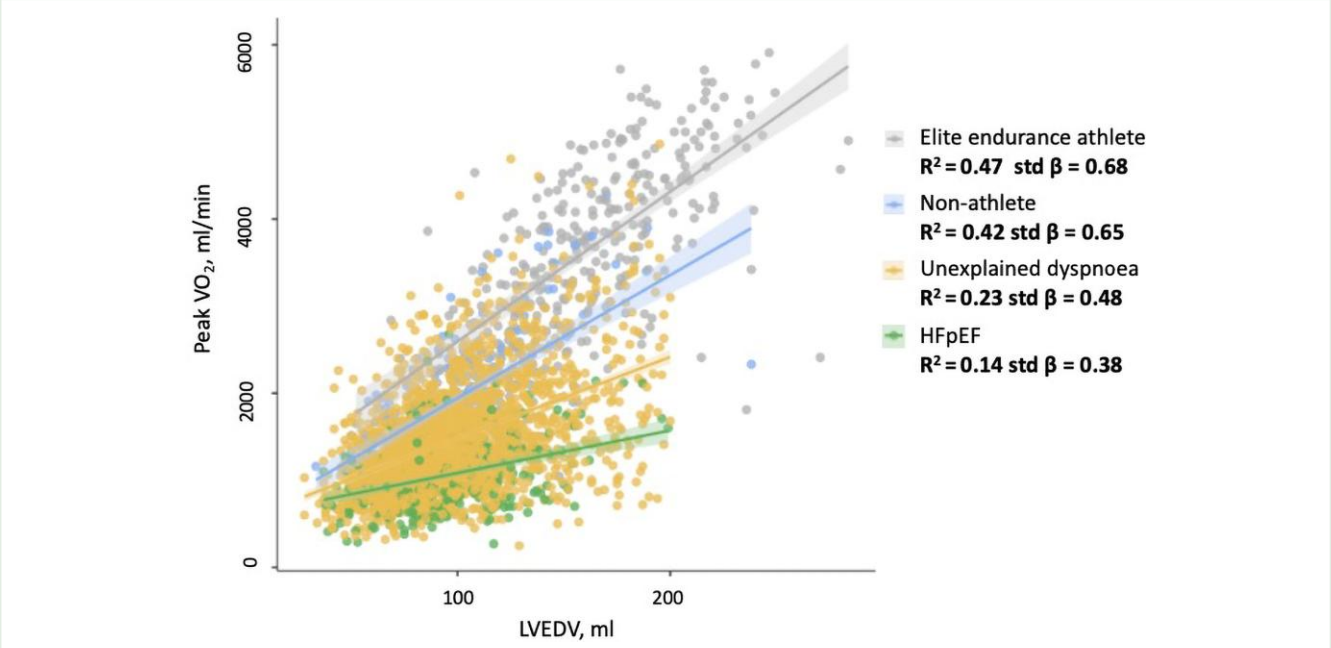


Figure 1 Association between ventricular size and cardiorespiratory fitness by health/disease status. Univariable linear regression with standard errors. Grey circles, elite endurance athletes; blue circles, non-athletes; yellow circles, participants with unexplained dyspnoea; green circles, participants with heart failure with preserved ejection fraction. $P < 0.0001$ for all. LVEDV, left ventricular end-diastolic volume; std β, standardized β.

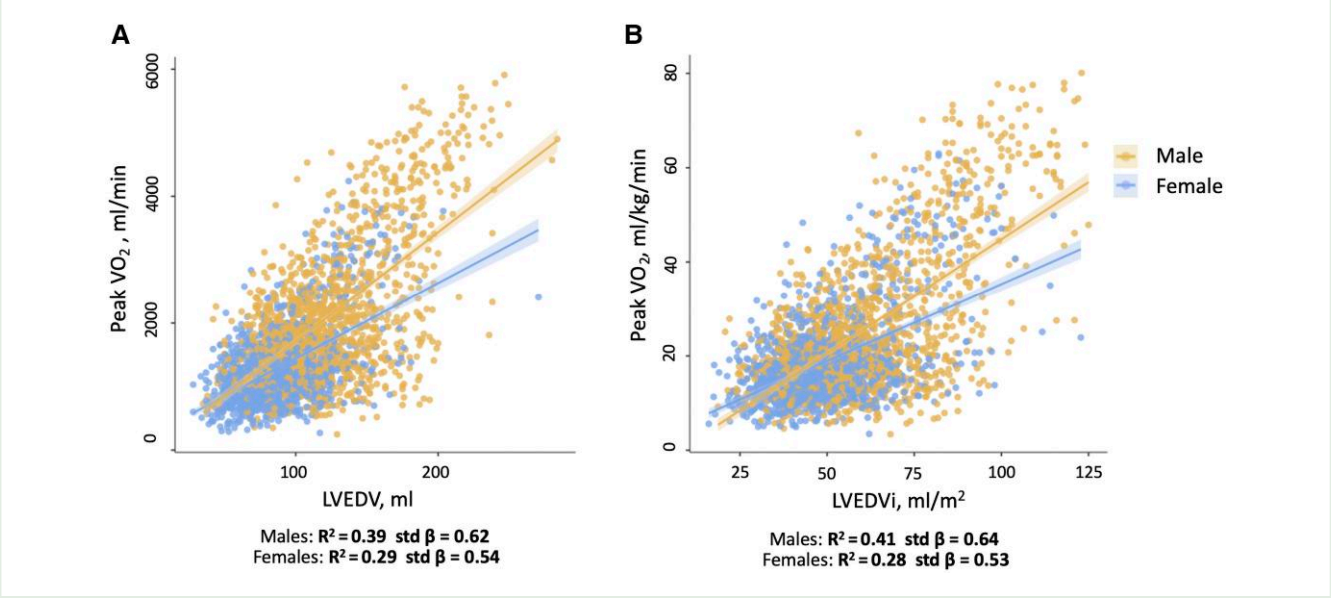


Figure 2 Association between ventricular size and cardiorespiratory fitness by sex. Univariable linear regression by sex showing association between (*A*) left ventricular end-diastolic volume and absolute peak oxygen uptake and (*B*) left ventricular end-diastolic volume indexed to body surface area and peak oxygen uptake indexed to body weight. Yellow circles, male participants; blue circles, female participants. $P < 0.0001$ for both males and females. Std β, standardized β.

illustrated in *Figure 4A* and *B*. The cut-points for ventricular size that optimize the differentiating ability to predict CRF status were 88 mL and 57 mL/m^2 for LVEDV and LVEDVi, respectively. The probability of achieving a peak VO_2 below the threshold required for functional independence was highest for smaller absolute and indexed ventricular volumes. In contrast, larger LV volumes were associated with a lower probability of having a peak VO_2 below the functional independence threshold. Indeed, there was an 83% probability that an individual with an LVEDV >88 mL and a 72% probability that an individual with an LVEDVi > 57 mL/m^2, had a peak VO_2 sufficient to maintain activities of daily living.

Table 2 Associations between clinical and echocardiographic variables and peak volume of oxygen uptake (mL/min)

	Adjusted R^2	Unstandardized β (SE)	Standardized β	*P*-value
Univariable associations				
Age, years	0.41	−37.3 (0.9)	−0.64	<0.001
Sex	0.17	797 (32.7)	0.83	<0.001
BMI, kg/m^2	0.02	−19.2 (2.7)	−0.13	<0.001
LVEDV, mL	0.45	17.1 (0.4)	0.67	<0.001
LVEDVi, mL/m^2	0.38	32.7 (0.8)	0.62	<0.001
LAVi, mL/m^2	0.12	24.6 (1.4)	0.34	<0.001
LVEF, %	0.02	−19.4 (−8.4)	−0.16	<0.001
LVMi, g/m^2	0.03	5.9 (0.7)	0.17	<0.001
E/e′ septal	0.17	−86.9 (3.6)	−0.42	<0.001
Multivariable associations (adjusted for age, sex, and BMI)				
LVEDV, mL	0.70	7.7 (0.4)	0.30	<0.001
LAVi, mL/m^2		12.5 (0.9)	0.18	<0.001
LVEF, %		−0.86 (1.5)	−0.01	0.568
LVMi, g/m^2		0.24 (0.5)	0.01	0.609
E/e′ septal		−29.3 (3.0)	−0.13	<0.001
Multivariable associations (adjusted for age, sex, BMI, and health/disease status)				
LVEDV, mL	0.70	12.2 (0.89)	0.23	<0.001
LAVi, mL/m^2		11.1 (1.0)	0.16	<0.001
LVEF, %		−0.96 (1.5)	−0.01	0.522
LVMi, g/m^2		1.16 (0.48)	0.03	0.015
E/e′ septal		−21.5 (3.1)	−0.10	<0.001

BSA, body surface area; LVEDV, left ventricular end-diastolic volume; LVEDVi, left ventricular end-diastolic volume indexed to BSA; LAVi, left atrial systolic volume indexed to BSA; LVEF, left ventricular ejection fraction; LVMi, left ventricular mass indexed to BSA; E/e′, septal E/e′ ratio.

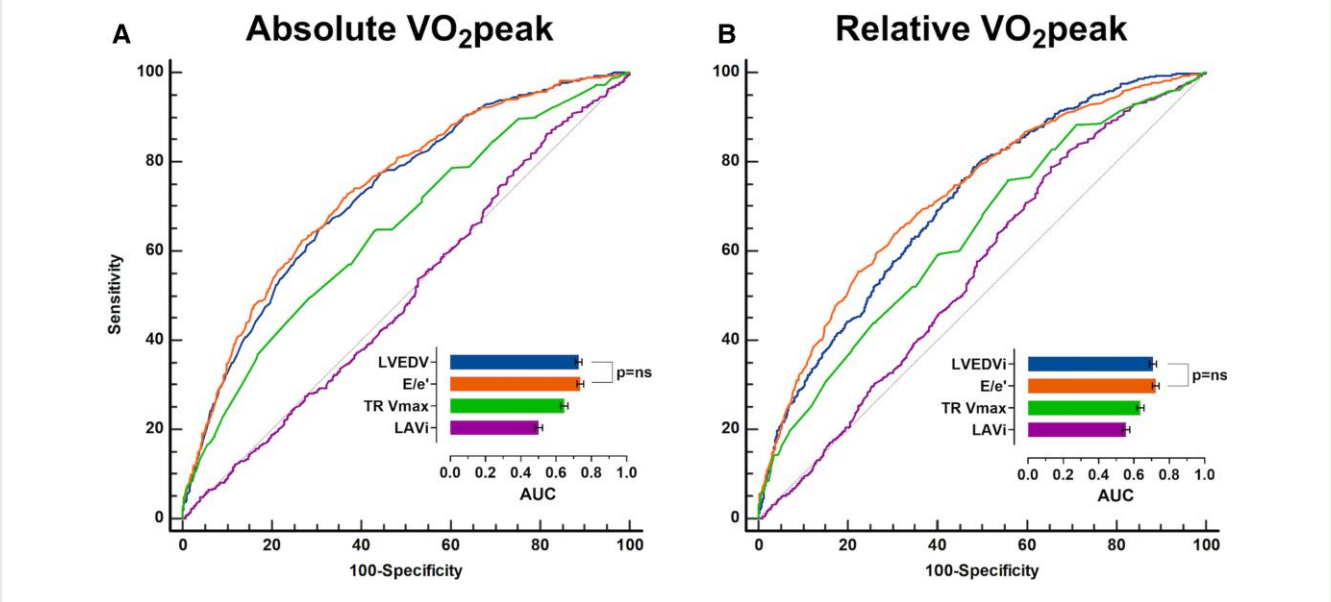


Figure 3 Utility of resting echocardiographic measures in discriminating between cardiorespiratory fitness statuses. Receiver operating characteristic analysis for echocardiographic variables and ability to discriminate between (*A*) absolute peak oxygen uptake <1100 mL/min and ≥1100 mL/min and (*B*) peak oxygen uptake <18 mL/kg/min and ≥18 mL/kg/min. Bar charts demonstrate the area under the receiver operating characteristic curve and 95% confidence interval for each variable. All differences in the area under the receiver operating characteristic curve between variables were significant ($P < 0.0001$), except for septal mitral valve E/e′ ratio and left ventricular end-diastolic volume ($P = 0.55$) and septal mitral valve E/e′ ratio and left ventricular end-diastolic volume indexed to body surface area ($P = 0.30$). LAVi, left atrial systolic volume indexed to body surface area; TR Vmax, maximal tricuspid valve velocity at rest; ns, non-significant.

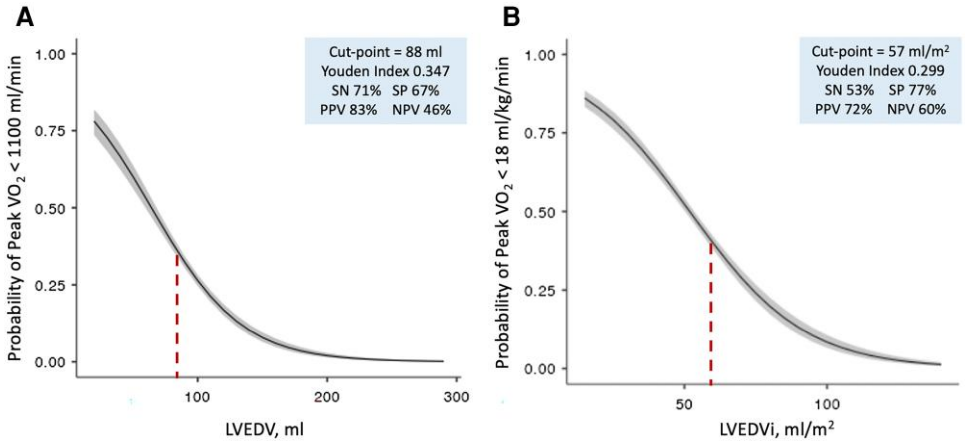


Figure 4 Cut-point for ventricular size associated with cardiorespiratory fitness needed for functional independence. Plot of marginal means with 95% confidence interval illustrating (*A*) the predicted probabilities of peak oxygen uptake <1100 mL/min based on left ventricular end-diastolic volume and (*B*) the probability of peak oxygen uptake <18 mL/kg/min based on left ventricular end-diastolic volume indexed to body surface area. The cut-point (dash line) is identified as the left ventricular end-diastolic volume or left ventricular end-diastolic volume indexed to body surface area measure that maximizes the Youden index. SN, sensitivity; SP, specificity; PPV, positive predictive value; NPV, negative predictive value.

Discussion

Our findings provide further evidence for the association between low cardiac size and poor CRF. In a comprehensive evaluation of peak VO_2 and echocardiographic measures of cardiac structure and function across the health and disease spectrum, (i) LVEDV was identified as the strongest echocardiographic predictor of peak VO_2 and (ii) a cut-off of LVEDV differentiated functional independence and functional disability with greater accuracy than most echocardiographic measures used in routine clinical practice. Taken together, these findings highlight the importance of considering small LV volumes as a possible mechanism of exercise limitation.

The relationship between ventricular size and CRF has traditionally been studied in endurance athletes. However, recent research has shifted towards examining individuals with lower CRF due to the clinical significance of this phenotype.[12,13,15] Our study found that both absolute and LVEDVi are valuable measures for predicting CRF across the entire spectrum of exercise capacity. Specifically, a 10 mL decrement in LVEDV was associated with a ~12% reduction in absolute peak VO_2. In previous studies, every 1-MET (metabolic equivalent of task) decrement in CRF has been associated with a 10–20% lower survival.[1,27] Our findings, therefore, highlight the clinical relevance of resting ventricular size in predicting CRF and, potentially, future health outcomes.

The small heart as a cause of unexplained dyspnoea

Our previous research found that the mechanism linking small LV size and low CRF was likely a lower SV reserve and hypothesized that insufficient physical activity and a lack of cardiac remodelling could be a predisposing factor.[12] We referred to this as the 'small heart' phenotype, in contrast to the athlete's heart. During exercise cardiac magnetic resonance imaging, left ventricular end-systolic volume reserve (the change from rest to exercise) was blunted in smaller hearts than in larger hearts indexed for body size. As a result, the lesser SV in smaller hearts at rest was exacerbated by the lack of SV reserve during exercise, an effective 'dual insult' that drastically limits the ability to increase cardiac output and deliver sufficient oxygen to meet the metabolic demands of daily activities.[12] Compared with the elite endurance athlete with large LV volume that results in superior SV reserve, an individual with a small ventricular volume may be unable to produce sufficient SV required for activities of daily living, such as walking up a flight of stairs, despite having a 'preserved' or 'normal' ejection fraction. In the current study, we determined a threshold for distinguishing individuals with low CRF based on two methods of measuring ventricular size and peak VO_2 (cut-point of 88 mL for LVEDV and 57 mL/m^2 for LVEDVi, *Figure 4*). This highlights the link between smaller ventricular size and failure to achieve a cardiac output required to perform the tasks of daily living through a cardiac limitation. This novel finding suggests that small ventricular size on an otherwise normal resting echocardiogram in patients with unexplained dyspnoea requires the clinician's attention—as they likely have a lesser SV and lower SV reserve as a significant contributing mechanism of their exercise limitation.[20,28]

Ventricular size and cardiorespiratory fitness

Ventricular size had the strongest positive relationship with CRF among other echocardiographic measures of cardiac structure and function, even after adjustment for age, sex, and BMI. Additionally, measures of resting cardiac structure primarily outperformed measures of cardiac function (*Table 2*), with the exception of the E/e′ ratio, reflective of LV filling pressure (*Figure 3*). Overall, LVEDV explained nearly half (45%) of the variation in peak VO_2 (*Table 2*). However, this relationship was attenuated in those with unexplained dyspnoea and HFpEF. Individuals with the smallest LV volumes had the highest probability of achieving a peak VO_2 below that which is required for daily tasks and functional independence (peak VO_2 <1100 mL/min and peak VO_2 <18 mL/kg/min).

Oxygen delivery during exercise is commonly considered the main limiting factor to CRF.[29,30] However, exercise capacity is determined

by both central and peripheral factors, and the degree to which these factors limit exercise differs among individuals. Exercise-induced cardiac remodelling is the hallmark adaptation to exercise in the elite athlete,[31] as demonstrated by the strong association between ventricular size and CRF in this subgroup ($r^2 = 0.47$, std $\beta = 0.68$; *Figure 1*). In contrast, participants with unexplained dyspnoea and HFpEF displayed a less steep but significant correlation of peak VO_2 with LVEDV. The weaker relationships seen in HFpEF compared with athletes may be due to the greater contribution of concomitant peripheral limitations such as reduced oxygen extraction and utilization by skeletal muscle to their reduced peak VO_2.[32] Indeed, ventricular size and its relationship to cardiac output is only one metric involved in CRF, and abnormalities in peripheral factors are known to play a significant role in exercise intolerance in HFpEF.[32,33] Given the differences in the role of ventricular size in determining CRF based on health status, this raises the question of which individuals will benefit from the physiological cardiac benefits of exercise. The relationship between fitness and end-diastolic volumes was present in both males and females. However, females with the same LVEDVi had a lower peak VO_2 than males, possibly due to poorer peripheral oxygen extraction and utilization or additional factors such as chronotropic incompetence (*Figure 2*).

Exercise to prevent functional disability and low cardiorespiratory fitness

Our study emphasizes the valuable link among exercise, ventricular size, and CRF and supports the concept of intervening at a young age to reduce the risk of low CRF and functional dependence. Lifelong exercise can mitigate the cardiac changes of ageing, including the reduction in ventricular size and compliance.[34] However, exercise started mid-late in life fails to induce similar physiological remodelling, suggesting the optimal time to intervene with the purpose of stimulating physiologic cardiac remodelling is early to mid-life.[35,36] Exercise trials in the HFpEF population show discordant results; however, they suggest that endurance training likely does not result in physiological LV cardiac remodelling or improved cardiac compliance, even though modest improvements in peak VO_2 may be achieved via peripheral adaptations, and that there may be evidence of atrial reverse remodelling.[37–39] Our study supports this concept, whereby the healthy and athletic population has a stronger relationship between ventricular size and CRF compared with those already impacted by unexplained dyspnoea and HFpEF—in which case peripheral factors likely contribute greatly to the variability in peak VO_2. Prevention with regular physical activity or exercise training is therefore a key in reducing the chance of disability associated with lower CRF, and this study supports the clinician in explaining to patients with unexplained dyspnoea and small LV volume that exercise may be beneficial. Scrutinizing the need for beta-blockers in patients with the small heart phenotype is also an important therapeutic question, as individuals with small LV volume may have a greater reliance on an increase in heart rate during exercise to compensate for the lack of SV reserve.[40]

Study limitations

This study addressed the role of resting echocardiographic assessment in predicting CRF and, as such, was not designed to assess the peripheral contributions to CRF directly or echocardiographic measures during exercise. Similarly, peak VO_2 is only one determinant of functional independence and focuses on the concept of dyspnoea with activities of daily living. Aside from peak VO_2, functional independence also relies on adequate muscle strength and balance, which were not assessed in this study. All individuals underwent an individualized ramp protocol on cycle ergometer; however, there was no infrastructure to test all athletes in a sport-specific manner. Participants were classified as HFpEF based on H_2PEF and HFA-PEFF scores, given the challenge of non-invasive assessment of HFpEF. E/e′ quantification was limited to only septal mitral annular tissue Doppler imaging. Last, many potential measures of cardiac size could be used to determine associations with peak VO_2, such as SV or whole heart volume. We utilized the two most commonly applied methods in clinical practice for each measure, which were LVEDV and LVEDVi, and absolute peak VO_2 and peak VO_2 indexed to body weight. Importantly, similar results were seen irrespective of the method utilized. Our data do not determine the end-diastolic pressure–volume relationship in patients with the small heart phenotype, and therefore, the contribution of preload and LV stiffness to decreased LV size and its relationship with peak VO_2 remain unknown.

Conclusions

Larger ventricular size is positively associated with CRF in individuals with LVEF $\geq$ 50% across the health–disease continuum. Conversely, small ventricular size is associated with a higher probability of low CRF and failure to achieve the peak VO_2 required for functional independence. Left ventricular size is the strongest independent predictor of CRF compared with other measures of cardiac structure and function. Small ventricular size in the setting of an otherwise 'normal' echocardiogram could be considered a potential mechanism of unexplained dyspnoea.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology*.

Author contribution

S.R., A.L.G., and J.V. contributed to the design, acquisition, analysis, and interpretation of data and drafted the manuscript. S.R., M.M., and J.V. analysed the data. W.L., M.M., L.S., S.F., E.P., K.J., J.S., B.D., R.P., S.M.-F., M.F., Y.B., L.H., M.J.H., and G.C. contributed to collection and interpretation of data and critically revised the manuscript. All authors gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

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Data availability

The data underlying this article may be shared on reasonable request with the corresponding author.

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