ESC European Society of Cardiology

European Heart Journal - Cardiovascular Imaging (2023) **24**, 721–729
https://doi.org/10.1093/ehjci/jead034

ORIGINAL PAPER

Indexing cardiac volumes for peak oxygen uptake to improve differentiation of physiological and pathological remodeling: from elite athletes to heart failure patients

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Received 21 December 2022; revised 11 January 2023; accepted 24 January 2023; online publish-ahead-of-print 19 April 2023

See the editorial comment for this article 'New data to differentiate physiological vs. pathological left ventricular dilatation in athletes', by D. Niederseer *et al.*, https://doi.org/10.1093/ehjci/jead050.

Aims Cardiovascular structures adapt to meet metabolic demands, but current methodology for indexing by body size does not accurately reflect such variations. Therefore, we aimed to investigate how left ventricular end-diastolic volume (LVEDV) and left atrial maximal volume (LAVmax) are associated with absolute (L/min) peak oxygen uptake (VO_{2peak}) and fat-free mass (FFM) compared to body surface area (BSA). We subsequently assessed the impact of indexing by absolute VO_{2peak}, FFM, and BSA to discriminate pathological from physiological remodeling.

Methods and results We used data from 1190 healthy adults to explore relationships for BSA, FFM, and absolute VO_{2peak} with LVEDV and LAVmax by regression and correlation analyses. We then compared these indexing methods for classification to normalcy/pathology in 61 heart failure patients and 71 endurance athletes using the chi-squared and Fisher exact tests and the net reclassification and integrated discrimination indices. Absolute VO_{2peak} correlated strongly with LVEDV, explaining 52% of variance vs. 32% for BSA and 44% for FFM. Indexing LVEDV for VO_{2peak} improved discrimination between heart failure patients and athletes on top of indexing to BSA. Seventeen out of 18 athletes classified to pathology by BSA were reclassified to normalcy by VO_{2peak} indexing ($P < 0.001$), while heart failure patients were reclassified to pathology (39–95%, $P < 0.001$). All indexing methods explained below 20% of the variance in LAVmax in univariate models.

Conclusions Indexing LVEDV to VO_{2peak} improves the ability to differentiate physiological and pathological enlargement. The LVEDV to absolute VO_{2peak} ratio may be a key index in diagnosing heart failure and evaluating the athlete's heart.

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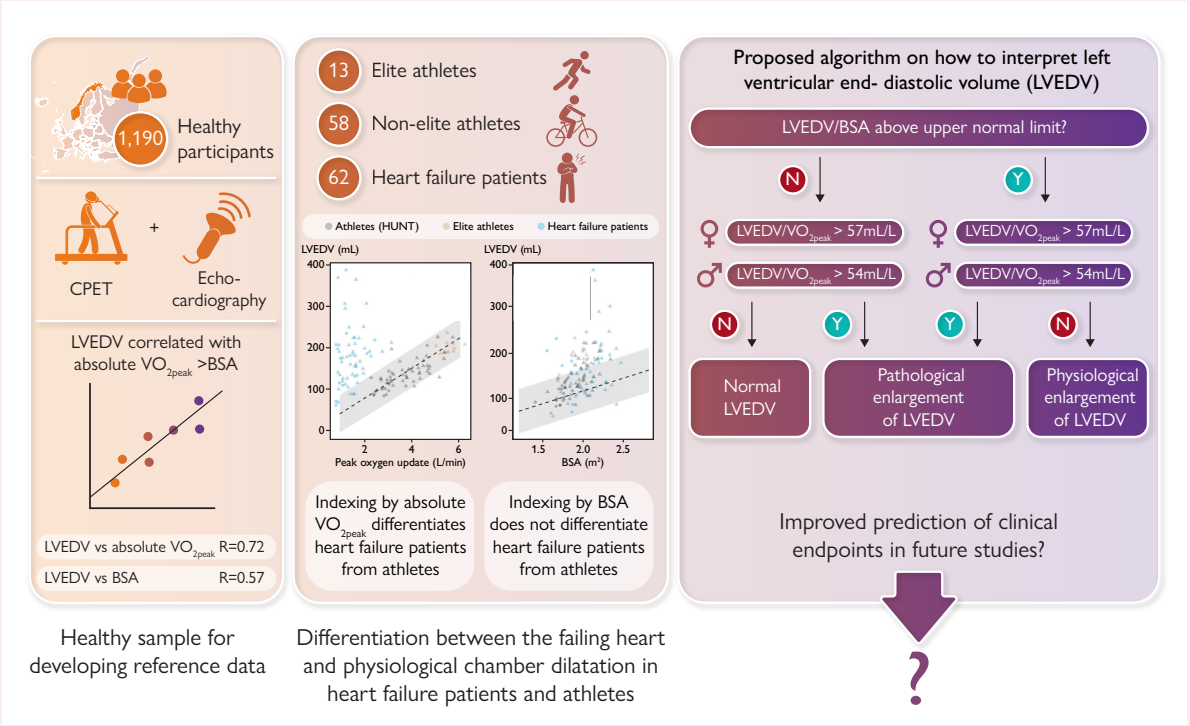
Graphical Abstract



Development of reference ranges for left ventricular end-diastolic volume (LVEDV) by absolute peak oxygen uptake (VO_{2peak}) (left panel), visualization of the impact of differentiation between chamber dilatation due to heart failure and physiological remodeling (middle panel), and impact on interpretation of LVEDV normalcy (right panel). BSA = body surface area; CPET = cardiopulmonary exercise testing.

Keywords scaling • echocardiography • VO_{2max} • body composition • heart failure

Introduction

Cardiovascular structures continuously adapt to meet specific metabolic demands. These demands are related to body size, and thus, cardiovascular structures are commonly indexed to body surface area (BSA).[1] However, ratiometric indexation for one body size measure usually does not remove the dependency of others.[1] It has therefore been argued that cardiovascular structures should be scaled to the amount of metabolically active tissue such as lean body mass or fat-free mass (FFM), or by allometrically indexing of such measures to a scalar exponent.[1] Independent of body size, exercise training leads to improved fitness and enlargement of cardiac chambers, which is a common finding in endurance athletes.[2] The *absolute* (L/min) peak oxygen uptake (VO_{2peak}) reflects the metabolic demands both from body size *and* exercise training status. Thus, considering VO_{2peak} may be a better way to scale cardiovascular structures for interpreting normalcy. The commonly used indexing to BSA often leads to conclusions of athletes having (pathologically) enlarged cardiovascular structures,[2,3] not considering the very different body composition and metabolic stress from exercise training between athletes and persons from the general population. Similarly, BSA does not consider differences in body composition leading to over-correction of body size in obesity that may reduce the sensitivity to detect pathology.[4] Overall, there are reasons to believe that indexing cardiac measures to VO_{2peak} would improve diagnostic accuracy both in athletes, in the general population, and in heart failure patients.

We aimed to compare the relationships of left-sided cardiac chamber volumes with absolute VO_{2peak} and the body size measures BSA and FFM in a healthy sample of the general population recruited from the Trøndelag Health Study (HUNT). We hypothesized that chamber volumes correlate better with absolute VO_{2peak} and FFM than BSA. Secondly, we aimed to investigate how using cut-offs for left atrial (LA) and left ventricular (LV) volumes indexed to VO_{2peak} vs. BSA would affect classification to normalcy or pathology in (i) a subpopulation of endurance athletes and (ii) in heart failure patients, using these groups as proxies of physiological and pathological remodeling.

Methods

The present study was approved by the regional ethical committee (REK) (REK mid-Norway IDs 11276, 13083, and 15409), and all participants provided their written informed consent before participation.

Healthy reference sample for main analyses

The healthy reference sample was based on participants from the fourth wave of the Trøndelag Health Study (HUNT4), where 56 042 (54%) of the county's inhabitants participated,[5] and specifically participants from the HUNT4 Fitness Study (2017–2018, $n = 2448$), a sub-study of HUNT4 (see Supplementary data online for detailed inclusion and exclusion criteria). For this study, participants without a medical history of angina pectoris, myocardial infarction, heart failure, atrial, stroke, chronic obstructive pulmonary disease, use of antihypertensives, and diabetes were selected. Also, participants with LV ejection fraction <50% were excluded, as well as participants with a respiratory exchange ratio <1.0 during cardiopulmonary

exercise testing (CPET). Participants reporting to be actively competing in endurance sports were retained in a separate sample ($n = 58$, see below). After exclusions, including missing data from key variables, 1190 participants were retained in the healthy reference sample.

At the initial visit at HUNT4 baseline, trained health personnel performed clinical examinations and blood sampling for biochemical analyses, and participants filled in questionnaires. Weight was measured wearing light clothes without shoes. Height was measured to the nearest centimetre. Measure of FFM was derived from body composition analysis using bioelectrical impedance (InBody 770, Cerritos, CA, USA). Further details regarding these procedures have been published.[5]

Endurance athletes

HUNT athletes

Participants in the HUNT4 Fitness Study reporting by questionnaires to be actively participating in endurance sports competitions (e.g. running, cross-country skiing, cycling, and swimming) were included in a separate data set ($n = 58$) (see *Supplementary data* online).

Elite athletes

In a separate data collection, 13 elite endurance athletes competing at national, international, and Olympic levels in cross-country skiing ($n = 7$), speed skating ($n = 3$), triathlon ($n = 1$), and cycling ($n = 2$) were invited to undergo echocardiography after performing CPET as a part of their regular follow-up at the Centre for Elite Sports Research in Trondheim.

Heart failure patients

We also used baseline data from a sample of 61 heart failure patients with reduced ($n = 44$), mildly reduced ($n = 12$), or preserved ($n = 5$) ejection fraction from a randomized clinical trial performed by our group aiming to evaluate the effect of telerehabilitation on a primary outcome of improvement in long-term physical activity (the ITISHOPE4HF trial; Implementation of Telerehabilitation In Support of HOme-based Physical Exercise for Heart Failure).[6] Heart failure diagnoses were made according to guidelines, including symptoms or signs of heart failure and reduced or mildly reduced ejection fraction or findings of preserved ejection fraction with diastolic dysfunction.[7]

An overview of the four cohorts is shown in *Figure 1*.

Echocardiography

Transthoracic echocardiography was performed with participants examined in the left lateral decubitus position using a Vivid E95 scanner (GE Ultrasound) with a 4Vc-D matrix transducer for both 2D and 3D imaging. Study-specific protocols aligned to the present recommendations[8] were followed for all image acquisitions and measurements in both the sample from the HUNT study, elite athletes, and the heart failure sample.[6,9] Each recording included at least three cardiac cycles acquired during quiet respiration or breath hold. Two experienced sonographers performed all echocardiographic analyses in the HUNT population, and one cardiologist expert accredited in transthoracic echocardiography by the European Association of Cardiovascular Imaging (EACVI) performed the analyses in the heart failure and elite endurance athlete population. All involved echocardiographic personnel were affiliated with the EACVI-accredited echocardiographic laboratory at St. Olavs Hospital, Trondheim, Norway. For 2D quantification of LA maximal volume (LAVmax), atrial-specific views were obtained aiming to centralize the image plane of the LA and avoid atrial foreshortening. The endocardial border was traced in two- and four-chamber views in end-systole excluding the pulmonary veins and the LA appendage, closing the mitral valve annulus by a straight line. LAVmax was calculated by the method of disc summation (MOD). For 2D quantification of LV end-diastolic volume (LVEDV), two- and four-chamber acquisitions were obtained aiming to avoid foreshortening with sector depth and width adjusted to focus on the LV to reduce errors when tracing the endocardial tissue–blood interface. LV volumes and ejection fraction were calculated using the Simpson's method. Information on acquisition of other echocardiographic measures and data on reproducibility of the other measurements have been published.[9,10]

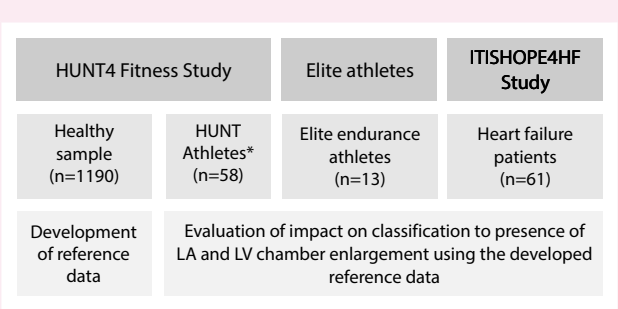


Figure 1 Cohorts included in the present study. *HUNT athletes were identified by questionnaire self-report of actively competing in endurance sports competitions. HUNT = Trondelag Health Study; ITISHOPE4HF = Implementation of Telerehabilitation In Support of HOme-based Physical Exercise for Heart Failure; LA = left atrium; LV = left ventricle.

Cardiopulmonary exercise testing

In the healthy reference sample, CPET was performed by running or walking on a calibrated treadmill after a 10-min warm-up, increasing inclination or speed every minute until voluntary exhaustion. Continuous gas analysis was performed with the Metalyzer (Cortex Biophysik Gmbh, Leipzig, Germany) portable mixing chamber system using Metasoft studio software. Further details regarding CPET have been published.[11] The heart failure patients used an individualized and constant walking speed with inclination increasing every other minute until voluntary exhaustion using the Vyntus CPX system (Erich Jaeger GmbH, Hoechberg, Germany).[6] Using the same Vyntus system, the elite endurance athletes performed CPET after a thorough warm-up using their preferred modality (e.g. cyclists and speed skaters on a stationary bike and cross-country skiers on a roller ski treadmill). The protocol consisted of an incremental exercise test with 1.0 kmt or 25 W increase per minute for the skiers and cyclists, respectively, with individualized starting points. Tests for all three samples were individualized to achieve exhaustion within ~10 min. We defined VO_{2peak} as the highest average oxygen uptake over 30 s. The respiratory exchange ratio was defined as the ratio between exhaled carbon dioxide (L) and oxygen uptake (L) per time unit, and peak oxygen pulse (mL O_2/beat) was calculated as VO_{2peak} (mL/min) divided by peak heart rate (b.p.m.).

Statistical analyses

Descriptive data are represented as means and standard deviations (SD) or counts and percentages. Univariate Pearson's correlations between LAVmax/LVEDV and BSA, FFM, and absolute VO_{2peak} were explored for the total sample and by age groups of <40, 40–60, and >60 years. The correlation coefficients were compared using the method by Hittner *et al.*[12] Linear regression was performed by adding age and sex as covariates and exploring effect modification using two-way interactions in several models, examining model fits by adjusted coefficients of determination (R^2) and through traditional significance testing with the significance level set at $P < 0.05$. We compared classification to normal or enlarged LAVmax and LVEDV indexed to BSA, FFM, and VO_{2peak} based on upper limits of normal (mean + 2SD) from the healthy reference sample for the heart failure patients and athletes using the chi-squared and Fisher exact tests. We investigated discrimination between LVEDV enlargement related to heart failure and athletic remodeling by adding LVEDV indexed to VO_{2peak} on top of LVEDV indexed to BSA using the continuous net reclassification index (NRI) and the integrated discrimination index (IDI).[13] Due to the impact of age and sex on LAVmax we used age (<40, 40–60, and >60 years) and sex-specific reference ranges for assessment of LAVmax normalcy. We did not

have data on FFM from the heart failure patients. Graphically presented prediction intervals are based on linear regression analyses forced through the origin to align their interpretation with reference values (based on ratios between chamber volumes and indexing measure). We also included analyses on peak oxygen pulse planned *post hoc* to explore the impact of considering the age-related decline in peak heart rate on VO_{2peak}. Analyses were performed with R 4.0.5 (www.r-project.org) using the packages *stats*, *cocor*, *ggeffects*, *ggplot2*, *ggpubr*, *gtsummary*, and *predictabel*.

Results

The 1190 included participants from the healthy general population [mean (SD) age of 58 (12) years] had a body mass index of 25.6 (3.4) kg/m^2, an absolute VO_{2peak} of 2.84 (0.83) L/min, and relative VO_{2peak} 37.4 (8.6) mL/kg/min. General characteristics and key CPET and echocardiographic data are shown in *Table 1*.

LV volume in the healthy general population

In univariate models, BSA explained 32% of the variance for LVEDV ($R^2 = 0.32$, $P < 0.001$), FFM explained 44% ($R^2 = 0.44$, $P < 0.001$), whereas absolute VO_{2peak} explained 52% ($R^2 = 0.52$, $P < 0.001$). The univariate Pearson's correlation coefficient for VO_{2peak} vs. LVEDV was significantly higher compared to those for BSA and FFM vs. LVEDV (both $P < 0.001$) (*Table 2*, *Figure 2*). The correlation between LVEDV and VO_{2peak} was stronger than for BSA both for those with a BMI < 25 kg/m^2 (0.74 vs. 0.59, $P < 0.001$) and those with a BMI ≥ 25 kg/m^2 (0.69 vs. 0.55, $P < 0.001$). Multiple linear regression for the relationship between LVEDV and absolute VO_{2peak} showed a significant contribution of sex including effect modification between absolute VO_{2peak} and sex, while age did not significantly influence LVEDV ($P = 0.46$). The best-fit model for LVEDV for absolute VO_{2peak} (including sex and the interaction between absolute VO_{2peak} and sex) did not improve R^2 compared to the univariate model. The best-fit model for FFM (including age and sex and the interaction between the two) explained 50% of the variance, whereas the best model with BSA (including age, sex, and the interaction between age and BSA) explained 46% of variance. Adding BSA and FFM to the model with absolute VO_{2peak} did not increase the explained variance notably. Using peak oxygen pulse (mL O_2/beat) as the explanatory variable gave a slightly higher explained variance of LVEDV compared to VO_{2peak} ($R^2 = 0.53$, $P < 0.001$), with the best-fit model with age and sex explaining 55% of variance. The final models are shown in Supplementary data online, *Table S1*.

LAVmax in the healthy general population

For LAVmax, BSA explained 16% of the variance ($R^2 = 0.16$, $P < 0.001$), FFM explained 17% ($R^2 = 0.17$, $P < 0.001$), and absolute VO_{2peak}

Table 1 General characteristics

Characteristic	HUNT, $n = 1190$	HUNT athletes, $n = 58$	Elite athletes, $n = 13$	Heart failure patients, $n = 61$
Age (years)	58 (12)	54 (12)	23 (5)	68 (11)
Women	691 (58%)	18 (31%)	1 (7.7%)	10 (16%)
Body mass (kg)	76 (13)	74 (12)	77 (8)	85 (23)
BMI (kg/m^2)	25.6 (3.4)	23.8 (2.6)	23.5 (1.5)	27.9 (4.9)
BSA (m^2)	1.88 (0.20)	1.90 (0.19)	1.98 (0.13)	2.02 (0.21)
Fat-free mass (kg)	54 (11)	60 (11)	69 (8)	NA
Systolic BP (mmHg)	128 (18)	124 (18)	124 (9)	121 (20)
Diastolic BP (mmHg)	75 (9)	75 (9)	69 (4)	73 (13)
Resting heart rate (b.p.m.)	65 (10)	58 (12)	55 (11)	70 (13)
Current smoker	41 (3.5%)	0 (0%)	NA	7 (11%)
PA above recommendations	422 (36%)	41 (72%)	NA	NA
Peak oxygen uptake (L/min)	2.84 (0.83)	3.71 (0.89)	5.37 (0.51)	1.51 (0.51)
Peak oxygen uptake (mL/kg/min)	37 (9)	49 (8)	70 (4)	18 (5)
Peak oxygen pulse (mL O_2/beat)	16.4 (4.6)	21.1 (4.9)	27.4 (2.9)	12.2 (3.6)
Respiratory exchange ratio	1.11 (0.05)	1.11 (0.04)	1.09 (0.06)	1.03 (0.09)
Peak heart rate (b.p.m.)	174 (14)	177 (11)	194 (10)	124 (19)
Ventilation (L/min)	100 (29)	122 (28)	195 (29)	61 (17)
$EqVO_{2peak}$ (L/L/min)	33.0 (4.0)	31.3 (4.0)	36.2 (3.5)	38.9 (8.0)
$EqVCO_{2peak}$ (L/L/min)	30.2 (3.5)	28.7 (3.4)	33.2 (3.4)	36.6 (6.9)
LVEDV biplane 2D (mL)	108 (30)	134 (34)	197 (22)	176 (72)
LVEDV 3D (mL)	115 (29)	136 (27)	192 (19)	NA
LV EF biplane 2D (%)	60.5 (4.3)	60.2 (4.9)	54.3 (4.4)	34.9 (11.4)
LAVmax MOD 2D (mL)	54 (19)	65 (23)	98 (29)	108 (39)
LAVmax 3D (mL)	56 (15)	66 (14)	85 (18)	NA

Numbers are mean (SD); *n* (%).
BMI, body mass index; BP, blood pressure; BSA, body surface area; EF, ejection fraction; $EqVCO_2$, ventilatory equivalent for carbon dioxide; $EqVO_2$, ventilatory equivalent for oxygen; LAVmax, left atrial maximal volume; LV, left ventricle; LVEDV; left ventricle end-diastolic volume; MOD, method of discs; PA, physical activity.

(L/min) explained 12% ($R^2 = 0.12$, $P < 0.001$) in univariate models. For those with a BMI ≥ 25 kg/m^2, BSA correlated better with LAVmax (0.35) than VO_{2peak} (0.28), P for comparison = 0.027. However, for BMI < 25 kg/m^2, VO_{2peak} correlated better with LAVmax than BSA (0.35 vs. 0.28, $P = 0.046$). In multiple linear regression models, the best-fit model for absolute VO_{2peak} explained 22% of the variance in LAVmax (including age, sex, the interaction between VO_{2peak} and sex, the interaction between VO_{2peak} and age, and the interaction between age and sex). The best-fit model for FFM explained 20% of the variance (including age, sex, and the interaction between FFM and sex and the interaction between FFM and age). For BSA, the best-fit model explained 18% of the variance (including age and the interaction between age and BSA). Across the age groups, peak oxygen pulse generally correlated better with LAVmax than BSA, FFM, and VO_{2peak}, and in the best-fit model (see Supplementary data online, *Table S1*) including age and sex, 26% of variance was explained.

Table 2 Pearson correlation coefficients for LAVmax and LVEDV towards BSA, FFM, absolute VO_{2peak}, and peak oxygen pulse in the healthy reference sample ($n = 1190$)

		All	<40 years	40–60 years	>60 years
LVEDV	BSA	0.57	0.61	0.52	0.59
	FFM	0.67*	0.67*	0.63*	0.67*
	VO_{2peak}	0.72*,#	0.70*	0.71*,#	0.64
	Peak oxygen pulse	0.73*,#	0.69	0.73*,#,‡	0.65*
LAVmax	BSA	0.39	0.27	0.39	0.42
	FFM	0.41	0.35*	0.41	0.44
	VO_{2peak}	0.35*,#	0.45*,#	0.42	0.37#
	Peak oxygen pulse	0.42‡	0.52*,#,‡	0.47*,#,‡	0.43‡

All correlation coefficients are significant at $P < 0.02$.
BSA, body surface area (m^2); FFM, fat-free mass; LAVmax, left atrial maximal volume; LVEDV, left ventricular end-diastolic volume; VO_{2peak}, peak oxygen uptake (L/min).
*Significantly different from BSA at $P < 0.05$.
#Significantly different from FFM at $P < 0.05$.
‡Significantly different from VO_{2peak} at $P < 0.05$.

Relationships with age and sex in the healthy general population

The LVEDV declined with higher age (see Supplementary data online, *Table S2A*) and also when indexed to BSA. When indexed to absolute VO_{2peak} (LVEDV/VO_2), LVEDV was relatively unchanged with increasing age, except for men beyond 60 years of age. Using linear regression, age explained 6% of the variance in LVEDV/VO_2 ($R^2 = 0.06$, $P < 0.001$), compared to 13% for LVEDV/BSA ($R^2 = 0.13$, $P < 0.001$) and 9% for LVEDV/FFM ($R^2 = 0.09$, $P < 0.001$). Age had no influence on LVEDV/O_2pulse ($R^2 = 0.00$, $P = 0.63$). On the other hand, LAVmax was larger with higher age, especially for men, also when indexed to absolute VO_{2peak} (see Supplementary data online, *Table S2B*). The descriptive data showed that LVEDV/VO_2 was generally higher in women, corresponding to 3.5 mL/L/min VO_2 in a general linear model (beta: −3.5 mL/L/min, $P < 0.001$), but after adjusting for blood haemoglobin concentration, there was no significant difference across sex (beta: −0.8 mL/L/min, $P = 0.22$). The upper and lower limits of normalcy for LVEDV and LAVmax, indexed to absolute VO_{2peak} and BSA, are shown in *Table 3*.

Endurance athletes and heart failure patients

When assessing classification to normalcy, HUNT athletes and elite athletes were pooled ($n = 71$). Indexing LVEDV to VO_{2peak} compared to BSA significantly increased the proportion classified as enlarged among heart failure patients (95% vs. 39%, $P < 0.001$) while indexing LVEDV to VO_{2peak} compared to BSA significantly decreased the proportion classified as abnormal among athletes (1% vs. 25%, $P < 0.001$) when indexing to absolute VO_{2peak} compared to BSA (*Table 4*, *Figure 3*, *Graphical Abstract*). The same patterns were also seen for the data on LAVmax for heart failure patients ($P < 0.001$), but not for athletes ($P = 0.26$). The NRI for discrimination between LVEDV enlargement related to heart failure and athletic remodeling was 1.97 (95% CI 1.92–2.03, $P < 0.001$) and the IDI was 0.93 (95% CI 0.89–

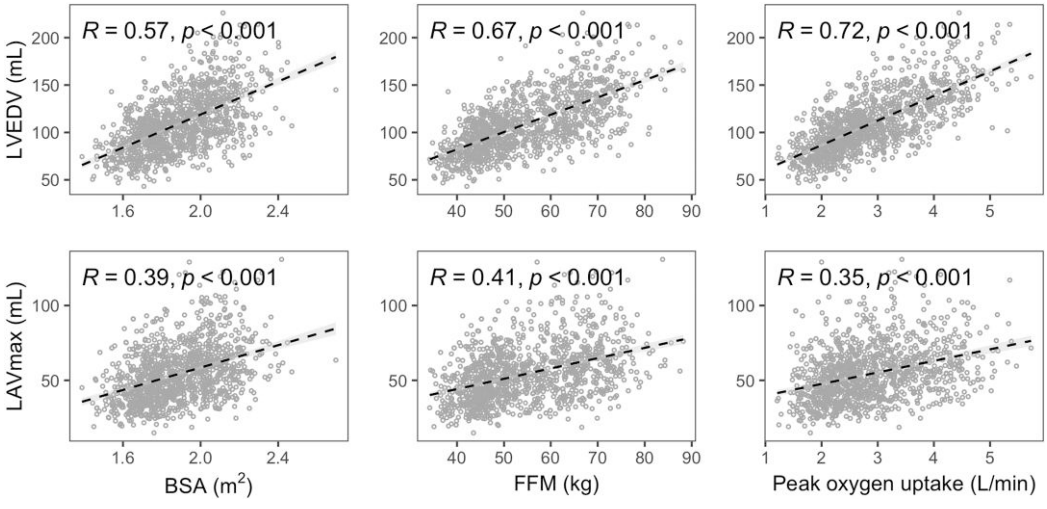


Figure 2 Scatter plots and Pearson's correlation coefficients for left ventricular end-diastolic volume (LVEDV) and left atrial maximal volume (LAVmax) vs. body surface area (BSA), fat-free mass (FFM), and absolute peak oxygen uptake (VO_{2peak}).

Table 3 Mean and lower (mean – 2SD) and upper (mean + 2SD) limits of normalcy for LVEDV and LAVmax indexed by VO_{2peak} and BSA

	Women	Men
LVEDV/VO_2	40.7 (24.2–57.2)	37.2 (20.1–54.2)
LVEDV/BSA	53.6 (30.3–76.8)	62.6 (35.2–89.9)
LAVmax/VO_2		
<40 years	16.4 (6.7–26.1)	12.5 (6.8–18.2)
40–60 years	19.7 (8.4–31)	15.7 (6.2–25.2)
>60 years	23.7 (6.6–40.8)	21.4 (5.2–37.6)
LAVmax/BSA		
<40 years	26.6 (9.4–43.9)	26.3 (11.5–41.2)
40–60 years	28.1 (12.1–44.2)	29.5 (11.9–47.1)
>60 years	27.5 (9.4–45.6)	30.9 (10.3–51.5)

Values are mean (lower limit of normal to upper limit of normal).
BSA, body surface area (m^2); LAVmax; left atrial maximal volume; LVEDV, left ventricular end-diastolic volume; VO_2, peak oxygen consumption (L/min).

Table 4 Proportions with enlarged LVEDV and LAVmax indexed by BSA, FFM, and VO_{2peak}

	HUNT athletes, $n = 58$	Elite athletes, $n = 13$	Heart failure patients, $n = 61$
Enlarged LVEDV indexed to			
BSA	6 (10%)	12 (92%)	24 (39%)
FFM	4 (6.9%)	5 (38%)	–[a]
VO_{2peak}	1 (1.7%)	0 (0%)	58 (95%)
Peak oxygen pulse	4 (7.0%)	5 (45%)	46 (78%)
Enlarged LAVmax indexed to			
BSA	6 (10%)	9 (75%)	30 (51%)
FFM	7 (12%)	9 (75%)	–[a]
VO_{2peak}	4 (6.9%)	5 (42%)	57 (97%)
Peak oxygen pulse	4 (7.0%)	5 (45%)	46 (78%)

Mean (SD); *n* (%).
BSA, body surface area; FFM, fat-free mass; LAVmax, left atrial maximal volume; LVEDV; left ventricular end-diastolic volume; VO_{2peak}, peak oxygen uptake.
[a]Fat-free mass was not measured in the heart failure sample.

0.98). Findings were similar for peak oxygen pulse vs. BSA, but indexing to peak oxygen pulse reduced the number of heart failure patients classified with abnormalcy. For athletes, indexing to FFM vs. BSA did not significantly reduce the number of participants classified with enlarged LVEDV ($P = 0.087$), and for LAVmax, there was no numeric or statistical difference between indexing to BSA or FFM ($P = 1.0$).

We compared our data to other studies reporting data on both LVEDV by the biplane Simpson's method and absolute VO_{2peak} in endurance athletes and normal subjects. Data from all these studies were well within the presented normal ranges from the present study (*Figure 4*).[14–22] The correlation between VO_{2peak} and LVEDV/BSA found in this study was also present in the previous studies, meaning that at high absolute VO_{2peak}, the LVEDV/BSA was above current upper limits of normalcy[23] (*Figure 5*).

Sensitivity analyses

Results were replicated in 1035 and 888 participants from the healthy reference sample with 3D measures of LVEDV and LAVmax, respectively, showing the same patterns (see Supplementary data online, *Table S3* and *Table S4*). We also performed sensitivity analyses on heart failure patients where we adjusted the absolute VO_{2peak} to a standardized level of blood haemoglobin concentration (15 g/dL) without notable effects on our results. Lastly, performing analyses by including only heart failure patients with sinus rhythm at baseline ($n = 25$) did not change the main findings (data not shown).

Discussion

In a large sample of healthy subjects from the HUNT Study, we found that LV volumes were more closely related to absolute VO_{2peak} and FFM than BSA, the most commonly used measure of body size when indexing cardiovascular structures. This was especially evident for LVEDV where absolute VO_{2peak} explained >50% of its variance, significantly more than BSA. Indexing LVEDV and LAVmax to absolute VO_{2peak} classified more heart failure patients to having enlarged chambers compared to BSA. Similarly, indexing to VO_{2peak} in athletes significantly reduced classification to enlarged LVEDV, but not LAVmax. When indexing to FFM, the results were more in line with absolute VO_{2peak} than BSA, which is important to note as FFM may be easier to implement in clinical practice than measurements of VO_{2peak}.

LVEDV and peak oxygen uptake

A main finding of the current study was that indexing LVEDV for absolute VO_{2peak} may drastically improve evaluation of athletes with enlarged cardiac chambers with respect to normal or pathological LV enlargement compared to indexing for BSA. Current recommendations suggest indexing cardiac chambers to body size measures such as BSA for the evaluation of the athlete's heart,[24] similar to the general recommendations for assessing cardiac chamber volumes.[8] As shown with our data and with the data from previous studies illustrated in *Figures 4* and *5*, athletes, or individuals with a high absolute VO_{2peak}, are currently defined as having (pathologically) enlarged LVs.[2] Our data suggest that assessing normalcy of LV size might best be performed by indexing to VO_{2peak}, especially for athletes or others with high volumes of endurance training. We further show that indexing to VO_{2peak} based on normal reference data from a large general population may be helpful for evaluation of endurance athletes' LV volumes. This adds strength to the findings. Further, the strong correlations of absolute and relative VO_{2peak} with LVEDV and even the total heart size from previous studies are in line with suggestions that cardiac structural characteristics are stronger determinants of VO_{2peak} than measures of cardiac function.[17,21,25] Larger LV volumes allow for larger stroke volumes and higher cardiac output, both being key determinants of VO_{2peak} as shown by the classical Fick equation. Furthermore, the theory of similarities, stating that relative geometries in part determine the relationship between body size variables,[1] supports indexing of cardiac volumes to VO_{2peak}. Following the theory of similarities, 3D variables such as LV volumes should theoretically be indexed towards a 3D variable, e.g. a volume such as VO_{2peak} (with dimensions raised to the third power, cm^3), and not a 2D variable such as BSA (raised to the second power, m^2).

Observations based on descriptive data from longitudinal studies also support our findings. Bjerring *et al.*[15] found that the LVEDV measured by 3D was 100 mL at 12 years of age and increased by 43% in a follow-up 3 years later. Correspondingly, VO_{2peak} increased by 43% from 2.53 to 3.62 L/min. Thus, even in adolescents, the LVEDV/VO_{2peak} was unchanged (39.2 and 39.5 mL/L/min, respectively), while LVEDV/BSA increased ~10% from 76 to 84 mL/BSA. The same pattern was found by Arbab-Zadeh *et al.*,[26] who performed a 1-year single-arm exercise training study on 12 sedentary adults and found that absolute

VO_{2peak} and cardiac magnetic resonance imaging (cMRI)-derived LVEDV both increased by 18%, leaving the LVEDV/VO_{2peak} unchanged.

Indexing LVEDV to VO_{2peak} identified a considerably larger proportion of the heart failure patients as having enlarged LVEDV than indexing for BSA. This finding was consistent also for HFpEF patients. These findings relate pathophysiologically to the need of a larger end-diastolic volume to compensate for the reduced systolic function in order to maintain adequate stroke volume. This leads to the key question when assessing normalcy: is the cardiac chamber size proportional to cardiovascular function expected to follow the given chamber size? Our data indicate that considering VO_{2peak} may answer whether the given LVEDV reflects physiological or pathological enlargement, and we see a potential for the LVEDV to absolute VO_{2peak} *coupling* to address a key question in the definition of heart failure. A previous study found that the ratio between VO_{2peak} to total heart volume measured by cMRI identified patients with heart failure.[27] Although using a different design, the mentioned study supports that indexing cardiac volumes to absolute VO_{2peak} may identify heart failure patients at an earlier stage of the disease. From a physiological point of view, indexing to peak oxygen pulse could be even more robust than indexing for absolute VO_{2peak} as it considers the age-related decline in heart rate, leading to the *post hoc* inclusion of these data in the manuscript. The reason for the lower discriminatory capacity of peak oxygen pulse is not clear to us, and these findings require further study and validation in other populations.

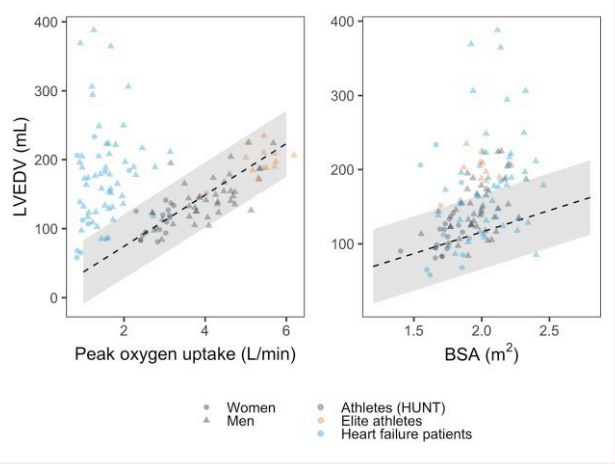


Figure 3 Left ventricular end-diastolic volume (LVEDV) in relation to absolute peak oxygen uptake (VO_{2peak}) and body surface area (BSA), showing how athletes and heart failure patients are effectively differentiated by assessing LVEDV in relation to VO_{2peak}, compared to BSA.

Another typical clinical example is the athlete with a large LVEDV where the clinician is uncertain whether the adaptation is related to a developing cardiomyopathy or physiological chamber dilatation. Detraining, with a consequent reduction in VO_{2peak}, has been suggested for assessing whether cardiac alterations in athletes represent physiological or pathological adaptions. Similarly, exercise echocardiography has been proposed to distinguish between normalcy and pathology in athletes with sub-normal LV ejection fraction.[28] We suspect that indexing the LVEDV by VO_{2peak} may reduce the need to perform both detraining interventions and exercise echocardiography, and a proposed algorithm for interpretation of physiological or pathological LVEDV enlargement is shown in the *Graphical Abstract*. Still, the proposed method remains to be proven in further studies including evaluation of the prognostic value of different indexing approaches.

Contributions by age and sex

Other studies have found how LVEDV is reduced with higher age.[23] However, when indexing to VO_{2peak}, the LVEDV remains relatively unchanged across age, signifying that the lower LVEDV with higher age is

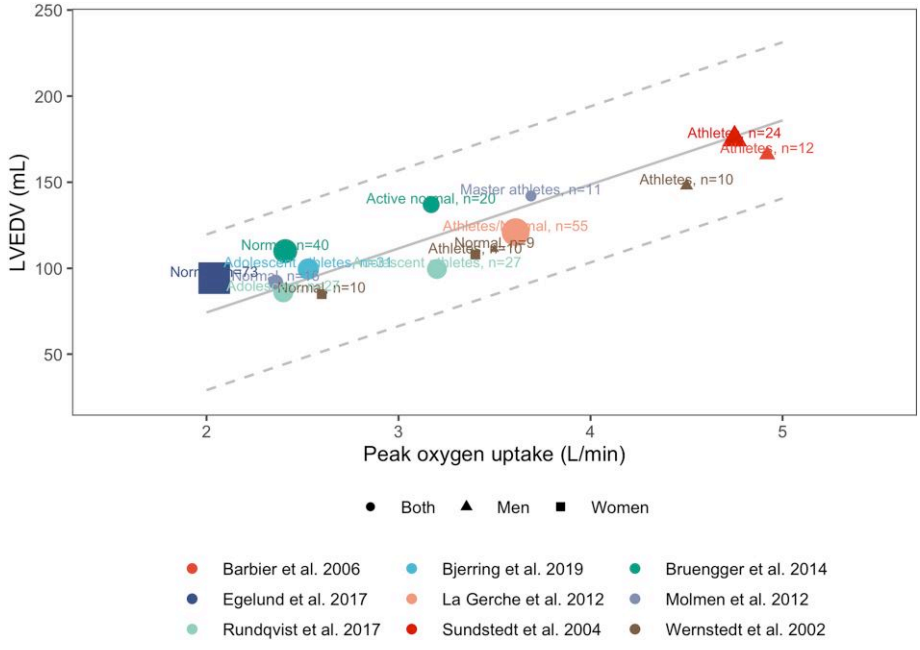


Figure 4 Comparison of absolute peak oxygen uptake and echocardiographic left ventricular end-diastolic volume based on descriptive data from healthy normal subjects and endurance athletes from various studies. The fit line shows the best linear fit among the studies. The dotted lines show the 95% prediction interval from the current study.

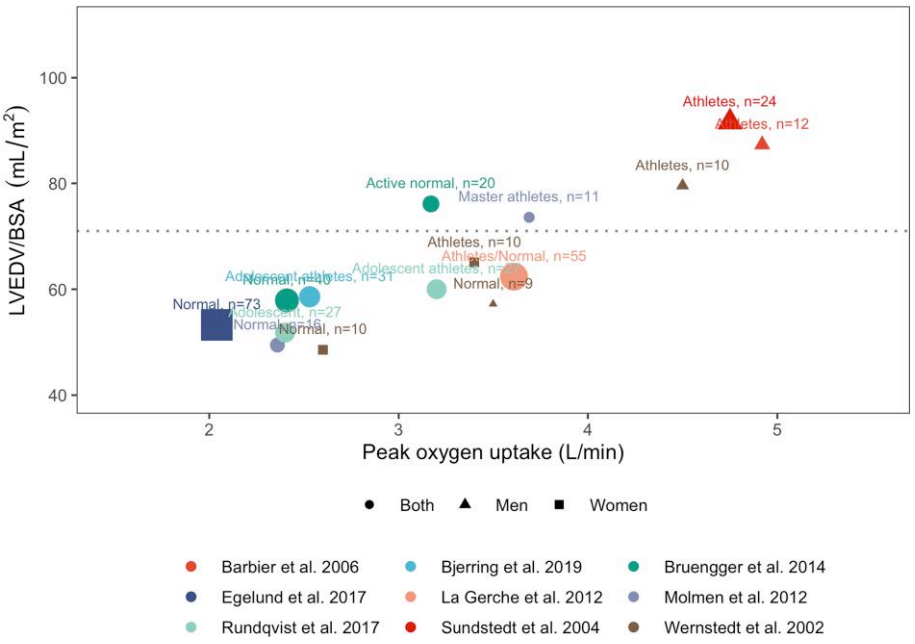


Figure 5 Echocardiographic left ventricular end-diastolic volume indexed to body surface area (BSA) by absolute peak oxygen uptake from various studies on healthy normal subjects and endurance athletes. The dotted line shows the cut-off for normalcy based on the study by Kou et al. from the NORRE population.[23]

more related to reduced metabolic demands than to concentric LV remodeling. Furthermore, our analyses on oxygen pulse showed that the effect of age on the LVEDV/VO_2 relationship was explained by the decline in peak heart rate with age. Molmen[18] found that VO_{2peak} increased from 2.36 to 2.65 L/min with a concurrent balanced increase in LVEDV preserving the LVEDV/VO_2 ratio in an exercise study of older adults.[18] A control sample of master athletes in the same study showed similar LVEDV/VO_2 values. In the present study, differences by sex were small, and after adjusting for haemoglobin concentration, there was no sex difference. Thus, absolute VO_{2peak} explains important age- and sex-related differences in LV adaptation.

Determinants of LAVmax

Our results did not show the same strong relationship between VO_{2peak} or body size measures and LAVmax as for LVEDV. The relationship between VO_{2peak} and LAVmax was most evident at young age, while the effect of age was opposite for body size measures. The explained variance was <20% for all measures in the univariate models, and in models including age and sex, the model with VO_{2peak} explained most of the variance. Thus, somewhat contrary to LV, other factors than fitness are of importance for LA size. Although the LA may be enlarged due to higher exercise capacity caused by endurance training as found in previous studies,[3,29] it is also influenced by the presence of elevated filling pressures over time.[30,31] These conflicting pathways to LA enlargement may also be present in apparently healthy populations through clustering of risk factors or through accumulated volumes of vigorous physical activity. This may explain one reason for the lower correlation with VO_{2peak} compared to the findings for the LV. Findings from the CARDIO-FIT study showed that LAVmax/BSA *decreased* from 38 to 32 mL/m^2 by increasing exercise capacity with >2 metabolic equivalents over 4 years in low-fit obese subjects with atrial fibrillation.[32] Conversely, LAVmax has been shown to increase in individuals with normal risk factor levels over a 2-year training intervention.[33] The latter study also showed that the LA seemed to remodel more than the LV in the last year of intervention, which may hint to different mechanisms affecting LA compared to LV remodeling.

Limitations

Self-selection to participating in exercise testing implies a risk of selection bias. Also, some features regarding this study are important to note when assessing generalizability of the findings. First, CPET was performed using treadmill testing, and cycle ergometry testing typically yields lower values in non-athletes, which should be acknowledged when interpreting data from cycle modalities. Using submaximal CPET data such as VO_2 at the ventilatory threshold could also have a role in settings where maximal exercise is contraindicated or impractical. Exploring this could have a role in further studies as we did not have these data available. Furthermore, reduced pulmonary function, anaemia, or cardiac arrhythmias during VO_{2peak} testing may impact the studied relationships. Whether these relationships are similar across different ethnicities also remains to be explored, as the participants included in this study were mainly of Caucasian origin. Whether the improved discriminatory capability shown by indexing LV volumes to VO_{2peak} compared to BSA translates to improved prognostication for heart failure patients as well as athletes must be evaluated in adequately powered clinical endpoint studies. Lastly, we do not have data to support if mechanisms and the effect of reverse remodeling are different for the LA compared to the LV.

Conclusions

Absolute VO_{2peak} reflects both body size and fitness level and is a strong determinant of left-sided cardiac volumes. Our data suggest that indexing LV volumes to VO_{2peak} is significantly better than indexing to BSA, with FFM performing more in line with VO_{2peak} than BSA. Indexing LVEDV by VO_{2peak} compared to BSA significantly improved the differentiation of physiological from pathological adaptations compared to BSA when endurance athletes and heart failure patients were

used as proxies for physiological and pathological remodeling. Thus, discovering uncoupling of the relationship between LVEDV and absolute VO_{2peak} may be a key to diagnosing heart failure. Compared to findings for the LVEDV, neither VO_{2peak} nor body size measures explained the same amount of variation in LA volumes. Further studies should examine whether indexing to VO_{2peak} (or peak oxygen pulse) or FFM translates to improved prognostication over BSA.

Supplementary data

Supplementary data are available at *European Heart Journal - Cardiovascular Imaging* online.

Acknowledgements

The HUNT (Nord-Trøndelag Health Study) is a collaboration between the HUNT Research Centre (Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology), Nord-Trøndelag County Council, Central Norway Regional Health Authority, and the Norwegian Institute of Public Health. We recognize the invaluable effort by employees and students from our research group throughout data collection in the presented studies.

Funding

The work was funded by Helse Midt-Norge (The Liaison Committee for Education, Research and Innovation in Central Norway), the Norwegian Research Council, Helse Nord-Trøndelag (Nord-Trøndelag Hospital Trust), Norwegian University of Science and Technology, Landsforeningen for Hjerte- og Lungesyke (National Association for Heart and Lung Diseases), and Simon Fougner Hartmann's Family Fund (Copenhagen, Denmark).

Conflict of interest: Institutional partnership with GE Ultrasound in Centre for Innovative Ultrasound Solutions. Håvard Dalen has research contract with GE Ultrasound. None of the disclosures were related to this work. The remaining authors have nothing to disclose.

Data availability

The data from HUNT used in this study are available on application to the HUNT Data Access Committee in accordance with the policy on data availability (further information and contact information: https://www.ntnu.edu/hunt/data).

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