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ORIGINAL ARTICLE

# Left atrial volume index is an independent predictor of hypertensive response to exercise in patients with hypertension

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**A hypertensive response to exercise (HRE) is known to be associated with higher risk of heart failure and future cardiovascular events in patients with hypertension. Left atrial volume index (LAVI) is associated with the diastolic dysfunction, indicating exercise intolerance. Therefore, we investigated whether LAVI is relevant to HRE during cardiopulmonary exercise test (CPET). We studied 118 consecutive hypertensive patients (61 men, 57 ± 11 years) and 45 normotensive control subjects (16 men, 54 ± 8 years). Clinical characteristics, CPET, echocardiographic and laboratory findings were assessed at the time of enrollment. HRE was defined as maximum systolic blood pressure (SBP) ⩾ 210 mm Hg in men and ⩾ 190 mm Hg in women. HRE was more prevalent in hypertensive patients compared with normotensive control subjects (50.8% *vs.* 20.0%, $P<0.001$). Age and baseline SBP were shown to be associated with HRE in normotensive control subjects, as were baseline SBP and LAVI in hypertensive group. In multivariate analysis, LAVI was found to be an independent predictor of HRE in hypertensive patients ($P=0.020$) but not in normotensive control subjects ($P=0.936$) when controlled for age, sex, body mass index and peak oxygen consumption. Higher LAVI, reflecting the duration and severity of increased left atrial pressure is independently associated with HRE in hypertensive patients, but not in normotensive control subjects.**
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## INTRODUCTION

Hypertensive response to exercise (HRE) predicts the future development of essential hypertension,[1–4] coronary disease,[5] left ventricular (LV) hypertrophy,[6] cardiovascular events[7,8] and mortality,[9] independent of resting blood pressure (BP) in apparently healthy, normotensive individuals. HRE was also associated with multiple metabolic risk factors in normotensive patients even before clinical manifestation of arterial hypertension.[10] However, the underlying mechanism of an exaggerated HRE remains poorly characterized.

In a recent study, patients with HRE had impaired exercise tolerance and LV longitudinal diastolic dysfunction, irrespective of the presence of resting hypertension.[11] Thus, it is plausible to assume that echocardiographic parameters of LV diastolic dysfunction are correlated to the development of HRE. However, only a few studies have attempted to evaluate the direct correlation between HRE and echocardiographic diastolic indices.[12,13]

Performance during treadmill testing is largely influenced by the individual's exercise capacity, a parameter that has routinely been measured by the metabolic equivalent tasks (MET). However, previous studies have not adjusted for these factors,[1–6] and only a few studies have adjusted for the functional capacity of the patient by using MET.[14] As conventional treadmill testing has been used in most HRE studies,[1–9] no adequate method exists to objectively adjust for the patient's effort. By using the cardiopulmonary exercise test (CPET), an objective criterion of effort[15,16]—the peak respiratory exchange ratio (RER) and peak oxygen consumption ($VO_2$)—can be adjusted while assessing the HRE. We therefore investigated whether LV diastolic dysfunction is equally relevant to HRE in both groups, the hypertensive patients and the normotensive control subjects, by utilizing CPET.

## METHODS

### Patient selection

One-hundred and eighteen hypertensive patients without diabetes, who underwent the CPET at our institution between November 2011 and May 2013, were enrolled. Resting two-D echocardiogram and tissue Doppler measurements were obtained within 24 h of CPET. We recruited hypertensive subjects with either a documented systolic BP (SBP) >140 mm Hg and/or a diastolic BP

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>90 mm Hg, taken after resting at least 5 min in a sitting position, over three distinct visits prior to commencing BP medication. Patients currently taking antihypertensive medications for treatment of hypertension were also enrolled. Patients with any of the following conditions were excluded from participation: prior myocardial infarction, unstable angina, congestive heart failure, valvular heart disease, peripheral vascular disease, malignant disease, severe respiratory disease, renal failure (creatinine $>1.4\ mg\ dl^{-1}$), anemia (hemoglobin $<12\ g\ dl^{-1}$), history of inflammatory disease and/or on anti-inflammatory medications, clinically significant atrioventricular conduction disturbance, history of atrial fibrillation or other serious arrhythmia, and/or malignant hypertension (>200/140 mm Hg). Patients with other diseases that could limit exercise tolerance (for example, emphysema, bronchitis, severe renal dysfunction and severe liver dysfunction) were excluded. Patients with peak RER <1.10 were also excluded.[17,18]

A control group, consisting of 45 healthy subjects without hypertension, was selected retrospectively from among patients who underwent the CPET for general health examinations during the same period.

### Protocol

Each subject provided informed, written consent to the protocol. The institutional review board of Yonsei University College of Medicine approved the study protocol.

### Cardiopulmonary exercise test

A symptom-limited CPET was performed on a treadmill according to the modified Bruce ramp protocol. Patients were strongly encouraged to achieve a peak RER >1.10. Expired gases were collected continuously throughout exercise and analyzed for ventilator volume, oxygen ($O_2$) content, and carbon dioxide ($CO_2$) content using a calibrated metabolic cart (Quark CPET, COSMED, Chicago, IL, USA). Expired gases were measured every 15 s. During the exercise test, monitoring consisted of continuous 12-lead electrocardiography, manual BP measurements every stage and heart rate recordings every stage via the ECG. CPET was terminated based on the following criteria: patient request, ventricular tachycardia, horizontal or downsloping ST segment depression of $\geqslant 2$ mm, or a drop in SBP $\geqslant 20\ mm\ Hg^{-1}$ during exercise. A qualified exercise physiologist conducted each test, under supervision of a physician.

The following variables were derived from the CPET results: peak $VO_2$; peak RER, defined by the ratio of $CO_2$ production to $O_2$ consumption at peak effort; the minute ventilation–carbon dioxide production ($VE/VCO_2$) slope, defined as the slope of the increase in peak ventilation/increase in $CO_2$ production throughout exercise. Peak RER had the highest 30-s average value during the last stage of the test. Heart rate reserve is defined as the difference between basal and peak heart rate.

An HRE is defined as a peak exercise SBP of $\geqslant 210$ mm Hg in men, and $\geqslant 190$ mm Hg in women, in line with the Framingham criteria.[19] Recent studies using the technique of 24-h ambulatory BP monitoring have shown that BP is higher in men than in women at similar ages.[20,21] Moreover, gender difference exists in arterial stiffness both at rest and after acute physical stress.[22] Therefore, we used the different definition of HRE for men and female based on previous studies which is mostly used in recent studies.

### Echocardiography protocol

Left ventricular ejection fraction was measured using the modified Quinones method.[23] In patients with regional-wall motion abnormalities, the left ventricular ejection fraction was calculated using Simpson's biplane method with apical four- and two-chamber views.[24] Left atrial volume index (LAVI) was measured using the prolate ellipsoid method.[25] Pulsed-wave Doppler echocardiography of mitral inflow, and tissue Doppler imaging from the apical four-chamber view with 2- to 5-mm sample volumes placed at the septal corner of the mitral annulus, were used to determine the peak velocity of early diastolic filling (E), late filling (A), peak systolic velocity (S′) and early diastolic velocity (E′).[26]

### Statistical analyses

Continuous variables were tested for normal distribution by the Kolmogorov–Smirnov test; continuous data are reported as mean and s.d. We compared continuous variables using Student's *t*-test or Mann–Whitney *U*-test between groups. Categorical variables were summarized as percentages and compared with the $\chi^2$-test. Correlation analyses between parametric and non-parametric variables were tested using Pearson's and Spearman's correlation coefficients, respectively. Linear regression analysis was performed to estimate the proportional contribution of LAVI. Logistic regression analysis was performed to estimate predictors of HRE. A two-sided *P*-value <0.05 was considered significant, with confidence intervals of 95%. All statistical analyses were performed with SPSS, version 15 (SPSS, Chicago, IL, USA).

## RESULTS

There were 118 patients (mean age $57 \pm 11$; 51.7% men) in the hypertensive group, and 45 healthy volunteers (mean age $54 \pm 8$; 35.6% men) in the control group. Baseline characteristics and laboratory findings for both groups are presented in Table 1. Subjects belonging to the hypertensive group were older, had higher body mass index and lower estimated glomerular filtration rate, than those in the control group. Baseline SBP was higher in patients with HRE in both control and hypertensive groups. The medication history, including antihypertensive drugs and antiplatelet agents was similar in patients with and without HRE (Table 2).

Table 3 shows CPET parameters and echocardiographic indices of study population. HRE was more frequent in the hypertensive group than in the control group (50.8% *vs.* 20.0%, $P<0.001$). When hypertensive patients were divided on the basis of HRE, most of the parameters related to LV diastolic function, except for LAVI, did not show significant difference. In the control group, the parameters A, E/A, decelerating time (DT) , E′ and E/E′ were all significantly different between patients with and without HRE.

To identify the factors correlated to HRE in the hypertensive and control groups, univariate logistic regression analyses were performed (Table 4). In the hypertensive group, the $VE/VCO_2$ slope and baseline BP were associated with HRE ($P<0.05$); LAVI was the only significantly related parameter among other echocardiographic variables ($P=0.017$). In the control group, age, E/A, DT, E′ and E/E′ were all associated with HRE. Interestingly, pulse pressure, a marker for arterial stiffness, was independently associated with HRE in both hypertensive subjects and control group.

Multivariate logistic regression test was performed to identify factors independently related to HRE (Table 5); age, sex,[22] body mass index and peak $VO_2$ were adjusted. Although none of the echocardiographic parameters were found to be independently related to HRE in the normotensive group (all $P>0.050$), LAVI was independently correlated with HRE in hypertensive group ($P=0.020$). In hypertensive patients, pulse pressure and delta BP also had an independent relationship with HRE (all $P<0.001$). However, in linear regression analysis, delta BP had statistically meaningful relationship with LAVI in only hypertensive patients without HRE ($P=0.020$).

We also investigated the independent correlation of LAVI with HRE as a function of age. When hypertensive patients were divided into two subgroups according to age, independent correlation diminished between LAVI and HRE in hypertensive patients younger than 55 years. However, in patients older than 55 years, HRE was independently correlated with LAVI ($P=0.042$) (Table 6).

## DISCUSSION

In the present study, we have shown an independent correlation between the HRE and LAVI in hypertensive patients. HRE was more

**Table 1 Baseline characteristics and laboratory findings of study subjects**

| | *Control group* (n = *45*) | | | *Hypertensive group* (n = *118*) | | | *Control vs. hypertensive group* |
|---|---|---|---|---|---|---|---|
| | *HRE (−)* (n = *36*) | *HRE (+)* (n = *9*) | P-*value* | *HRE (−)* (n = *58*) | *HRE (+)* (n = *60*) | P-*value* | P-*value* |
| Age (year) | 52±7 | 61±10 | 0.006 | 58±12 | 56±11 | 0.510 | 0.044 |
| Male sex, *n* (%) | 14 (38.9) | 2 (22.2) | 0.456 | 33 (56.9) | 28 (46.7) | 0.266 | 0.065 |
| BMI ($kg\,m^{-2}$) | 22.5±3.0 | 24.7±4.3 | 0.104 | 25.2±3.5 | 25.4±3.4 | 0.572 | <0.001 |
| Baseline SBP (mm Hg) | 112±12 | 125±17 | 0.011 | 121±13 | 139±14 | <0.001 | <0.001 |
| Dyslipidemia, *n* (%) | 4 (11.1) | 4 (44.4) | 0.039 | 11 (19.0) | 18 (30.0) | 0.164 | 0.354 |
| CVA, *n* (%) | 0 (0.0) | 0 (0.0) | — | 2 (3.4) | 5 (8.3) | 0.439 | |
| WBC ($\times10^9$ cells $l^{-1}$) | 8.2±15.8 | 5.6±1.2 | 0.575 | 6.5±1.8 | 6.4±1.6 | 0.630 | 0.413 |
| Hemoglobin ($g\,dl^{-1}$) | 13.9±1.6 | 13.5±2.0 | 0.583 | 14.1±1.7 | 14.4±1.4 | 0.305 | 0.118 |
| Hematocrit (%) | 40.7±4.7 | 40.3±4.9 | 0.844 | 41.3±4.4 | 42.4±3.6 | 0.182 | 0.105 |
| MCV (fL) | 92.0±4.7 | 90.2±6.1 | 0.349 | 91.8±4.3 | 91.4±4.0 | 0.617 | 0.897 |
| RDW (%) | 13.4±2.8 | 13.3±1.7 | 0.823 | 13.0±0.7 | 12.9±0.6 | 0.645 | 0.902 |
| hsCRP ($mg\,dl^{-1}$) | 1.37±2.02 | 0.78±0.38 | 0.885 | 1.43±1.94 | 4.60±12.87 | 0.127 | 0.325 |
| BUN ($mg\,dl^{-1}$) | 14.0±3.1 | 13.4±4.0 | 0.511 | 14.3±4.7 | 14.7±4.3 | 0.441 | 0.733 |
| Cr ($mg\,dl^{-1}$) | 0.72±0.19 | 0.65±0.11 | 0.290 | 0.84±0.19 | 0.81±0.17 | 0.357 | <0.001 |
| Uric acid ($mg\,dl^{-1}$) | 4.7±1.2 | 4.2±0.7 | 0.304 | 5.2±1.4 | 5.3±1.4 | 0.717 | 0.006 |
| Total cholesterol ($mg\,dl^{-1}$) | 192±31 | 195±32 | 0.773 | 179±34 | 187±35 | 0.197 | 0.131 |
| Albumin ($g\,dl^{-1}$) | 4.3±0.2 | 4.3±0.2 | 0.609 | 4.3±0.4 | 4.4±0.3 | 0.070 | 0.721 |
| Na ($mEq\,l^{-1}$) | 141±2 | 142±2 | 0.508 | 141±2 | 141±2 | 0.113 | 0.909 |
| eGFR ($ml\,min^{-1}$ per $1.73\,m^2$) | 98±16 | 98±14 | 0.992 | 85±17 | 87±14 | 0.555 | <0.001 |

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BUN, blood urea nitrogen; CCB, calcium channel blocker; Cr, creatinine; CVA, cardiovascular accident; eGFR, estimated glomerular filtration rate; HRE, hypertensive response to exercise; hsCRP, high-sensitivity C-reactive protein; MCV, mean corpuscular volume; RDW, red cell distribution width; SBP, systolic blood pressure; WBC, white blood cell.

**Table 2 Medication history of hypertensive group**

| | *Hypertensive group* (n = *118*) | | |
|---|---|---|---|
| | *HRE (−)* (n = *58*) | *HRE (+)* (n = *60*) | P-*value* |
| Beta blockers, *n* (%) | 7 (12.1) | 8 (13.3) | 0.837 |
| ACEIs, *n* (%) | 2 (3.4) | 5 (8.3) | 0.439 |
| ARBs, *n* (%) | 17 (29.3) | 17 (28.3) | 0.907 |
| CCBs, *n* (%) | 15 (25.9) | 16 (26.7) | 0.921 |
| Antiplatelet agents, *n* (%) | 9 (15.5) | 11 (18.3) | 0.684 |
| Diuretics, *n* (%) | 5 (8.6) | 7 (11.7) | 0.584 |
| Nitrates, *n* (%) | 10 (17.2) | 6 (10.0) | 0.251 |
| Lipid-lowering drugs, *n* (%) | 12 (20.7) | 13 (21.7) | 0.897 |

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; HRE, hypertensive response to exercise.

strongly associated with diastolic dysfunction in older (>55 years) hypertensive patients.

### Relationship between HRE and diastolic dysfunction

In general, echocardiographic indices of LV diastolic function were significantly different between the hypertensive and normotensive groups. This is inconsistent with previous reports,[27–29] which have demonstrated a positive correlation between arterial hypertension and LV diastolic dysfunction in patients with hypertension. Specifically, LAVI was found to be independently correlated with HRE in hypertensive patients, but not in normotensive subjects.

Among several indices of left ventricular diastolic function, only LAVI, which reflects the chronicity and severity of increased left atrium (LA) pressure,[30] showed a correlation with HRE in the hypertensive group. An increased LA size has been consistently reported in patients with hypertension,[31] and LAVI is reported to be a sensitive marker of LV diastolic dysfunction.[30] Moreover, there is a significant relationship between LA remodeling and echocardiographic indices of diastolic function.[32] While time intervals and doppler velocities are largely influenced by the volume status of the patient at the time of measurement, LA volume reflects the cumulative effects of filling pressures over time.[33] Because all echocardiographic measurements were done within 24 h of the CPET in this study, the fact that only LAVI was correlated with HRE is in line with this finding.

Zanettini *et al.*[14] have shown that patients in the top tertile of SBP response corrected by the METs (⩾11.3 mm Hg per MET), had higher LV septal and posterior wall thickness than individuals classified in the lower tertiles. However, these parameters are an insignificant predictor in multivariate models. In this study, LAVI was independently correlated with HRE after adjusting for exercise capacity, age, sex and work load in hypertensive patients. Body mass index was also adjusted because there is a direct correlation between weight and BP.[34] Thus, our finding strengthens the association between LV diastolic dysfunction and development of HRE, which has been previously suggested.[35,36]

### Effect of aging on the development of HRE

Our results show that the association between LAVI and HRE is more statistically significant in hypertensive patients older than 55 years, upon multivariate analysis. Diastolic dysfunction is strongly associated with aging,[37] and it contributes to LA remodeling and other echocardiographic indices of diastolic function.[32,38,39] As LAVI is one of the most reliable parameters of diastolic dysfunction,[30] our finding is in line with the fact that age is likely the most significant determinant of the prevalence and prognosis of diastolic heart failure.[37] It is plausible to assume that HRE accompanies the development of diastolic failure with aging. Pulse pressure amplification may also account for the stronger correlation between LAVI and HRE in older patients. Because pulse pressure amplification reduces

**Table 3 Cardiopulmonary exercise test and echocardiographic variables of study population differentiated by hypertensive response to exercise**

| | *Control group (n = 45)* | | | *Hypertensive group (n = 118)* | | | *Control vs. Hypertensive group* |
|---|---|---|---|---|---|---|---|
| | *HRE (−) (n = 36)* | *HRE (+) (n = 9)* | P-*value* | *HRE (−) (n = 58)* | *HRE (+) (n = 60)* | P-*value* | P-*value* |
| *Cardiopulmonary test* | | | | | | | |
| Exercise duration (s) | 766 ± 145 | 695 ± 149 | 0.196 | 729 ± 185 | 767 ± 138 | 0.209 | 0.882 |
| Peak $VO_2$ (ml kg$^{-1}$ min$^{-1}$) | 30.1 ± 5.4 | 27.7 ± 5.6 | 0.251 | 27.6 ± 6.5 | 29.4 ± 5.3 | 0.097 | 0.291 |
| METs | 8.6 ± 1.5 | 7.9 ± 1.6 | 0.242 | 7.9 ± 1.9 | 8.4 ± 1.5 | 0.099 | 0.292 |
| VE/$VCO_2$ slope | 29.0 ± 4.4 | 28.6 ± 3.5 | 0.900 | 29.7 ± 5.0 | 27.8 ± 3.4 | 0.049 | 0.909 |
| Peak RER | 1.18 ± 0.07 | 1.16 ± 0.05 | 0.393 | 1.17 ± 0.07 | 1.17 ± 0.05 | 0.219 | 0.844 |
| Base SBP (mm Hg) | 112 ± 12 | 125 ± 17 | 0.011 | 121 ± 13 | 139 ± 14 | <0.001 | <0.001 |
| Peak SBP (mm Hg) | 165 ± 19 | 207 ± 19 | <0.001 | 178 ± 17 | 219 ± 15 | <0.001 | <0.001 |
| Delta BP (mm Hg) | 54 ± 18 | 82 ± 15 | <0.001 | 58 ± 20 | 79 ± 14 | <0.001 | 0.009 |
| Pulse pressure (mm Hg) | 41 ± 9 | 49 ± 9 | 0.047 | 43 ± 10 | 52 ± 11 | <0.001 | 0.022 |
| Peak HR (b.p.m.) | 158 ± 17 | 160 ± 19 | 0.743 | 152 ± 20 | 163 ± 16 | 0.003 | 0.755 |
| HRR (b.p.m.) | 88 ± 15 | 89 ± 17 | 0.841 | 79 ± 20 | 90 ± 18 | 0.002 | 0.253 |
| Recovey HR 5 min | 88 ± 15 | 89 ± 16 | 0.843 | 94 ± 13 | 95 ± 19 | 0.728 | 0.029 |
| HR recovery 5 min | 81.0 ± 8.9 | 78.8 ± 10.0 | 0.606 | 76.3 ± 17.8 | 77.3 ± 9.4 | 0.504 | 0.013 |
| *Echocardiography parameters* | | | | | | | |
| EF (%) | 67 ± 5 | 69 ± 6 | 0.353 | 69 ± 6 | 68 ± 5 | 0.408 | 0.246 |
| LVEDD (mm) | 48 ± 4 | 47 ± 4 | 0.567 | 48 ± 4 | 49 ± 4 | 0.111 | 0.538 |
| LVESD (mm) | 31 ± 3 | 30 ± 2 | 0.293 | 30 ± 3 | 31 ± 4 | 0.069 | 0.676 |
| IVSd (mm) | 8 ± 1 | 8 ± 1 | 0.459 | 9 ± 1 | 9 ± 1 | 0.325 | <.001 |
| PWd (mm) | 8 ± 1 | 9 ± 1 | 0.334 | 9 ± 1 | 9 ± 1 | 0.732 | <.001 |
| LVMI (g m$^{-2}$) | 81.8 ± 16.0 | 77.8 ± 12.7 | 0.481 | 86.2 ± 15.9 | 92.3 ± 19.2 | 0.063 | 0.007 |
| LAVI (ml m$^{-2}$) | 22.4 ± 5.3 | 22.2 ± 4.6 | 0.918 | 23.1 ± 6.0 | 25.9 ± 6.5 | 0.014 | 0.049 |
| E (cm s$^{-1}$) | 0.62 ± 0.13 | 0.59 ± 0.13 | 0.548 | 0.61 ± 0.12 | 0.62 ± 0.13 | 0.604 | 0.939 |
| A (cm s$^{-1}$) | 0.53 ± 0.12 | 0.78 ± 0.09 | <0.001 | 0.71 ± 0.16 | 0.73 ± 0.15 | 0.727 | <0.001 |
| E/A | 1.23 ± 0.38 | 0.76 ± 0.13 | <0.001 | 0.90 ± 0.28 | 0.88 ± 0.26 | 0.677 | <0.001 |
| DT (s) | 196 ± 35 | 230 ± 35 | 0.012 | 209 ± 36 | 218 ± 39 | 0.198 | 0.107 |
| S′ (cm s$^{-1}$) | 7.5 ± 1.1 | 7.4 ± 1.8 | 0.748 | 8.0 ± 1.4 | 8.1 ± 4.2 | 0.053 | 0.198 |
| E′ (cm s$^{-1}$) | 8.1 ± 2.1 | 6.3 ± 1.4 | 0.038 | 6.8 ± 1.8 | 6.6 ± 2.3 | 0.260 | 0.002 |
| A′ (cm s$^{-1}$) | 8.2 ± 1.9 | 9.0 ± 1.8 | 0.138 | 9.4 ± 1.6 | 9.0 ± 1.8 | 0.201 | 0.003 |
| E/E′ | 7.94 ± 1.62 | 9.74 ± 2.01 | 0.017 | 9.49 ± 2.59 | 10.17 ± 3.19 | 0.232 | 0.001 |

Abbreviations: A, late diastolic filling velocity; A′, the late diastolic annular velocity; BP, blood pressure; DT, deceleration time of early filling velocity; E, the peak early filling velocities; E′, the early diastolic annular velocity; EF, ejection fraction; HR, heart rate; HRE, hypertensive response to exercise; HRR, heart rate reserve; IVSd, interventricular septal end-diastolic dimension; LAVI, left atrial volume index; LVEDD, left ventricle end-diastolic dimension; LVESD, left ventricle end-systolic dimension; LVMI, left ventricle mass index; MET, metabolic equivalent task; peak $VO_2$, peak oxygen consumption; PWd, pulse wave Doppler; RER, respiratory exchange ratio; SBP, systolic blood pressure; S′, the peak systolic annular velocity; VE, ventilation; $VCO_2$, $CO_2$ production.

with age,[40,41] in older patients, brachial BP is a more accurate predictor of central BP. Therefore, HRE may be overestimated in younger patients who have higher pulse pressure amplification, which might result in the insignificant correlation between HRE and LAVI in younger patients.

**Correlation between vascular stiffness and HRE**

In this study, higher pulse pressure was found to be independently associated with HRE. Pulse pressure indirectly represents vascular function, and abnormal vascular function has been suggested as a possible mechanism for HRE. The major determinants of pulse pressure are arterial stiffness and the timing, and intensity of wave reflections.[42] However, only a few studies have evaluated the direct association between arterial stiffness,[43–45] or endothelial dysfunction,[46] with HRE. Although direct measurements of arterial stiffness were not performed in this study, our finding agrees with those of previous studies that have demonstrated the correlation of HRE with vascular function.

To properly evaluate the independent associations of various parameters to HRE, we have used CPET instead of the treadmill test. Zanettini *et al.*[14] have reported the influence exerted by the correction for work performance over HRE associations; however, they used METs, and echocardiographic parameters showed no correlation when adjusted with clinical parameters. By using CPET, we have corrected for the individual's exercise capacity and work load with objective parameters (RER and peak $VO_2$). Therefore, the fact that LAVI has an independent correlation which strengthens the association between LV diastolic dysfunction and HRE .

This study has several limitations. First, this is a human observational study, rather than an interventional study, which makes identifying a direct cause and effect relationship difficult. Due to the cross-sectional design of the study, we could not directly assess the effect of increased LAVI on HRE. Also medications could not be controlled. Second, as there is no universal definition of HRE, results may vary when other definitions are used. Third, endothelial function and arterial stiffness were not evaluated in this cohort.

Despite the fact that HRE is a risk factor for future hypertension and cardiovascular events, CPET is not a recommended preliminary assessment for hypertension. However, HRE might be an easily available clinical marker of LV diastolic dysfunction or impaired arterial stiffness.

**Table 4 Univariate logistic regression analysis for predictors of hypertensive response to exercise**

| | *Control group* | | *Hypertensive group* | |
|---|---|---|---|---|
| | *Unstandardized β coefficient (95% CI)* | P-*value* | *Unstandardized β coefficient (95% CI)* | P-*value* |
| Age | 1.146 (1.029–1.277) | 0.013 | 0.989 (0.958–1.021) | 0.989 |
| Sex | 2.227 (0.403–12.294) | 0.358 | 1.509 (0.730–3.118) | 0.267 |
| BMI | 1.209 (0.971–1.505) | 0.089 | 1.016 (0.914–1.129) | 0.775 |
| Total cholesterol | 1.004 (0.980–1.028) | 0.767 | 1.007 (0.996–1.018) | 0.196 |
| Exercise duration | 0.997 (0.991–1.002) | 0.198 | 1.001 (0.999–1.004) | 0.210 |
| METs | 0.740 (0.448–1.223) | 0.240 | 1.202 (0.965–1.498) | 0.101 |
| Peak $VO_2$ | 0.919 (0.797–1.060) | 0.919 | 1.054 (0.990–1.123) | 0.099 |
| Pet $CO_2$ | 1.054 (0.905–1.228) | 0.501 | 1.070 (0.988–1.157) | 0.095 |
| VE-$VO_2$ slop | 0.982 (0.817–1.179) | 0.843 | 0.896 (0.815–0.985) | 0.024 |
| Baseline BP | 1.073 (1.010–1.140) | 0.023 | 1.110 (1.067–1.154) | <0.001 |
| Delta BP | 1.105 (1.036–1.178) | 0.002 | 1.079 (1.047–1.112) | <0.001 |
| Pulse pressure | 1.087 (1.002–1.180) | 0.045 | 1.087 (1.041–1.134) | <0.001 |
| Ejection fraction | 1.074 (0.925–1.248) | 0.347 | 0.972 (0.908–1.040) | 0.405 |
| LVEDD | 0.934 (0.767–1.138) | 0.499 | 1.078 (0.985–1.179) | 0.102 |
| IVSd | 0.771 (0.388–1.533) | 0.458 | 1.194 (0.867–1.645) | 0.277 |
| LV mass index | 0.982 (0.934–1.032) | 0.473 | 1.020 (0.999–1.042) | 0.066 |
| LA volume index | 0.992 (0.858–1.148) | 0.916 | 1.080 (1.014–1.150) | 0.017 |
| E/A | 0.000 (0.000–0.192) | 0.022 | 0.806 (0.208–3.124) | 0755 |
| DT | 1.027 (1.004–1.051) | 0.023 | 1.007 (0.997–1.017) | 0.198 |
| E′ | 0.512 (0.279–0.941) | 0.031 | 0.966 (0.810–1.152) | 0.700 |
| E/E′ | 1.756 (1.104–2.794) | 0.017 | 1.087 (0.955–1.236) | 0.207 |

Abbreviations: A, late diastolic filling velocity; BMI, body mass index; BP, blood pressure; CI, confidence interval; DT, deceleration time of early filling velocity; E, the peak early filling velocities; E', the early diastolic annular velocity; IVSd, interventricular septal end-diastolic dimension; LA, left atrium; LV, left ventricle; LVEDD, left ventricle end-diastolic dimension; MET, metabolic equivalent task; peak $VO_2$, peak oxygen consumption; PET $CO_2$, end-tidal $CO_2$ pressure; VE, ventilation; $VCO_2$, $CO_2$ production.

**Table 5 Multivariate analysis for predictors of hypertensive response to exercise (Adjusted for age, sex, BMI, peak $VO_2$)**

| | *Control group* | | *Hypertensive group* | |
|---|---|---|---|---|
| | *Unstandardized β coefficient (95% CI)* | P-*value* | *Unstandardized β coefficient (95% CI)* | P-*value* |
| Baseline BP | 1.190 (1.007–1.406) | 0.041 | 1.121 (1.072–1.172) | <0.001 |
| Delta BP | 1.307 (0.981–1.740) | 0.067 | 1.104 (1.062–1.147) | <0.001 |
| LV mass index | 0.958 (0.893–1.029) | 0.238 | 1.021 (0.997–1.045) | 0.082 |
| LA volume index | 1.008 (0.826–1.230) | 0.936 | 1.082 (1.013–1.157) | 0.020 |
| E/A | 0.000 (0.000–6.596) | 0.091 | 0.369 (0.058–2.356) | 0.292 |
| DT | 1.027 (0.992–1.064) | 0.133 | 1.007 (0.996–1.018) | 0.210 |
| E′ | 0.965 (0.466–1.997) | 0.923 | 0.908 (0.713–1.156) | 0.433 |
| E/E′ | 1.301 (0.748–2.262) | 0.352 | 1.122 (0.960–1.311) | 0.149 |
| Pulse pressure | 1.099 (0.985–1.227) | 0.092 | 1.119 (1.063–1.177) | <0.001 |

Abbreviations: A, late diastolic filling velocity; BMI, body mass index; BP, blood pressure; CI, confidence interval; DT, deceleration time of early filling velocity; E, the peak early filling velocities; E', the early diastolic annular velocity; LA, left atrium; LV, left ventricle; peak $VO_2$, peak oxygen consumption.

**Table 6 Independent correlates of left atrial volume index in hypertensive patients**

| | *Age < 55* | | *Age ⩾ 55* | |
|---|---|---|---|---|
| *Independent variable* | *Standardized β* | P-*value* | *Standardized β* | P-*value* |
| Age | 0.146 | 0.456 | 0.013 | 0.931 |
| Sex | 0.166 | 0.470 | 0.302 | 0.046 |
| Body mass index | 0.293 | 0.110 | 0.185 | 0.128 |
| Peak $VO_2$ | 0.087 | 0.753 | 0.068 | 0.679 |
| HRE | 0.221 | 0.181 | 0.270 | 0.026 |

Abbreviations: HRE, hypertensive response to exercise; peak $VO_2$, peak oxygen consumption.

In conclusion, higher LAVI, a marker for the increased duration and severity of left atrial pressure, is independently correlated with HRE in patients with hypertension. The present study provides an important mechanistic relationship between HRE and impaired LV diastolic function, which can be measured by echocardiographic parameters.

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