Original Article

Increased aortic augmentation index is associated with reduced exercise capacity after heart transplantation

Kyeong-Hyeon Chun[a], Chan Joo Lee[a], Jaewon Oh[a], Chihyeong Won[b], Taeyoon Lee[b], Sungha Park[a], Sang-Hak Lee[a], and Seok-Min Kang[a]

Objective: Exercise capacity is often reduced after heart transplantation. We aimed to investigate the association between aortic stiffness and exercise capacity after heart transplantation.

Methods: We retrospectively analyzed the data of patients who underwent a cardiopulmonary exercise test and central hemodynamic measurements over 1 year following heart transplantation, from Janary 2011 to June 2018.

Results: A total of 54 patients (mean age, 49 years; 72% men) were analyzed. The median peak oxygen uptake level was 21.1 ml/kg per min at a median time of 13 months after heart transplantation. In univariate linear regression, recipient age, pulmonary arterial pressure, pulmonary capillary wedge pressure, hemoglobin level, estimated glomerular filtration rate, aortic augmentation index, and pulse wave velocity were significant predictors for peak oxygen uptake level. After adjustment for other confounding variables, heart rate-corrected aortic augmentation index was a significant predictor for peak oxygen uptake ($\beta = -0.141$, 95% confidence interval, -0.263 to -0.058, $P = 0.003$).

Conclusion: In the present study, increased aortic augmentation index was associated with reduced exercise capacity after heart transplantation. Therefore, this simple measurement of aortic stiffness should be periodically used for the evaluation of exercise capacity after heart transplantation.

Keywords: aortic stiffness, cardiopulmonary exercise test, heart transplantation, oxygen consumption

Abbreviations: Aix, augmentation index; Aix@75, augmentation index standardized to heart rate of 75 beats per minute; CPET, cardiopulmonary exercise test; PCWP, pulmonary capillary wedge pressure; peak VO_2, peak oxygen uptake; PWV, pulse wave velocity

INTRODUCTION

Cardiopulmonary exercise test (CPET) is a reliable test for evaluation of the cardiopulmonary fitness, even in elderly patients with cardiovascular diseases [1]. It provides gas exchange measures of O_2 uptake, CO_2 output and ventilation. Measured maximum value of O_2 uptake during exercise, peak oxygen uptake (peak VO_2), is the most objective assessment of exercise capacity. Peak VO_2 is not only an important predictor of survival in heart failure with reduced ejection fraction patients but also determines whether heart transplantation may be needed [2,3].

In addition, posttransplant peak VO_2 is well known to be associated with functional capacity and long-term survival [4]. Although exercise capacity usually improves after heart transplantation, some recipients experience less recovery of peak VO_2 [5]. This may be because of physical deterioration resulting from previous heart failure, comorbidities, and impairment of hemodynamics after heart transplantation. However, there is a lack of studies about factors that play a role in determining exercise capacity in heart transplantation recipients.

Aortic stiffness is a measure of the elastic property of large arteries and wave reflection, and its role has been proven as a cardiovascular risk assessment marker [6]. A recent study has shown that aortic stiffness is associated to impaired exercise capacity in coronary artery disease patients [7]. Aortic stiffness can be assessed easily by noninvasive technique, therefore, it may be measured in the early postoperative period.

To our knowledge, the clinical implication of aortic stiffness has not been assessed in heart transplantation recipients. Therefore, we set out to investigate the association between aortic stiffness and exercise capacity in heart transplantation recipients.

METHODS

Study population and baseline characteristics

We retrospectively analyzed the clinical data of the patients who underwent CPET and central hemodynamic measurements following heart transplantation from January 2011 to

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[a]Division of Cardiology, Department of Internal Medicine, Severance Cardiovascular Hospital, Cardiovascular Research Institute, Yonsei University College of Medicine and [b]School of Electrical and Electronic Engineering, Yonsei University, Seoul, Republic of Korea

Correspondence to Seok-Min Kang, MD, PhD, Division of Cardiology, Department of Internal Medicine, Yonsei University College of Medicine, 50-1, Yonsei-Ro, Seodaemun-gu, Seoul, 03722, Republic of Korea. Tel: +82 2 2228 8450; fax: +82 2 2227 7732; e-mail: smkang@yuhs.ac

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June 2018 in a single tertiary university hospital. A total of 143 patients received heart transplantation during the study period, and recipients and donors' information were collected. In the present study, we included the patients who underwent both the CPET and central hemodynamic measurements between 1 and 2 years after heart transplantation. Finally, a total of 54 patients could be analyzed. They underwent CPET after a median time of 13 months [interquartile range (IQR) 12–14] and central hemodynamic test after a median of 6 months (IQR 1–13) after heart transplantation. Hypertension was defined as both previously diagnosed essential hypertension before heart transplantation and the need for antihypertensive agents to control blood pressure after heart transplantation. Endomyocardial biopsy for graft rejection evaluation and coronary angiography to evaluate cardiac allograft vasculopathy were performed according to the schedule for each patient. Rejection grade was reported based on the revised rejection grading system by the International Society of Heart and Lung Transplantation (ISHLT) and cardiac allograft vasculopathy grade was reported according to the previous ISHLT document [8,9]. At the same time as the biopsy, we performed right-sided cardiac catheterization to measure pulmonary capillary wedge pressure (PCWP), pulmonary artery pressure (systolic, mean), right ventricular (RV) pressure, and central venous pressure.

Eligibility was confirmed and written informed consent were obtained from all participants and the study was approved by the Institutional Review Board of the Yonsei University Health System (4-2013-0665, 4-2019-1203).

Cardiopulmonary exercise test

Functional exercise capacity was evaluated during maximal treadmill exercise test using the Bruce RAMP protocol with exercise testing system CASE T2100 (GE Healthcare, Chicago, Illinois, USA) under the supervision of a cardiologist. Respiratory gas exchange analysis was performed throughout exercise protocol with an ergospirometry system Quark CPET corival (COSMED, Rome, Italy). The heart rate (HR) and heart rhythm were continuously monitored via 12-lead electrocardiogram during exercise and recovery phases. Peak VO_2 was defined as the highest VO_2 achieved by the patient during the test (values for VO_2 were indexed to body weight) and obtained by averaging the last 30 s of the CPET data. Measured gas exchange variables included peak VO_2, lactate threshold, carbon dioxide production (VCO_2), minute ventilation (VE), respiratory exchange ratio, and HR reserve. The value of VE/VCO_2 slope was determined with rest-peak values for minute ventilation and VCO_2 [10]. Baseline brachial blood pressure (BP) was measured in the sitting position just before the test.

Trans-thoracic echocardiography

All patients underwent trans-thoracic echocardiography. Two-dimensional and Doppler echocardiography were performed with a commercially available echocardiographic unit equipped with a 2.5 MHz transducer having both pulsed wave and tissue Doppler capability (Vivid 7; GE Medical System, Milwaukee, Wisconsin, USA). Left ventricle (LV) diastolic and systolic dimensions, LV ejection fraction (LVEF), left atrial volume index (LAVI), mitral inflow velocity (E velocity), and early diastolic velocity of the mitral annulus (E' velocity) were measured.

Noninvasive central hemodynamic measurements

Central hemodynamics were evaluated in the sitting position after 10 min of rest using the SphygmoCor system (AtCor Medical, Sydney, Australia). A high-fidelity micromanometer (Millar Instruments, Houston, Texas, USA) was used to record peripheral pressure waveforms from the radial arteries as reported previously [11,12]. The SphygmoCor system obtains the ascending aortic pressure waveform from the radial artery waveform using its validated mathematical transfer function. Central SBP, DBP, pulse pressure, augmentation pressure, and augmentation index (Aix) were acquired from the aortic pressure waveform analyses and brachial cuff BP measured by oscillometric devices, and radial BP was calibrated from radial artery waveform and mean brachial BP in the supine position. Augmentation pressure is the difference between the second and first systolic peak pressures, and Aix is defined as the ratio of augmentation pressure to the aortic pulse pressure. Also, we calculated the Aix, standardized to HR of 75 beats per minute (Aix@75), as previously described [13]. During the measurements, normal sinus rhythm was maintained in all patients. To control for the quality of recorded waveforms, visually acceptable recordings of a peripheral pulse-waveform were only accepted if the variations in pulse height, diastole, and pulse length were equal or less than 5% and if the mean pulse height was above 80 mV as expressed by an operator index (%) provided by the SphygmoCor software. Only measurements with an index greater than 80% were accepted, and the exam was repeated to get the best operator index [14].

The pressure waveforms were exported, and waveform analysis was performed using custom-designed software and MATLAB algorithms (MathWorks, Natick, Massachusetts, USA) [15]. The PU-loop method was used to determine the relationship between aortic pressure and aortic flow velocity. During early systole, local wave velocity was estimated from the slop of the PU-loop, which is equal to ρc. The aortic flow shape was then simulated by c, the wave speed, and by ρ, the density of blood, which is virtually constant. The central aortic pressure wave was separated into forward (Pf) and backward pressure waves (Pb) using measured pressure (P_m), simulated flow (S_f), and characteristic impedance (Z_c). Z_c was calculated as the ratio of pressure and flow. The Pf and Pb values were calculated using the following equation:

$$\mathrm{Pf} = [\mathrm{P_m} + \mathrm{S_f} \times \mathrm{Z_c}]/2, \quad \mathrm{Pb} = [\mathrm{P_m} - \mathrm{S_f} \times \mathrm{Z_c}]/2.$$

Reflection magnitude was calculated as $100 \times (\mathrm{Pb}/\mathrm{Pf})$ (%) [16].

The pulse wave velocity (PWV) was measured as specified previously [17]. The electrocardiogram and carotid/femoral pulse waves were obtained simultaneously to calculate the transit time using the foot-to-foot method. The distance traveled by the pulse wave was calculated by subtracting the distances between the sternal notch-right carotid site from the right femoral site-sternal notch [17].

Statistical analysis

Data are presented as mean ± standard deviation (SD) or frequency (percentage) wherever applicable. Correlation analysis with peak VO_2 was performed with Pearson's method. Comparisons between the groups were made with the Student's *t*-test for unpaired data for continuous variables and by the chi-square test for categorical variables. In case of serious deviation from the normal distribution, median value and IQR and a Wilcoxon rank-sum test were used. Clinical and hemodynamic differences were compared among these groups. Clinically relevant variables associated with peak VO_2 in the comparison analysis were evaluated with a univariate linear regression model, and then clinically relevant variables with *P* value of less than 0.1 were entered into multivariate model as significant covariates. In multivariate linear regression model, among central hemodynamic measurements, which represent aortic stiffness, Aix@75, and PWV were first entered into the model as representatives considering a multicollinearity of augmentation pressure, Aix, and Aix@75. Then, reflection magnitude was entered into another model, instead of PWV, for analysis of contributing factors. Also, mean arterial BP (MAP) was entered into the model and calculated from brachial cuff BP and radial artery waveform at the time of central hemodynamic measurements, using following equation:

$$\mathrm{MAP} = \sum_{t=T0}^{Tf} \frac{Pi}{n}$$

(*Tf*, time period of one cardiac cycle; *Pi*, pressure points; *n*, number of pressure points). In the supplementary data, we divided the study population into four groups by age and Aix@75, and used Bonferroni correction for the purpose of a post hoc analysis. Statistical analysis was carried out with R software (version 3.5.3, R Foundation for Statistical Computing, Vienna, Austria), assuming a threshold of significance at *P* less than 0.05.

TABLE 1. Baseline characteristics of the study patients

Variables	Total (*N* = 54)
Clinical characteristics	
Age (years)	49 ± 15
Male sex (*n*, %)	39 (72%)
Follow-up duration (months)	34 ± 14
BMI (kg/m^2)	23.2 ± 3.3
Height (cm)	165.9 ± 7.1
NYHA class (%)	
I	52 (96%)
II	2 (4%)
Donor characteristics	
Age (years)	40 ± 10
Male sex (*n*, %)	32 (59%)
BMI (kg/m^2)	24.1 ± 3.5
Height (cm)	166.7 ± 8.6
LV EF (%)	62.1 ± 8.0
Cause (*n*, %)	
Ischemic CMP	11 (20%)
Nonischemic CMP	
DCMP	23 (43%)
HCMP	7 (13%)
VHD	7 (13%)
Others	6 (11%)
Comorbidities (*n*, %)	
Hypertension	32 (59%)
Diabetes	31 (57%)
CKD	23 (43%)
Medication (*n*, %)	
Mycophenolate	47 (87%)
Tacrolimus	52 (96%)
Cyclosporin	2 (4%)
Everolimus	7 (13%)
Prednisolone	27 (50%)
RAS inhibitors	2 (4%)
Beta-blockers	3 (6%)
CCBs	19 (35%)
Diuretics	5 (9%)
Statins	44 (82%)

BSA, body surface area; NYHA, New-York Heart Association; LV EF, LV ejection fraction; CMP, cardiomyopathy; DCMP, dilated cardiomyopathy; HCMP, hypertrophic cardiomyopathy; HF, heart failure; CKD, chronic kidney disease; RAS, renin–angiotensin–aldosterone system; CCBs, calcium-channel blockers.

RESULTS

Baseline characteristics

The characteristics of study patients are shown in Table 1. Mean (±SD) age of recipients was 49 ± 15 years with 39 (72%) of male and mean LV EF was 67.3 ± 5.9%. The most common cause for heart transplantation was dilated cardiomyopathy (43%), followed by ischemic cardiomyopathy (20%). Thirty-two (59%) of the patients have been diagnosed with hypertension or are currently on antihypertensive medications. All coronary angiographies showed no significant lesion of severe cardiac allograft vasculopathy, and all endomyocardial biopsy showed no grade 2 or more acute rejection. The CPET data, laboratory tests, echocardiographic parameters, right-sided cardiac catheterization, and noninvasive central hemodynamic measurements are also shown in Table 2. The mean value of operator indices of the central hemodynamic measurements was 97.7%, and all measurements were acceptable. At the time point of central hemodynamic measurement, central and radial SBP/DBP were 112.3 ± 13.4/82.5 ± 11.3 and 127.2 ± 15.1/80.6 ± 9.7 mmHg, respectively, and hazard ratio was 88.3 ± 9.2 bpm. In terms of medication, three patients (9%) of the study population had been prescribed beta-blockers.

Differences according to peak oxygen uptake in cardiopulmonary exercise test data

The CPET data showed that the median peak VO_2 level was 21.1 ml/kg per min. When we divided these variables into low exercise capacity (peak $VO_2 < 21.1$ ml/kg per min, $n = 27$) and high exercise capacity (peak $VO_2 \geq 21.1$ ml/kg per min, $n = 27$) group according to the peak VO_2 value, there were no significant differences in these baseline variables between the two groups (Supplementary Table 1, http://links.lww.com/HJH/B332). Echocardiographic findings had no significant differences between the two groups, but there were significant differences in hemoglobin levels, the right-sided cardiac catheterization measurements including PCWP, pulmonary artery pressure (systolic, mean) and central venous pressure, and central hemodynamic parameters including Aix and Aix@75 (shown in Supplementary Table 2, http://links.lww.com/HJH/B332). These results suggest that the

TABLE 2. Cardiopulmonary exercise, laboratory, echocardiographic, and hemodynamic findings

Variables	Total ($N = 54$)
Cardiopulmonary exercise test	
Peak VO_2 (ml/kg per min)	21.8 ± 6.2
RER	1.1 ± 0.1
Lactate threshold (ml/kg per min)	18.2 ± 7.3
VE/VCO_2 slope	35.0 [29.4, 39.7]
Base SBP/DBP (mmHg)	118.9 ± 13.5/79.4 ± 13.2
Base heart rate (bpm)	94 [88, 102]
Peak heart rate (bpm)	150 [131, 160]
HR reserve (bpm)	51 [41, 65]
HR reserve, % predicted (%)	71.5 [53.3, 86.0]
Laboratory findings	
Hemoglobin (g/dl)	12.5 ± 1.8
BUN (mg/dl)	21.1 ± 8.0
eGFR (ml/min per 1.73 m^2)	74.0 ± 16.4
NT-proBNP (pg/ml)	282 [137, 405]
Echocardiographic parameters	
LVEDD (mm)	43.7 ± 4.0
LV EF (%)	67.3 ± 5.9
LAVI (ml/m^2)	42.2 ± 15.7
E/e′	10.4 ± 3.3
RV systolic pressure (mmHg)	29.1 ± 6.8
Right-sided cardiac catheterization	
PCWP (mmHg)	8.8 ± 5.1
Pulmonary arterial pressure (systolic) (mmHg)	22.0 ± 8.0
Pulmonary arterial pressure (mean) (mmHg)	14.0 ± 5.9
RV systolic pressure (mmHg)	24.2 ± 7.2
Central venous pressure (mmHg)	2.9 ± 3.2
Noninvasive central hemodynamic measurements	
Central/radial SBP (mmHg)[a]	112.3 ± 13.4/127.2 ± 15.1
Central/radial DBP (mmHg)[a]	82.5 ± 11.3/80.6 ± 9.7
Central pulse pressure (mmHg)	30.4 ± 11.3/47.7 ± 13.4
Base heart rate (bpm)	88.3 ± 9.2
PWV (m/s)	8.8 ± 2.5
Aortic augmentation pressure (mmHg)	3.1 ± 5.4
Aortic augmentation index (%)	7.7 ± 15.7
Aix@75 (%)	14.5 ± 14.7
Waveform analysis	
Forward wave amplitude (mmHg)	26.0 ± 5.6
Backward wave amplitude (mmHg)	14.9 ± 5.7
Reflection magnitude (%)	58.8 ± 22.6

RER, respiratory exchange ratio; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; LVEDD, LV end-diastolic dimension; LVESV, LV end-systolic dimension; LV EF, LV ejection fraction; LAVI, left atrium volume index; PCWP, pulmonary capillary wedge pressure; BP, blood pressure; PWV, pulse wave velocity; Aix@75, Aortic augmentation index (at heart rate 75 beats per minute).
[a]Radial systolic/diastolic BP calibrated from mean brachial BP.

patients in low exercise capacity group had increased aortic stiffness compared with the high exercise capacity group.

Association of aortic augmentation index with peak oxygen uptake

Scatter diagram and a Pearson's correlation analysis showed the association between surrogate markers of aortic stiffness and peak VO_2 level, and it revealed that there were significant correlations, respectively (AP, $R = -0.41$, $P = 0.003$; Aix, $R = -0.45$, $P = 0.001$; Aix@75, $R = -0.53$, $P < 0.001$; PWV, $R = -0.37$, $P = 0.006$, Fig. 1). As the absolute coefficient value was highest and *P*-value was lowest in the correlation between Aix@75 and peak VO_2 among these central hemodynamic measurements, we analyzed peak VO_2 value according to Aix@75. heart transplantation recipients with high Aix@75 (≥16.5%) had a lower peak VO_2 (19.2 ± 5.6 vs. 24.1 ± 6.1 ml/kg per min, $P = 0.004$, Fig. 2a).

Univariate linear regression analysis revealed that recipient age, PCWP, pulmonary arterial pressure, hemoglobin level, estimated glomerular filtration rate, AP, Aix, Aix@75, and PWV were significant predictors for peak VO_2 (Table 3). As shown in Supplementary Table 3, http://links.lww.com/HJH/B332, multivariate linear regression analysis showed Aix@75 was an independent determinant of peak VO_2 level (model 1, $\beta = -0.148$, 95% CI −0.255 to −0.041, $P = 0.008$) when adjusting for PWV as a contributing factor, and the significant association of Aix@75 remained (model 2, $\beta = -0.141$, 95% CI −0.263 to −0.058, $P = 0.003$) after adjustment for reflection magnitude as another contributing factor. When adjusted for HR at baseline, Aix was also an independent determinant (Supplementary Table 4, http://links.lww.com/HJH/B332) when analyzed with PWV or reflection magnitude as a contributing factor. Additionally, we adjusted for sex, MAP, and body height, all of which are known as confounding factors for Aix [18–21]. As shown in Table 4, Aix@75 was still significantly associated with the peak VO_2 level when analyzed with PWV or reflection magnitude as a contributing factor (model 1, $\beta = -0.127$, 95% CI −0.253 to −0.002, $P = 0.047$, model 2, $\beta = -0.124$, 95% CI −0.245 to −0.003, $P = 0.045$, respectively). Taken together, we deemed that HR-adjusted Aix has a significant association with peak VO_2 in heart transplantation recipients.

In addition, we analyzed the effect of age and aortic stiffness on exercise capacity by subgroup analysis according to age (age below or above 50 years) of the study population. There was a linear positive correlation in PWV with recipient age ($R = 0.57$, $P < 0.001$), but there were no significant correlations in other aortic stiffness parameters with recipient age (Supplement Figure 1, http://links.lww.com/HJH/B332). In the relatively young age group (<50 years), low Aix@75 (<16.5%) had significantly higher peak VO_2 level (27.2 ± 6.4 vs. 19.0 ± 2.7, $P = 0.006$ by Bonferroni correction, Fig. 2b) than high Aix@75 group.

The female sex had a greatest absolute value of the coefficient in univariate analysis, however, there was a no statistical significance ($\beta = -2.537$, $P = 0.179$, Table 3) in the present study. When we analyzed the effect of sex difference on association of exercise capacity with aortic stiffness, there was no significant difference of peak VO_2 level in the subset of each sex and the Aix@75 groups (data not shown).

DISCUSSION

The main findings of the present study show that Aix has a negative correlation with exercise capacity in the heart transplantation recipients. We found that the HR-adjusted Aix was a still significant determinant for peak VO_2 value. Among the parameters of central hemodynamic measurements, Aix was a significant independent predictor for peak VO_2 value in the study population. As Aix@75 is a value of Aix standardized to a HR of 75 bpm and easy to calculate from the aortic pressure waveform calculated by software performing central hemodynamic measurement, it is a single meaningful parameter in heart transplantation recipients, considering they have variable baseline HR [22]. This

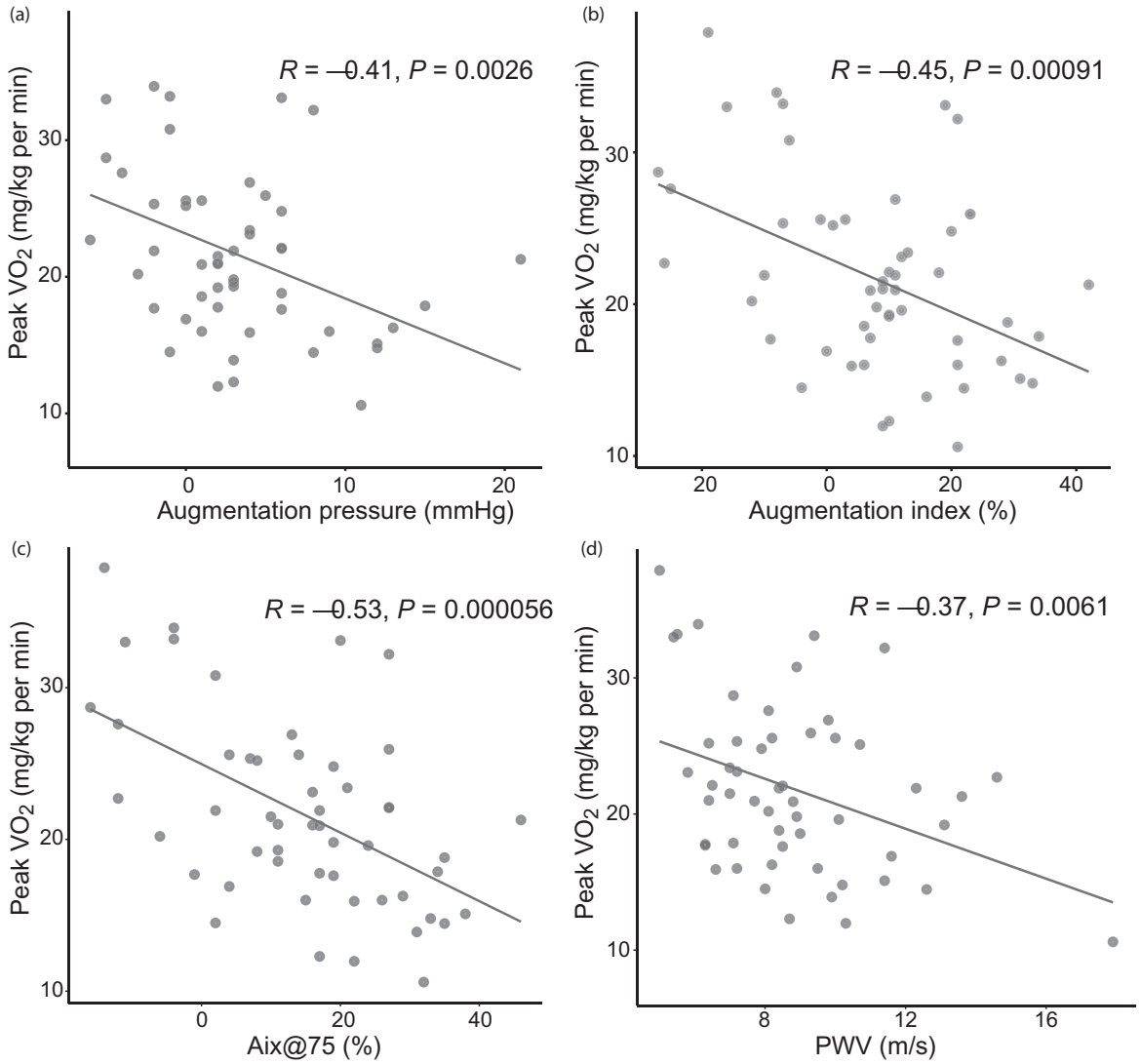

FIGURE 1 Correlation plot between aortic stiffness parameters and peak VO_2. Peak VO_2 level was significantly correlated with augmentation pressure (a), augmentation index (b), Aix@75 (c), and pulse wave velocity (d). Aix@75, aortic augmentation index (at heart rate 75 beats per minute).

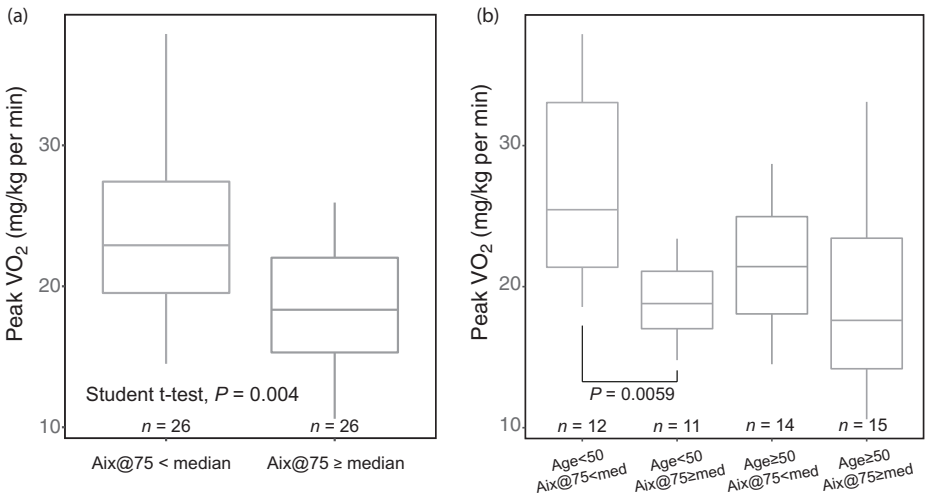

FIGURE 2 (a) Values of peak VO_2 between high and low Aix@75 (cutoff = 16.5%: median value of Aix@75). (b) Values of peak VO_2 in younger and older recipients with high and low Aix@75. Peak VO_2 of high Aix@75 patients was significantly lower than those with low Aix@75 in younger (<50 years) age group ($P = 0.0059$). Aix@75, aortic augmentation index (at heart rate 75 beats per minute).

TABLE 3. Univariate linear regression analysis to determine factors for peak VO_2

Variables	Coefficient	95% CI	*P* value
Demographics			
Recipient age	−0.162	−0.272 to −0.052	0.005
Donor age	−0.023	−0.202 to 0.155	0.793
Female sex	−2.537	−6.278 to 1.204	0.179
Height	0.203	−0.034 to 0.439	0.091
BMI	0.089	−0.438 to 0.617	0.735
Usage of beta-blockers	−5.582	−12.862 to 1.699	0.130
Echocardiographic parameter			
LV EF	0.007	−0.284 to 0.299	0.961
E/*e*′	−0.164	−0.727 to 0.400	0.561
LAVI	−0.072	−0.183 to 0.039	0.199
Right-sided cardiac catheterization			
PCWP	−0.380	−0.720 to −0.041	0.029
Pulmonary arterial pressure (systolic)	−0.243	−0.449 to −0.036	0.022
Pulmonary arterial pressure (mean)	−0.357	−0.635 to −0.080	0.013
RV systolic pressure	−0.216	−0.449 to 0.018	0.070
Central venous pressure	−0.607	−1.123 to −0.091	0.022
Laboratory findings			
Hemoglobin	1.271	0.395–2.147	0.005
eGFR	0.148	0.050–0.246	0.004
Noninvasive central hemodynamic measurements			
PWV	−0.917	−1.561 to −0.274	0.006
Aortic augmentation pressure	−0.474	−0.775 to −0.174	0.003
Aortic augmentation index	−0.179	−0.281 to −0.077	0.001
Aix@75	−0.226	−0.329 to −0.123	<0.001
Waveform analysis			
Forward wave amplitude	−0.001	−0.313 to 0.301	0.968
Backward wave amplitude	−0.226	−0.522 to 0.070	0.132
Reflection magnitude	−0.063	−0.137 to 0.011	0.094

Aix@75, aortic augmentation index (at heart rate 75 beats per minute); eGFR, estimated glomerular filtration rate; LAVI, left atrium volume index; LV EF, left ventricle ejection fraction; PCWP, pulmonary capillary wedge pressure; PWV, pulse wave velocity.

is the first study to show an association of exercise capacity with Aix in heart transplantation recipients.

In heart transplantation recipients, postoperative exercise capacity is meaningful as it is associated with quality of life and it is one of prognostic factors for long-term clinical outcome [4,22]. However, specific conditions related to heart transplantation can affect the measurement of oxygen uptake at peak exercise. In the early phase after heart transplantation, cardiac denervation status diminishes exercise capacity as a slow increase in HR in response to exercise [23]. Although the exercise capacity improves over time even after the first year, peak VO_2 value in heart transplantation recipient usually is below 20 ml/kg per min [24]. There have been a few reports that address the clinical determinants for VO_2 in de novo heart transplantation recipients. From a cross-sectional study of 140 heart transplantation recipients, Osada *et al.* [25] demonstrated that preoperative peak VO_2 and the younger age of recipients were significant predictors of a 1-year postoperative improvement in peak VO_2. From another study of 85 heart transplantation recipients, Douard *et al.* [26] has shown that donor age was also a significant predictor of postoperative peak VO_2 level. In addition, Leung *et al.* [24] showed in their analysis of 95 heart transplantation recipients that the male sex is also an independent factor for high posttransplant peak VO_2 value. In addition to these clinical demographics, other CPET parameters, such as O_2 pulse, HR reserve, and muscular exercise capacity were shown to be independent predictors for the posttransplant peak VO_2 value [5]. However, in the present study, we focused on the effect of the vascular system, especially the

TABLE 4. Multivariate linear regression analysis including the clinically meaningful variables to determine factors for peak VO_2 according to aortic augmentation index (at heart rate 75 beats per minute)

Variables	Model 1 coefficient beta [95% CI]	*P* value		Model 2 coefficient beta [95% CI]	*P* value
Recipient age	−0.089 [−0.236 to 0.059]	0.231	Recipient age	−0.134 [−0.261 to −0.007]	0.039
Hemoglobin	0.664 [−0.246 to 1.575]	0.148	Hemoglobin	0.628 [−0.246 to 1.501]	0.154
Egfr	0.050 [−0.076 to 0.176]	0.429	eGFR	0.042 [−0.073 to 0.156]	0.468
PCWP	−0.275 [−0.583 to 0.033]	0.079	PCWP	−0.185 [−0.480 to 0.114]	0.215
PWV	−0.436 [−1.174 to 0.301]	0.238	RM	−0.064 [−0.133 to 0.005]	0.067
Aix@75	−0.127 [−0.253 to −0.002]	0.047	Aix@75	−0.124 [−0.245 to −0.003]	0.045
Female sex	−3.039 [−7.725 to 1.648]	0.197	Female sex	−3.40 [−7.845 to 1.049]	0.130
MAP	−0.011 [−0.163 to 0.140]	0.880	MAP	−0.043 [−0.188 to 0.103]	0.555
Height	−0.122 [−0.395 to 0.172]	0.430	Height	−0.055 [−0.323 to 0.214]	0.681

Aix@75, aortic augmentation index (at heart rate 75 beats per minute); eGFR, estimated glomerular filtration rate; MAP, mean arterial blood pressure; PCWP, pulmonary capillary wedge pressure; PWV, pulse wave velocity; RM, reflection magnitude.

aorta/arterial bed function. The aorta contributes most of the compliance in the systemic arterial bed and the decreased aortic distensibility affects the ventricular afterload.

This association may have a unique point in that denervated hearts do not initially have sufficient chronotropic response that tends to improve gradually after heart transplantation. The HR reserve is known to be an important determinant of peak VO_2 early after heart transplantation [5]. In our study population, chronotropic response was significantly impaired as the median percentage of age-predicted HR reserve was 71.5%, which is usually considered to be reduced at 80% or lower [27]. Thus, it is important to find another factor related to exercise capacity in the patients with restored cardiac contractility and impaired chronotropic response following heart transplantation.

In the present study, the results showed that the recipients with stiff arterial system have reduced peak VO_2 level. Among the several parameters, Aix@75 is the most powerful parameter, which was associated with peak VO_2 level, independent of the other variables. As heart transplantation recipients may have a wide range of baseline HR because of their heterogeneous cardiac reinnervation status and individual difference of sympathetic tone, indexed parameter corrected with HR (75 beats per minute) could be the most powerful and easily obtained predictor among aortic stiffness measurements. In general, stiffened arteries reduce the cushioning effect of the arterial system, which attenuate the force from stroke volume, leading to increase aortic systolic pressure and pulse pressure, and therefore, increased left ventricular afterload and myocardial workload and oxygen demand [28]. There have been a few studies that showed the inverse association between exercise capacity and surrogate markers of arterial stiffness in general population and also in coronary artery disease with a history of myocardial infarction [7,29]. However, there was no data regarding the association between aortic stiffness and exercise capacity in heart transplantation recipients.

There are several factors that may affect aortic stiffness after solid organ transplantation. After heart transplantation, as with other organ transplant recipients, immunosuppressive therapy is needed, and most treatment regimens are based on the use of calcineurin inhibitors (CNI) and corticosteroids. As studied in kidney transplant recipients, CNI is known to contribute to vascular stiffness acceleration [30]. In addition, tacrolimus, one of the CNI, and corticosteroid are known to develop posttransplant diabetes, and consequently, it can affect aortic stiffness after transplant [31]. However, these results have not been studied in heart transplantation recipients, and no studies have shown that other medical interventions improved the progress of arterial stiffness after heart transplantation.

Aging is another factor to consider in both impaired exercise capacity and increased aortic stiffness after heart transplantation. As changes in vascular wall and increased aortic stiffness are associated with the process of atherosclerosis, aging is one of the most important factors [7]. Then, it is meaningful that Aix, not PWV, was a major determinant of exercise capacity in heart transplantation recipients. In fact, Aix is known to increase with MAP and age, and is inversely related to HR and body height [18–21]. In the present study, Aix was an independent predictor for peak VO_2 level after adjusting for age, MAP, height, and HR.

In general, both PWV and Aix are known as markers of arterial stiffness [32,33]. Moreover, as Aix is a composite measure of the magnitude of wave reflection and arterial stiffness, analysis with reflection magnitude was important to derive clinical implications. The waveforms of increased aortic Aix have higher magnitudes of reflection waves and shorter times to the second systolic peaks. As the reflection times (time to return of the reflected wave) differed among the study population, we obtained the magnitude of forward and backward pressure wave and calculated reflection magnitude. Introducing reflection magnitude into a new model, the significant association of Aix with peak VO_2 level remained even with adjusting for reflection magnitude as a contributing factor in the analysis. In addition, Aix@75 had significant association with peak VO_2 level in relatively young (<50 years) patients among the population. This finding is consistent with the result of other studies in cardiovascular disease in that increased arterial stiffness in younger patients represents a different biological vascular aging process compared with older patients [7,34,35]. Also, the previous study showed a similar result in the normal population that the influence of age is higher on the Aix than on aortic PWV in relatively young (<50 years) patients and higher on aortic PWV than on the Aix in older patients (>50 years) [36]. As higher Aix is a result of higher magnitudes of reflection waves from the peripheral arterial system and as it is possibly because of high peripheral vascular resistance in the same arterial stiffness, it could be inferred that reduced exercise capacity in relatively young heart transplantation recipients could be associated with their high peripheral vascular resistance. Moreover, it may be explained by the suggestion that the process of impaired exercise capacity is more complex in elderly patients because there are several confounding factors not only in the process of vascular aging but in other risk factors, such as peripheral factors (skeletal muscle exercise capacity) or respiratory function.

Taken together, Aix, which is dependent on the duration and pattern of ventricular ejection in addition to the nature of PWV, which represents intrinsically arterial stiffness [37], showed the significant association with exercise capacity owing to the interaction of restored ventricular function with aortic vascular bed after heart transplantation, especially in relatively young patients.

Limitation

As this study was a cross-sectional retrospective observational study, there were several limitations. First, missing data of CPET and central hemodynamic measurements in heart transplantation recipients within the study period might be a selection bias and no causal relationships should be drawn with the only association between aortic stiffness and peak VO_2 level. Second, we just observed the results around the 1-year time point after heart transplantation and did not show the long-term outcome of the study population. Also, we could not evaluate any change in aortic stiffness following heart transplantation because of lacking aortic stiffness data before heart transplantation and we did not have control patients. If we can assess the relationship between the long-term outcomes with aortic stiffening in heart transplantation recipients, it could be more meaningful

clinically. Moreover, as described above, measurements were performed in two different moments after heart transplantation: central hemodynamic data were obtained on a median of 6 months after heart transplantation and CPET on a median of 13 months after heart transplantation. This time difference could be a limiting factor to demonstrating the causal link between increased Aix and reduced peak VO_2 level in this study. Although there was a difference in measured BP between the two examinations, the position of BP measurement has affected the difference. Previous studies have shown that BP in the sitting position (measured during CPET) is significantly lower than supine BP (measured during SphygmoCor measurement) [38,39]. Therefore, a direct comparison between the two BP measurements may not accurately reflect the difference in BP. Also, even though there may be some differences in the value of Aix over time, Aix has been shown to be relatively consistent over time [40]. For this reason, we can carefully suggest that the value of Aix would provide useful information to expect the exercise capacity in this population. Finally, we could not show the effect of improved aortic stiffness on the exercise capacity by any interventions. For example, in patients with established coronary heart disease, there has been a study that aortic stiffness index was improved over a 20-week cardiac rehabilitation program [35]. Further prospective studies with cardiac rehabilitation or medical intervention, such as an alternative immunosuppressant other than CNI as mentioned above, are needed to better understand the improvement of arterial stiffness as well as exercise capacity after heart transplantation.

In conclusion, in the present study, central aortic Aix was associated with exercise capacity after heart transplantation. As cardiorespiratory exercise capacity is a major predictor of long-term mortality in heart transplantation recipients, the association of exercise capacity with Aix emphasizes the importance of the assessment of central hemodynamic measurement after heart transplantation. Further research is needed to validate this explanation and determine whether lowering Aix may improve not only exercise tolerance but also long-term outcomes in heart transplantation recipients.

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Conflicts of interest

There are no conflicts of interest.

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