Effect of Stiffened and Dilated Ascending Aorta on Aerobic Exercise Capacity in Repaired Patients With Complex Congenital Heart Disease

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Several studies have reported aortic dilation and increased stiffness of the ascending aorta in patients after repair of congenital heart disease (CHD), which may be a predominant cardiovascular risk. However, the clinical significance has not been described in detail. In this retrospective study, 175 repaired patients with complex CHD achieving biventricular circulation and age-matched 39 control subjects were reviewed (median age: 14.9 and 15.7 years, respectively). We measured the diameters of the ascending aorta and descending aorta from catheterization angiograms to yield Z-scores and stiffness indexes (β) using diameter fluctuations corresponding to pulsatile pressures. Clinical profile, peak oxygen uptake during the cardiopulmonary exercise test, and incidence of unscheduled hospitalization during follow-up was also reviewed. Compared with controls, patients with complex CHD, except for those with aortic coarctation, exhibited significant dilation and increased stiffness of the aortic root and ascending aorta, but not of the descending aorta. In this CHD population (n = 147, including 112 conotruncal anomalies), exercise capacities correlated independently with the diameter Z-score and stiffness index of the ascending aorta along with the history of repetitive thoracotomies, reduced forced vital capacity, and right ventricular hypertension. During a follow-up period (median 15.6 years), either dilation (Z-score >3.5) or increased stiffness (β >6.0) of the ascending aorta stratified morbidity, but no synergistic impact was detected. In conclusion, in repaired patients with complex CHD, a stiffened and dilated ascending aorta was frequently found, exerting significant adverse impacts on diminished exercise capacity and morbidity. **(Am J Cardiol 2020;129:87−94)**

A major issue that adults with congenital heart disease (CHD) face as they age is heart failure, which is a major cause of death.[1] One of the notable physiological characteristics in CHD patients is aortopathy, which is defined as dilation and stiffened ascending aorta (AAo).[2] In the older patients without CHD, vascular stiffening of the great arteries is a predominant cardiovascular risk that predicts all-cause mortality.[3] Adverse influence on the coronary flow[4] and increased systolic load with exaggerated wave reflections[5] are importantly coupled to maladaptation of the heart, resulting in ventricular−arterial stiffening.[6] Aortopathy in patients with CHD, for whom progressive dilation of AAo has been the main focus, can also be associated with diminished cardiac output.[7,8] However, the clinical significance has not been analyzed in detail. We hypothesized that the size and stiffness of the aorta would influence aerobic exercise capacity and clinical events in repaired CHD patients who have achieved biventricular circulation.

Methods

This study was a single-center, retrospective study that conformed to the principles outlined in the Declaration of Helsinki and was approved by the institutional review board (M24-001-5, M28-021). In total, 175 consecutive patients with complex CHD were eligible. Inclusion criteria were as follows: patients who underwent diagnostic cardiac catheterization more than 1 year after surgical repair to achieve biventricular circulation; clinically stable condition without taking inotropic agents except for digoxin and without residual shunt; functional evaluation using cardiopulmonary exercise tests; and follow-up until >16 years old in our institute. All patients with complex CHD undergoing catheterization for any indication were included; these indications comprised follow-up examinations (n = 72), and diagnostic assessments of the need for interventions (n = 103). Patients with simple CHD (i.e., Bethesda 1 complexity class[9]) and those whose systemic ventricles were not morphological left ventricle (such as atrioventricular discordance after the physiologic repair, transposition of great arteries after atrial switch operation, and double-inlet left ventricle after the ventricular septation procedure) were excluded. The eligible patients with complex CHD were categorized into 4 based on basic anatomical features:

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Table 1
Anatomic categories and diagnosis of patients with complex congenital heart disease undergoing biventricular repair

	n
Conotruncal anomalies	112 (64%)
Tetralogy of Fallot‡	65
Double-outlet right ventricle with pulmonary valvular obstruction†	15
Transposition of great arteries with pulmonary valvular obstruction†	13
Truncus arteriosus†	7
D-transposition of the great arteries after arterial switch operation†	12
Corrected transposition	12 (7%)
L-transposition of the great arteries after double-switch procedure†	12
Aortic valve disease	23 (13%)
Aortic stenosis after Ross operation†	19
Aortic regurgitation after Ross operation†	4
Aortic coarctation	28 (16%)
Interrupted aortic arch§	9
Coarctation of the aorta*	19

Disease complexity according to Bethesda classification:
* Bethesda 2 (moderate severity).
† Bethesda 3 (great complexity).
‡ As for Tetralogy of Fallot, 28 (43%) patients in Bethesda 2 and 37 (57%) in Bethesda 3.
§ As for Interrupted aortic arch, 2 (22%) patients in Bethesda 2 and 7 (78%, conduit interposition) in Bethesda 3.

conotruncal anomalies, corrected transposition, aortic valve disease after Ross operation, and aortic coarctation (Table 1). A total of 39 age- and sex-matched control subjects were also reviewed as referents. All had a past history of Kawasaki disease without stenotic coronary arterial lesions, although some had a history of dilated coronary arteries. Subjects who had undergone diagnostic catheterization at around the same period as the CHD group were included. All catheterizations were performed more than 1 year after disease onset. Because this was a retrospective observational study based on data collected for routine clinical care, individual informed consent was not required. We provided patients with the appropriate opportunity to decline consent under the opt-out method on the institutional website and bulletin board, in accordance with Japanese Ministries' Ethical Guidelines.[10]

Diagnostic cardiac catheterizations were conducted from January 2000 to March 2004 under mild procedural sedation as previously described.[11] We estimated oxygen consumption from age, sex, and heart rate and measured cardiac index using the Fick principle under the assumption that the oxygen content of mixed venous blood was the averaged amount of contents in bilateral pulmonary arteries. Mean pulmonary arterial pressure was the averaged values in bilateral pulmonary arteries. End-diastolic ventricular volumes and ejection fractions of the right ventricle and left ventricle were measured using Simpson's method from biplane angiogram. Ventricular volume was indexed to body surface area. Moderate valvular regurgitation was determined by traditional angiographic grading according to Sellers' classification $\geq$ 3+ degree.[12]

Aortic size and stiffness were measured using the angiogram, as previously described.[13] In brief, using aortography in the lateral projection digitally obtained at 30 frames/s in 512×512 pixels, we measured aortic annulus diameter, minimum diameter in diastole of the sinus of Valsalva, that of the sinotubular junction (STJ), that of the AAo, and that of the descending aorta (DAo) (see Supplemental Figure 1). These diameters were standardized for sex and body surface area to yield Z-scores,[14,15] and are denoted as Z-Annulus, Z-Sinus, Z-STJ, Z-AAo, and Z-DAo, respectively. Three patients who underwent Damus−Kaye−Stansel anastomosis were excluded from analyses of the aortic annulus, sinus of Valsalva, and sinotubular junction. Arterial stiffness index β, a nondimensional, blood pressure-independent parameter, was calculated using distensible changes in diameter and corresponding pressures, as also previously reported.[13,16] Aortic stiffness was examined at AAo and DAo, and denoted as β-AAo and β-DAo, respectively.

All patients underwent symptom-limited treadmill exercises within 1 month of catheterization, as previously reported.[17] Peak oxygen uptake was measured and calculated as the percentage of the predicted normal value according to sex and body weight.[17]

In total, 137 (78%) subjects underwent pulmonary function testing using conventional spirometry (FUDAC-77; Fukuda Denshi, Tokyo, Japan) within 1 month of the cardiopulmonary exercise test. Forced vital capacity and forced expiratory volume in 1 second were measured according to the recommendation.[18] Predicted values for forced vital capacity were calculated with reference equations for healthy Japanese adolescents and adults[19,20] based on age, sex, and height. The severity of obstructive lung disease is evaluated using forced expiratory volume in 1 second standardized by forced vital capacity and expressed in percentage form.

Adverse clinical events, representing a composite of death from all causes, unscheduled hospitalization, and surgical intervention, were monitored during follow-up until March 2017. Day zero was defined as the day of catheterization. Any scheduled hospitalizations for diagnostic examination or catheter intervention were not included for events of interest.

Statistical analyses were performed using JMP version 12.0.1 software (SAS Institute, Cary, North Carolina) and R version 3.6.1. Categorical variables are expressed as frequencies and percentages and were compared using Fisher's exact test. Continuous variables are expressed as the median and interquartile range and compared using the Wilcoxon rank-sum test or Kruskal−Wallis H test. The Steel −Dwass post-hoc test was used for multiple comparisons. Pearson's correlation analysis was used to evaluate relationships between continuous variables. Multivariable linear regression analysis of the least-square method was used to detect major determinants of exercise capacity. We included the independent variable for each aspect (i.e., demographics, medication, hemodynamic parameters, pulmonary function, aortic size, and aortic stiffness) that showed a significant correlation in univariable analysis. We limited the number of independent variables to less than 12 to avoid overfitting. Missing data of pulmonary function parameters were imputed based on the multivariate normal

distribution platform. Stiffness index β was log-transformed to approximate normality, as appropriate. The event-free rate was estimated using the Kaplan−Meier method, and differences between groups were assessed using log-rank tests. Intraobserver reliability of measurements of diameters and stiffness indexes of the aorta was performed on 30 randomly selected subjects with repeated analyses over 4 weeks apart, with the investigator blinded to the previous measurement. Reliability was expressed as intraclass correlation coefficients, and the Bland−Altman method provided 95% limits of agreement. Statistical significance was accepted for values of $p < 0.05$.

Results

In 175 complex CHD patients eligible for the study, basic anatomical diagnoses are summarized in Table 1. Patient characteristics are summarized in Table 2. Most patients were in middle adolescence with good functional status. Reproducibility in the measurements of aortic diameters and stiffness indexes was satisfactory (Supplemental Table 1, Supplemental Figure 2).

Table 3 displays hemodynamic parameters, structural and functional properties of the aorta, and parameters of exercise physiology in complex CHD patients compared with control subjects. The aortic root and AAo of CHD patients were dilated and stiffened compared with control subjects, whereas the sizes and stiffness indexes of DAo were comparable between the 2 groups. Detailed profiles of aortic structure and stiffness according to basic anatomical features are depicted in Figure 1. Dilation and increased stiffness of aortic root and AAo were commonly found in patients with complex CHD except for aortic coarctation.

Table 2
Patient characteristics based on anatomic diagnoses and comparison with control subjects

	Total	Conotruncal anomalies	Corrected transposition	Aortic valve disease	Aortic coarctation	Control
n	175	112	12	23	28	39
Age (years)	14.9 [12.1, 17.8]	15.1 [12.4, 19.6]	14.6 [12.6, 16.4]	13.0 [9.2, 16.9]	14.3 [11.4, 16.5]	15.7 [11.2, 19.8]
Male	102 (58%)	63 (56%)	7 (58%)	16 (70%)	16 (57%)	29 (74%)
Body weight (kg)	45.4 [36.6, 52.9]	45.2 [37.1, 52.0]	40.6 [28.2, 55.0]	49.0 [25.3, 62.0]	46.2 [38.0, 53.3]	53.0 [37.0, 59.0] §
Body mass index (kg/m^2)	18.4 [16.2, 21.3]	18.3 [16.4, 20.8]	16.4 [14.2, 20.7]	20.4 [16.2, 23.0]	18.8 [15.9, 21.7]	19.4 [17.6, 20.7]
New York Heart Association classification (I/II/III)	154/19/2	96/14/2	9/3/0	22/1/0	27/1/0	39/0/0
Number of thoracotomies‡	2 [1, 3]	2 [2, 3]	3 [3, 4]	1 [1, 2]	1.5 [1, 2]	-
Number of open-heart surgeries‡	1 [1, 2]	1.5 [1, 2]	1.5 [1, 2]	1 [1, 2]	1.5 [1, 2]	-
History of aortopulmonary shunt‡	66 (38%)	55 (49%)	11 (92%)	0 (0%)	0 (0%)	-
Age at primary repair (years) ‡	3.5 [1.2, 6.1]	3.5 [1.9, 5.6]	5.7 [4.7, 6.8]	6.4 [1.5, 13.4]	0.2 [0.1, 1.9]	-
Age at final surgery (years)†	8.2 [3.2, 13.2]	9.1 [4.0, 13.1]	9.7 [5.2, 15.4]	10.9 [6.7, 15.5]	2.4 [0.6, 11.3]	-
Bethesda classification (2/3) ‡	49/126	28/84	0/12	0/23	21/7	-
Procedure for the pulmonary valve‡						
Transannular patch	38 (2%)	37 (33%)	0 (0%)	1 (4%)	0 (0%)	-
Right ventricle-to-pulmonary artery conduit	99 (57%)	65 (58%)	12 (100%)	0 (0%)	0 (0%)	-
Open pulmonary valvotomy	1 (1%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	-
Pulmonary valve replacement	1 (1%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	-
No intervention	36 (21%)	8 (7%)	0 (0%)	0 (0%)	28 (100%)	39 (100%)
Right aortic arch‡	32 (18%)	27 (24%)	5 (42%)	0 (0%)	0 (0%)	0 (0%)¶
Pulmonary atresia‡	50 (29%)	42 (38%)	8 (67%)	0 (0%)	0 (0%)	0 (0%)**
Bicuspid aortic valve‡	8 (5%)	2 (2%)	0 (0%)	0 (0%)	6 (21%)	0 (0%)
Damus-Kaye-Stansel anastomosis	3 (2%)	2 (2%)	1 (8%)	0 (0%)	0 (0%)	0 (0%)
Prosthetic aortic valve replacement	4 (2%)	4 (4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Tricuspid regurgitation ≥ moderate	19 (11%)	13 (12%)	1 (8%)	4 (17%)	1 (4%)	0 (0%)§
Pulmonary regurgitation ≥ moderate‡	99 (57%)	78 (70%)	5 (42%)	16 (70%)	0 (0%)	0 (0%)**
Mitral regurgitation ≥ moderate	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Aortic regurgitation ≥ moderate*	8 (5%)	4 (4%)	0 (0%)	2 (9%)	2 (9%)	0 (0%)
Diuretics‡	35 (20%)	24 (21%)	5 (42%)	6 (26%)	0 (0%)	0 (0%)¶
Angiotensin-converting enzyme inhibitor	18 (10%)	10 (9%)	1 (8%)	2 (9%)	5 (18%)	0 (0%)§
Beta-blocker	10 (6%)	7 (6%)	0 (0%)	0 (0%)	3 (11%)	0 (0%)

Values are expressed as median [interquartile range] or as number (percentage).
* $p < 0.05$.
† $p < 0.01$.
‡ $p < 0.001$ represent significant difference among four anatomic features in patients with complex congenital heart disease.
§ $p < 0.05$.
¶ $p < 0.01$.
** $p < 0.001$ for comparison between patients and control subjects.

Table 3
Comparison between repaired patients with congenital heart disease and control subjects

	Complex congenital heart disease (n = 175)	Control (n = 39)	p-Value
Hemodynamic parameters			
Cardiac index (l/min/m^2)	3.0 [2.6, 3.5]	3.4 [3.2, 4.0]	< 0.001
Right ventricular peak systolic pressure (mmHg)	46 [37, 64]	25 [22, 28]	< 0.001
Right ventricular end-diastolic pressure (mm Hg)	9 [7, 11]	6 [4, 8]	< 0.001
Right ventricular end-diastolic volume index (ml/m^2)	82.8 [70.9, 100.4]	88.6 [72.8, 94.9]	n.s.
Right ventricular ejection fraction (%)	52 [47, 58]	52 [46, 58]	n.s.
Mean pulmonary arterial pressure (mm Hg)	16 [13, 19]	13 [11, 14]	0.002
Left ventricular peak systolic pressure (mm Hg)	110 [101, 120]	115 [104, 125]	n.s.
Left ventricular end-diastolic pressure (mm Hg)	11 [9, 13]	11 [8, 13]	n.s.
Left ventricular end-diastolic volume index (ml/m^2)	89.2 [78.0, 108.6]	78.0 [70.4, 88.0]	< 0.001
Left ventricular ejection fraction (%)	62 [55, 70]	61 [55, 68]	n.s.
Mean aortic pressure (mm Hg)	86 [80, 92]	89 [80, 92]	n.s.
Aortic pulse pressure (mm Hg)	39 [35, 45]	37 [35, 39]	0.005
Size and stiffness of the aorta			
Z-score for the aortic annulus diameter (SD)	3.3 [2.1, 4.9]	0.7 [0.0, 1.4]	< 0.001
Z-score for the sinus of Valsalva diameter (SD)	2.9 [1.9, 3.7]	0.7 [0.2, 1.4]	< 0.001
Z-score for the sinotubular junction diameter (SD)	1.9 [0.5, 3.2]	−0.2 [−0.7, 0.7]	< 0.001
Z-score for the ascending aortic diameter (SD)	3.0 [1.6, 4.1]	1.2 [0.2, 1.8]	< 0.001
Z-score for the descending aortic diameter (SD)	0.0 [−1.0, 1.0]	0.3 [−0.3, 0.8]	n.s.
Diameter ratio of the ascending aorta to descending aorta	1.83 [1.58, 2.13]	1.49 [1.34, 1.63]	< 0.001
Ascending aortic stiffness index	5.3 [3.7, 9.9]	2.8 [2.1, 3.8]	< 0.001
Descending aortic stiffness index	2.8 [2.2, 3.4]	2.9 [2.0, 3.7]	n.s.
Stiffness index ratio of the ascending aorta to descending aorta	1.93 [1.29, 3.50]	0.99 [0.68, 1.33]	< 0.001
Pulmonary function test			
Forced vital capacity (% of predicted)	77 [64, 89]	-	-
Forced expiratory volume in first second (% of forced vital capacity)	89 [83, 93]	-	-
Exercise test			
Exercise duration (min)	7.5 [6.2, 8.5]	10.0 [9.5, 10.5]	< 0.001
Heart rate at rest (beats/min)	82 [74, 91]	80 [67, 86]	n.s.
Systolic blood pressure at rest (mm Hg)	106 [100, 116]	110 [104, 124]	0.034
Heart rate at peak exercise (beats/min)	169 [156, 180]	190 [181, 195]	< 0.001
Systolic blood pressure at peak exercise (mm Hg)	164 [146, 186]	172 [158, 196]	0.035
Peak oxygen uptake (% of predicted)	63 [55, 74]	92 [84, 105]	< 0.001

Values are expressed as median [interquartile range]. SD = standard deviation; n.s. = not significant.

Next, we analyzed the relation of exercise capacity with an aortic abnormality in complex CHD. Since linear regression analysis is highly sensitive to outliers, we excluded 28 patients with aortic coarctation in the following analysis; that is, study from this point forward only comprised the population with dilated and stiffened AAo (n = 147). Table 4 shows the association of clinical variables with exercise capacity. In multivariable regression analysis, dilation and increased stiffness of the AAo, as well as repeated thoracotomies, hypertension of the right ventricle, reduced forced vital capacity, and taking diuretics and/or β-blockers, were major determinants of reduced exercise capacity. Scatter plots and the relationship of clinical correlates are also shown in Figure 2.

In addition, we examined whether the structural and functional abnormalities in AAo synergistically influence exercise capacity and morbidity in the complex CHD population. We separated 4 subgroup categories according to good cut-off points around medians of Z-AAo (= 3.5 standard deviations) and β-AAo (= 6.0); that is, patients with relatively mild abnormality in the AAo (n = 49), those with stiff AAo (n = 34), those with dilated AAo (n = 24), and those with dilated stiff AAo (n = 40) as schematized in Figure 3. Demographics of the 4 subgroups are summarized in Supplemental Table 2; patients with dilated AAo underwent primary repair at an older age, whereas hemodynamics at rest were comparable. Compared with a subgroup with a relatively mild abnormality in the AAo, exercise capacity was significantly decreased in patients with stiff and/or dilated AAo despite large overlap (Figure 3).

During follow-up (median 15.6 years; interquartile range 11.8 to 17.5 years), 9 (6%) patients diedand 55 (37%) patients experienced clinical events; additional cardiac surgeries for pulmonary stenosis or insufficiency in 22 patients, arrhythmia and pacemaker implantation in 16, faintness or malaise in 6, right-sided heart failure in 3, prosthetic aortic valve replacement in 2, angina suggestive of myocardial ischemia in 2, hemorrhagic event in 2, and noncardiac surgery in 2. Compared with the subgroup with a relatively mild abnormality in the AAo, patients with stiff and/or dilated AAo exhibited significant morbidity, although no difference was detected among the 3 subgroups (Figure 3). We could not examine mortality due to insufficient statistical power.

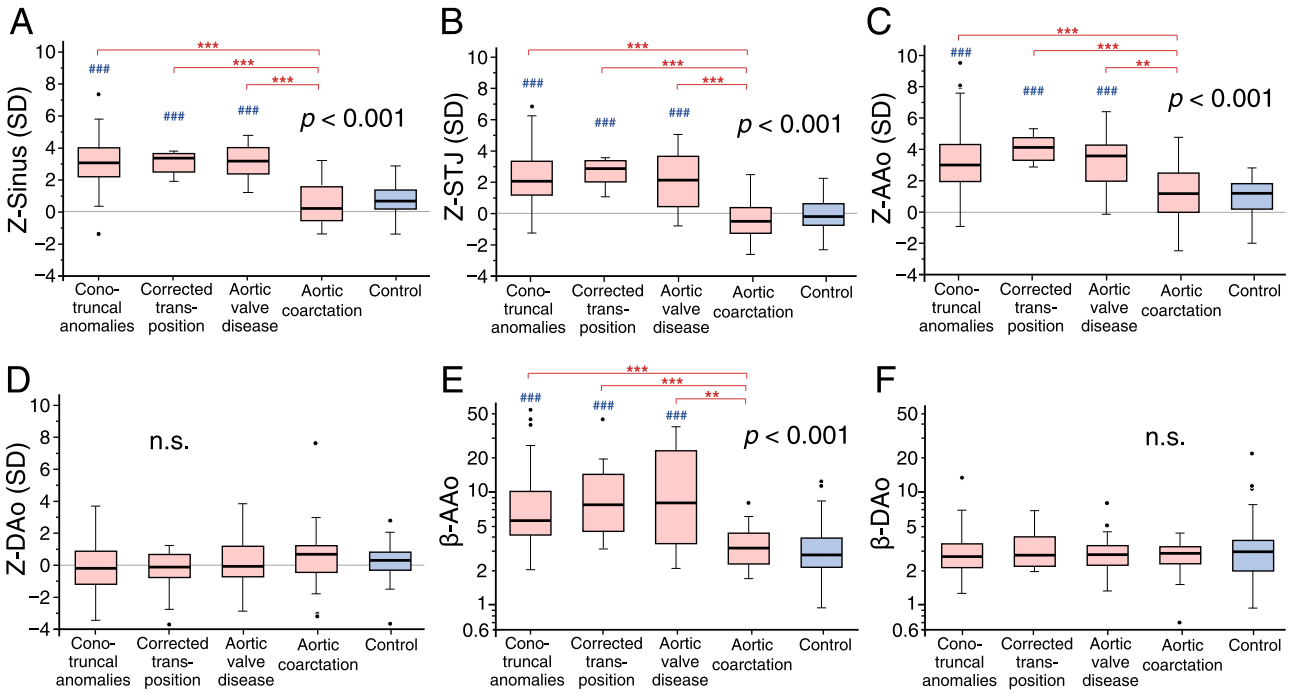

Figure 1. Aortic size and stiffness in patients with complex congenital heart disease (CHD) and comparison with control subjects. Box-and-whisker plots display the distributions of Z-scores for sinus of Valsalva diameter *(Z-Sinus, Panel A)*, sinotubular junction diameter *(Z-STJ, Panel B)*, ascending aorta diameter *(Z-AAo, Panel C)*, descending aorta diameter *(Z-DAo, Panel D)*, stiffness index of the ascending aorta *(β-AAo, Panel E)*, and stiffness index of the descending aorta *(β-DAo, Panel E)* among patients with conotruncal anomalies, corrected transposition, aortic valve disease, and aortic coarctation as complex CHD groups (red boxes), and control subjects *(gray boxes)*. The stiffness index is presented on a logarithmic scale. The p-value in each panel represents the significance of difference among the five groups. $^{**}p < 0.01$, $^{***}p < 0.001$ for comparison among complex CHD patients, $^{\#\#\#}p < 0.001$ for comparison between CHD patients and control subjects. SD = standard deviation; n.s. = not significant. (Color version of figure is available online.)

Discussion

This study represents the first study to demonstrate the association of aortic abnormality with decreased exercise capacity in repaired patients with complex CHD. The present study revealed several important characteristics of aortic abnormality. Increased size and stiffness of AAo, but not of DAo, were confirmed as characteristic features in patients with complex CHD except for aortic coarctation. Among this complex CHD population, dilated and stiff AAo predicted reduced exercise capacity and morbidity, suggesting the clinical importance of the aortic abnormality as a cardiovascular risk factor.

Aortopathy in CHD patients, which is characterized by dilation, impaired compliance, and histological abnormalities of the AAo,[21] is an intrinsic feature in patients with conotruncal defects.[2,22] Aortic volume overload by right-to-left and aortopulmonary shunting before a repair is a primary mechanism in the pathogenesis, consistent with our results (Figure 1). Increased size and stiffness of AAo, as well as residual right ventricular hypertension, exhibited negative associations with exercise capacity (Table 4). Restrictive respiratory impairment due to repetitive thoracotomies,[23] chronotropic incompetence characterized by reduced heart rate response during exercise (Table 3),[24] and the aortopathy would be associated interdependently with exercise intolerance. After surgical repair, a disproportionately enlarged AAo connected to a normal DAo represents a rapidly converging shape of the aorta. It may employ the left ventricular afterloads with augmented wave reflection (also known as impedance mismatch governed by the cross-sectional area of the vessel),[25] which might result in the inappropriate distribution of blood flow to the lower body during stress.[26]

Numerous studies, mainly in the elderly, have demonstrated that reduced aortic compliance is responsible for increased ventricular pulsatile workload,[5] impaired coronary blood flow reserve,[4] exercise intolerance,[27] and adverse cardiovascular events.[3] Although this may hold in CHD patients, whether decreased arterial compliance localized to only the AAo shows an adverse clinical impact has not been well-described. Some cross-sectional studies have demonstrated an association between decreased compliance of the proximal aorta and reduced cardiac output in patients with tetralogy of Fallot.[7,8] We determined that the stiff AAo predicted exercise intolerance and reduced morbidity in populations with complex CHD.

No synergistic impact of dilation and stiffening of AAo was observed on exercise intolerance and morbidity (Figure 3). Possible explanations for this result is that the stiffening (increase in impedance) of the dilated AAo (low impedance) may offset the impedance mismatch between AAo and DAo.[26] Although dilation and stiffening of AAo are closely associated with each other, as has been histologically confirmed,[21] our findings suggested that either of

Table 4
Association of clinical variables with exercise capacity in patients with complex congenital heart disease except for aortic coarctation (n = 147)

(Dependent variable = peak oxygen uptake [% of predicted])	Univariable		Multivariable (model 1)		Multivariable (model 2)	
	r	p	β	p	β	p
Patient characteristics						
Age (year)	−0.15	0.069				
Gender (male)	-	0.007	0.07*	n.s.	0.11*	n.s.
Body weight (kg)	0.20	0.015	0.09*	n.s.		
Bethesda classification (2 or 3)	-	0.009				
Number of thoracotomies	−0.37	< 0.001	−0.21	0.006	−0.20	0.004
Number of open-heart surgeries	−0.07	0.39				
History of aortopulmonary shunt (yes)	-	< 0.001				
Diuretics use (yes)	-	< 0.001			0.22	0.002
Angiotensin-converting enzyme inhibitor use (yes)	-	< 0.001				
Beta-blocker use (yes)	-	< 0.001			0.20	0.004
Hemodynamic parameters						
Cardiac index (l/min/m^2)	0.17	0.042	0.11*	n.s.		
Right ventricular peak systolic pressure (mm Hg)	−0.21	0.011	−0.15	0.030	−0.19	0.003
Right ventricular ejection fraction (%)	0.22	0.010	0.07*	n.s.		
Mean pulmonary arterial pressure (mmHg)	−0.24	0.005			0.03*	n.s.
Left ventricular peak systolic pressure (mmHg)	0.23	0.006	0.08*	n.s.	0.08	0.019
Left ventricular end-diastolic volume index (ml/m^2)	−0.18	0.033				
Left ventricular ejection fraction (%)	0.27	0.001	0.11*	n.s.	0.03*	n.s.
Size and stiffness of the aorta						
Z-score for the sinus of Valsalva diameter (SD)	−0.17	0.036				
Z-score for the sinotubular junction diameter (SD)	−0.31	< 0.001				
Z-score for the ascending aortic diameter (SD)	−0.33	< 0.001	−0.17	0.030	−0.14	0.048
Z-score for the descending aortic diameter (SD)	0.11	0.17				
Diameter ratio of the ascending aorta to descending aorta	−0.40	< 0.001				
Ascending aortic stiffness index	−0.32	< 0.001	−0.19	0.024	−0.15	0.026
Descending aortic stiffness index	−0.10	0.24				
Stiffness index ratio of the ascending aorta to descending aorta	−0.26	0.002				
Pulmonary function†						
Forced vital capacity (% of predicted)	0.50	<0.001	0.27	<0.001	0.17	0.026
Forced expiratory volume in first second (% of forced vital capacity)	0.14	0.14				

Patient characteristics and hemodynamic parameters that did not display any significant correlation with peak oxygen uptake are not shown.
* Variables in the analysis but not in the model. Adjusted R^2 were 0.35 and 0.50 for the multivariable model 1 and model 2, respectively.
† As for pulmonary function, missing data in 32 patients (22%) were imputed based on the multivariate normal distribution platform in multivariable analysis.

these abnormalities would predict potentially unfavorable clinical conditions. In addition, because adults with complex CHD are reportedly at high risk of glucose intolerance,[28] aortopathy may suggest subclinical processes such as inflammation[29] and metabolic abnormality[30] that are an interdependent mechanism underlying ventricular-arterial stiffening and are potentially preventable by appropriate life-long management.

The present study has some limitations which should be acknowledged. First, because this was a retrospective observational study, we could not prove a cause-and-effect relation between aortopathy and decreased exercise capacity. Our data only suggested that the enlarged and stiffened AAo predicted diminished exercise tolerance and morbidity. Because clinical events in complex CHD patients are often associated with pulmonary valve abnormality and arrhythmia originating from the right atrium, the impact of aortopathy may be indirect. Second, patient heterogeneity was inevitably subject to selection biases that would have affected the results of this study. The cohort included in this study was the specific population referred to a tertiary center who underwent diagnostic cardiac catheterization. Third, aortic size and stiffness were measured under resting conditions. Lack of data on hemodynamics during exercise in the CHD population will not allow an assumption of the exact exercise physiology. Fourth, our control subjects were not entirely healthy individuals. The increase in left ventricular end-diastolic pressure in controls (Table 3) may be due to the previous angiitis. Finally, although reproducibility was good, our classical methods of measuring aortic size, stiffness, and ventricular volume from the angiogram represent a major limitation. Some future studies using modalities such as cardiovascular magnetic resonance imaging are warranted to validate our findings regarding the long-term impact of aortopathy in CHD patients.

In conclusion, in complex CHD patients achieving biventricular circulation, except for those with aortic coarctation, the stiffened and dilated ascending aorta is commonly found and has a significant adverse impact on aerobic exercise capacity and morbidity.

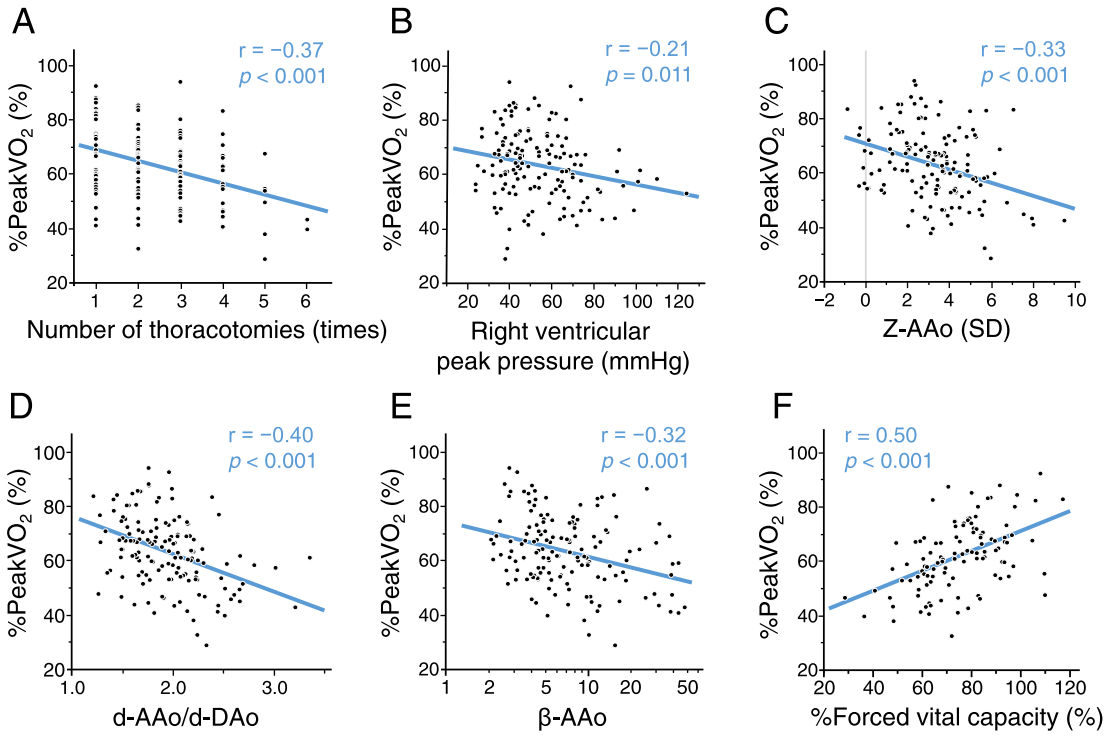

Figure 2. Association between clinical correlates and exercise capacity in 147 patients with complex congenital heart disease except for aortic coarctation. Scatter plots and linear relationships between the number of thoracotomies including final surgery *(Panel A)*, right ventricular peak pressure *(Panel B)*, Z-score for ascending aorta diameter *(Z-AAo, Panel C)*, diameter ratio of AAo to descending aorta *(d-AAo/d-DAo, Panel D)*, stiffness index of AAo *(β-AAo, Panel E)*, percentage predicted forced vital capacity in pulmonary function test *(Panel F)* and percentage predicted peak oxygen uptake (%PeakVO$_2$). The *β*-AAo is presented on a logarithmic scale.

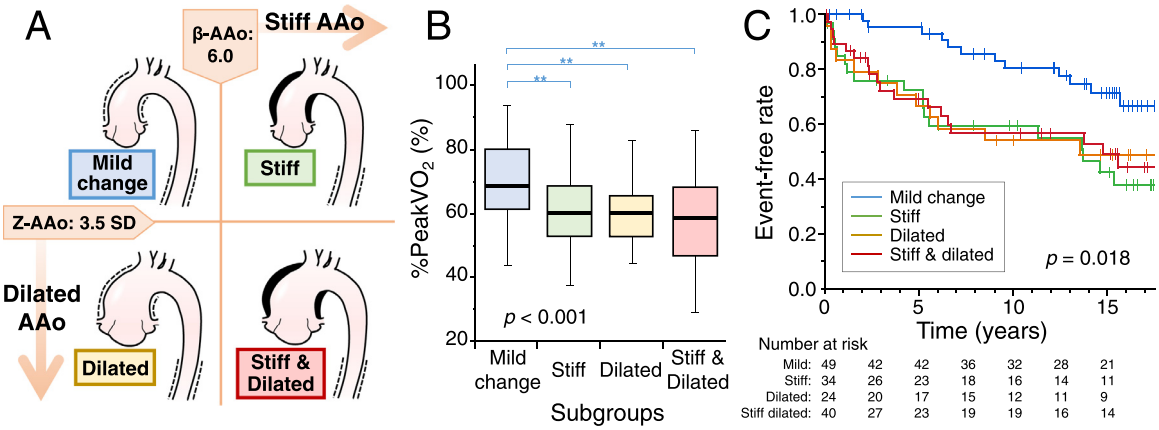

Figure 3. Impact of aortic structural and functional abnormalities on exercise capacity and morbidity in patients with complex congenital heart disease (CHD) except for aortic coarctation. *(A)* We categorized complex CHD patients into 4 subgroups according to good cut-off points around median Z-scores (Z-AAo = 3.5 standard deviations) and stiffness index (*β*-AAo = 6.0) of the ascending aorta (AAo); i.e., patients with relatively mild abnormality in the AAo (n = 49, *in blue*), stiff AAo (n = 34, *in green*), dilated AAo (n = 24, *in yellow*), and dilated stiff AAo (n = 40, *in red*). *(B)* Box-and-whisker plots of percentage predicted peak oxygen uptake (%PeakVO$_2$) among 4 subgroups. **p <0.01 in post-hoc analysis. *(C)* Kaplan−Meier curve of clinical events among 4 subgroups. The event endpoint is a composite of death from all causes, unscheduled hospitalization, and surgical intervention. (Color version of figure is available online.)

Author Contributions

Yohsuke Hayama: Investigation, Data Curation, Writing - Original Draft, Visualization, Funding acquisition. **Hideo Ohuchi:** Conceptualization, Methodology, Writing - Review & Editing, Project administration. **Jun Negishi, Toru Iwasa, Heima Sakaguchi, Aya Miyazaki, Etsuko Tsuda:** Resources. **Kenichi Kurosaki:** Resources, Supervision.

Disclosures

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Supplementary materials

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