

Elastic properties of the ascending aorta in young children after successful coarctoplasty in infancy

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Abstract

Background: Based on the hypothesis that vascular dysfunction in the ascending aorta can cause morbidity, we undertook this study on the elastic properties of ascending aorta and left ventricular (LV) function in young children who received coarctoplasty in early infancy. **Methods:** Blood pressures (BP) in the right arm and ascending aortic internal diameters determined by M-mode ultrasound at rest and after exercise were measured in 25 patients (mean age, 6.4 ± 3 years) and 22 control subjects (mean age, 5.8 ± 2.4 years). Ascending aortic stiffness index and distensibility were calculated using BP measurements and ascending aortic internal diameters. In addition, LV parameters (systolic and diastolic function, mass index) were evaluated. **Results:** Compared with control subjects, patients had increased stiffness index (at rest: 4.87 ± 1.94 versus 3.57 ± 1.19 , $P=0.021$; after exercise: 4.33 ± 1.91 versus 3.2 ± 1.26 , $P=0.034$) and decreased distensibility (at rest: 6.90 ± 3.15 versus 8.72 ± 2.77 , $P=0.02$; after exercise: 5.69 ± 2.39 versus 7.88 ± 3.44 $\text{cm}^2 \text{dyn}^{-1} 10^{-6}$, $P=0.023$). BP and LV parameters showed no consistent differences between the two groups. In patients, distensibility was significantly correlated with systolic BP (at rest: $P=0.008$; after exercise: $P=0.014$) and pulse pressure (at rest: $P=0.013$; after exercise: $P=0.001$). **Conclusions:** This study suggests that vasculopathy of ascending aorta is possible in some young children despite early correction. However, long-term tracking study is needed to clarify the significance of the study.

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1. Introduction

Although coarctation of the aorta has been considered a curable disease since the first surgical repair was reported in 1944 [1], there have been a number of reports of cardiovascular morbidity and mortality even after successful repair [2,3]. Persistent resting and exercise-induced hypertension have been reported in 10–46% [4,5] and 30–60% [6,7], respectively, and these have been suggested to be the main cause of post-operative cardiovascular events [8]. Although several mechanisms of persistent arterial hypertension have been suggested, the underlying pathophysiology has not yet been clearly defined [9–13]. Among the proposed mechanisms, vasculopathy consisting of increased vascular reac-

tivity and changes in the elastic properties of the aorta proximal to the coarctoplasty site have been recently emphasized [10,11,14]. Although previous studies [15,16] have demonstrated low frequencies of late hypertension among patients repaired in infancy, long-term follow-up results in this group are not well defined. The present study was undertaken to evaluate the elastic properties of the aorta proximal to the coarctoplasty site, and its subsequent effect on the left ventricle in young children operated in early infancy.

2. Materials and methods

2.1. Study subjects

The clinical characteristics of the study population are shown in Table 1. The medical records of children who

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Table 1
Clinical characteristics of subjects and BP profiles at rest and after exercise in the right arm

	Patients	Control	<i>P</i>
Number (<i>N</i>)	25	22	
Age (year)	6.40±2.99	5.86±2.39	0.685
Weight (kg)	20.5±8.99	21.9±5.56	0.077
Height (m)	113.2±18	113.6±14	0.685
BSA (m ²)	0.79±0.23	0.83±0.15	0.176
<i>At rest</i>			
SBP, mm Hg	99.3±13.5	96±8.4	0.557
DBP, mm Hg	50±6.9	51±6.2	0.608
PP, mm Hg	48.9±12	45±7.5	0.224
<i>After exercise</i>			
SBP, mm Hg	135±23.7	129±17.1	0.281
DBP, mm Hg	68.7±16.3	69±17.1	0.839
PP, mm Hg	66.3±22.7	59±13.7	0.765

Values are mean±S.D. BSA, body surface area; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure.

underwent coarctoplasty in infancy at The Seoul National University Children's Hospital from January 1, 1989 to December 31, 1997 were reviewed. Patients with residual cardiac defects (significant left ventricular (LV) outflow tract obstruction with Doppler velocity of more than 2.5 m s⁻¹, more than mild aortic or mitral insufficiency, or some other significant lesions influencing hemodynamics) and on medication were excluded. Twenty-five asymptomatic patients (16 boys and 9 girls; mean age at the time of study 6.40±2.99 years, mean age at operation 0.22±0.24 years and with a range of 1 to 11 months) without residual coarctation were enrolled. Residual coarctation was defined to be present when Doppler tracing along the coarctoplasty site was associated with: (1) a diastolic tail or (2) a systolic velocity of over 3.5 m s⁻¹. Associated lesions were present in 23 patients (ventricular septal defect, 18; atrial septal defect, 11; patent ductus arteriosus, 14) and were corrected at the time of coarctoplasty. Four patients with a bicuspid aortic valve unassociated with significant stenoinufficiency or gross pathology of the ascending aorta were included. Repair was achieved by end-to-end anastomosis in 17, subclavian flap angioplasty in 5, and end-to-side anastomosis in 3. Mean duration of the post-operative follow-up was 6.34±2.99 years. For comparison purposes, 22 age- and sex-matched control subjects (12 boys, and 10 girls; mean age at the time of study 5.8±2.4 years) were recruited. Our institutional ethics committee approved the present study and informed consent was obtained from each subject.

2.2. Study protocol

All studies were performed in the afternoon, and regular diet was allowed before study. Height and body weight were recorded. Each child was placed in a supine position before acquiring data to ensure a resting state. After confirming the resting state by heart rate, data acquisition commenced. At

the time of echocardiographic examination, blood pressure (BP) was also measured in the right arm using an automatic oscillometric device (Agilent CMS V24 and V26, Germany) with an adequately sized cuff. BP was measured five times on each occasion and averaged. Children were considered to be hypertensive if their BP values were above the 95th percentile of normal BP of corresponding age and sex [17].

2.3. Acquisition of echocardiographic data

Each subject underwent complete baseline echocardiography (Acuson Sequoia C256 echocardiography system or Acuson 128XP echocardiography system) using an appropriate transducer. After screening for significant cardiac lesions, the following continuous variables were measured. LV internal diameters and interventricular septal and posterior wall thickness were measured at end-diastole and end-systole according to the methods set forth by the American Society of Echocardiography [18]. To determine LV diastolic function, Doppler profiles using a sample volume at the tip of the mitral valve were acquired from an apical four-chamber view. Ascending aortic internal diameters were measured using an M-mode ultrasound under 2-D echocardiography with discerning intima. LV echocardiographic data were acquired once at rest and ascending aortic data twice at rest and again just after exercise. All echocardiographic findings were analyzed by one of the authors who was blind to subjects' past histories. All data presented represent the averages of at least five separate cardiac cycles.

2.4. Exercise test

Subjects underwent an exercise test, which involved running 150 m at a speed suitable for the subject's age. This method was adopted because we expected better cooperation from the young children. Immediately after running, subjects were placed in a supine position and BP and ascending aortic data were acquired from the same site within 1 min.

2.5. Elastic properties of the aorta

Using M-mode ultrasound with discerning intima and a perpendicular beam projection angle to the aorta, internal diameters were measured at the ascending aorta just proximal to the origin of the innominate artery in the high parasternal area. We did not acquire data in suprasternal notch view because of patch correction of the hypoplastic transverse arch and difficulty in placing echocardiographic beam tangentially to the aorta in many patients. Systolic internal diameters (AS) were measured at the point of maximal anterior motion of the aortic wall, and diastolic internal diameters (AD) were measured at the beginning of the QRS complex. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were also obtained at the time of M-mode ultrasound. Using the following formulas,

the elastic properties of the ascending aorta at rest and after exercise were calculated.

$$\text{Aortic stiffness index}(\beta \text{ index}) [19] = \ln(\text{SBP}/\text{DBP}) / [(\text{AS}-\text{AD})/\text{AD}]$$

$$\text{Aortic distensibility}(\text{cm}^2\text{dyn}^{-1}10^{-6}) [20] = 2(\text{AS}-\text{AD}) / [\text{AD}(\text{SBP}-\text{DBP})]$$

2.6. LV systolic and diastolic function

To evaluate the LV systolic function, we calculated fractional shortening (FS) and the velocity of circumferential fiber shortening (VCF) [21] which was defined as $\text{FS}/[\text{ET}/(\text{RR})^{1/2}]$. Peak systolic wall stress (WS) [22] was also calculated using: $\text{Wall stress} (\times 10^3 \text{ dyn cm}^{-2}) = \text{SBP} \times \text{LVIDs} (\text{mm}) / [\text{LVPWs} (\text{mm}) \times (1 + \text{LVPWs} (\text{mm}) / \text{LVIDs} (\text{mm}))]$ where LVIDs is the LV end-systolic internal diameter, LVPWs is the LV end-systolic posterior wall thickness, ET is the ejection time, and RR is the RR interval in the electrocardiogram. To evaluate the LV diastolic function, the peak early and late transmitral flow velocities (the E and A velocities), the ratio of early to late peak velocities (E/A ratio), the deceleration time of the early transmitral flow velocity (DT), and the isovolumic relaxation time (IVRT) were obtained [23].

2.7. LV mass index (LVMI)

LV mass was calculated by using the M-mode ultrasound method described by Devereux et al. and was indexed by using body surface area (BSA) [24]. $\text{LV mass index} (\text{gm}/\text{m}^2) = \{ (0.8) [(1.04)(\text{LVIDd} + \text{LVPWd} + \text{LVSDd})^3 - (\text{LVIDd}^3)] + 0.6 \} / \text{BSA}$, where LVSDd represents LV end-diastolic septal thickness.

2.8. Statistical analysis

Data analysis was performed using the SPSS statistical package (version.10) and the SAS statistical package (version.8.1). All descriptive data are expressed as mean \pm S.D. The Mann–Whitney test was used to compare continuous variables between groups. Linear regression analyses and bivariate correlation analyses were used to compare variables using the Spearman test. Comparisons concerning linear regressions between the two groups were performed using the general linear model procedure in the SAS statistical package. A *P* value of <0.05 was considered statistically significant.

3. Results

3.1. Blood pressure

BP profiles at rest and after exercise are presented in Table 1.

No statistically significant difference was found in SBP, DBP and pulse pressure (PP) between patients and control subjects. However, 3 (12%) among 25 patients showed systolic hypertension for their age. In addition, the PP in the right arm of patients had a wider tendency

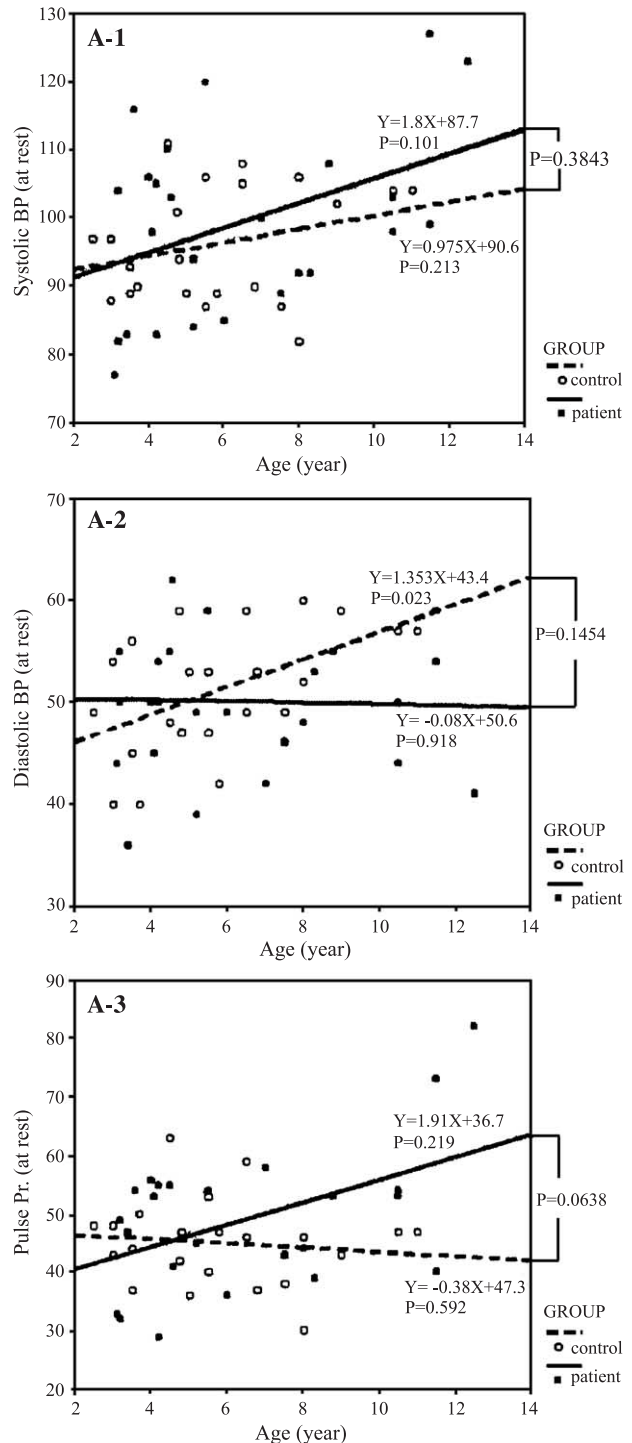


Fig. 1. Changes in systolic blood pressure (SBP), diastolic blood pressure (DBP) and pulse pressure (PP) with increasing age at rest (A1, 2, 3). Patients showed a tendency to have a wider PP and relative decrease in DBP at rest with increasing age.

Table 2
Elastic properties of the aorta proximal to the coarctoplasty site

	Patients	Control	P
<i>At rest</i>			
Stiffness index	4.87±1.94	3.57±1.19	0.021
Distensibility, cm ² ·dyn ⁻¹ ·10 ⁻⁶	6.9±3.15	8.72±2.77	0.02
<i>After exercise</i>			
Stiffness index	4.33±1.91	3.2±1.26	0.034
Distensibility, cm ² ·dyn ⁻¹ ·10 ⁻⁶	5.69±2.39	7.88±3.44	0.023

Values are mean±S.D.

of amplitude with increasing age unlike the control subjects at rest. The relative increase of PP in patients was mainly because of the relative decrease in DBP with increasing age (Fig. 1).

3.2. Elastic properties of the aorta

The aortic elastic properties at ascending aorta are presented in Table 2 and Fig. 2.

Table 3
LV systolic and diastolic function, LV mass index

	Patients	Control	P
<i>Systolic</i>			
FS	0.33±0.05	0.33±0.05	0.921
ET, ms	275±20	275±23	0.812
VCF, circ s ⁻¹	0.94±0.24	0.98±0.14	0.8
WS (×10 ³), dyn cm ⁻²	46±12.8	48.6±15.7	0.159
<i>Diastolic</i>			
IVRT, ms	42.2±5.3	41.1±1.9	0.38
DT, ms	139±35	138±11	0.38
A velocity, m·s ⁻¹	0.49±0.14	0.46±0.11	0.138
E velocity, m·s ⁻¹	1.07±0.19	0.95±0.15	0.025
E/A ratio	2.4±1.06	2.12±0.42	0.843
LVMI, g m ⁻²	65±28.9	59.6±11.6	0.792

Values are mean±S.D. FS, fractional shortening; ET, ejection time; VCF, velocity of circumferential fiber shortening; WS, peak systolic wall stress; IVRT, isovolumic relaxation time; DT, deceleration time; LVMI, LV mass index.

The ascending aortic stiffness index was increased significantly and ascending aortic distensibility was decreased significantly in patients versus the controls

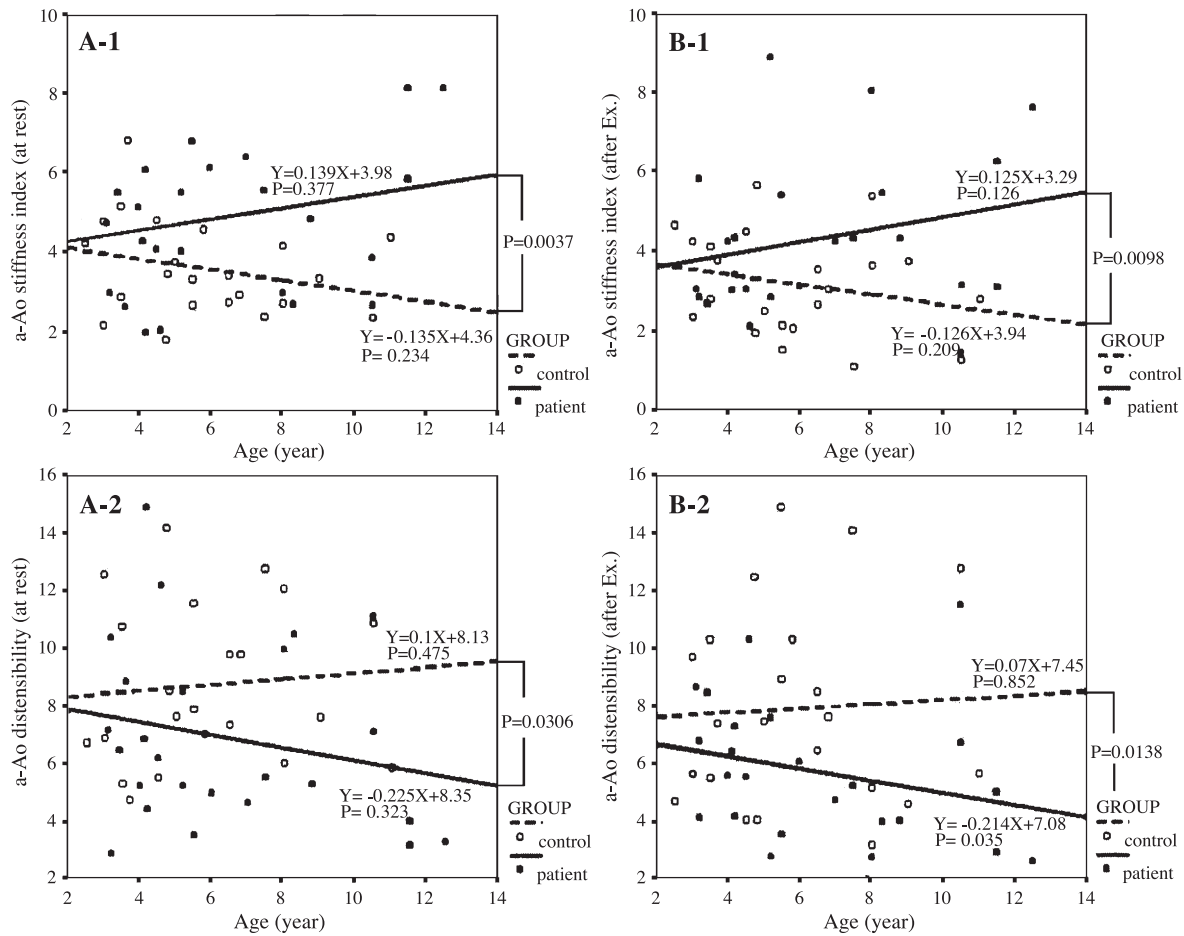


Fig. 2. Changes in the ascending aortic stiffness index and distensibility with increasing age at rest (A1, 2) and after exercise (B1, 2). Patients showed a tendency to have a higher ascending aortic stiffness index and lower distensibility at rest with increasing age than the controls. Moreover, decreased distensibility became significant after exercise ($P=0.035$).

at rest and after exercise. In addition, unlike the controls, patients had a tendency towards an increasing ascending aortic stiffness index and a decreasing distensibility with increasing age. Decreased distensibility in patients became significant after exercise ($P=0.035$).

3.3. LV systolic and diastolic function and mass index

The parameters representing LV systolic and diastolic function were not significantly different in the two groups. Consistent changes in transmitral flow velocity were not identified in patients. There was no significant difference in LVMI between the two groups as a whole (Table 3), despite a significant increase in LVMI in patients with increasing age ($P=0.002$, Fig. 3). The LVMI was found to be significantly and positively correlated with SBP and PP in patients ($P=0.002$; $P=0.027$, respectively).

3.4. Correlation of the elastic properties of the ascending aorta with BP

SBP and PP were found to be related to the elastic properties of the ascending aorta. SBP showed a tendency to increase as the ascending aortic stiffness index increased in both patients and controls and decreased significantly in patients as ascending aortic distensibility increased (at rest, $P=0.008$; after exercise, $P=0.014$). As the ascending aortic stiffness index increased, PP in patients showed a tendency to increase at rest ($P=0.084$) and a significant increase after exercise ($P=0.042$). PP also decreased significantly in patients as ascending aortic

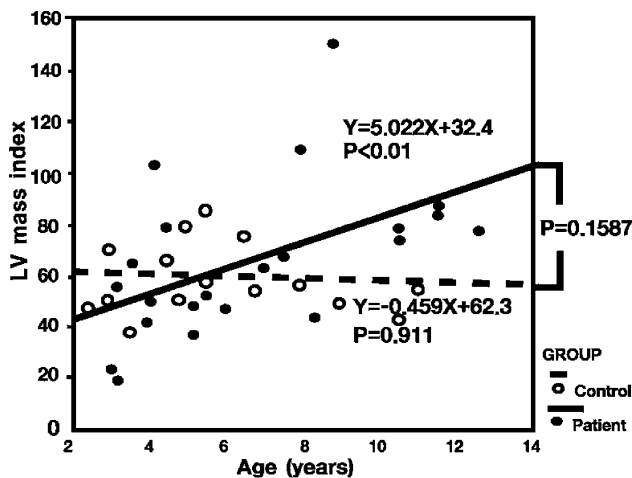


Fig. 3. Correlations of the left ventricular mass index (LVMI) with increasing age. A significant increase in LVMI was observed in patients with increasing age ($P=0.002$) differently from normal children.

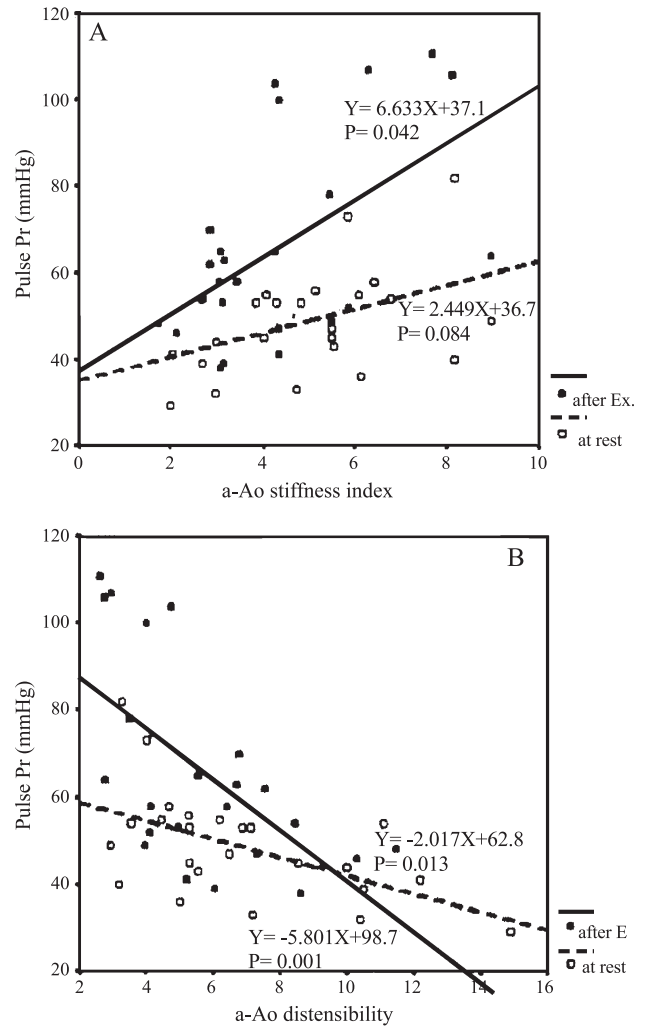


Fig. 4. Correlations between the elastic properties and PP of right arm at rest (A) and after exercise (B) in patients. As the ascending aortic stiffness index increased, PP showed an increasing tendency at rest and a significant increase after exercise (A). PP decreased significantly as ascending aortic distensibility increased (B).

distensibility increased (at rest, $P=0.013$; after exercise, $P=0.001$) (Fig. 4).

4. Discussion

In this study, we found that even in young children repaired in early infancy, significant changes in the elastic properties of ascending aorta (increased stiffness and decreased distensibility) could occur. These elastic properties were statistically different between the two groups. LV mass index in patients also significantly increased with increasing age and correlated with SBP and PP.

Changes in the elastic properties, including stiffness and distensibility, which is inversely correlated with stiffness, have often been regarded as the mechanisms of late hypertension and cardiovascular morbidity and mortality [25,26].

Ong et al. [11] reported a high prevalence of exercise-induced arm-leg pressure gradients and increased stiffness in the pre-coarctation aorta even in normotensive patients at rest, which was related to the fact that functional re-coarctation at a coarctoplasty site due to decreased distensibility is a cause of late hypertension [12,13]. With increasing stiffness and decreasing distensibility, the cushioning effect of the aorta is lost, which leads to increased SBP and PP [27]. In turn, increased SBP and PP would increase myocardial oxygen demand by augmenting LV afterload. On the other hand, a diminution of ascending aorta distensibility decreases myocardial oxygen supply by decreasing aortic diastolic backflow, which contributes to coronary perfusion [28]. In this context, Sutton [25] commented that aortic stiffness was the most powerful independent predictor of acute coronary events in the adult population. It has not yet been confirmed whether the same scenario can be applied to the younger population. In our study, we found that the PP in the right arm of patients had a wider tendency of amplitude with increasing age unlike the control subjects at rest and the relative increase of PP in patients was mainly because of the relative decrease in DBP with increasing age (Fig. 1). These changes of pressure in young children after successful coarctoplasty in infancy seem to be the same pattern of elderly hypertensive patients. Structural alteration of the pre-coarctation arterial bed has been reported to cause changes in elastic properties. Sehested et al. [9] demonstrated in an *in vitro* study that pre-coarctation tissue has greater contractility to potassium, norepinephrine, and prostaglandin $F_{2\alpha}$ than post-coarctation tissue, and that histologically, pre-coarctation tissue consists of more collagen and less smooth muscle than post-coarctation tissue. In our study, which involves subjects confined to young children operated upon in early infancy, we also found a significant alteration in the elastic properties of ascending aorta. Recently, de Divitiis et al. [14] also demonstrated modification in the elastic properties of conduit arteries, specially reduced flow-mediated vasodilation and nitroglycerin response in some patients operated upon in early infancy, and suggested that endothelial and smooth muscle functional abnormalities could persist despite early repair.

Minimal anatomical stenosis and dynamic narrowing, due to differences in the elastic properties proximal and distal to the repair site, both could cause pressure gradients in patients [29]. In the present study, having adhered to the current definition of a successful repair, we found differences in the aortic properties proximal to the coarctoplasty site. The fact that not all cases with such minimal stenosis have the same pressure gradient argues against structural stenosis as a culprit. We believe that significant dynamic narrowing, secondary to differences in the elastic properties between two sites, is the primary cause of pressure gradients. However, we cannot exclude a possible relation between residual structural narrowing, even though insignificant according to current

diagnostic methods, and subsequent changes in aortic properties.

In addition to late hypertension, persistent LV dysfunction and increased LV mass even in post-operative patients with normal BP have been reported [30,31]. In contrast, we could not demonstrate statistically consistent differences in LV parameters between patients and control subjects. We believe that this is because of the relatively short-term follow-up of patients in our study.

4.1. Limitations of this study

This study has several limitations. First, since the post-operative follow-up duration was short (mean, 6.34 ± 2.99 years) and the study population size was not large enough, many variables might not differ significantly from those of the controls. It is necessary that we acquire tracking data over a prolonged period in a large group of patients to reach a clearer answer. Second, although we ruled out residual stenosis tenaciously by physical and echocardiographic examination, we did not perform MRI and/or aortogram in all cases, and therefore, some study subjects may have had minor structural stenosis. However, we do not believe that the conclusion would have been different, because we adhered to the current criteria of successful coarctoplasty when selecting study subjects. Third, the data of four patients with bicuspid aortic valve may have influenced the total analysis. However, considering the small number and young age of the patients and insignificant statistical differences between patients with and without bicuspid aortic valve, we believe that our conclusions are unaffected.

5. Conclusions

In the context of vasculopathy of ascending aorta even after successful coarctoplasty in early infancy, we recommend that careful follow-up and tailored therapy through adulthood is mandatory to reduce morbidity and mortality, even in children with successful coarctoplasty in early infancy. However, long-term tracking study is needed to clarify the significance of the study.

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