Endothelial Dysfunction of Conduit Arteries in Patients with Repaired Coarctation of the Aorta

Yoshihiro Nozaki,1 MD, Kasumi Nakayama-Inaba,2 BA, Tomoko Ishizu,3 MD, Noriko Iida,4 BA, Yoshiaki Kato,1 MD, Yuji Hiramatsu,4 MD and Hitoshi Horigome,1 MD

Summary
Adult patients with repaired coarctation of the aorta (r-CoA) show high prevalence of late hypertension, but the exact mechanisms of this phenomenon are unknown. Endothelial dysfunction has been implicated in this paradoxical hypertension. We evaluated the endothelial function of both conduit and resistance arteries by using flow-mediated dilation (FMD) and digital peripheral artery tonometry (PAT).

Seventeen patients with r-CoA and one patient with repaired interrupted aortic arch (r-CoA group) aged 22.0 ± 6.9 years (5 females) underwent FMD of the right brachial artery, PAT of the right finger, blood marker tests, ambulatory blood pressure monitoring, echocardiography, carotid ultrasonography, and brachio-ankle pulse wave velocity measurement. The median age at aortic arch reconstruction was 2.0 months (interquartile range: 15 days to 7.0 years). Results were compared with 17 age-matched healthy subjects (control group).

Eight (44%) patients of the r-CoA group were hypertensive (5 received antihypertensive drugs). Patients in the r-CoA group showed significantly lower FMD (3.8 ± 1.5 versus 6.6 ± 2.5%, P < 0.001), larger intima-media thickness (0.63 ± 0.17 versus 0.47 ± 0.09 mm, P = 0.001), and higher left ventricular mass index (91.4 ± 24.6 versus 73.4 ± 17.3 g/m², P = 0.017) than those in the control group. There were no significant differences in PAT (refractory hyperemia index, 1.86 ± 0.43 versus 1.99 ± 0.59, P = 0.48) and brachio-ankle pulse wave velocity between the two groups.

Vascular dysfunction in r-CoA patients, particularly endothelial dysfunction, tends to occur more significantly in conduit arteries than in resistance arteries.

Key words: Flow-mediated dilation, Hypertension, Peripheral artery tonometry

The prevalence of hypertension in adult patients with coarctation of the aorta (CoA) or aortic arch interruption is high, and this condition is associated with cardiovascular morbidity and mortality even in the absence of recoarctation after surgical or interventional repair.1-3) More than half of CoA patients older than 30 years old are reportedly hypertensive.2,3) However, the mechanisms of this late hypertension need to be clarified.

Several studies have evaluated vascular function, including endothelial function in patients with repaired CoA (r-CoA) by using flow-mediated dilation (FMD). Most of these studies showed impaired endothelial function.4-6) However, only a few studies have investigated refractory hyperemia by using reactive hyperemia-peripheral artery tonometry (RH-PAT), and their results are inconsistent.7,8) FMD tends to reflect the endothelial function of large arteries (conduit arteries), whereas RH-PAT reflects the endothelial function of the peripheral microvasculature (resistance arteries).9) We are not aware of any studies that compared the vascular responsiveness between FMD and RH-PAT in patients with r-CoA. The present study investigated the vascular function of a group of r-CoA patients, particularly the regional differences in endothelial function.

Methods

Study population: The study subjects included 20 patients aged 13 to 40 years old who underwent surgical repair or percutaneous transcatheter angioplasty for CoA or aortic arch interruption between February 2016 and March 2017 at our hospital. None of the patients had evidence of recoarctation at their last visit (defined as > 3 m/second velocity in the aortic arch with a diastolic tail or > 20 mmHg pressure gradient between the upper and lower limbs, as measured by continuous wave Doppler echocardiography). However, two patients were excluded: RH-PAT was contraindicated in one patient because of the use...
of anticoagulants for mechanical aortic valve replacement, whereas the vascular function of the section proximal to the repair lesion could not be evaluated in the other patient with aortic arch interruption because the left and right subclavian arteries originated from the distal site of the repaired portion. In addition to the above 18 patients (r-CoA group), our study recruited 17 age-matched control subjects (control group) through leaflets, the department website, and word of mouth. Among the 18 patients of the r-CoA group, 8 showed hypertension, and 5 had been treated with antihypertensive drugs.

Ethics: The study protocol conformed to the ethical guidelines set forth by the 1975 Declaration of Helsinki and was approved by the Ethics Committee of Tsukuba University Hospital. All study subjects provided written informed consent (for subjects younger than 20 years of age, their parents provided the written informed consent).

Study protocol: The participants underwent FMD, RH-PAT, transthoracic echocardiography, carotid ultrasonography, hematological tests, 24-hour ambulatory blood pressure monitoring (ABPM), and brachio-ankle pulse wave velocity (baPWV) measurement. One patient declined ABPM. Participants were instructed to fast, refrain from caffeine, alcohol, and tobacco, and avoid exercise from midnight until the start of the study at 9:00 a.m. Furthermore, the administration of antihypertensive vasodilators was avoided for 24 hours before the FMD and RH-PAT tests. FMD, RH-PAT, and baPWV were evaluated in the right-side extremities because the left subclavian artery of some patients had been sacrificed for aortic arch reconstruction with subclavian artery flap procedure or modified Blalock-Park procedure.

FMD of the brachial artery  FMD was performed in conjunction with PAT and was measured using UNEXEF18G (UNEX, Nagoya, Japan) with a high-resolution 10 MHz linear probe and by semiautomated vessel tracking; the equipment is designed to be consistent with the published recommendations\(^9,10\) and showed acceptable reliability.\(^\text{11,12}\)

On the basis of the guidelines provided by the manufacturer, the study was performed in a quiet, dimmed, and temperature-controlled room. The right arm was placed on a supporting cradle, an occlusion cuff was placed on the forearm 1-2 cm distal to the elbow crease, and the ultrasound transducer was placed on the arm proximal to the elbow where the brachial artery could be clearly visualized. ECG was monitored simultaneously to display the phase of the cardiac cycle. The one minute baseline period of scanning of the brachial artery was recorded prior to cuff inflation. The cuff was then inflated to at least 50 mmHg above systolic blood pressure (SBP) for 5 minutes to achieve total brachial artery occlusion. The scanning was continued for 5 minutes after deflation (postocclusion period).

The diameters of the brachial arteries were measured from the adventitia signals of A-mode in endo-diastole by automated edge detection and were corrected manually whenever necessary (Figure). The adventitia-adventitia diameter was defined as the vessel diameter because it is often difficult to obtain the intima-media complex signal in young adults. The FMD was calculated using the following equation:

\[
\text{FMD (\%)} = \frac{\text{[peak diameter - baseline diameter]}}{\text{baseline diameter}} \times 100
\]
PAT PAT tests were performed using the EndoPAT device (Tamar Medical, Caesarea, Israel) by placing the fingertip plethysmography probe on the index finger, in addition to the FMD. The pulse wave amplitude was measured continuously during three phases: the quiet baseline period, five-minute forearm occlusion period (as mentioned above in FMD), and the reactive hyperemia period following cuff release. The recordings were then analyzed using the proprietary software of the device. The reactive hyperemia index (RHI) was computed by the device using the method described previously.13

ABPM A validated oscillometric device (TM-2431, A&D, Toshima, Japan) with an appropriate cuff size was used in this study. Although almost all subjects wore the cuff on the left brachial arm (nondominant arm), seven patients in whom the left subclavian artery had been sacrificed for aortic arch repair wore it on the intact right arm. Blood pressure was measured automatically every 20-30 minutes according to the published guidelines.14 Hypertension was defined as the 24-hour average SBP and/or diastolic blood pressure of > 130/80 mmHg for adults [13] and > 95th percentile of published values for children.15

Carotid ultrasonography The intima-media thickness (IMT) of the common cervical arteries was measured using an ultrasound machine (AplioXG, Toshiba Medical Systems, Ootawara, Japan) with a 12 MHz linear transducer.16

baPWV baPWV was measured using a volume-plethysmographic apparatus (BP-203RPE II form PWV/ABI, Omron Healthcare, Kyoto, Japan), as described previously.17

Echocardiography All participants underwent comprehensive standardized echocardiographic evaluation and confirmation of the absence of recoarctation by ultrasonography (Vivid E9, GE Healthcare, Little Chalfont, UK). The left ventricular dimensions were measured according to the recommendation of the American Society of Echocardiography.18 Ejection fraction was calculated by the modified Simpson method. LV mass was calculated from the linear dimensions obtained from the M-mode images.19

Hematological tests Blood samples were collected to evaluate the factors related to arterial sclerosis, including glucose intolerance (fasting plasma glucose, HbA1c), lipid metabolism (total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglyceride), alanine aminotransferase, uric acid, and high-sensitive C-reactive protein.

Statistics analysis: Data are expressed as mean ± standard deviation. All data were stored and analyzed using SPSS statistical package version 22 (IBM, New York, NY). Statistical analysis was performed with t test, Mann-Whitney U test, Kruskal-Wallis test, and one-way analysis of variance (depending on the data distribution pattern), followed by multiple comparison and Fisher’s exact test as appropriate. Correlations were evaluated using Spearman’s rank order coefficient. In all analyses, a two-sided value of P < 0.05 was considered statistically significant.

Results

Subject characteristics: Table I summarizes the clinical characteristics of the subjects. The study included 17 patients with r-CoA and 1 patient aged 22.0 ± 6.9 years old with interrupted aortic arch (New York Heart Association class I). The median age at the first repair of aortic arch was 2.0 months (interquartile range: 15 days to 7.0 years). Thirteen patients (72%) underwent the first procedure during infancy, and six patients underwent multiple therapies. The time from the last repair was 16.7 ± 6.2 years. Five patients (28%) had known arterial hypertension requiring antihypertensive treatment (angiotensin converting enzyme inhibitor (n = 2), angiotensin receptor blocker (n = 2), calcium antagonist (n = 1), and beta blocker (n = 1); drugs overlapped in one case). One of the patients had type 2 diabetes mellitus (DM) and hyperlipidemia. Seven patients had bicuspoid aortic valve, three patients had mild aortic valve stenosis, and eight patients had aortic valve regurgitation (mild (n = 6), moderate (n = 1), and severe (n = 1)). There was no significant difference in gender and body mass index (BMI) between the r-CoA and control groups; however, obesity (defined as BMI > 25 kg/m²) was noted in five patients in the r-CoA group compared with one patient subject in the control group. None of the subjects had history of coronary artery disease or stroke, and all subjects were nonsmokers at the time of the study.

Hematological tests: HbA1c was higher in the r-CoA group than the control group, but only one patient had DM with HbA1c of > 6.5%. There was no significant difference between the two groups in lipid metabolism markers, alanine aminotransferase, uric acid, and high-sensitive C-reactive protein (Table II).

Vascular function: With regard to the parameters of endothelial function, FMD was significantly lower in the r-CoA group than in the control group (3.8 ± 1.5% versus 6.6 ± 2.5%, P < 0.001), but the RHI between the groups was comparable (1.86 ± 0.43 versus 1.99 ± 0.59, P = 0.480) (Table III). ABPM showed that the patients of the r-CoA group tended to be hypertensive, but the difference was not statistically significant. Three of the patients were newly diagnosed with hypertension by ABPM. The IMTs were thicker in both the right and left arteries in the r-CoA group. However, in most patients, the IMT of the common carotid artery was within the reference values and was thicker than 0.9 mm in only three patients.21 None of the patients had plaque. There was no significant difference in the baPWV value.

Echocardiography: The left ventricle mass index was greater in the r-CoA group than the control group, but the ejection fraction was not significantly different (Table III).

Correlations of endothelial function and other parameters: The parameters of the endothelial function (FMD and RHI) were compared with blood pressure, HbA1c, IMT, and LV mass index. A significant correlation was observed only between FMD and IMT (right IMT, r = −0.357, P = 0.035; left IMT r = −0.439, P = 0.008).

Discussion

Endothelial function: The main findings of the present
study show that almost half of the patients (8/18, 44%) were hypertensive. FMD was impaired in the r-CoA group, whereas the results of RH-PAT were comparable with the control group of healthy subjects. The results
confirmed the presence of endothelial dysfunction, which was evaluated by FMD, in patients with r-CoA. The impairment of FMD in these patients has been described with or without evidence of high BP. The RHI from RH-PAT in CoA were preserved, similar to that in a previous report.

Although both FMD and RH-PAT could reflect endothelial function, we should consider the differences in reactivity between conduit and resistance arteries. Reduced nitric oxide (NO) release in response to stimuli plays a central role in the pathophysiology of endothelial dysfunction in the conduit arteries. In resistance arteries, endothelium-dependent vasodilation is maintained not only by NO but also by prostacyclin and various endothelium-derived hyperpolarizing factors. Furthermore, FMD is particularly sensitive to traditional risk factors (age, hypertension), whereas RH-PAT is more sensitive to metabolic risk factors, particularly BMI and DM.

Our results suggest that endothelial dysfunction in patients with r-CoA may occur more significantly in conduit arteries than in resistance arteries; however, it is difficult to confirm whether this difference is the cause or consequence. It is necessary to elucidate the mechanisms in which endothelial dysfunction occurs in r-CoA, e.g., decreased production of NO or decreased responsiveness to NO. The effectiveness of treatment strategies based on endothelial function in the prevention of hypertension and improvement of long-term cardiovascular morbidity, mortality, and quality of life remains to be investigated. Furthermore, whether the strategies improve cost effectiveness, such as angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and beta blockers for heart failure, should be analyzed.

In this study, the parameters of endothelial function (FMD and RHI) were comparable between patients treated with angioplasty and those with surgery. Those values were not affected by the number of times of interventions. The comparison between patients treated with antihypertensive drugs and those treated without antihypertensive drugs showed no significant difference in the values of FMD, blood pressure, HbA1c, IMT, and LV mass index. However, it was difficult to elucidate the influence of the abovementioned factors on endothelial function in r-CoA patients because of the small number of subjects in each group.

### Aortic stiffness: Our results showed larger IMT in the r-CoA group, thus confirming the findings of previous studies. Previous experimental studies showed increased medial thickness in the proximal arteries obtained from rabbits with repaired experimentally induced coarctation. The same study demonstrated the presence of significant endothelial dysfunction, which was reflected by acetylcholine-induced relaxation (endothelial dependent), whereas the peak of sodium nitroprusside-induced relaxation (endothelial independent) was unchanged. Whether there is an interaction between endothelial dysfunction and increased aortic stiffness remains to be seen. Although a weak but significant negative correlation between FMD and IMTs was observed in this study, it is difficult to clarify the exact mechanisms of this interaction because of the cross-sectional design of the study.

Our results showed no differences in baPWV between the r-CoA and control groups. Although baPWV does not require professional skills compared with carotid-femoral PWV, baPWV reflects the mechanics at both the proximal and distal sides of coarctation. A number of studies investigated the PWV of the proximal side to coarctation, such as the brachial to radial artery, and demonstrated the acceleration of the regional velocity. It is likely that BaPWV is not suitable for the assessment of the aortic stiffness of the proximal side of coarctation.

### Study limitations: This study is a cross-sectional observational study with a small sample size and consists of heterogeneous patients with regard to treatment procedures, timing of treatment, age at examination, and duration from the procedures to examinations. Furthermore,
some patients were on antihypertensive medications, including angiotensin converting enzyme inhibitors, angiotensin receptor blockers, calcium antagonists, and beta blockers, which might have improved FMD to some extent\textsuperscript{28}, however, these agents were stopped at least 24 hours before the study. FMD was reduced in the r-CoA group in our study relative to the control.

**Conclusion**

FMD, which is a conduit artery-sensitive endothelial function, was significantly impaired in patients in the r-CoA group, whereas RH-PAT, which reflects resistance arteries, was comparable with the control group. The results suggest the presence of vascular dysfunction mainly in the conduit arteries of patients with r-CoA.

**Disclosures**

**Conflicts of interest:** None.

**References**