Ventricular–Vascular Stiffening in Patients With Repaired Coarctation of Aorta
Integrated Pathophysiology of Hypertension

Hideaki Senzaki, MD; Yoichi Iwamoto, MD; Hirotaka Ishido, MD; Satoshi Masutani, MD; Mio Taketazu, MD; Toshiki Kobayashi, MD; Toshiyuki Katogi, MD; Shunei Kyo, MD

Background—Despite successful repair, patients with coarctation of the aorta (COA) often show persistent hypertension at rest and/or during exercise. Previous studies indicated that the hypertension is mainly due to abnormalities in the arterial bed and its regulatory systems. We hypothesized that ventricular systolic stiffness also contributes to the hypertensive state in these patients in addition to increased vascular stiffness.

Methods and Results—The study involved 43 patients with successfully repaired COA and 45 age-matched control subjects. Ventricular systolic stiffness (end systolic elastance) and arterial stiffness (effective arterial elastance) were measured invasively by ventricular pressure–area relationship during varying preload before and after β-adrenergic stimulation. The mean systolic blood pressure was significantly higher with concomitant increases in both end systolic elastance and effective arterial elastance in patients with COA compared with control subjects (113.2±16.8 versus 91.0±9.1 mm Hg, 44.5±17.0 versus 19.2±6.7 mm Hg/mL/m², and 27.8±11.4 versus 20.2±4.8 mm Hg/mL/m², respectively; P<0.01 for each). End systolic elastance and effective arterial elastance of patients with COA showed exaggerated responses to β-adrenergic stimulation, further amplifying blood pressure elevation. Quantification analyses assuming that ventricular systolic stiffness of patients with COA is equal to that of the control revealed that ventricular systolic stiffness accounts for approximately 50% to 70% of the elevated blood pressure in patients with COA. Furthermore, combined ventricular–arterial stiffening amplified systolic pressure sensitivity to increased preload during abdominal compression and limited stroke volume gain/relaxation improvement induced by β-adrenergic stimulation.

Conclusions—Increased ventricular systolic stiffness, coupled with increased arterial stiffness, plays important roles in hypertension in patients with repaired COA. Thus, ventricular systolic stiffness is a potentially suitable target for reduction of blood pressure and improvement of prognosis of patients with COA. (Circulation. 2008;118[suppl 1]:S191–S198.)

Key Words: blood pressure ▪ congenital ▪ hemodynamics ▪ heart defects ▪ patients

There is a general agreement that hypertension often persists or develops after successful anatomic repair of coarctation of the aorta (COA).1,2 Old age at repair appears to be associated with a higher incidence of hypertension.2,3,4 However, a recent study has emphasized the high prevalence of hypertension in a large cohort of patients treated for COA even in early childhood (nearly 30% incidence of hypertension at 10 years follow-up).5 Previous studies have postulated the potential roles of various factors in the hypertensive state after COA repair. These factors include mechanical,7,8 functional,9,10 and structural10 abnormalities in the systemic arterial bed, particularly of the precoarctation region and malfunctions of blood pressure (BP) regulatory systems,11–13 some of which appear to exist within the fetal or neonatal period before repair.14,15

However, systolic BP is determined not only by the status of arteries, but also by the properties of the ventricles to which the blood vessels are coupled. Chronic cardiac ejection into stiff arteries may induce ventricular adaptation to confront the high systolic load by increasing ventricular systolic stiffness.16 Increased ventricular systolic stiffness coupled with increased arterial stiffness could contribute to the generation of higher levels of systolic BP. In addition, the combination of ventricular–systolic and arterial stiffening can interact to augment systolic BP instability to changes in loading conditions and/or changes in ventricular and arterial properties. The importance of such heart–arterial interaction has indeed been implicated in several pathophysiological conditions such as aging-related BP elevation and control.17

In the present study, we tested the hypothesis that ventricular systolic stiffness as well as vascular stiffness are increased and significantly contribute to elevated BP and enhanced sensitivity of systolic BP to altered cardiac
Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Control Subjects</th>
<th>Patients With COA</th>
</tr>
</thead>
<tbody>
<tr>
<td>BSA, m²</td>
<td>0.77±0.45*</td>
<td>0.78±0.52*</td>
</tr>
<tr>
<td>Range</td>
<td>0.40 to 1.80</td>
<td>0.34 to 1.81</td>
</tr>
<tr>
<td>Age at study, years</td>
<td>5.9±5.5*</td>
<td>5.9±5.2*</td>
</tr>
<tr>
<td>Range</td>
<td>6 months to 16</td>
<td>7 months to 16</td>
</tr>
<tr>
<td>Age at repair, years</td>
<td>2.9±4.2*</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>1 month to 14</td>
<td></td>
</tr>
<tr>
<td>Interval from repair to study, years</td>
<td>3.0±2.5*</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>5 months to 8</td>
<td></td>
</tr>
</tbody>
</table>

Methods for repair

- Balloon angioplasty, n
- Stent implantation, n
- Surgery, n

Medications

- ACEI, n
- ARB, n
- ß-blocker, n
- ACEI + ß-blocker, n

*Data are mean±SD.

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin type 1 receptor blocker.

Table 2. Baseline Hemodynamic Data and Changes After Dobutamine Infusion

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>COA</th>
<th>Control</th>
<th>COA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, beats/min</td>
<td>99.1±10.5</td>
<td>101.1±12.1</td>
<td>2.6±3.3</td>
<td>2.1±3.1</td>
</tr>
<tr>
<td>SAI, L/min/m²</td>
<td>4.7±0.8</td>
<td>4.6±0.9</td>
<td>0.64±0.16†</td>
<td>0.20±0.09†</td>
</tr>
<tr>
<td>ESVI, cm²/m²</td>
<td>3.6±0.7</td>
<td>3.2±0.8</td>
<td>-0.79±0.18†</td>
<td>-0.35±0.1†</td>
</tr>
<tr>
<td>EDI, cm²/m²</td>
<td>8.3±1.8</td>
<td>7.8±2.3</td>
<td>-0.17±0.09†</td>
<td>-0.16±0.09†</td>
</tr>
<tr>
<td>FS, %</td>
<td>57.7±6.4</td>
<td>59.1±9.1</td>
<td>8.1±1.1†</td>
<td>2.9±0.8†</td>
</tr>
<tr>
<td>ESP, mm Hg</td>
<td>91.0±9.1</td>
<td>113.2±16.8*</td>
<td>24.9±6.5†</td>
<td>46.3±10.1†</td>
</tr>
<tr>
<td>EDP, mm Hg</td>
<td>8.1±2.1</td>
<td>11.5±3.6*</td>
<td>-0.2±0.8</td>
<td>1.2±1.8</td>
</tr>
<tr>
<td>ß, mm Hg/cm²/m²</td>
<td>0.32±0.07</td>
<td>0.45±0.13*</td>
<td>0.03±0.06</td>
<td>0.02±0.07</td>
</tr>
<tr>
<td>τ, ms</td>
<td>18.5±3.9</td>
<td>20.9±4.2</td>
<td>-1.8±0.4†</td>
<td>0.9±1.2*</td>
</tr>
</tbody>
</table>

Data are mean±SD.

*P<0.05 versus control.
†P<0.05 versus baseline.

SAI indicates stroke area index; ESVI, end systolic area index; EDI, end diastolic area index; FS, fractional shortening; ESP, end systolic pressure; EDP, end diastolic pressure; ß, stiffness coefficient for end diastolic P-A relationship.

Procedures

After routine cardiac catheterization and before angioventriculography, the left ventricular P-A relationship was constructed by simultaneously measuring ventricular chamber pressure and area both at rest and during preloads varied by brief balloon obstruction of the inferior vena cava. Details of this procedure have been reported previously and validated.

Briefly, ventricular pressure was measured with a high-fidelity pressure transducer mounted on a 0.014-inch guide wire (RADIAL Medical Systems, Uppsala, Sweden) in a 4- or 5-French pigtail catheter. Instantaneous ventricular cavity area was obtained using an automated border detection echocardiographic system (Sonos 5500; Hewlett-Packard) with a 3.5- or 5.0-MHz phased-array transducer. Transhpecric 2-dimensional images were recorded from the midventricular short-axis plane using the papillary muscle as an anatomic landmark. P-A data were displayed in real time and stored for subsequent offline analysis. P-A analysis was repeated after ß-adrenergic stimulation by dobutamine (5 μg/kg/min).

Data Analysis

P-A data were digitized at 500 Hz and analyzed using custom-designed software. Three to 5 steady-state beats during expiration over 2 respiratory cycles were signal-averaged and used to calculate hemodynamic parameters, including end diastolic and end systolic pressures and areas, stroke area, fractional shortening, and time constant of ventricular relaxation (τ). Area data were normalized to body surface area (BSA) and expressed as area indices. The value τ was calculated using a logistic fit, which provides a more stable parameter than monoeponential fits.

The effective arterial elastance (Ea), defined as the ratio of end systolic pressure and stroke area index, was also computed as a measure of arterial stiffness. Both the mean and pulsatile components of arterial impedance are manifest in Ea.

Data obtained during preload changes induced by transient inferior vena cava occlusion yielded the end systolic elastance (Ees) as a measure of systolic ventricular stiffness. Using an iterative method, end systole was defined as the point of maximal stiffness regardless of the timing of P-A data, and perpendicular regression for each end systolic P-A data provided the slope (Ees) and area axis intercept of

preload in patients who had undergone COA repair. For this purpose, we used ventricular pressure–area (P-A) analysis during varying preload both at rest and under ß-adrenergic stimulation.

Methods

Patients

Cardiac catheterization was performed in postcoarctectomy patients who were suspected of having recoarctation based on examination in the outpatient clinic, including echocardiography, persistent heart murmur, or high BP. Of 61 consecutive such patients, 43 patients without residual pressure gradient across the repaired site were enrolled in the present study. The characteristics of the enrolled patients are listed in Table 1. Data were compared with those of 45 age-matched control subjects who had a small ventricular septal defect with a calculated shunt ratio of <5% (Table 1). All control patients had a subpulmonic ventricular septal defect, which can potentially cause aortic valve prolapse with resultant aortic regurgitation.

All patients with ventricular septal defect had undergone cardiac catheterization previously to check for deformities of the aortic valves and their relations to ventricular septal defect. This was based on the management protocol adopted by our institution for all such patients before 2000. All medications for patients with COA were withheld 24 hours before the study, and the same anesthesia protocol was used in all study subjects (premedication with intramuscular pethidine combined with atropine and sedation with continuous infusion of sodium thiamylal during catheterization). Written informed consent was obtained from the parents of all patients, and the procedures were approved by the Committee on Clinical Investigation of Saitama Medical University.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.
end systolic P-A relationship. Ventricular diastolic stiffness was also computed from the data obtained during inferior vena cava occlusion by fitting the end diastolic P-A relationship to a monoeXponential function \( P = P_0 - \alpha (e^{-\beta DAI}) \) yielding passive diastolic chamber stiffness (\( \beta \)).

**Statistical Analysis**

All values were expressed as mean±SD. Differences between groups were compared by unpaired \( t \) test. Data obtained before and after dobutamine infusion were compared by the paired \( t \) test. A probability value of \( <0.05 \) was considered significant. All statistical analyses were performed using Systat version 6.0.

**Results**

**Ventricular–Vascular Stiffening and Blood Pressure**

Baseline hemodynamics and ventricular–vascular stiffness indices for each group are summarized in Table 2 and Figure 1A, respectively. BP and both Ees (44.5±17.0 versus 19.2±6.7 mm Hg/mL/m², \( P<0.01 \)) and Ea (27.8±11.4 versus 20.2±4.8 mm Hg/mL/m²; \( P<0.05 \)) were significantly higher in patients who underwent repair of COA compared with the control subjects. The increases in Ees and Ea were disproportionate, with Ees rise being more prominent as shown by the significantly higher value of the coupling ratio (Ees/Ea) in patients with COA than in the control subjects (1.58±0.36 versus 0.95±0.16, \( P<0.01 \)). The mean values of diastolic ventricular posterior wall thickness measured by echocardiography were significantly higher in patients with COA than in control subjects (6.3±1.5 versus 5.5±0.6 mm, \( P<0.05 \)). However, there was no significant correlation between ventricular wall thickness and Ees in patients with COA, suggesting that ventricular systolic stiffness is increased independent of ventricular hypertrophy in patients with COA. There were no significant differences in other hemodynamic parameters between the 2 groups, except for significant increases in end diastolic pressure and diastolic chamber stiffness (\( \beta \)) in patients with COA compared with the control subjects. Figure 2 demonstrates representative P-A relations of a control subject and a patient with repaired COA. Compared with the control subject, the patient with COA had steeper slopes of both Ees and Ea with marked elevation of systolic BP, suggesting that both systolic–ventricular and vascular wall stiffening contribute to the increased BP in patients after repair of COA.

We further quantified the contribution of increased ventricular systolic stiffness to the elevated BP in patients with COA using 2 different approaches as illustrated in Figure 3. In the first approach (Figure 3A), we estimated systolic BP by assuming that Ees of the patients with COA was equal to the mean Ees value of the control subjects. Using this method, systolic BP in patients with COA was significantly decreased

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**Figure 1.** A, Ees, Ea, and their coupling (Ees/Ea) for each group at baseline. B, Absolute changes in Ees, Ea, and Ees/Ea after dobutamine infusion. Data are mean±SD of 43 patients with repaired COA and 45 control subjects.
Changes in hemodynamic variables and ventricular–vascular stiffness after \( \beta \)-adrenergic stimulation with dobutamine are shown in Table 2 and Figure 1B, respectively. Dobutamine infusion significantly increased both \( E_{es} \) and \( E_{es} \) in patients with COA, whereas it significantly increased \( E_{es} \) only in the control subjects. The delta changes in \( E_{es} \) and \( E_{es} \) were significantly greater in patients with COA than in control subjects. The delta changes in \( E_{es} \) and \( E_{es} \) were significantly and positively correlated with changes in systolic BP (\( \Delta E_{es} = 0.04 \Delta \text{systolic pressure} + 0.2, r=0.40, P<0.05 \)), suggesting elevated systolic BP-induced delayed relaxation.

**Blood Pressure During Acute Increase in Preload**

Increased \( E_{es} \) coupled with increased \( E_{es} \) further implies enhanced sensitivity of systolic BP change to a given change in ventricular preload. This was directly tested by examining systolic BP changes during acute increase in preload induced by abdominal compression in randomly selected 21 patients with COA and 29 patients of the control group both before and after dobutamine infusion. Table 3 summaries such data, showing that despite smaller increases in preload (end diastolic area index) with abdominal compression, patients with COA exhibited significantly greater increases in systolic BP than the control subjects both at rest and under \( \beta \)-adrenergic stimulation. In both groups of subjects, the sensitivity of systolic BP to preload was significantly augmented under dobutamine compared with that at rest before dobutamine infusion.

**Discussion**

Based on the narrowing of the aorta in COA, most previous studies have focused on the abnormalities in the arterial bed as an important determinant of persisting hypertensive state after COA repair. Attention has also been paid to abnormalities of BP regulation systems, but this still appears to be limited within the concept that these abnormalities should affect BP control through the arterial system. Although this concept appears to be indeed relevant to the mechanisms of rest and exertional hypertension in patients with repaired COA, there is less emphasis on the role of the ventricle, including interaction with the arterial system, as a potential determinant of BP regulation. The present study provided for the first time evidence that ventricular systolic stiffness significantly contributes to the elevated BP in patients with repaired COA and that increased ventricular systolic stiffness coupled with increased arterial stiffness enhances pressure lability to preload alterations. We also demonstrated that basal elevation of ventricular systolic stiffness limits the...
increase in stroke volume under β-adrenergic stimulation. These findings would better explain the underlying mechanism of hypertension after COA repair and help broaden its pathophysiological and therapeutic focus.

Ventricular–Systolic and Arterial Stiffening and Hypertension in Patients With Repaired Coarctation of the Aorta

Several studies reported increased arterial stiffness in patients with repaired but with mild residual COA by showing increased pulse wave velocity of the forearm artery or increased elastic modulus of the ascending and transverse aorta. The present study further demonstrated that arterial stiffness assessed by Ea is markedly increased and is associated with increased systolic BP in postcoarctectomy patients even without apparent residual coarctation. We also demonstrated exaggerated arterial stiffening under adrenergic stimulation. These mechanical and functional abnormalities in the arterial bed of postcoarctectomy patients may be linked to the structural abnormalities that hold characteristics compatible with the loss of vessel elasticity. In addition, abnormalities in BP regulatory

Table 3. Hemodynamic Changes After Abdominal Compression

<table>
<thead>
<tr>
<th></th>
<th>At Rest (before dobutamine)</th>
<th>Dobutamine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>COA</td>
</tr>
<tr>
<td>Δ EDAI, cm²/m²</td>
<td>0.95±0.51†</td>
<td>1.06±0.50†</td>
</tr>
<tr>
<td>Δ ESP, mm Hg</td>
<td>16.4±7.6†</td>
<td>28.3±13.6† ‡</td>
</tr>
</tbody>
</table>

Data are mean±SD.
*P<0.05 versus control.
†P<0.05 versus before abdominal compression.
‡P<0.05 versus before dobutamine.

EDAI indicates end diastolic area index; ESP, end systolic pressure.
systems, including augmented responsiveness of the renin–angiotensin system, sympathetic hyperactivity, and baroreflex dysfunction, may also be involved in both rest and exertional hypertension in patients with post-COA repair.

However, the present study clearly demonstrated that ventricular systolic stiffening also significantly contributes to BP regulation in patients with repaired COA. The Ees depends on both active contraction and passive structural factors, and enhanced contractility in postcoarctectomy patients has been suggested by previous reports using different systolic indices. None of these studies, however, related systolic ventricular property to BP status. Our method using the Ees in the ventricular P-A diagram has an advantage in that it enables us to clarify the heart–arterial interaction and its net hemodynamic consequence, including BP and cardiac output. Without an increase in Ees, systolic BP expected from the elevated arterial stiffness alone was much lower than the observed systolic BP in our patients, highlighting the importance of ventricular properties in the elevated BP after COA repair. We also demonstrated that there was an exaggerated rise in Ees in response to β-adrenergic stimulation, further amplifying BP elevation under increased stiffness of arteries into which the ventricle ejects flow volume. This may be importantly associated with the reported hypertensive response to exercise. Figure 4 shows an example of the P-A relationships in a representative patient with COA before and after dobutamine infusion. The steeper Ees and Ea after dobutamine makes systolic BP markedly elevated compared with baseline. Because ventricular preload is generally preserved during exercise and appears also preserved in postcoarctectomy patients, the ventricular P-A loop in this patient during exercise can be estimated by the dashed line in Figure 4, leading to a noticeable hypertension (this particular patient indeed had hypertensive response of >200 mm Hg during treadmill exercise testing, data not shown). Thus, increased ventricular systolic stiffness and exaggerated response to adrenergic stimuli importantly contribute to the hypertensive state at rest and possibly during exertion in patients after COA repair.

Other Implications of Systolic Ventricular and Vascular Stiffness

Importantly, the combination of ventricular–arterial stiffness alters the way in which the cardiovascular system can respond to stress demands, changes in volume, and pressure loading. As shown by the results of BP changes during abdominal compression, higher Ees and Ea increase the sensitivity of BP changes to a given change in cardiac preload. Furthermore, the higher Ees implies higher sensitivity of BP changes to a given change in ventricular afterload (Ea), and higher Ea does so to a given change in ventricular systolic property or contractility (Ees). Based on the exaggerated ventricular and vascular response during adrenergic stimulation, or exercise, the combined systolic ventricular–arterial stiffness could also lead to augmented pressure rise through changes in ventricular and vascular properties. Superimposed on the reported abnormalities in neurohumoral and baroreflex regulation of ventricular preload, afterload, and contractility, ventricular systolic, and arterial stiffening would induce BP liability in patients with repaired COA.

This notion is indeed supported by several previous studies. Schroeder et al reported that high volume status significantly contributes to the development of paradoxic hypertension after COA repair and suggested the importance of fluid management in stabilizing BP control after COA repair. Furthermore, Polson et al reported increased BP variability in patients with COA despite significantly reduced heart rate variability. Because increased BP variability is associated with increased risk of end organ damage, reducing stiffness of both systems could be an effective therapeutic target to reduce morbidity and mortality in postcoarctectomy patients not only by reducing the level of BP, but also by reducing BP lability.

Another implication of the combined ventricular systolic and arterial stiffening in patients with COA is that exertional capacity may be limited due to a limited gain in stroke volume and amplified rise in BP. Indeed, decreased exercise tolerance has been reported in patients with repaired COA. Although hypertension was phenomenologically linked to this abnormality, the underlying mechanisms remain unclear. The present study has clearly demonstrated that high basal Ees limits ability to increase stroke volume despite greater increase in Ees during β-adrenergic stimulation, whereas further increases in both Ees and Ea with adrenergic stimulation augment the rise in systolic BP. Increased systolic ventricular–vascular stiffness and the consequential rise in systolic pressure may also worsen diastolic function during exercise by pressure load-induced prolongation of relaxation. Our results indeed demonstrated compromised improvement of relaxation after dobutamine in patients with COA, which was significantly associated with increased systolic BP. This may induce synergistic rise in end diastolic pressure under increased ventricular diastolic stiffness as observed in the present patients with COA. Thus, the stiff
ventricular-arterial system of patients with COA may also explain in part the exercise intolerance noted in this population. Interestingly, Chen et al. demonstrated that verapamil improves exercise performance by reducing ventricular systolic and vascular stiffening in the elderly. Whether such agents also improve exercise capacity in postcoarctectomy patients deserves future investigation.

**Limitations**

There are several limitations to this study that deserve consideration. The present study does not implicate cause-effect relationships among ventricular systolic stiffening, arterial stiffening, and hypertension. In particular, arterial stiffening alone can cause elevation of systolic BP, which may cause ventricular stiffening. Although increased ventricular systolic stiffness may not be primary, this does not undermine the notion that the underlying pathophysiology of elevated BP after COA includes not only the arterial bed, but also the ventricular systolic property. Second, although the data of pharmacological β-adrenergic stimulation suggest their implications in pathophysiology during exercise (exercise intolerance and hypertension), they cannot be extrapolated to directly explain such phenomena. Comparative study with exercise testing is needed to define the role of ventricular-vascular stiffening during exercise in patients with COA. Third, although we normalized area data to BSA, area changes are not necessarily linear with BSA. If the BSA is smaller, the area indexed to BSA tends to be overestimated. However, the distribution of BSA was similar in the COA and control groups, and therefore the potential error should be equal in the 2 groups. Furthermore, even if the BSA were smaller in patients with COA than in control subjects, this could lead to underestimation of the Ees value rather than overestimation. Fourth, it is well known that Ees exhibits ventricular size dependency. Although there was no significant difference in end diastolic area index between the patients with COA and control subjects, the tendency for a smaller of end diastolic area index in patients with COA could potentially cause higher Ees, even if the “true” stiffness is the same. However, the difference in end diastolic area index was much smaller than that in Ees between the 2 groups. Furthermore, even if the P-A loop of the COA group in Figure 3B is shifted to the right to match end diastolic area index between the 2 groups, this produces only a modest decline in Ees from 44.5 to 37.2 mm Hg/cm²/m², which is still much higher than the Ees of the control subjects. Thus, it is unlikely that ventricular size alone explains the higher Ees values of patients with COA than those of the control subjects. Lastly, patients in the present study do not reflect the entire cohort of postcoarctectomy patients (more than half of patients with COA do not show hypertension), and the enrollment of a limited number of patients does not allow us to identify the effect of timing or operative procedure of coarctectomy on the ventricular-vascular pathophysiology after COA repair. These issues should be addressed in future studies with noninvasive methodology that allow data to be obtained repeatedly in a large population.

**Conclusions**

Kass has recently proposed the concept of “coupling disease” in which stiffness of both the heart and arteries interacts to limit performance and generate clinical symptoms. COA may also belong to this disease entity. Cardiovascular and cerebrovascular complications are evident late after anatomic repair of COA, resulting in premature death in this population. Hypertension and atherosclerosis are the main determinants of this adverse outcome. Recognition that changes in both ventricular-systolic and vascular stiffening contribute to increased BP and to its enhanced sensitivity to loading conditions both at rest and perhaps during exertion may open new avenues for the treatment of postcoarctectomy patients to reduce morbidity and mortality. Prospective studies examining the effects of therapies aimed at “destiffening” both the ventricle and arteries of postcoarctectomy patients are warranted.

**Sources of Funding**

Supported by a National Grant (No 8025127) from the Japan Society for the Promotion of Science (H.S.) and Medical Research Grants from Nipro Corporation (H.S.), Kawano Memorial Foundation (H.S.), and Tenshino Medical Institute (H.S.).

**Disclosures**

None.

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_Circulation_. 2008;118:S191-S198
doi: 10.1161/CIRCULATIONAHA.107.757096

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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The four articles listed below have been retracted due to ethical violations. The corresponding author’s institution, Saitama Medical University, reported to the editors of Circulation, that Dr. Hideaki Senzaki did not receive approval for these studies from the institutional internal ethics committee. Furthermore, in each of the articles referenced below, it was determined that Dr. Senzaki misinformed the editors and readers of Circulation by stating that the studies had received the necessary approval from his institutional review board.