Sympathetic Denervation and Reinnervation After Arterial Switch Operation for Complete Transposition

Chisato Kondo, MD; Makoto Nakazawa, MD; Kazuo Momma, MD; Kiyoko Kusakabe, MD

Background—Sympathetic cardiopulmonary nerves arise from the cervical sympathetic trunks and the stellate ganglia and subsequently course along the origin of the great arteries and the coronary arteries to innervate the ventricles. Therefore, the sympathetic nerves may be obligatorily interrupted by the arterial switch operation (ASO) for complete transposition of the great arteries.

Methods and Results—To demonstrate and characterize the possible sympathetic denervation, 51 patients after ASO, 4.8 years old (range, 1 month to 10.1 years), underwent [123I]metaiodobenzylguanidine (MIBG) imaging of the sympathetic nerve terminal. MIBG uptake to the heart was graded by quantitative analysis using the heart-to-mediastinum (H/M) ratio of MIBG uptake. A quantitative criterion for absent uptake of MIBG was set to 1.48 in the H/M ratio. Four patients, 1 month after ASO showed complete absence of MIBG uptake, which had been observed preoperatively. In contrast, 47 patients late after ASO (range, 15 months to 10.1 years) showed various degrees of uptake of MIBG. Patients operated on at <55 days of age showed positive MIBG uptake much more frequently than those operated on at later ages. Heart rate and rate-pressure product at peak exercise on a treadmill exercise test were significantly greater in patients with positive uptake than in those with absent uptake of MIBG.

Conclusions—Cardiac sympathetic nerves were denervated early after and reinnervated late after ASO. Neonatal ASO may be favorable to facilitate sympathetic reinnervation, which may affect exercise tolerance late after surgery. (Circulation. 1998;97:2414-2419.)

Key Words: transposition of great vessels ■ heart defects, congenital ■ nervous system, autonomic ■ nuclear medicine ■ exercise
removing 47 patients, with a mean age of 4.9 years (range, 15 months to 10.1 years) and operated on at a mean age of 5 months (range, 7 days to 1.5 years), underwent an MIBG scan only once late after the surgery at a mean interval of 4.5 years (range, 1.3 to 9.8 years). No additional surgeries after ASO were performed in any of the patients. Anatomic diagnosis of the heart included simple transposition in 27 patients and association with ventricular septal defect in 20. Because the study subjects included an early series of ASOs in our institution, hearts in 14 patients with simple transposition were repaired after the neonatal period with two-stage operations with initial pulmonary arterial banding and aortopulmonary shunting. Conversely, hearts in 6 patients with associated malformations were repaired during the neonatal period.

Standard cardiac catheterization and thallium scintigraphy with dipyridamole infusion were performed on separate days within 1 week from the day of an MIBG scan. Twenty-eight patients >5 years old also underwent a treadmill exercise test with Bruce protocol.

As a negative control of the patients early after ASO in this study, 4 infants with an isolated ventricular septal defect with a mean age of 3 months (range, 2 to 6 months) who had undergone intracardiac repair without ASO were also studied with MIBG scintigraphy within 1 month after the surgery.

Possible risks associated with the present study related to nuclear studies, cardiac catheterization, and treadmill exercise were thoroughly explained to the patients’ guardians, and informed consent was obtained from them for each patient. The study protocol was approved by our institutional committee on human clinical investigations.

Cardiac MIBG Scintigraphy

$^{123}$I-MIBG (37 MBq) (Dai-ichi Radio Isotope Inc) was injected intravenously into the patients. The absorbed dose per unit radioactivity administered of $^{123}$I-MIBG to a target organ (liver) of pediatric patients is 0.19 mGy/MBq for those 5 years old and 0.34 mGy/MBq for those 1 year old. The absorbed dose from $^{123}$I-MIBG to human organs is only $0.10$ that of $^{131}$I-MIBG. At 15 minutes and at 4 hours after injection, static data were acquired in the anterior and 45° left anterior oblique views with a single-head gamma camera (Sophy DS 7, Sopha Medical Co) equipped with a low-energy, high-resolution, parallel-hole collimator. Static images on a 128×128 matrix were collected for 5 minutes with a 20% window centered on 159 keV, corresponding to the $^{123}$I photopeak. After the static planar images were acquired 4 hours after injection, SPECT of the heart was performed with the patient under complete sedation with intravenous administration of 5 mg/kg pentobarbital. The camera was rotated over 180° from the 45° right anterior oblique to the 45° left posterior oblique position in 32 views with an acquisition time of 25 seconds per view. Scans were acquired in a 64×64 matrix by a filtered back-projection method for reconstruction. The final reconstructed images for displays were of the horizontal long axis, vertical long axis, and short axis of the heart. No attenuation or scatter correction was utilized.

Data Processing and Interpretation of MIBG Images

Cardiac MIBG uptake was measured independently by two experienced nuclear physicians unaware of the patients’ clinical information. Left ventricular uptake was assessed by quantitative analysis performed by manually drawing a region of interest over the left ventricle in the anterior view. Rectangular regions of interest with 9×9 pixels were placed over the upper mediastinum and the left lung. Counts per pixel were calculated from each region of interest located at the heart, lung, and mediastinum. The H/M and H/L ratios were computed to quantify cardiac uptake of MIBG. We used a value of 1.48 in the H/M ratio as a criterion to define positive and absent uptake of MIBG in the present study (Figure 1).

Regional uptake of MIBG in the left ventricle was assessed on the short-axial SPECT images. Each short-axial slice was divided into four segments by axes from a central point in the midcavity separately at the base, midventricle, and apex. The lateral segment was defined between $-45^\circ$ and $+45^\circ$ to the horizontal, the inferior segment between $+45^\circ$ and $+135^\circ$, the septal segment between $+135^\circ$ and $+225^\circ$, and the anterior segment between $+225^\circ$ and $-45^\circ$ (Figure 2). The uptake was graded into two categories (absent or positive) on visual inspection.

Other Cardiac Evaluations

Each patient late after ASO underwent cardiac catheterization, including cardiac output measurements with a thermodilution method, biplane cineangiography of the left and right ventricles, and selective coronary angiography by transfemoral approaches.

Thallium myocardial perfusion scintigraphy with dipyridamole infusion was also performed for each patient as described previously.

Statistical Analysis

The data are presented as mean±SD. Comparisons of the H/M ratios between positive and absent MIBG uptake were made by the nonpaired $t$ test. $\chi^2$ analysis was used to assess frequencies of the absent uptake of MIBG depending on the age at ASO and abnormal exercise responses. ANOVA was used to compare the hemodynamic data at rest with those during exercise. A value of $P<0.05$ was considered significant.
Results

MIBG Findings Early After ASO
All 4 patients showed positive MIBG uptake in the right and left ventricles before ASO but showed complete absence in the delayed images 4 hours after injection shortly (<1 month) after ASO (Figure 3).

In contrast, all of the 4 control patients operated on with closure of an isolated ventricular septal defect showed significant uptake of MIBG in the left ventricle shortly after the surgery.

MIBG Uptake Late After ASO
Fifteen of the 47 patients (32%) late after ASO showed absent uptake of MIBG. We found that patients operated on during the neonatal or early infantile period showed positive MIBG uptake more frequently than those operated on at later ages (P<0.01) (Figure 4). The cutoff value of age at ASO for showing positive MIBG uptake was found to be \( \leq 4 \) in the natural logarithm of age in days at operation, which corresponded to \( \leq 55 \) days of age. However, the interval from surgery to the MIBG study did not show a significant difference between the patient subgroups with absent or positive MIBG uptake. The H/M ratio was not significantly different between the patients with primary ASO or staged repair, ie, with preceding pulmonary arterial banding and aortopulmonary shunt (1.60±0.19 versus 1.56±0.28).

Relationships Between Cardiac Function at Rest and MIBG Uptake
Left ventricular ejection fraction and end-diastolic volume expressed as percent of normal did not differ significantly between the patient subgroups with an absent or positive MIBG (ejection fraction, 60±7% versus 63±6%; end-diastolic volume, 146±25% versus 137±28% of normal).

Regional Myocardial MIBG Uptake Late After ASO
Regional uptake of MIBG in the left ventricle was distributed most frequently at the anterior (32 of 47 patients, 68%) and subsequently less at the lateral (28 of 47 patients, 60%), septal (22 of 47 patients, 47%), and inferior (10 of 47 patients, 21%) segments. Coronary arterial patterns, especially in regard to whether the left circumflex artery arose from the left main trunk or the right coronary artery, did not affect the regional distribution of MIBG.

A localized coronary stenosis >75% in percent narrowing and a corresponding reversible perfusion defect on thallium scans were found in 3 patients. The locations of the transient perfusion defect and the absent MIBG accumulation were matched at the inferior wall in 2 of the 3 patients. The other patient showed reversible perfusion defect at the anteroseptal wall, although this was positive in MIBG accumulation.

Relationship Between MIBG Uptake and Blood Pressure and Heart Rate on Exercise
Changes in blood pressure and heart rate during exercise are summarized in the Table. Heart rate and rate-pressure product were significantly greater in patients with positive uptake than in those with absent uptake of MIBG. Com-

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**Exercise Capacity of Patients With Absent or Positive MIBG Uptake**

<table>
<thead>
<tr>
<th></th>
<th>Absent MIBG (n=10)</th>
<th>Positive MIBG (n=18)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex, n (%)</td>
<td>7 (70)</td>
<td>15 (83)</td>
<td>NS</td>
</tr>
<tr>
<td>Age, mo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At ASO</td>
<td>8.2±4.4</td>
<td>5.3±5.2</td>
<td>NS</td>
</tr>
<tr>
<td>At MIBG</td>
<td>82±20</td>
<td>77±7</td>
<td>NS</td>
</tr>
<tr>
<td>Late surgery,* n (%)</td>
<td>9 (90)</td>
<td>11 (61)</td>
<td>NS (0.10)</td>
</tr>
<tr>
<td>Two-stage repair, n (%)</td>
<td>4 (40)</td>
<td>5 (28)</td>
<td>NS</td>
</tr>
<tr>
<td>Rest</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>96±17</td>
<td>95±12</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>112±23</td>
<td>108±12</td>
<td>NS</td>
</tr>
<tr>
<td>Exercise</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>144±23</td>
<td>168±15</td>
<td>0.03</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>127±16</td>
<td>132±13</td>
<td>NS</td>
</tr>
<tr>
<td>RPP, bpm×mm Hg</td>
<td>18 189±2723</td>
<td>22 276±2976</td>
<td>0.02</td>
</tr>
</tbody>
</table>

BP indicates blood pressure; RPP, rate-pressure product.
*ASO after 55 days of age.
pared with the normal values obtained from 128 age- and sex-matched, healthy subjects at our institution, none of the patients in the two groups had abnormal heart rate or blood pressure values at rest. With abnormal exercise response defined as heart rate or blood pressure lower than −2.5 SD of the control values, the abnormality was observed more frequently in those with absent MIBG than those with positive MIBG in heart rate (71% versus 25%, \(P=0.04\)) and in blood pressure (43% versus 0%, \(P=0.02\)), respectively.

The number of surgical procedures did not affect the exercise responses. Postoperative residual abnormalities in the 28 patients who performed exercise tests included aortic regurgitation of grade ≥2 in 2 patients, pulmonary stenosis ≥50 mm Hg in pressure gradient in 1, and coronary stenosis in 1. No patients showed depressed contraction <0.45 in ejection fraction and regional wall motion abnormalities of the left ventricle. Because the number of patients with such residual abnormalities was very small, any statistical difference depending on the presence of the residue could not be found in exercise responses.

**Discussion**

The major finding of this study was that cardiac MIBG uptake completely disappeared within 1 month after and reappeared to various degrees late after ASO. Late after the surgery, almost all of the patients operated on in early infancy showed positive uptake of MIBG, which was observed in only half of those operated on at later ages. Among the patients late after ASO, subnormal cardiovascular responses on peak exercise were more frequently observed in the patients with absent MIBG uptake than in those with positive uptake. These findings suggested that the process of sympathetic denervation and reinnervation occurred with arterial switching for complete transposition of the great arteries. The scarcity of reinnervation may have physiological and clinical importance in the long term after this type of surgery.

**Possible Pathogenesis of Absent MIBG Uptake After ASO**

Cardiac MIBG uptake is reduced under various pathological conditions, such as ischemic heart disease,\(^{16,17}\) valvular heart disease,\(^{18}\) heart transplantation,\(^{11,19}\) and diabetic neuropathy.\(^{16}\) MIBG uptake is totally absent from the heart early after transplantation.\(^{11}\) An experimental study using a canine model confirmed that MIBG uptake accurately indicates the presence or absence of myocardial sympathetic innervation established by neuroelectrophysiological testing.\(^{17}\) Complete disappearance of MIBG uptake indicates the global denervation of the ventricle. Because myocardial infarction or contractile failure was not observed in our subjects early after ASO, ischemic myocardial injury associated with the surgery is unlikely to be the reason for the absent MIBG uptake after ASO. The use of the cardiopulmonary bypass for infants did not abolish cardiac MIBG uptake after surgery, as shown in the negative control subjects of this study. Therefore, sympathetic denervation after ASO must be related to the nature of the surgical procedure itself, which obligatorily interrupts the neural pathways along the vascular walls.

**Ventricular MIBG Uptake Late After ASO**

Restoration of MIBG uptake in the left ventricle varied significantly among the patients late after ASO not only in magnitude but also in location. According to the reports on cardiac transplantation, reinnervation of the ventricle is regionally heterogeneous\(^{3,20–22}\) and a gradient in the degree of reinnervation from the base to the apex of the left ventricle has been observed in animal models.\(^{22}\) Studies using PET of late transplant survivors demonstrated that the uptake of a norepinephrine analogue is found mostly at the anterobasal wall of the left ventricle.\(^{21}\) All these findings are compatible with the present results late after ASO, showing a gradient in the magnitude of MIBG uptake from the anterobasal to the inferoposterior wall of the left ventricle.

The present results indicated that the patients who underwent ASO during the neonatal period showed a greater MIBG uptake than those operated on at a later age, suggesting that there is a greater ability for reinnervation in early infancy. Previous investigations on the development of cardiac sympathetic innervation have shown that in dogs, the sympathetic innervation develops through mid to late gestation, continues after birth,\(^{23–27}\) and matures to the adult status by 6 weeks of age.\(^{24}\) Working myocardium of the ventricle is innervated from the epicardial to the endocardial side through para-arterial routes, with the great majority of sympathetic nerves appearing throughout the ventricular wall by 2 months of age\(^{23,28}\) As shown in the present study, ASO before 55 days of age resulted in positive uptake of MIBG late after surgery. Therefore, it is very likely that arterial transection during the neonatal period in humans does not influence the physiological processes of normal sympathetic innervation to the ventricle.

**Relationships Between MIBG Uptake and Exercise Cardiovascular Response**

The present study showed that heart rate responses on exercise were attenuated in those with absent MIBG uptake. A recent preliminary report showed that presence or absence of reinnervation after transplantation correlated with the magnitude of peak heart rate and oxygen consumption during exercise.\(^{29}\) However, we also noted that absent uptake of MIBG after ASO was not always associated with attenuated heart rate response at peak exercise. After cardiac transplantation, the heart rate response to exercise might be affected by several factors, such as heterogeneity of the reinnervation within the heart, variability of the reinnervation among subjects, and the magnitude of the reinnervation to the sinus node.\(^{10,30}\) After ASO, the effects of autonomic nerves on the sinus node function may be even more variable. Cardiac nerves (the right stellate cardiopulmonary nerves), which include sympathetic and parasympathetic axons,\(^{1}\) course along the posteromedial surface of the superior vena cava and
project onto the junction of the superior vena cava and the right atrium. Therefore, the sympathetic as well as the parasympathetic innervation from the right stellate cardio-pulmonary nerve to the sinus node may well be preserved after ASO and influence heart rate changes during exercise. Conversely, positive chronotropic action due to norepinephrine release into the sinus node artery may be attenuated after ASO. Hence, the heart rate response during exercise is likely to be much more variable among patients after ASO than after transplantation.

Study Limitation and Future Issues

The present study showed that restoration of sympathetic neural function was variable in magnitude, as assessed by MIBG scintigraphy in patients after ASO. However, whether the neuronal innervation is returned to normal levels is not clear, even in patients with a homogeneous, intense uptake of MIBG. Theoretical and methodological limitations should be considered to assess the “normality” of sympathetic nerve function after ASO. MIBG uptake is influenced by not only the neuronal function but also the amount of myocardial mass. To precisely identify the normality of patients after ASO, the normal value of MIBG uptake should be established from control subjects matched for age, sex, cardiac anatomy, and hemodynamic status. On the contrary, sympathetic activity may be evaluated more directly by measurements of cardiac catecholamine, such as intracoronary tyramine injection to release cardiac norepinephrine, or endomyocardial biopsies and high-performance liquid chromatography to measure myocardial catecholamine content.

The physiological significance of the sympathetic denervation should be investigated more thoroughly in patients with complete transposition after ASO. Ventricular performance on exercise, which may be influenced by ventricular sympathetic denervation, can be studied by radionuclide ventriculography at peak exercise. Abnormal cardiac sympathetic nerve activity may influence heart rate spectral changes and cardiac norepinephrine spill over. Heart rate variability of the present study group is currently under investigation at our laboratory. Recent studies of cardiac transplant recipients by PET scans showed that increases in coronary blood flow in response to sympathetic stimulation correlated with the regional norepinephrine content. The magnitude of sympathetic innervation was suggested to play an important role in modulating the ability of the coronary vasculature to dilate and thus increase the myocardial blood flow during the periods of sympathetic activation, such as occurs during exercise and mental stress. Further evaluations may be required to determine whether or not an increase of coronary flow during exercise is limited at the sympathetically denervated myocardium observed in the patients after ASO.

References


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