Severely Impaired Cardiac Autonomic Nervous Activity After the Fontan Operation

Hideo Ohuchi, MD; Satoshi Hasegawa, MD; Kenji Yasuda, MD; Osamu Yamada, MD; Yasuo Ono, MD; Shigeyuki Echigo, MD

Background—Elevated neurohumoral activity and an abnormal cardiopulmonary response to exercise are well-established characteristics in patients after the Fontan operation. However, there have been few studies addressing cardiac autonomic nervous activity (CANA) in these patients.

Methods and Results—We evaluated CANA in 63 post-Fontan patients and 44 controls. Cardiac parasympathetic nervous activity (PSNA) was estimated by heart rate (HR) changes after cholinergic blockade, HR variability, and arterial baroreflex sensitivity. Cardiac sympathetic nervous activity was estimated by the heart to mediastinum \(^{121}\)I-metaiodobenzylguanidine activity ratio (H/M) and the HR increase (ΔHR) after isoproterenol infusion (β). ΔHR and peak oxygen uptake (V\(_{\text{O}_2}\)) were measured by exercise test. There was no difference in β between the Fontan group and controls. PSNA and H/M were markedly lower than in controls (P<0.001). PSNA and β were related to ΔHR (P<0.05); however, peak V\(_{\text{O}_2}\) was not correlated with ΔHR. Neither PSNA nor H/M was associated with clinical features, including hemodynamics, type of repair, number of surgical procedures, age at Fontan operation, or follow-up period, and administration of an angiotensin-converting enzyme inhibitor did not improve the impaired CANA in these patients.

Conclusions—After the Fontan procedure, postsynaptic β-sensitivity is maintained and is important in ΔHR during exercise as is PSNA, although ΔHR does not determine exercise capacity. The lack of a relationship between CANA and clinical features implies that, in addition to surgical damage, the Fontan circulation per se may impair CANA. Angiotensin-converting enzyme inhibitor administration does not change this abnormality. (Circulation. 2001;104:1513-1518.)

Key Words: heart defects, congenital □ nervous system, autonomic □ exercise □ heart rate □ Fontan procedure

Abnormal hemodynamics, such as elevated systemic venous pressure and low cardiac output, causes an abnormal cardiorespiratory response to exercise, reduced exercise capacity,\(^1,2\) and increased neurohumoral activity.\(^3,4\) However, the influence of the Fontan operation on cardiac autonomic nervous activity (CANA) has never been evaluated precisely, although its abnormality can be anticipated because of the impaired heart rate (HR) response during exercise as observed after right ventricular outflow tract reconstruction.\(^5\)

We hypothesized that the type of surgical procedure influenced CANA in these patients and that they would have a significantly impaired CANA without subsequent improvement because of the palliative nature of the Fontan circulation. We also evaluated the influence of an angiotensin-converting enzyme inhibitor (ACEI), which improves HR variability (HRV) and the prognosis of patients with chronic heart failure,\(^5,7\) on CANA in these patients.

Methods

Subjects

We studied 63 patients after the Fontan operation and 44 controls. Of the Fontan patients, a total cavopulmonary connection (TCPC) was created in 45 and an atrio pulmonary connection (APC) in 18 (Table 1). Medications included digoxin (n=13), diuretics (n=31), and antiplatelet agents (n=31), and 4 were taking ACEIs. No patients were receiving chronotropic or antiarrhythmic medications, and 5 patients with significant arrhythmias, such as junctional rhythm or ventricular tachycardia, were excluded from the present study. The total number of surgical procedures, including the Fontan operation, ranged from 1 to 6 per patient (mean 2.6 times). Before the Fontan, a systemic to pulmonary shunt(s) was done in 37 patients, pulmonary arterial banding in 10, a Glenn anastomosis in 7, creation of an atrial septal defect in 3, and other palliative procedures, such as reconstruction of the pulmonary artery. Four patients were converted from APC (n=2) or total cavopulmonary shunt (n=2) to TCPC. All patients were in sinus rhythm. The control group consisted of patients with a history of Kawasaki disease without stenotic coronary arterial lesions. None of the controls had abnormal findings suggesting cardiac lesions, as shown by physical examination, chest x-ray, ECG, echocardiogram, or treadmill exercise testing.

Subgroup Analysis

To further investigate the influence of the ACEI (enalapril, 0.1 mg · kg\(^{-1}\) · d\(^{-1}\)) on CANA, we investigated 10 of 63 Fontan patients (mean age±SD, 14±3 years; 3 APC, 7 TCPC) before and after ACEI administration for at least 6 months (mean, 6.8 months) and compared their changes in CANA with those in 8 Fontan patients.

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(mean age, 13±4 years; 3 APC, 5 TCPC) without medical intervention with a mean follow-up of 1.8 years. There were no defined criteria used to select the ACEI patients, who were given a full explanation of the potential benefits of an ACEI before its administration.

Cardiac Catheterization

Cardiac catheterization was performed in 59 Fontan patients and 42 controls under light sedation with pethidine and promethazine hydrochlorides for patients <12 years old. Patients older than 12 years were sedated with oral pentobarbital calcium. Parameters determined included right atrial (central venous) and systemic ventricular end-diastolic pressures, ejection fraction of the systemic ventricle measured by cineventriculography, and cardiac output by the Fick principle. Oxygen consumption was estimated from the age, sex, and HR data, and cardiac index (in L · m⁻² · min⁻¹) was measured by using the Fick principle with the assumption that right atrial oxygen saturation was equal in patients with a Glenn anastomosis or a TCPC.

Natriuretic Peptides

The end-diastolic pressure of the systemic ventricle; CI, cardiac index; TA, tricuspid atresia; PA, pulmonary atresia; MA, mitral atresia; UVH, univentricular heart; DORV, double-outlet right ventricle; and Hx of KD, history of Kawasaki disease.

†P<0.05, †P<0.01, and ‡P<0.001 vs control.
§P<0.001 vs TCPC.

Measurement of Norepinephrine and Natriuretic Peptides

An indwelling angiocatheter was inserted into the antecubital vein for sampling. After at least 10 minutes of rest, the plasma norepinephrine level (NE) was determined by high-performance liquid chromatography.9 The plasma levels of atrial and brain natriuretic peptides (ANP and BNP, respectively) were assayed by radioimmunoassay.10,11 Secretion of ANP and BNP is stimulated by stretching the atrium and ventricle, respectively, and is a sensitive marker of failing hemodynamics.12

Measurement of HRV and Arterial Baroreflex Sensitivity

The method for measuring HRV and arterial baroreflex sensitivity was reported previously.5,13 In brief, after a 10-minute supine rest, ECG signals were recorded for 5 minutes, and beat-to-beat fluctuations were transformed into frequency domains by using a fast Fourier transformation. The spectral HRV was expressed as a low-frequency (LF) component (0.04 to 0.15 Hz) and a high-frequency (HF) component (0.15 to 0.40 Hz), and their respective logarithmic values, log LF and log HF, were used.14 When premature contractions were detected, removal of ectopy was performed.15 After measuring HRV, the bolus phenylephrine (1 to 4 μg/kg) injection method was used to measure arterial baroreflex sensitivity.16 The ECG, arterial blood pressure (Finapres, Ohmeda), and respiration (by impedance device) were recorded continuously at a speed of 100 mm/s until the peak blood pressure was reached. The R-R intervals obtained during expiration were plotted against the systolic blood pressures on a beat-to-beat basis to determine the linear slope of the regression line (arterial baroreflex sensitivity).16 and the mean value of at least 2 measurements (ms/mm Hg) was used.

[123I]Metaiodobenzylguanidine Scintigraphy

The method used for this index was also identical to that previously reported.17 Metabolobenzylguanidine scintigraphy was performed in 39 Fontan patients and 14 controls to evaluate myocardial adrenergic nerve activity. There were no definitive criteria for subject selection, and the reason why all patients did not undergo this procedure was the limited capacity of our laboratory. After injection of 74 to 148 MBq metaiodobenzylguanidine, myocardial images were acquired 15 minutes and 4 hours after tracer injection; to evaluate the myocardial accumulation of metaiodobenzylguanidine, the heart to mediastinal activity ratio (H/M) was calculated. Because metadobenzylguanidine is an analogue of NE and shares its uptake and storage mechanisms, decreased metadobenzylguanidine uptake (low H/M) suggests decreased sympathetic innervation and has been demonstrated in patients with heart failure18 and in cases of denervation caused by ischemia. Dividing the cardiac sympathetic nerves also results in a low H/M, as occurs after cardiac transplantation.18

Radionuclide Angiography

To evaluate the effect of the ACEI on ventricular systolic function, radionuclide angiography was used instead of echocardiography because of the difficulty in calculating the ejection fraction of the right-ventricle type and the 2-ventricle type systemic ventricle. Systemic ventricular end-diastolic and end-systolic volumes and
ejection fractions were calculated by 2 experienced technologists using a semiautomated edge-detection algorithm. The patients received radiolabeled $^{99m}$Tc by a standard technique and were imaged in the supine position. In preliminary studies, we had obtained acceptable correlations between values of end-diastolic and end-systolic volumes as measured by cineangiography and as determined with this system (ECG-gated single-photon emission CT, n=35, r=0.85 and 0.86, respectively; P<0.01).

**Determination of Cardiac Parasympathetic Nervous Tone and Postsynaptic β-Sensitivity**

The method for measuring cardiac parasympathetic nervous tone (α) and postsynaptic β-sensitivity (β) was identical to that previously reported. In 27 Fontan patients and 11 controls after at least a 10-minute rest, baseline HR was taken as the control value, the HR 1 minute after an atropine infusion (0.04 mg/kg) was determined, and α was defined as the change in HR. Two minutes after the atropine infusion, a 6-minute continuous infusion of isoproterenol was administered (3 μg·kg$^{-1}$·min$^{-1}$), and β was defined as the increase in HR from 1 minute after the full-dose atropine infusion to 6 minutes after the isoproterenol continuous infusion. These pharmacological studies were limited to hospitalized patients without significant tachyarrhythmias.

**Exercise Protocol**

All subjects were exercised to the end of their tolerance on a motor-driven, programmable treadmill (Q-5000 system, Quinton) and were displayed along with the HR and $\dot{V}O_2$ on a monitor. The method for measuring cardiac parasympathetic nervous tone (α) and postsynaptic β-sensitivity (β) was identical to that previously reported. 5 In 27 Fontan patients and 11 controls after at least a 10-minute rest, baseline HR was taken as the control value, the HR 1 minute after an atropine infusion (0.04 mg/kg) was determined, and α was defined as the change in HR. Two minutes after the atropine infusion, a 6-minute continuous infusion of isoproterenol was administered (3 μg·kg$^{-1}$·min$^{-1}$), and β was defined as the increase in HR from 1 minute after the full-dose atropine infusion to 6 minutes after the isoproterenol continuous infusion. These pharmacological studies were limited to hospitalized patients without significant tachyarrhythmias.

**Informed Consent**

After adequate explanation of the purpose of the study and its clinical significance (mentioned in the Clinical Implications section), informed consent was obtained from all Fontan subjects and/or their parents. In controls in whom metaiodobenzylguanidine scintigraphy and a pharmacological evaluation were performed, we asked them and/or their parents to take part in the present study as a volunteer. We obtained consent for 11 pharmacological and 14 metaiodobenzylguanidine scintigraphic evaluations. The study protocol was approved by the Ethics Committee of the National Cardiovascular Center.

**Statistical Analysis**

Differences in hemodynamic variables, parameters of CANA, and cardiorespiratory variables during exercise were evaluated with a factorial 1-way ANOVA with Sheffe’s procedure. Simple regression analysis was used to determine correlations between ΔHR and other parameters. The change in CANA after ACEI treatment was evaluated with a paired t test. Correlation between the number of surgical procedures and indexes of CANA was evaluated by Spearman rank correlation analysis. Data are expressed as the mean±SD. A P value <0.05 was considered statistically significant.

**Results**

**Hemodynamic Variables and Natriuretic Peptides**

For the Fontan patients, right atrial pressure was significantly higher than in controls, whereas systemic ejection fraction and cardiac index were significantly lower (Table 1). ANP was significantly higher in both Fontan groups, BNP was significantly higher in APC patients, and BNP in TCPC patients tended to be higher than in controls (P<0.07). The low cardiac index and ejection fraction of the ventricle in the Fontan groups indicated mild heart failure.

**Impaired CANA and Influences of the Type of Repair, Number of Surgical Procedures, Age at Time of Fontan, and Follow-Up Period on CANA**

All CANA indexes, except β, in both Fontan groups were significantly lower than in controls (P<0.01 to 0.001), and NE was significantly higher in Fontan groups than in controls (P<0.01 to 0.05; Table 2). β was well maintained and was correlated inversely with NE in Fontan patients (r = −0.38, P<0.05). There was no difference in CANA indexes between APC and TCPC groups. None of the CANA indexes was

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**TABLE 2. Comparison of Cardiac Autonomic Nervous Activity Among the Study Groups**

<table>
<thead>
<tr>
<th>Variables</th>
<th>APC n</th>
<th>TCPC n</th>
<th>Control n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log HF</td>
<td>1.1±0.7‡</td>
<td>18</td>
<td>1.4±0.5‡</td>
</tr>
<tr>
<td>Log LF</td>
<td>1.4±0.5‡</td>
<td>18</td>
<td>1.7±0.5‡</td>
</tr>
<tr>
<td>BRS, ms/mm Hg</td>
<td>3.1±3.1‡</td>
<td>18</td>
<td>3.2±3.1‡</td>
</tr>
<tr>
<td>α, bpm</td>
<td>11±8‡</td>
<td>8</td>
<td>16±12‡</td>
</tr>
<tr>
<td>H/M</td>
<td>1.6±0.4‡</td>
<td>13</td>
<td>1.8±0.4‡</td>
</tr>
<tr>
<td>β, bpm</td>
<td>27±13</td>
<td>8</td>
<td>28±11</td>
</tr>
<tr>
<td>NE, pg/ml</td>
<td>226±181†</td>
<td>18</td>
<td>229±130*</td>
</tr>
</tbody>
</table>

BRS indicates arterial baroreflex sensitivity. Groups are the same as in Table 1. Values are mean±SD.

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*P<0.05, †P<0.01, and ‡P<0.001 vs control.
correlated with the number of surgical procedures, age at the time of Fontan operation, or length of follow-up.

Influence of Medication on CANA

Although NE was significantly higher in patients on digoxin than in those not taking this drug, no difference in natriuretic peptides or in any CANA index between these 2 groups was observed. NE tended to be higher in patients on diuretics than in those not taking diuretics, whereas β was significantly lower (22±10 vs 32±10, P<0.02). Because peak VO₂ in patients on digoxin and/or diuretics was significantly lower than in those not taking these drugs, medication may have been given to sicker Fontan patients.

Cardiovascular Response During Exercise, Exercise Capacity, and CANA

Because the average gas exchange ratio at peak exercise exceeded 1.10 in all groups, we are confident that all patients performed at their near-maximal exercise tolerance, although the average gas exchange ratio at peak exercise was significantly lower in both Fontan groups than in controls (Table 3). Rest HR was elevated and ΔHR was significantly lower in both Fontan groups vs controls. Systolic blood pressures both at rest and at peak exercise were significantly lower in Fontan groups than in controls (P<0.05 and 0.001, respectively). In all Fontan patients, all CANA indexes except H/M were correlated with the value was significantly lower than in controls. Endurance time and peak VO₂ were significantly lower in both Fontan groups than in controls. Systolic blood pressures both at rest and at peak exercise were significantly lower in both Fontan groups vs controls. Endurance time and peak VO₂ were significantly lower in both Fontan groups vs controls. NE levels after treatment were higher than those before treatment, although the difference was not significant. These indexes were also unchanged in Fontan patients without ACEI administration during 1.8 years of follow-up.

Discussion

Our major findings include the following: (1) Fontan patients exhibit severely impaired CANA; (2) in contrast to our hypothesis, because the degree of impaired CANA is not associated with hemodynamics, surgical procedures, follow-up period, or type of repair, it is the Fontan circulation per se, along with surgery-related damage, that impairs CANA, and no further improvement in CANA may be expected in the future; and (3) although CANA is related to ΔHR, ΔHR is not a determinant of aerobic exercise capacity; moreover, (4) a beneficial effect of ACEI therapy on CANA cannot be proved.

Change in CANA After ACEI Administration and During Follow-Up

Log HF and arterial baroreflex sensitivity in 10 ACEI study patients before drug administration were significantly lower than in the other 53 patients without ACEI (P<0.05), and ventricular ejection fraction in the former group tended to be lower compared with those without ACEI (43±17% with ACEI vs 52±12% without ACEI, P<0.1). After ACEI administration, no significant change in ventricular ejection fraction was observed (46±17% before vs 49±20% after, NS), nor did CANA change (Table 4). Natriuretic peptide and NE levels after treatment were higher than those before treatment, although the difference was not significant. These indexes were also unchanged in Fontan patients without ACEI administration during 1.8 years of follow-up.

| TABLE 3. Exercise Capacity and Heart Rate Response During Exercise |
|-------------------|------------------|------------------|
| **Variables**     | **APC (n=18)**   | **TCPC (n=45)**  | **Control (n=44)** |
| Endurance time, min | 6.2±1.1†       | 6.2±1.6†        | 10.3±1.3          |
| Peak VO₂, mL·kg⁻¹·min⁻¹ | 22.8±3.4‡       | 24.2±4.8‡       | 42.6±5.8          |
| Heart rate, bpm   | 70±12‡          | 71±23‡          | 112±10            |
| Systolic BP, mm Hg | 101±7†          | 104±14*         | 112±11            |
| Peak gas exchange ratio | 1.12±0.07‡      | 1.14±0.07†      | 1.20±0.06         |

BP indicates blood pressure. Values are mean±SD. *P<0.05, †P<0.01, ‡P<0.001 vs control.

Correlations between increase in heart rate (ΔHR) during peak exercise and parasympathetic tone (α) (left), between ΔHR and β-sensitivity (β) (middle), and between predicted peak oxygen uptake (VO₂) and ΔHR.

**TABLE 4. Change in Cardiac Autonomic Nervous Activity Before and After ACEI Therapy and in Those During Follow-Up Without ACEI Therapy**

<table>
<thead>
<tr>
<th><strong>ACEI Status/Variables</strong></th>
<th><strong>Before</strong></th>
<th><strong>After</strong></th>
<th><strong>n</strong></th>
<th><strong>P</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>With ACEI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Log HF</td>
<td>0.9±0.6</td>
<td>1.2±0.4</td>
<td>10</td>
<td>NS</td>
</tr>
<tr>
<td>BRS, ms/mm Hg</td>
<td>2.1±1.6</td>
<td>2.3±2.1</td>
<td>10</td>
<td>NS</td>
</tr>
<tr>
<td>NE, pg/mL</td>
<td>231±137</td>
<td>279±268</td>
<td>10</td>
<td>NS</td>
</tr>
<tr>
<td>AMP, pg/mL</td>
<td>120±80</td>
<td>162±219</td>
<td>10</td>
<td>NS</td>
</tr>
<tr>
<td>BNP, pg/mL</td>
<td>139±153</td>
<td>159±252</td>
<td>10</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Without ACEI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Log HF</td>
<td>1.2±0.6</td>
<td>1.3±0.5</td>
<td>8</td>
<td>NS</td>
</tr>
<tr>
<td>BRS, ms/mm Hg</td>
<td>2.6±2.3</td>
<td>3.3±1.5</td>
<td>8</td>
<td>NS</td>
</tr>
<tr>
<td>NE, pg/mL</td>
<td>173±70</td>
<td>299±223</td>
<td>8</td>
<td>NS</td>
</tr>
<tr>
<td>AMP, pg/mL</td>
<td>70±39</td>
<td>76±49</td>
<td>8</td>
<td>NS</td>
</tr>
<tr>
<td>BNP, pg/mL</td>
<td>50±29</td>
<td>58±47</td>
<td>8</td>
<td>NS</td>
</tr>
</tbody>
</table>

BRS indicates arterial baroreflex sensitivity.
Impaired CANA

Three possible explanations can be offered for the severely impaired CANA in Fontan patients: (1) surgery-related direct and/or subclinical damage, such as ischemia and/or denervation, as reported in patients after the arterial switch operation or right ventricular outflow tract reconstruction; (2) heart failure, as demonstrated in adult cardiac patients; and (3) preoperative pathology, such as hypoxia. Some patients need reconstructions of the pulmonary artery and/or a Glenn anastomosis at or before their Fontan operation. These procedures entail some unavoidable damage to cardiopulmonary nerves around the vessels and atrium, along with subclinical ischemia during cardiac surgery. A relatively maintained β may be further proof that the major cause of abnormal CANA is cardiac denervation, because a similar observation has been reported after cardiac transplantation. In addition, reduced lung volume (small tidal volume) may be related to a decrease in inhibitory signals from the stretch receptor against cardiac sympathetic nervous activity. However, the lack of a relationship between CANA abnormalities and surgical procedures, age at Fontan operation, or follow-up period implies that the Fontan circulation per se is responsible for impaired CANA. Along with elevated neurohumoral factors, evidence of high central venous pressure, low ventricular ejection fraction, and low cardiac output are consistent with chronic heart failure due to pump failure. Low blood pressure at rest and during exercise, probably due to low cardiac output, causes persistent activation of the sympathetic nervous system, which may be essential not only to maintain systemic blood pressure but also to ensure an efficient systemic blood flow distribution by regulating vascular tone of the peripheral arteries, as it does during exercise. Therefore, in addition to surgical damage of CANA, including pulmonary autonomic nerves, it is likely that specific hemodynamics characterized by low cardiac output are responsible for diminished parasympathetic and sympathetic nervous system activation. These persisting abnormalities prevent future reinnervation of the cardiac nerves. Because of the vulnerability of CANA to ischemia, long-standing preoperative hypoxia may also have some influence on abnormal CANA in these patients.

HR Response During Exercise and CANA

As in patients after right ventricular outflow tract reconstruction, our study demonstrates that even in Fontan patients, CANA is closely related to ΔHR, and a relatively maintained β has an important role for ΔHR.

ACEI Administration and CANA

Administration of ACEI not only does not change exercise capacity but also has no effect on systemic vascular resistance, resting cardiac index, or diastolic function in Fontan patients. Because these indexes may be somewhat insensitive markers, we hoped that, in addition to relatively long-term administration of ACEI, the use of sensitive biochemical markers and CANA indexes would enable us to detect a significant benefit of ACEIs on Fontan patients. However, our results were negative. Therefore, ACEIs do not positively influence the parameters measured in this study, even after their long-term administration. Reducing systemic arterial resistance and breaking the vicious circle of excess activation of the renin-angiotensin-aldosterone system are beneficial mechanisms of ACEIs. Preventing the remodeling of the left ventricle by ACEIs is considered another important mechanism to improve prognosis. Serious supraventricular arrhythmias late after the Fontan operation are of great concern, and there may be some benefit from ACEI administration not only on the geometric but also on the electrical remodeling in the atrium, thereby reducing occurrences of such arrhythmias. We need a longer observation period to conclude that ACEI administration benefits Fontan patients.

Study Limitations

First, we did not demonstrate a direct influence of surgical procedures on CANA. Evaluations before and after the Fontan operation may provide more precise information on CANA. Because of methodology limitations, relatively older patients were enrolled; ie, only a small number of up-to-date Fontan patients were examined. However, the lack of correlation between CANA indexes and the number of surgical procedures, including palliative operations, indicates that a major determining factor is the Fontan circulation itself. Thus, even in Fontan patients who have undergone surgery with the most modern procedures, CANA is likely to be severely impaired. Second, our control patients were not entirely “normal,” and microangitis may have existed even when there was no overt aneurysm; this may also have had some influence on CANA. However, because cardiorespiratory response, exercise capacity, α, and β in our control subjects were equivalent to those previously reported, we believe that our present data are comparable to those from healthy subjects. Third, the present ACEI study was not prospective. A randomized, double-blind, placebo-controlled crossover study is preferable. We believe that comparing Fontan patients with and without ACEI administration may give us objective information. However, we need a more sophisticated protocol and/or special techniques to examine the electrical properties of the atrium. Finally, a difference in NE between arterial and coronary sinus vein samples should be measured, whereas direct stimulation of the sympathetic nerves of the sinus node and the ventricle with tyramine is preferable to assess cardiac sympathetic nervous activity. Therefore, a future study investigating the correlation between indexes obtained by measuring NE, direct stimulation, and those used in our study is needed.

Clinical Implications

We should remember that patients may not complain of chest pain even when they develop ischemic heart disease because of cardiac nerve denervation, such as that which occurs after cardiac transplantation. Another important and serious concern is the relationship between arrhythmias, especially supraventricular arrhythmias, late sudden death, and CANA. Severely diminished parasympathetic nerve activity and a maintained or accelerated sympathetic nerve activity may be arrhythmogenic, especially in APC patients, and may be a possible cause of sudden death during follow-up. Considering
the degree of deterioration of cardiac function, administration of a β-receptor blocker along with an ACEI may be more beneficial, but we need further studies to address this issue.

Acknowledgments
We are grateful to Dr Peter M. Olley, Professor of Pediatrics, University of Alberta, and Dr Setsuko Olley for assistance in preparing the manuscript. We also thank Drs H. Takaki and M. Sugimachi, Department of Cardiovascular Dynamics, National Cardiovascular Center Research Institute, for their data analysis of HRV.

References
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/content/109/25/3257.2.full.pdf

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In the article, “Cost Effectiveness of Defibrillation by Targeted Responders in Public Settings,” by Nichol et al, which appeared in the August 12, 2003, issue of the journal (Circulation. 2003;108:697–703), an error appeared. This economic evaluation of defibrillation in various public settings was based on incorrect interpretation of the number of defibrillators required at each site.1 The following Table corrects this error. The revised incremental costs are less than previously estimated. However, the authors reconfirm that those making decisions to implement lay responder defibrillation should consider the likelihood of cardiac arrest and the number of defibrillators required at the site.

Reference

DOI: 10.1161/01.CIR.0000135145.84484.7B

The article, “Clinical Correlates and Heritability of Flow-Mediated Dilation in the Community: The Framingham Heart Study,” by Benjamin et al, which appeared in the February 10, 2004, issue of the journal (Circulation. 2004;109:613–619), the authors regret that they incorrectly described the method of blood pressure ascertainment. In the regression models, instead of using the automatic blood pressure device (Dinamap, Critikon, Inc), they actually used the average of the physician’s first and second blood pressures from the same morning as the brachial testing. The regression models using the Dinamap blood pressure produced very similar results. Hence, for Table 1, the correct mean systolic and diastolic blood pressures were 128/76 for men and 122/67 for women. (The reported values were 128/75 for men and 122/67 for women.) The corrected rows of Table 1 appear below.

Sample Characteristics

<table>
<thead>
<tr>
<th>Location Category</th>
<th>Average Annual Site Incidence (No.)</th>
<th>Defibrillators Required per Site (No.)</th>
<th>Incremental Cost-Effectiveness ($/QALY), Median (IQR)</th>
<th>Probability ICER &lt;$100 000/QALY</th>
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<td>International airport</td>
<td>7</td>
<td>15</td>
<td>$55 200 ($42 600, $76 300)</td>
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<td>0.1</td>
<td>1</td>
<td>$130 900 ($77 500, $228 700)</td>
<td>0.37</td>
</tr>
<tr>
<td>Public sports venue</td>
<td>0.4</td>
<td>4</td>
<td>$136 500 ($78 100, $257 400)</td>
<td>0.35</td>
</tr>
<tr>
<td>County jail</td>
<td>1</td>
<td>11</td>
<td>$159 800 ($77 700, $437 400)</td>
<td>0.34</td>
</tr>
<tr>
<td>Health club/gym</td>
<td>0.08</td>
<td>1</td>
<td>$153 900 ($87 900, $286 100)</td>
<td>0.30</td>
</tr>
<tr>
<td>Large shopping mall</td>
<td>0.6</td>
<td>9</td>
<td>$162 100 ($90 300, $298 000)</td>
<td>0.29</td>
</tr>
<tr>
<td>Large industrial site</td>
<td>0.4</td>
<td>5.75</td>
<td>$162 500 ($89 000, $318 600)</td>
<td>0.29</td>
</tr>
<tr>
<td>Community center</td>
<td>0.03</td>
<td>1</td>
<td>$378 600 ($172 900, $832 100)</td>
<td>0.15</td>
</tr>
</tbody>
</table>

QALY indicates quality-adjusted life year.
*2003 US dollars rounded to nearest $100.

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3256
In the article, “Abnormal Cardiac Autonomic Nervous Activity After Right Ventricular Outflow Tract Reconstruction,” by Ohuchi et al, which appeared in the November 28, 2000, issue of the journal (Circulation. 2000;102:2732–2738), the authors regret that the administration dose of isoproterenol to determine β sensitivity of the sinus node was incorrect. On page 2733, on the tenth line under the heading Determination of Cardiac Parasympathetic Nervous Tone and Postsynaptic β-Sensitivity, “3 µg · kg⁻¹ · min⁻¹” should instead read “0.5 µg · kg⁻¹ · min⁻¹.”

DOI: 10.1161/01.CIR.0000135147.97462.57

In the article, “Severely Impaired Cardiac Autonomic Nervous Activity After the Fontan Operation,” by Ohuchi et al, which appeared in the September 25, 2001, issue of the journal (Circulation. 2001;104:1513–1518), the authors regret that the administration dose of isoproterenol to determine β sensitivity of the sinus node was incorrect. On page 1515, on the eighth line under the heading Determination of Cardiac Parasympathetic Nervous Tone and Postsynaptic β-Sensitivity, “3 µg · kg⁻¹ · min⁻¹” should instead read “0.5 µg · kg⁻¹ · min⁻¹.”

DOI: 10.1161/01.CIR.0000135148.97462.B3

In the article, “Serum Total Cholesterol Concentrations and Awareness, Treatment, and Control of Hypercholesterolemia Among US Adults: Findings From the National Health and Nutrition Examination Survey, 1999 to 2000,” by Ford et al, which appeared in the May 6, 2003, issue of the journal (Circulation. 2003;107:2185–2189), the authors regret that an error occurred in the age-specific mean total cholesterol concentration for women in Table 1. The correct means are shown in the following Table. These data indicate that women aged 55 to 64 years and ≥75 years also enjoyed significant decreases in total cholesterol concentrations.

<table>
<thead>
<tr>
<th>Age-Specific and Age-Adjusted Mean Total Cholesterol Concentrations by Selected Sociodemographic Characteristics Among US Adults Aged ≥20 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Women</strong></td>
</tr>
<tr>
<td>Age, y</td>
</tr>
<tr>
<td>20–34</td>
</tr>
<tr>
<td>35–44</td>
</tr>
<tr>
<td>45–54</td>
</tr>
<tr>
<td>55–64</td>
</tr>
<tr>
<td>65–74</td>
</tr>
<tr>
<td>≥75</td>
</tr>
</tbody>
</table>

DOI: 10.1161/01.CIR.0000135149.05086.9A
In the article, “Hypertrophic Cardiomyopathy: Distribution of Disease Genes, Spectrum of Mutations, and Implications for a Molecular Diagnosis Strategy,” by Richard et al, which appeared in the May 6, 2003, issue of the journal (Circulation. 2003;107:2227–2232), the authors regret that errors occurred in Tables 2 and 4. In Table 2, Exon 30, Nucleotide Change C19222T, the value listed under Coding Effect (E1377M) should be replaced with T1377M. In Table 4, row 3, the value listed under Troponin T (P120V) should be replaced with F110V. Also in Table 4, row 4, the value listed under Regulatory Light Chain (D166L) should be replaced with D166V. The corrected rows of Tables 2 and 4 appear below.

**TABLE 2. MYH7 Mutations**

<table>
<thead>
<tr>
<th>Exon</th>
<th>Nucleotide Change*</th>
<th>Coding Effect</th>
<th>Index Patient</th>
<th>Active Sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>C19222T</td>
<td>T1377M</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

Novel mutations are indicated in bold.
*GenBank accession No. X52889.

**TABLE 4. Cardiac Troponin T, Cardiac Troponin I, and Regulatory and Essential Myosin Light Chain Mutations**

<table>
<thead>
<tr>
<th>Row</th>
<th>Troponin T</th>
<th>Troponin I</th>
<th>Regulatory Light Chain</th>
<th>Essential Light Chain</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>F110V</td>
<td>R162P</td>
<td>IVS5–2: a&gt;g</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Del E160</td>
<td>Del K 177</td>
<td>D166V</td>
<td></td>
</tr>
</tbody>
</table>

Novel mutations are indicated in bold. Del indicates deletion.

DOI: 10.1161/01.CIR.0000135150.43204.25

Dr Kereiakes wishes to disclose that he is CEO of Ohio Heart Health Center (OHHC), but his position with OHHC did not influence the commentary, “Doctors and Hospitals: Health Care’s Rubik’s Cube” (Circulation. 2004;109:2381–2385).

DOI: 10.1161/01.CIR.0000136550.73761.99

Drs Gami and Ammash (“Double Aortic Arch,” Circulation. 2004;109:2370–2371) would like to acknowledge that the imaging study was performed by Dr John Lesser at the Minneapolis Heart Institute Foundation.

DOI: 10.1161/01.CIR.0000136805.53910.0B