Abnormal Cardiac Autonomic Nervous Activity After Right Ventricular Outflow Tract Reconstruction

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Background—There are few studies of cardiac autonomic nervous activity (CANA) in patients with congenital heart disease. Methods and Results—We evaluated CANA in 54 patients after closure of an atrial/ventricular septal defect (group A), 54 patients after successful right ventricular outflow tract reconstruction (RVOTR) (group B1), 35 RVOTR patients with residual stenosis (group B2), and 47 controls. Cardiac parasympathetic nervous activity (PSNA) was estimated by heart rate (HR) change after cholinergic blockade, HR variability, and arterial baroreflex sensitivity (BRS). Cardiac sympathetic nervous activity was estimated by the heart-to-mediastinum \( ^{123} \text{I}-\text{metaiodobenzylguanidine} \) activity ratio (H/M) and HR increase after isoproterenol infusion (\( \beta \)). HR response (\( \Delta \text{HR} \)) and peak oxygen uptake (\( \text{VO}_2 \)) were measured by exercise test. There was no difference in \( \beta \) among study groups. Group A exhibited mildly impaired PSNA, which recovered 1 year after surgery, and no change in H/M. Impaired PSNA and low H/M were found in groups B1 and B2 compared with controls (\( P<0.001 \)), although the PSNA tended to recover 1 year after re-RVOTR. In group B1, PSNA and \( \beta \) were related to \( \Delta \text{HR} \), and BRS correlated inversely with the number of surgical procedures and age at RVOTR and positively correlated with the follow-up period, whereas \( \Delta \text{HR} \) correlated with peak \( \text{VO}_2 \) (\( P<0.01 \) to 0.001).

Conclusions—After RVOTR, postsynaptic \( \beta \)-sensitivity is maintained and is important in \( \Delta \text{HR} \) during exercise, as is PSNA, although ventricular sympathetic denervation is common. Impaired PSNA immediately after RVOTR improves with improved \( \Delta \text{HR} \) and results in future amelioration of aerobic capacity, whereas ventricular sympathetic reinnervation is uncertain. (Circulation. 2000;102:2732-2738.)

Key Words: heart defects, congenital ■ nervous system, autonomic ■ exercise ■ heart rate ■ surgery

The blunted heart rate (HR) response during exercise in patients with congenital heart disease (CHD), especially those with complex CHD, is well demonstrated.\(^1\)\(^2\)\(^3\) Because the cardiac autonomic nervous system regulates HR,\(^5\) it is predictable that cardiac autonomic nervous activity (CANA) is abnormal in patients with CHD after definitive surgery. It is not known how much the sympathetic (SNA) and parasympathetic (PSNA) nervous activity are impaired and whether reinnervation occurs. Therefore, the purpose of our present study was as follows: (1) to evaluate PSNA and SNA in patients who have undergone right ventricular outflow tract reconstruction (RVOTR), which is a common procedure to correct CHD, and to compare the results with patients undergoing atrial or ventricular septal defect repair and with control subjects; (2) to investigate the relationships between CANA and clinical profiles, such as surgical procedure and HR response during exercise; and (3) to investigate the influence of surgery on both PSNA and SNA in these patients.

Methods

Subjects in the Cross-Sectional Study

No patients were receiving inotropic, chronotropic, or antiarrhythmic medications. We studied 142 patients, who were divided into 4 groups. Group A consisted of 54 patients, 38 of whom had undergone closure of an atrial septal defect (ASD) and 16 of whom had closure of a ventricular septal defect (VSD). Group B1 consisted of 54 patients after RVOTR with no significant residual right ventricular outflow (pulmonary) stenosis. Group B2 consisted of 35 patients after RVOTR with significant residual pulmonary stenosis. Patients with a pressure gradient >30 mm Hg during cardiac catheterization or a transpulmonary valve flow velocity >3.0 m/s on Doppler echocardiography were included in this group. Group C, the controls, consisted of 47 patients with a history of Kawasaki disease but no stenotic coronary arterial lesions. None of the controls had abnormal findings on physical examination, chest radiograph, ECG, 2D echocardiogram, or treadmill exercise test. In the CHD groups, the follow-up period from the last operation to the time of study was ≥1 year. Antiplatelet agent was given to 3 patients in group B1. (See Table 1.)

Subjects in the Longitudinal Study

We investigated the change in CANA in 31 group A patients (group X, age 14.3±6.1 years; ASD=28, VSD=3) and 19 group B2 patients (group Y, age 13.2±3.8 years; tetralogy of Fallot=8, others=11). CANA was measured before (n=50) and 1 month (n=50) and 1 year (n=41) after the last definitive operation. In group X, ASD or VSD closure was performed, whereas all group Y patients underwent re-RVOTR because of progressive severe stenosis of the right ventricular outflow tract.

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Subgroup Analysis
To further investigate the influence of RVOTR on CANA, we investigated 62 patients in groups B1 and B2 (group Z) who had undergone 1 definitive RVOTR without re-RVOTR (age 14.3±3.7 years; age at RVOTR 4.9±3.7 years; follow-up 9.6±3.6 years).

Cardiac Catheterization
Cardiac catheterization was performed in 102 CHD patients and 41 controls. Parameters determined included central venous and systolic right ventricular pressures, ejection fraction of right and left ventricles measured by cineventriculography, and cardiac output by the Fick principle.

Measurement of Norepinephrine and Natriuretic Peptides
An indwelling angiocatheter was inserted into the antecubital vein for sampling. After ≥10 minutes’ rest, the plasma norepinephrine (NE) level was determined by high-performance liquid chromatography. The plasma levels of atrial (ANP) and brain (BNP) natriuretic peptides were assayed by radioimmunoassay to evaluate the severity of hemodynamic impairment. ANP and BNP are sensitive markers of failing ventricular pump function.

Measurement of HR Variability and Arterial Baroreflex Sensitivity
Methodology for measuring HR variability (HRV) and baroreflex sensitivity (BRS) was identical to that reported previously. After a 10-minute supine rest, ECG signals were recorded for an additional 5 minutes at a rate of 1000 samples per second. Beat-to-beat fluctuations were transformed into frequency domains by a fast Fourier transformation. Spectral HRV was expressed as a low-frequency (LF) component at 0.04 to 0.15 Hz and a high-frequency (HF) component at 0.15 to 0.40 Hz, and the logarithmic values of the frequency components, log LF and log HF, were used. When premature contractions were detected, removal of ectopy was performed. After HRV was measured, the bolus phenylephrine (1 to 4 μg/kg) injection method was used to measure BRS. ECG, arterial blood pressure (by Finapres, Ohmeda), and respiration (by impedance device) were recorded continuously on a multichannel recorder at a speed of 100 mm/s until peak blood pressure was reached. The R-R intervals obtained during expiration were plotted against the systolic blood pressures of the preceding beats on a beat-to-beat basis. A linear fit was performed to establish the linear portion of the line of best fit. Only regression lines that were statistically significant (P<0.05) were accepted for analysis. The final slope (BRS) was obtained by calculating the mean value of ≥2 measurements (ms/mm Hg).

[123I]Metaiodobenzylguanidine Scintigraphy
Metaiodobenzylguanidine (MIBG) scintigraphy was performed in 81 CHD patients and 14 controls to evaluate myocardial adrenergic nervous activity. There were no definitive criteria for subject selection, but all patients did not undergo this scintigraphy owing to the capacity of our laboratory. Seventy-four to 148 MBq of MIBG was injected, and myocardial images were acquired with a standard-field gamma camera equipped with a low-energy, parallel-hole collimator. Static planar imaging was performed 15 minutes and 4 hours after tracer injection, and to evaluate the myocardial accumulation of MIBG, the heart-to–mediastinal activity ratio (H/M) was calculated. Because MIBG is an analogue of NE and shares its uptake and storage mechanisms, decreased MIBG uptake (low H/M) suggests decreased sympathetic innervation, and it has been demonstrated in patients with heart failure and denervation caused by ischemia. Division of the cardiac sympathetic nerves results in a low H/M, as occurs after cardiac transplantation.

Determination of Cardiac Parasympathetic Nervous Tone and Postsynaptic β-Sensitivity
In 66 patients with CHD and 11 controls, atropine (0.04 mg/kg) was administered intravenously to determine the cardiac parasympathetic nervous tone (PNT) not less than 3 hours postprandially. After at least a 10-minute rest, baseline HR was taken as the control value. HR was recorded continuously at 25 mm/s on a strip chart recorder, and the HR 1 minute after a full-dose atropine infusion was determined. PNT was defined as the change in HR after complete cholinergic blockade by atropine. Two minutes after the atropine infusion, a continuous infusion of isoproterenol was administered at a rate of 3 μg·kg⁻¹·min⁻¹ for 6 minutes, and β was defined as the increase in HR from 1 minute after full-dose atropine infusion to 6
minutes after isoproterenol continuous infusion. In principle, we performed this approach in series. After that, to investigate the influence of basal SNA on PNT, propranolol (0.2 mg/kg) was administered to determine intrinsic HR in 14 of 66 patients (group A, n=4; B1, n=1; B2, n=8; and C, n=1). These pharmacological studies were limited to hospitalized patients with relatively preserved ventricular function and without significant tachyarrhythmias.

Exercise Protocol
All subjects exercised to the end of their tolerance on a motor-driven, programmable treadmill (Q-5000 system, Quinton) using a 30-second incremental protocol described previously.\(^1\)\(^2\) Endurance time (in minutes) and peak oxygen uptake (\(V\dot{O}_2\), mL·kg\(^{-1}\)·min\(^{-1}\)) were measured. A 12-lead ECG was recorded at rest and throughout exercise and used to determine HR. Ventilation and gas exchange were measured by a computerized breath-by-breath method. The subjects breathed through a tight-fitting mask connected to a hot-wire anemometer (Riko AS500, Minato Medical Science) to measure inspired and expired volume continuously. A mass spectrometer (MG-300, Perkin Elmer) was used to continuously measure \(O_2\) and \(CO_2\) partial pressures. In the breath-by-breath protocol, ventilatory equivalents for oxygen and carbon dioxide, as well as respiratory gas exchange ratio, were computed in real time and displayed with the HR and \(V\dot{O}_2\) for oxygen and carbon dioxide, as well as respiratory gas exchange pressures. In the breath-by-breath protocol, ventilatory equivalents [inspired \(O_2\) and \(CO_2\) partial pressures, expired \(O_2\) and \(CO_2\) partial pressures, and respiratory gas exchange ratio] were computed in real time and displayed with the HR and \(V\dot{O}_2\).

Change in HR from rest to peak exercise (ΔHR) was calculated.

Informed Consent
In CHD groups, after adequate explanation of the purpose of the study and clinical significance (mentioned in the clinical implication), informed consent was obtained from all subjects and/or their parents. In controls who performed MIBG scintigraphy and pharmacological evaluation, we asked them and/or their parents to take part in the present study as a volunteer, and we obtained consent from 11 pharmacological and 14 MIBG 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 by a factorial 1-way ANOVA with Scheffé’s procedure. Simple regression analysis was used to determine correlations between HR response and other parameters. Change in CANA after surgery was evaluated with a paired t test or Wilcoxon signed rank test. Correlation between number of surgical procedures and indices of CANA was evaluated by Spearman rank correlation analysis. Univariate and stepwise multivariate linear regression analyses were used to detect independent indices affecting the change of CANA during follow-up. Data are expressed as mean±SD. A P value of <0.05 was considered statistically significant.

Hemodynamic Variables and Natriuretic Peptides
All hemodynamic variables in groups B1 and B2, except right ventricular ejection fraction, were abnormal compared with those from groups A and C. A significant increase in systolic right ventricular pressure was observed in group B2, but no obstructive pulmonary arterial lesions were demonstrated (pulmonary arterial resistance <3.0 U/m\(^2\)). Natriuretic peptides were significantly higher in CHD groups, which suggests the presence of mild heart failure. (See Table 1.)

Influence of the Number of Surgical Procedures, Age at Time of RVOTR, and Follow-Up Period on CANA
In group Z, log LF, BRS, and PNT were significantly higher in patients without prior palliative surgeries than in patients with prior palliative surgeries (log LF, \(P<0.005\); BRS, \(P<0.0001\); and PNT, \(P<0.005\)). Although log HF and H/M tended to be higher in the former group than the latter (log HF, \(P<0.07\); H/M, \(P<0.08\)), no difference in \(\beta\) was observed between the 2 groups. Log LF, BRS, and PNT correlated inversely with the number of surgical procedures \((P<0.05\text{ to }0.0001; \text{BRS is shown in Figure 1}),\) whereas age at the time of RVOTR also inversely correlated with log LF, BRS, and \(\beta\) \((P<0.05\text{ to }0.01)\). BRS significantly correlated with the follow-up duration after RVOTR (BRS, \(r=0.42, P=0.001\); Figure 2). However, no significant correlation was demonstrated between H/M and follow-up duration (Figure 3). Among these 3 factors, the number of surgical procedures and age at the time of RVOTR were the independent indices of BRS. However, no predictive indices for H/M were determined.
Change in CANA After Operation
In group X, log HF and BRS decreased 1 month after definitive repair, but both values increased significantly 1 year after surgery (P<0.001). BRS increased significantly compared with its preoperative value, whereas no change in H/M was observed. In group Y, log HF, BRS, and H/M decreased significantly 1 month after re-RVOTR (P<0.05 to 0.01). Log HF increased significantly (P<0.05), and the value of BRS tended to increase (P<0.1). H/M was unchanged 1 year after re-RVOTR compared with its value 1 month after surgery. (See Table 3.)

HR Response During Exercise and Exercise Capacity
Because the gas exchange ratio at peak exercise exceeded 1.00 in all patients, we are confident that all patients performed near-maximal exercise. Endurance time and peak VO2 were significantly lower than for controls in all CHD groups. ΔHR was significantly lower in any CHD group, especially B1 and B2, than in controls. (See Table 4.)

Peak HR and ΔHR correlated well with peak VO2 in group B1 (Figure 4). However, no significant relationship was demonstrated between ΔHR and peak VO2 in groups A and B2.

Relationship Between CANA and HR Response
All indices of CANA except H/M correlated with ΔHR in groups A and B1, whereas these correlations were weak in group B2. PNT and β correlated more closely with ΔHR in group B1. (See Table 5.)

Influence of Basal SNA on PNT
PNT (27±17) was significantly greater than the difference in HR between intrinsic HR and HR after full dose of atropine (20±15, P<0.005), which is considered a true PSNA, but correlation between the 2 variables was very tight (r=0.92, P<0.0001).

Discussion
Our major findings are as follows. First, relatively severe sympathetic denervation of the ventricle is common after RVOTR, relating to the number of surgical procedures and not to ventricular function. Ventricular sympathetic reinnervation after RVOTR is uncertain. In addition, there is a small contribution of the sympathetic denervation to HR response during exercise. Second, with regard to the sinus node, β is relatively maintained in the majority of these patients, whereas impaired PSNA immediately after surgery recovers 1 year later. Both β and the recovery in PSNA are crucial to the HR response during exercise and are a major determinant of individual exercise capacity in these patients long after definitive RVOTR.

Abnormal CANA
Possible explanations for the sympathetic denervation of the ventricle include ventricular failure and/or surgery-related damage. Because H/M did not correlate with NE, natriuretic peptides, or ventricular function but correlated closely with the number of surgical procedures, the latter explanation is more likely. Surgical damage includes 2 factors: one is direct damage due to transection and/or dissection, and the other is subclinical myocardial damage, such as ischemia during cardiac surgery. Central sympathetic and parasympathetic cardiopulmonary nerves pass along the posteromedial surface of the superior vena cava, the right atrium, and both the ascending aorta and main pulmonary artery. Many small nerves arise from the cardiopulmonary plexuses and innervate the adjacent atria, aorta, pulmonary artery, and pulmonary veins. Consequently, removal of pericardium overlying the surface of the right atrium and the superior vena cava during cardiac surgery must cause abnormal CANA even in
patients with an ASD or VSD. In addition to vulnerability of the cardiac sympathetic nerves to ischemia, direct damage of CANA may be inevitable. Significant deterioration of PSNA immediately after closure of an ASD or VSD, although it soon recovers, supports this hypothesis. Because there is no change in H/M after closure of an ASD or VSD, possibly the surgical technique used for RVOTR and/or surgical time is responsible for sympathetic denervation of the ventricle. Even in an initial RVOTR (although re-RVOTR in the present study), extensive surgical manipulation, such as transection and/or dissection of the main and branch pulmonary arteries, is sometimes needed to repair stenosis of the right ventricular outflow tract and is both time consuming and potentially traumatic to adjacent innervation. Hence, significant sympathetic denervation must be associated with re-RVOTR and probably also with first RVOTR. Our study also supports this possibility, because a significant decrease in H/M immediately after re-RVOTR was demonstrated. Finally, preoperative hypoxia may be related to sympathetic denervation because of its vulnerability to ischemia.

Although it is unclear whether abnormal CANA of the sinus node results from cardiac nerve denervation, well-maintained β can be further proof that the major cause of abnormal CANA is cardiac nerve denervation, because a similar observation has been reported after cardiac transplantation. As shown in the ventricle, subclinical ischemia during cardiac surgery may cause abnormal CANA in the sinus node. In addition, the significant inverse correlation between age at the time of RVOTR and HRV, BRS, and β suggests some influence of preoperative factors, including hypoxia, on postoperative CANA.

Reinnervation of Cardiac Autonomic Nerves

Significant sympathetic reinnervation of the ventricle was not shown in patients after 1-staged RVOTR. Possible sympathetic reinnervation in infants after an arterial switch operation has been demonstrated. The higher age of our subjects compared with that study may explain the different outcome. However, because some studies have demonstrated sympathetic reinnervation in adults after cardiac transplantation, it may be anticipated that sympathetic reinnervation occurs in patients after RVOTR.

CANA of the sinus node followed a quite different course from that of the ventricle. In addition to well-maintained β, PSNA improves, at least during the first year after closure of ASD or VSD. Abolition of the intracardiac shunt may improve PSNA in these patients. Even in patients after RVOTR, the present study demonstrated recovery in PSNA, and the significant positive correlation between BRS and the follow-up period also suggests further parasympathetic reinnervation long after RVOTR. Hemodynamic improvement could explain this, but this seems unlikely because the rate of sympathetic reinnervation is slow, as in the ventricle, even in cardiac transplant patients who enjoy a remarkable hemody-

### Table 3: Change in CANA After Surgery

<table>
<thead>
<tr>
<th>Variable</th>
<th>Before Surgery</th>
<th>1 Month After Surgery</th>
<th>1 Year After Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Value n</td>
<td>Value n</td>
<td>Value n</td>
</tr>
<tr>
<td>Group X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Log HF</td>
<td>1.9±0.5 31</td>
<td>1.6±0.5* 31</td>
<td>2.0±0.5§ 31</td>
</tr>
<tr>
<td>BRS, ms/mm Hg</td>
<td>10.0±4.0 27</td>
<td>8.2±4.3* 27</td>
<td>12.8±4.2†§ 27</td>
</tr>
<tr>
<td>H/M</td>
<td>2.3±0.4 10</td>
<td>2.5±0.5 10</td>
<td>2.4±0.4 10</td>
</tr>
<tr>
<td>Group Y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Log HF</td>
<td>1.5±0.4 16</td>
<td>1.2±0.4† 16</td>
<td>1.5±0.4† 11</td>
</tr>
<tr>
<td>BRS, ms/mm Hg</td>
<td>4.6±2.8 19</td>
<td>2.9±2.5† 19</td>
<td>5.2±5.0 11</td>
</tr>
<tr>
<td>H/M</td>
<td>1.8±0.5 10</td>
<td>1.5±0.3* 10</td>
<td>1.4±0.3* 5</td>
</tr>
</tbody>
</table>

*P<0.05, †P<0.01 vs before surgery; ‡P<0.05, §P<0.001 vs 1 month after surgery.

### Table 4: Exercise Capacity and HR Response During Exercise

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group A (n=50)</th>
<th>Group B1 (n=54)</th>
<th>Group B2 (n=35)</th>
<th>Group C (n=47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endurance time, min</td>
<td>9.3±0.9*</td>
<td>8.2±1.8†‡</td>
<td>7.0±1.61§‡</td>
<td>10.5±1.3</td>
</tr>
<tr>
<td>Peak $V_O_2$, mL · kg$^{-1}$ · min$^{-1}$</td>
<td>38±5*</td>
<td>31±7§</td>
<td>26±5§</td>
<td>42±6</td>
</tr>
<tr>
<td>HR, bpm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>82±12</td>
<td>82±12</td>
<td>81±12</td>
<td>78±11</td>
</tr>
<tr>
<td>Peak</td>
<td>184±12</td>
<td>171±16§</td>
<td>160±15§∥</td>
<td>191±7</td>
</tr>
<tr>
<td>ΔHR</td>
<td>102±14*</td>
<td>89±19§</td>
<td>80±17§∥</td>
<td>113±11</td>
</tr>
<tr>
<td>Peak gas exchange ratio</td>
<td>1.19±0.09</td>
<td>1.17±0.07</td>
<td>1.13±0.07‡</td>
<td>1.20±0.06</td>
</tr>
</tbody>
</table>

Values are mean±SD.

*P<0.01, †P<0.001 vs group C; ‡P<0.01, §P<0.001 vs group A; ||P<0.05, ¶P<0.01 vs group B1.
namic improvement. Parasympathetic reinnervation, along with sympathetic reinnervation, occurs in cardiac transplant patients22; therefore, the most likely mechanism for temporary deterioration with subsequent recovery of PSNA along with maintained may be surgery-related subclinical damage of the sinus node based on ischemia, rather than denervation as occurs in the ventricle. Accepting the evidence that nerves regenerate only if they are cut,23 the type of surgery used, ie, the extent to which the cardiac parasympathetic and/or sympathetic nerve fibers are cut, may also determine the degree of cardiac nerve reinnervation in these patients.

**HR Response During Exercise and CANA**

Impaired CANA is one of the serious consequences of RVOTR because it is closely related to exercise capacity. We have demonstrated, for the first time, the close relationship between and HR response during exercise. Although the mechanism of impaired is undetermined, downregulation of the -receptor24 is unlikely because did not correlate with NE. If cardiac parasympathetic reinnervation occurs, late improved exercise capacity may be expected in patients long after RVOTR. The weak relationship between and CANA in group A is probably due to the smaller range of peak , ie, there were few patients with low aerobic capacity.

**Study Limitations**

The present study is limited by the small number of patients in the longitudinal study. Another important issue is the method of evaluating CANA. Direct stimulation of the sympathetic nerves of the sinus node and the ventricle with tyramine is preferable,21 and a future study investigating the correlation between indices obtained by direct stimulation and those used in our study is needed. Because the increase in HR after a full dose of atropine and propranolol strongly correlates with PNT, we believe that basal SNA has no major influence on the present results. PSNA may be somewhat underestimated by log HF,25 because patients who underwent several surgical procedures showed a restrictive ventilatory impairment. In contrast, BRS may be a more valid approach to estimate PSNA, because its value is uninfluenced by respiration, and this reflex directly activates the cardiac parasympathetic nerves26 and is almost abolished by atropine. 27

**Clinical Implication**

When monitoring adults after RVOTR, in addition to the greater contribution of CANA to exercise capacity, we should also be aware that they may not complain of chest pain even if they develop ischemic heart disease because of cardiac nerve denervation, as occurs in patients after cardiac transplantation. This may apply to other kinds of CHD, including patients after the arterial switch operation and postoperative complex CHD. Another important and serious concern is the relationship between arrhythmia and CANA. Arrhythmias have been implicated in sudden cardiac death long after RVOTR28; therefore, further studies of life-threatening arrhythmias and their relationship to CANA are needed.

**Acknowledgments**

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

**References**


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_Circulation_. 2000;102:2732-2738
doi: 10.1161/01.CIR.102.22.2732

_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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