Predictors of Disease Course in Patients With Acute Myocarditis

Koichi Fuse, MD; Makoto Kodama, MD; Yuji Okura, MD; Masahiro Ito, MD; Satoru Hirono, MD; Kiminori Kato, MD; Haruo Hanawa, MD; Yoshifusa Aizawa, MD

Background—Clinical manifestations of acute myocarditis, with distinct onset, vary from asymptomatic to fatal. The predictors of the course of the disease in patients with acute myocarditis at initial presentation have not yet been established. In this study, we examined the predictive values of various parameters in the disease course of patients with myocarditis.

Methods and Results—Twenty-one consecutive patients who had been diagnosed as having acute myocarditis by histological examinations were analyzed. The patients with myocarditis were divided into the survival group (n=13) and the fatal group (n=8). We examined the parameters of the clinical state, hemodynamic variables, required therapies, biochemical laboratory data, and cytokines. The control groups were composed of 23 patients with old myocardial infarction and 20 healthy volunteers. The fatal group had lower blood pressure and higher pulmonary capillary wedge pressure compared with those values in the survival group. Mechanical ventilation support was more frequently required in the fatal group. Serum levels of soluble Fas (sFas) and soluble Fas ligand (sFasL) were significantly higher in the myocarditis group than in the 2 control groups. Furthermore, levels were significantly higher in the fatal group than in the survival group for sFas (13.93±4.77 versus 3.77±0.52 ng/mL, respectively; P<0.001) and sFasL (611.4±127.7 versus 269.5±37.3 pg/mL, respectively; P<0.05). Other clinical states, hemodynamic variables, required therapies, and biochemical laboratory parameters were not different between the 2 groups.

Conclusions—Elevation of sFas and sFasL levels at initial presentation appear to be a good serological marker to predict the prognosis of acute myocarditis. (Circulation. 2000;102:2829-2835.)

Key Words: myocarditis □ prognosis □ Fas

Clinical manifestations of acute myocarditis vary from flulike symptoms to the fulminant fatal forms. Most acute myocarditis, with distinct onset, follows a monophasic clinical course, and the majority of patients recover spontaneously after several days of congestive heart failure. On the other hand, some patients with acute myocarditis rapidly progress into cardiogenic shock before or after admission to the hospital. Serious complications, such as ventricular arrhythmias, cardiac arrest, or cardiogenic shock, appear unexpectedly during the acute phase. Some patients progress into subacute or chronic forms, which ultimately lead to death. The mechanisms of diversity in the clinical manifestation of acute myocarditis have not been fully elucidated. Moreover, the predictors of the disease course in acute myocarditis have not yet been established. In the present study, we examined various clinical parameters, ie, clinical states, hemodynamic variables, required therapies, biochemical laboratory data, cytokines, and immunologic markers, as the predictors of the disease course in patients with histology-proven acute myocarditis.

Received May 23, 2000; revision received July 20, 2000; accepted July 25, 2000.
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Clinical Course and Hemodynamics
Heart rate, systolic and diastolic blood pressures, and hemodynamic variables on admission were evaluated. In all the patients with acute myocarditis, pulmonary capillary wedge pressures were measured by use of a thermodilution method (7F Swan-Ganz catheter), and the cardiac index was calculated as the ratio of cardiac output to body surface area. Therapeutic strategies were not formulated. Patients in severe congestive heart failure were managed by use of mechanical ventilation, and those in cardiogenic shock were treated by an intra-aortic balloon pump or a percutaneous cardiopulmonary support system. Required therapies during the clinical course were analyzed.

Serum Samples and Biochemical Assay
Blood samples were obtained from the patients of the myocarditis group immediately after admission to the hospital. Blood samples were immediately centrifuged to separate serum and were kept at −80°C until assay. Biochemical laboratory data on admission were analyzed to determine their predictive values for disease outcome.

Measurement of TNF-α
Tumor necrosis factor (TNF)-α, a proinflammatory cytokine and a product of activated macrophages and inducer of apoptosis, was increased in the serum of patients with severe congestive heart failure.1–13 For the measurement of serum TNF-α, a TNF-α Enzyme Immunoassay Kit (Code No. 1121, Immunotech) was used. After completion of the reaction, the samples were subjected to electrophotometry to measure absorbency at a wavelength of 405 nm. The sensitivity limit of the assay was 5 pg/mL. The cross-reactivity of interference with either TNF-β or the p55 and p75 forms of the TNF receptor was not observed. Intra-assay and interassay coefficients of variation were 5.9% and 7.0%, respectively.

Measurements of sFas and sFasL Levels by ELISA
Recently, elevations of serum soluble Fas (sFas) and soluble Fas ligand (sFasL) levels have been demonstrated in patients with myocarditis and dilated cardiomyopathy.14–19 However, it remains uncertain whether the increased serum levels of these proteins are related to the pathogenesis or the prognosis of such cardiac diseases. We examined whether serum levels of sFas and sFasL proteins at initial presentation could be serological markers to predict the prognosis of patients with acute myocarditis.

In the present study, sFas and sFasL levels were measured in the sera obtained at admission to the hospital. Serum sFas levels were measured by use of an sFas (S) ELISA Kit (Code No. 5251, Medical & Biological Laboratories Co Ltd). The kit uses the sandwich ELISA technique with a monoclonal antibody recognizing the extracellular domain of sFas protein and polyclonal antibodies recognizing the intracellular domain of the protein. Thus, the kit specifically detects only interactive sFas molecules, which do not have a membrane-penetrating domain, and does not detect impaired molecules whose extracellular domain is degraded by protease. After completion of the reaction, the samples were subjected to electrophotometry to measure absorbency at a wavelength of 450 nm. The minimum concentration of sFas for detection was 0.5 ng/mL. The average within-run and between-run coefficients of variation were 4.5% and 5.2%, respectively. Recovery of the sFas added to the serum ranged between 94% and 109%. sFasL was measured by use of an sFas-Ligand ELISA Kit (Code No. 5255, Medical & Biological Laboratories Co Ltd), which also used the sandwich ELISA technique with 2 monoclonal antibodies recognizing different epitopes of sFasL molecules. After completion of the reaction, the samples were also subjected to electrophotometry to measure absorbency at a wavelength of 450 nm. The minimum concentration of sFasL for detection was 0.1 ng/mL. The average within-run and between-run coefficients of variation were 4.2% and 6.3%, respectively. Recovery of the sFasL added to the serum ranged between 96% and 111%. When data exceeded the maximum limit measurable in the detection assay or went beyond the range of the spectrophotometer, the samples were diluted and measured again.

Control Group
Two control groups were set up. One group consisted of 23 age- and sex-matched patients, which was composed of 15 men and 8 women with old myocardial infarction (OMI) but not congestive heart failure or myocarditis. They were diagnosed by physical examination, echocardiography, and cardiac catheterization. In addition, all subjects had no clinical or laboratory evidence of neoplasm and autoimmune disease. The other group was composed of 20 age- and sex-matched healthy volunteers, including 10 men and 10 women. They had no evidence of cardiac diseases and served as the normal control. The mean age of the OMI group was 61.0±2.3 years (range 27 to 78 years), and that of the healthy control group was 46.5±3.5 years (range 24 to 76 years).

All the patients and healthy volunteers selected for the present study were given a full explanation about the study and agreed to participate in the study, which was approved by the local ethics committee on human research (Niigata University).

Statistical Analysis
Data were statistically analyzed by use of the software program Statview J-5.0 (Abacus Concepts, Inc.). Serum sFas, sFasL, and TNF-α levels in the myocarditis group, the OMI group, and the healthy control group were analyzed by the Kruskal-Wallis test, which was followed by the Mann-Whitney U test. Statistical analysis of several vari able parameters between the subgroups of the patients with myocarditis was performed with the Mann-Whitney U test. Each value is shown as the mean±SEM. We judged values as significantly different at P<0.05.

Results
Clinical Manifestations and Hemodynamics of Patients With Myocarditis
The cardiac index of the patients with myocarditis in the present study was 2.2±0.2 L·min⁻¹·m⁻² and the mean pulmonary capillary wedge pressure was 20.5±1.3 mm Hg on admission (Table 1). Five patients (24%) were classified into subset II according to Forrester’s criteria; 2 patients (10%), into subset III; and 7 patients (33%), into subset IV. Nine patients (43%) had complications of complete atrioventricular block, and 4 (19%) had ventricular tachycardia or fibrillation during hospitalization. In addition, 14 (67%) patients were treated with an intra-aortic balloon pump, and 8 (38%) of these 14 patients were managed by use of a percutaneous cardiopulmonary support system because of severe arrhythmia, refractory heart failure, or cardiogenic shock. The mean value of the maximum serum creatine phosphokinase (CPK) levels in the myocarditis group was 4001±1575 IU/L. The first histopathologic examinations were performed 27.1±5.7 days (range 3 to 83 days) from the onset of myocarditis and demonstrated lymphocytic myocarditis in 18 (86%) patients; 2 (10%) were affected with giant cell myocarditis, and 1 (5%) was affected with eosinophilic myocarditis. All patients showed infiltration of inflammatory cells in the myocardium with necrosis or degeneration of cardiomyocytes, and these findings met the criterion for active myocarditis as established by the Dallas criteria. A viral study was performed in 13 patients by the measurement of neutralizing antibody titers in the paired sample; only 1 patient was positive for Coxsackievirus B4. Ten patients (48%) were treated with steroid hormones during the active phase. The doses of steroid hormones were not significantly different between the fatal group and the survival group. The immunosuppressive therapy for patients with distinct-onset
The cardiac index of the patients with OMI in the present study was 2.6±0.4 L·min⁻¹·m⁻², which was significantly higher than that of the myocarditis group. The mean pulmonary capillary wedge pressure was 8.7±0.8 mm Hg, which was significantly lower than that of the myocarditis group (Table 2).

**Profiles of Patients With OMI**

The cardiac index of the patients with OMI in the present study was 2.6±0.4 L·min⁻¹·m⁻², which was significantly higher than that of the myocarditis group. The mean pulmonary capillary wedge pressure was 8.7±0.8 mm Hg, which was significantly lower than that of the myocarditis group (Table 2).

**Serum TNF-α, sFas, and sFasL Concentrations**

The serum TNF-α levels were significantly elevated in the myocarditis group (28.9±14.1 pg/mL) compared with the OMI group (8.2±0.8 pg/mL) and the healthy control group (6.8±0.4 pg/mL) (Table 2). The serum sFas and sFasL levels of the myocarditis group (7.64±2.09 and 399.7±63.8 pg/mL, respectively) were also significantly higher than those of the OMI group (1.83±0.09 and 122.7±11.4 pg/mL, respectively) and those of the healthy control group (1.68±0.08 and 108.0±19.0 pg/mL, respectively) (Table 2, Figure 1). There were no significant differences in levels of TNF-α, sFas, and sFasL between the OMI group and the healthy control group. The serum sFas and sFasL levels of the lymphocytic myocarditis group (7.98±2.43 and 418.2±73.2 pg/mL, respectively) were significantly higher than those of the OMI group (P<0.0001) and those of the healthy control group (P<0.0001).

**Predictive Values of Clinical and Humoral Parameters in the Course of Acute Myocarditis**

Various parameters at the time of admission, ie, clinical state, hemodynamic variables, biochemical laboratory data, serum
levels of TNF-α, sFas, and sFasL, were evaluated for their predictive values for disease outcome (Table 3). Some parameters, such as required therapies, maximal CPK, and maximum CPK-MB, were not obtained at admission but were estimated after the entire clinical course. Systolic blood pressure and diastolic blood pressure of the fatal group were significantly lower than those of the survival group. Pulmonary capillary wedge pressure of the fatal group was significantly higher than that of the survival group. Biochemical laboratory data at the time of admission were not significantly different between both groups. No significant difference was observed in the levels of TNF-α between the survival group and the fatal group of patients with myocarditis. The serum sFas and sFasL levels of the fatal group were significantly higher than those of the survival group (for sFas, 16.58 ± 6.06 versus 3.69 ± 0.56 ng/mL, respectively [P = 0.0027]; for sFasL, 735.7 ± 132.9 versus 259.4 ± 39.1 pg/mL, respectively [P = 0.0076]) (Figure 2). We did not sample all patients’ sera sequentially during the clinical course, so we were not able to clarify the sequential changes of sFas and sFasL levels in the natural course of acute myocarditis. However, in 2 patients who recovered from acute myocarditis, the levels of sFas and sFasL gradually decreased in accordance with the clinical course (for 1 of the 2 patients, sFas decreased from 3.74 to 0.99 ng/mL, and sFasL decreased from 122 to 80 pg/mL; for the other patient, sFas decreased from 5.63 to 3.64 ng/mL, and sFasL decreased from 370 to 118 pg/mL). Because of the small sample size, the multivariate techniques to balance dissimilarities between the survival group and the fatal group were not possible.

**Discussion**

Clinical diagnosis of acute myocarditis is occasionally difficult at the initial presentation of patients; this is because acute myocarditis shows a wide variety of clinical courses, from minimum symptoms to fulminant or fatal courses.1 Even if the initial hemodynamic status was stable, catastrophic deterioration might appear during the acute phase. There are some reports indicating reliable predictors of the course of histology-proven acute myocarditis20–23; however, good sero-

<table>
<thead>
<tr>
<th></th>
<th>Myocarditis (n=21)</th>
<th>OMI (n=23)</th>
<th>Healthy Control (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>50.5 ± 4.0</td>
<td>55.0 ± 2.3</td>
<td>46.5 ± 3.5</td>
</tr>
<tr>
<td>Male/female, n/n</td>
<td>15/6</td>
<td>15/8</td>
<td>10/10</td>
</tr>
<tr>
<td>Hemodynamic data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac index, L · min⁻¹ · m⁻²</td>
<td>2.2 ± 0.2†</td>
<td>2.6 ± 0.4</td>
<td>...</td>
</tr>
<tr>
<td>PCWP, mm Hg</td>
<td>20.5 ± 1.3†</td>
<td>8.7 ± 0.8</td>
<td>...</td>
</tr>
<tr>
<td>Serum concentrations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum TNF-α level, pg/mL</td>
<td>28.9 ± 14.4*†</td>
<td>8.2 ± 0.8</td>
<td>6.8 ± 0.4</td>
</tr>
<tr>
<td>Serum sFas level, ng/mL</td>
<td>7.64 ± 2.09†</td>
<td>1.83 ± 0.09</td>
<td>1.68 ± 0.08</td>
</tr>
<tr>
<td>Serum sFasL level, pg/mL</td>
<td>399.7 ± 63.8†</td>
<td>122.7 ± 11.4</td>
<td>108.0 ± 19.0</td>
</tr>
</tbody>
</table>

Values are mean ± SEM or number of patients. PCWP indicates mean pulmonary capillary wedge pressure. *P < 0.05 vs healthy control group; †P < 0.05 vs OMI group.
logical markers at admission to the hospital were not yet established. McCarthy et al\textsuperscript{23} recently reported the prognosis of histology-proven myocarditis. Fulminant myocarditis, which they defined as myocarditis with distinct onset, showed a favorable prognosis, and acute myocarditis, which was defined as a disease of indistinct onset, had a poor prognosis. The present study population might be classified into “fulminant myocarditis” according to the classification of McCarthy et al. Patients in the present study showed high values of serum CPK and high prevalence of life-threatening arrhythmia, and compared with the populations in the study of McCarthy et al and in other reports from the United States, they had been frequently managed with use of a respirator and an intra-aortic balloon pump. The prognosis of myocarditis in our study population was poor compared with that in the study of McCarthy et al. Thus, clinical manifestations and prognosis for patients with myocarditis may vary among races or countries.

In the present study, hypotension and elevation of pulmonary capillary wedge pressure on admission were associated with a fatal clinical course. These parameters imply that the patients are already in the condition of cardiogenic shock or severe congestive heart failure at the time of admission to the hospital. Physicians can agree with these results. Intensive care will start when patients show symptoms of hypotension or high pulmonary capillary wedge pressure. The main interest of the present study was to determine whether any biochemical or humoral factors at the time of admission are able to predict the fatal outcomes in patients with acute myocarditis.

Extremely high levels of serum CPK at presentation would reflect severe myocardial damage and would be associated with a poor prognosis. However, some patients with fulminant myocarditis have revealed a rather mild elevation of CPK on admission, as shown in the present study (Table 1). Progressive elevation of CPK was frequently observed in patients with severe acute myocarditis. Therefore, the initial CPK levels could not predict the disease course of the patients with acute myocarditis. Other biochemical variables on admission were also not able to predict the disease course of patients with acute myocarditis.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Survival Group (n=13)</th>
<th>Fatal Group (n=8)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female, n/n</td>
<td>10/3</td>
<td>5/3</td>
<td>NS</td>
</tr>
<tr>
<td>Age, y</td>
<td>50.2±4.9</td>
<td>51.1±7.5</td>
<td>NS</td>
</tr>
<tr>
<td>Clinical and hemodynamic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>variables</td>
<td>Heart rate, bpm</td>
<td>86±8</td>
<td>78±10</td>
</tr>
<tr>
<td></td>
<td>Systolic blood pressure, mm Hg</td>
<td>100±4</td>
<td>84±7</td>
</tr>
<tr>
<td></td>
<td>Diastolic blood pressure, mm Hg</td>
<td>62±3</td>
<td>49±3</td>
</tr>
<tr>
<td></td>
<td>CI, L·min(^{-1})·m(^{-2})</td>
<td>2.4±0.2</td>
<td>2.0±0.3</td>
</tr>
<tr>
<td></td>
<td>PCWP, mm Hg</td>
<td>18.3±1.3</td>
<td>24.1±2.0</td>
</tr>
<tr>
<td>Required therapies, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steroid</td>
<td>4 (31%)</td>
<td>6 (75%)</td>
<td>NS</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>4 (31%)</td>
<td>8 (100%)</td>
<td>0.0024</td>
</tr>
<tr>
<td>IABP</td>
<td>8 (62%)</td>
<td>6 (75%)</td>
<td>NS</td>
</tr>
<tr>
<td>PCPS</td>
<td>4 (31%)</td>
<td>4 (50%)</td>
<td>NS</td>
</tr>
<tr>
<td>Biochemical and humoral factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial WBC level, mm(^3)</td>
<td>8031±974</td>
<td>7913±1728</td>
<td>NS</td>
</tr>
<tr>
<td>Initial CRP level, mg/dL</td>
<td>5.5±2.2</td>
<td>6.5±2.2</td>
<td>NS</td>
</tr>
<tr>
<td>Initial GOT level, IU/L</td>
<td>305.2±100.4</td>
<td>1464.0±1184.7</td>
<td>NS</td>
</tr>
<tr>
<td>Initial LDH level, IU/L</td>
<td>1300.6±255.3</td>
<td>4257.1±2421.2</td>
<td>NS</td>
</tr>
<tr>
<td>Initial BUN level, IU/L</td>
<td>21.8±2.7</td>
<td>30.8±3.4</td>
<td>NS</td>
</tr>
<tr>
<td>Initial creatinine level, IU/L</td>
<td>1.0±0.1</td>
<td>1.3±0.2</td>
<td>NS</td>
</tr>
<tr>
<td>Initial CPK level, IU/L</td>
<td>814.0±306.5</td>
<td>1341.4±414.9</td>
<td>NS</td>
</tr>
<tr>
<td>Maximum CPK level, IU/L</td>
<td>1253.0±340.3</td>
<td>8465.6±3699.1</td>
<td>NS</td>
</tr>
<tr>
<td>Maximum CPK-MB level, IU/L</td>
<td>93.4±25.9</td>
<td>175.0±40.2</td>
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</tr>
<tr>
<td>Initial TNF-(\alpha) level, pg/mL</td>
<td>10.2±0.9</td>
<td>59.4±36.6</td>
<td>NS</td>
</tr>
<tr>
<td>Initial sFas level, ng/mL</td>
<td>3.77±0.52</td>
<td>13.93±4.77</td>
<td>0.0009</td>
</tr>
<tr>
<td>Initial sFasL level, pg/mL</td>
<td>269.5±37.3</td>
<td>611.4±127.7</td>
<td>0.0326</td>
</tr>
</tbody>
</table>

Values are mean±SEM or number (percentage) of patients. PCWP indicates mean pulmonary capillary wedge pressure; IABP, intra-aortic balloon pump; PCPS, percutaneous cardiopulmonary support; WBC, white blood cell; CRP, C-reactive protein; GOT, glutamic-oxaloacetic transaminase; LDH, lactate dehydrogenase; and BUN, blood urea nitrogen.
Serum levels of TNF-α in patients with acute myocarditis were significantly higher than those of the healthy control subjects. These data confirmed previous reports that serum concentrations of TNF-α are increased in patients with congestive heart failure compared with normal subjects. However, there was no significant difference in the serum TNF-α levels between the survival group and the fatal group. A few cases of fulminant myocarditis showed extremely high levels of serum TNF-α, but other cases revealed only slight elevations of TNF-α. The levels of serum TNF-α and CPK may reflect the severity of myocardial damage at the time of examination in acute myocarditis, but they seem to be unable to predict whether the myocardial damage is progressive or not.

Serum sFas and sFasL levels of patients with acute lymphocytic myocarditis were significantly higher than those of the OMG group and those of the healthy control group (Figure 1), confirming previously reported data. Furthermore, serum levels of sFas and sFasL showed significant correlations with the prognosis (Figure 2). We also added the data for patients with giant cell myocarditis and eosinophilic myocarditis (each with distinct symbols in the figures), because sFas and sFasL of those specific types of myocarditis have not yet been reported; however, the statistical tendency did not change. Both humoral factors, especially sFas, are strong predictors of the disease course in patients with acute myocarditis, although we could not apply the multivariate analyses.

It is uncertain why sFas and sFasL are able to predict the outcome of acute myocarditis. Recently, several studies have demonstrated that various viruses could stimulate the expression of mRNA and protein production of Fas or FasL in blood mononuclear cells as well as infected organ cells. A similar enhancement of the production of Fas or FasL molecules was also demonstrated in Coxsackievirus and encephalomycarditis virus infection. This evidence suggests that a part of the elevation of serum sFas or sFasL may be determined in the phase of viremia preceding the phase of target organ injury. Accordingly, sFas and sFasL may reflect the severity of preceding viremia and not merely the myocardial damage at the time of examination. If so, these factors may be partially able to suggest the future progression of the disease. Another possibility is that apoptosis of cardiomycocytes via the Fas/Fas ligand pathway may be involved in the pathogenesis of acute myocarditis. Some experimental studies have implied the involvement of apoptosis in myocardial damage in myocarditis. We could not confirm these hypotheses in clinical cases reported in the present study.

In conclusion, elevation of sFas and sFasL levels was strongly associated with the fatal outcomes of the patients with acute myocarditis. Thus, measurement of the levels of sFas and sFasL can be quite valuable when treating patients with acute myocarditis.

**Acknowledgments**

This study was supported in part by a grant for scientific research from the Ministry of Education, Science, and Culture of Japan (No. 10670636). We gratefully acknowledge the following doctors for their cooperation and collaboration in this study: Niigata Prefectural Shibata Hospital, Kaoru Suzuki, MD, Yasuhiko Tanabe, MD, and Eiichi Ito, MD; Niigata City General Hospital, Hirotaka Oda, MD, Norio Higuma, MD, Tetsuro Toeda, MD, Tsutomu Miida, MD, and Kazuyoshi Takahashi, MD; Tachikawa General Hospital, Maseaki Okabe, MD, Masahito Sato, MD, Junji Ishiguro, MD, Minoru Takahashi, MD, Hitoshi Kitazawa, MD, and Osamu Ogawa, MD; Niigata Koho Hospital, Hideaki Otsuka, MD, Mitsuru Oshima, MD, and Yasushi Miyakita, MD, and Niigata Prefectural Center Hospital, Fumiaiku Masami, MD, Masatake Suzuki, MD, and Michiko Kudo, MD.

**References**


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Circulation. 2000;102:2829-2835
doi: 10.1161/01.CIR.102.23.2829

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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