Time Course of Sympathetic Neural Hyperactivity After Uncomplicated Acute Myocardial Infarction

Lee N. Graham, MB ChB; Paul A. Smith, MB ChB; John B. Stoker, BSc, MB ChB; Alan F. Mackintosh, MA, MD; David A.S.G. Mary, MB ChB, PhD

Background—Little information is available on sympathetic activity after acute myocardial infarction (AMI), despite the belief that sympathetic drive is important in relation to morbidity and mortality. Indirect indices such as plasma catecholamines are transiently elevated after uncomplicated AMI, whereas other prognostically important autonomic indices may be affected longer. We planned to quantify central sympathetic output to the periphery after uncomplicated AMI and to investigate its progress over time.

Methods and Results—After uncomplicated AMI, 13 patients had muscle sympathetic nerve activity (MSNA) assessed from multiunit discharges and from single units with defined vasoconstrictor properties (s-MSNA). Measurements were obtained 2 to 4 days after AMI and were repeated after 3 and 6 months. We also examined 3 matched control groups comprising normal subjects, patients with coronary artery disease, and hospitalized patients without AMI. MSNA and s-MSNA after AMI (84±4.6 bursts/100 beats and 95±5.8 impulses/100 beats) were unchanged at 3 months but decreased (P<0.01 and P<0.001) after 6 months (75±4.0 bursts/100 beats and 80±4.4 impulses/100 beats). These were still greater (at least P<0.01) than values in normal subjects, patients with coronary artery disease, and hospitalized patients without AMI (51±3.9 bursts/100 beats, 58±4.7 impulses/100 beats; 56±2.2 bursts/100 beats, 61±2.2 impulses/100 beats; and 55±3.6 bursts/100 beats, 61±3.3 impulses/100 beats, respectively). This sympathetic hyperactivity was inversely correlated to left ventricular ejection fraction but not to changes in blood pressure.

Conclusions—A protracted state of sympathetic hyperactivity was shown to occur after uncomplicated AMI. It is suggested that this hyperactivity may explain delayed cardiovascular morbidity and mortality and that it arises because of an impairment of reflexes from cardiac receptors. (Circulation. 2002;106:793-797.)

Key Words: nervous system, sympathetic myocardial infarction action potentials

There has been virtually no information on the magnitude of sympathetic nerve activity and its changes over time in patients after acute myocardial infarction (AMI). Although it has been possible to quantify vasoconstrictor muscle sympathetic nerve activity (MSNA) directly by the technique of microneurography in a variety of cardiovascular conditions,1 so far it has not been used systematically to quantify MSNA after AMI. This information is needed because autonomic dysfunction in the form of sympathetic activation and impairment of vagal control of the heart have been repeatedly associated with an adverse outcome after AMI.2-4

All the information on autonomic function after AMI has been derived from the use of indirect indices such as plasma catecholamine levels,2,5 heart rate variability, and cardiovagal baroreceptor reflex sensitivity.6 Notwithstanding their value in the prediction of clinical outcome after AMI, there are limitations to the use of these indices to quantify sympathetic or vagal mechanisms. For instance, the levels of plasma catecholamines may be affected by regional variations in their release and by changes in their clearance rate,6 whereas changes in heart rate may be affected by the responsiveness of the sinoatrial node to vagal output.7 It is also notable after uncomplicated AMI that plasma catecholamine levels return to normal within days,2,5 whereas impairment of baroreceptor reflex sensitivity6 and heart rate variability6 may require months to recover.

The present investigation was therefore designed to quantify the magnitude of central sympathetic vasoconstrictor output to the peripheral vascular bed in patients after uncomplicated AMI and to investigate its progress over time. For this purpose, the mean frequency of MSNA was measured by microneurography between 2 to 4 days, 3 months, and 6 months after AMI.

Methods

Subjects

A total of 55 white subjects were examined. They included 18 patients who had uncomplicated AMI between January 2000 and

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TABLE 1. Details of the 4 Study Groups

<table>
<thead>
<tr>
<th>Group</th>
<th>AMI Group</th>
<th>NC Group</th>
<th>CAD Group</th>
<th>NMI Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (men)</td>
<td>13 (10)</td>
<td>13 (7)</td>
<td>13 (10)</td>
<td>11 (8)</td>
</tr>
<tr>
<td>Age, y</td>
<td>60±2.4</td>
<td>57±1.9</td>
<td>56±2.6</td>
<td>56±1.6</td>
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<tr>
<td>Weight, kg</td>
<td>74±2.7</td>
<td>78±4.0</td>
<td>82±3.9</td>
<td>77±4.3</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26±0.8</td>
<td>27±0.8</td>
<td>26±0.9</td>
<td>25±1.0</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>56±1.9</td>
<td>64±2.3</td>
<td>58±1.4</td>
<td>61±4.0</td>
</tr>
<tr>
<td>Blood pressure, mm Hg Mean</td>
<td>89±2.6</td>
<td>102±1.3</td>
<td>94±2.1</td>
<td>94±2.4</td>
</tr>
<tr>
<td></td>
<td>&lt;0.001</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic</td>
<td>116±4.4</td>
<td>135±2.1</td>
<td>129±3.3</td>
<td>128±2.8</td>
</tr>
<tr>
<td></td>
<td>&lt;0.01</td>
<td>&lt;0.05</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic</td>
<td>76±2.1</td>
<td>85±1.1</td>
<td>76±1.9</td>
<td>78±2.5</td>
</tr>
<tr>
<td></td>
<td>&lt;0.01</td>
<td>NS</td>
<td>&lt;0.01</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Data are expressed as mean±SEM. AMI indicates acute myocardial infarction; NC and CAD, matched normal and coronary artery disease patients, respectively; NMI, patients hospitalized with chest pain in which AMI was excluded; and NS, P>0.05. Analyses were performed using ANOVA post-tests, except for sex difference in which χ² test was used.

May 2001, 13 normal subjects, 13 patients with stable coronary artery disease (CAD) who had no prior history of AMI, and 11 patients hospitalized with chest pain in whom AMI was subsequently excluded (NMI). Of the 18 patients who had AMI, two developed clinical complications, and stable microneurographic data could not be obtained in a further three. The investigations were therefore completed in 13 patients with uncomplicated AMI, 13 normal subjects, 13 patients with stable CAD, and 11 patients with NMI who were matched in terms of age and body mass index to the AMI patients (Table 1). All patients were screened by history, physical, and laboratory examination. Patients were excluded if they had a history of previous myocardial infarction, hypertension, diabetes, or other chronic disease that could influence the autonomic nervous system. Those patients with evidence of arrhythmia, conduction abnormalities, heart failure, or cardiogenic shock were also excluded.

AMI was confirmed by at least 2 of the following 3 criteria: (1) a clinical history of ischemic-type chest pain, (2) changes on serially obtained electrocardiograms, and (3) a rise in serum creatine kinase levels to >400 IU/L and its subsequent fall. The latter 2 criteria were absent in the NMI group. All AMI patients were in Killip class I, and none had frequent ventricular ectopic beats or conduction defects, chest rales, or radiographic evidence of pulmonary vascular congestion. Also, none had a left ventricular ejection fraction (LVEF) <40%, as determined by echocardiography. Six had anterior and 7 had inferior infarcts. Patients received conventional therapy in the form of thrombolysis (n=12), and angiotensin-converting enzyme (ACE) inhibitors (n=9). All patients were entered into an individualized physical rehabilitation program twice a week for 4 weeks, starting on day 7 after AMI. Exercise intensity was adjusted to increase the heart rate to 70% of maximum. CAD was confirmed both by exercise treadmill testing and coronary angiography. A positive exercise test was defined by horizontal ST depression of at least 2 mm during exercise with associated chest pain. Coronary angiography demonstrated significant CAD in these patients (>70% stenosis of at least one major epicardial coronary artery). Seven patients had single vessel disease, 5 had 2-vessel disease, and one patient had 3-vessel disease. All CAD patients were on β-blockers. Six of those in the NMI group were on β-blockers. The investigation was performed with the approval of St James University Hospital’s Ethics Committee, and all subjects provided informed written consent.

General Protocol

Sympathetic activity was assessed at 2 to 4 days after admission and was repeated at 3 and 6 months. The details of the protocol and data analysis have been published previously.10 Briefly, all investigations were performed under similar conditions between the hours of 9 AM and 12 PM (midday) to avoid circadian autonomic variation. Subjects were asked to have a light breakfast and to empty their bladder before commencing the study. The subjects maintained a normal dietary sodium intake of ~400 mmol/d, and they were requested to avoid nicotine and caffeine products for 12 hours and alcohol and strenuous exercise for 24 hours before investigation.

During each session, the subjects were studied in the semisupine position. Measurements were made in a darkened laboratory in which the temperature was constant at 22°C to 24°C. Resting blood pressure was measured from the arm using a standard mercury sphygmomanometer. Heart rate and arterial blood pressure were monitored and recorded using a standard ECG and a Finapres device, and blood flow to the muscle of the left calf was obtained using standard strain-gauge plethysmography.

**Microneurography**

Postganglionic MSNA was recorded from the right peroneal nerve as previously described.1,10 Briefly, the neural signal was amplified (×50 000) and, for the purpose of generating bursts representing multunit discharge, the signal was filtered (bandwidth of 700 to 2000 Hz) and integrated (time constant of 0.1 s). The output of action potentials and bursts from this assembly were passed to a data-acquisition system, which digitized the action potentials at 12 000 samples/s and other data channels at 2000 samples/s (8 bits).

MSNA was differentiated from skin sympathetic activity and afferent activity by previously accepted criteria.1,10 Single units (s-MSNA) in the raw action potential neurogram were obtained by adjusting the electrode position while using fast monitor sweep and online storage oscilloscope to confirm the presence of a consistent action potential morphology, as previously described.10,11 Only vasoconstrictor units were accepted and examined; the criteria of acceptance was appropriate responses to spontaneous changes in arterial blood pressure, the Valsalva maneuver, and isometric hand-grip exercise. Simultaneous measurement of calf vascular resistance confirmed the vasoconstrictor function of the observed neural activity. During the Valsalva maneuver, sympathetic activity increased during the latter part of phase II and/or phase III and decreased during phase IV (increase and overshoot of blood pressure). Isometric hand-grip exercise, performed using a dynamometer, produced a late increase in arterial blood pressure and sympathetic neural activity.

An electronic discriminator was used to count the spikes of s-MSNA objectively, and s-MSNA was quantified as mean frequency of impulses/min and also as impulses/100 cardiac beats to avoid any interference by the length of the cardiac cycle.12 The bursts of MSNA were identified by inspection when the signal-to-noise ratio was >3, and they were quantified in a similar manner. The
variability of measuring both s-MSNA and MSNA in this laboratory did not exceed 10%.10

Other assessments were performed independently and without knowledge of the results from the microneurography data. LVEF was determined using 2D echocardiography (Toshiba SSA-380A, Toshiba Corp). Briefly, left ventricular wall motion was visually assessed using a 9-segment model and graded as previously described in patients with myocardial infarction.13,14 The following scores were used: 3, hyperkinesia; 2, normokinesia; 1, hypokinesia; 0, akinesia; and –1, dyskinesia. Wall motion index was calculated by dividing the sum of the scores in each individual segment by 9; when multiplied by 0.3, this index gave the estimate of LVEF.

Statistics

One-way ANOVA with Newman-Keuls post-tests were used to compare data between patients and subjects and to test changes of data during follow-up in patients (repeated measures). The least square technique was used for assessing the linear relationship between variables. P<0.05 was considered statistically significant. Data are presented as mean±SEM.

Results

There were no significant differences between the AMI, normal, CAD, and NMI groups (Table 1) with respect to age, body weight, body mass index, or heart rate. There were no significant differences in the sex ratio between the 4 groups (χ²=2.25; P>0.5). AMI, CAD, and NMI patients had a lower arterial pressure than normal subjects. The mean LVEF in the AMI group was 52±2.4%, and the peak creatine kinase rise was 1348±198 IU/L.

During follow up, there were no changes in the therapeutic agents given. Also, no significant changes occurred in indices of body weight or arterial blood pressure (Table 2). There was a small but significant decrease in heart rate at 3 months, but this returned to baseline values at 6 months after AMI. All indices of sympathetic neural discharge significantly decreased (at least P<0.01) at 6 months relative to baseline values obtained 2 to 4 days after AMI (Table 2 and Figure). There was a trend for mean indices of sympathetic discharge per minute to decrease gradually during follow-up, although a significant decrease occurred only at 3 months after AMI relative to baseline values, reflecting the small decrease in heart rate at the same time. By accounting for the changes in heart rate, the mean frequency of activity per 100 beats did not change at 3 months but did significantly decrease thereafter (Table 2 and Figure).

The significant decrease in sympathetic activity at 6 months relative to baseline values and that occurring between 3 and 6 months after AMI did not significantly correlate to

<table>
<thead>
<tr>
<th>TABLE 2. Changes in Data of the 13 AMI Patients</th>
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<tbody>
<tr>
<td>2–4 Days</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td><strong>Body weight, kg</strong></td>
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<tr>
<td><strong>Body mass index, kg/m²</strong></td>
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<tr>
<td><strong>Heart rate, bpm</strong></td>
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<td><strong>Blood pressure, mm Hg</strong></td>
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<tr>
<td>Mean</td>
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<tr>
<td>Systolic</td>
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<tr>
<td>Diastolic</td>
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<tr>
<td><strong>s-MSNA, impulses/min</strong></td>
</tr>
<tr>
<td><strong>s-MSNA, impulses/100 beats</strong></td>
</tr>
<tr>
<td><strong>MSNA, bursts/min</strong></td>
</tr>
<tr>
<td><strong>MSNA, bursts/100 beats</strong></td>
</tr>
</tbody>
</table>

Values of s-MSNA (top) and MSNA (bottom) in the 13 patients with AMI during the initial 2 to 4 days, at 3 months (3m), and at 6 months (6m) after admission. Also shown are the corresponding values obtained in 13 matched normal subjects (NC), 13 patients with stable CAD, and 11 hospitalized patients without AMI (NMI). The height of the column indicates the mean value of the group, and the bars indicate SEM. Compared with data at 2 to 4 days, *P<0.001, †P<0.01. Compared with data at 3 months, ‡P<0.001, §P<0.01. Compared with data at 6 months, ||P<0.001, ¶P<0.01.
any changes in indices of arterial pressure or body mass index (respectively, at least \( r = 0.39, P > 0.18 \); \( r = -0.10, P > 0.70 \);
\( r = 0.31, P > 0.30 \); \( r = -0.34, P > 0.25 \)). However, the baseline values of all indices of sympathetic activity, obtained 2 to 4 days after AMI, showed an inverse correlation to LVEF (at least \( r = -0.65; P < 0.02 \)). In both the patients and the controls, there was a positive correlation with age (at least \( r = 0.58; P < 0.04 \)).

The indices of sympathetic activity in normal subjects were not significantly different from those in CAD or NMI patients, and all were smaller than the indices obtained during the 3 follow-up examinations in the AMI patients. Thus, values of \( s - \text{MSNA} \) in normal subjects of \( 36 \pm 2.8 \) impulses/min and \( 58 \pm 4.7 \) impulses/100 beats, in CAD patients of \( 35 \pm 1.4 \) impulses/min and \( 61 \pm 2.2 \) impulses/100 beats, and in NMI patients of \( 37 \pm 2.1 \) impulses/min and \( 61 \pm 3.3 \) impulses/100 beats were significantly less than all values obtained in AMI patients (at least \( P < 0.05 \)). Similarly, values of multiunit MSNA in normal subjects of \( 32 \pm 2.4 \) bursts/min and \( 51 \pm 3.9 \) bursts/100 beats, in CAD patients of \( 33 \pm 1.3 \) bursts/min and \( 56 \pm 2.2 \) bursts/100 beats, and in NMI patients of \( 33 \pm 2.0 \) bursts/min and \( 55 \pm 3.6 \) bursts/100 beats were significantly less than all values obtained in the AMI patients (at least \( P < 0.05 \)).

**Discussion**

The present investigation has shown for the first time that uncomplicated AMI is associated with a protracted sympathetic neural hyperactivity. This sympathetic hyperactivity was inversely related to LVEF and was not significantly related to changes in arterial blood pressure or body weight. These findings suggest that the increase of sympathetic neural discharge in AMI may involve mechanisms related to central and reflex control from cardiac receptors.

The sympathetic hyperactivity after AMI was found both in single-unit activity and in multiunit bursts. The multiunit bursts have been used to provide an estimate of the function of sympathetic activity representing a number of different firing units. This allows the assessment of changes in sympathetic neural output, which include fiber recruitment arising from central or reflex effects and also an insight into the overall effect of different units. The single-unit activity seems to provide a more quantitative estimation of central sympathetic discharge, because it allows an estimate of the mean firing frequency of any single unit\(^{10,11,15} \) and is obtained objectively.\(^{10,15} \) This contention has been used to infer a central sympathetic hyperactivity in early hypertension when the proportion of single-unit hyperactivity was greater than that of multiunit bursts.\(^{19} \) In the present study, the magnitude of single-unit hyperactivity relative to normal values was similar to that of multiunit bursts, perhaps suggesting that the mechanism of increased sympathetic output involved peripheral reflex effects.

To avoid interference by confounding factors, only white subjects were examined because race can affect responses of MSNA.\(^{16} \) Also, assessments were undertaken within the same controlled laboratory conditions while avoiding the known effects on sympathetic activity of age, body weight, time of day, dietary sodium intake, large meal and visceral distension, alcohol, nicotine, and exercise.\(^{17–24} \) These criteria were satisfied both by closely matching the study and the control groups and when determining changes in the same patients. There were, however, some differences regarding the cross-sectional analysis between the AMI, normal, CAD, and NMI groups. For instance, all the AMI and CAD patients required \( \beta \)-blocker or ACE inhibitor therapy, which resulted in a slightly lower heart rate and arterial pressure than the normal subjects. None of these would unequivocally explain the sympathetic hyperactivity in the AMI patients. Acute intravenous administration of \( \beta \)-blocking agents has been reported to increase MSNA in hypertensive subjects\(^{25} \) but not in normal subjects.\(^{26} \) However, all our patients were given oral therapy at least 1 to 3 days before the studies. Chronic administration of \( \beta \)-blocking agents has been reported to decrease MSNA in hypertensive subjects\(^{25} \) but not in patients with congestive heart failure.\(^{27} \) Also, chronic ACE inhibitor therapy has been reported not to affect MSNA in hypertensive subjects\(^{28,29} \) but to decrease it in patients with congestive heart failure.\(^{30} \) The effects of these drugs on MSNA in AMI and CAD are unknown, but they are unlikely to have caused the sympathetic hyperactivity after AMI because the hyperactivity occurred early, persisted at 3 months, and decreased only at 6 months despite continuing with the same therapy. In addition, the sympathetic activity in the CAD group was similar to that in the normal group despite \( \beta \)-blocker therapy.

The new findings of the present study of protracted sympathetic neural hyperactivity have important implications. This may provide an explanation for the delayed cardiovascular morbidity and mortality after AMI. Furthermore, our findings make it possible to suggest a mechanism for this protracted sympathetic hyperactivity. The changes in sympathetic hyperactivity could not be related to an effect of arterial blood pressure because this did not significantly change during the follow-up period and there was no significant correlation between arterial pressure and sympathetic activity. Although this does not completely exclude an influence of baroreceptor reflexes, our findings contain information that indicates that cardiac reflexes may be involved. Evidence in support of the latter is our finding that the magnitude of sympathetic hyperactivity was greater in patients with lower values of LVEF. There have also been reports showing that cardiac sympathetic output, as assessed by norepinephrine spillover rate, is increased in unstable angina, in left ventricular dysfunction after ventricular arrhythmias, and during exercise-induced myocardial ischemia but is normal in patients with stable CAD.\(^{31–33} \) Indeed, plasma norepinephrine levels have been found to be greatly raised in patients with AMI who developed left ventricular failure.\(^{2} \) When taken together, these findings suggest an association between sympathetic hyperactivity and cardiac receptors. It has been shown that myocardial infarction may lead to impairment of reflexes from receptors in the heart,\(^{34} \) which are known to inhibit efferent sympathetic activity.\(^{35} \)

In conclusion, it was shown for the first time that central sympathetic hyperactivity occurs after AMI and that, despite an absence of complications, this hyperactivity remains for months before returning toward normal values. It is suggested that the mechanism of this sympathetic hyperactivity may at
least in part involve impairment of reflexes from cardiac receptors.

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References
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