

Sympathetic Drive in Anterior and Inferior Uncomplicated Acute Myocardial Infarction

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Background—The sympathetic activation that follows acute myocardial infarction (AMI) has been associated with increased morbidity and mortality. Because the prognosis after anterior AMI (ant-AMI) is worse than that after inferior AMI (inf-AMI), we planned to determine whether the magnitude of sympathetic hyperactivity differs between the two.

Methods and Results—Thirty-nine patients with uncomplicated AMI, comprising 2 matched groups of 17 patients with ant-AMI, and 22 patients with inf-AMI were examined. Measurements were obtained 2 to 4 days after AMI and compared with 20 normal subjects (NC) who were matched in terms of age and body weight to the AMI groups. Resting muscle sympathetic nerve activity was quantified from multiunit bursts (MSNA) and from single units (s-MSNA). Both groups of AMI patients were matched with regard to hemodynamic variables, left ventricular function, and infarct size. Both groups had greater (at least $P<0.01$) sympathetic nerve activity than NC (60±4.3 bursts/100 cardiac beats and 68±4.9 impulses/100 cardiac beats), but the magnitude of sympathetic nerve hyperactivity in ant-AMI (81±4.0 bursts/100 cardiac beats and 91±4.9 impulses/100 cardiac beats) was similar ($P>0.05$) to that in inf-AMI (80±3.2 bursts/100 cardiac beats and 90±4.0 impulses/100 cardiac beats).

Conclusions—Both ant-AMI and inf-AMI resulted primarily in a similar magnitude of sympathetic nerve hyperactivity. These findings suggest that the worse prognosis after ant-AMI compared with after inf-AMI would not be related primarily to the degree of sympathetic hyperactivity. (Circulation. 2004;109:2285-2289.)

Key Words: nervous system, sympathetic ⋅ myocardial infarction ⋅ action potentials

Sympathetic hyperactivity has been shown to occur early after acute myocardial infarction (AMI), although very little is known about whether its magnitude differs between anterior wall (ant-AMI) and inferior wall (inf-AMI) infarction. This information is important because it may be relevant to the prognosis after AMI and to the mechanisms of associated sympathetic activation.

Adverse prognosis after AMI has been associated with factors such as advanced age, larger infarcts, and left ventricular systolic dysfunction, conditions in which a disproportionate sympathetic activation is known to occur. However, although the prognosis after ant-AMI is poorer than after inf-AMI, it is as yet unknown whether sympathetic nerve hyperactivity occurs to a greater extent in the former than the latter. The only available information has been derived from experimental studies in animals. For instance, after the demonstration of a sympatho-sympathetic cardiac reflex, other reports have reported that excitation of left ventricular sympathetic afferents is a significant mechanism leading to sympathetic activation after acute myocardial ischemia and infarction. These afferents are evenly distributed in the walls of the left ventricle, such that their excitation at any site causes similar reflex efferent sympathetic activation. Indeed, in humans, plasma norepinephrine levels have been reported to increase to a similar extent in patients who sustain either an ant-AMI or inf-AMI. However, plasma norepinephrine levels are a crude estimate of sympathetic output and there are no available data from direct measurements of sympathetic nerve activity.

The present investigation was therefore designed to determine whether the magnitude of sympathetic nerve hyperactivity early after ant-AMI is different from that after inf-AMI. For this purpose, we quantified sympathetic nerve hyperactivity relative to normal controls in 2 groups of patients within 4 days of sustaining ant-AMI or inf-AMI who were closely matched in terms of age, body weight, left ventricular systolic function, and peak cardiac enzyme levels.

Methods

Subjects
A total of 59 white subjects were examined (Table). They comprised 39 patients who had uncomplicated AMI, 17 with ant-AMI and 22 with inf-AMI. In addition, 20 normal control subjects (NC) were examined. All patients were screened by history, physical, and laboratory examination. They were excluded if there was a history of previous myocardial infarction, hypertension, diabetes, or other
chronic disease that might influence the autonomic nervous system. Patients with evidence of arrhythmia, conduction abnormalities, heart failure, or cardiogenic shock were also excluded.

AMI was confirmed by the following criteria: (1) a clinical history of ischemic-type chest pain, (2) changes on serially obtained ECGs, and (3) a rise in serum creatine kinase (CK) levels to >400 IU/L and their subsequent fall. The location of the infarct was obtained from analysis of the ECG according to the Minnesota code and was subsequently confirmed by the finding of a regional wall motion abnormality with 2D echocardiography and by coronary angiography and left ventriculography. In all patients, coronary artery disease was confirmed by both exercise treadmill testing and coronary angiography. A positive exercise test was defined by horizontal ST-segment depression of at least 2 mm during exercise with associated chest pain. Coronary angiography demonstrated significant coronary artery disease in these patients (>70% stenosis of at least 1 major epicardial coronary artery).

All 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) of <40% as determined by echocardiography. Patients with ant-AMI and inf-AMI received conventional therapy in the form of thrombolysis (n=15 and 21), β-blockers (n=15 and 18), and ACE inhibitors (n=13 and 15). None had undergone any revascularization procedure. The 2 groups, respectively, had single-vessel disease (n=10 and 14), 2-vessel disease (n=4 and 7), and 3-vessel disease (n=3 and 1). The investigation was performed with the approval of St James’s University Hospital Ethics Committee, and all subjects provided informed written consent.

**General Protocol**

Sympathetic activity in AMI patients was assessed at 2 to 4 days after admission. The same protocol was performed between the hours of 9:00 AM and 12:00 noon for all groups as previously reported.4 Subjects were asked to have a light breakfast and to empty their bladder before commencing the study and were requested to avoid alcohol, nicotine, and caffeine products for 12 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 with a standard mercury sphygmomanometer. Heart rate and arterial blood pressure were monitored and recorded with a standard ECG and a Finapres device, and blood flow to the muscle of the left calf was obtained by use of standard strain-gauge plethysmography.

**Microneurography**

Postganglionic muscle sympathetic nerve activity (MSNA) was recorded from the right peroneal nerve for 5 minutes after subjects had attained steady state for at least 30 minutes with regard to measured variables as previously described.4 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, 0.1 second). 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 per second and other data channels at 2000 samples per second (8 bits).

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.24,25 Only vasocostructor units were accepted and examined, the criteria of acceptance being appropriate responses to spontaneous changes in arterial blood pressure, the Valsalva maneuver, and isometric handgrip exercise. Simultaneous measurement of calf vascular resistance confirmed the vasocostructor 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 with a dynamometer, produced a late increase in arterial blood pressure and sympathetic neural activity.
An electronic discriminator was used objectively to count the spikes of s-MSNA and 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. The bursts of MSNA were identified by inspection when the signal-to-noise ratio was >3 and were quantified in a similar manner. The variability of measuring both s-MSNA and MSNA in this laboratory did not exceed 10%. LVEF was determined by 2D echocardiography (Toshiba SSA-380A, Toshiba Corp). Briefly, left ventricular wall motion was assessed visually by use of a 9-segment model and graded as previously described in patients with myocardial infarction. The following scores were used: 3 for hyperkinesia, 2 for normokinesia, 1 for hypokinesia, 0 for akinesia, and −1 for dyskinesia. Wall motion index was calculated by dividing the sum of the scores in each individual segment by 9. Wall motion index multiplied by 0.3 gave the estimate of LVEF.

Statistics
One-way ANOVA with Newman-Keuls post hoc tests was used to compare data between the 3 groups of subjects. Student’s t test was used to compare unpaired data available only in patients with anti-AMI and inf-AMI. The least-squares technique was used for assessing the linear relationship between variables. Values of P<0.05 were considered statistically significant. Data are presented as mean±SEM.

Results
The 3 groups of subjects were not significantly different with regard to age, body weight, body mass index, or heart rate (Table). Also, there were no significant differences in the gender ratio between the 3 groups (χ²=0.58; P>0.1). The indices of arterial blood pressure in ant-AMI were similar to those with inf-AMI, although as expected, they were lower in the 2 AMI groups than in NC. There were also no significant differences between ant-AMI and inf-AMI with regard to LVEF or peak CK levels (Table).

All indices of sympathetic nerve activity were significantly greater in ant-AMI and inf-AMI than in NC. However, all indices of sympathetic activity in ant-AMI were similar to those in inf-AMI (Table; Figure). In both of the AMI groups, there was a significant negative correlation between indices of sympathetic activity and LVEF (at least r=-0.45, P<0.02), although there was no correlation between sympathetic activity and peak CK levels (at least r=0.06; P>0.40).

In each of the 3 groups, the indices of sympathetic nerve activity were positively correlated to age (at least r=0.59; P<0.008) but not to indices of arterial blood pressure (at least r=0.34; P>0.07).

Discussion
The present investigation has shown for the first time that the site of infarction does not affect the magnitude of sympathetic nerve hyperactivity seen 2 to 4 days after uncomplicated AMI. These findings indicate that sympathetic nerve hyperactivity alone would not primarily account for the poorer prognosis observed after ant-AMI compared with inf-AMI. Furthermore, the findings are consistent with the proposals that the mechanism of efferent sympathetic hyperactivity to the periphery after AMI involves excitation of ventricular sympathetic afferents, which are evenly distributed within the walls of the left ventricle.

Although MSNA is limited to exploring efferent peripheral discharge, our findings that both groups of AMI had greater sympathetic activity than normal controls is consistent with previous reports using different techniques, showing sympathetic activation early after AMI. All 3 groups in the present study were examined under the same laboratory conditions to avoid confounding influences related to circadian variation, alcohol, visceral distension, and a large meal. In addition, all groups were closely matched to avoid confounding factors such as age, gender, race, body weight, and heart rate. Unavoidably, the 2 groups with AMI were receiving β-blocker or ACE inhibitor therapy and as a result had a slightly lower arterial pressure than the NC subjects. However, we found no correlation between sympathetic nerve activity and indices of arterial pressure as previously reported in other clinical conditions, supporting the proposal that sympathetic excitation was independent of baroreceptor reflex function. Also, we have previously shown that the sympathetic hyperactivity early after AMI persisted for at least 3 months despite normalization of arterial pressure. With regard to therapy, it has been reported in patients with heart failure that ACE inhibitors decrease sympathetic nerve activity and that β-blockers have no effect on MSNA.
Also, we have previously shown that after AMI, MSNA was greater than in control groups receiving the same therapeutic agents, including patients with stable coronary artery disease and patients hospitalized with chest pain in whom AMI was excluded. These treated control groups had the same level of MSNA as that in untreated matched controls. These considerations make it likely that no single factor other than AMI could have resulted in the observed sympathetic hyperactivity.

With regard to the site of the infarct, our findings were obtained 2 to 4 days after AMI, at a time when patients had no discernible clinical complications and their LVEF was >40%. Both groups were closely matched to avoid interfering effects on sympathetic nerve activity by factors including arterial pressure, peak serum CK levels, and degree of left ventricular dysfunction. In addition, both groups received similar therapy. Such considerations make it unlikely that confounding factors would have unequivocally explained the similarity of the magnitude of sympathetic hyperactivity between ant-AMI and inf-AMI.

Our findings have implications with regard to the mechanism of the sympathetic nerve hyperactivity observed after AMI. One of the postulated mechanisms of sympathetic activation after acute myocardial ischemia or infarction has involved chemical activation or impairment of sympathetic or vagal afferents, respectively, and their interaction. There has been experimental evidence showing that sympathetic afferents are evenly distributed throughout the anterior and inferoposterior walls of the left ventricle and that their activation by chemicals or ischemia in any of these locations leads to a similar reflex sympathetic activation. In contrast, the chemosensitive vagal afferents, the excitation of which leads to sympathetic inhibition, are located primarily in the inferoposterior walls of the left ventricle.

Reports in humans seem to support the view that excitation of ventricular sympathetic afferents is the predominant mechanism of efferent sympathetic activation after AMI. For instance, plasma norepinephrine levels increase to a similar extent in patients developing either ant-AMI or inf-AMI. Within the first hours of developing infarction, excessive vagal discharge has been related to bradyarrhythmia and sudden death that occur in the case of posterior AMI. Using changes in heart rate and arterial pressure that occurred within 1 hour after the onset of posterior AMI, a predominance of parasympathetic effects was found to occur early, whereas sympathetic predominance occurred late within the hour after ant-AMI. In addition, sympathetic activation and diminished vagal modulation of the heart period have been reported 3 hours after ant-AMI and inf-AMI, although they occurred to a greater extent in ant-AMI. Taken together, these reports indicate that any vagal overactivity and its confounding effect on sympathetic activation was short-lasting. The present study was therefore conducted 2 to 4 days after AMI, with the patients in a stable condition, to avoid the volatile phase of autonomic disturbance very early after infarction and also any other confounding factors that might interfere with the sympathetic drive, such as the complications of arrhythmia and heart failure. Our finding in each of the 2 AMI groups of an inverse correlation between sympathetic hyperactivity and LVEF is consistent with a predominant effect of excitation of sympathetic over vagal afferents, because the former leads to efferent sympathetic activation, whereas the latter leads to sympathetic inhibition. These considerations make it possible to propose that the efferent sympathetic activation after AMI has involved excitation of ventricular sympathetic afferents.

The other implications of the present study relate to reported factors that may potentially result in a greater mortality and morbidity in association with ant-AMI than with inf-AMI. These factors have included age, extent of left ventricular dysfunction, infarct size, and development of heart failure. It is notable that most of these factors result in sympathetic activation, which in turn is believed to lead to an adverse outcome. In addition, it is known that the increased mortality associated with ant-AMI occurs during the first few hours after the onset of infarction. However, both AMI groups in the present study were clinically stable, had no complications, and were matched for confounding factors, particularly LVEF and peak CK levels.

In conclusion, the findings of the present study indicate that the magnitude of sympathetic nerve hyperactivity seen 2 to 4 days after uncomplicated AMI is similar between ant-AMI and inf-AMI. The findings suggest that excitation of the evenly distributed sympathetic afferents within the left ventricle constitute an important mechanism for efferent sympathetic activation.

Acknowledgments
This work was funded by the British Heart Foundation (grant FS/2000069). The authors thank J. Bannister, J. Corrigan, and G. McGawley for technical assistance.

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Circulation. 2004;109:2285-2289; originally published online April 26, 2004;
doi: 10.1161/01.CIR.0000129252.96341.8B
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2004 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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