Serial Determination of Plasma Catecholamines in Myocardial Infarction

By Jørgen Videbaek, M.D., Niels Juel Christensen, M.D., and Bent Sterndorff, M.D.

SUMMARY
By the use of a precise and sensitive double-isotope derivative technic, plasma catecholamine concentration was measured at 2-hour intervals in 10 patients during the first 48 hours of myocardial infarction.

Plasma catecholamine concentration was elevated in most patients, but to an extremely variable degree. In each patient, however, the values were rather stable during the study period. High levels of plasma catecholamines were correlated to the clinical state of the patients. Patients who received antiarrhythmic treatment on admission to the hospital had higher values than untreated patients. There was no temporal correlation between plasma catecholamine concentration and ventricular arrhythmias. In contrast to the plasma catecholamine level, the heterotopic ventricular activity declined spontaneously in the untreated patients within the study period.

It is emphasized that the plasma catecholamine concentration in patients with acute myocardial infarction is considerably lower than the level necessary to produce arrhythmias in experimental myocardial infarction.

Additional Indexing Words:
Plasma epinephrine
Plasma norepinephrine
Heart failure
Ventricular ectopic beat
Double-isotope technic
Ventricular tachycardia

It is generally accepted that the urinary excretion of catecholamines1-6 and the plasma catecholamine levels7-10 are elevated in most patients during the acute stage of myocardial infarction.

A high level of catecholamines appears to be associated with the clinical state of the patient, and especially with heart failure.4-10 Catecholamine excretion is also elevated in congestive heart failure unrelated to myocardial infarction.11

Studies of urinary catecholamine excretion have shown that arrhythmias occur most frequently in patients with high excretion rates.4-6 Such patients, in addition, often show varying degrees of heart failure. However, McDonald et al.8 found raised norepinephrine levels in patients with early ventricular arrhythmias independent of the presence or absence of pulmonary venous congestion. Siggers et al.9 found a relationship only between peak levels of epinephrine and ventricular arrhythmias but not with mean values of norepinephrine and epinephrine, nor with peak norepinephrine levels.

The aforementioned studies are based on estimations of urinary excretion of catecholamines or a few plasma determinations in the individual patients within the first 1 or 2 days of myocardial infarction where significant arrhythmias are likely to occur.

More information about the role of elevated plasma catecholamine levels in the development of cardiac arrhythmias might be obtained by studying more closely the temporal
relationship between the degree of arrhythmias and the plasma catecholamine level. Serial determinations of plasma catecholamines cannot be performed using fluorimetric methods, as large amounts of blood have to be collected each time.

These problems regarding plasma catecholamine methodology have recently been overcome by the introduction of a sensitive and precise double-isotope derivative technic for the determination of the total plasma catecholamine concentration as well as norepinephrine and epinephrine separately.\textsuperscript{12}

We have studied the relationship between ventricular arrhythmias as evaluated by continuous monitoring of the electrocardiogram and the plasma catecholamine concentration measured at 2-hour intervals during the first 48 hours of myocardial infarction.

**Patients**

Ten patients with acute myocardial infarction, five control patients, and eight normal subjects were studied. The selection of the patients with myocardial infarction was based on the following criteria: (1) a history of classical myocardial infarction of less than 12-hours duration, with a well-defined onset; (2) an ECG pattern unmistakably compatible with acute myocardial infarction; and (3) none of the patients had, prior to the admission, taken drugs which are known to influence the autonomic nervous system, and none of them had shown diabetes mellitus or systemic hypertension.

Control patients were admitted with precordial pain within 12 hours after the onset of pain. The initial electrocardiograms were normal and remained so, and subsequent studies excluded the presence of angina pectoris and myocardial infarction.

All the normal subjects enjoyed good health, and none had cardiopulmonary complaints.

**Methods**

The patients with myocardial infarction and the control patients with chest pain were admitted to a coronary care unit. A bipolar precordial ECG lead was continuously monitored, and simultaneously the ECG signal was shown in the control room and stored on magnetic tape. Later, by replaying the tape, supraventricular, junctional, and ventricular extrasystolic beats were counted in ½-hour periods. Runs of ventricular tachycardia were noted when at least 10 abnormal QRS complexes in succession were observed in connection with A-V dissociation and a ventricular rate greater than that of the atrial rate. Furthermore, we noted the time when P-Q changes emerged, either in the form of increasing block or wandering pacemaker. None of the patients had atrial flutter or fibrillation.

The blood pressure was measured with the indirect auscultatory method, and the heart rate was read on a tachometer and continuously recorded.

The clinical state of the patients with myocardial infarction was evaluated by a cardiologist who had no knowledge of the results of the plasma catecholamine determination. The assessment was based (1) on the magnitude of the infarction as judged from the ECG and enzyme analysis, and (2) on the presence or absence of clinical signs of heart failure.

Six milliliters of blood was collected every second hour in the patients with myocardial infarction and in the control subjects through an indwelling catheter inserted via the vena basilica to the superior vena cava. All the patients rested in the supine position throughout the investigation period. The exact time of drug administration was recorded.

In the normal subjects a blood sample was taken in the morning after a fast of at least 8 hours. The subjects were not allowed to leave their beds before the experiments. Smoking was prohibited, but fluid intake was not limited. Blood was collected from an antecubital vein via an indwelling catheter, and at least 15 min elapsed between the time when the catheter was inserted and the withdrawal of venous blood.

For the measurement of the total plasma catecholamine concentration, i.e. the sum of norepinephrine and epinephrine, and for the separate determinations of these two catecholamines, the double-isotope derivative technic described by Engelman and Portnoy\textsuperscript{12} was employed with minor modifications.

This method permits the determination of the plasma catecholamine content in a sample without the use of standard solutions. In order to insure continuous control of the method we have, however, included in each analysis one or two samples containing a known amount of catecholamine: 0.8 ng/ml of norepinephrine for the determination of the total plasma catecholamine concentration and 0.6 ng/ml of both norepinephrine and epinephrine for separate determination. Ten-milliliter aliquots of the samples were used in these determinations.

The precision of the method was calculated on the basis of 19 double determinations performed on 19 consecutive days. The samples contained 0.8 ng/ml of norepinephrine, and 10 ml of this sample was used in each analysis. The standard
deviation of the single determination was ± 0.03 or 4%. The mean recovery was 99 ± 8% (sd of the single recovery).

In the present study considerably less than 10 ml of plasma was used in most cases for the total plasma catecholamine determination (3 ml). For this reason the precision of the method was evaluated at lower concentrations by analysis of eight standard solutions with a total norepinephrine content of 2.40 ng and eight standard solutions of 4.80 ng of norepinephrine. These amounts of norepinephrine may alternatively be looked upon as 10-ml aliquots of samples containing 0.24 and 0.48 ng/ml, respectively, or 3-ml samples containing 0.80 and 1.60 ng/ml, respectively. The results are presented in figure 1. It appears that the estimated concentration equals the expected, with a reasonable small variance.

Twenty-four-hour urinary excretion of norepinephrine and epinephrine was measured in eight of the patients with myocardial infarction employing the fluorometric method of Lund.13

Other laboratory determinations included hemoglobin, sedimentation rate, serum creatinine, white cell count, electrolytes, plasma glucose, glutamic oxaloacetic transaminase, and lactic acid dehydrogenase.

Results

The mean plasma catecholamine value obtained in the group of normal subjects was 0.23 ng/ml. The upper 95% confidence limit was 0.40 ng/ml in accordance with previous findings.14 There were four males, four females, and the mean age was 55.8 years (range 46–75 years). No correlation was obtained between the plasma catecholamine concentration and age. In four of the subjects norepinephrine and epinephrine were measured separately and averaged 0.21 and 0.04 ng/ml, respectively.

Pertinent clinical and laboratory data from the two groups of monitored patients are given in table 1. It is evident that all of the infarction patients showed typical laboratory findings of myocardial infarction. The S-T values represent the average of the numerical sum of the S-T segment deviation in leads I and III. All infarctions were transmural; two patients had posterior wall infarctions with BBB, two had posterior inferior wall infarctions, three had anterior septal infarctions, and three had anterior wall infarctions.

Table 1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>AMI</th>
<th>Controls (with chest pain)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>8/2</td>
<td>5/0</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>60.4</td>
<td>48–75</td>
</tr>
<tr>
<td>S-T&lt;sub&gt;i+III&lt;/sub&gt; (mv)</td>
<td>0.197</td>
<td>0.01–0.60</td>
</tr>
<tr>
<td>GOT&lt;sub&gt;max&lt;/sub&gt; units</td>
<td>276</td>
<td>139–381</td>
</tr>
<tr>
<td>LDH&lt;sub&gt;max&lt;/sub&gt; units</td>
<td>1318</td>
<td>825–2150</td>
</tr>
<tr>
<td>White cell (μliter)</td>
<td>15130</td>
<td>9000–21000</td>
</tr>
<tr>
<td>Plasma glucose (mg/100 ml)</td>
<td>162.7</td>
<td>132–211</td>
</tr>
</tbody>
</table>

Abbreviations: AMI = acute myocardial infarction; S-T<sub>i+III</sub> = numerical sum of S-T deviation in standard ECG; GOT = glutamic oxaloacetic transaminase; LDH = lactic acid dehydrogenase.

Circulation, Volume XLVI, November 1972
Figure 2 shows the plasma catecholamine curves in the individual infarction patients, controls, and normal subjects. There was a great scatter in the plasma catecholamine levels in the different patients with myocardial infarction, but in each patient the values were rather stable within the 48-hour study period. The catecholamine values in the control subjects with chest pain were slightly outside the upper normal range, with a tendency to lower values in the latter part of the study period.

Table 2 presents the mean values of plasma catecholamines obtained from the patients with myocardial infarction during the first 24 hours, as well as the mean values obtained in the controls and in the normal group. The plasma catecholamine concentrations are significantly higher in the controls than in the normal subjects (Student's t test, P < 0.001).

![Figure 2]

*Results of serial determinations of plasma catecholamines in 10 patients with acute myocardial infarction (upper curve) and in control subjects with chest pain (lower curve). The shaded area denotes the 95% range in the normal group.*
Table 2

Mean Plasma Catecholamine Values in Different Groups of Patients during First 24 Hours after Onset of AMI

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Mean (ng/ml)</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Normal</td>
<td>8</td>
<td>0.23</td>
<td>0.08</td>
</tr>
<tr>
<td>2. Control (with chest pain)</td>
<td>5</td>
<td>0.53</td>
<td>0.11</td>
</tr>
<tr>
<td>3. AMI without antiarrhythmic treatment</td>
<td>6</td>
<td>1.00</td>
<td>0.45</td>
</tr>
<tr>
<td>4. AMI, with antiarrhythmic treatment</td>
<td>3</td>
<td>2.07</td>
<td>0.50</td>
</tr>
</tbody>
</table>

Abbreviations: AMI = acute myocardial infarction.

The infarction patients have been divided into two subgroups according to whether they received treatment with antiarrhythmic drugs. Six patients did not receive such treatment and exhibited a mean plasma catecholamine value of 1.00 ng/ml. With one exception, these

Figure 3

The temporal relationship between the plasma catecholamine concentration in the individual patients with myocardial infarction who did not receive antiarrhythmic treatment during the first 24 hours after admission to hospital, and the number of ectopic ventricular beats counted at ½-hour periods. Black columns: untreated period. Hatched columns: treatment with lidocaine. Arrows indicate runs of ventricular tachycardia.
patients had mean plasma catecholamine levels exceeding the highest value observed in the controls. The mean values in the controls and in the patients with myocardial infarction who did not receive antiarrhythmic treatment on admission to the hospital differ significantly (median test by chi-square, \( P < 0.05 \)).

Three patients received treatment with lidocaine immediately after admission to the hospital, because of serious arrhythmias. The mean plasma catecholamine level was 2.07 ng/ml, and all patients exhibited mean values above the 99.9% confidence limit of the controls and of the normal subjects. The mean value is also significantly higher than the corresponding value in the untreated group of patients (Student's \( t \) test, \( P < 0.02 \)). One patient could not be satisfactorily classified into one of these groups due to intermittent treatment. This patient had a mean plasma catecholamine concentration of 0.94 ng/ml.

Figures 3 and 4 show the temporal relationship in the individual infarction patients between plasma catecholamines and the number of ventricular ectopic beats counted at 30-min intervals. All of the untreated patients (fig. 3) exhibited a moderate number of ventricular ectopic beats. It appears from figure 3 that there is no correlation nor even a tendency toward correlation between the degree of ectopic ventricular activity and the plasma catecholamines. It is striking that the heterotopic activity disappeared almost completely in one patient (upper left curve) while the plasma catecholamine concentration remained rather high and unchanged. Another patient (middle upper curve) developed a short period of ventricular tachycardia despite plasma catecholamine values within normal range. It should be emphasized that serum potassium, calcium, and blood gases were also normal in this patient.

Figure 4 shows corresponding values in the lidocaine-treated group of subjects. It was not possible, of course, to analyze the relationship between the degree of arrhythmia and plasma catecholamines in these patients. It might be mentioned, however, that in one patient (upper right curve) the arrhythmias did not reappear when lidocaine treatment was discontinued after approximately 24 hours despite an unchanged and rather high level of plasma catecholamines.
Figure 5 shows the mean values of plasma catecholamines and the number of ectopic ventricular beats in the untreated group of patients (excluding a patient who received treatment after approximately 20 hours and a patient with idiopathic ventricular rhythm with a frequency of about 70 beats/min). The figure clearly shows the spontaneous fall in heterotopic arrhythmic activity during the first 24–48 hours of myocardial infarction, in contrast to the nearly constant and elevated mean level of plasma catecholamines.

Figure 6 shows the correlation between the clinical state of the patients evaluated as described above and the peak plasma catecholamine concentration ($P < 0.01$). A significant correlation was also obtained when the mean plasma catecholamine values were employed ($P < 0.05$).

There was no correlation between mean plasma catecholamine concentration and the urinary excretion of catecholamines. This was obviously due to one patient who exhibited a mean plasma catecholamine level above 2 ng/ml but a very low urinary excretion. The urinary concentration of catecholamine was high, but the diuresis is only 250 ml/24 hours. A significant correlation was obtained between the urinary concentration of catecholamine and mean plasma catecholamine concentration ($P < 0.05$).

In five of the six patients who had not received antiarrhythmic treatment on admission to hospital, plasma norepinephrine and epinephrine were measured separately from one or two of the samples obtained during the 48 hours. The plasma epinephrine averaged 0.03 ng/ml while plasma norepinephrine was 0.88 ng/ml. The mean urinary excretion of epinephrine in these patients was 2 μg/24 hours.

Separate determinations of plasma epinephrine and norepinephrine were available only in one of the three patients who had received antiarrhythmic treatment on admission to the hospital. Plasma epinephrine and norepinephrine were 0.21 and 2.02 ng/ml, respectively. In another patient belonging to this group urinary excretion of epinephrine was 38 μg/24 hours.

These data, although very limited, suggest that the epinephrine concentration was elevated in patients with the highest catecholamine concentrations. In one of the control subjects with chest pain several determinations of both epinephrine and norepinephrine were performed. The norepinephrine concentration averaged 0.53 ng/ml and the epinephrine concentration, 0.05 ng/ml.

**Discussion**

The present study differs from previous
studies in this field in the way that catecholamine determinations were performed at short intervals in the first 48 hours of acute myocardial infarction. Furthermore, in the individual patients a detailed analysis of the temporal relationship between plasma catecholamines and the degree of arrhythmias was carried out.

In accordance with earlier studies of plasma catecholamines in acute myocardial infarction,7-10 we found a correlation between the clinical state of the patients and the plasma catecholamine concentration. This result is also indirectly in agreement with results of analysis of urinary excretion of catecholamines in such patients.4-6

The significance of plasma catecholamines in the genesis of heterotopic ventricular activity in acute myocardial infarction is difficult to settle. Studies of urinary catecholamine excretion have shown that arrhythmias occur more frequently in patients with high excretion rates.4-6 Unfortunately, these patients are also those with more severe degree of myocardial damage. The established correlation between elevated urinary catecholamine excretion and arrhythmias might be an expression of a more severe state of the disease in the patients rather than an expression of a causal relationship.15 However, McDonald et al.9 obtained results suggesting an arrhythmogenic activity of circulating catecholamines unrelated to the presence of pulmonary venous congestion. Siggers et al.9 found a relationship only between peak levels of epinephrine and ventricular arrhythmias, but not with mean levels of epinephrine and norepinephrine, nor with peak levels of norepinephrine.

Our study is consistent with previous studies of urinary catecholamines and plasma catecholamines in the way that patients in whom antiarrhythmic treatment was considered a necessity on admission to the hospital showed significantly higher values of plasma catecholamines than the patients who did not receive antiarrhythmic treatment. However, our results do not support the hypothesis that elevated plasma catecholamines are of major importance in the development of heterotopic ventricular activity in acute myocardial infarction.

This opinion is based, (1) on the absence of a correlation or a tendency toward correlation in the individual untreated patients between heterotopic ventricular activity and serial determinations of plasma catecholamines (fig. 3).

(2) It is evident that that there is a different time course of plasma catecholamines, which is fairly stable within the experimental period, and the heterotopic activity, which is reduced spontaneously in the same period of time. The shape of the curves in figure 5 is in accordance with the general impression gained from previous studies, although based on results obtained in few patients. The spontaneous fall in heterotopic activity during the first 24-48 hours of acute myocardial infarction has been reported in animal experiments16, 17 as well as in clinical studies.18-20 A fairly constant mean level of plasma catecholamines during the first 5 days of acute myocardial infarction was reported by Siggers et al.9 However, Griffiths et al.10 reported a gradual fall in mean plasma norepinephrine concentration during the first 24 hours of acute myocardial infarction. In none of these studies were data obtained in the individual patients presented. Almost every patient with acute myocardial infarction shows some degree of arrhythmia when examined by continuous monitoring. In our opinion, the degree of arrhythmias in our untreated group of patients was of such magnitude that a correlation or a tendency toward correlation between plasma catecholamines and arrhythmias should have appeared if it existed.

(3) We would like to emphasize that the dose of catecholamines which can induce arrhythmias in experimental myocardial infarction is considerably above the plasma concentrations found in our patients. The maximum value we observed was approximately 3 ng/ml plasma corresponding to an estimated infusion rate of 0.3 μg/kg/min (or 0.0016 μM/kg/min21), a dose which is very
unlikely to produce arrhythmias in experimental myocardial infarction. Szekereres and Papp have shown that infusion of 1 µg/kg/min of epinephrine or norepinephrine did not change the fibrillation threshold in dog hearts.

We are aware of the fact that the blood samples were taken from the superior vena cava and not from the arterial system. The arterial-venous difference in the upper extremity is, however, very small. Data have shown that the arteriovenous difference in the upper extremity and in the brain is insignificant even at high plasma catecholamine concentrations obtained during vigorous exercise (Trap-Jensen J, Christensen NJ: Unpublished data).

Both epinephrine and norepinephrine appear to be elevated in acute myocardial infarction although McDonald found no increase in plasma epinephrine, and Gazes et al. observed elevated epinephrine values in only seven of 13 patients, all of whom demonstrated elevated norepinephrine concentrations. Siggers et al. observed elevated mean plasma epinephrine concentrations while Griffiths et al. observed minor changes in plasma epinephrine. Increased urinary excretion rates of epinephrine are a consistent finding in acute myocardial infarction. Only a few separate determinations of plasma epinephrine and norepinephrine were performed in the present study, but our very limited data suggest that epinephrine is elevated in patients with high plasma catecholamine concentrations.

We have preferred to measure the total plasma catecholamine concentration rather than epinephrine and norepinephrine separately because the arrhythmic effect of these hormones is very similar. A greater amount of blood is necessary to obtain reliable determinations of epinephrine and norepinephrine separately, and this amount could hardly have been obtained at the short sample intervals employed in the present study.

One of us has previously shown that in normal subjects there is a correlation between rise in plasma norepinephrine and rise in pulse rate. During exercise the plasma norepinephrine concentration can be correlated to the pulse rate. There is also a close relationship between sympathetic nervous impulses and pulse rate. In the patients with myocardial infarction there was no correlation between pulse rate and plasma catecholamine concentration. This may be at least partially due to widely varying degrees of vagal influence in these patients. As mentioned previously, the plasma catecholamine concentration in the patients with myocardial infarction was correlated to the clinical state of the patients.

The mechanism of catecholamine secretion after acute myocardial infarction has been studied in animal experiments. Epinephrine secretion from the adrenal gland seems to be induced reflexly from receptors at the site and the boundary of the ischemic area of the heart. Norepinephrine is probably released, partly by reflexes, from the postganglionic sympathetic nerve endings in the heart, perhaps as a compensatory phenomenon, increasing the inotropic state of the heart muscle. It seems probable that baroreceptor mechanisms are involved, particularly in patients with hemodynamic changes.

Acknowledgment

The authors are grateful to the nurses of the CCU who have contributed to the success of this study.

References


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Circulation. 1972;46:846-855
doi: 10.1161/01.CIR.46.5.846

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

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