Br Heart J 1988;**60**:117–24

Neuroendocrine activation after acute myocardial infarction

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SUMMARY The extent of neuroendocrine activation, its time course, and relation to left ventricular dysfunction and arrhythmias were investigated in 78 consecutive patients with suspected acute myocardial infarction. High concentrations of arginine vasopressin were found within six hours of symptoms, even in the absence of myocardial infarction (n = 18). Plasma catecholamine concentrations also were highest on admission, whereas renin and angiotensin II concentrations rose progressively over the first three days, not only in those with heart failure but also in patients with no clinical complications. Heart failure, ventricular tachycardia, and deaths were associated with extensive myocardial infarction, low left ventricular ejection fraction, and persistently high concentrations of catecholamines, renin, and angiotensin II up to 10 days after admission, whereas in uncomplicated cases concentrations had already returned to normal.

The clinical presentation of acute myocardial infarction varies widely. Some patients have only mild constitutional upset, while others suffer intense vasoconstriction, arrhythmias, heart failure, or shock. In common with other major acute illnesses, myocardial infarction is accompanied by many metabolic and hormonal changes which may be related to the severity of illness and clinical outcome.[1] Although stimulation of neuroendocrine systems may be an appropriate response to acute myocardial injury, those hormones that promote vasoconstriction or tachycardia might also be harmful.

Of the vasoconstrictor mechanisms, catecholamine release has been the most extensively studied. Numerous reports have confirmed the initial observations in 1952 by Forssman[2] of raised concentrations of urinary[3–5] and plasma[6–8] catecholamines after myocardial infarction. High concentrations of catecholamines are frequently associated with the presence of heart failure, shock, or ventricular arrhythmias,[4 7 8] and the potential for reducing infarct size and arrhythmias by interference with the catecholamine response by β blockers has attracted much interest.[9–11]

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Accepted for publication 15 February 1988

Other vasoconstrictor hormones also may be important after myocardial infarction, and compared with catecholamines little is known of the role of the renin-angiotensin system. Preliminary observations indicate that concentrations of plasma renin are raised in some patients after myocardial infarction, particularly in association with heart failure, shock, or ventricular fibrillation.[12–14] Furthermore, inhibition of angiotensin II formation in those with heart failure may confer haemodynamic benefit.[15 16]

Nausea, vomiting, and administration of morphine[17 18] may stimulate release of another potent vasoconstrictor, arginine vasopressin, but little is known about the activation of arginine vasopressin in this clinical setting. The vasoconstrictor effects of these neuroendocrine systems on the coronary and peripheral circulations may be mutually facilitatory,[19–21] and they may have the potential to decrease myocardial and peripheral perfusion as well as lowering cardiac output.

We studied the extent and time course of the stimulation of the release of renin, angiotensin II, catecholamines, and arginine vasopressin in a large consecutive series of patients admitted to the coronary care unit with suspected myocardial infarction.

Patients and methods

We studied 78 consecutive patients with suspected

acute myocardial infarction admitted to our coronary care unit within six hours of the onset of symptoms. We excluded those patients with a previous history of cardiac failure and those who were maintained on long term diuretic treatment, because neuroendocrine activation may have been present before the onset of acute myocardial infarction. We also excluded those with atrial fibrillation or frequent extrasystoles on admission because they were unsuitable for radionuclide ventriculography.

All patients included for study had a gated technetium-99m radionuclide scan performed on admission to measure the left ventricular ejection fraction (normal >45%), and venous blood samples were taken to measure the concentrations of plasma active renin (normal range 10–50 μU/ml), angiotensin II (normal range 3–12 pmol/l), arginine vasopressin (normal range 0·3–0·7 pg/ml), adrenaline (normal range undetectable −0·2 nmol/l), and noradrenaline (normal range 0·2–3·0 nmol/l). Plasma was separated within 15 minutes and frozen for assay later. To avoid the discomfort of repeated venepuncture we inserted an indwelling venous cannula. Venous blood sampling was repeated during bed rest on days 1, 2, and 3 after admission, and again after 30 minutes' supine rest on day 10. The diagnosis of acute myocardial infarction was based on standard electrocardiographic features on the serial electrocardiograms and on a significant rise of serum creatine kinase and its MB isoenzyme.

Clinical examination and chest *x* rays were performed on admission and at frequent intervals thereafter to detect the presence of heart failure. For the purposes of this study we defined clinical left ventricular failure as the presence of either basal crepitations or a third heart sound together with radiological pulmonary venous congestion sufficient to warrant treatment with frusemide. We made a note of the use of frusemide, which was the only diuretic used, and other drugs that might influence neuroendocrine activation during the period of study. Sustained ventricular tachycardia, symptomatic non-sustained ventricular tachycardia, and ventricular fibrillation were noted during routine monitoring in the coronary care unit over the first 48 hours.

Results

CLINICAL COURSE

Acute myocardial infarction was confirmed in 60 patients (mean (SEM) age 52·9 (1·2) years). Those patients in whom myocardial infarction was subsequently excluded acted as a control group for this study (n = 18, age 53·6 (1·9) years). Most of these patients were discharged from the coronary care unit on their second day; so for the control group there are no data for day three. Thirteen patients (age 56·6 (1·9) years) with myocardial infarction developed clinical evidence of left ventricular failure during the study period, including two with cardiogenic shock. Four patients died during their hospital admission—one within 24 hours in cardiogenic shock, two with intractable left ventricular failure on days seven and 11, and one, who had previously had uncomplicated infarction, from late ventricular fibrillation on day 14.

Four patients had one or more episodes of ventricular fibrillation within 24 hours of admission. One of these patients died in cardiogenic shock, whereas the others subsequently had an uneventful clinical course. Two patients, one of whom was in heart failure, developed complete heart block on day four that required temporary cardiac pacing. In both cases, sinus rhythm had returned within 72 hours. Three patients who had no other clinical complications had atrial flutter or fibrillation in the first two days. Because these episodes lasted <1 hour, no treatment was given. Late ventricular tachycardia occurred in two patients, both of whom had sustained extensive myocardial damage with evidence of heart failure.

Satisfactory radionuclide scans were available for 69 of the 78 patients studied. In those with acute myocardial infarction left ventricular ejection fraction correlated inversely with the cumulative release of creatine kinase isoenzyme MB over the first three days ($r = -0·62$; $p < 0·001$). Mean (SEM) peak release of creatine kinase MB was higher (316·6 (42·1) U/l) in patients with left ventricular failure and ejection fractions were lower (23·3 (3·9)%) than in those without heart failure (192·5 (20·5) U/l and 33·5 (1·6)% respectively; both $p < 0·01$). In the control group the mean ejection fraction was 49·6 (2·8)%. On admission there were no significant differences in blood pressure between those with acute myocardial infarction and the control group. Although all groups showed a fall in blood pressure, those with left ventricular failure had significantly lower systolic pressures at day 2 than the control group (108 (4) mm Hg *v* 127 (3·4) mm Hg respectively; $p = 0·002$) and these differences were maintained at day 10.

Three patients who developed heart failure had been on β blockers that were stopped at admission. None of the patients with uncomplicated myocardial infarction was on β blockers at admission, and treatment with β blockers or diuretics was not started during the study period. Twenty patients without heart failure were given intravenous nitrates for a period of 24–48 hours because of persisting or recurrent cardiac pain without evidence of reinfarction. For those with clinical evidence of left ventricular failure during their admission the mean

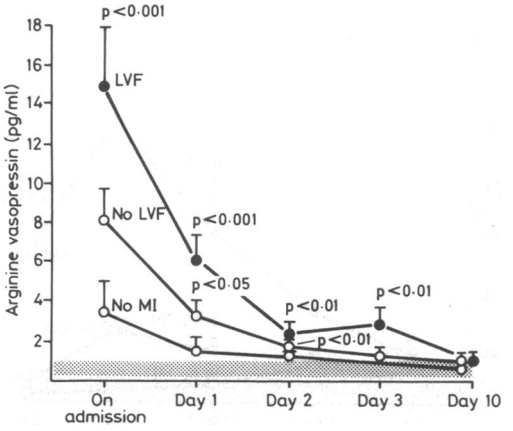

Fig 1 *Changes (mean (SEM)) in arginine vasopressin concentration over 10 days in patients with heart failure (LVF), those without heart failure (no LVF), and those without myocardial infarction (no MI). Shaded area is normal range.*

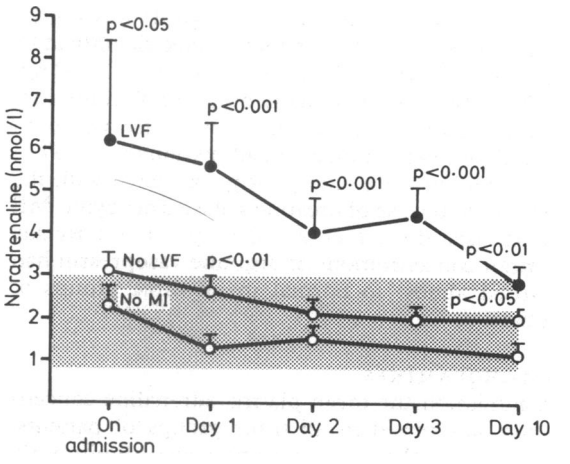

Fig 3 *Changes (mean (SEM)) in noradrenaline concentration over 10 days in patients with heart failure (LVF), those without heart failure (no LVF), and those without myocardial infarction (no MI). Shaded area is normal range.*

frusemide dosage at day 3 was 95 (22·7) mg. Figures 1–4 show the pattern of neuroendocrine activation for the control group and for those with myocardial infarction in the presence and absence of heart failure. Significance values were derived from Student's paired and unpaired *t* tests, and r values from Pearson's correlation coefficients.

ARGININE VASOPRESSIN

Concentrations of arginine vasopressin were highest at admission and declined rapidly over the next 48 hours (fig 1). In those with proven myocardial infarction, arginine vasopressin concentrations were higher in 50 patients who were given narcotic analgesics before admission to the coronary care unit (range 0·15–39·98 pg/ml, median 7·19 pg/ml) than in 10 patients whose pain had spontaneously settled (range 0·17–2·92 pg/ml, median 1·31 pg/ml; p = 0·007). Arginine vasopressin concentrations also tended to be higher in the seven controls on narcotic analgesics (range 0·22–19·9 pg/ml, median 4·2 pg/ml) than in the eleven controls who did not require analgesia (range 0·02–16 pg/ml; median 1·41 pg/ml). This difference was not statistically significant. Ten patients required one or more further doses of diamorphine in the 12 hours before blood sampling on day 1, and although arginine vasopressin concentration had fallen significantly the median concentra-

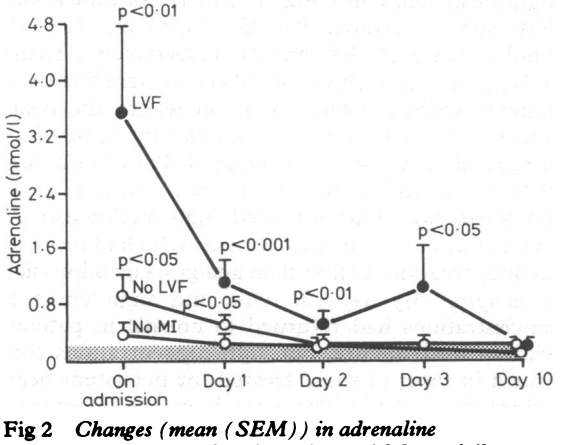

Fig 2 *Changes (mean (SEM)) in adrenaline concentration over 10 days in patients with heart failure (LVF), those without heart failure (no LVF), and those without myocardial infarction (no MI). Shaded area is normal range.*

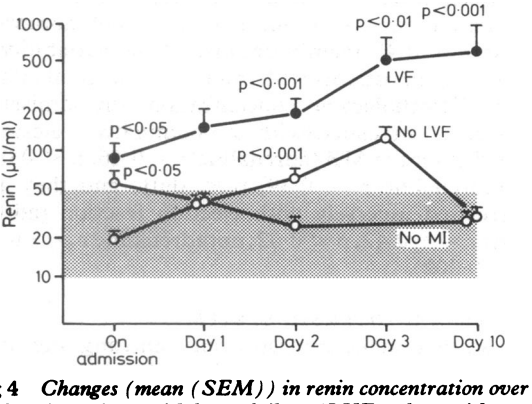

Fig 4 *Changes (mean (SEM)) in renin concentration over 10 days in patients with heart failure (LVF), those without heart failure (no LVF), and those without myocardial infarction (no MI). Shaded area is normal range.*

tion (3·63 pg/ml, range 0·3–9·9 pg/ml) was higher than in those (n = 40) who had analgesia only at or before admission (median 2·84, range 0·12–20·02 pg/ml; NS). In those with acute myocardial infarction, arginine vasopressin concentrations correlated with adrenaline concentrations on admission (r = 0·57, p < 0·001), but were only poorly correlated with the cumulative release of creatine kinase isoenzyme MB over the first three days (r = 0·37, p < 0·01). By day 10 mean concentrations of arginine vasopressin had returned almost to normal in all three groups of patients.

CATECHOLAMINES

On admission the mean plasma adrenaline concentration was raised in all three groups of patients. Plasma adrenaline concentration was significantly higher in those with heart failure (mean 3·54 (1·3) nmol/l, range 0·03–15·9) than in those without (0·96 (0·25) nmol/l, range undetectable −7·4 nmol/l) and also in those in whom myocardial infarction was excluded (0·35 (0·05) nmol/l, range undetectable −0·61 nmol/l). During the course of the admission all three groups showed a progressive decline in mean adrenaline concentrations towards normal (fig 2). Plasma noradrenaline concentrations also fell significantly during the course of the hospital stay in patients without heart failure and in the control group; in those without heart failure mean concentrations were just above the upper limit of normal on admission (3·12 (0·43) nmol/l (range 0·05–11·93 nmol/l), but they were within the normal range in the controls (2·34 (0·31) nmol/l) range 0·7–4·6 nmol/l). On admission mean plasma noradrenaline concentrations were at twice the upper limit of normal in patients with heart failure (mean 6·2 (2·3) nmol/l range 0·16–29·9 nmol/l), and high concentrations persisted over the next three days (fig 3). Correlations between heart rate and catecholamine release on admission were poor (adrenaline r = 0·3, noradrenaline r = 0·4), mainly because of the variability in heart rate in patients with inferior myocardial infarction. Catecholamine concentrations on admission, however, correlated with the cumulative release of creatine kinase MB (adrenaline r = 0·46, p < 0·001; noradrenaline r = 0·39, p < 0·01) and they also correlated inversely with ejection fraction (adrenaline r = −0·42, p < 0·02; noradrenaline r = −0·53, p < 0·002).

RENIN-ANGIOTENSIN SYSTEM

On admission mean plasma renin and angiotensin II concentrations were normal in the patients with myocardial infarction, but they rose by the third day to more than three times the upper limit of the normal range (203 (69) μ U/ml and 43·5 (8·6) pmol/l

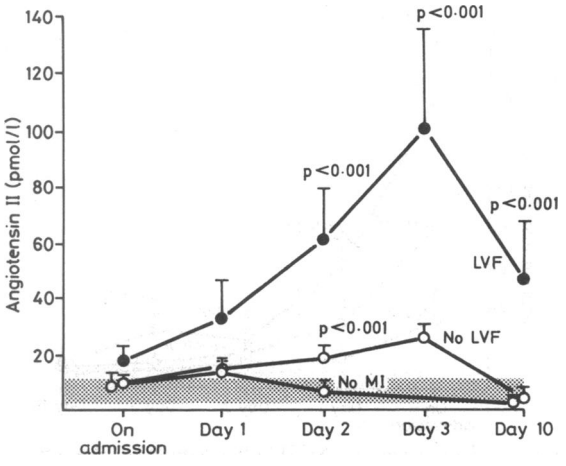

Fig 5 *Changes (mean (SEM)) in angiotensin II concentration over 10 days in patients with heart failure (LVF), those without heart failure (no LVF), and those without myocardial infarction (no MI). Shaded area is normal range.*

respectively). In the control group, mean concentrations of renin and angiotensin II remained normal throughout the study period, apart from a transient rise in angiotensin II on day 1 to 13·2 (3·5) pmol/l (range 1·9–48 pmol/l). Left ventricular failure was clinically present on admission in nine patients, and occurred later in four patients. Three patients had been treated with frusemide before blood sampling at admission (range 40–80 mg dose); plasma concentrations of angiotensin II were raised in only one. Two patients with cardiogenic shock and four patients with acute heart failure had not received diuretics; angiotensin II concentrations were raised in five of them. By day 3 the group treated for heart failure had high mean renin and angiotensin II concentrations (559 (303) μU/l (range 95–3855 μU/ml) and 102 (33) pmol/l (range 16–400 pmol/l) respectively). Renin and angiotensin II, however, also rose significantly in patients without heart failure in whom the mean concentrations were more than twice the upper limit of normal (104 (14) μU/l (range 4–455 μU/ml) and 26·8 (3·3) pmol/l (range 1–90 pmol/l) respectively) at the third day. This included high angiotensin II concentrations in 16 of 27 patients who had received no drug treatment other than analgesia on admission to hospital. By day 10, renin and angiotensin II concentrations had returned to normal in patients without heart failure, but high concentrations continued in most of those treated for persistent heart failure (figs 4 and 5). The table shows the angiotensin II concentrations in all 13 patients with heart failure and their respective diuretic dosages. Renin and angiotensin II concentrations correlated well on admission (r = 0·56), at day 3 (r = 0·83), and at day

Table *Individual angiotensin II concentrations (pmol/l) and frusemide dosage (mg) over the previous 24 hours in patients with heart failure. Shading indicates presence of clinical heart failure*

Case No	OA	F	Day 1	F	Day 2	F	Day 3	F	Day 10	F	Outcome
1	50·0	0	126·0	80	124·0	160	132·0	200	100·0	160	Cardiogenic shock
2	34·4	0	Died								Cardiogenic shock
3	15·2	0	8·1	80	41·0	80	52·0	80	66·0	80	Severe failure
4	26·0	0	30·8	160	157·1	240	255·0	240	Died		Severe failure
5	14·0	0	20·0	0	65·0	160	78·0	200	180·0	160	Severe failure—died
6	30·0	0	140·0	80	200·0	160	400·0	80	33·2	80	Moderate failure
7	3·6	80	2·2	80	9·8	80	16·2	80	10·5	80	Moderate failure
8	3·2	40	20·0	40	29·7	40	29·0	80	29·7	40	Moderate failure
9	16·6	0	14·8	40	55·2	80	68·6	80	3·9	40	Moderate failure
10	4·1	0	3·7	0	10·0	40	35·0	80	45·0	40	Moderate failure
11	7·2	0	14·0	80	18·0	0	75·0	0	3·1	0	Mild failure
12	25·0	80	22·0	0	28·0	0	48·0	0	12·0	40	Mild failure
13	3·5	0	11·4	0	16·9	0	32·1	20	7·0	40	Mild failure

OA, on admission; F, frusemide.

10 ($r = 0·80$) ($p < 0·001$). Renin on admission correlated with catecholamines (adrenaline, $r = 0·59$, $p < 0·001$; noradrenaline, $r = 0·37$, $p < 0·01$) and also with peak creatine kinase MB ($r = 0·43$, $p < 0·001$). We found no significant correlations between concentrations of arginine vasopressin or ejection fraction and activation of the renin-angiotensin system.

RELATIONS WITH ARRHYTHMIAS AND DEATH

Ventricular fibrillation occurred in four patients within the first 24 hours. Three had normal noradrenaline concentrations and only mildly raised adrenaline concentrations on admission. This included one patient in whom ventricular fibrillation developed during blood sampling (adrenaline 0·21 nmol/l, noradrenaline 3·01 nmol/l). They subsequently had an uneventful recovery. The fourth patient was in cardiogenic shock and died within 24 hours. Angiotensin II concentration on admission was markedly raised in this patient (34·4 pmol/l), as were adrenaline (4·4 nmol/l) and noradrenaline (3·4 nmol/l).

Three other patients died in hospital. Two had progressive intractable heart failure with high angiotensin II and noradrenaline concentrations at day 3. The clinical condition of the third patient had been uncomplicated despite a low ejection fraction (13%) and he died on day 14 from late ventricular fibrillation. At day 10 he had raised catecholamine concentrations (adrenaline 0·45 nmol/l, noradrenaline 7·7 nmol/l) and also high angiotensin II (17 pmol/l).

Two patients with symptomatic episodes of ventricular tachycardia had very high catecholamine concentrations on admission (adrenaline 1·25 and 7·44 nmol/l, noradrenaline 6·43 and 6·15 nmol/l) and raised angiotensin II concentrations (15·2 and 25 pmol/l). Furthermore, both of these patients had low left ventricular ejection fractions (7% and 22%), although only one had clinical signs of heart failure. Atrial flutter and fibrillation were seen in two patients with inferior myocardial infarction, and these were not associated with raised catecholamine concentrations. Late ventricular tachycardia occurred in a further two patients, both of whom had been treated for heart failure and had persistently high catecholamine and angiotensin II concentrations at day 3.

Thus in this small group of patients with arrhythmias, primary ventricular fibrillation was not closely related to the magnitude of neuroendocrine activation, although episodes of ventricular tachycardia on admission were accompanied by very high catecholamine concentrations. Late life threatening ventricular arrhythmias and deaths occurred only in those with major left ventricular dysfunction, which was also associated with persistently high catecholamine and angiotensin II concentrations.

Discussion

This study describes for the first time in a large consecutive series the extent, time course, and interrelations of neuroendocrine activation after acute myocardial infarction. Although raised urinary aldosterone had been noted as early as 1956,[22] the role of the renin-angiotensin system after myocardial infarction has been neglected until recently. Preliminary studies measuring renin show a very wide range of individual responses. Vaney *et al* described raised renin and catecholamine concentrations on admission in 19 patients with acute myocardial infarction; concentrations were highest in four of eight patients who subsequently developed cardiogenic shock or ventricular fibrillation.[12] Wenting *et al*, however, found normal renin concentrations in four patients with heart failure within 12 hours of

acute myocardial infarction in the absence of diuretic treatment, although high renin concentrations were seen at 48–72 hours in two other patients who received inotropes and vasodilators.[15] A much larger study by Michorowski and Ceremuzynski of 95 patients showed raised renin concentrations in 20 of 22 patients within six hours of chest pain in the presence of heart failure, arrhythmias or shock, but no significant increase in patients without clinical complications.[14]

These findings are extended and confirmed in our study, in which most patients had normal concentrations of renin and angiotensin II within six hours of symptoms, with the exception of those with severe heart failure or shock. Sequential measurements in patients without clinical complications, however, showed a significant increase in renin and angiotensin II by day 3, in the absence of treatment with vasodilators or diuretics. Those treated for heart failure had very much higher angiotensin II concentrations at day 3, which persisted at ten days and presumably for longer.

Stimulation of renin secretion during the first three days after myocardial infarction is likely to be dependent on several interacting variables. The initially very high arginine vasopressin concentration may have suppressed renin release,[23,24] whereas acute reduction in renal blood flow, together with increased renal nerve activity may stimulate the renin-angiotensin system.[25,26] There seems little doubt that contraction of blood volume associated with diuretic treatment contributed to the extremely high concentrations of renin and angiotensin II in those with heart failure, but concentrations of these hormones were raised on admission in nearly half of this group before diuretic treatment. We confirmed previous observations of a relation between catecholamines and initial renin concentration,[14] which suggests that this may be one of the more important initial stimuli to renin secretion in this clinical setting.

As shown previously,[4,7,8] catecholamine release was also related to the extent of left ventricular damage as assessed by cardiac release, ejection fraction, and the presence of heart failure. Whether catecholamines have any direct influence on infarct size remains uncertain, but raised urinary and plasma catecholamine concentrations have been reported to be related to the frequency of early ventricular arrhythmias.[4,5] In our study only six out of 60 patients had ventricular fibrillation or haemodynamically important ventricular tachycardia in the first 24 hours, and short salvos of ventricular extrasystoles were not documented. β Blockade at an early stage when catecholamine concentrations are highest seems a logical tactic both to reduce arrhythmias and limit the extent of infarct damage, and this has been the focus of several studies.[9–11] In our study, however, catecholamine concentrations were highest in a group in whom β blockers are generally contraindicated—that is those patients in whom heart failure is developing.

Arginine vasopressin release during acute myocardial infarction has received little attention. We found markedly raised arginine vasopressin concentrations at admission, not only in those with myocardial necrosis but also in some patients in whom myocardial infarction had been excluded. Furthermore, the correlation between arginine vasopressin concentrations and creatine kinase release was poor, suggesting that factors other than myocardial necrosis are responsible for arginine vasopressin release. Administration of morphine was strongly associated with the considerable increase in arginine vasopressin in both those with myocardial infarction and in the control group. In contrast, in patients with myocardial infarction who were not given morphine arginine vasopressin was only slightly raised, and this is also true of the control patients who did not receive morphine. Thus after myocardial infarction arginine vasopressin is more likely to be high as a result of treatment than as a primary response to acute myocardial infarction. The explanation for the correlation between initial concentrations of adrenaline and arginine vasopressin might also be that those under greater stress because of pain or nausea and vomiting had received higher doses of morphine.

The antidiuretic effect of arginine vasopressin is well recognised and probably contributes to the low urine volumes in the first 24 hours after myocardial infarction. It has been estimated that approximately 760 ml water is gained then.[27] Although infusion of arginine vasopressin does not raise blood pressure, except in very high concentration (100 ng/l),[28] it is an extremely potent arterial vasoconstrictor. Arginine vasopressin has been given as a provocative test for angina and coronary artery spasm,[29] and in other situations in which there is an excess of arginine vasopressin, myocardial infarction, arrhythmias, and sudden death have been reported.[30–32] We do not know whether the concentrations of arginine vasopressin seen after myocardial infarction in this study had important haemodynamic effects, but the vasoconstrictor properties of arginine vasopressin may be enhanced by noradrenaline, and both of these hormones were at their highest in the first 24 hours after admission.

The interaction of raised plasma concentrations of angiotensin II, arginine vasopressin, and catecholamines could be harmful in several ways. Arginine vasopressin, noradrenaline, and angiotensin II are potent arterial vasoconstrictors that could increase left ventricular afterload and lower coronary

perfusion. Similarly tachycardia and arrhythmias induced by catecholamine excess could be disadvantageous. Furthermore, the combination of vasoconstriction mediated by these hormones and volume expansion through the sodium retaining effects of increased renal sympathetic nerve activity, stimulation of aldosterone secretion, and antidiuresis in the presence of raised arginine vasopressin concentration provides the setting for the development of acute heart failure. Treatment with angiotensin converting enzyme produced short term and long term haemodynamic improvements in patients with chronic heart failure.[33-35] Inhibition of angiotensin II production in chronic heart failure has also been associated with reduction of arrhythmias,[36] a significant rise in body potassium,[37] and a reduction in plasma catecholamine concentrations.[36 37] More recently beneficial haemodynamic changes have been shown with angiotensin converting enzyme inhibitors in heart failure complicating myocardial infarction.[15 16 38] These findings suggest that clinical trials of early intervention with angiotensin converting enzyme inhibitors in patients with extensive myocardial infarction and heart failure should be considered.

In addition to these more obvious adverse haemodynamic consequences, neuroendocrine activation could have other subtle effects on myocardial structure and function. Experimentally, high concentrations of catecholamines and angiotensin II cause diffuse microscopic myocardial cellular necrosis in rabbits, and in man can cause similar lesions even in the absence of coronary disease.[39] Recent studies show that infarct expansion and progressive ventricular dilatation occur in some patients after myocardial infarction.[40-42] In animal models angiotensin converting enzyme inhibitors may reduce infarct size,[43-45] increase collateral blood flow to the infarct zone,[43] reduce the incidence of reperfusion arrhythmias,[46] and through improved ventricular remodelling in rats[47-49] can lead to an increase in survival.[49]

Thus persisting high concentrations of angiotensin II after myocardial infarction could have important implications not only for the development of acute heart failure, but also for long term cardiac structure and function. The observations reported here provide a logical basis for the cautious exploration of the effects of angiotensin converting enzyme inhibition given early in acute myocardial infarction on ventricular structure and function.

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