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Plasma concentration of atrial natriuretic peptide at admission and risk of cardiac death in patients with acute myocardial infarction

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Abstract

***Objective*—To compare the concentration of plasma atrial natriuretic peptide in patients with acute myocardial infarction with a healthy population and to determine whether a raised concentration of plasma atrial natriuretic peptide at admission was a predictor of mortality after acute myocardial infarction.**

***Design*—Patients with acute myocardial infarction were divided into a group with no congestion (class I) and a group with congestion (class II-IV) according to their highest Killip classification in the first 24 hours after infarction. The concentration of plasma atrial natriuretic peptide was measured at admission. On the basis of the concentration of atrial natriuretic peptide measured in the healthy population, patients were separated into two groups: a group with a high (>200 pg/ml) and a group with a low concentration of atrial natriuretic peptide (≤200 pg/ml). The patients were followed for three years.**

***Patients*—55 patients admitted to the coronary care unit within 12 hours of the appearance of symptoms of acute myocardial infarction were compared with 51 healthy individuals.**

***Main outcome measures*—Plasma atrial natriuretic pepetide, Killip class, mortality.**

***Results*—The patients had significantly higher concentrations of atrial natriuretic peptide than the healthy controls. Furthermore, patients with congestion had a significantly higher concentration of atrial natriuretic peptide than the uncongested group of patients. Total mortality was 34·5%. In the group with a low concentration of atrial natriuretic peptide the mortality was only 13·6%, whereas mortality was significantly higher (48·5%) in the group with a high concentration.**

***Conclusions*—The measurement of atrial natriuretic peptide separated the patients into low and high risk groups after acute myocardial infarction.**

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During the past 30 years the hospital stay for uncomplicated acute myocardial infarction has progressively shortened.[1] To identify those patients at high risk of an early death after acute myocardial infarction many risk factors have been evaluated including the emergency electrocardiogram,[2] early exercise test,[3] predischarge maximal exercise test,[4] the concentration of creatine kinase,[5] and haemodynamic measurements.[6] Since the establishment of coronary care units about 20 years ago, the number of deaths primarily attributed to cardiac arrhythmias has decreased and clinical heart failure, or more accurately left ventricular impairment, has emerged as the prime factor responsible for most deaths after acute myocardial infarction.[7-9]

The concentration of plasma atrial natriuretic peptide is reported to be higher in patients with left ventricular dysfunction and to correlate well with the function of the left ventricle in both chronic[10-12] and acute heart disease.[13]

We have compared the concentration of plasma atrial natriuretic peptide in patients with acute myocardial infarction with that in a group of healthy controls. Because left ventricular dysfunction determines mortality after myocardial infarction,[14] we wanted to examine whether a raised concentration of atrial natriuretic peptide at admission predicted mortality after acute myocardial infarction and could be used as an easily measured indicator of left ventricular function.

Patients and methods

From 1 April 1987 to 31 March 1988, 191 patients were admitted to our hospital with acute myocardial infarction. In this study we included all patients admitted to the coronary care unit who fulfilled the following criteria: (*a*) infarction diagnosed according to the criteria of the World Health Organisation,[15] (*b*) clinical evaluation and blood samples taken within 12 hours of the onset of symptoms, (*c*) no vasoactive drugs given at admission before the blood samples were taken, (*d*) serum creatinine concentration <200 μmol/l at admission, (*e*) no history of chronic liver disease, (*f*) no permanent or temporary pacemaker treatment, (*g*) no resuscitation before admission, (*h*) informed consent. Patients were excluded if they did not meet the inclusion criteria. The patients we studied were followed up to determine mortality. The study was approved by the local ethics committee.

Blood samples were collected at admission from a cubital vein into EDTA-coated tubes

containing aprotinin 500 IU/ml and kept in an ice bath. The plasma was centrifuged within an hour and then stored at −20°C until analysis. We used a highly specific and reproducible radioimmunoassay from INC, Holland that included plasma extraction before analysis.[16] The kit was tested in our laboratory: intra and inter assay variation was 5% and 10% respectively. Recovery of added atrial natriuretic peptide was 99% (sensitivity, 0·8 pg/tube = 4 pg/ml plasma).

A normal range of atrial natriuretic peptide was established in 51 healthy controls (20 women) (mean age 54·9, range 27–82 years). They were not taking any medication, had no history of chronic liver or heart disease, and had a serum creatinine concentration of < 200 μmol/l. The concentration of plasma atrial natriuretic peptide ranged from 25 to 200 pg/ml (mean (SD) 83 (38·4) pg/ml). On the basis of the concentration of atrial natriuretic peptide in the healthy controls we divided the patients with acute myocardial infarction into two groups: one group with low (≤200 pg/ml) and one with a high atrial natriuretic peptide concentration (>200 pg/ml).

Patients with acute myocardial infarction were divided into an uncongested (Killip class I) group and congested (Killip class II–IV) group in order to compare the concentration of atrial natriuretic peptide in the two groups.[17] Patients were classified according to the highest Killip class attained during the first 24 hours after myocardial infarction. The patients were classified by two of the authors (JS and KA-N) without knowing the concentration of plasma atrial natriuretic peptide.

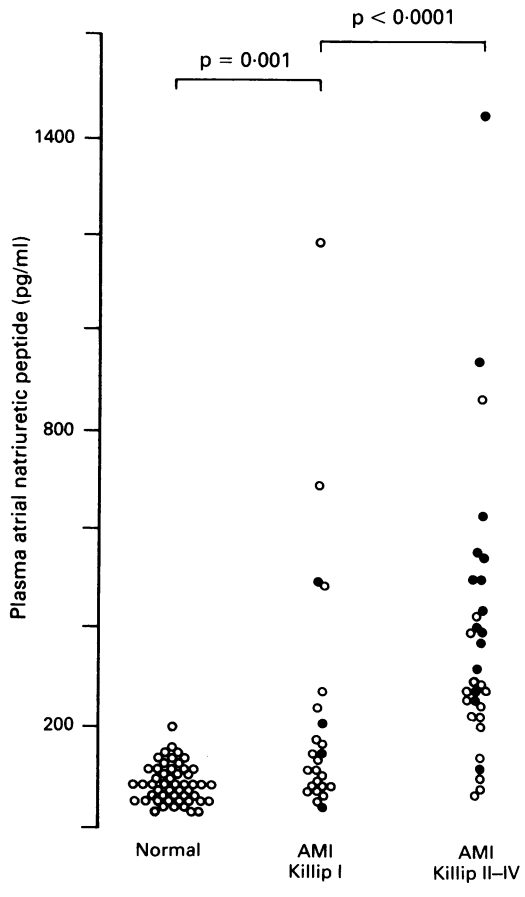

Figure 1 Concentration of plasma atrial natriuretic peptide in 51 healthy controls compared with 24 patients in Killip class I and 31 patients in Killip class II-IV with acute myocardial infarction (AMI). Solid circles indicate patients who died.

STATISTICAL ANALYSIS

We used the two-sample rank sum test (Mann-Whitney test). The differences in survival curves were calculated by a log rank test.[18] Dichotomised data were analysed by a χ^2 test. We compared the concentration of atrial natriuretic peptide in healthy controls and patients by analysis of covariance after adjusting for age. We used the Cox model for regression in survival to analyse the concentration of atrial natriuretic peptide as a continuous value. The relative risk of death for a given increase in the concentration of atrial natriuretic peptide was calculated from the slope of the regression line.[19]

Results

We studied 55 patients (15 women) admitted to the coronary care unit with acute myocardial infarction. They were all admitted within 12 hours (median time 3·0 hours) from the onset of symptoms of myocardial infarction. Atrial natriuretic peptide was significantly higher in the patients with acute myocardial infarction than in the healthy controls (p < 0·00001). In the first 24 hours after infarction 24 patients were in Killip class I (uncongested) and 31 patients were in Killip class II–IV (congested). Table 1 shows the age, mean concentration of atrial natriuretic peptide, and sex in the controls and patients. In the controls there was a significant correlation between age and atrial natriuretic peptide (regression line for atrial natriuretic peptide (pg/ml) = 1·32 × age (years) + 9·8; r = 0·53, p = <0·001). The concentration of atrial natriuretic peptide was similar in men and women (p = 0·19). The concentration of atrial natriuretic peptide in the uncongested patients (Killip class I) was significantly different from that in the controls and in the congested patients (Killip class II–IV) with acute myocardial infarction (fig 1). Three (43%) of the seven uncongested patients with a high concentration of atrial natriuretic peptide at admission became congested 24–48 hours after infarction, compared with three (18%) of the 17 uncongested patients in whom the concentration of atrial natriuretic peptide was low at admission. This difference was not statistically significant.

The mean observation time for all patients was 1094 days (range 929–1273 days). Nineteen

Table 1 Mean values for age, sex, and atrial natriuretic peptide in healthy controls and patients with acute myocardial infarction

	Healthy controls (n = 51)	*Patients Killip class I (n = 24)*	*Patients Killip class II-IV (n = 31)*
Age (mean (SD))	54·9 (15·6)	61·7 (11·7)	66·1 (8·7)
Females (%)	20 (39)	7 (29)	8 (26)
ANP (pg/ml)	82·9	221·3	390·0

ANP, atrial natriuretic peptide.

Table 2 Basic characteristics of the patients

	Deaths (n = 19)	*Survivors (n = 36)*	*p Value*
Age (mean (SD))	68 (11·2)	62 (9·2)	0·052
Women (%)	6 (32)	9 (25)	0·83
Pre-existing factors:			
AMI (%)	6 (32)	4 (11)	0·13
Angina pectoris (%)	11 (58)	11 (31)	0·09
Hypertension (%)	10 (53)	8 (22)	0·047
Atrial flutter (%)	1	0	
Congestion (%)	3 (16)	3 (8)	0·7

patients died during the follow up period. Table 2 shows the salient clinical characteristics of those who died and those who survived.

Figure 2 shows the relations between the groups with low (≤200 pg/ml) and high (above 200 pg/ml) values of atrial natriuretic peptide and survival in the follow up period. Three (13·6%) of 22 patients in the group with a low value of atrial natriuretic peptide died. Mortality was significantly higher 16/33 (48·5%) in the group with a high value.

Figure 2 also shows the relation between the highest Killip classification in the first 24 hours after myocardial infarction and survival. Four (16·7%) of the 24 uncongested patients in Killip class I died compared with 15 (48·4%) of 31 patients with congestion (Killip class II–IV). We used the Cox model for regression in survival to avoid arbitrary cut off points between groups and to use the concentration of atrial natriuretic peptide as a continuous value. This gave a relative risk of 1·7 for death for a doubling of the concentration of atrial natriuretic peptide (p = 0·0056).

When both plasma atrial natriuretic peptide and the Killip classification were included as covariates they did not explain significantly more of the survival rates than the values of atrial natriuretic peptide alone, but the values of atrial natriuretic peptide gave more information than the Killip values alone.

Discussion

Atrial natriuretic peptide was higher in the patients (both uncongested and congested) with acute myocardial infarction than in the healthy controls. We found that the concentration of plasma atrial natriuretic peptide immediately after infarction was significantly higher in congested patients than in patients without congestion and that the concentration of atrial natriuretic peptide of both groups was higher than in healthy controls. It seems to be the severity of the left ventricular dysfunction rather than the degree of myocardial ischaemia that determines the concentration of atrial natriuretic peptide. During percutaneous transluminal coronary angioplasty, which always causes ischaemia of a part of the heart muscle, the concentration of atrial natriuretic peptide was higher in patients in whom pulmonary capillary wedge pressure increased whereas it remained normal in patients in whom it did not increase. Furthermore, myocardial ischaemia provoked by dynamic exercise did not in itself increase the concentration of atrial natriuretic peptide in plasma.[20] There was a good correlation between atrial natriuretic peptide and capillary wedge pressure in uncongested patients during dynamic exercise 10 hours after the onset of symptoms of acute myocardial infarction.[13]

In a rat model of myocardial infarction neither atrial natriuretic peptide nor the left ventricular end diastolic pressure correlated linearly with infarct size, whereas there was a good linear correlation between atrial natriuretic peptide and left ventricular end diastolic pressure ($r = 0·89$, $p < 0·001$) during volume expansion.[21] An increased concentration of atrial natriuretic peptide is likely to aggravate congestive heart failure because intravenous administration of atrial natriuretic peptide reduced blood pressure and increased haemoconcentration in healthy individuals.[22] Because atrial natriuretic peptide increases transcapillary water shifts by altering vascular permeability, it has been proposed that a high concentration of atrial natriuretic peptide could contribute to pulmonary oedema in left sided myocardial disease and valve disease. This does not seem to be true of chronic heart failure where "acute" atrial natriuretic peptide infusion in several studies was associated with potentially beneficial renal, endocrine, and haemodynamic effects.[23,24] The vasodilatation and decrease in systemic vascular resistance that have been demonstrated could explain the harmful effect of atrial natriuretic peptide in healthy individuals. We know of no studies of the infusion of atrial natriuretic peptide in patients with acute heart failure.

We found a weak but significant increase in atrial natriuretic peptide with age in our healthy controls. Others, however, found no correlation in 124 younger healthy blood donors.[25] This might be because of differences in methods: we and others[26,27] found a positive correlation in healthy controls at all ages. It has been suggested that this positive correlation with age reflects increasing morbidity from other causes. To ensure that we used a cut off value that was independent of age we chose the highest value in the healthy controls (200 pg/ml).

Plasma atrial natriuretic peptide has already

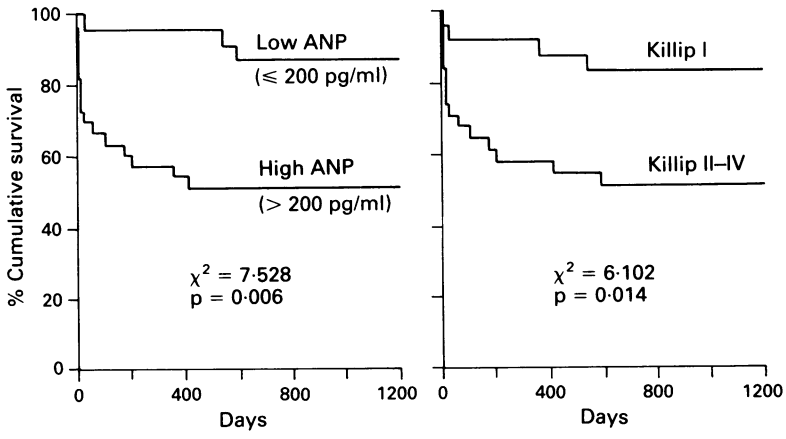

Figure 2 Relation between plasma atrial natriuretic peptide (ANP) and cumulative survival (left) and relation of Killip classification and cumulative survival (right).

been used as a prognostic indicator in chronic heart failure, where in 102 patients those with concentrations above the median concentration of atrial natriuretic peptide had a significantly lower two year survival rate than those with a lower concentration.[28]

We found that the Killip classification in the first 24 hours after myocardial infarction was a reliable prognostic indicator. All but four of those who died were in clinical heart failure at this time. This accords with the results of a study by Califf *et al*, who found that mortality in patients with coronary disease was strongly associated with left ventricular dysfunction. The detection of ventricular arrhythmias during a 24 hour monitoring period gave no further information on the prognosis if the haemodynamic indices were known.[29] The methods of assessing left ventricular dysfunction differ from one investigation to another, but in all mortality was associated with the degree of heart failure. A combination of physiological markers such as low left ventricular ejection fraction measured by radionuclide ventriculography, clinical heart failure, and radiological heart failure enhances the reliability of evidence of heart failure as a marker of mortality after acute myocardial infarction.[30] Pulmonary capillary wedge pressure measured at admission to the hospital gives a better indication of subsequent mortality than later measurements.[31] This might explain why radionuclide ventriculography performed 10 days after infarction in 39 patients with overt pulmonary oedema (Killip class III) was unable to predict the larger mortality in patients with an ejection fraction lower than 0·45 than in patients with a larger ejection fraction. The correlation between ejection fraction and pulmonary capillary wedge pressure was poor because pulmonary capillary wedge pressure in the two groups did not differ.[32] The difficulties in estimating heart failure several days after an acute myocardial infarction could be caused by treatment given soon after admission. Compared with other methods of predicting mortality atrial natriuretic peptide has the advantage that the blood sample can be drawn immediately at admission (day or night) by regular staff. The Killip classification is also a simple, reliable and easy way to predict mortality after a myocardial infarction. We found that atrial natriuretic peptide was as good and maybe was better than the Killip classification in predicting outcome. There will always be some inter-observer variability in assigning patients to the Killip classification. Furthermore we found that when the concentration of atrial natriuretic peptide doubled the relative risk of death increased by a factor 1·7.

We were not able to prove that the measurement of atrial natriuretic peptide can be used to predict congestion, because clinical evidence of congestion developed in too few patients after the first 24 hours to allow such a conclusion. If the plasma concentration of atrial natriuretic peptide is to be clinically useful in predicting congestion it must be available in minutes or hours, like an arterial gas analysis. At present a reliable analysis of atrial natriuretic peptide takes a couple of days.

We conclude that the increase in plasma atrial natriuretic peptide at admission in patients with acute myocardial infarction depends on their degree of heart failure. Furthermore, atrial natriuretic peptide measured at entry to the hospital before treatment is started is a good predictor of mortality and therefore good at identifying patients with acute myocardial infarction who are at a low and a high risk. However, it is important not to rely on a single blood test to risk-stratify patients. Like any other test plasma natriuretic peptide should be considered in conjunction with clinical information.

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