Current perspectives
Risk stratification after acute myocardial infarction: role of neurohormones, inflammatory markers and albumin excretion rate

Giuseppe Berton, Paolo Palatini*

Cardiology Department, Conegliano General Hospital, Conegliano Veneto (TV), Clinica Medica IV, University of Padua, Padua, Italy

Activation of several neurohormonal systems occurs during acute myocardial infarction (AMI) and is associated with short- and long-term outcomes. In the last few years, many circulating factors have received close attention but it is not clear which are the best prognostic indicators of mortality. Renin and natriuretic cardiac peptides appeared to be strong predictors of outcome in patients with AMI, and could represent helpful markers of risk in these patients. Though the role of acute inflammatory markers has been investigated only recently, mounting evidence indicates that C-reactive protein is also associated with an adverse outcome after AMI. Recent research from our laboratory indicates that the albumin excretion rate (AER) is a powerful predictor of the in-hospital and 3-year mortality in patients with AMI and that its prognostic power is stronger than that shown by other humoral markers of risk or by clinical and echocardiographic signs of congestive heart failure. The reason why AER is so closely associated with an adverse prognosis is not completely understood, but the available data support the hypothesis that it reflects both the hemodynamic as well as the inflammatory changes which accompany AMI. The determination of the brain natriuretic peptide and of C-reactive protein appears to be a valuable tool in the risk stratification of subjects with AMI. Even though available evidence is still limited, the evaluation of AER could be useful for the identification of those patients at higher risk for whom additional preventive and therapeutic measures would be advisable.

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Address:

Dr. Giuseppe Berton

*U.O. di Cardiologia
Dipartimento di Medicina
Interna e Cardiologia
Ospedale Civile
31015 Conegliano Veneto (TV)
E-mail: giube.s@tin.it*

Introduction

The identification of those individuals at high risk of mortality represents one of the most challenging issues in the care of patients with acute myocardial infarction (AMI) and multiple clinical variables have been proposed to improve the assessment of patients in this clinical setting[1-8]. Furthermore, in this era of cost containment, it appears crucial to identify those subgroups of patients who are at higher risk in order to target the most aggressive pharmacological and interventional therapies towards these patients. Most of the studies on risk stratification after AMI are based on signs of cardiac muscle injury but electrocardiographic and echocardiographic findings and the levels of traditional serum markers of myocyte necrosis, such as the creatine kinase MB fraction and troponin I and T, proved to be only partially successful in risk stratification[6,9,10].

In the last few years, our understanding of the pathophysiology of the acute coronary syndromes has made considerable progress and our ability to stratify patients according to risk should improve in tandem. Many circulating factors have received close attention and have been tested as prognostic indicators of mortality in the setting of AMI (Table I)[11-39]. Among these, the inflammatory markers and humoral factors reflecting heart failure have gained more credit.

This review attempts to summarize the clinical value of the main neurohormones, inflammatory markers and albumin excretion rate (AER), which have been proposed for the risk stratification of subjects with AMI and to determine a practical approach for a better definition of the risk profile in the individual patient.

Humoral factors reflecting heart failure

Clinical signs of congestive heart failure and a decreased left ventricular ejection fraction (LVEF) are known to be major in-

Table I. Main studies reporting on the association between neurohormones, inflammatory markers and albumin excretion rate (AER), measured during acute myocardial infarction (AMI), and outcomes.

Study authors	No. patients	Patient selection	Main marker(s)	Time of measurement	Follow-up	Results
Humoral factors reflecting heart failure						
Svanegaard et al.[11], 1992	55	<12 hours after symptom onset. Exclusion of subjects receiving CV drugs before blood sampling	ANP	Admission	3 years	Higher global mortality rate in patients with an ANP > 200 pg/ml.
Nakamura et al.[12], 1993	130	Unselected	ANP	Day 1 after admission	37 months	ANP was independently associated with cardiac death.
Omland et al.[13], 1993	145	Severe CHF, cardiogenic shock, pts in NYHA class IV excluded	ANP, E, NE	Day 3	1 year	At univariate analysis ANP, E and NE were associated with cardiac mortality; at multivariable analysis only ANP remained associated with outcome.
Omland et al.[14], 1993	139	Severe CHF, cardiogenic shock, pts in NYHA class IV excluded	ANP, N-ANP	Day 3	1 year	N-ANP shows a higher predicting power than ANP for global mortality.
Rouleau et al.[15], 1994	534	LVEF 40% and no overt HF	PRA, aldosterone, E, NE, dopamine, ANP, arginine vasopressin	Hospital discharge (mean 12 days, range 3-16)	38 months (range 24 to 55)	At univariate analysis PRA, aldosterone, NE and ANP were associated with CV mortality; at multivariable analysis PRA and ANP remained independently associated.
Hall et al.[16], 1994	246	LVEF 40% and no overt HF	ANP, N-ANP	Hospital discharge (mean 12 days, range 3-16)	38 months (range 24 to 55)	N-ANP was a stronger predictor for global and CV mortality than ANP both at univariate and multivariable analyses including clinical variables, the Killip class and LVEF.
Omland et al.[17], 1994	142	Severe CHF, cardiogenic shock, pts in NYHA class IV excluded	Endothelin, ANP	Day 3	1 year	Endothelin was independently associated with global mortality and yielded additional information to clinical HF and ANP.
Omland et al.[18], 1995	142 / 76	Severe CHF, cardiogenic shock, pts in NYHA class IV excluded	Endothelin, ANP, NE	Day 3	Median 3.7 years	At univariate analysis ANP, NE and endothelin were associated with CV mortality; at multivariable analysis including clinical HF, ANP and endothelin were independent predictors. When LVEF (n=85) was included in the model, neurohormones lost statistical significance.
Hall et al.[19], 1995	131	Pts treated with rt-PA admitted <4 hours from symptom onset	N-ANP	Within 8 hours of admission	1 year (retrospective)	At multivariable logistic regression N-ANP was independently associated with global mortality.
Omland et al.[20], 1996	70	Severe CHF, cardiogenic shock, pts in NYHA class IV excluded	BNP, ANP, N-ANP	Day 3	Median 3.7 years	BNP, but not ANP or N-ANP, was stronger than LVEF in predicting CV mortality.
Arakawa et al.[21], 1996	121	Unselected	BNP, ANP	Admission and day 2	18 months	BNP was associated with cardiac death, and was a stronger predictor than ANP.
Richards et al.[22], 1998	1390	Pts > 80 years and with cardiogenic shock excluded	N-BNP, BNP, adrenomedullin, N-ANP, ANP, catecholamines	Day 2 to 4	2 years	N-ANP, ANP, N-BNP, BNP and adrenomedullin were predictors of mortality at univariate analysis; N-BNP and BNP independently predicted global mortality and were superior to any other neurohormone and to LVEF.
de Lemos et al.[23], 2001		Unselected	BNP	<72 hours from symptom onset (median 40 hours)	10 months	In NSTEAMI and STEAMI, BNP was associated with global mortality at univariate analysis. The results of multivariable analysis were not reported.

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(Continued Table I)

Study authors	No. patients	Patient selection	Main marker(s)	Time of measurement	Follow-up	Results
Blood markers reflecting inflammation						
Casl et al.[24], 1995	40	Unselected	SAA, CRP, α₁-acid glycoprotein	Peak values	In-hospital	SAA and CRP were associated with early fatal events. Survival regressions were not reported.
Pietila et al.[25], 1996	188	Pts with thrombolytic therapy	CRP	Peak values	24 months	High CRP predicted an increased mortality up to 6 months. Survival regressions were not reported.
Furman et al.[26], 1996	2863	Unselected	WBC count	Admission	In-hospital	WBC count was an independent predictor for in-hospital mortality.
Anzai et al.[27], 1997	220	First Q-wave AMI	CRP	Peak values	1 year	CRP was independently associated with cardiac deaths.
Gheno et al.[28], 1999	205	Women aged 75 years	CRP	Admission	In-hospital	CRP was independently associated with early mortality.
Tommasi et al.[29], 1999	64	First uncomplicated AMI	CRP	Admission	13 ± 4 months	CRP was an independent predictor of combined cardiac events (cardiac death, recurrent angina, reinfarction).
Tomoda and Aoki[30], 2000	234	Pts with symptom onset < 6 hours treated with PTCA	CRP	Admission	In-hospital	Higher rate of adverse coronary events in patients with CRP > 0.3 mg/dl.
Nikfardjam et al.[31], 2000	729	Unselected	CRP	Admission	3 years (retrospective)	Higher CV mortality for higher CRP values. At multivariable Cox analysis a weak, non-significant association with mortality.
Mariotti et al.[32], 2001	55	First uncomplicated AMI	CRP, WBC count, ESR, α₁-acid glycoprotein	Admission	5 years (retrospective)	At multivariable Cox analysis CRP and α₁-acid glycoprotein were independent predictors of cardiac death.
Barron et al.[33], 2001	153 213	Pts aged 65 years	WBC count	Day 1	30 days	WBC count was an independent predictor for in-hospital and 30-day mortality.
Mueller et al.[34], 2002	1042	No-ST elevation - ACS with primary PTCA	CRP	Admission	Mean 20 months	At multivariable analysis CRP was independently associated with global mortality.
Zebrack et al.[35], 2002	319	Unselected	CRP	Hospital discharge	Mean 2.8 years	CRP was not associated with death/AMI neither at univariate nor at multivariable analysis.
Berton et al.[36], 2003	220	Unselected	CRP	Peak values	1 year	CRP was independently associated with global and HF mortality.
Albumin excretion rate						
Berton et al.[37], 1997	360	Unselected	AER	Day 1 and 3	In-hospital	ACR was independently associated with CV and global mortality. More powerful than the Killip class and LVEF.
Berton et al.[38], 1998	147	Hypertensives AMI	AER	Day 1 and 3	In-hospital	The combination of hypertension and microalbuminuria was independently associated with a greater risk of in-hospital mortality (1% in low-AER vs 25% in high-AER hypertensives).
Berton et al.[39], 2001	432	Unselected	ACR, renin, aldosterone, CRP	Day 1, 3 and 7	1 year	ACR was independently associated with CV and global mortality. More powerful than the Killip class and LVEF.

ACR = albumin to creatinine ratio; ACS = acute coronary syndrome; ANP = atrial natriuretic peptide; BNP = brain natriuretic peptide; CHF = congestive heart failure; CRP = C-reactive protein; CV = cardiovascular; E = epinephrine; ESR = erythrocyte sedimentation rate; LVEF = left ventricular ejection fraction; N-ANP = N-terminal atrial natriuretic peptide; N-BNP = N-terminal brain natriuretic peptide; NE = norepinephrine; NSTEAMI = non-ST-segment elevation acute myocardial infarction; PRA = plasma renin activity; PTCA = percutaneous transluminal coronary angioplasty; Pts = patients; rt-PA = recombinant tissue-type plasminogen activator; SAA = serum amyloid A; STEAMI = ST-segment elevation acute myocardial infarction; WBC = white blood cell.

dependent predictors of an adverse outcome after AMI and remain a cornerstone in the prognostic assessment of AMI patients[1-3,40,41].

During the past few years several investigations documented an association between mortality and the activation of a number of neurohumoral systems reflecting heart failure during AMI. These include catecholamines, renin-angiotensin-aldosterone system hormones, natriuretic cardiac peptides, and endothelins. Although all of these markers were found to be associated with a high risk of mortality after AMI, for some of them no independent prognostic information was found in multivariable models which included clinical signs of heart failure or LVEF.

Catecholamines. That the elevation of plasma levels of catecholamines is associated with increased early and late mortality in AMI has been known for long[42,43]. However, it is not yet clear whether this association holds true when other markers of risk are accounted for. In a CONSENSUS II substudy, which aimed at evaluating the prognostic value of neurohumoral measurements, Omland et al.[13] measured plasma epinephrine and norepinephrine concentrations in 145 AMI patients. Epinephrine and norepinephrine were found to be associated with 1-year cardiac death at univariate survival analysis, but this association did not reach statistical significance after adjustment for other clinical variables including clinical signs of heart failure. Though exclusion of severely ill patients at enrolment represents a potential limitation of this observation, more recent studies confirmed the association of catecholamines with mortality at univariate but not at multivariable analysis in which other neurohormones or clinical signs of heart failure were taken into account[15,18,22]. Thus, from these studies it appears that plasma catecholamines do not serve as a useful prognostic tool in the general AMI population.

Renin-angiotensin-aldosterone system. The association between the activity of the renin-angiotensin-aldosterone system and an adverse outcome after AMI was investigated in the SAVE study[15] which enrolled AMI patients with a LVEF 40% and no overt heart failure. In this study, a number of neurohumoral factors were evaluated (plasma renin activity, aldosterone, epinephrine, norepinephrine, dopamine, atrial natriuretic peptide-ANP and arginine vasopressin at the time of hospital discharge). The mean follow-up was 38 months. At univariate analysis plasma renin activity and aldosterone, along with the other factors but not epinephrine and norepinephrine, were related to cardiovascular mortality. At multivariable analysis, only plasma renin activity and ANP, but not aldosterone, were found to be associated with the overall cardiovascular mortality[15]. These results were obtained in a highly selected AMI population with a depressed left ventricular function, so that they are not directly transferable to all AMI patients. Furthermore, the neurohumoral assessment was performed in the subacute phase of AMI (mean time 12 days after admission) and this could have weakened the strength of the association between neurohumoral activation and outcome. However, it is noteworthy that we obtained similar results in a sample of 220 unselected AMI patients, in whom renin and aldosterone serum levels were measured on the third day after admission to the intensive care unit. At Cox regression analysis both renin (p = 0.02) and aldosterone (p = 0.04) showed a significant predictive power for the 3-year global mortality, but at multivariable analysis including LVEF only renin remained in the model (unpublished data). Overall, these data indicate that renin more than aldosterone carries useful prognostic information for mortality after AMI.

Endothelins. The role of endothelins in the risk assessment after AMI has recently been subject of evaluation. The endothelin family consists of four closely related 21-amino acid peptides (ET-1, ET-2, ET-3 and ET-4). They are produced in a variety of tissues where they act as modulators of the vasomotor tone, cell proliferation and hormone production. Endothelins have been implicated in the pathogenesis of several, mainly cardiovascular disorders, in view of their powerful vasoconstrictor and growth-promoting properties[44,45]. The first observation of a prognostic power of endothelin after AMI was made in the CONSENSUS study in which 142 patients were enrolled[17]. Endothelin serum levels measured on the third day after admission were found to be associated with the 1-year global mortality both at univariate analysis and at multivariable analysis which included Killip class assessment, indicating that it may yield additional prognostic information to that provided by other variables including clinically overt heart failure. Subsequently, in the same sample of patients, Omland et al.[18] also measured the serum levels of other neurohormones and confirmed the independent prediction of endothelin for outcome. However, in the subgroup of 85 patients in whom LVEF was also measured, the association between all neurohormones and outcome failed to reach statistical significance[18]. The latter analysis does not allow, however, one to draw definite conclusions, owing to the small size of the sample studied. Further research in larger samples will clarify whether plasma endothelin measurement adds independent prognostic information in AMI.

Cardiac peptides. Among neurohumoral factors, the cardiac peptides are by far those which received more attention in the risk assessment after AMI. ANP is a 28-amino acid peptide synthesized and secreted by the atria stimulated by wall stress and stretch. On secretion, the ANP prohormone is split into an N-terminal moiety (N-ANP) and the biologically active ANP[46]. Brain natriuretic peptide (BNP) is a 32-amino acid peptide structurally similar to ANP and secreted predominant-

ly from the ventricle, although smaller amounts are also released from atrial myocytes. On secretion, its pro-hormone is split into an N-terminal moiety (N-BNP) and the biologically active BNP. The release of BNP is predominantly mediated by ventricular wall stress, and its synthesis is increased with cardiac injury especially in the peri-infarct zone[47,48].

The first observation on the prognostic value of ANP was provided as early as 10 years ago by Svane-gaard et al.[11] who noted that among 55 AMI patients with low plasma concentrations of ANP measured on admission, the mortality rate was significantly lower than among patients with higher ANP levels. This finding was not validated by a survival regression analysis. However, similar results were obtained in a later study including 130 patients followed for 37 months after controlling data in a Cox regression model for the base-line characteristics[12]. In the CONSENSUS II substudy for neurohormones, Omland et al.[13] showed that ANP serum levels were independently associated with 1-year cardiac mortality after data adjustment for anamnestic, biochemical and clinical variables including clinical signs of heart failure. Even in the SAVE study, at univariate analysis, ANP along with other neu-rohumoral factors but not epinephrine and norepineph-rine, was related to cardiovascular mortality. At multi-variable analysis, as mentioned above, only ANP together with plasma renin activity were found to be associated with cardiovascular mortality[15]. In keeping with the results by others, this study indicates that the activation of several neurohumoral systems is associated with an adverse prognosis after AMI and that when several markers are simultaneously analyzed, plasma renin activity and ANP are the most precise predictors of outcome[15]. Even the N-ANP moiety measured in the same setting has shown to have a high prognostic power for mortality. In a multivariable model which included the patients' baseline variables and clinical signs of heart failure, Omland et al.[14] showed that N-ANP provided prognostic information superior to that obtained from ANP. Accordingly, in the patients of the SAVE study, N-ANP was found to be a stronger predictor of survival than ANP and at multivariable analysis, N-ANP in contrast to ANP and other neurohormones was still an independent predictor when the model included the baseline clinical variables, Killip class and LVEF evaluation[16]. This observation is in keeping with the results of a retrospective TIMI II substudy which compared the N-ANP serum levels measured on admission in 76 AMI patients who died after 1 year of follow-up and in 76 patients who survived[19]. However, in this study LVEF was not included among the predictors.

Because of its predominant ventricular secretion, it has been suggested that after AMI circulating concentrations of BNP may increase more than those of ANP[49]. Omland et al. measured BNP serum levels on day 3 after symptom onset in 131 patients of the CONSENSUS study and, at multivariable analysis including LVEF (performed in 79 patients), plasma BNP, but not ANP or N-ANP provided additional prognostic information beyond that provided by the evaluation of LVEF. These results suggest that plasma BNP determination may have a greater potential than ANP in complementing the standard prognostic indicators used in risk stratification after AMI[20]. Similar results were obtained in another study including 70 patients followed for 18 months[21]. Richards et al.[22] evaluated both BNP and N-BNP together with several other neurohumoral markers in 121 patients followed for 2 years. They found that both BNP and the N-BNP moiety were associated with the global mortality at univariate and at multivariable analyses including LVEF. A recently published study by de Lemos et al.[23] conducted in a large cohort of patients with acute coronary syndrome showed an association of BNP with the 10-month global mortality across the spectrum of acute coronary syndromes, independently of age, troponin I levels and the presence of heart failure, renal insufficiency and ST-segment deviation. In the subgroups of patients with ST-segment elevation AMI (n = 825) and no ST-segment elevation AMI (n = 565), this association was still present at univariate analysis, while no data are available with regard to multivariable analysis[23].

Overall, these studies indicate that both ANP and BNP along with their N-terminal moieties, measured within a few days after AMI, carry important prognostic information for the short- and long-term risk stratification. In this respect, BNP and N-BNP, probably because of their ventricular origin, appear to be stronger predictors of outcome than ANP and N-ANP.

Humoral factors reflecting inflammation

In contrast to the long-standing knowledge that neurohormonal activation is deleterious in AMI, the demonstration that inflammation has a critical role in the pathogenesis of this syndrome is relatively recent. Inflammation contributes at several levels to the rupture of vulnerable atherosclerotic plaques or to their superficial erosion, both of which may be followed by coronary thrombosis[50]. Many patients with AMI have multiple complex unstable plaques that are associated with adverse clinical outcomes, thereby suggesting that inflammation may have widespread effects throughout the coronary vasculature[51,52]. A number of inflammatory markers acting during AMI such as C-reactive protein (CRP), white blood cell count, erythrocyte sedimentation rate, α_1-acid glycoprotein, and serum amyloid A, have been linked to the outcomes after AMI. Of these, CRP, an acute-phase reactant which can be regarded as a component of the primitive innate immune system, is by far the most widely studied[53]. During AMI, CRP levels markedly increase, peaking 48-96 hours after symptom onset and returning towards normal around 7 days later[25].

Although there are no large studies on the association between CRP and mortality after AMI, some reports have shown that CRP may be of value even in this clinical setting. In 1995, Casl et al.[24] showed that peak CRP (and amyloid A) levels in patients with AMI was higher in those who had an early fatal outcome. Subsequently, Pietila et al.[25] studying patients with ST-segment elevation AMI and receiving thrombolytic agents reported that high serum CRP concentrations during the first days after AMI were associated with a higher mortality rate up to 6 months after the infarction. In these two studies, however, survival analyses for risk assessment were not used. Similar results were obtained by Anzai et al.[27] in patients with a first Q-wave AMI. At multivariable Cox analysis, peak CRP was found to be independently associated with the 1-year cardiac mortality. A very recent study by our group confirmed the independent prognostic significance of elevated peak CRP levels over and above that defined by traditional risk predictors after AMI. Notably, the CRP level proved to be a strong predictor chiefly for mortality due to heart failure[36]. Other studies showed that even when measured upon admission CRP levels are associated with mortality. Gheno et al.[28] reported that the admission CRP levels in elderly females were independently associated with in-hospital mortality. Tommasi et al.[29] obtained similar results for long-term mortality in patients with a first, uncomplicated AMI. In keeping with the above results, two studies performed in subgroups of AMI patients who underwent primary percutaneous transluminal coronary angioplasty showed that the admission CRP levels were independently associated with both in-hospital and long-term global mortality[30,34]. In contrast, negative results were observed in two studies with an almost 3-year follow-up. Nikfardjam et al.[31], in a retrospective evaluation, found at multivariable Cox analysis, that the association between the admission CRP levels and outcomes was largely explained by other baseline clinical variables and, after data adjustment, the predictive power of CRP was found to be weakened and not significant. Similarly, Zebrack et al.[35] did not find any association between the pre-discharge CRP measurements and death and/or non-fatal AMI in unselected patients. However, it should be pointed out that in the latter study, the lack of prognostic power could be due to the delay in measuring CRP levels after AMI, when the acute inflammatory process is almost extinguished.

Though much less investigated than CRP, even white blood cell count was found to be associated with outcomes after AMI. In the Worcester Heart Attack Study, Furman et al.[26] found an association between white blood cell count on admission and in-hospital mortality at multivariable Cox analysis. Similarly, in the Cooperative Cardiovascular Project study including a large cohort of elderly AMI patients, an increased white blood cell count was found to be independently associated with a higher risk of in-hospital and 30-day mortality[33].

Since it is unclear which inflammatory marker is more closely associated with mortality, a small retrospective study in patients with a first uncomplicated AMI compared CRP, white blood cell count, erythrocyte sedimentation rate and α_1-acid glycoprotein. At multivariable analysis, α_1-acid glycoprotein and CRP were found to be independently associated with long-term cardiac mortality while the white blood cell count and erythrocyte sedimentation rate were not[32]. These data suggest that CRP is a stronger predictor for an adverse outcome after AMI than the white blood cell count or erythrocyte sedimentation rate.

The timing of sampling seems to be crucial in order to fully exploit the predictive power of CRP. Admission sampling is of practical use for early risk assessment, but may not express the real extent of the acute inflammatory process and pre-discharge sampling showed a weak prognostic power. In agreement with the results by others[25,27], data from our group obtained in 220 AMI patients showed that the third day CRP measurement was more closely associated with the 1-year global mortality than the first or seventh day measurements[36].

Albumin excretion rate in acute myocardial infarction

Several studies have suggested that a subclinical increase in AER predicts the all-cause (largely cardiovascular) mortality in patients with diabetes mellitus[54-56]. Recent reports indicate that the presence of microalbuminuria may be a marker of cardiovascular disease even in patients with hypertension or in normotensive subjects[57-60]. Only very recently was AER investigated in the setting of AMI.

In 1991, Gosling et al.[61], at the Birmingham Hospital (UK), observed in 44 patients that initially AER increased during AMI. AER then fell rapidly over the subsequent 3 days. In 1995, our group examined the AER profile in 135 unselected AMI patients[62]. AER was measured by radioimmunoassay in 24-hour urine samples on day 1, 3 and 7 after admission. The 24-hour AER on day 1 and 3 after admission was found to be much higher in the AMI group than in the non-AMI controls and the differences were strongly significant even after adjusting for baseline variables. The AER profile shown by our patients during the first days after AMI closely overlapped the data firstly reported by Gosling et al.[61]. More recently, other studies confirmed the sharp increase in AER during AMI[63-65].

Pathophysiology. Gosling's[61] hypothesis suggested that ischemia produces a systemic increase in vascular permeability, including the vessels in the kidney, as part of the early acute inflammatory process accompanying AMI. In the above-mentioned study by our group, AER

was independently correlated with the creatine kinase and transaminase peak levels and with clinical signs of heart failure (evaluated according to the Killip classification)[62]. To better clarify the possible mechanisms for the AER increase in AMI, in a subsequent study we also measured the serum levels of renin, CRP and aldosterone, the number of neutrophil granulocytes and the erythrocyte sedimentation rate in 220 AMI patients[39]. At multivariable regression analysis AER was found to be related to the renin and aldosterone levels chiefly during the first 3 days after admission, while the inflammatory markers were found to be related to AER especially during the subsequent days (Fig. 1). These results support the hypothesis that urinary albumin may represent a comprehensive marker of the pathophysiological changes which occur during AMI reflecting both the severity of inflammation and the degree of heart failure[39]. AER could be regarded as an early marker of generalized endothelial dysfunction and observations in diabetic and hypertensive patients support this hypothesis[45,66-69]. Recently, Buffon et al.[52] showed that the acute inflammatory process during AMI involves not only the ischemic infarct-related coronary artery but also the unrelated coronary vessels. This observation is in keeping with the hypothesis of a widespread acute endothelial dysfunction during AMI.

Predictive value of albumin excretion rate for mortality. The association between AER and mortality has been well documented in diabetes and other clinical conditions, and the determination of AER is routinely used in the care management of diabetics[55,56]. Only a few studies investigated whether there is a relationship between AER and outcome in patients with AMI. In 1997, in a study in which we divided a sample of 360 AMI patients according to whether they had a normal AER, microalbuminuria or overt albuminuria (AER < 30, between 30 and 300 or > 300 mg/24 hours respectively), we observed that mortality progressively increased with increasing AER levels. In a Cox survival

model, AER was a better predictor of in-hospital mortality than other clinical variables including the Killip class or LVEF evaluation[37]. These results showed for the first time that measurement of AER during AMI yields additional prognostic information for short-term mortality to that provided by the clinical or echocardiographic evaluation of left ventricular performance. Even among hypertensive patients, who are known to be at greater risk for an adverse outcome after AMI, we observed that subjects with an AER < 30 mg/24 hours on the third day after AMI had a very low in-hospital mortality (1%) compared to those with AER 30 mg/24 hours (25%). The AER-mortality association was confirmed at multivariable survival analysis[38]. These data documented that the worse prognosis of hypertensive subjects in AMI is related to the presence of microalbuminuria. AER also appeared to be a powerful predictor of long-term mortality, as shown by our group in an unselected sample of 432 patients followed for 1 year[39]. AER, expressed as the albumin to creatinine ratio (ACR), was found to be 3.9 to 5.5 times higher in the patients who died than in those who survived. At Cox analysis, the ACR was closely associated with the global mortality in all regressions, and the ACR measured on the third day emerged as the strongest predictor of death among several clinical variables including the creatine kinase-MB peak, the Killip class and echocardiographic LVEF evaluation (p < 0.0001)[39].

To compare the predictive power of different humoral factors in AMI, we studied 220 unselected AMI patients followed for 3 years and compared the prognostic power of renin, CRP and ACR for the global mortality (unpublished data). All three indicators (analyzed by tertiles) were univariate predictors of long-term mortality after AMI (Fig. 2). When these three variables were included in a survival Cox model, the adjusted χ^2 values were 7.0, p = 0.008 for renin, 10.7, p = 0.001 for CRP, and 32.7, p < 0.0001 for ACR. The adjusted relative risk values were 1.5 (95% confidence limit-CL 1.1-2.1) for renin, 1.7 (95% CL 1.2-2.4) for CRP, and 2.6 (95% CL 1.8-3.8) for ACR. These data confirmed the independent prognostic value of renin and CRP, and documented that ACR is the strongest prognostic humoral factor in subjects with AMI.

Conclusions and perspectives

Activation of several neurohormonal systems occurs during AMI and is associated with short- and long-term outcomes. Among the several markers which have been tested, some have been shown to carry independent information for the mortality risk. Renin and cardiac peptides appear to be the strongest associates, and could represent helpful markers of risk in these patients. Though the role of acute inflammatory markers has been investigated only recently, mounting evidence indicates that CRP is also associated with an adverse
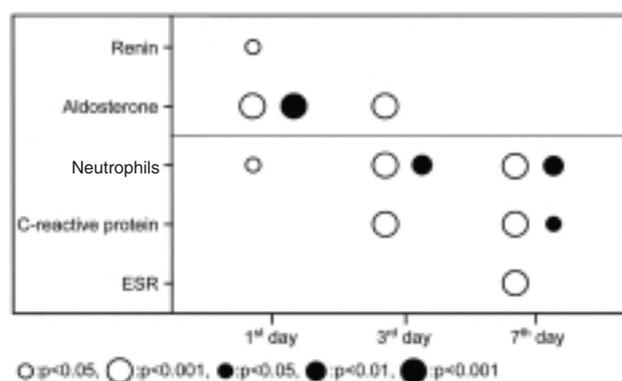
Figure 1. *Independent predictors of the albumin to creatinine ratio during the first week after admission to hospital for myocardial infarction at multivariable regression analysis. ESR = erythrocyte sedimentation rate. Data from Berton et al.[39].*
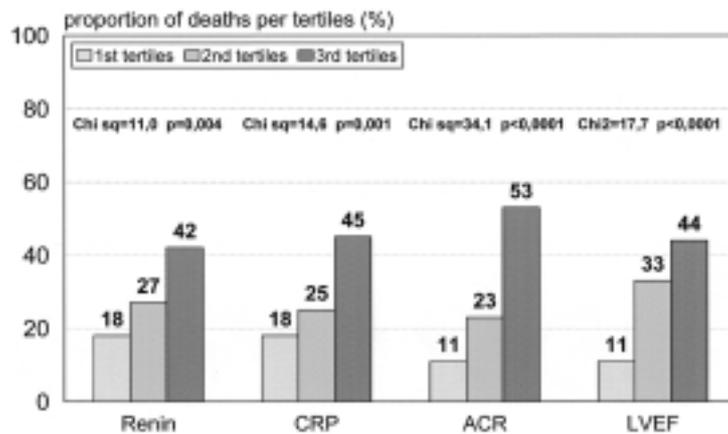
Figure 2. *Global mortality after 3 years of follow-up in 220 patients with acute myocardial infarction by tertiles of renin, C-reactive protein (CRP), albumin to creatinine ratio (ACR), and left ventricular ejection fraction (LVEF). Data from Berton et al. (unpublished results).*

outcome after AMI. The evidence for the association between AER and mortality in AMI has been provided only by recent results from our group. In our experience, AER has a strong independent association both with in-hospital and long-term mortality[37,39], and its prognostic power was found to be stronger than that shown by other humoral markers of risk or by the clinical and echocardiographic signs of congestive heart failure. The reason why AER is so closely associated with an adverse prognosis is still largely unknown, but the available data support the hypothesis that it reflects both the hemodynamic and inflammatory changes which accompany AMI.

From a clinical standpoint, the measurement of BNP and CRP during the first few days after admission appears to be a valuable tool in subjects with AMI. Even though the available evidence is still limited, we suggest that even the evaluation of AER should be included in the assessment of the overall cardiovascular risk in AMI patients, as this test appears to be a cost-effective means of identifying those patients at higher risk for whom additional preventive and therapeutic measures would be advisable. In our hands, AER showed a specificity of 76% and a sensitivity of 67% for the 3-year global mortality, and an accuracy of 73%, which was similar to that shown by CRP (72%), and greater than that provided by echocardiographic LVEF (62%) or renin (55%). Hopefully, to bridge the gap between research and practice the clinical value of AER in AMI will be validated in large prospective trials.

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