Albumin Excretion Rate Increases During Acute Myocardial Infarction and Strongly Predicts Early Mortality

Giuseppe Berton, MD; Tiziana Citro, MD; Rosa Palmieri, MD; Stefania Petucco, MD; Renzo De Toni, DBSc; Paolo Palatini, MD

Background This study was undertaken to assess whether albumin excretion rate (AER) increases during acute myocardial infarction (AMI) and whether it predicts in-hospital mortality.

Methods and Results The study was carried out in 496 subjects admitted to hospital for suspected AMI. Of these, 360 had evidence of AMI. The other 136 were studied as control subjects. AER was assessed by radioimmunoassay in three 24-hour urine collections performed on the first, third, and seventh days after admission. Left ventricular ejection fraction was measured by two-dimensional echocardiography in 254 subjects. AER adjusted for several confounders was higher in the AMI than the non-AMI group on the first (69.2±5.2 versus 27.3±8.5 mg/24 h, $P<.0001$) and third (30.3±2.7 versus 12.5±4.4 mg/24 h, $P=.001$) days, whereas no difference was present on the seventh day. When the subjects with heart failure were excluded, the difference between the two groups remained significant (first day, $P<.0001$; third day, $P=.001$). On the basis of classification of the 26 AMI patients who died in hospital according to whether they had normal AER, microalbuminuria, or overt albuminuria, mortality rate progressively increased with increasing levels of AER ($P<.0001$). In a Cox's proportional hazards model, AER was a better predictor of in-hospital mortality than Killip class or echocardiographic left ventricular ejection fraction. A cutoff value of 50 mg/24 h for first-day AER and 30 mg/24 h for third-day AER yielded a sensitivity of 92.3% and of 88.5% and a specificity of 72.4% and of 79.3%, respectively, for mortality. Adjusted relative risks for the two cutoff values were 17.3 (confidence limits, 4.6 to 112.7) and 8.4 (confidence limits, 2.4 to 39.3), respectively.

Conclusions These data show that AER increases during AMI and that it yields prognostic information additional to that provided by clinical or echocardiographic evaluation of left ventricular performance. (***Circulation*. 1997;96:3338-3345.**)

Key Words • myocardial infarction • heart failure • mortality • microalbuminuria

Several studies have suggested that a subclinical increase in AER, so-called microalbuminuria, predicts all-cause (largely cardiovascular) mortality in patients with diabetes mellitus.[1-3] In patients with hypertension or in normotensive subjects, the clinical relevance of microalbuminuria is less clear. However, recent reports indicate that in these subjects, as in diabetic patients, the presence of microalbuminuria may be a marker of cardiovascular disease, hypertensive left ventricular hypertrophy, or peripheral arterial obstructive disease.[4-7]

It is also clear that several factors, such as increased body weight, high triglyceride levels, low HDL cholesterol levels, and raised serum insulin levels, are statistically correlated to microalbuminuria in general population studies. The clustering of these factors in microalbuminuric individuals may help to explain the increased mortality associated with AER in the background population.[8,9]

Received April 23, 1997; revision received July 21, 1997; accepted August 1, 1997.

From the Divisione di Cardiologia, Ospedale di Conegliano Veneto (G.B.), Divisione di Medicina, Ospedale di Conegliano Veneto (T.C.), Divisione di Medicina, Ospedale di Adria (R.P.), Divisione di Cardiologia, Ospedale di Bassano del Grappa (S.P.), and Clinica Medica 1a, Università di Padova (R. De T., P.P.), Italy.

Presented at the 68th annual Scientific Sessions of the American Heart Association, Anaheim, Calif, November 13-16, 1995.

Correspondence to Prof Paolo Palatini, Clinica Medica 1a, Via Giustiniani 2, 35126 Padova, Italy.

Recently, increased AER was found to be an early and proportional response to AMI.[10] The rise in AER associated with AMI was attributed to a systemic increase in vascular permeability, including the renal vessels, as part of the early acute inflammatory process that accompanies AMI.[10]

The present study was a prospective cross-sectional analysis of a large number of patients admitted to three coronary care units for AMI. The aims of the study were to (1) examine whether and for how long AER was increased after AMI, (2) assess its relationship with thrombolytic therapy and the presence of congestive heart failure, and (3) report on the predictive power of AER for in-hospital mortality in these subjects.

Methods

Patients

Five-hundred forty-eight patients consecutively admitted to the intensive care units at Bassano del Grappa (n=228), Adria (n=179), and Conegliano Veneto (n=141) Hospitals (Northeast Italy) for suspected AMI were prospectively studied. Thirty-five patients with urinary tract infections or other concomitant clinical situations that could affect AER were excluded from the study. Seventeen other patients were excluded because of insufficient data collection; thus, the final analysis was performed in 496 subjects. Having given informed consent, the patients were interviewed by a physician who completed a standard record form covering details of past medical history. The study was approved by the hospital ethics committees.

The criteria for AMI diagnosis were based on fulfillment of at least two of the following: central chest pain lasting >30

Selected Abbreviations and Acronyms

AER = albumin excretion rate
AMI = acute myocardial infarction
CL = confidence limits
LVEF = left ventricular ejection fraction

minutes, typical changes in serum enzymes (total CK, CK-MB, AST, LDH), typical ECG changes with occurrence of pathological Q waves, and/or localized ST-T changes in at least two contiguous leads.[11]

On admission and thereafter every 4 hours, serum enzymes and 12-lead ECG were recorded. Starting from the third day of admission, these examinations were performed daily. On the first and seventh days after admission, venous blood was drawn for determination of blood glucose and serum levels of total and HDL cholesterol, triglycerides, creatinine, and uric acid. Urinalysis was performed on the first, third, and seventh days. Blood pressure was measured by specially trained nurses with a mercury sphygmomanometer with a cuff of appropriate size. The mean of three recordings was used. Heart rate was measured by palpation of the radial pulse. The presence and degree of heart failure were assessed on the first, third, and seventh days after admission according to Killip classification.[12] The in-hospital length of bedrest was similar for AMI patients and control subjects during the 7 days of the study.

Echocardiography

To evaluate LVEF, a two-dimensional echocardiogram was performed in 282 AMI patients within 7 days after admission. Patients were examined while lying in the left lateral position. Four- and two-chamber apical views were recorded onto VHS cassettes. Centralized determination of LVEF (%) was performed according to Simson's method.[13] Calculations were obtained by two physicians who had no knowledge of patients' clinical data and evaluated the mean of the two measurements. Twenty-eight subjects in whom the echocardiographic images were technically unsatisfactory were discarded from the analysis; thus, LVEF could be obtained for 254 patients.

AER Assessment

AER was assessed in three 24-hour urinary collections, performed on the first, third, and seventh days after admission. For collection of the urine sample, a 2-L plastic container was used, and the volume of urine was measured to the nearest 50 mL. Urine aliquots were stored deep-frozen at −20°C and sent to the laboratory of Clinica Medica 1a of Padua University (Italy), where albumin levels were determined through radioimmunoassay with a human ALB. KIT double-antibody (TechnoGenetics, Cassina De Pecchi).[14] The detection limit of the method was 0.5 mg/L, and the between-batch coefficient of variation was 243.5%. AER was expressed as mg/24 h. Patients with AER of 30 to 300 mg/24 h were said to have microalbuminuria.[2] The analyst was unaware of patients' diagnoses at the time of the measurement.

Measurement of Hormones

In the last 68 consecutive AMI patients and 22 control subjects, plasma renin was measured with immunoradiometric assay and aldosterone was measured with radioimmunoassay on the first and third days after admission with the use of kits from Nichols Institute and Radim, respectively. Thirty-four patients were classified as Killip class of >1, and 34 patients were classified as Killip class 1. The clinical characteristics of the three groups of subjects were comparable to those of the entire sample. Venous blood samples were placed on ice and centrifuged within 20 minutes at +4°C; plasma was stored at −20°C until assayed.

Data Analysis

Statistical analysis was carried out with Biomedical Data Package (BMDP) for Windows, Version 1.1, and Systat Version 5.01 package. To correct for skewed distribution (positive) AER, renin and aldosterone were log-transformed. Differences in mean values were tested with unpaired Student's t test. Between-group comparisons on the first, third, and seventh days of admission were performed using repeated-measure ANCOVA and Tukey's posthoc test. The covariates used in each comparison are reported in "Results."

Proportions were compared with the use of the χ^2 test. Variables significantly associated in correlation analysis with log-AER were entered as independent variables in a forward stepwise multiple regression analysis with log-AER as the dependent variable (minimum tolerance for entry into model, 0.01; α to enter and α to remove=.15). When considering in-hospital mortality, the Cox's proportional hazards regression model was used. Analyses were performed using a significance level of α=.05 (two-sided). The categorical variables were grouped into classes such that smoking, having hypertension, and so forth were scored 1, and the opposite was scored 0. Killip class was considered a four-class variable. AMI site was fitted as a two-dummy variable. The risk factors considered in the model were all entered into a first model. This model was reduced by removing the variable causing the least change in significance. This procedure was continued until no further variables could be removed without producing a significant change of the model.[15] AMI patients were divided into two groups according to their Killip class (≤2 or >2) and LVEF (≥40% or <40%). Kaplan-Meier life-table methods were used to estimate mortality rates for these groups. Relative risks were adjusted for all clinical confounders, including Killip class in the subjects stratified according to LVEF and LVEF in the subjects stratified according to Killip class. In the adjustments, Killip class on the day of AER assessment was used. Sensitivity was calculated as the proportion of dead patients and specificity was calculated as the proportion of alive patients correctly identified by AER measurement. Positive predictive value was calculated as the proportion of patients with a positive test who died, and negative predictive value was calculated as the proportion of patients with a negative test who survived. Discriminant analysis was used to identify the optimal cutoff value for AER to divide patients into a high-risk group and a low-risk group.

Data are presented as mean±SD unless otherwise specified. All P values are two-tailed. Statistical significance was established at P<.05.

Results

Subject Characteristics

Of the 496 patients included in the study, 360 had evidence of AMI on the basis of the aforementioned criteria. The other 136 subjects were used as a control group. Of these, 57 manifested signs of unstable angina, 42 had chronic ischemic heart disease, and 37 had nonischemic cardiac diseases (valvular disease, dilated cardiomyopathy, and so forth). The main clinical characteristics of the two groups are reported in Table 1. The AMI patients were slightly older than the non-AMI subjects, were more frequently diabetics or smokers, and less frequently reported prior angina. Blood pressure was lower in the AMI group. The between-group differences remained significant after adjustment for age, previous angina, current smoking, and presence or absence of diabetes. HDL cholesterol was lower in AMI group, whereas total cholesterol, triglyceride, creatinine, and uric acid levels were similar in the two groups. Heart failure was more prevalent among the AMI patients

TABLE 1. Clinical Characteristics of Patients With AMI and of Control Subjects

	AMI Patients (n=360)	Control Subjects (n=136)	P
Age, y	66.4±12.4	63.6±12.0	.019
Sex, F	112 (31%)	48 (35%)	NS
Body mass index, kg/m^2	25.8±3.7	26.0±4.0	NS
Prior AMI, n	87 (24%)	44 (32%)	NS
Prior angina, n	88 (24%)	47 (34%)	.024
Current smoking, n	136 (38%)	36 (26%)	.018
Hypertensive, n	168 (47%)	67 (49%)	NS
Diabetics, n	93 (26%)	19 (14%)	.005
SBP, mm Hg	121±16	128±16	<.0001
DBP, mm Hg	73±12	77±10	<.0001
Heart rate, bpm	75±16	74±13	NS
Total cholesterol, mg/dL	210±53	206±43	NS
HDL cholesterol, mg/dL	44±11	47±12	.014
Triglycerides, mg/dL	152±107	154±111	NS
Serum creatinine, mg/dL	1.0±0.3	1.0±0.3	NS
Uric acid, mg/dL	5.8±1.8	5.6±1.5	NS
Heart failure (1st week), n	149 (41%)	34 (25%)	.001
Therapy, n			
Nitrate	328 (91%)	93 (68%)	<.0001
β-Blockers	87 (24%)	33 (24%)	NS
Calcium channel blocker	50 (14%)	53 (39%)	<.0001
Diuretic	91 (25%)	23 (17%)	.048
ACE inhibitor	113 (31%)	38 (28%)	NS
Digitalis	38 (11%)	20 (15%)	NS
Antiarrhythmic	46 (13%)	19 (14%)	NS
Antiplatelet	291 (81%)	76 (57%)	<.0001
Anticoagulant	332 (92%)	82 (60%)	<.0001

SBP indicates systolic blood pressure; DBP, diastolic blood pressure.

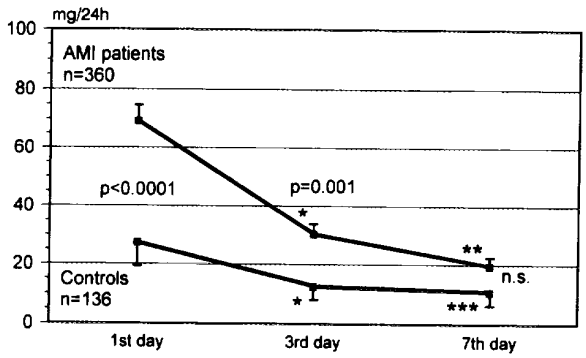
than the control subjects. Nitrates, diuretics, antiplatelets, and anticoagulants were more frequently used in the AMI patients, and calcium channel blockers were used in the non-AMI group.

Among the AMI subjects, there were 248 men and 112 women. The women were older than the men (73.8±10.8 versus 63.1±11.8 years; $P<.0001$), had a greater frequency of anterior AMI (40.2% versus 29.8%; $P=.02$) and heart failure (60.7% versus 32.7%; $P<.0001$), and were less commonly treated with thrombolytic agents (26.8% versus 41.5%; $P=.007$). LVEF was similar in the two sexes (men, 50.7±11.7%; n=179; women, 50.0±11.9%, n=75).

AER Levels

The 24-hour excretion of albumin was significantly higher in the AMI than the control group after adjustment for age, blood pressure, previous angina, presence or absence of diabetes, current smoking, and administration of the various drugs ($F=12.3$, $P<.0001$) (Figure). Tukey's test showed that the between-group differences were significant on the first (69.2±5.2 versus 27.3±8.5 mg/24 h) and third (30.3±2.7 versus 12.5±4.4 mg/24 h) days. AER progressively fell from the first to the seventh day in the AMI patients, so on the seventh day, the difference between the two groups was no longer significant.

AER was slightly higher in the women than the men, but after adjustment for clinical variables, no significant differences were observed throughout the period of observation. The AMI site did not influence the levels of



AER in patients with AMI and control subjects on the first, third, and seventh days after admission to the coronary care unit. *$P<.0001$, vs first day, **$P<.0001$ vs first and third days, ***$P=.004$ vs first day.

AER; the administration of thrombolytic agents; or the use of nitrates, ACE inhibitors, β-blockers, and calcium channel blockers.

Effect of Heart Failure on AER

The levels of AER in the subjects with AMI (n=211) and the control subjects (n=102) who did not manifest signs of heart failure (Killip class 1) were also calculated. After adjustment for sex, previous angina, current smoking, blood pressure, and administration of various drugs, AER was higher in the AMI than the non-AMI patients ($F=18.1$, $P<.0001$). Tukey's test showed that the between-group differences were significant on the first (38.0±3.7 versus 13.2±5.3 mg/24 h) and third (14.7±1.5 versus 7.0±2.1 mg/24 h) days. One hundred forty-nine patients in the AMI group and 34 patients in the control group belonged to Killip classes 2 to 4. Even though there was a tendency for AER to be higher in the subjects with AMI than the control subjects, no between-group difference turned out to be statistically significant in any of the 3 days.

AER and LVEF

The mean age of the patients with echocardiographic LVEF (n=254) was similar to that of the entire group (65.4±12.3 versus 66.4±12.4 years, P=NS). After adjustment for confounders, the levels of AER in the patients divided according to whether LVEF was ≥50% (n=132) or <50% (n=122) were higher in the low-LVEF group ($F=8.32$, $P=.004$). The between-group differences were significant on the first (93.0±9.6 versus 38.5±9.2 mg/24 h, $P<.0001$), third (39.7±4.3 versus 15.5±4.1 mg/24 h, $P=.001$), and seventh (26.9±3.6 versus 8.5±3.6 mg/24 h, $P=.04$) days.

Multiple Regression Analysis

In a multiple regression analysis, which considered AER as the dependent variable and the continuous (age, blood pressure, heart rate, serum enzymes) and categorical (Killip class, presence or absence of diabetes mellitus, β-blocker, and ACE inhibitors therapy) variables significant at the univariate level as the independent ones, age ($P=.025$), CK peak ($P<.0001$), Killip class ($P<.0001$), and heart rate ($P=.088$) correlated with AER measured on the first day after admission. These variables also correlated with AER on the third day

TABLE 2. Plasma Renin and Aldosterone in 68 Subjects With AMI Divided by Killip Class and 22 Control Subjects

	Renin, pg/mL		Aldosterone, pg/mL	
	day 1	day 3	day 1	day 3
AMI, Killip class >1 (n=34)	33.5±4.3*	22.6±3.8	186.7±17.6*	132.0±13.6
AMI, Killip class 1 (n=34)	16.5±3.9	11.8±3.1	83.4±17.6*	41.5±13.6
Control subjects (n=22)	18.1±5.1	15.2±4.0	79.9±23.7*	59.5±18.7

Data adjusted for age, sex, history of IMA or angina, thrombolysis, therapy with ACE inhibitors, diuretics, β-blockers, or calcium antagonists.

Results of repeated-measures ANCOVA: $P<.01$ for AMI, Killip class >1 vs the other two groups.

*$P<.001$ vs day 3 (Tukey's test). Data are mean±SEM.

($P<.0001$, $<.0001$, $<.0001$, and.030, respectively) and the seventh day after admission ($P=.038$, .023, .002, and .008, respectively). Furthermore, on the third day, presence of diabetes also correlated with AER ($P=.045$).

In the subgroup with LVEF, age ($P=.025$), CK peak ($P=.002$), Killip class ($P=.003$), and ACE inhibitors therapy ($P=.014$) were independent predictors of AER on the first day. On the third day, age ($P<.0001$), CK peak ($P=.005$), Killip class ($P=.054$), LVEF ($P=.081$), and presence of diabetes ($P=.024$) showed a significant association with AER. On the seventh day, age ($P=.010$) and LVEF ($P=.017$) remained significant predictors of AER. When the same regression was made in the subjects of Killip class of >1 (n=98), LVEF remained a significant predictor of AER on the first and third days ($P=.018$ and.022, respectively). In contrast, in the subjects of Killip class 1 (n=156), LVEF was not associated with AER in any of the three samples.

Hormones

In the AMI patients in Killip class of >1, plasma renin and aldosterone adjusted for confounders (Table 2) were more elevated on the first day than on the third day and higher than in the AMI patients in Killip class 1 or the control subjects. No differences were found between the AMI patients in Killip class 1 and the control subjects. In multivariate regression analyses, which included treatment with ACE inhibitors, diuretics, and β-blockers in the models, first-day renin ($P=.09$) and aldosterone ($P=.02$) were positively related to Killip class and negatively related to LVEF ($P=.09$ and $P=.0001$, respectively). Similar results were obtained for third-day hormones. Such relations were present also within the subjects in Killip class of >1 but not in Killip class 1 patients. In subjects of Killip class of >1, plasma aldosterone showed a significant positive association with AER in multivariate analysis ($P=.02$ on third day), whereas renin did not. No relationship was found between hormones and AER in Killip class 1 patients.

In-Hospital Mortality

During the hospital stay (range, 3 to 62 days), 25 AMI patients died from cardiovascular complications, and 1 died from esophageal variceal bleeding (Table 3).

On the first day, AER in the AMI patients who died was 191.7±32.0 versus 59.7±5.5 mg/24 h in the survivors ($P<.0001$); on the third day, it was 105.4±22.8 versus 24.4±2.5 mg/24 h, respectively ($P<.0001$). By classifying the 26 AMI patients who died according to whether they had normal AER, microalbuminuria, or overt albuminuria, mortality rate progressively increased from the first to the third group (Table 4).

Possible predictors of in-hospital mortality were examined in a Cox proportional hazards regression analysis. The continuous variables tested included age, CK-MB and AST peaks, heart rate, and log-AER. The following categorical variables were also examined: sex; preexisting hypertension; presence of diabetes, smoking, previous myocardial infarction, and/or angina; AMI site; thrombolysis; arrhythmias; and Killip class. In univariate analysis, log-AER was significantly related to mortality rate ($P<.0001$). Age ($P<.0001$), sex ($P=.003$), preexisting hypertension ($P=.004$), CK-MB peak ($P=.0006$), AST peak ($P=.001$), heart rate ($P<.0001$), clinical heart failure ($P<.0001$), arrhythmias ($P=.03$), thrombolysis ($P=.04$), and LVEF in the group of the 254 subjects who had echocardiographic examination ($P<.0001$) were also significantly related to mortality. In a multivariate model, on the first day after admission, death was predicted by log-AER, age, Killip class, and CK-MB peak (Table 5). AER measured on the third day remained the strongest predictor of in-hospital mortality, again followed by Killip class and age (Table 5). Also in the subgroup of subjects with LVEF, AER was the most important predictor of mortality (Table 5). In this subgroup, LVEF excluded Killip class from the model.

To assess whether the predictive value of AER was also present in the subjects who manifested clinical signs of heart failure, Cox analysis was repeated in the 149 patients with Killip class of >1. In this clinical setting, AER emerged as a strong predictor of mortality (Table 5).

The estimated probability of early mortality as a function of AER according to a discriminant analysis model showed that the AER cutoff points that gave the highest odds ratios approximated 50 mg/24 h on the first day and 30 mg/24 h on the third day. For first-day AER, a value of ≥50 mg/24 h was associated with a highly increased risk of death. Unadjusted and adjusted relative risks were 27.8 (CL, 8.3 to 173.1) and 17.3 (CL, 4.6 to 112.7), respectively. Relative risks for AER of ≥30 mg/24 h on the third day were 25.1 (CL, 8.7 to 105.9) and 8.4 (CL, 2.4 to 39.3), respectively. The 50 mg/24 h cutoff value on the first day gave a sensitivity of 92.3% and a specificity of 72.4%. The corresponding positive and negative predictive values were 20.7% and 99.2%, respectively. For the 30 mg/24 h third-day AER cutoff value, sensitivity and specificity were 88.5% and 79.3%, respectively, with a positive predictive value of 25.0% and a negative predictive value of 98.9%.

The probability of mortality as a function of AER was also studied in the patients divided according to Killip class (≥2 or >2) (Table 6). AER measured on the first and third days was a predictor of mortality in both groups, especially in the patients in the Killip classes of ≤2. When only the subjects in Killip class 1 were considered, AER again was a strong predictor of mortality, with adjusted relative risks of 12.3 (CL, 1.6 to 247.9; $P=.005$) on the first day and 22.4 (CL, 2.9 to 453.9; $P=.0001$) on the third day. Also, in the subjects divided according to whether their LVEF was ≥40% or <40%, increased AER was associated with a higher rate of mortality in both groups (Table 6).

TABLE 3. Characteristics, AER, and Causes of Death for the 26 AMI Patients Who Died In-Hospital

Patient	Sex	Age, y	CK Peak, UI/L	Thrombolysis	AMI Site	Killip Class (first week)	LVEF, %	Arrhythmias (week 1)	AER 1st, mg/24 h	AER 3rd, mg/24 h	AER 7th, mg/24 h	Death	
												Day	Cause
1	M	67	978	+	Inf	1	62	−	236.0	102.3		4th	Stroke
2	M	71	974	−	non-Q wave	1	49	−	99.0	49.2		4th	Cardiac rupture
3	M	75	806	−	Ant	1	48	−	15.2	11.7		4th	Cardiac rupture
4	F	80	1597	−	Ant	4	35	+++	52.5	39.0		4th	Shock
5	F	86	1040	−	Inf	2	...	−	105.0	47.5		5th	Reinfarction shock
6	F	71	2333	−	Inf	3	...	+	344.0	99.4		6th	Esophageal bleeding
7	F	85	725	−	Ant	4	...	−	203.4	109.8		7th	Cardiac rupture
8	F	87	561	−	Inf	2	...	−	235.0	121.0		7th	Shock
9	M	77	585	−	Non-Q wave	4	30	+	110.7	36.0	35.6	8th	Shock
10	F	82	5110	+	Ant	3	52	−	312.0	154.8	36.8	8th	Ven. septum rupture
11	F	73	4145	−	Ant	3	34	+	62.5	88.4	72.0	9th	Shock
12	M	84	354	−	Inf	3	48	+	95.0	16.9	49.6	9th	Stroke
13	F	79	1336	−	Inf	3	...	−	480.0	153.0	160.0	10th	Shock
14	M	88	1618	−	Ant	2	32	−	71.5	63.7	29.7	10th	Shock
15	F	89	1636	−	Inf	2	49	+++	166.4	81.2	22.8	10th	Stroke
16	M	73	4540	+	Inf	3	26	−	330.0	232.0	220.0	11th	Shock
17	F	75	3760	−	Inf	4	46	+	68.2	51.3	...	11th	Shock
18	F	48	8680	+	Ant	3	...	−	543.4	601.6	187.2	13th	Stroke
19	M	79	472	−	Inf	2	28	+	165.7	208.6	...	13th	Ven. fibrillation
20	M	77	5350	−	Ant	2	...	+	12.9	13.3	7.2	14th	Cardiac rupture
21	F	95	655	−	Non-Q wave	2	45	−	52.8	126.0	14.6	21th	Shock
22	M	66	3246	+	Ant	4	25	+++	472.6	133.9	57.2	34th	Shock
23	M	76	1620	−	Inf	2	41	++	508.7	43.3	52.8	35th	Ven. septum rupture
24	M	73	1532	−	Ant	2	43	−	67.2	75.4	25.6	39th	Reinfarction/ shock
25	F	82	522	−	Ant	3	...	−	103.4	51.0	127.3	45th	Ven. septum rupture
26	M	67	4710	−	Ant	4	31	+	70.2	31.0	16.2	62th	Ven. fibrillation

Ant indicates anterior; Inf, inferior; 1st, 3rd and 7th, on the 1st, 3rd, and 7th hospital day, respectively; Ven., ventricular; +, tachyarrhythmia; ++, bradyarrhythmia; +++, tachyarrhythmia and bradyarrhythmia; and ..., not measured.

Discussion

The results of the present study showed a marked increase in AER in the acute phase of AMI. After the initial rise, urinary albumin progressively fell toward normal during the week after admission to hospital. These data are in agreement with those by Gosling et al,[10] who found a transient increase in AER in 44 subjects admitted for AMI. In the present study, the differences in AER between the patients with AMI and the control subjects remained significant on the first and third days after admission, also after adjustment for several clinical confounders. Because 41% of our AMI patients versus 24% of the non-AMI subjects had signs of heart failure, we wanted to determine whether the difference in AER between the two groups was also present after exclusion of the patients with heart failure. In fact, it is known that this clinical condition is accompanied by an enhanced urinary excretion of albumin.[16,17] The elevated glomerular capillary pressure, which is present in congestive heart failure, facilitates the transglomerular passage of albumin.[16] The increased activity of the renin-angiotensin system seems to account for this effect.[16] In addition, the high levels of atrial natriuretic peptide also contribute to the renal escape of albumin in heart failure by increasing capillary permeability.[18,19] It is therefore crucial to know whether the increased levels of AER associated with AMI are due to myocardial infarction per se or to its hemodynamic consequences.

Our results showed that the increase in AER on the first and third days after admission was also present in the AMI subjects who had no signs of heart failure. This aspect was not taken into account by Gosling at al.[10] In a recent report, Ellekilde et al[17] found greater levels of AER in a group of AMI patients with heart failure compared with a group without heart failure, but no information was provided as to whether the AMI patients without heart failure had greater AER than the

TABLE 4. In-Hospital Mortality Rate in Patients With AMI Divided According to Whether They Had Normal AER, Microalbuminuria, or Overt Albuminuria on the First and Third Days After Admission to the Hospital

First Day	AER <30 (n=204)	AER 30-299 (n=135)	AER ≥300 (n=21)
Alive, n (%)	202 (99.0)	118 (87.4)	14 (66.7)
In-Hospital mortality rate, n (%)	2 (1.0)	17 (12.6)	7 (33.3)

Third Day	AER <30 (n=268)	AER 30-299 (n=90)	AER ≥300 (n=2)
Alive, n (%)	265 (98.9)	68 (75.6)	1 (50)
In-Hospital mortality rate, n (%)	3 (1.1)	22 (24.4)	1 (50)

χ^2=39.0, P<.0001 and χ^2=60.2, P<.0001 for first and third day, respectively.

TABLE 5. Cox Proportional Hazards Model for Mortality in All Subjects, in the Subjects With Clinical Signs of Heart Failure, and in the Subjects With Echocardiographic LVEF

	First Day Assessment			Third Day Assessment		
Independent Variable	Regression Coefficient ±SEM	χ^2	P	Regression Coefficient ±SEM	χ^2	P
All subjects (n=360)						
log-AER	.74±.20	16.6	<.0001	.85±.23	15.9	<.0001
Age	.10±.03	11.0	.0009	.08±.03	6.9	.008
Killip class (1-4)	.60±.27	4.2	.03	.95±.31	9.1	.002
CK-MB peak	.01±.01	4.8	.02	NS		
Subjects with heart failure (n=149)						
log-AER	.84±.25	14.8	<.0001	.86±.28	11.9	.0005
Age	.11±.04	8.9	.002	.11±.04	7.7	.005
CK-MB	.01±.01	6.7	.009	.01±.01	4.7	.02
Hypertension	1.28±.60	5.4	.02	NS		
Killip class (2-4)	.66±.31	4.5	.03	1.24±.40	10.8	.001
Thrombolysis	−1.37±.76	3.8	.05	NS		
Subjects with LVEF (n=254)						
log-AER	.54±.24	5.0	.02	.76±.30	7.3	.007
Age	.12±.04	11.9	.0005	.09±.04	4.8	.02
LVEF	.06±.03	4.1	.04	−.05±.03	3.6	.05

Data were collected on the first and third day after admission.

control subjects. In agreement with the results by von Eyben et al,[20] no effect of thrombolytic therapy was observed on urinary albumin.

A possible limitation of the present analysis is that patients in Killip class 1 may be not identical hemodynamically and may have a broad range of effective arterial volumes, which might be responsible for the observed differences in AER.[21-23] This issue was dealt with by measuring renin and aldosterone taken as estimates of the effective arterial volume in 90 patients. In agreement with the data from the literature, in the patients with heart failure (Killip class of >1), both hormones were elevated on the first day after admission, decreased during the following days, and were inversely related to LVEF.[21,23] In these subjects, plasma aldosterone was related to AER. However, in the patients without clinical signs of heart failure, both renin and aldosterone levels were similar to those in the control subjects and were unrelated to the level of AER, indicating that AER cannot be considered a mere indicator of inadequate arterial volume. Furthermore, after division of the patients according to the Killip class, the difference between the AMI patients and the control subjects remained significant only for the subjects in Killip class 1, whereas it lost the statistical significance for the patients in classes 2 to 4. These data suggest that the main discriminant between the two groups was AMI per se and not heart failure. The more frequent administration of nitrates to the AMI patients than to the control subjects might be another factor potentially affecting the difference in AER between the two groups. However, AER differences remained significant after adjustment of the data for nitrate administration or exclusion of subjects not taking nitrates.

The reason why AER increases in AMI subjects with no signs of heart failure remains a matter of dispute. The normal levels of renin and aldosterone and the lack of correlation between these hormones and AER in the

TABLE 6. Kaplan-Meier Estimates and Relative Risk of In-Hospital Mortality in the Subjects Divided by Killip Class or LVEF

First-Day Assessment				Third-Day Assessment			
AER, mg/24 h	% of Death	P (log-rank test)	RR (CL)	AER, mg/24 h	% of Death	P (log-rank test)	RR (CL)
Killip class ≤2 (n=328)							
<50	0.8			<30	1.1		
≥50	12.1	<.00001	12.9 (2.7-100.1)	≥30	14.9	<.00001	6.9 (1.7-37.3)
Killip class >2 (n=32)							
<50	0.0			<30	0.0		
≥50	52.0	.02	3.1 (1.3-8.3)	≥30	52.0	.02	2.6 (1.1-7.2)
LVEF ≥40% (n=213)							
<50	0.6			<30	1.2		
≥50	15.5	<.00001	8.6 (2.1-57.6)	≥30	19.0	<.00001	9.6 (1.7-83.3)
LVEF <40% (n=41)							
<50	0.0			<30	0.0		
≥50	36.4	.003	4.5 (1.3-22.1)	≥30	42.1	.0008	8.3 (1.2-111.5)

RR=relative risk adjusted for clinical confounders (Killip same day, see methods).

subjects in Killip class 1 suggest that AER elevation is not due to subtle degrees of heart failure. According to Gosling et al,[10] microalbuminuria is the consequence of the inflammatory reaction that accompanies AMI and involves the renal vascular system. A systemic release of thromboxanes and leukotrienes has been reported in patients with severe unstable angina and AMI.[24,25] Furthermore, the increase in plasma C-reactive protein and serum amyloid A, which has recently been documented in patients with unstable angina and AMI,[26] points to the existence of an important inflammatory component in these clinical conditions.

In-Hospital Mortality

The results of the present study indicate that in AMI, even a slight-to-moderate increase in urinary albumin concentration measured on the first 3 days after admission is associated with a considerable increase in early mortality. In fact, Cox's analysis showed that both first-day AER and third-day AER were the strongest independent predictors of in-hospital mortality.

Clinical signs of congestive heart failure and decreased LVEF are known to be major independent predictors of adverse outcome after AMI.[27,28] In the present study, urinary albumin concentration also held a strong predictive power for in-hospital mortality in the subgroup of patients in classes 2 to 4 of the Killip classification, suggesting that AER is not merely a marker of heart failure. During the past few years, several investigations have documented an association between mortality and a number of neurohumoral measurements during the first few days after AMI, independent of Killip classification.[21,29] However, recent results showed that neurohumoral determination provided complementary prognostic information to clinical evaluation but not to LVEF.[22] In the present study, urinary albumin remained a strong predictor of in-hospital mortality in the patients with objective assessment of left ventricular systolic function, indicating that AER measurement for risk stratification purposes after AMI is justified in patients who undergo echocardiographic assessment of LVEF. The relevant complementary prognostic information to LVEF and Killip classification provided by urinary albumin suggests that AER should be regarded not merely as a marker of hemodynamic compromise but rather as an epiphenomenon of a more complex pathophysiological process. The lack of association found in the multivariate model between mortality and hypertension or diabetes, which are known to increase AER[1,2,4] and adversely affect outcome in AMI,[30-32] suggests that urinary albumin outweighed the predictive power of these diseases. Thus, AER appears as an integrative marker of several clinical conditions related to increased risk of mortality in AMI.

From our results, we could devise two different optimal cutoff points for first-day AER (50 mg/24 h) and third-day AER (30 mg/24 h) to divide patients into high- and low-risk groups. Only 2 of the 26 patients who died during the follow-up period had first-day AER of <50 mg/24 h, and 3 had third-day AER of <30 mg/24 h. In the literature, AER values of >30 mg/24 h are currently considered abnormal; they provided important prognostic information in diabetic patients.[2,3] The AER increase that accompanies AMI is a dynamic process, and thus it is conceivable that different threshold values may be identified in the days that follow AMI. The predictive value of the two AER cutoffs held true in the subjects stratified according to Killip class (≤2 or >2) or LVEF (≥40% or <40%) with the threshold levels more commonly used in the literature.[33,34] Even within the subjects without clinical signs of heart failure (Killip class of 1), an AER of ≥50 mg/24 h on the first day or of ≥30 mg/24 h on the third day was associated with a significantly higher risk of in-hospital mortality.

The AER cutoff values devised in the present study showed a remarkably high sensitivity for the identification of the patients who subsequently died and a negative predictive power of 99% for both AER measurements. Specificity was lower, as was the positive predictive value of the test. This finding has important clinical implications and suggests that subjects with low AER may be safely discharged from hospital at an early stage. Subjects with high AER are at increased risk, but they do not necessarily require aggressive intervention. The reason for the low positive predictive value of AER may be due to the confounding effect of factors affecting the level of urinary albumin. In the present study, care was taken to exclude subjects with diseases potentially affecting AER, but we cannot exclude that unrecognized infections of the urinary tract or other diseases influencing AER may have affected the results.

Regardless of the reason for the association between the levels of AER and mortality rate, our results suggest that measurement of AER may be an inexpensive and readily obtainable prognostic index in patients with AMI, independent of other major risk factors. In particular, AER showed a strong negative predictive value for in-hospital mortality, as the risk of dying appeared very low in the patients with urinary albumin of <50 mg/24 h on the first day after admission and with albumin of <30 mg/24 h on the third day.

Acknowledgments

We are deeply indebted to Dr Sigismondo Pianca, Adelia Berton, Paola Michelazzo, Jessica Civiero, and Gianfranco Barro for their help with the data. We thank the nurses of the Emergency Care Units of the Conegliano Veneto, Adria, and Bassano City Hospitals for the efforts in the collection of the blood and urine samples. We are very grateful to Dr Paolo Mormino for his help in statistical analysis.

References

1. Viberti GC, Hill RD, Jarret RJ, Mahmud U, Argyropoulos A, Keen H. Microalbuminuria as a predictor of clinical nephropathy in insulin-dependent diabetes mellitus. *Lancet*. 1982;1:1430-1432.
2. Mogensen CE. Microalbuminuria predicts clinical proteinuria and early mortality in maturity-onset diabetes. *N Engl J Med*. 1984;310: 356-360.
3. Mattock MB, Morrish NJ, Viberti G, Keen H, Fitzgerald AP, Jackson G. Prospective study of microalbuminuria as predictor of mortality in NIDDM. *Diabetes*. 1992;41:736-741.
4. Gerber LM, Shmukler C, Alderman MH. Differences in urinary albumin excretion rate between normotensive and hypertensive, white and nonwhite subjects. *Arch Intern Med*. 1992;152:373-377.
5. Kuusisto J, Mykkänen L, Pyörälä, Markku L. Hyperinsulinemic microalbuminuria: a new risk indicator for coronary heart disease. *Circulation*. 1995;91:831-837.
6. Damsgaard EM, Froland A, Jorgensen OD, Mogensen CE. Microalbuminuria as predictor of increased mortality in elderly people. *BMJ*. 1990;300:297-300.
7. Gosling P, Shearman CP. Increased levels of urinary proteins: markers of vascular permeability? *Ann Clin Biochem*. 1988;25: 150s-151s.

8. UK Prospective Diabetes Study Group. Urinary albumin excretion over 3 years in diet-treated type 2 (non-insulin-dependent) diabetic patients, and association with hypertension, hyperglicaemia and hypertriglyceridaemia. *Diabetologia*. 1993;36:1021-1029.
9. Schnack C, Pietschmann P, Knobl P, Schuller E, Prager R. Apolipoprotein levels and atherogenic lipid fractions in relation to the degree of urinary albumin excretion in type 2 diabetes mellitus. *Nephron*. 1994;66:272-277.
10. Gosling P, Hughes EA, Reynolds JP, Fox JP. Microalbuminuria is an early response following acute myocardial infarction. *Eur Heart J*. 1991;12:508-513.
11. Pasternak RC, Braunwald E, Sobel BE. Acute myocardial infarction. In: Braunwald E, ed. *Heart Disease*, 4th ed. Philadelphia, Pa: WB Saunders; 1992:1200-1223.
12. Killip T III, Kimball JT. Treatment of myocardial infarction in a coronary care unit: a two year experience with 250 patients. *Am J Cardiol*. 1967;20:457-464.
13. Erbel R. Comparison of single-plane and biplane volume determination by two-dimensional echocardiography, 1: asymmetric model hearts. *Eur Heart J*. 1982;3:469-474.
14. Bradows RG, Nichols D, Shaker G, Kubasik NP. Evaluation of a new radioimmunoassay for urinary albumin. *Diabetes Care*. 1986;9: 189-193.
15. Altman DG. Modelling survival, the Cox regression model. In: Practical Statistics for Medical Research. Chapman & Hall 1992: 387-394.
16. Eiskjaer H, Bagger JP, Mogensen CE, Schmitz A, Pedersen EB. Enhanced urinary excretion of albumin in congestive heart failure: effect of ACE-inhibition. *Scand J Lab Invest*. 1992;52:193-199.
17. Ellekilde G, von Eyben FE, Holm J, Hemmingsen L. Above-normal urinary excretion of albumin and retinol-binding protein in patients with acute myocardial infarction. *Clin Chem*. 1993;39:2350-2351.
18. Eiskjaer H, Mogensen CE, Schmitz A, Pedersen EB. Enhanced urinary excretion of albumin and α2-microglobulin in essential hypertension induced by atrial natriuretic peptide. *Scand J Lab Invest*. 1991;51:359-366.
19. Zimmerman RS, Trippodo NC, MacPhee AA, Martinez AJ, Barbee RW. High-dose atrial natriuretic peptide enhance albumin escape from the systemic but not the pulmonary circulation. *Circ Res*. 1990;67:461-468.
20. von Eyben FE, Holm J, Hemmingsen L, Ellekilde G. Albuminuria with or without streptokinase. *Lancet*. 1993;342:365-366.
21. Rouleau JL, Packer M, Moyè L, de Champlain J, Bichet D, Klein M, Rouleau JR, Sussex B, Arnold JM, Sestier F, Parker JO, McEwan P, Bernstein V, Cuddy TE, Lamas G, Gottlieb S, McCans J, Nadeau C, Delage F, Wun CC, Pfeffer MA. Prognostic significance of neurohumoral activation in patients with an acute myocardial infarction: effect of captopril. *J Am Coll Cardiol*. 1994;24: 583-591.
22. Omland T, Bonarjee VVS, Lie RT, Caidahl K. Neurohumoral measurements as indicators of long-term prognosis after acute myocardial infarction. *Am J Cardiol*. 1995;76:230-235.
23. Foy SG, Crozier IG, Richards AM, Nicholls MG, Turner JG, Frampton CM, Ikram H. Neurohumoral changes after acute myocardial infarction: relationships with haemodynamic indices and effects of ACE inhibition. *Eur Heart J*. 1995;16:770-778.
24. Nash GB, Thomas PRS, Dormandy JA. Abnormal flow properties of a white blood cells in patients with severe ischaemia of the leg. *BMJ*. 1988;296:1699-1701.
25. Lucchesi Br, Mullane KM. Leukocytes and ischaemia-induced myocardial injury. *Annu Rev Pharmacol Toxicol*. 1986;26:201-224.
26. Liuzzo G, Biasucci LM, Gallimore JR, Grillo RL, Rebuzzi AG, Pepys MB, Maseri A. The prognostic value of C-reactive and serum amyloid A protein in severe unstable angina. *N Engl J Med*. 1994; 331:417-424.
27. Madsen EB, Gilpin E, Henning H. Evaluation of prognosis one year after myocardial infarction. *J Am Coll Cardiol*. 1983;1:985-993.
28. Gottlieb S, Moss AJ, McDermott M, Eberly S. Interrelation of left ventricular ejection fraction, pulmonary congestion and outcome in acute myocardial infarction. *Am J Cardiol*. 1992;69:977-984.
29. Omland T, Bonarjee VS, Nilsen DWT, Sundsfjord JA, Lie RL, Thibault G, Dickstein K. Prognostic significance of N-terminal pro-atrial natriuretic factor (1-98) in acute myocardial infarction: comparison with atrial natriuretic factor (99-126) and clinical evaluation. *Br Heart J*. 1993;70:409-414.
30. Herlitz J, Karlson BW, Richter A, Wiklund O, Jablonskiene D, Hjalmarson A. Prognosis in hypertensives with acute myocardial infarction. *J Hypertens*. 1992;10:1265-1271.
31. Zuanetti G, Latini R, Maggioni AP, Santoro L, Franzosi MG. Influence of diabetes on mortality in acute myocardial infarction: data from the GISSI-2 study. *J Am Coll Cardiol*. 1993;22:1788-1794.
32. Granger CB, Califf RM, Young S, Candela R, Samaha J, Worley S, Kereiakes DJ, Topol EJ. Outcome of patients with diabetes mellitus and acute myocardial infarction treated with thrombolytic agent. *J Am Coll Cardiol*. 1993;21:920-925.
33. Willerson JT, Cohn JN. *Cardiovascular Medicine*. New York, NY: Churchill Livingstone; 1995.
34. Launbjerg J, Berning J, Fruengaard P, Eliasen P, Bork-Johnsen K, Eiken P, Appleyard M. Risk stratification after acute myocardial infarction by means of echocardiographic wall motion scoring and Killip classification. *Cardiology*. 1992;80:375-381.