Prognostic significance of hypertension and albuminuria for early mortality after acute myocardial infarction

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Objective **To assess the risk of mortality associated with hypertension and microalbuminuria in patients with acute myocardial infarction.**

Design **A prospective study.**

Setting **Intensive care units in three Italian general hospitals.**

Patients **In total 309 consecutive patients (including 97 women) aged 66.6 ± 12.5 years, admitted to hospital for acute myocardial infarction.**

Main outcome measures **Albumin excretion rate measured by radioimmunoassay of 24 h urine samples, on the first and third days after admission to hospital. In-hospital mortality rate among the patients stratified according to their history of hypertension and albumin excretion rate.**

Results **Of the patients, 147 had histories of hypertension. Forty-four per cent of the normotensive and 43% of the hypertensive subjects had microalbuminuria on the first day. On the third day the percentages were 25 and 29%, respectively. Twenty-two patients died before discharge from hospital. Patients were divided into four groups according to whether they had microalbuminuria or not and likewise for hypertension. Mortality rate among the subjects with hypertension and microalbuminuria combined was greater than those among the other three groups ($P < 0.0001$ on the first and third days). The relative hazard ratio was 11.7 on the first day, and 15.6 on the third day. In a multivariate Cox's model hypertension and microalbuminuria combined had a greater predictive power for mortality than either variable alone. Killip class, age, and creatinine kinases MB level were other significant predictors of death.**

Conclusions **These results show that the combination of hypertension and microalbuminuria is associated with a greater risk of in-hospital mortality among subjects with acute myocardial infarction, independently of degree of heart failure and other possible confounders.**
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Introduction

Several factors such as age, female sex, diabetes, and prior angina can adversely affect prognosis of subjects with acute myocardial infarction (AMI) [1–3]. A deleterious effect on patient survival has been described by some investigators also for a history of hypertension [4,5], but authors of other reports did not mention any relation between a history of hypertension and mortality after AMI [6].

A greater than normal albumin excretion rate (AER) is a well-known predictor of mortality among patients with diabetes [7,8]. AER was found to be higher than normal also for many subjects with hypertension, but the clinical significance of microalbuminuria (AER > 30 mg/24 h) in this clinical entity has not been established [9,10].

Higher than normal AER have recently been reported for subjects admitted to hospital for AMI [11], with a rapid decline in AER towards normal values during the first week of hospitalization [12]. The aim of this study was to assess the prevalence of microalbuminuria and of a history of hypertension among subjects admitted to hospital for AMI, and to investigate whether these clinical features are associated with a greater than normal risk of in-hospital mortality.

Methods

Patients

Three hundred and thirty-three patients consecutively admitted to the intensive care units at Bassano del Grappa (n = 123), Adria (n = 135) and Conegliano Veneto (n = 75)

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Hospitals (northeast Italy) for AMI were prospectively studied. Seventeen patients with concomitant clinical conditions that could affect AER were excluded from our study [urinary tract infections (n = 8), chronic renal failure (n = 1), a need for dialytic treatment (n = 1), myocardial reinfarction within 7 days of admission (n = 2), neoplastic disease (n = 2), traumatic diseases (n = 2), and menstrual flow (n = 1)]. Data for seven other patients were excluded from our study because we had collected insufficient data for them. Thus, the final analysis was performed on data for 309 subjects. After they had given their informed consent to participate in our study, the patients were interviewed by a physician who completed a standard record form covering details of their past medical history. All patients were asked whether they had a documented history of hypertension (administration of antihypertensive therapy or a doctor's report on blood pressure values). Furthermore, the date of first documentation of high blood pressure was reported. The study was approved by the ethics committees of the three hospitals. The criteria for diagnosis of AMI were at least two of the following: central chest pain lasting > 30 min, typical changes in serum enzymes [total creatinine kinase, CK-MB, aspartate aminotransferase (AST), lactate dehydrogenase], typical electrocardiographic changes with occurrence of pathological Q waves or localized ST–T changes for at least two contiguous leads [1]. On the first day after admission venous blood was drawn for determination of serum levels of total and high-density lipoprotein cholesterol and triglycerides. On the first and third days, blood pressure was measured by especially trained nurses, using 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 and third day after admission according to the Killip classification [13].

AER assessment

AER was assessed from two 24 h urinary collections, performed on the first and third 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 the Clinica Medica 1 of the Padua University (Italy), where albumin was measured by radioimmunoassay [14], using a Human ALB. KIT-double antibody (Techno Genetics, Cassina De Pecchi, Milan, Italy). The detection limit of the method was 0.5 mg/l and the between-batch coefficient of variation was ⩽ 5%. AER was expressed as mg/24 h. Patients with AER > 30 mg/24 h were said to have microalbuminuria [15].

Data analysis

Statistical analysis was carried out with Biomedical Data Package [16] new system for windows, version 1.1 and Systat version 5.01 package [17]. To correct for skewed distribution (positive), AER was logarithmically transformed. Differences in mean values were tested with unpaired Student's t test. Between-group comparisons for data on the first and third days after admission were performed using repeated-measures analysis of covariance and Tukey's post-hoc test. The covariates used in each comparison are reported in the Results.

Proportions were compared with Pearson's two-way χ^2 test. When considering in-hospital mortality, Cox's proportional hazards regression model was used. Analyses were performed using a significance level of $\alpha = 0.05$ (two-sided). The categorical variables were grouped into classes such that smoking, being a man, and so on scored 1 and the opposite scored 0. Killip class was considered as to be a four-class 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. In Cox's analysis AER was treated either as a categorical or as a continuous variable.

Data are presented as means ± SD unless otherwise specified. All P values are two-tailed. $P < 0.05$ was considered statistically significant.

Results

Of the 309 patients, 147 had histories of hypertension, with a mean duration of 11.5 ± 9.0 years. The main clinical characteristics of the normotensive and hypertensive subjects are reported in Table 1. The hypertensives were older than the normotensives and were more likely to be diabetic. Smoking was more common among the normotensives. Creatinine kinase peak levels, prevalences of non-Q-wave AMI, and presence and degree of heart failure and arrhythmias did not differ between the two groups. Use of thrombolysis was more common among the normotensives. Diuretics, converting enzyme inhibitors and digoxin were more commonly used by the hypertensives.

Proportions of subjects with microalbuminuria did not differ between the normotensive and hypertensive patients [44 versus 43% on the first day (NS), and 25 versus 29% on the third day (NS)].

During the hospital stay (range 3–62 days, mean 16.3 ± 15.9), 22 AMI patients (12 men and 10 women) died. The causes of death were cardiogenic shock (n = 9), reinfarction (n = 1), ventricular fibrillation (n = 3), rupture of ventricular septum (n = 2), rupture of free cardiac wall (n = 3), strokes (n = 3), and esophageal variceal bleeding (n = 1). Patients who died in hospital were older than survivors, and more often had histories of hypertension,

Table 1 Clinical characteristics of the patients with acute myocardial infarction by presence/absence of a history of hypertension

Variable	Normotensives (n = 162)	Hypertensives (n = 147)	Significance
Age (years)	63.6 ± 12.6	70.1 ± 11.4	$P < 0.0001$
Sex (females)	32 (20)	65 (44)	$P < 0.0001$
Body mass index (kg/m^2)	25.6 ± 3.5	25.8 ± 3.8	NS
Prior AMI	35 (22)	42 (29)	NS
Prior angina	35 (22)	44 (30)	NS
Current smoking	73 (45)	39 (26)	$P = 0.001$
Diabetics	35 (22)	47 (32)	$P = 0.03$
Total cholesterol (mmol/l)	5.5 ± 1.5	5.4 ± 1.2	NS
HDL cholesterol (mmol/l)	1.2 ± 0.3	1.1 ± 0.2	NS
Triglycerides (mmol/l)	1.7 ± 1.5	1.7 ± 1.0	NS
First day:			
SBP (mmHg)	118 ± 15	124 ± 16	
DBP (mmHg)	72 ± 11	76 ± 11	
Heart rate (beats/min)	74 ± 15	79 ± 18	$P = 0.02$
Third day			
SBP (mmHg)	117 ± 15	127 ± 20	
DBP (mmHg)	72 ± 10	76 ± 11	
Heart rate (beats/min)	71 ± 14	77 ± 16	$P = 0.002$
Creatinine kinase peak (UI/l)	1334 ± 1118	1298 ± 1235	NS
Non-Q-wave	35 (22)	35 (24)	NS
Heart failure[a]	58 (36)	64 (43)	NS
Arrhythmias[b]	49 (30)	35 (24)	NS
Thrombolysis	67 (41)	39 (26)	$P = 0.006$
Nitrates	145 (89)	133 (90)	NS
β-Blockers	36 (22)	35 (24)	NS
Ca antagonists	23 (14)	22 (15)	NS
Diuretics	33 (20)	47 (32)	$P = 0.02$
ACE inhibitors	40 (25)	61 (41)	$P = 0.002$
Digitalis	11 (7)	25 (17)	$P = 0.005$
Antiarrhythmics	22 (14)	19 (13)	NS
Antiplatelets	136 (84)	107 (73)	$P = 0.01$
Anticoagulants	149 (92)	133 (90)	NS

Values are expressed as means ± SD and numbers (percentages). [a]First 3 days after admission; [b]either tachy-arrhythmias or brady-arrhythmias. HDL, high-density lipoproteins; SBP, systolic blood pressure; DBP, diastolic blood pressure; AMI, acute myocardial infarction.

Table 2 Clinical characteristics of the patients who died during their stay in hospital and survivors

	Alive (n = 287)	Dead (n = 22)	Significance
Age (years)	65.9 ± 12.3	76.6 ± 9.9	$P < 0.0001$
Sex (Female)	87 (30)	10 (45)	NS
Body mass index (kg/m^2)	25.8 ± 3.6	25.0 ± 4.1	NS
Prior AMI	73 (25)	4 (18)	NS
Prior angina	74 (26)	5 (23)	NS
Current smoking	105 (37)	7 (32)	NS
Diabetics	74 (26)	8 (36)	NS
Hypertension	130 (45)	17 (77)	$P = 0.004$
Total cholesterol (mmol/l)	5.5 ± 1.4	5.0 ± 1.5	NS
HDL cholesterol (mmol/l)	1.1 ± 0.3	1.0 ± 0.3	NS
Triglycerides (mmol/l)	1.7 ± 1.3	1.8 ± 0.8	NS
First day			
SBP (mmHg)	121 ± 15	124 ± 21	NS
DBP (mmHg)	74 ± 11	74 ± 11	NS
Heart rate (beats/min)	75 ± 16	90 ± 19	$P < 0.0001$
Third day			
SBP (mmHg)	122 ± 18	114 ± 19	NS
DBP (mmHg)	74 ± 11	69 ± 12	$P = 0.02$
Heart rate (beats/min)	72 ± 14	92 ± 18	$P < 0.0001$
Creatinine kinase peak (UI/l)	1254 ± 1050	2145 ± 2102	$P = 0.001$
Non-Q-wave	67 (23)	3 (14)	NS
Heart failure[a]	102 (35)	20 (91)	$P < 0.0001$
Arrhythmias[b]	74 (26)	10 (45)	NS
Thrombolysis	102 (35)	4 (18)	NS
First day AER (mg/24 h)	62.6 ± 6.4	201.3 ± 23.3	$P < 0.0001$
First day microalbuminuria	114 (40)	21 (95)	$P < 0.0001$
Third AER (mg/24 h)	25.8 ± 3.4	109.3 ± 12.3	$P < 0.0001$
Third day microalbuminuria	64 (22)	20 (91)	$P < 0.0001$

Values are expressed as means ± SD and numbers (percentages). [a]First 3 days after admission; [b]either tachy-arrhythmias or brady-arrhythmias. HDL, high-density lipoprotein; SBP, systolic blood pressure; DBP, diastolic blood pressure; AMI, acute myocardial infarction. AER, albumin excretion rate. Microalbuminuria: AER ⩾ 30 mg/24 h.

signs of heart failure and higher heart rates. Proportion of microalbuminuric patients and AER level were higher among the patients who died in hospital than they were among the survivors, both on the first day and on the third day assessment (Table 2).

By dividing the patients into four groups according to the absence or presence of a history of hypertension and albuminuria (group 1, normoalbuminuric normotensives; group 2, normoalbuminuric hypertensives; group 3, microalbuminuric normotensives; group 4, microalbuminuric hypertensives), mortality rate progressively increased on going from the first to the fourth group for data collected both on the first and on the third day (Table 3).

In Table 3 relative hazard ratios and confidence limits for the four groups are also shown. Relative risk proved to be much higher for the patients with hypertension and

Table 3 In-hospital mortality rate and relative hazard ratios for the patients with acute myocardial infarction divided according to whether they had hypertension, microalbuminuria, the two situations combined or neither of them, on the first and third days after admission to the hospital

	Normotensives without microalbuminuria	Hypertensives without microalbuminuria	Normotensives with albuminuria	Hypertensives with albuminuria
First day				
Alive	91 (100)	82 (99)	67 (93)	47 (75)
Dead	0 (0)	1 (1)	5 (7)	16 (25)
Relative hazard ratio	0.000003 (∞–0.2)	0.1 (0.007–0.6)	1.0 (0.3–2.5)	11.7 (4.8–32.5)
Third day				
Alive	121 (100)	101 (98)	37 (88)	28 (65)
Dead	0 (0)	2 (2)	5 (12)	15 (35)
Relative hazard ratio	0.000003 (∞–0.1)	0.2 (0.03–0.7)	1.9 (0.6–4.9)	15.6 (6.6–40.9)

Values are expressed as numbers (percentages) and relative hazard ratios (confidence intervals). Two-way Pearson's χ^2 test for the four-class comparisons: first day 42.3, $P < 0.0001$; and third day 65.2, $P < 0.0001$.

Table 4 Relative hazard ratios for the patients with acute myocardial infarction divided according to whether they had hypertension, microalbuminuria (in separate and bivariate models) or the two situations combined, on the first and third days after admission to the hospital

	Separate models		Bivariate models		Combined effects
	Hypertension	Albuminuria	Hypertension	Albuminuria	
Unadjusted					
First day	3.9 (1.5–11.8)	5.2 (2.8–9.7)	3.4 (1.3–10.5)	4.7 (2.6–8.7)	11.7 (4.8–32.5)
Third day	3.9 (1.5–11.8)	10.2 (5.0–20.9)	3.9 (1.5–11.9)	10.7 (5.1–22.7)	15.6 (6.6–40.9)
Adjusted for confounders					
First day	3.3 (1.1–11.6)	5.4 (2.3–13.7)	4.2 (1.3–16.4)	5.4 (2.4–12.7)	11.1 (3.5–39.3)
Third day	2.6 (0.9–9.1)	7.0 (2.0–31.0)	4.1 (1.3–15.9)	9.8 (2.6–47.4)	10.2 (3.7–30.8)

Values are expressed as relative hazard ratios (confidence limits).

microalbuminuria combined than it was for the other three groups, both on the first and on the third day after admission.

To evaluate the prognostic significances of hypertension and microalbuminuria, isolated or combined, taking into account clinical confounders, possible predictors of in-hospital mortality were examined in a Cox's proportional hazards regression analysis. The continuous variables tested included age, creatinine kinase MB and AST peaks, and heart rate. The following categorical variables were also examined: sex, presence of diabetes, current smoking, previous myocardial infarction and angina, AMI site, thrombolysis, therapy with converting enzyme inhibitors, arrhythmias, Killip class, presence of hypertension, and microalbuminuria. In univariate analysis age ($P < 0.0001$), creatinine kinase MB peak level ($P = 0.01$), AST peak level ($P = 0.0002$), heart rate ($P = 0.0005$), clinical heart failure ($P < 0.0001$), arrhythmias ($P = 0.04$), hypertension alone (0.003), and microalbuminuria alone ($P < 0.0001$) were significantly related to mortality. Relative hazard ratios for hypertension and for microalbuminuria in separate models are reported in Table 4. When they were examined in bivariate models, hypertension ($P = 0.008$ on the first day and $P = 0.003$ on the third day) and microalbuminuria ($P < 0.0001$ on both days) remained significant predictors of death, as did the combination of the two ($P < 0.0001$ on both days). The related odds ratios are reported in Table 4.

In a multivariate model, on the first day after admission hypertension and microalbuminuria remained significant predictors of in-hospital mortality when examined separately ($P = 0.03$ and 0.0001, respectively) and together ($P = 0.01$ and < 0.0001, respectively). The combination of hypertension with microalbuminuria ($P < 0.0001$) had an additive effect, with an increase in the relative risk of death (Table 4). On the third day, the predictive power of hypertension was of borderline significance in separate analysis ($P = 0.09$) and significant ($P = 0.01$) when microalbuminuria was included in the model. Third day microalbuminuria was a significant predictor of mortality in both models ($P = 0.002$ and 0.0004, respectively), as was the combined effect of hypertension with microalbuminuria ($P = 0.0007$). Killip class ($P = 0.003$ on both days), age ($P = 0.01$ on the first day and $P = 0.003$ on the third day), and creatinine kinase MB peak ($P = 0.01$ on both days) were other predictors of mortality. Similar results were obtained when AER (logarithmically transformed) was entered into Cox's analysis as a continuous instead of a categorical variable. Both in separate and in bivariate models, either unadjusted or adjusted for confounders, AER appeared as a strong predictor of mortality (all $P < 0.0001$). Hypertension also remained significantly associated with mortality when it was entered into the bivariate models with logarithm of AER (on both days, $P = 0.01$ for unadjusted data, and $P = 0.04$ for data adjusted for confounders).

Discussion

A history of arterial hypertension has been shown to influence outcome after AMI [4–6]. Gottlieb *et al.* [18] showed that a history of hypertension was associated with a greater than normal risk of cardiac death for postinfarction patients during a 2-year follow-up, at any level of left ventricular ejection fraction and irrespective of degree of clinical heart failure. Similar results were obtained by Herlitz *et al.* [4] in a 1-year follow-up of 917 AMI patients. However, in the latter authors' study a history of hypertension did not affect early in-hospital mortality, which was 14% both among normotensive and among hypertensive individuals. The results of the present study confirm that hypertension in itself does not necessarily imply a worse outcome during hospitalization for patients admitted for AMI. In Cox's analysis hypertension emerged as a predictor of in-hospital mortality both in univariate and in multivariate models. However, it should be pointed out that, among the subjects without microalbuminuria, the relative risk of in-hospital mortality was low also for the patients with positive histories of hypertension. On the other hand, hypertension is not a uniform condition, and the risk related to it greatly varies in relation to the blood pressure levels and the degree of the associated target organ damage. Low level urinary albumin has been shown to be related to the severity of hypertension [9,10] and the degree of hypertensive complications [14,19]. This association probably reflects damage to the glomerular capillaries and the endothelial

injury which occur during the more advanced stages of the disease [7].The high in-hospital mortality among the hypertensive subjects with microalbuminuria found in the present study suggests that these were the most compromised patients, who were most at risk of developing life-threatening complications during the first weeks after AMI. These subjects had a mortality of 25% when first-day data were used compared with 0–1% for nonmicroalbuminuric individuals and 7% for normotensive subjects with microalbuminuria. When third-day data were used mortality among the microalbuminuric hypertensive patients rose to 35%. Subjects who died in hospital were older and had a greater degree of heart failure than did those who survived. However, microalbuminuria had a strong prognostic power also after we had controlled for these clinical variables.

AER of a large proportion of subjects with AMI dramatically increases even in the absence of clinical signs of heart failure [12,20]. According to Gosling *et al.* [11] this phenomenon is the consequence of the inflammatory reaction which accompanies AMI and involves the renal vascular system. Systemic release of thromboxanes and leukotrienes has been observed during the first days after AMI [21,22]. It is thus conceivable that the AMI-related inflammatory injury causes leakage of albumin from the glomerulus in subjects with hypertension and associated glomerular damage.

Of the subjects in our AMI population, 47.6% had a history of hypertension, a proportion a little greater than that found in previous studies, in which the prevalence of hypertension varied in the range 29–37%. In agreement with the reports by other authors, hypertensives differed from normotensives in being older and more likely to have diabetes. Clinical signs of heart failure, however, were equally common for the two groups. This can account for the similar prevalences of microalbuminuria found among the normotensive and the hypertensive patients. It is known that congestive heart failure is accompanied by an increase in urinary excretion of albumin [23] due to the increase in glomerular capillary pressure which occurs in this clinical condition. The more common use of converting enzyme inhibitors among the hypertensives than among the normotensives might have reduced the prevalence of microalbuminuria among these subjects, thereby offsetting the effect of hypertension on AER [24]. In spite of these possible confounders microalbuminuria associated with hypertension emerged as a strong independent risk factor for death in Cox's proportional hazards model, in which also diabetes, previous cardiovascular events and therapy with converting enzyme inhibitors were included. Microalbuminuria was associated with a greater than normal risk of mortality also among the normotensives, but its predictive power was lower than that among the hypertensives. The mechanism behind this observation could only be speculated upon. It is known that several confounding factors may affect the level of urinary albumin [7,9]. It is, thus, possible that the number of false-positive microalbuminuric patients among the normotensives was proportionally greater than that among the hypertensives and that microalbuminuria in the latter more often reflected the existence of true glomerular damage.

In conclusion, for a consecutive series of patients admitted to hospital for AMI, a history of hypertension and detection of microalbuminuria strongly predicted subsequent in-hospital mortality, regardless of heart failure, diabetes, and other possible confounders. Our results suggest that the association of these two clinical findings yields additional prognostic information to that provided by traditional assessment of patients with AMI.

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