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Impact of hypertension on short- and long-term prognoses in patients with ST elevation myocardial infarction and without previously known diabetes

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Abstract Hypertension is well established as a risk factor for the development of atherosclerosis. Data on the impact of hypertension in patients with ST elevation myocardial infarction are so far inconsistent, and are mainly related to studies performed in the thrombolytic era. We assessed the impact of hypertension over the short and long term in 560 patients with ST elevation myocardial infarction (STEMI) and without previously known diabetes, all of whom were submitted to mechanical revascularization and consecutively admitted to our Intensive Cardiac Care Unit. Hypertensive patients were older ($p < 0.001$), more frequently male (0.005), and they showed a reduced eGFR ($p < 0.001$). Smoking was more frequent in nonhypertensive patients ($p < 0.001$), while the incidence of three-vessel coronary artery disease was higher in hypertensive patients ($p = 0.003$). No difference in the in-hospital mortality rates for the two subgroups was detected. At follow-up (median 32.5 months, 25th–75th percentile 16.9–47.3 months), Kaplan–Meier survival analysis detected no differences in mortality between hypertensive and nonhypertensive patients (log rank $\chi^2 0.38$, $p = 0.538$). According to our data, obtained from a large series of consecutive STEMI patients without previously known diabetes, all of whom were submitted to primary PCI, a history of hypertension does not affect mortality over either the short or the long term. Moreover, hypertensive patients showed an altered glucose response to stress, as indicated by higher admission glucose

values, poorer in-hospital glucose control, and a higher incidence of acute insulin resistance (as indicated by the HOMA index). Hypertensive patients therefore appear to warrant careful metabolic management during their hospital courses.

Keywords Hypertension · ST elevation myocardial infarction · Nondiabetic · Prognosis · Acute glucose dysmetabolism

Introduction

Hypertension is well established as a risk factor for the development of atherosclerosis [1–3], and for increased incidence of cerebrovascular disease [4] and coronary artery disease [5]. In the INTERHEART study, the strength of the association of hypertension with risk of first myocardial infarction (MI) was greater in women than in men [6]. Hypertension is also an important risk factor for death and ischemic events after presentation with acute coronary syndromes (ACS) [7].

In the SYMPHONY study [8], which assessed sex-related differences in the prevalence and treatment of hypertension among patients presenting with ACS, hypertension was more prevalent in women than in men, while mortality did not show any gender-related difference.

Data on the impact of hypertension in patients with ST elevation myocardial infarction (STEMI) are so far inconsistent, and are mainly related to studies performed in the thrombolytic era [7, 9–13].

The present investigation was therefore aimed at assessing the impact of hypertension over the short and long term in 560 patients with STEMI and without previously known diabetes, all of whom were submitted to

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mechanical revascularization and consecutively admitted to our Intensive Cardiac Care Unit (ICCU).

Methods

Study population

From 1 January 2008 to 30 June 2010, 560 consecutive patients with STEMI (within 12 h from the onset of symptoms) but without previously known diabetes were admitted to our ICCU, which is located at a tertiary center. In our hospital, in Florence, the reperfusion strategy of STEMI patients is represented by primary PCI [14–19]. STEMI patients are first evaluated by the Medical Emergency System staff in the prehospital setting and then directly admitted to the catheterization laboratory or transferred to it after rapid stabilization in First Aid. After primary PCI, they are admitted to our ICCU. Patients were defined as hypertensive if they had a known history of hypertension or were being treated with antihypertensive medication at the time of the qualifying event [8].

A successful procedure was defined as an infarct artery stenosis <20% associated with thrombolysis in myocardial infarction (TIMI) grade 3 flow; TIMI grade 0 to 2 flow, regardless of the residual stenosis, was regarded as unsuccessful PCI [20].

The diagnosis of STEMI was based on the criteria of the American College of Cardiology/American Heart Association [20, 21].

On ICCU admission, after PCI, the following parameters were measured in a fasting blood sample: glucose (mg/dl), insulin values (mIU/l) [15, 17], glycated hemoglobin (HbA1c, %), troponin I (ng/ml), C-reactive protein (mg/dl) (normal values <9), alanine aminotransferase (ALT, UI/l), aspartate amino transferase (AST, UI/l) [22], NT-pro brain natriuretic peptide (NT-pro BNP) (pg/ml) [18], total cholesterol (mg/dl), triglycerides (mg/dl), HDL (mg/dl), LDL (mg/dl), and fibrinogen (mg/dl). Creatinine (mg/dl) was also measured in order to calculate the glomerular filtration rate (eGFR, ml/min/1.73 m², MDRD formula) [23]. Glucose and Tn I were measured three times a day during the ICCU stay, and peak values for each variable were considered. Glucose measured at discharge was also considered. Intensive insulin therapy was administered in patients with significant hyperglycemia (that is, plasma glucose >180 mg/dl) [24].

Definition of insulin resistance

Criteria used for the definition of insulin resistance are in accordance with the recently published guidelines proposed by the European Group for the Study of Insulin

Resistance (EGIR). HOMA was calculated according to the following formula: {[fasting insulin (microU/ml)] × [fasting glucose (mmol/l)]}/22.5. Subjects whose values exceeded the sex-specific 75th percentile (i.e., 1.80 for women and 2.12 for men) were considered to have insulin resistance (HOMA-IR) [17, 25–27].

Transthoracic two-dimensional echocardiography was performed in order to measure left ventricular ejection fraction (LVEF) on ICCU admission and at discharge.

The study protocol was in accordance with the Declaration of Helsinki and approved by the local ethics committee. Informed consent was obtained in all patients before enrollment.

Statistical analysis

Analysis was performed using SPSS 13.0 statistical package (SPSS Inc., Chicago, IL, USA). Categorical data are expressed as frequencies and percentages; continuous data are reported as the mean ± SD or the median (25th–75th percentile [IR]), depending on whether the distribution is normal or not. Data have been analyzed by means of χ^2 (or Fisher's exact test when the expected count in a cell was <5) for categorical data and Student's *t* test or the Mann–Whitney *U* test for continuous data, according to the shape of their distribution. When χ^2 was calculated in a table with >2 × 2 cells, the differences between the cells were assessed with the Z-score. Logistic regression analysis was performed in order to identify predictor(s) of in-hospital mortality; variables for inclusion were chosen carefully among those considered clinically relevant and those which showed a univariate relationship with in-hospital death, given the number of events available, to ensure parsimony of the final models. Taking into account the number of deaths, a bivariate analysis was performed. Candidate variable(s) that were non-normally distributed were entered as their log-transformed values. The Hosmer–Lemeshow goodness-of-fit test and Nagelkerke's *R*² have been reported. We used Kaplan–Meier survival analysis to assess differences (if any) in death at follow-up between hypertensive and nonhypertensive patients; results of the logrank test are reported. A *p* value <0.05 was considered statistically significant.

Results

Our population comprises 300 STEMI patients with hypertension (53.6%) and 260 patients without a history of hypertension (46.4%) (Table 1). Hypertensive patients were older (*p* < 0.001), more frequently male (*p* ≤ 0.005), and they showed a reduced eGFR (*p* < 0.001) and a higher BMI (*p* = 0.025). Smoking was more frequent in

Table 1 Clinical characteristics of the 560 nondiabetic patients with ST elevation myocardial infarction included in the study

	Hypertensive patients (<i>n</i> = 300, 53.6%)	Nonhypertensive patients (<i>n</i> = 260, 46.4%)	<i>p</i> value
Age (years)	70.1 ± 11.2	62.2 ± 13.2	<0.001
Males/females <i>n</i> (%)	200/100 (66.7/33.3)	201/59 (77.3/22.7)	0.005
BMI (kg/m ²)	26.1 (23.8–28.9)	25.5 (23.5–27.7)	0.025
History of <i>n</i> (%)			
Smoking	168 (56.0)	188 (72.3)	<0.001
COPD	30 (10.0)	18 (6.9)	0.195
Previous PCI	47 (15.7)	29 (11.2)	0.120
Previous MI	50 (16.7)	31 (11.9)	0.111
Symptom to balloon time (min)	234 (160–350)	200 (150–300)	0.053
Killip class <i>n</i> (%)			
I–II	268 (89.3)	238 (91.5)	0.378
III–IV	32 (10.7)	22 (8.5)	
In-hospital mortality <i>n</i> (%)	8 (2.7)	10 (3.8)	0.430
Follow-up mortality <i>n</i> (%)	42 (14.4)	32 (12.9)	0.594

Values are frequencies (percentages), mean ± SD or median (25th–75th percentile) *Pct* percentile, *BMI* body mass index, *COPD* chronic obstructive pulmonary disease, *PCI* percutaneous coronary intervention, *MI* myocardial infarction

Table 2 Angiographic characteristics of the 560 nondiabetic patients with ST elevation myocardial infarction included in the study

	Hypertensive patients (<i>n</i> = 300, 53.6%)	Nonhypertensive patients (<i>n</i> = 260, 46.4%)	<i>p</i> value
AMI location <i>n</i> (%)			
Anterior	150 (50.0)	142 (54.6)	0.255
Inferior	124 (41.3)	104 (40.0)	
Other	26 (8.7)	14 (5.4)	
Coronary artery disease <i>n</i> (%)			
1-vessel	108 (36.0)	113 (43.5)	0.003
2-vessel	90 (30.0)	92 (35.4)	
3-vessel	102 (34.0) [§]	55 (21.2) [§]	
Left main <i>n</i> (%)	20 (6.7)	15 (5.8)	0.648
CABG <i>n</i> (%)	6 (2.8)	1 (0.4)	0.085 [§]
PCI failure <i>n</i> (%)	16 (5.4)	19 (7.4)	0.350
Admission EF (%)	42.6 ± 9.2	43.9 ± 9.8	0.100
Discharge EF (%)	43.9 ± 8.5	45.3 ± 8.6	0.068

Values are frequencies (percentages), mean ± SD or median (25th–75th percentile)

AMI acute myocardial infarction, *CABG* coronary artery bypass graft, *PCI* percutaneous coronary intervention, *EF* ejection fraction

[§] Fisher's exact test. *Z* score *p* < 0.05

nonhypertensive patients (*p* ≤ 0.001). No difference was observed in door-to-balloon time and in Killip class between the two subgroups. Mortality rates over the short and long term did not differ between the two subgroups.

Table 2 shows the angiographic data. No difference in AMI location was detectable between hypertensive and nonhypertensive STEMI patients. The incidence of three-vessel coronary artery disease was higher in hypertensive patients (*p* = 0.003). Left ventricular ejection fraction (both on admission and at discharge) did not differ between the two subgroups.

As depicted in Table 3, hypertensive STEMI patients showed lower eGFR (*p* < 0.001), higher values of both admission and peak glycemia (*p* < 0.001 and *p* < 0.001, respectively) and of glycosylated hemoglobin (*p* = 0.006), and a higher incidence of HOMA positivity (*p* = 0.015). The percentage of patients with glycosylated Hb ≥ 6.5% was higher

in the hypertensive group (*p* = 0.047). Higher levels of NT-pro BNP (*p* ≤ 0.001) and uric acid (*p* ≤ 0.001), fibrinogen (*p* = 0.024), total cholesterol (*p* = 0.028) and LDL (*p* = 0.024) were observed in hypertensive patients.

After excluding patients with HbA1c ≥ 6.5% (*n* = 103, 18.4%), higher values of admission glycemia [nonhypertensive 120 (108–146); hypertensive 132 (114–162) mg/dl; *p* = 0.002] and peak glycemia [nonhypertensive 139 (122–166); hypertensive 151 (129–190) mg/dl; *p* = 0.001] were observed in STEMI patients with hypertension, whereas no significant differences were detectable between the two subgroups in terms of insulinemia [nonhypertensive 8.2 (5.5–13.6); hypertensive 8.2 (5.4–15.9) mIU/l] and the incidence of HOMA index positivity (nonhypertensive 51.3%, hypertensive 60.0%).

Table 4 shows medications on admission and at discharge in both hypertensive and nonhypertensive patients.

Table 3 Comparison of laboratory data between hypertensive and nonhypertensive patients

	Hypertensive patients (<i>n</i> = 300, 53.6%)	Nonhypertensive patients (<i>n</i> = 260, 46.4%)	<i>p</i> value
Estimated GFR (ml/min/1.73 m ²)	76.3 ± 28.9	88.9 ± 27.5	<0.001
Admission glucose (mg/dl)	144 (118–197)	126 (110–156)	<0.001
Peak glucose (mg/dl)	167 (135–224)	145 (125–185)	<0.001
Insulinemia (mUI/l)	10.5 (5.8–20.0)	9.0 (5.5–15.6)	0.111
Glycated hemoglobin (%)	6.0 (5.7–6.6)	5.9 (5.5–6.3)	0.006
Glycated hemoglobin ≥6.5%, <i>n</i> (%)	65 (21.7)	38 (14.6)	0.047
HOMA positivity <i>n</i> (%)	57 (19.0)	30 (11.5)	0.015
AST (UI/l)	67 (66–144)	71 (34–177)	0.456
ALT (UI/l)	40 (25–74)	40 (25–75)	0.906
Peak Tn I (ng/ml)	103.5 (39.9–226.1)	89.0 (46.7–165.9)	0.449
NT-proBNP (pg/ml)	1721 (684–4448)	1066 (362–2504)	<0.001
Uric acid (mg/dl)	6.0 ± 1.5	5.4 ± 1.7	<0.001
ESR (mm/h)	26 (14–40)	20 (12–36)	0.078
CRP (mg/dl)	11.0 (9.0–37.0)	10.0 (8.0–23.0)	0.100
CRP positivity <i>n</i> (%)	155 (55.8)	137 (54.4)	0.748
Leucocytes (×10 ³ /μl)	10.6 (8.7–13.3)	11.0 (9.0–14.0)	0.326
Fibrinogen (mg/dl)	409 (353–501)	389 (330–473)	0.024
Total cholesterol (mg/dl)	183 ± 45	192 ± 45	0.028
HDL cholesterol (mg/dl)	40 (35–47)	41 (35–48)	0.581
LDL cholesterol (mg/dl)	118 ± 38	125 ± 37	0.024
Triglycerides (mg/dl)	102 (75–140)	102 (78–140)	0.612

Values are frequencies (percentages), mean ± SD or median (25th–75th percentile) *GFR* glomerular filtration rate, *HOMA* homeostatic model assessment, *AST* aspartate transferase, *ALT* alanine transferase, *Tn* troponin, *NT-pro BNP* N-terminal pro-brain natriuretic peptide, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein

Table 4 Medications in hypertensive and nonhypertensive patients on admission and at discharge

	Hypertensive (<i>n</i> = 300, 53.6%)	Nonhypertensive (<i>n</i> = 260, 46.4%)	<i>p</i> value
Admission <i>n</i> (%)			
β-blockers	260 (86.7)	232 (89.2)	0.354
ACEi-ARB	273 (91.0)	232 (89.2)	0.483
Calcium channel blockers	19 (6.3)	7 (2.7)	0.041
Diuretics	248 (82.7)	189 (72.7)	0.004
ASA	289 (96.3)	251 (96.5)	0.896
At discharge <i>n</i> (%)			
β-blockers	254 (84.7)	219 (84.2)	0.887
ACEi-ARB	263 (87.7)	218 (83.8)	0.195
Calcium channel blockers	12 (4.0)	4 (1.5)	0.081
Diuretics	197 (65.7)	125 (48.1)	<0.001
ASA	281 (93.7)	238 (91.5)	0.335
Clopidogrel	286 (95.3)	247 (95.0)	0.854

Values are frequencies (percentages) *ACEi* angiotensin-converting enzyme inhibitors, *ARB* angiotensin receptor blockers, *ASA* acetylsalicylic acid

On admission and at discharge, hypertensive STEMI patients were more often on diuretics.

The logistic regression analysis indicated that, in the overall population, admission EF (1% increase; OR 0.906, 95% CI 0.859–0.956, *p* < 0.001) and peak glycemia (10 mg/dl increase; OR 1.113, 95% CI 1.049–1.181, *p* ≤ 0.001) were independent predictors of in-hospital

mortality (Hosmer–Lemeshow χ^2 8.3, *p* = 0.407; Nagelkerke's *R*² 0.28).

At follow-up (median 32.5 months, 25th–75th percentile 16.9–47.3 months), Kaplan–Meier survival analysis detected no differences in mortality between hypertensive and nonhypertensive patients (logrank χ^2 0.38, *p* = 0.538) (Fig. 1).

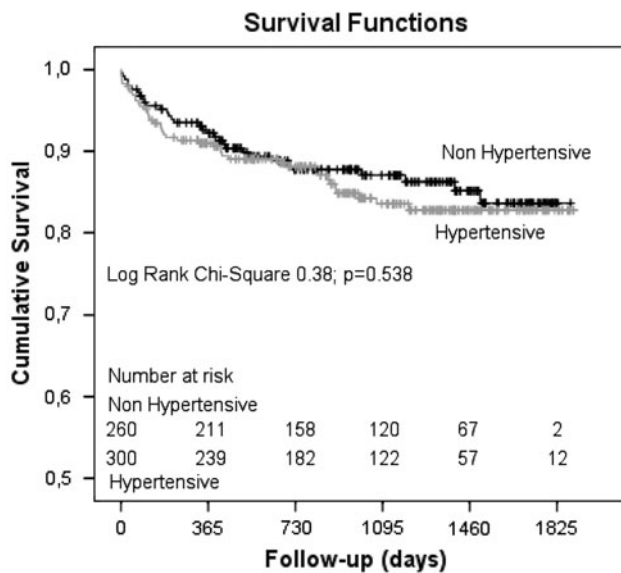


Fig. 1 Kaplan–Meier survival curves in hypertensive and nonhypertensive patients

Discussion

The main finding of the present investigation, performed in consecutive hypertensive STEMI patients without previously known diabetes, all of whom were submitted to PCI, is that history of hypertension is not able to affect mortality over both the short and long term. Hypertensive patients were older and exhibited an altered glucose response to stress, as indicated by higher admission glycemic values, poor in-hospital glycemic control (as inferred by peak glycemia) and a higher incidence of insulin resistance (as indicated by HOMA index positivity).

In our series, the prevalence of a history of hypertension was comparable to that reported in previous studies [8, 28, 29], being detectable in half of the population. Moreover, as previously described [8, 28, 29], in our study, hypertensive patients were older and exhibited reduced renal function (as inferred by eGFR). Interestingly, unlike the GREECS study [30], no significant difference in time to presentation was observed between hypertensive and nonhypertensive patients. In regard to medications, like previous reports, no significant difference was observed between hypertensive and nonhypertensive patients at both admission and discharge, apart from the increased use of diuretics in hypertensives.

Available data on the effects of hypertension on mortality in STEMI are so far inconsistent.

In the thrombolytic era, Rabkin et al. [9] showed adverse short- and long-term outcomes in hypertensive patients. In the GISSI-2 study, in-hospital and 6-month mortality in hypertensive MI patients was significantly higher than for normotensives [10], as was the rate of left ventricular

failure, recurrent angina and recurrent MI. In contrast, elevated blood pressure was not an independent prognostic factor for 30-day mortality among MI patients in the GUSTO-1 study [8]. Nevertheless, patients with very high blood pressure were excluded from the GUSTO-1 study due to the use of thrombolytic treatment (though systolic blood pressure exceeded 180 mmHg in 602 patients). Ayward et al. [11], evaluating all patients participating in the GUSTO-1 study, observed that the risk of an early death was higher in patients with elevated systolic BP. In a study by Majahalme et al. [12], in-hospital and 6-month mortality were both similar in hypertensive and normotensive ACS patients, while the rates of recurrent angina, paroxysmal atrial fibrillation and acute renal failure were higher among hypertensives. Jonas et al. [13] analyzed three groups of patients admitted due to MI (with normal, high normal or elevated BP), and found no significant differences in in-hospital mortality (5% among normotensives, 4% in patients with high normal BP, and 1.9% among hypertensives).

In the era of mechanical revascularization, data on this topic are scarce and conflicting, and have mainly been reported from small observational studies.

Abrignani and colleagues [30] observed that hypertensive subjects with first AMI have a better in-hospital outcome than age- and gender-matched normotensive subjects, perhaps due to a less severe extension of the infarction area or to a different pathophysiological mechanism. On the other hand, according to a recent paper by Rembeck [28] regarding 366 STEMI patients who were submitted to mechanical revascularization, no difference was observed in in-hospital mortality between hypertensive and normotensive patients.

In our series, comprising a larger group of consecutive STEMI patients without previously known diabetes, we confirmed that early mortality rates did not differ between hypertensive and normotensive patients. Furthermore, we observed that hypertensive patients exhibited an altered glycemic response to stress, as indicated by increased values of admission and peak glycemia and a higher incidence of acute insulin resistance (as indicated by the HOMA index). This phenomenon can be related to three main contributory factors. First, the older ages of the hypertensive patients. In a recent paper [27], we documented that during the early phase of STEMI, the acute glucose response to myocardial injury differs according to age, since older patients showed the highest glucose levels and the poorest glycemic control during their ICCU stay. Second, the higher incidence of acute insulin resistance (as indicated by HOMA positivity) observed in hypertensive patients may be related to higher BMI, since insulin secretion in the acute phase of STEMI seems to be strictly related to BMI [32]. Third, the percentage of patients with

glycated hemoglobin $\geq 6.5\%$ was higher in the hypertensive group, thus indicating a higher number of patients with poor glycemic control in the previous months. Interestingly, after excluding patients with glycated Hb $\geq 6.5\%$, the hypertensive patients still showed increased values of admission and peak glycemia.

Finally, we observed, for the first time, that hypertensive STEMI patients without previously known diabetes who were submitted to primary PCI exhibit a comparable survival rate at long-term follow-up to that of nonhypertensive STEMI patients. This can probably be related to the fact that hypertensive STEMI patients did not show a larger infarct size or a higher incidence of unsuccessful PCI, and that medications administered at discharge did not substantially differ between the two subgroups.

In conclusion, in the era of mechanical revascularization, we observed that the mortality rates over both the short and long term in a large series of consecutive nondiabetic STEMI patients did not differ between hypertensive and normotensive patients. Moreover, hypertensive patients showed an altered glucose response to stress, as indicated by higher admission glucose values, poorer in-hospital glucose control (as inferred from peak glycemia), and a higher incidence of acute insulin resistance (as indicated by the HOMA index). Hypertensive patients seem therefore to warrant careful metabolic management during their hospital courses.

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