Heart Failure and Left Ventricular Remodeling After Reperfused Acute Myocardial Infarction in Patients With Hypertension

Guido Parodi, Nazario Carrabba, Giovanni M. Santoro, Gentian Memisha, Renato Valenti, Piergiorgio Buonamici, Emilio V. Dovellini, David Antoniucci

Abstract—In the thrombolytic era, hypertension has been shown to adversely affect the development of heart failure after acute myocardial infarction (AMI). We sought to examine the relation between antecedent hypertension and heart failure after mechanical reperfusion and to test the impact of postinfarction left ventricular remodeling on heart failure in hypertensive patients. A series of 953 patients (324 hypertensives) with AMI treated with successful primary percutaneous coronary intervention underwent a 5-year follow-up. A subgroup of 325 subjects underwent 2D echocardiography at admission, 1 month, and 6 months. From day 1 to 6 months, despite similar improvement in regional and global left ventricular function and similar 6-month infarct artery patency rate, left ventricular end-diastolic volume increased in the normotensives (122±36 mL to 131±47 mL; P<0.001) but not in the hypertensives (127±41 mL to 128±51 mL; P=0.768). At 6 months, the incidence of left ventricular remodeling in hypertensive and normotensive patients was not different (22% versus 28%; P=0.210). However, at 5 years, the incidences of hospitalization for heart failure (7% versus 3%; P=0.014) and of New York Heart Association functional class ≥2 (53% versus 40%; P<0.001) were higher in hypertensive as compared with normotensive patients. Hypertension was found to be a predictor of heart failure (hazard ratio, 2.23; P=0.015). In conclusion, patients with antecedent hypertension are at higher risk to develop heart failure after AMI, even when successfully reperfused by primary percutaneous coronary intervention. However, the increased incidence of heart failure in hypertensive patients is not associated with a greater propensity to postinfarction left ventricular remodeling. (Hypertension. 2006;47:706-710.)

Key Words: heart failure • hypertrophy • remodeling • coronary artery disease • myocardial infarction

Hypertension is a well-known risk factor for coronary artery disease and heart failure. It has been shown that after thrombolysis for acute myocardial infarction (AMI), antecedent hypertension increases the risk of heart failure (HF) and other adverse events.1–5 The progression to HF after AMI is mainly related to left ventricular (LV) remodeling.6 However, animal7,8 and human studies5,9,10 evaluating the relation between hypertension and early LV remodeling after AMI have yielded conflicting or inconclusive results.

Several studies have demonstrated that mechanical reperfusion (primary percutaneous coronary intervention, PCI) is superior to pharmacological reperfusion (thrombolysis), because it allows brisk and sustained flow achievement in the infarct-related artery (IRA) in a higher proportion of patients with subsequent improved myocardial salvage and better long-term outcome.11 Thus, in the last decade, an increasing number of centers have adopted primary PCI as the preferred reperfusion therapy for AMI.

In this study, we sought to examine the relation between antecedent hypertension and the development of HF after successful primary PCI for AMI. Ancillary aim of the present study was to test whether the increased incidence of HF in hypertensive patients was related to a greater propensity for LV remodeling. To test this hypothesis and to avoid the confounding impact of IRA patency on subsequent changes in LV volumes, we performed a prospective echocardiographic study in a consecutive sample of patients who had fully restored anterograde IRA flow by primary PCI.

Methods

Patients and Study Protocol

The study population included a series of consecutive patients referred to our catheterization laboratory for primary PCI between January 1995 and December 1999, who met the following criteria: (1) confirmed ST segment elevation AMI, (2) successful primary PCI (defined as Thrombolysis in Myocardial Infarction Trial [TIMI] grade 3 flow and residual stenosis in the IRA <30%) within 12 hours of the onset of symptoms, and (3) no history or presence at admission of congestive HF or significant other cardiac disease. The study cohort consisted of 953 patients. Six-month coronary angiography was scheduled for all of the patients. In a subgroup of 400...
consecutive patients, regional and global LV function, as well as LV volumes, were scheduled to be evaluated at baseline and 1 month and 6 months after the index infarction. The ethics committee of the hospital approved the research protocol, and informed consent was obtained from each patient.

Echocardiographic Examination
Complete 2D echocardiography examinations were performed using commercially available imaging systems (Aloka model SSD-830; HP SONOS model 5500; 2.5 and 3.5-MHz transducers). 2D echocardiographic images were transferred to the hard disk of a Tomtec P90 analysis system and digitized. LV volumes and LV ejection fraction (EF) were then calculated by the modified Simpson’s rule algorithm.\textsuperscript{12} The mean values of 3 measurements of the technically best cardiac cycles were taken from each examination. Intraobserver and interobserver variability values in the evaluation of end-systolic volume (ESV) and end-diastolic volume (EDV) have been reported to be <5% in our laboratory, indicating the good reproducibility of the measurements.\textsuperscript{13} To evaluate regional systolic function, the left ventricle was divided according to a 16-segment model.\textsuperscript{12} For each segment, wall motion was scored from 1 (normal) to 4 (dyskinetic). Anterior and inferior infarct zones were constructed, and an infarct zone wall motion score index (IZ WMSI) was derived for baseline and follow-up 2D echocardiograms. To evaluate diastolic function, the E and A wave and the E-wave deceleration time (DT) were measured from the mitral inflow Doppler echocardiograms. LV restrictive filling pattern was recognized in the presence of DT $\leq$130 ms.\textsuperscript{14}

Definitions and Outcome Measures
Patients were categorized as having antecedent hypertension if this diagnosis was known by the patient to have been made by the family physician or after specialist referral and/or the admission note indicated a history of hypertension. Restenosis was defined as a $\geq$50% diameter stenosis of the culprit lesion at follow-up angiogram. LV dilatation was defined as an increase in EDV $\geq$20%, based on repeated measurements in individual patients and on the upper 95% confidence limit of the intraobserver variability in our laboratory.\textsuperscript{15} According to the presence or absence of LV dilatation 6 months after the infarction, patients were divided into LV remodeling group and no LV remodeling group, respectively.

Major cardiac adverse events were death, nonfatal reinfarction, documented hospitalization for congestive HF, and additional coronary revascularization procedures, as described previously.\textsuperscript{14} After hospital discharge, patients were referred to their private physician, who regulated therapy. No attempt was made to standardize therapy. All of the patients were asked to return to our outpatient clinic for evaluation by 1 of the investigators 6 months after discharge and annually thereafter. For those patients not returning to the clinic at the designated time, follow-up information was collected by telephone interview. The primary end point of the study was the incidence of documented hospitalization for HF.

Statistical Analysis
Continuous data are expressed as mean±SD. Baseline data were compared by means of the $\chi^2$ test for categorical variables and unpaired $t$ test for continuous variables. ANOVA with the Tukey post-hoc test was used to analyze repeated measures of LV EF, IZ WMSI, and LV volumes. Forward stepwise Cox regression analysis was used to identify independent predictors of hospitalization for HF. Forward stepwise multiple logistic regression analysis was used to identify independent predictors of 6-month LV remodeling within the subgroup of patients with complete echocardiographic data. A value of $P<0.05$ was considered statistically significant. Statistical analysis was performed with SPSS 11.5 for Windows (SPSS Inc).

Results

Clinical Characteristics and Medical Treatment
Hypertension was present in 324 patients (34%). Hypertensive patients were older, had a higher body mass index, and were more frequently women, diabetics, and nonsmokers as compared with normotensive subjects (Table 1). There was no significant difference in the enzymatic infarct size between hypertensive and normotensive patients (peak creatine kinase value: 2386±2110 U/L versus 2524±2310 U/L; $P=0.375$). At discharge, angiotensin-converting enzyme (ACE) inhibitors were more frequently prescribed in hypertensive than normotensive patients (80% versus 66%; $P=0.01$), and their use remained higher at 6 months (78% versus 58%; $P=0.006$). $\beta$ blockers were less frequently used in both hypertensive and normotensive patients, without significant differences at discharge (17% versus 14%; $P=0.48$) and at 6 months (14% versus 10%; $P=0.51$).

 Angiographic Results
Angiographic and procedural characteristics, such as multi-vessel disease, Rentrop collateral flow grade, associated chronic occlusion, use of stent, and PCI success, were similar between the 2 groups (Table 1). Coronary angiography was repeated in 722 (84%) of the 855 eligible patients 6 months after the index infarction. Overall, restenosis or reocclusion rates were not significantly different between hypertensive and normotensive patients (25% versus 23%; $P=0.58$).

| TABLE 1. Baseline Clinical, and Angiographic Characteristics of the Study Patients |
|-----------------------------------|-----------------|-----------------|---------------|
| Characteristic                    | Hypertensives   | Normotensives   | P Value       |
| Age, years                        | 65±11           | 62±13           | 0.013         |
| Female                            | 88 (27)         | 126 (20)        | 0.012         |
| Diabetes                          | 57 (18)         | 81 (13)         | 0.047         |
| Cholesterolemia >200 mg/dl        | 91 (28)         | 158 (25)        | 0.303         |
| Smoker                            | 99 (32)         | 292 (48)        | 0.001         |
| Body mass index                   | 27.1±3.6        | 26.5±3.7        | 0.019         |
| Previous myocardial infarction    | 36 (11)         | 78 (12)         | 0.561         |
| Previous PCI                      | 9 (3)           | 21 (3)          | 0.609         |
| Symptom-to-reperfusion time, min  | 158±95          | 160±113         | 0.787         |
| Left ventricular EF, %            | 42±10           | 43±10           | 0.210         |
| Anterior infarct location         | 171 (53)        | 327 (52)        | 0.817         |
| Multivessel CAD                   | 155 (48)        | 309 (49)        | 0.722         |
| Associated chronic occlusion      | 32 (10)         | 76 (12)         | 0.360         |
| Infarct artery TIMI flow grade $\geq$2 | 57 (18)     | 113 (18)        | 0.878         |
| IABP use                          | 32 (10)         | 87 (14)         | 0.079         |
| Infarct artery stenting           | 232 (71)        | 454 (72)        | 0.750         |
| Peak CK value, U/L                | 2386±2110       | 2524±2310       | 0.375         |
| Time-to-peak CK, hours            | 7.8±4.4         | 7.6±4.4         | 0.699         |

Data are presented as the mean±SD or numbers (%) of patients. PCI indicates percutaneous coronary intervention; EF, ejection fraction; CAD, coronary artery disease; TIMI, thrombolysis in myocardial infarction; IABP, intra-aortic balloon pump; CK, serum creatine kinase.
Long-Term Clinical Outcome and Relation Between Hypertension and HF

Follow-up data were collected for all of the 953 patients but 4. The mean follow-up length was 52.1100620 months. The incidence of hospitalization for HF was 7% (n=21) in the hypertensives and 3% (n=19) in the normotensives (P=0.014). Overall, New York Heart Association functional class ≥2 was higher in hypertensives as compared with normotensive patients (53% versus 40%; P=0.001). Major cardiac adverse event rate was higher in hypertensive patients (Table 2).

At multivariate Cox analysis, significant clinical predictors of 5-year hospitalization for HF were age (odds ratio [OR], 1.068; 95% CI, 1.032 to 1.104; P<0.0001), peak creatine kinase value (OR, 1.001; 95% CI, 1.001 to 1.001; P<0.0001), and hypertension (OR, 2.296; 95% CI, 1.175 to 4.485; P=0.015).

Changes in LV Regional and Global Function and Volumes

Of the 400 consecutive patients initially selected for the echocardiographic substudy, 13 (3.2%) were excluded for death within the first 6 months, 30 (7.5%) for inadequate echocardiographic image quality, and 31 (7.7%) for not having been adherent to the echocardiographic follow-up protocol. One patient underwent heart transplantation. Thus, 325 patients (111 hypertensives) underwent serial 2D echocardiogram from admission to 1 and 6 months. The subgroup of 325 patients with complete follow-up echocardiographic data showed similar baseline clinical and angiographic characteristics as compared with the entire patient cohort. From baseline to 6 months, a significant progressive improvement in regional (IZ WMSI; Figure A) and global LV function (EF; Figure B) was observed in both groups of patients. At baseline, LV volumes were higher, albeit not significantly, in the hypertensive patients than in the normotensive patients (ESV, 74.4±25.5 mL versus 69.9±27.2 mL, P=0.15; EDV, 127±41 mL versus 122±36 mL, P=0.14). LV ESV progressively decreased from baseline to 1 month in both groups. An additional reduction in LV ESV was observed between 1

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Changes in IZ WMSI (A), EF (B), and LV volumes (C and D) during 6 months after AMI in patients with (——) and without (----) hypertension (P<0.01 versus baseline, by ANOVA analysis).

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Hypertension and LV Remodeling

Our data suggest that the higher incidence of HF after AMI in patients with antecedent hypertension is not explained by a greater propensity to LV dilation and remodeling. In our study, 6-month LV remodeling rate was similar in hypertensive and normotensive patients. After AMI, normotensive subjects showed an upsloping LV EDV change-over-time curve that can be considered a natural compensatory adaptation to the reduced contractile mass. Surprisingly, hypertensive patients, despite enzymatic infarct size and 6-month IRA patency rate similar to normotensive patients, showed a flat LV EDV change-over-time curve, which suggests a reduced capability to remodel appropriately.

Perspectives

During the acute phase, there were no differences in the echocardiographic indexes of diastolic function between hypertensive and normotensive patients. Many factors may contribute to this finding, such as myocardial ischemia, LV systolic function, volumes, and mass, as well as mitral regurgitation grade and medical therapy. This finding cannot exclude that the persistence or the development of diastolic dysfunction after the acute phase of AMI could have contributed to the development of HF in hypertensive patients. Interestingly, hypertensive patients showed an increased incidence of late HF despite the fact that 6-month LV volumes and systolic function were similar between hypertensive and normotensive patients. However, in hypertensive patients, HF may be because of either LV systolic or diastolic dysfunction.

Previous reports established that HF with normal EF is common in hypertensive patients, particularly at old age, and most studies in humans with diastolic HF reported normal LV volumes. When challenged by hemodynamic stress, the LV of hypertensive patients is unable to increase the EDV (ie, it has limited preload reserve) because of decreased LV relaxation and compliance. Consequently, a cascade begins in which LV end-diastolic pressure rises, left atrial pressure increases, and pulmonary stasis develops.

Clinical Implications

There are some potentially important clinical implications of this study. First, as in patients treated with thrombolysis, a simple information as the history of antecedent hypertension can be used to identify, among patients treated with primary PCI, those at risk for postinfarction HF. The results of the present study may have implications for secondary prevention. In hypertensive patients, more effective blood pressure control may improve the outcome in the event that an AMI occurs. Second, in patients with antecedent hypertension, a progressive reduction in ESV was seen, but this finding does not necessarily imply that HF will not occur during the following months. Thus, a small ESV after AMI should not be considered routinely as a favorable sign. These patients should be carefully serially evaluated, and therapeutic measures aimed to prevent HF should not be neglected or postponed. Third, the simple observation that LV is significantly dilated or not at 6 months after the index AMI do not allow us to identify hypertensive patients who will experience HF.

Discussion

Hypertension and Long-Term Outcome

Our study shows that patients with antecedent hypertension are at higher risk to develop HF after AMI, even when successfully reperfused by primary PCI. During long-term follow-up, patients with antecedent hypertension were more frequently hospitalized for overt HF than normotensive patients, and antecedent hypertension was an independent predictor of overt HF. Moreover, at 5-year follow-up, patients with antecedent hypertension were more likely to have a worse functional class and a higher rate of major cardiac adverse events than normotensive patients. In hypertensives, the higher long-term adverse event rate was related to the higher incidence of HF hospitalization, as well as to the higher, although not significant, incidence of death and additional revascularization procedures. Antecedent hypertension may be associated with adverse outcome after AMI because of its multiple associations. Hypertensive patients are likely to have a high prevalence of other risk factors that, in addition to their high blood pressure, predispose them to a more severe and progressive atherosclerosis; furthermore, other comorbid conditions and hypertension-related end-organ damage are frequently found in patients with antecedent hypertension.

LV Diastolic Function

At baseline, a similar E wave/A wave ratio (1.02±0.27 versus 1.06±0.46; P=0.399), a similar DT (164±41 ms versus 161±43 ms; P=0.544), and a similar rate of LV restrictive filling pattern (29% versus 27%; P=0.803) were found in the hypertensives and in normotensives.
Study Limitations
Our results must be evaluated in the light of some study limitations. First, the definition of hypertension used may have led to an underestimation of the true prevalence of antecedent hypertension. However, our observed prevalence of 34% matches other reports,2–4 and our follow-up data indicate that antecedent hypertension, as defined in the current report, is of clinical relevance. Second, we cannot assess the impact of ACE inhibitor therapy on the attenuation of LV dilation in hypertensive patients. The inhibition of the renin–angiotensin system immediately after AMI has been shown to prevent the development of LV dilation.25 However, the absence of ACE inhibitor recommendation at discharge was not an independent predictor of 6-month LV remodeling. Third, we did not calculate LV mass (a not-trivial component of LV remodeling), because the conventional formulas used to calculate this parameter assume fixed cavity geometry, uniform wall thickness, and myocardial contractility, which are unusual after AMI. 3D echo and MRI imaging data would have provided more detailed and complete analysis of LV remodeling in this setting.24 However, LV remodeling, as defined in the current report, has been shown to be of prognostic value.13–15 Finally, we did not evaluate the impact of vascular remodeling and function on long-term clinical status. As is well known, arterial load influences systolic and diastolic LV performance, and clinical studies indicate that arterial stiffness may be increased in diastolic HF.25

Conclusions
Our study shows that patients with antecedent hypertension are at higher risk to develop HF after AMI, even when successfully reperfused by primary PCI. Our data suggest that the increased incidence of postinfarction HF in hypertensive patients is not associated with a greater propensity to LV remodeling.

Acknowledgments
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