

The New England Journal of Medicine

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VOLUME 338

APRIL 2, 1998

NUMBER 14



EFFECT OF REPERFUSION ON BIVENTRICULAR FUNCTION AND SURVIVAL AFTER RIGHT VENTRICULAR INFARCTION

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ABSTRACT

Background Although the salutary effects of reperfusion in patients with left ventricular infarction are well documented, the benefits in patients with acute right ventricular infarction are less clear.

Methods To determine whether primary angioplasty improves right ventricular function and the clinical outcome in patients with right ventricular infarction, we performed echocardiographic studies before and after angioplasty in 53 patients with acute right ventricular infarction.

Results Complete reperfusion, defined as normal flow in the right main coronary artery and its major right ventricular branches, was achieved in 41 patients (77 percent), leading to prompt and striking recovery of right ventricular function (mean [\pm SE] score for free-wall motion, 3.0 ± 0.4 at base line and 1.4 ± 0.1 at three days; $P < 0.001$). Twelve patients (23 percent) had unsuccessful reperfusion, defined as the failure to restore right ventricular branch flow, with or without patency of the right main coronary artery. Unsuccessful reperfusion was associated with lack of recovery of right ventricular function (score for free-wall motion, 3.2 ± 0.6 at base line and 3.0 ± 0.9 at three days; $P = 0.55$), as well as persistent hypotension and low cardiac output (in 83 percent of the patients, vs. 12 percent of those with successful reperfusion; $P = 0.002$) and a high mortality rate (58 percent, vs. 2 percent for those with successful reperfusion; $P = 0.001$).

Conclusions In patients with right ventricular infarction, complete reperfusion of the right coronary artery by angioplasty results in the dramatic recovery of right ventricular performance and an excellent clinical outcome. In contrast, unsuccessful reperfusion is associated with impaired recovery of right ventricular function, persistent hemodynamic compromise, and a high mortality rate. (N Engl J Med 1998;338:933-40.)

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RIGHT ventricular infarction is common in patients with acute inferior-posterior left ventricular myocardial infarction and may depress right ventricular function, resulting in right-heart failure and low cardiac output.¹⁻⁷ Despite the potentially life-threatening acute hemodynamic effects, however, most patients with ischemic right ventricular dysfunction have spontaneous early hemodynamic improvement and subsequent recovery of right ventricular function, regardless of the patency of the infarct-related artery.⁵⁻¹⁴ This resilience of the right ventricle is in marked contrast to the effects of coronary occlusion on regional and global left ventricular function.¹⁵⁻¹⁷ Nevertheless, right ventricular infarction is associated with increased rates of morbidity and mortality.^{5,6,18-23} Furthermore, spontaneous recovery of right ventricular function and hemodynamic and clinical improvement may be slow^{9-14,24} and in some cases incomplete.²⁵

Although the salutary effects of timely reperfusion in patients with left ventricular infarction are well documented,²⁶⁻³⁰ the benefits in patients with ischemic right ventricular dysfunction are less clear. Some studies suggest that right ventricular function is recovered only after successful reperfusion,^{11,12,22,31,32} whereas others report improvement even in the absence of a patent infarct-related artery.^{5,8,9,13,14} Unfortunately, it is difficult to draw firm conclusions from these studies because of the small numbers of patients or the lack of serial measurements of right ventricular performance. Recent studies in laboratory animals have shown that reperfusion of the right coronary artery enhances the recovery of right ventricular function, even after prolonged ischemia.^{33,34}

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If reperfusion improves right ventricular performance in patients with ischemic right ventricular dysfunction, the clinical benefits may be substantial. We performed a study designed to assess the effect of primary percutaneous transluminal coronary angioplasty (PTCA) of the occluded right coronary artery on right ventricular function and clinical outcome in patients with acute ischemic right ventricular dysfunction.

METHODS

The study group consisted of 53 patients who presented to William Beaumont Hospital, Royal Oak, Michigan, between September 1994 and December 1996 with acute inferior myocardial infarction (defined as chest pain with an ST elevation ≥ 1 mm in leads II, III, and aVF), and ischemic right ventricular dysfunction (defined as the combined presence of right ventricular free-wall dysfunction, dilatation, and depressed global performance) on transthoracic two-dimensional echocardiography. A total of 290 patients with inferior myocardial infarction were screened. Of these patients, 125 were excluded because a base-line echocardiogram could not be obtained without an unacceptable delay, and 41 were excluded because of technically inadequate images at base line (38 patients) or follow-up (3). Of the 124 remaining patients, 53 with echocardiographic evidence of right ventricular infarction were enrolled in the study and underwent emergency cardiac catheterization and primary PTCA according to standard techniques.^{29,32}

Assessment of Ventricular Function

Serial echocardiograms were obtained to assess right and left ventricular function before and 1 hour, 24 hours, three to five days, and one month after PTCA. The echocardiograms were analyzed according to previously described methods.^{24,33,34} From the apical four-chamber view, right ventricular performance was assessed by measuring the ventricular area at end diastole and end systole and calculating the fractional change in area. The right ventricular free wall was divided into three segments, and the motion of each segment was scored on a scale of 1 to 4 (1, normal; 2, hypokinetic; 3, akinetic; and 4, dyskinetic). The overall score for right ventricular free-wall motion was calculated as the average score for the three segments. Left ventricular dimensions and the change in the fractional area were also calculated. The left ventricular inferoposterior wall was divided into apical, middle, and posterior segments, and the overall score for left ventricular inferior-wall motion was calculated as the average score for the three segments. The left ventricular ejection fraction was determined by cineangiography.

Assessment of Perfusion

Coronary angiograms were analyzed to determine the severity of stenosis and the extent of flow, which was graded according to the Thrombolysis in Myocardial Infarction (TIMI) classification.²⁸⁻³⁰ Previous studies of reperfusion in patients with right-coronary-artery occlusion have focused on the restoration of flow in the right main coronary artery and its left ventricular branches, largely ignoring flow in the right ventricular branches.^{11-14,17,28-32} In our study, we defined successful reperfusion of the right coronary artery as less than 50 percent residual stenosis and restoration of TIMI grade 3 flow in the right main coronary artery, its left ventricular branches, and all major (≥ 1 mm) right ventricular branches. To assess right ventricular free-wall reperfusion, we calculated an overall grade for branch flow by averaging the flow grades for all major right ventricular branches. Similarly, an overall grade for left ventricular inferior-wall perfusion was calculated by averaging the flow grades for the posterior descending artery and posterolateral left ventricular branches.

In-Hospital Outcome

Adverse clinical events were recorded, including recurrent ischemia (defined as recurrent chest pain with new electrocardiographic changes or recurrent myonecrosis as indicated by enzyme tests), high-grade atrioventricular block, the need for a pacemaker for more than one hour, ventricular arrhythmias requiring treatment, hemodynamic abnormalities (elevated right atrial pressure, low cardiac output, or hypotension for more than one hour), and death.

Statistical Analysis

All data are expressed as means \pm SD, except the results of paired comparisons, which are reported as means \pm SE. Comparisons were made with use of the chi-square test for categorical variables and a two-tailed Student t-test for continuous variables. A paired t-test was used to compare base-line and subsequent values in each patient. Analysis of variance was used to compare serial echocardiographic wall-motion data, including right and left ventricular wall-motion scores, within each group over time, and a paired t-test was used for comparisons at each interval. Comparisons between groups at the same point in time were made with a two-tailed Student t-test.

RESULTS

Base-Line Characteristics

The 53 patients with acute inferior infarction and ischemic right ventricular dysfunction had a mean age of 63 ± 10 years. Eight patients had had previous myocardial infarctions, 12 had undergone PTCA, and 1 had undergone bypass surgery. The patients presented a mean of 2.2 ± 3.4 hours (range, 1.3 to 12.5) after the onset of symptoms.

Before PTCA was performed, bradyarrhythmias occurred in 21 patients (40 percent). Ventricular tachyarrhythmias, defined as recurrent ventricular tachycardia (>15 beats) or ventricular fibrillation or both, occurred in 16 patients (30 percent). Twenty-three patients (43 percent) had hypotension (aortic systolic pressure, <90 mm Hg), which responded to volume infusion, treatment of bradycardia, or both in 12 patients but required inotropic or vasopressor support in 11.

Angiographic Findings and Perfusion Status

Coronary angiography documented single-vessel disease in 29 patients, two-vessel disease in 22, and three-vessel disease in 2. The right coronary artery was the infarct-related artery in all cases, and the culprit lesion (initial stenosis, 97 ± 7 percent; TIMI flow grade, 0.8 ± 1.2) was proximal to the major right ventricular branches in 50 patients (94 percent) (Fig. 1). Perfusion of the right ventricular free wall and the left ventricular inferior wall was severely reduced (flow grades, 0.5 ± 0.8 and 0.8 ± 1.2 , respectively).

According to the traditional criteria (i.e., regardless of the flow in the right ventricular branches), reperfusion of the right main coronary artery and its left ventricular branches was successful in 48 patients (91 percent): residual stenosis, 19 ± 13 percent a mean of 3.4 ± 3.0 hours after the onset of symp-

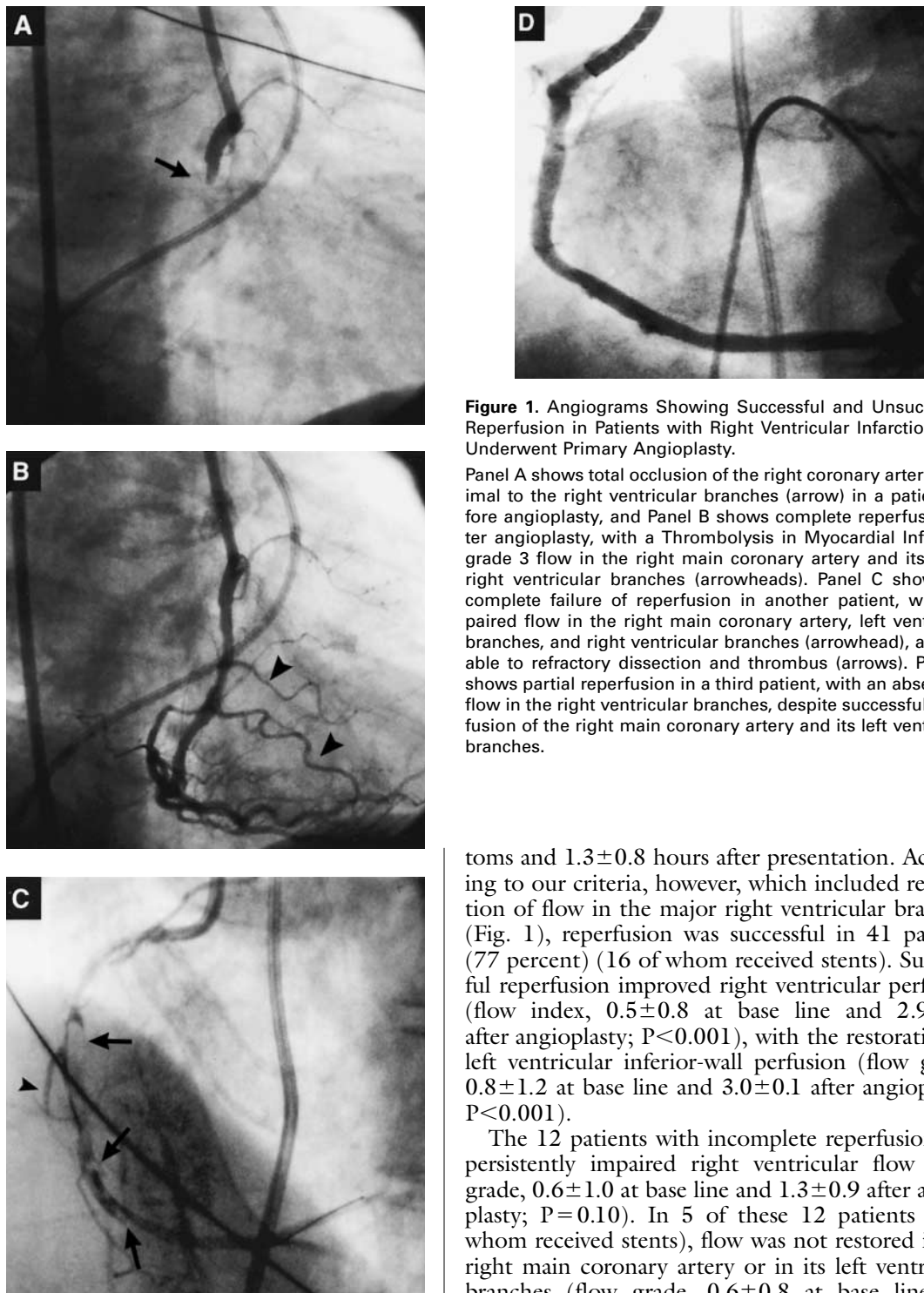


Figure 1. Angiograms Showing Successful and Unsuccessful Reperfusion in Patients with Right Ventricular Infarction Who Underwent Primary Angioplasty.

Panel A shows total occlusion of the right coronary artery proximal to the right ventricular branches (arrow) in a patient before angioplasty, and Panel B shows complete reperfusion after angioplasty, with a Thrombolysis in Myocardial Infarction grade 3 flow in the right main coronary artery and its major right ventricular branches (arrowheads). Panel C shows the complete failure of reperfusion in another patient, with impaired flow in the right main coronary artery, left ventricular branches, and right ventricular branches (arrowhead), attributable to refractory dissection and thrombus (arrows). Panel D shows partial reperfusion in a third patient, with an absence of flow in the right ventricular branches, despite successful reperfusion of the right main coronary artery and its left ventricular branches.

toms and 1.3 ± 0.8 hours after presentation. According to our criteria, however, which included restoration of flow in the major right ventricular branches (Fig. 1), reperfusion was successful in 41 patients (77 percent) (16 of whom received stents). Successful reperfusion improved right ventricular perfusion (flow index, 0.5 ± 0.8 at base line and 2.9 ± 0.5 after angioplasty; $P < 0.001$), with the restoration of left ventricular inferior-wall perfusion (flow grade, 0.8 ± 1.2 at base line and 3.0 ± 0.1 after angioplasty; $P < 0.001$).

The 12 patients with incomplete reperfusion had persistently impaired right ventricular flow (flow grade, 0.6 ± 1.0 at base line and 1.3 ± 0.9 after angioplasty; $P = 0.10$). In 5 of these 12 patients (2 of whom received stents), flow was not restored in the right main coronary artery or in its left ventricular branches (flow grade, 0.6 ± 0.8 at base line and 1.0 ± 1.0 after angioplasty; $P = 0.50$) or right ventricular branches (flow grade, 0.6 ± 1.0 at base line and 1.0 ± 1.0 after angioplasty; $P = 0.54$). The failure of PTCA to restore perfusion was attributable to recurrent intracoronary thrombus in three patients and refractory flow-limiting dissections in two. In the seven patients with partial reperfusion (three of whom

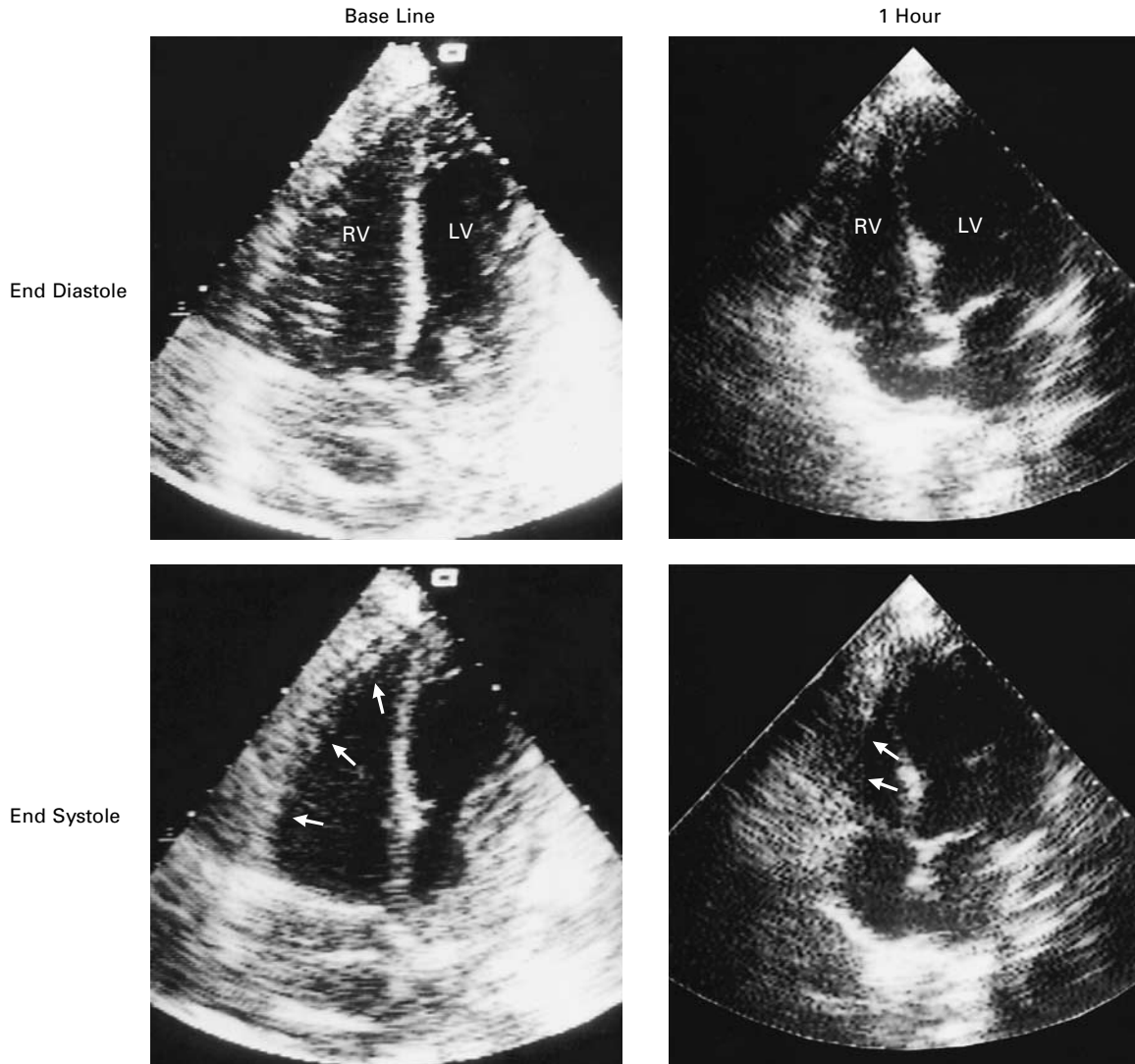


Figure 2. Echocardiographic Images from a Patient with Acute Inferior Myocardial Infarction and Right Ventricular Ischemia in Whom Angioplasty Was Successful.

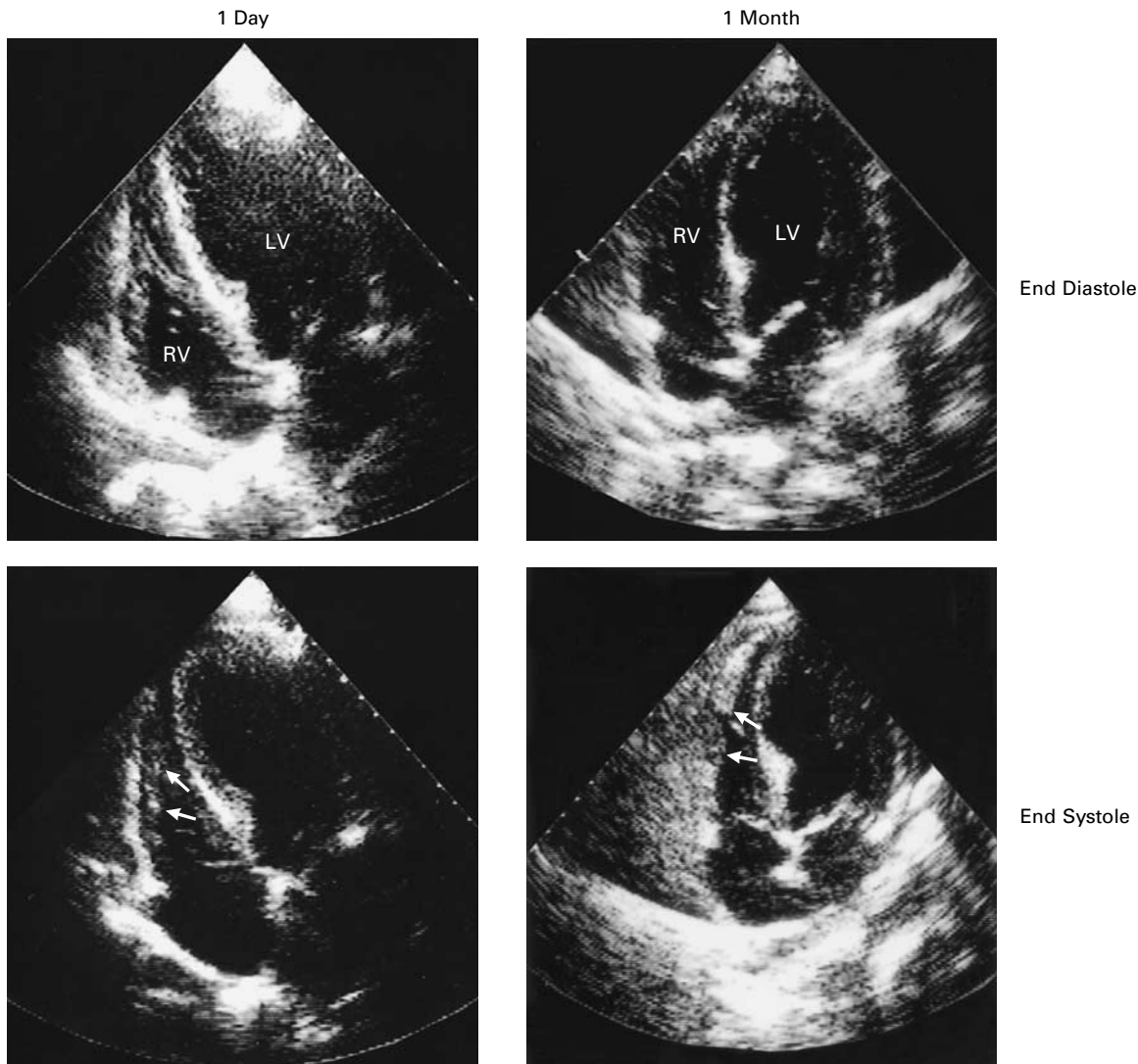
Images at end diastole and end systole were obtained from the transthoracic apical four-chamber view. At base line, there was severe right ventricular dilatation with reduced left ventricular diastolic size at end diastole. At end systole, there was right ventricular free-wall dyskinesia (arrows), intact left ventricular function, and compensatory paradoxical septal motion. One hour after angioplasty, there was a striking recovery of right ventricular free-wall contraction (arrows), resulting in marked improvement in global right ventricular performance, with a markedly reduced right ventricular size and an increased left ventricular size at end diastole. At one day, there was further improvement in right ventricular function (arrows), and at one month right ventricular size and function (arrows) were normal. RV denotes right ventricle, and LV left ventricle.

received stents), normal flow was restored in the right main coronary artery and its left ventricular branches (flow grade, 0.8 ± 1.0 at base line and 3.0 ± 0.1 after angioplasty; $P < 0.001$) but not in one or more major right ventricular branches (flow grade, 0.8 ± 1.0 at base line and 1.4 ± 0.5 after angioplasty; $P = 0.18$). The impaired flow in the right ventricular branches was attributable to the “no reflow” phenomenon (in which there is flow into the epicardial vessels but diminished flow into the myocardi-

um) in five patients and severe residual branch stenoses in two.

Ventricular Performance

Before PTCA, all the patients had severe inferior left ventricular dysfunction (motion score, 2.9 ± 0.4), but overall left ventricular performance was preserved (fractional change in area, 38 ± 5 percent; ejection fraction, 50 ± 8 percent). In all cases, there was severe right ventricular dysfunction (motion



score, 3.1 ± 0.6 ; fractional change in area, 25 ± 8 percent), with paradoxical septal motion reflecting compensatory systolic interactions.^{24,33-36} Right ventricular diastolic dysfunction was indicated by right ventricular dilatation (Fig. 2), reversed septal curvature, and elevated right-heart diastolic pressures (mean atrial pressure, 14.0 ± 4.3 mm Hg). In 80 percent of the patients, a right ventricular dip-and-plateau pattern and equalized diastolic filling pressures indicated adverse diastolic interactions.^{3,6,33-37}

In all cases of successful right-coronary-artery reperfusion, right ventricular function recovered dramatically at one hour (wall-motion score, 3.0 ± 0.6 at base line and 2.0 ± 0.5 at one hour, $P < 0.01$; change in the fractional area, 25 ± 4 percent at base line and 32 ± 5 percent at one hour, $P < 0.001$) (Fig. 2 and 3). As in laboratory models,^{32,33} successful reperfusion led to lower right-heart filling pressures (right

atrial pressure, 12.4 ± 1.9 at base line and 10.3 ± 1.6 mm Hg at one hour; $P = 0.05$), reduced right ventricular dilatation (Fig. 2), and resolution of the right ventricular dip-and-plateau pattern and equalized diastolic pressures. As right ventricular systolic and diastolic function recovered, left ventricular filling was enhanced, and systemic cardiac output improved (3.6 ± 0.7 liters per minute at base line and 5.6 ± 1.1 liters per minute at one hour, $P = 0.04$). There was further recovery of right ventricular function during the next 23 hours, and at 3 to 5 days, right ventricular performance was normal in 95 percent of the patients (Fig. 2 and 3). Remarkably, even though flows in the right and left ventricular branches were restored to similar levels after successful reperfusion, the recovery of right ventricular function was greater and more rapid than the recovery of left ventricular function (Fig. 4). Immediately

after PTCA, there was demonstrable improvement in right ventricular contraction in 76 percent of the patients with successful reperfusion, whereas left ventricular wall motion improved in only 2 percent ($P=0.001$). At one month, right ventricular wall motion was completely normal in 98 percent of the patients with successful reperfusion, whereas left ventricular inferior wall motion recovered completely in only 8 percent ($P=0.001$).

In contrast, the patients with unsuccessful reperfusion had impaired recovery of right ventricular function, regardless of whether reperfusion was achieved in part or not at all. Lack of complete reperfusion was associated with persistent, severe right ventricular dysfunction at 24 hours (wall-motion score, 3.2 ± 0.6 at base line and 2.8 ± 1.0 at 24 hours, $P=0.26$; fractional change in area, 24 ± 7 percent and 27 ± 8 percent, respectively, $P=0.34$) (Fig. 3). Unsuccessful reperfusion was associated with persistently elevated right-heart filling pressures (atrial pressure, 16.4 ± 4.7 mm Hg at base line and 15.6 ± 4.5 mm Hg at 24 hours; $P=0.67$) and depressed cardiac output (2.8 ± 0.8 liters per minute at base line and 3.6 ± 1.0 liters per minute at 24 hours, $P=0.16$). However, although unsuccessful reperfusion led to a higher rate of in-hospital mortality (see below), patients surviving to discharge ultimately had complete recovery of right ventricular function, although the recovery was slower than in those with successful reperfusion (Fig. 3).

Clinical Outcome

Adverse in-hospital events were infrequent in the patients with successful reperfusion. Sustained hypotension occurred in five patients (12 percent), with inotropic support for more than 24 hours required in one. Ventricular arrhythmias occurred in 10 patients (24 percent). Most important, 40 of the patients with successful reperfusion (98 percent) survived and were discharged from the hospital after a mean stay of 8.7 ± 7.7 days (range, 3 to 45). At one month, all 40 were alive and had no evidence of right-heart failure.

Conversely, the 12 patients with unsuccessful reperfusion had a poor clinical outcome. Lack of recovery of right ventricular function in these patients was associated with persistent severe hemodynamic compromise, and 10 of the 12 patients (83 percent) required high-dose inotropic support and intraaortic balloon pumping to maintain blood pressure ($P=0.002$ for the comparison with the successful-reperfusion group). Although these supportive measures initially stabilized blood pressure, seven patients (58 percent) had progressively reduced output leading to refractory hypotension and death ($P=0.001$ for the comparison with the successful-reperfusion group), despite intact left ventricular function (ejection fraction, 49.3 ± 6.7 percent). Of the seven pa-

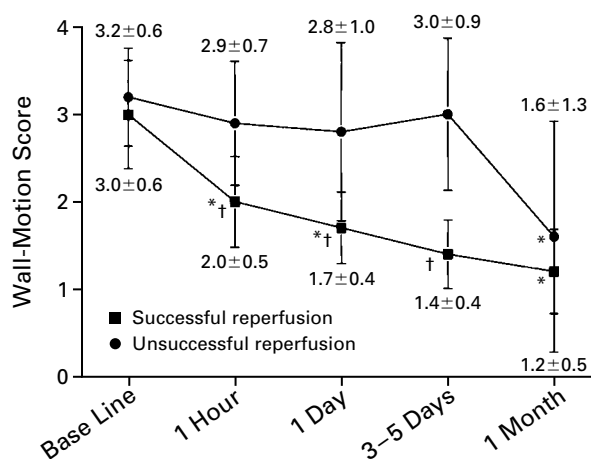


Figure 3. Mean (\pm SD) Changes over Time in the Score for Right Ventricular Free-Wall Motion in Patients with Successful Reperfusion and Those with Unsuccessful Reperfusion.

An asterisk denotes $P\leq 0.01$ for the comparison with the most recent score in the same group. A dagger denotes $P\leq 0.02$ for the comparison between groups at one point in time.

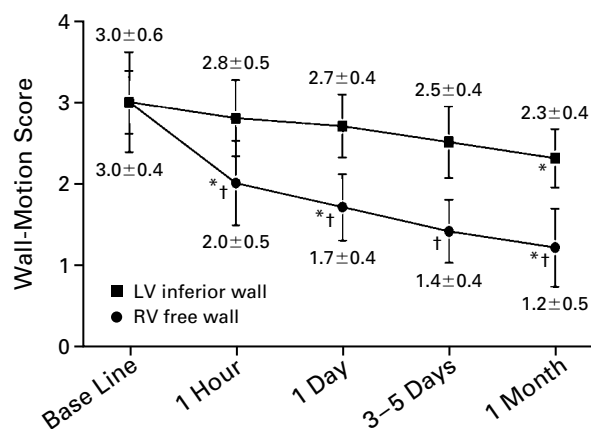


Figure 4. Mean (\pm SD) Changes over Time in the Score for Right Ventricular (RV) Free-Wall Motion and Left Ventricular (LV) Inferior-Wall Motion in the Patients with Complete Reperfusion.

An asterisk denotes $P\leq 0.01$ for the comparison with the most recent score for the same ventricle. A dagger denotes $P\leq 0.003$ for the comparison between the scores for the right and left ventricles at one point in time.

tients who died, four had no reperfusion, and three had partial reperfusion. Ventricular arrhythmias were more common in these patients, occurring in 6 of 12 (50 percent, $P=0.09$ for the comparison with the successful-reperfusion group). The five patients with unsuccessful reperfusion who survived to discharge had prolonged hospital stays (11.8 ± 6.2 days; range, 6 to 24), but at 1 month, all five were alive and had no evidence of right-heart failure.

DISCUSSION

The results of our study document the effect of right ventricular reperfusion on the clinical outcome and survival and demonstrate the disparate responses of the ischemic ventricles to reperfusion. In our study, as in previous studies in animals and humans, the detrimental effects of right ventricular free-wall ischemia on right-heart function were striking.^{1-6,24,33-37} Right-coronary-artery occlusion proximal to the major right ventricular branches resulted in severe right ventricular dysfunction. Previous studies have defined successful reperfusion of the right coronary artery on the basis of the restoration of flow to the left ventricular branches only, largely ignoring the status of the right ventricular branches.^{1-14,17,28-32} Our study, in which we used new criteria for reperfusion of the occluded right coronary artery, suggests that complete reperfusion (including reperfusion of the major right ventricular branches) improves right ventricular function and the clinical outcome. In our study, complete reperfusion led to a striking immediate improvement in right ventricular function followed by complete recovery — findings consistent with the results of studies in animals^{33,34} and the few available data from clinical studies.^{11,12,31,32} Recovery of right ventricular function was associated with improved hemodynamic status, which is consonant with reperfusion-mediated attenuation of adverse diastolic interactions,^{6,24,33,34,37} since prompt recovery of right ventricular function reduces right ventricular dilatation and the constraining effects of the pericardium and enhanced right ventricular systolic performance augments left ventricular filling and improves cardiac output. Most important, unlike prior studies of right ventricular infarction,¹⁸⁻²³ our study suggests that successful reperfusion is associated with an uneventful clinical course and a high rate of survival.

In contrast to the benefits of successful reperfusion, failure to restore complete flow to the main right coronary artery and its major right ventricular branches was associated with impaired recovery of right ventricular function, persistent hemodynamic compromise, and a high rate of in-hospital mortality. Since the initial depression in right ventricular function was no greater in the patients with unsuccessful reperfusion than in those with successful reperfusion and since global left ventricular performance was intact in the patients with unsuccessful reperfusion, their poor clinical outcome must be predominantly attributable to persistent, severe right ventricular dysfunction. These observations emphasize the importance of complete right-coronary-artery reperfusion, since the failure to restore flow in the right ventricular branches was associated with adverse outcomes even if the main right coronary artery and its left ventricular branches were reperfused.

There are scant and conflicting clinical data on the

effects of interventions designed to achieve reperfusion in ischemic right ventricular myocardium. Some authors suggest that right ventricular function improves only after successful thrombolysis,^{11,12,22,31} whereas others report recovery even in the absence of early recanalization.^{5,9,13,14} There is a paucity of data on the effects of primary PTCA in patients with acute ischemic right ventricular dysfunction. Our findings are consistent with those of a recent study at our institution, which reported rapid hemodynamic improvement and an excellent clinical outcome after reperfusion in patients with right ventricular infarction who underwent primary angioplasty.³² Our observations are also consonant with prior studies of right ventricular infarction that have documented increased rates of morbidity and mortality attributable to arrhythmias and cardiogenic shock,¹⁸⁻²³ particularly in patients with unsuccessful reperfusion.^{31,38} We can only speculate about whether the adverse outcomes previously observed were related to unsuccessful reperfusion of the right ventricular branches and whether selective PTCA in unsuccessfully recanalized right ventricular branches will improve the clinical outcome.

It should be noted that our conclusions are based on a study of a limited number of nonconsecutive patients undergoing primary PTCA. Therefore, caution should be used when extrapolating the results of this study to reperfusion interventions in the broad population of patients with right ventricular infarction in general and in those undergoing primary thrombolysis in particular.

Previous studies support the concept that the right ventricle is more resistant to infarction than the left ventricle.^{8-12,24,33,34} However, previous studies of reperfusion have not correlated the mechanical responses of the ischemic ventricles over time with perfusion in the coronary branches. In our study, the dramatic recovery of right ventricular function contrasted sharply with the response of the left ventricle to equivalent ischemic insults. Remarkably, recovery of right ventricular function ultimately occurred even in the patients with unsuccessful reperfusion who survived. The superior recovery of the right ventricle is probably attributable, at least in part, to more favorable oxygen supply-demand characteristics, in general, and a greater capacity for rapid development of a functional collateral vascular supply, in particular.^{24,33,34,39,40} It is possible that other mechanisms underlie the different responses of the ventricles, such as different patterns of ventricular injury potentially mediated by a disproportionate distal distribution of emboli to the left and right ventricular branches, differences in the responses of myocytes to ischemia and reperfusion, and differences in recovery from stunning. In the aggregate, however, our observations suggest that the term “right ventricular infarction” is largely a misnomer, because

acute ischemic right ventricular dysfunction appears to represent predominantly viable myocardium that responds favorably to reperfusion.

Presented in part at the Scientific Session of the American College of Cardiology, March 16-18, 1997.

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