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STATE-OF-THE-ART PAPER

Pathophysiology and Management of Right Heart Ischemia

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Acute right coronary artery occlusion proximal to the right ventricular (RV) branches results in right ventricular free wall dysfunction, exerting mechanically disadvantageous effects on biventricular performance. Depressed RV systolic function decreases transpulmonary delivery of left ventricular (LV) preload, resulting in diminished cardiac output. The ischemic right ventricle is stiff, dilated, and volume dependent, resulting in pandiastolic RV dysfunction and septally mediated alterations in LV compliance, which are exacerbated by elevated intrapericardial pressure. Under these conditions, RV pressure generation and output are dependent on LV-septal contractile contributions, governed by both primary septal contraction and paradoxical septal motion. When the culprit coronary lesion is distal to the right atrial (RA) branches, augmented RA contractility enhances RV performance and optimizes cardiac output. Conversely, more proximal occlusions result in ischemic depression of RA contractility, which impairs RV filling and performance, resulting in more severe hemodynamic compromise. Bradyarrhythmias limit output generated by the rate-dependent noncompliant ventricles. Hemodynamic compromise may respond to volume resuscitation and restoration of physiologic rhythm. Vasodilators and diuretics should generally be avoided. In some patients, parenteral inotropic stimulation may be required. The right ventricle appears to be relatively resistant to infarction and recovers even after prolonged occlusion. The term RV "infarction" appears to be somewhat of a misnomer, for in most patients acute RV dysfunction represents ischemic but predominantly viable myocardium. Although RV performance improves spontaneously even in the absence of reperfusion, recovery of function may be slow and associated with high in-hospital mortality. Reperfusion enhances recovery of RV performance and improves the clinical course and survival.   (J Am Coll Cardiol 2002;40:841–53) © 2002 by the American College of Cardiology Foundation

On the basis of early experimental studies of right ventricular (RV) performance, it was felt for many years that RV contraction was unimportant in maintenance of the circulation (1). However, recognition of the profound hemodynamic effects of RV systolic dysfunction became evident with the description of severe right ventricular infarction (RVI) (2–9). Significant RVI typically occurs in association with acute transmural inferior-posterior left ventricular (LV) myocardial infarction (MI), and the right coronary artery (RCA) is almost always the culprit vessel (3,7–13). Necropsy studies demonstrate pathologic evidence of RVI in 14% to 60% of patients dying of inferior MI (3,4), typically inscribing a "tripartite" pathologic signature consisting of LV inferior-posterior wall, septal, and posterior right ventricular free wall (RVFW) necrosis contiguous with the septum, with less frequent extension into the anterolateral RVFW (3). In patients with anterior MI, the RV apex may be infarcted, but the extent of RVFW involvement is small and clinically insignificant (4). It must be emphasized that these patterns of RVI are derived from autopsy studies and do not necessarily reflect the status of the right ventricle

in the vast majority of patients who survive acute RV ischemic dysfunction.

Noninvasive studies demonstrate RV ischemic dysfunction characterized by RV dilatation and RVFW motion abnormalities in 40% to 50% of patients with acute inferior MI (6,11), although hemodynamic compromise develops in fewer than one-half of such cases. Patients with predominant severe RVI develop a distinct hemodynamic syndrome characterized by severe right heart failure, clear lungs, and low output despite intact global LV systolic function (2,5–9). Although in general the magnitude of hemodynamic derangements in patients with RVI is related to the extent of RVFW contraction abnormalities (7,8,9,11–13), some patients tolerate severe RV systolic dysfunction without hemodynamic compromise whereas others develop life-threatening low output, emphasizing that additional factors modulate the clinical expression of RVI.

Although acute ischemic RV dysfunction may result in hemodynamic compromise associated with higher in-hospital morbidity and mortality (12,14–17), most patients manifest spontaneous early hemodynamic improvement and later recovery of RV function, even in the absence of reperfusion of the infarct-related artery (7,18–21). In fact, chronic right heart failure attributable to RVI is rare (11). Thus, the term RV "infarction" is to an extent a misnomer, for in most cases acute RV ischemic dysfunction appears to

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Abbreviations and Acronyms

AV	=	atrioventricular
JVP	=	jugular venous pressure
LV	=	left ventricular
MI	=	myocardial infarction
RA	=	right atrial
RCA	=	right coronary artery
RV	=	right ventricular
RVFW	=	right ventricular free wall
RVI	=	right ventricular infarction

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represent viable myocardium. These responses are in marked contrast to the effects of ischemia on the left ventricle (22–25). This review will clarify the present understanding of fundamental issues regarding the pathophysiology, natural history, and clinical management of right heart ischemic dysfunction.

RV mechanics and oxygen supply-demand. Given that the right and left ventricles face dramatically different loading conditions, it should not be surprising that they differ markedly in their anatomy, mechanics, and metabolism. The left ventricle is a thick-walled bullet-shaped pressure pump ejecting into the high-resistance systemic arterial system. In contrast, the pyramidal-shaped right ventricle has a triangular base with a thin crescentic free wall and is designed as a volume pump, ejecting into the lower resistance pulmonary circulation. Under physiologic conditions, RV systolic pressure and flow are generated by RVFW shortening and contraction toward the septum from apex to outflow tract (26–28). The septum is an integral architectural and mechanical component of the RV chamber and, even under physiologic conditions, LV-septal contraction contributes to RV performance (26–28). The right ventricle has a more favorable oxygen supply-demand profile than the left ventricle. The RVFW has less myocardial mass and faces lower preload and afterload; therefore, RV oxygen demand is lower (29–31). Less oxygen extraction at rest also imparts to the right ventricle greater extraction reserve capabilities during stress (30). Right ventricular perfusion also is more favorable, in part because of a dual anatomic supply system whereby nearly one-third of RVFW flow is derived from left coronary branches (32,33). In addition, because the RVFW is thinner, develops lower systolic intramyocardial pressure, and faces less diastolic intracavitary pressure (29,31), it receives relatively homogeneous transmural perfusion in systole as well as diastole, both under physiologic conditions and with collateral perfusion during RCA occlusion. Furthermore, there is a comparatively greater likelihood of acute collateral development to the RCA (34–36), attributable in part to lower coronary resistance that favors a left-to-right transcoronary pressure gradient. The propensity for bridging ipsilaterals and the frequent presence of an independently arising conus branch further impart a greater anatomic reserve capacity for maintenance of perfusion.

Patterns of coronary compromise resulting in RVI. Although proximal RCA occlusion is accepted as the culprit commonly responsible for RVI (3,4,7–11), some patients with proximal occlusions develop minimal or no RVI ischemic dysfunction, whereas in others RVI develops in association with more distal occlusion. Furthermore, in those who develop RV ischemic involvement, the severity of RV dysfunction ranges broadly from mild RVFW contraction abnormalities to profound global depression of RV pump function. Recent observations from our laboratory have delineated the patterns of coronary compromise that determine the magnitude of RV ischemic dysfunction (12,13). In patients undergoing primary angioplasty for acute inferior-posterior MI, the RCA was the culprit vessel in all cases with RV ischemic dysfunction, the vast majority of whom showed proximal high-grade occlusion compromising flow to the major RV branches (Fig. 1). In contrast, patients without RVI tended to have more distal RCA lesions or circumflex culprits that spared RV branch perfusion (13). Although the proximity of the culprit lesion and its relationship to RVFW perfusion correlates with the presence or absence of RVI in most patients, there are exceptions in which proximal occlusions do not result in RV ischemic dysfunction, attributable in most cases to restoration of RVFW perfusion through prominent collaterals or spontaneous antegrade reperfusion. In the rare cases in which RV ischemic dysfunction occurs in association with culprit lesions distal to the major RV branches, RV branch flow is impaired by adjacent thrombus or RV branch stenosis. Occasionally, isolated RVI may develop from occlusion of a nondominant RCA (37) or selective compromise of RV branches during percutaneous coronary interventions (38).

Effects of RV systolic and diastolic dysfunction. The pathophysiologic mechanisms contributing to hemodynamic compromise with severe RVI are now well documented. In experimental animal models and in patients (9,12,34,35,39–45), proximal RCA occlusion compromises RVFW perfusion, resulting in RVFW dyskinesis and severely depressed global RV performance (Fig. 2), reflected in the RV waveform by a sluggish upstroke, depressed and broadened systolic peak, delayed relaxation phase, and markedly diminished RV stroke work (Figs. 3 and 4). Right ventricular systolic dysfunction diminishes transpulmonary delivery of LV preload, leading to decreased cardiac output despite intact LV contractility.

Biventricular diastolic dysfunction contributes to hemodynamic compromise associated with acute right heart ischemia (9,34,35,39–45). Depressed RV contractility results in RV dilation and ischemia intrinsically impairs RV relaxation. Therefore, the ischemic right ventricle is stiff and dilated early in diastole, resulting in increased impedance to initial RV inflow. As filling progresses, the noncompliant right ventricle ascends a steep pressure-volume curve, leading to a pattern of rapid diastolic pressure elevation. Right ventricular diastolic dysfunction adversely affects LV dia-
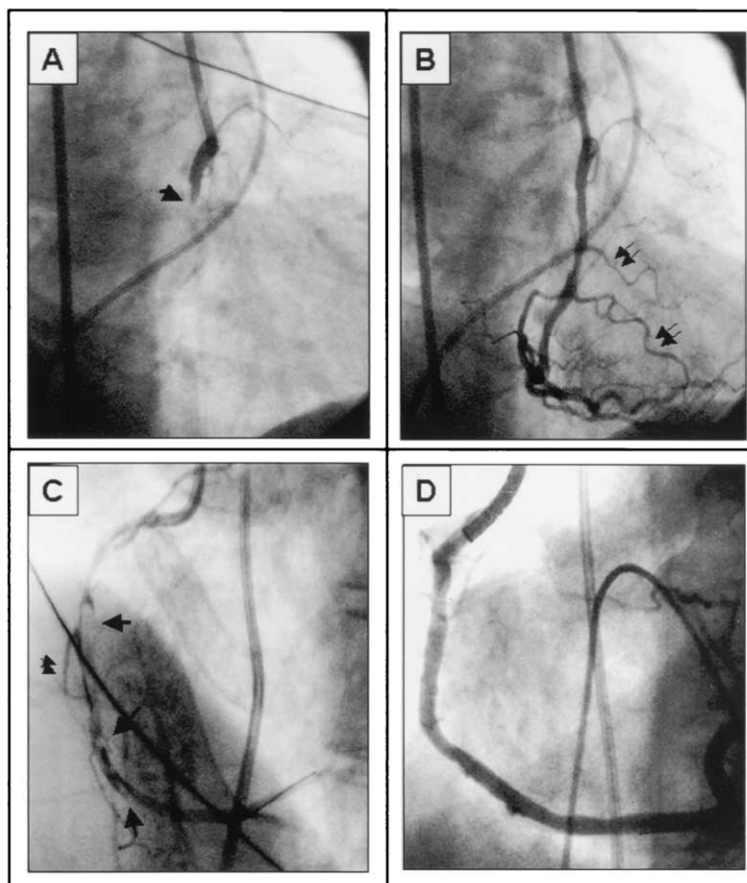
Figure 1. Angiograms showing successful and unsuccessful reperfusion in patients with right ventricular infarction who underwent primary angioplasty. **A** shows total occlusion of the right coronary artery proximal to the right ventricular branches **(arrow)** in a patient before angioplasty, and **B** 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)**. **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)**. **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. Reprinted with permission from reference 12.

stolic properties through diastolic interactions mediated by the reversed curved septum and exacerbated by elevated intrapericardial pressure (9,39–45). Acute RV dilation and elevated RV diastolic pressure shift the interventricular septum toward the volume-deprived left ventricle, thereby impairing LV compliance and further limiting LV filling. Abrupt RV dilation within the noncompliant pericardium leads to elevated intrapericardial pressure. The resultant pericardial constraint further impairs both RV and LV compliance and filling, both directly and by intensifying the adverse effects of diastolic ventricular interactions. Furthermore, as both ventricles fill and compete for space within the crowded pericardium, the effects of pericardial constraint contribute to the pattern of equalized diastolic pressures and RV "dip-and-plateau" characteristic of RVI (5,9,39).

The hemodynamic importance of abnormal RV compliance has been recognized in patients with significant RVI (2,5,6,9,46), who manifest distinctive alterations in right atrial (RA) waveform morphology, at one time thought to be characterized by a blunted X and prominent Y descent

(5,46). However, given that progressive increments in diastolic impedance imposed by the stiff dilated right ventricle reduce inflow velocity across the tricuspid valve, a blunted rather than a rapid Y descent would be expected. In contrast to these previous interpretations, in experimental animal studies (34,35,43–45) and patients with severe RVI (9), when RA waveform components are timed to mechanical correlates rather than the electrocardiogram alone, the RA Y descent is blunted (Figs. 3 and 4), reflecting pandiastolic RV dysfunction.

Determinants of RV performance in severe RVI. IMPORTANCE OF SYSTOLIC VENTRICULAR INTERACTIONS. For many years it was felt that under conditions of loss of RV contraction, pulmonary flow could be generated by passive gradient from a distended systemic venous system and by active RA contraction. Experimental and clinical studies of acute severe RVFW dysfunction now demonstrate that despite the absence of RVFW motion, an active albeit depressed RV systolic waveform (Fig. 3) is generated by global LV-septal contractile contributions transmitted through systolic interactions mediated by the septum
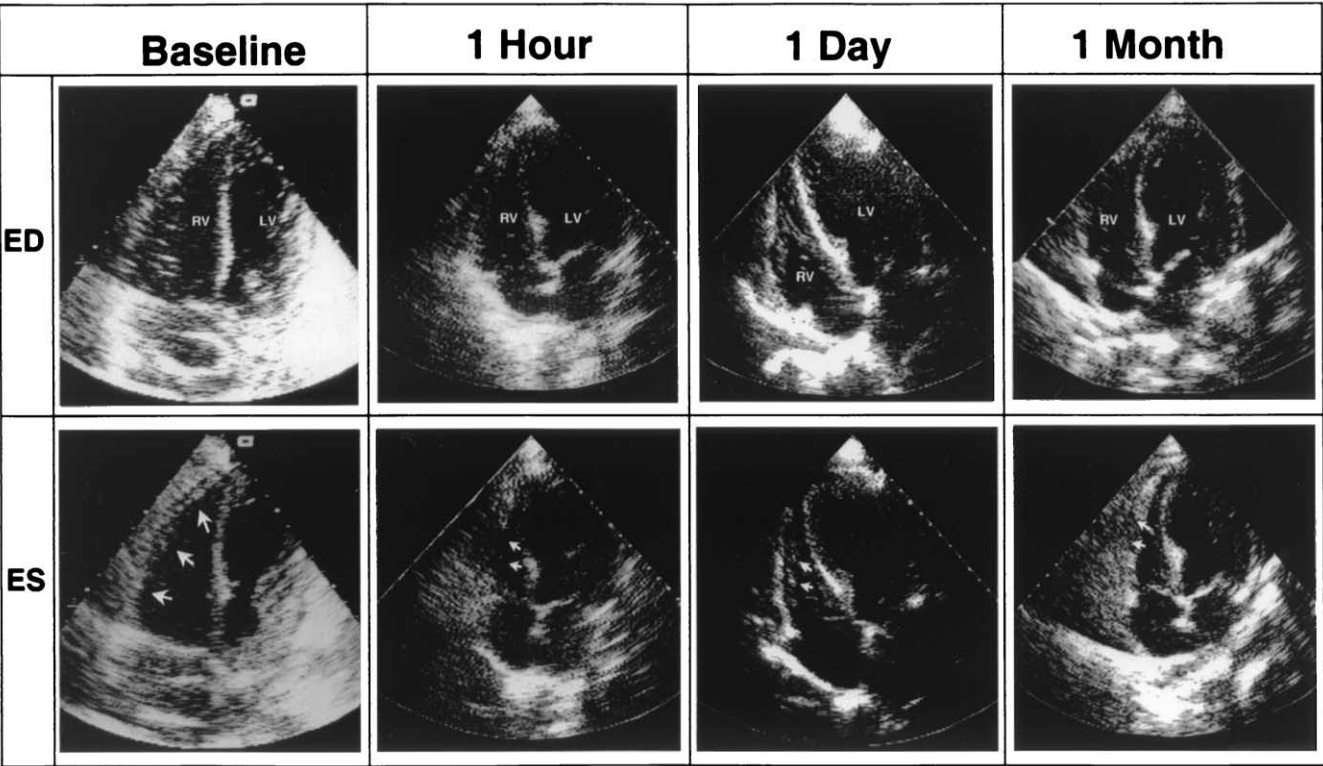
Figure 2. Echocardiographic images from a patient with acute inferior myocardial infarction and right ventricular ischemia in whom angioplasty was successful. Images at end-diastole (ED) and end-systole (ES) were obtained from the transthoracic apical four-chamber view. At baseline, there was severe right ventricular dilation with reduced left ventricular diastolic size at ED. At ES, there was right ventricular free-wall dyskinesis **(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 = right ventricle; LV = left ventricle. Reprinted with permission from reference 12.

(9,34,35,43–45). The septum constitutes an important anatomic component of the RV chamber and even in normal hearts is responsible for one-third of RV stroke work (26–28). When RVFW contraction is depressed, RV systolic pressure is generated by primary septal contraction and through mechanical displacement of the septum into the RV cavity associated with paradoxical septal motion (Fig. 2). The systolic behavior of the septum is fundamentally influenced by the instantaneous trans-septal gradient, and under conditions of severe RVFW dysfunction, paradoxical septal motion reflects the development of an early left-to-right systolic trans-septal gradient because depressed RV contraction allows unopposed LV septal tension development (34,35,43–45). Global RV performance is influenced by the extent of mechanical disadvantage imposed by the ischemic dyskinetic RVFW (34,35,43–45). Dyssynergic segments must be stretched to their maximal systolic length before providing a stable buttress upon which actively contracting segments can generate effective stroke work. Dyssynergic segments in the left ventricle undergo passive systolic lengthening and thereby impose a mechanical disadvantage on nonischemic zones because of regional intraventricular interactions that diminish the contribution of the contracting regions to overall ejection (47,48). The

ischemic dyskinetic RVFW behaves in an analogous manner, and must be stretched through interventricular interactions that reduce their contributions to both RV and LV performance (34,35,44,45). The critical compensatory contributions of LV-septal contraction to global RV systolic are emphasized by the deleterious effects of depressed LV septal function, which diminishes these compensatory systolic interactions, thereby further depressing both RV and LV performance (45). Not surprisingly, LV-septal contractile dysfunction exacerbates hemodynamic compromise associated with RVI. In contrast, inotropic stimulation enhances LV-septal contraction and thereby augments RV performance through augmented compensatory systolic interactions (45).

Compensatory role of augmented RA contraction. Augmented RA booster pump transport is an important compensatory mechanism that optimizes RV performance and thereby improves cardiac output (9,43–45). Under conditions of RVI attributable to occlusions compromising RV but sparing RA branches, RV diastolic dysfunction imposes increased preload and afterload on the right atrium, resulting in enhanced RA contractility reflected in the RA waveform as a "W" pattern characterized by a rapid upstroke and increased peak A-wave amplitude, sharp X descent
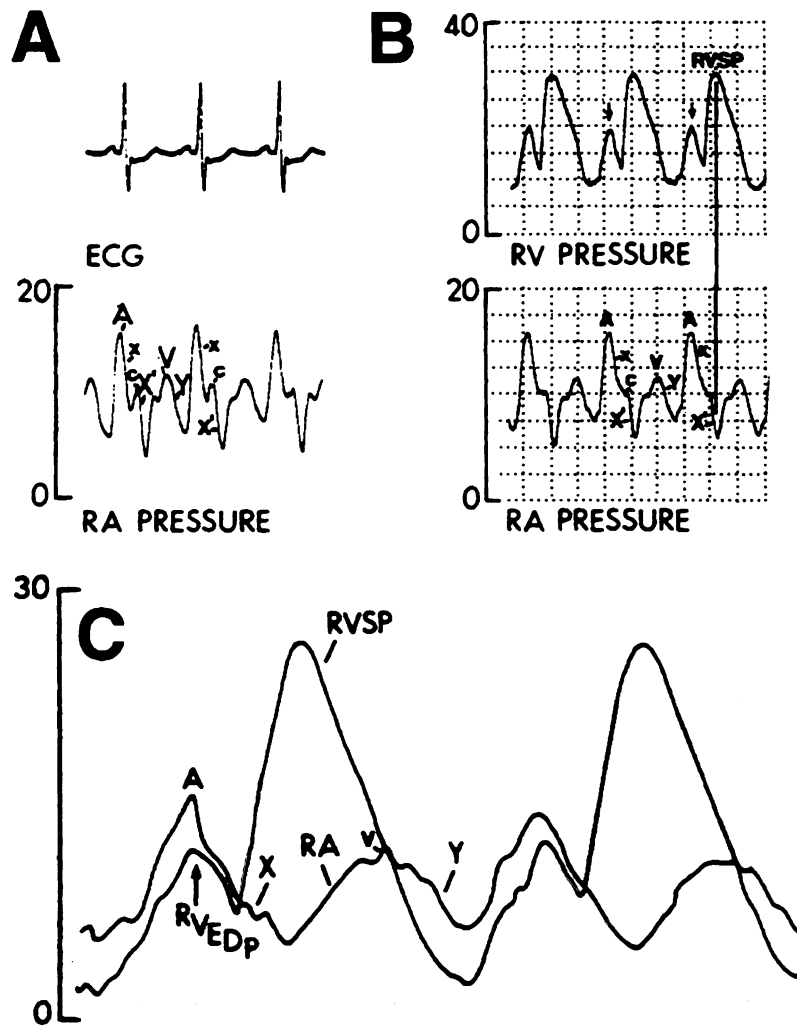
Figure 3. Hemodynamic recordings from a patient with a W pattern. Peaks of W are formed by prominent A-waves, and most prominent right atrial (RA) descent occurs just before T-wave of electrocardiogram (ECG) **(A)**. Simultaneous RA and right ventricular (RV) pressures **(B)** demonstrate that this prominent descent coincides with peak right ventricular systolic pressure (RVSP) and is therefore an "X" systolic descent, followed by a comparatively blunted Y descent. Peak RVSP is depressed, RV relaxation is prolonged, and there is a dip and rapid rise in RV diastolic pressure. Prominent RA A-waves are reflected in the right ventricle as an augmented end-diastolic pressure (EDP) rise **(arrows)**. These waveform relations are confirmed by simultaneous superimposed RA/RV pressure recordings **(C)**. Reprinted with permission from reference 9.

reflecting enhanced atrial relaxation, and blunted Y descent owing to pandiastolic RV dysfunction (Fig. 3) (9,43–45). Conversely, more proximal RCA occlusions compromising the atrial as well as the RV branches result in ischemic depression of atrial function (9,43–45), manifesting as more severely elevated mean RA pressure and inscribing an "M" pattern in the RA waveform characterized by depressed A-wave and X descent, as well as blunted Y descent (Fig. 4). Under conditions of acute RV dysfunction, loss of augmented RA transport because of ischemic depression of atrial contractility or AV dyssynchrony precipitates more severe hemodynamic compromise (9,43,49). Right atrial dysfunction decreases RV filling, which impairs global RV systolic performance, thereby resulting in further decrements in LV preload and cardiac output. Interventions that augment ventricular filling reduce the extent of systolic lengthening in the dyskinetic zone and the magnitude of isovolumetric shortening in the nonischemic zone, reducing regional dyssynergy and thereby improving ventricular performance (34,35,44,45,47,48). Because the end-diastolic length-tension relationship is steeper in ischemic segments, such zones are especially sensitive to changes in filling in general and more dependent on atrial transport in particular (50,51). Thus, depression of RA contractility further impairs RV performance not only because of the absolute reduction in RV preload resulting from diminished atrial transport, but also because of the increased mechanical disadvantage imposed on the septum by the dyskinetic right ventricle (34,35,44,45). Venous return is inversely proportional to the instantaneous RA pressure, which is itself dependent on atrial compliance and relaxation (52,53). Augmented RA contractility, by enhancing atrial relaxation, facilitates atrial inflow (9,44,45,52,53). Conversely, depressed atrial performance impairs relaxation, an effect
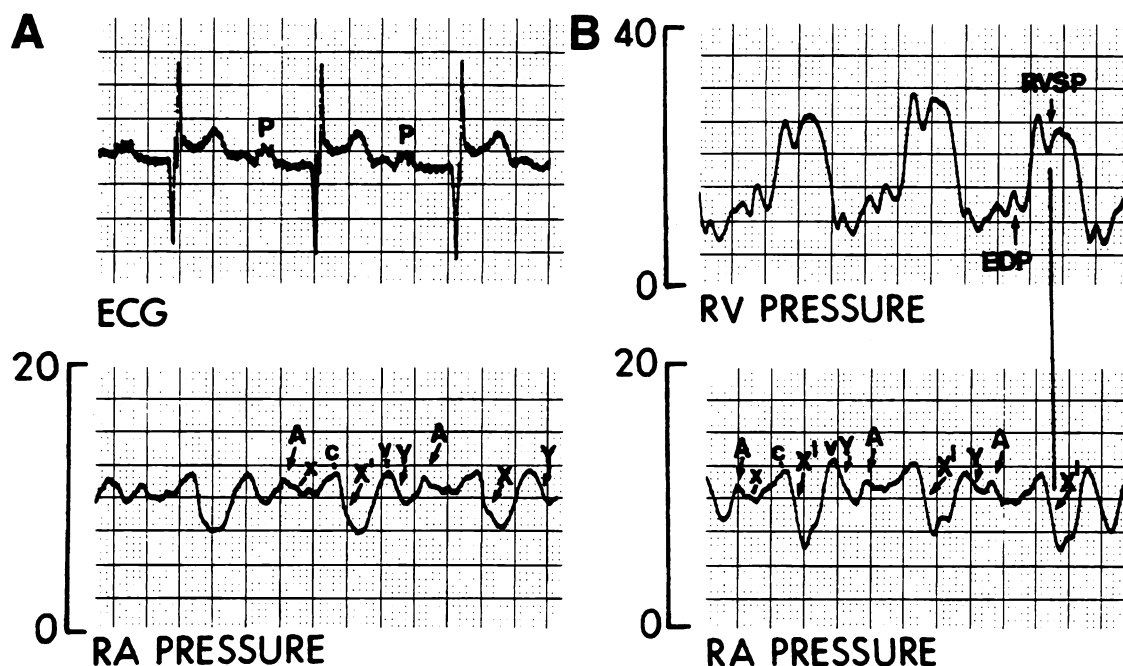
Figure 4. Tracings of M pattern of right atrial (RA) pressure. When timed by electrocardiogram **(A)**, most prominent negative deflection in right atrium is coincident with T-wave, suggesting a diastolic Y descent. In contrast, its relation to right ventricular (RV) pressure **(B)** demonstrates that this prominent descent coincides with peak RV systolic pressure (RVSP), indicating a systolic X descent, whereas diastolic Y descent is blunted. M pattern comprises a depressed A-wave, D descent before a small C-wave, a prominent X descent, a small V-wave, and a blunted Y descent. Peak RVSP is depressed and bifid (arrow) with delayed relaxation and an elevated end-diastolic pressure. (All pressures are measured in mm Hg). Reprinted with permission from reference 9.

evident by a diminished X descent (9,44,45). These effects, together with abnormalities induced by ischemia on RA compliance directly, impede venous return to the preload-dependent right heart. Furthermore, the increased loading conditions imposed on the right atrium by the stiff dilated right ventricle increase atrial oxygen demand at a time when the compressive effects of increased intracavitary filling pressure tend to diminish transmural perfusion (9,44,45), thereby increasing the ischemic burden on the thin-walled atrium. Not surprisingly, ischemic atrial involvement is not rare, with autopsy studies documenting atrial infarction in up to 20% of cases of ventricular infarction, with RA involvement five times commoner than left (9,54,55).

Rhythm disorders and reflexes associated with RVI.
High-grade atrioventricular (AV) block and bradycardia-hypotension without AV block commonly complicate infe-rior myocardial infarction (56–58) and have been attributed predominantly to the effects of AV nodal ischemia and cardioinhibitory (Bezold-Jarisch) reflexes arising from stim-ulation of vagal afferents in the ischemic LV inferoposterior wall (59–61). We and others have documented that in patients with acute RVI there is an increased incidence of high-grade AV block compared to those without right heart involvement (12,15,62–64). Recent observations from our laboratory now also document that bradycardia-hypotension without AV block is also more common in patients with RVI (65,66). Given that the AV nodal artery and branches to the inferoposterior LV wall typically arise distally from

the dominant RCA, if reflexes arising from the ischemic LV alone or together with AV nodal ischemia were responsible for bradycardia-hypotension and high-grade AV block, then occlusions just proximal to the origin of the AV nodal and LV branches should result in an incidence of these phenomena no different from more proximal RCA occlu-sions resulting in RV and LV ischemia. Recent findings from our laboratory document that both bradycardia-hypotension and AV block are far more common in patients with proximal RCA occlusion inducing right heart and LV inferior-posterior ischemia, compared to more distal occlu-sions compromising LV perfusion but sparing the RV branches (65,66). These findings suggest that the ischemic right heart may also be a trigger for cardioinhibitory-vasodilator reflexes. Receptors and reflexes arising from the RV have received little attention. Although fewer in num-ber, there are both myelinated and nonmyelinated nerves that terminate in the right ventricle, and some experimental studies suggest that RV afferents stimulated by RV disten-tion can result in bradycardia-hypotension (67–69).

It is important to consider separately bradycardia-hypotension induced by RCA reperfusion. Following suc-cessful thrombolysis or primary angioplasty of the acutely occluded RCA, transient but profound bradycardia-hypotension may paradoxically develop in a patient whose rhythm and blood pressure were stable during occlusion (66,70,71). Based on its abrupt and transient nature, reper-fusion induced bradycardia-hypotension appears to be reflex

mediated and, based on recent findings, also appears to be more common with proximal versus distal RCA occlusions (65,66), suggesting a right heart mechanism.

Patients with RVI are prone to ventricular tachyarrhythmias (12,14–17,72). In-hospital ventricular tachycardia should not be unexpected, given that the ischemic RV is often massively dilated. Autonomic denervation in the peri-infarct area may also play a role (72). However, RVI is unlikely to portend late ventricular arrhythmias, as RV function tends to recover completely. Supraventricular tachycardias including atrial fibrillation may develop, attributable to atrial ischemia/infarction, distension, and elevated atrial pressures (73).

Natural history of RV ischemic dysfunction. Although RVI may result in profound acute hemodynamic effects, arrhythmias, and higher in-hospital mortality, many patients manifest spontaneous clinical improvement within 3 to 10 days regardless of the patency status of the infarct-related artery (7,19). Furthermore, global RV performance typically recovers over several weeks, with subsequent return of RV ejection fraction to near-normal levels within 3 to 12 months (18–20). Moreover, chronic unilateral right heart failure secondary to RVI is rare. This favorable natural history of RV performance is in marked contrast to the effects of coronary occlusion on segmental and global LV function (20–25). Observations from experimental animal studies document that the spontaneous recovery of RV function despite chronic RCA occlusion is attributable to the more favorable oxygen supply-demand characteristics of the RV in general and the beneficial effects of collaterals in particular (34,35). In a canine model of persistent RCA occlusion (34), we demonstrated that despite persistent RCA occlusion, collateral restoration of RCA perfusion facilitates complete recovery of RVFW function and global RV performance, with minimal infarction by gross and histologic analysis. Although most previous clinical studies of chronic RCA occlusion demonstrate that resting RV performance is preserved (18–20), other studies suggest that a significant subset of patients exhibit RV contraction abnormalities during stress (74,75). Until recently, no study of chronic RCA occlusion has analyzed the site of RCA occlusion relative to the nutritive RV branches or the presence of collaterals, nor documented and correlated with detailed angiographic data the response of the RV to stress. We have recently shown that in patients with chronic proximal RCA occlusion, RV function is typically maintained at rest and augments appropriately during stress (21). This dramatic spontaneous recovery of RV function and trivial infarction contrast sharply with the response of the left ventricle to equivalent ischemic insults (76–78). The relative resistance of the RVFW to infarction is undoubtedly attributable to more favorable oxygen supply-demand characteristics. In fact, in patients with acute inferior MI, preinfarction angina is an independent risk factor that predicts the absence of RVI (79), an effect likely mediated by the development of protective collaterals.

Effects of reperfusion on ischemic RV dysfunction. It thus appears that acute ischemic RV dysfunction is largely reversible. Nevertheless, acute RV ischemia contributes to early morbidity and mortality (9,14–16). Furthermore, spontaneous recovery of RV contractile function and hemodynamics may be slow. The salutary effects of timely reperfusion on myocardial function and infarct size in the ischemic left ventricle are well documented in both experimental models (76–78) and in patients (22–25,80–83). Given the more favorable oxygen supply-demand characteristics of the right ventricle and the strength of observations supporting the notion that the preponderance of acutely dysfunctional RV myocardium is viable, it would be expected that reperfusion (even late) could have salutary effects on recovery of RV function and clinical outcome. Observations from our laboratory in experimental animals (35) and in humans (12) now demonstrate the beneficial effects of reperfusion on recovery of RV performance. In experimental models, RCA occlusion results in depressed RVFW function and global RV performance (35). Reperfusion after 1 h of occlusion reperfusion leads to immediate improvement in RVFW function and consequently global RV performance, with prompt resolution of the pattern of equalized diastolic filling pressures and lesser reversed septal curvature, indicating diminished effects of hemodynamically adverse diastolic ventricular interactions. These effects contribute to enhanced LV filling and performance. Reperfusion after 4 to 8 h of ischemia also results in acute improvement in global RV performance, but to a lesser extent. However, even after prolonged ischemia, reperfusion results in striking, albeit slower, improvement in function over time with minimal RV infarction (35).

Until recently, there were scant clinical data regarding the effects on ischemic RV myocardium of interventions designed to achieve reperfusion. In recent studies of patients with RVI undergoing primary angioplasty (12), we have now documented that successful complete reperfusion of the main RCA and the major RV branches leads to immediate improvement in and later complete recovery of RVFW function and consequently global RV performance (Figs. 1 and 2). Most importantly, reperfusion-mediated recovery of RV performance is associated with excellent clinical outcome. In contrast, failure to restore flow to the major RV branches was associated with lack of recovery of RV performance and refractory hemodynamic compromise leading to high in-hospital mortality, even if flow was restored in the main RCA (Fig. 1). These findings emphasize not only the crucial relationship between reperfusion-mediated recovery of RV performance and clinical outcome, but documents for the first time the importance of RV branch reperfusion. Previous definitions have largely ignored the reperfusion status of the RV branches (24,25,81,82). The dramatic recovery of RVFW function and global RV performance contrasts sharply with the response of the left ventricle. Despite comparable degrees of initial regional dysfunction in the ischemic RVFW and

inferior LV wall, in patients undergoing successful reperfusion the pace and extent of recovery of contraction in the left ventricle lags behind the right ventricle (12), undoubtedly related to oxygen supply-demand differences between the ventricles that influence resistance to ischemic damage (12,29–36).

Although evidence suggests that patients with inferior myocardial infarction benefit from timely thrombolytic reperfusion, the specific short- and long-term responses of the right ventricle have not been adequately evaluated. Some thrombolytic studies suggested that RV function improves only in patients in whom RCA patency is achieved (84–87), whereas others report little benefit (88,89). More recent prospective reports of patients with inferior MI undergoing thrombolytic therapy demonstrate that successful thrombolysis imparts survival benefit in those with RV involvement (90) and that failure to restore infarct related artery patency is associated with persistent RV dysfunction and increased mortality (90,91). Although successful thrombolysis appears to exert beneficial effects on RV function and mortality in patients with RVI, it is precisely such patients who may be resistant to fibrinolytic recanalization (89–92), due to proximal RCA occlusion with extensive clot burden which, together with impaired coronary delivery of fibrinolytic agents attributable to hypotension, leads to a higher incidence of primary thrombolytic failure in such patients. There also appears to be a higher incidence of reocclusion following thrombolysis of the RCA (89). In contrast, primary angioplasty is more likely to result in successful recanalization of the acutely occluded RCA (12,82,91) and has established salutary effects on RV performance and clinical outcome (12). Future controlled trials are needed to better define the role of thrombolysis in patients with RV infarction.

In aggregate, these results support the concept that, under conditions of ischemia and reperfusion, the right ventricle is more resilient than the left ventricle, consistent with the notion that RV "infarction" is to a great extent a misnomer, for the acutely ischemic dysfunctional right ventricle appears to represent predominantly viable myocardium which responds favorably to successful reperfusion, even late after the onset of occlusion (35).

Mechanical complications associated with RVI. Patients with acute RVI may suffer additional mechanical complications of acute infarction that may compound hemodynamic compromise and confound the clinical-hemodynamic picture. Ventricular septal rupture is a particularly disastrous complication, adding substantial overload stress to the ischemically dysfunctional right ventricle (93,94). As in other postinfarction myonecrotic septal ruptures, acute left-to-right shunting reduces effective forward LV output, precipitates pulmonary edema, and elevates pulmonary pressures and resistance. In aggregate, these effects exacerbate the RV dysfunction and low output associated with RVI. Surgical repair is imperative, but may be technically difficult. Furthermore, timing of repair, typically a challenging decision in the peri-infarction period, is further complicated in patients with RVI owing to RV dysfunction, which substantially increases the risks of any cardiac procedure and for which most surgeons prefer to wait to allow for recovery of RV performance, a luxury that may not be possible with acute septal rupture. Severe right heart dilation and diastolic pressure elevation associated with right heart ischemia may stretch open a patent foramen ovale, precipitating acute right-to-left shunting manifest as systemic hypoxemia or paradoxic emboli (95,96), which may resolve as right heart pressures diminish with recovery of RV performance, although some may require closure (97). Severe tricuspid regurgitation may also complicate RVI (98,99), developing as a result of primary papillary muscle ischemic dysfunction or rupture as well as secondary functional regurgitation attributable to severe RV and tricuspid valve annular dilation. Severe tricuspid regurgitation further impairs forward RV output and exaggerates right heart volume overload, thereby exacerbating low output, worsening systemic venous congestion and, owing to gross right heart dilation, impeding recovery of right heart performance. Although in most cases functional tricuspid regurgitation will improve as RV function recovers, some patients with severe papillary muscle dysfunction and dilated annulus require surgical repair, as do most with frank papillary muscle rupture.

Clinical presentations and evaluation. Although nearly 50% of patients with acute transmural inferior-posterior MI have ischemic RV involvement by echocardiography, RVI is often silent, as only 25% of patients overall develop clinically evident hemodynamic manifestations (6–8). Patients with inferior MI may initially present without evidence of hemodynamic compromise characteristic of RVI, but subsequently develop hypotension precipitated by preload reduction attributable to nitroglycerine (100) or associated with bradyarrhythmias (9,49,63,64). The physical exam provides important insights regarding the hemodynamic effects of RVI (101). Significant RV ischemic dysfunction results in increased mean RA pressure (>10 mm Hg), reflected as elevated jugular venous pressure (JVP). Pulsus paradoxus and Kussmaul sign have been reported in patients with RVI (101). Although the mechanisms underlying these phenomena in patients with RVI have not been delineated, they are likely related to the pericardial crowding and marked diastolic ventricular interactions evident in such patients. Under these conditions, it would not be unexpected that inspiratory augmentation of filling of the already distended right ventricle would intensify the adverse right-to-left septal mediated diastolic interactions, thereby resulting in respiratory oscillations of LV filling and output, resulting in pulsus paradoxus. In other cases, the stiff dilated right heart chambers, together with the effects of elevated intrapericardial pressure, may act to constrain the right heart such that inspiratory augmentation of right heart filling is blunted while venous return to the extrapericardial great veins is enhanced which, analogous to constrictive pericarditis, results in Kussmaul's sign (102).

Patients with severe RVI but preserved global LV function may be hemodynamically compensated, manifest by elevated JVP but clear lungs, normal systemic arterial pressure, and intact perfusion. When RVI leads to more severe hemodynamic compromise, systemic hypotension and hypoperfusion result. However, because LV preload is reduced, the lungs typically remain clear, even though LV filling pressure may be moderately elevated owing to adverse diastolic interactions. In patients with RVI and intact LV function, the carotid upstroke is intact but its volume is diminished. The precordial exam reveals an unimpressive LV impulse. Surprisingly, despite RV dilation, a RV heave is often not appreciated, likely owing to the constraining effects of the acutely noncompliant pericardium. Auscultation may reveal an RV S_3 or S_4 reflecting diastolic dysfunction. The presence of a holosystolic murmur suggests the development of ventricular septal rupture or tricuspid regurgitation. It is important to note that RVI may occur in the setting of global LV dysfunction, especially in patients with prior anterior myocardial infarction. In such cases, RVI may be masked by a presentation dominated by ischemic LV dysfunction characterized by low output and pulmonary congestion, with right heart failure ascribed to biventricular failure typical of ischemic cardiomyopathy.

Noninvasive and hemodynamic evaluation. The chest X-ray is not particularly helpful in detecting RVI. Although ST-segment elevation and loss of R-wave in the right-sided electrocardiographic leads (V_{3R} and V_{4R}) are sensitive indicators of the presence of RVI (15,90,103–105), they are not predictive of the magnitude of RV dysfunction or its hemodynamic impact. Two-dimensional echocardiography is the most effective tool for delineation of the presence and severity of RVI, demonstrating RVFW dysfunction and depression of global RV performance, the extent of RV dilation, and reversed septal curvature, which confirms the presence of significant adverse diastolic interactions, the degree of paradoxical septal motion indicative of compensatory systolic interactions, and the presence of severe RA enlargement that may indicate concomitant ischemic RA dysfunction and/or tricuspid regurgitation. Invasive hemodynamic assessment of the extent and severity of right heart ischemic involvement (Figs. 3 and 4) has been extensively discussed.

Therapy. Therapeutic options for management of right heart ischemia follow directly from the pathophysiology discussed. Treatment modalities include: 1) restoration of physiologic rhythm; 2) optimization of ventricular preload; 3) optimization of oxygen supply and demand; 4) parenteral inotropic support for persistent hemodynamic compromise; 5) reperfusion; and 6) mechanical support with intra-aortic balloon counterpulsation and RV assist devices.

Optimization of rhythm. Patients with RVI are particularly prone to the adverse effects of bradyarrhythmias. The depressed ischemic right ventricle has a relatively fixed stroke volume, as does the preload-deprived left ventricle (9,34,35,44,45). Therefore, biventricular output is exquis-

itely heart-rate dependent, and bradycardia even in the absence of AV dyssynchrony may be deleterious to patients with RVI. Severe RV systolic and diastolic dysfunction limit RV stroke volume and render RV output rate-dependent; the left ventricle is also stiff and has limited stroke volume reserve attributable to reduced preload. Therefore, chronotropic competence is critical in patients with acute inferior MI and ischemic RV dysfunction. However, not only are such patients notoriously prone to reflex-mediated frank bradycardia, they often manifest a relative inability to increase sinus rate in response to low output, owing to excess vagal tone, ischemia, or pharmacologic agents. Given that the ischemic right ventricle is dependent on atrial transport, the loss of RA contraction due to AV dyssynchrony further exacerbates difficulties with RV filling and contributes to hemodynamic compromise (9,43,49). In addition, AV dyssynchrony may precipitate tricuspid regurgitation, a mechanical defect likely to be devastating to performance of the ischemic right ventricle. Although atropine may restore physiologic rhythm in some patients, temporary pacing is often required. Ventricular pacing alone may suffice in some, especially if the bradyarrhythmias are intermittent. However, some patients require AV sequential pacing (9,49). Unfortunately, transvenous pacing can be difficult in patients with right heart ischemia because of problems in ventricular sensing, presumably related to diminished generation of endomyocardial potentials in the ischemic right ventricle, as well as difficulties in lead positioning and capture in the atrium, which may be ischemic and dilated. Reports suggest that rapid administration of intravenous aminophylline may restore sinus rhythm in some patients with acute AV block unresponsive to atropine (106,107), a response likely reflecting reversal of the adverse bradycardic effects of ischemia-induced adenosine elaboration. This pharmacologic maneuver may restore AV synchrony and thereby obviate the technical challenges of temporary AV sequential pacing.

Optimization of ventricular preload. In patients with RVI, the dilated noncompliant right ventricle is exquisitely preload dependent, as is the left ventricle, which is stiff but preload deprived. Therefore, any factor that reduces ventricular preload will tend to be detrimental, whereas measures that optimize cardiac filling tend to be beneficial. Accordingly, vasodilators and diuretics are contraindicated. Although experimental animal studies of RVI demonstrate hemodynamic benefit from volume loading (40), clinical studies have reported variable responses to volume challenge (2,6,7,9,108–110). These conflicting results may reflect a spectrum of initial volume status in patients with acute RVI, with those patients who are relatively volume depleted benefiting, and those who are more replete manifesting a flat response to fluid resuscitation. Nevertheless, an initial volume challenge is appropriate for patients manifesting low output without pulmonary congestion, particularly if the estimated central venous pressure is <15 mm Hg. For those unresponsive to an initial trail of fluids, determination of

filling pressures and subsequent hemodynamically monitored volume challenge may be appropriate. Caution should be exercised to avoid excessive volume administration above and beyond that documented to augment output, as the right heart chambers may operate on a "descending limb" of the Starling curve, resulting in further depression of RV pump performance as well as inducing severe systemic venous congestion. Abnormalities of volume retention and impaired diuresis may be related in part to impaired responses of atrial natriuretic factor (111,112).

Anti-ischemic therapy. Although hemodynamic compromise often dramatically dominates the clinical picture in severe RVI, it is important to keep in perspective the underlying ischemic pathophysiology that ultimately dictates recovery of both LV and RV function. Therefore, treatment of RVI should focus on optimizing oxygen supply and demand. However, given that virtually all anti-ischemic agents exert hemodynamic effects, caution must be exercised in administering these drugs to patients with RVI. Specially, beta-blockers and some calcium channel blockers may reduce heart rate and depress conduction, thereby increasing the risk of bradyarrhythmias and heart block in these chronotropically dependent patients. The vasodilator properties of nitrates and calcium-channel blockers may be deleterious to the stiff volume-dependent ventricles (100). Because in such patients RV performance is dependent on LV-septal systolic contraction, the potentially negative inotropic effects of beta-blockers and some calcium channel blockers can also be deleterious. Accordingly, these drugs should be avoided in patients with RVI resulting in manifest hemodynamic compromise, and in stable patients used only when clearly indicated and with careful monitoring to detect adverse hemodynamic effects.

Reperfusion therapy. The beneficial effects of successful reperfusion on RV function and clinical outcome, as well as the demonstrated efficacy and advantages of primary angioplasty versus thrombolysis in patients with acute right heart ischemic dysfunction, have been discussed.

Inotropic stimulation. Parenteral inotropic support is usually effective in stabilizing hemodynamically compromised patients not fully responsive to volume resuscitation and restoration of physiologic rhythm (9,108). The mechanisms by which inotropic stimulation improves low output and hypotension in patients with acute RVI have not been well studied. However, experimental animal investigations from our laboratory suggest that inotropic stimulation enhances RV performance by increasing LV-septal contraction, which thereby augments septal-mediated systolic ventricular interactions (43,45). Whether this mechanism is responsible for the improvement in patients treated with inotropic stimulation has not been delineated. Although an inotropic agent such as dobutamine that has the least deleterious effects on afterload, oxygen consumption, and arrhythmias is the preferred initial drug of choice, patients with severe hypotension may require agents with pressor effects (such as dopamine) for prompt restoration of adequate coronary perfusion pressure. The "inodilator" agents such as milrinone have not been studied in patients with RVI, but on the basis of their vasodilator properties, could exacerbate hypotension.

Mechanical assist devices. Intraaortic balloon pumping may be beneficial in patients with RVI and refractory low output and hypotension. Although balloon assist does not directly improve RV performance, it will improve coronary perfusion pressure in severely hypotensive patients. Because RV myocardial blood flow is dependent on perfusion pressure, balloon pumping may therefore also improve RV perfusion and thereby benefit RV function, particularly if the RCA has been recanalized or if there is collateral supply to an occluded vessel. Intra-aortic balloon pumping may also improve LV performance in those patients with hypotension and depressed LV function. As performance of the dysfunctional RV is largely dependent on LV septal contraction, RV performance may also benefit. Right ventricular assist devices have not been well studied in patients with RV infarction, but may improve hemodynamics and, in patients with life-threatening low output refractory to all other measures, such assist devices may be life-saving and serve as a bridge to transplant. Successful treatment of RV failure by atrial septostomy to augment left heart filling (113,114) should be considered only as a desperation intervention when all other measures have failed.

Summary. Acute RCA occlusion proximal to the RV branches results in RVFW dysfunction. The ischemic, dyskinetic RVFW exerts mechanically disadvantageous effects on biventricular performance. Depressed RV systolic function leads to a decrease in transpulmonary delivery of LV preload, resulting in diminished cardiac output. The ischemic right ventricle is stiff, dilated, and volume dependent, resulting in pandiastolic RV dysfunction and septally mediated alterations in LV compliance, which are exacerbated by elevated intrapericardial pressure. Under these conditions, RV pressure generation and output are dependent on LV-septal contractile contributions, governed by both primary septal contraction and paradoxical septal motion. When the culprit coronary lesion is distal to the RA branches, augmented RA contractility enhances RV performance and optimizes cardiac output. Conversely, more proximal occlusions result in ischemic depression of RA contractility, which impairs RV filling, thereby resulting in further depression of RV performance and more severe hemodynamic compromise. Bradyarrhythmias limit the output generated by the rate-dependent noncompliant ventricles. Patients with RVI and hemodynamic compromise often respond to volume resuscitation and restoration of a physiologic rhythm. Vasodilators and diuretics should generally be avoided. In some patients, parenteral inotropic stimulation may be required. The right ventricle appears to be relatively resistant to infarction and has a remarkable ability to recover even after prolonged occlusion. Therefore, the term RV "infarction" appears to be somewhat of a misnomer, for in most patients a substantial proportion of

acute RV dysfunction represents ischemic but viable myocardium. Although RV performance improves spontaneously even in the absence of reperfusion, recovery of function may be slow and associated with high in-hospital mortality. Reperfusion enhances the recovery of RV performance and improves the clinical course and survival of patients with ischemic RV dysfunction.

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