Effects of Reperfusion on Ischemic Right Ventricular Dysfunction
Disparate Mechanisms of Benefit Related to Duration of Ischemia

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**Background** Right ventricular free wall (RVFW) ischemia impairs global RV performance and may result in acute hemodynamic compromise. However, RV function and hemodynamic performance typically improve spontaneously over time. This study was designed to determine whether reperfusion facilitates recovery of function in the ischemic right ventricle.

**Methods and Results** Closed chest dogs underwent right coronary balloon occlusion for 1 hour (n=9), 4 hours (n=6), or 8 hours (n=7). In all animals, occlusion depressed RVFW function and global RV performance. After 1 hour of ischemia, reperfusion led to immediate improvement in RVFW function and consequently global RV performance, with complete recovery in part in 4 weeks and scar in <1% of total RVFW area. Reperfusion after 4- and 8-hour occlusions resulted in acute improvement in global RV performance but to a lesser extent and by different mechanisms, since RVFW contraction remained severely impaired. This disproportionate recovery of global RV function was attributable to diminished RVFW dyskinesis associated with reperfusion-induced increments in RVFW diastolic thickness (characterized histopathologically in 6 additional animals subjected to 4-hour occlusions but killed 1 hour after reperfusion by interstitial edema, contraction band necrosis, and hemorrhage). Although later reperfusion was associated with a slower pace and lesser extent of recovery, RVFW contraction improved markedly over time. At 4 weeks, there was trivial RVFW scar in 4-hour animals (2% of total RVFW area), and, although fibrosis was significantly greater in 8-hour animals (7% of RVFW area), infarction was minimal relative to the extent of jeopardized myocardium.

**Conclusions** The responses of ischemic RV myocardium to reperfusion are complex, with disparate effects according to the duration of preceding ischemia. Early reperfusion results in prompt improvement in and subsequent complete recovery of RVFW contraction and global RV performance, with trivial or no RVFW scar. Late reperfusion leads to little acute recovery of RVFW function, but global performance improves owing to diminished RVFW dyskinesis associated with reperfusion-induced increments in RVFW diastolic thickness. Nevertheless, RVFW function improves over time, with minimal evidence of infarction. Therefore, reperfusion facilitates recovery of RV function and minimizes the extent of infarction even after prolonged ischemia. *(Circulation. 1994;90:1398-1409.)*

**Key Words** reperfusion • ventricles • ischemia

Right ventricular free wall (RVFW) ischemia impairs global RV performance and may lead to hemodynamic compromise despite preserved global left ventricular (LV) function. However, despite potentially life-threatening acute hemodynamic effects, patients with ischemic RV dysfunction typically manifest spontaneous early clinical hemodynamic improvement and later recovery of global RV performance regardless of the patency status of the infarct-related artery. In fact, isolated chronic right heart failure related to RV infarction is exceedingly rare. This resilience of the right ventricle is in marked contrast to the effects of coronary occlusion on regional and global LV function. The concept that the right ventricle is relatively resistant to infarction is supported by recent observations from experimental studies on the effects of chronic right coronary artery (RCA) occlusion from our laboratory demonstrating that acute ischemic depression of RV function, global RV performance improves spontaneously over 1 week despite persistent severe RVFW dysfunction. This disproportionate recovery in global performance is attributable to reduction in the extent of RVFW dyskinesis associated with increased RVFW diastolic thickness, thought to be mediated in part by the effects of slow collateral reperfusion. However, restoration of perfusion by collaterals facilitates recovery of RVFW function over time and minimizes the extent of RVFW infarction.

It thus appears that acute ischemic RV dysfunction is largely reversible. Nevertheless, acute RV ischemia contributes to early morbidity and mortality in patients. Furthermore, in both experimental animals and in humans, recovery of RV contractile function and hemodynamics may be slow and incomplete. Therefore, interventions designed to hasten the pace and extent of recovery of RV function could be beneficial. The salutary effects of timely reperfusion on myocardial function and infarct size in the ischemic left ventricle are well documented in both experimental models and in patients. The potentially deleterious impact of reperfusion injury also has been emphasized. However, there are no experimental data on the short-
and long-term effects of reperfusion on ischemic RV dysfunction, and clinical studies have yielded conflicting results. 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 might be expected that reperfusion (even late) could have salutary effects on recovery of RV function. Accordingly, the present study was designed to evaluate the acute and chronic effects on RV performance of reperfusion induced after varying durations of RCA occlusion.

Methods

Experimental Preparation

Chronic closed chest studies were performed in 26 conditioned dogs (weight, 25 to 35 kg) subjected to proximal RCA balloon occlusions of 1 (n=9), 4 (n=6), or 8 (n=7) hours' duration, reperfused by balloon deflation and followed for 4 weeks. To delineate the acute effects on histological structure of reperfusion induced after prolonged ischemia, open chest studies were performed in 9 additional animals subjected to 4 hours of occlusion but killed 1 hour after reperfusion. All animals were anesthetized (thiopental, 12.5 mg/kg IV) and mechanically ventilated with a mixture of nitrous oxide and oxygen. Morphine sulfate (1 mg/kg subcutaneously every hour) was administered for analgesia. Both femoral arteries and veins, a carotid artery, and a jugular vein were surgically isolated and cannulated with vascular sheaths (Cordis Corp). A flotation right-heart thermodilution catheter (American Edwards Instruments) was positioned in the pulmonary artery. Dual-pressure, sensor micromanometer–tipped catheters (Millar Instruments) were inserted for measurement of cardiac pressures. A left atrial (LA) catheter (Cordis) was placed retrograde for pressure measurement and injection of radiolabeled microspheres. Ventilation was adjusted to maintain arterial blood gases within the physiological range. Core body temperature was maintained as close as possible to baseline temperature with the aid of a heating blanket.

Data Acquisition

In animals undergoing chronic studies, closed chest transthoracic two-dimensional echocardiograms were obtained in the short-axis view using techniques previously described. In animals subjected to acute studies only, an open chest preparation utilizing a left lateral thoracotomy incision was used to allow performance of transapical ultrasound, which not only provides high-quality two-dimensional resolution but also facilitates acquisition of M-mode measurements, which provide useful corroborative data regarding regional wall thickness and motion. All studies were recorded on videotape and analyzed off-line with a calibrated microcomputer system (Hewlett-Packard Instruments). Atrial and ventricular pressures and the ECG were recorded on a strip-chart recorder (Gould Medical Instruments) and photographed (Hewlett Visicorder) recorders and digitized on-line at 500 samples per second with a calibrated computer acquisition program (Gould Instruments). Coronary angiograms were recorded on cineangiographic film at 30 frames per second.

Experimental Protocols

Baseline Evaluation

After completion of instrumentation, intravenous lidocaine (50-mg bolus, followed by a 1 mg/min infusion) and heparin (5000-U bolus, followed by a 1000-U/h infusion) were administered. Baseline hemodynamic and echocardiographic measurements were recorded and microspheres injected. The RCA was engaged with an 8F JR4 guiding catheter (Advanced Cardiovascular Systems), and coronary angiography was performed with nonionic contrast. Acute RCA occlusion was induced using coronary angioplasty techniques. A 0.014-in, high-torque floppy guide wire (Advanced Cardiovascular Systems) was positioned in the distal RCA, and an appropriate-size angioplasty balloon catheter (2.0 to 2.5 mm, ACX balloon, Advanced Cardiovascular Systems) was advanced over the wire, positioned in the proximal RCA just beyond the ostium, and inflated to 6 to 8 atm pressure. Repeat angiography was performed to ensure optimal balloon positioning and confirm lack of antegrade flow. After occlusion, hemodynamic and echocardiographic parameters were recorded immediately and every 30 minutes for the duration of the occlusion interval. Microspheres were injected at the completion of the occlusion interval. Acute reperfusion was induced by balloon deflation; the balloon catheter and guide wire were removed and repeat angiography performed. Hemodynamic and echocardiographic measurements were recorded immediately, at 30 minutes, and 1 hour after reperfusion. In the chronic closed chest animals, microspheres were injected 1 hour after reperfusion. Open chest animals subjected to 4-hour balloon occlusions underwent echocardiographic study at 5, 30, and 60 minutes after reperfusion and were then killed and the hearts prepared for postmortem analysis. Radiolabeled microsphere injections were not performed in this acute group of animals. Animals undergoing 4-week follow-up were prepared for chronic survival as previously described. Serial transthoracic ultrasound was performed at 4 days and weekly thereafter over 4 weeks with animals conscious but sedated with morphine sulfate (0.5 mg/kg subcutaneously). Repeat invasive evaluation was performed at 4 weeks using the same preparation as described in the baseline studies. After completion of hemodynamic recordings, coronary angiography, and microsphere injections, animals were killed and the hearts excised for postmortem analysis. All experiments conformed to the position of the American Heart Association on research animal use and were conducted with the approval of the Washington University Committee on Humane Care of Laboratory Animals.

Analysis of Data

Echocardiographic and hemodynamic analyses were performed according to methods previously described. In animals subjected to chronic study, hearts fixed in formalin were sectioned into four transverse slices and prepared for radiolabeled microsphere determinations of myocardial blood flow as well as the pattern and extent of infarction. In brief, total RVFW infarct size was quantitated by gross planimetry of myocardial slices using a digitizing tablet (Jandel Scientific Corp). The RVFW slice at the midpapillary muscle level was cut into two transverse apical-basal layers, which were divided into anterior, middle, and posterior segments; segmental infarct size was then determined by gross planimetry. To perform correlative echocardiographic, blood flow, and histopathological analyses, the segments were subdivided into three equal sections, which were halved into epicardial and endocardial specimens. Individual specimens were processed for blood flow analysis measured from radiolabeled microspheres. To characterize the histopathological pattern of RVFW fibrosis, samples from each specimen were stained with hematoxylin and eosin as well as Mallory's trichrome and examined by light microscopy at a magnification of x100. Infarction was defined as scar seen on hematoxylin and eosin that stained positively with Mallory's trichrome; the pattern of fibrosis was analyzed with respect to transmural heterogeneity (patchiness) of scarring.

Hearts from animals subjected to 4-hour occlusions and killed after 1 hour of reperfusion were fixed in formalin and similarly sliced. Specimens from the middle segment of the RVFW slice at the midpapillary muscle level were stained with hematoxylin and eosin and examined by light microscopy to assess the extent of interstitial edema, contraction band necrosis, hemorrhage, and polymorphonuclear cell infiltration. Because the spatial distribution and regional severity of such
histological changes are often heterogenous, precise quantitative histomorphometry may be difficult. Traditional point counting methods using microscopic grids generate only binary (yes-no) data regarding the presence or absence of changes at a point locale and therefore do not take into account the variable severity of involvement within such zones. Accordingly, we modified this point counting approach by applying a qualitative scoring method to describe the extent and severity of each histopathological abnormality within the entire area of each individual grid zone. Briefly, specimens were analyzed by light microscopy at a magnification of ×100, with a grid consisting of 1-mm squares superimposed on the microscopic field. Within each square, the presence and severity of histopathological abnormalities (interstitial edema, hemorrhage, and neutrophil infiltration) were individually scored qualitatively as none (0), mild (1+), moderate (2+), or severe (3+). The total of all squares analyzed within the RFW area segment was determined and the percent of the segment involved by each abnormality calculated for each score category. Precise delineation and analysis of the extent of contraction band necrosis required higher magnification (×400). Accordingly, each square was visually divided into four quadrants, and the presence and extent of contraction bands within the entire square determined as none (none of four quadrants), 1+ mild (one of four quadrants), 2+ moderate (two of four quadrants) or 3+ severe (three of four or more quadrants). The extent and severity of contraction bands in the total RFW area segment then were similarly calculated. All data are expressed as mean±SEM. Comparisons were made by ANOVA for repeated measures with respect to changes in values within each animal. Comparisons were made between groups using a two-way ANOVA. A significant difference was considered to be present at the 95% confidence level.

Results

Chronic Closed Chest Studies: Effects of Acute Right Coronary Artery Occlusion

At baseline, all echocardiographic and hemodynamic measurements were normal (Figs 1 through 8). Four animals developed refractory ventricular tachycardia and died. In the 22 surviving animals constituting this analysis, acute RCA occlusion decreased perfusion throughout the RFW, resulting in a thinned and dyskinetic RFW and depressed global RV performance, as indicated by decreases in RV fractional area change (FAC), RV maximum (+)dP/dt, and peak RV systolic pressure (Figs 1 through 8). In systole, the interventricular septum thickened and bulged paradoxically into the right ventricle (Figs 1 through 3), generating an active albeit depressed RV systolic waveform. RV diastolic function was also impaired, as evidenced by gross RV dilation, depressed RV maximum (−)dP/dt, and elevated RV filling pressures (Figs 1 through 8). Interventricular septal curvature was reversed (Figs 1 through 3), and there was equalization of RA, RV, and LV diastolic filling pressures and a "dip and plateau" pattern in the RV waveform in all animals (Fig 4). In keeping with previous findings from similar models, depressed RV systolic function led to diminished LV preload (Figs 1 through 3, and Fig 7). Al-
though LV diastolic size was decreased, LV filling pressure was unchanged, indicating LV diastolic dysfunction. Despite intact LV-septal contractility, global LV performance declined, as did stroke volume and cardiac output (Figs 1 through 5). These changes were evident in all animals within 5 minutes of RCA occlusion and persisted throughout the occlusion interval without further significant change irrespective of the duration of ischemia. However, in 8-hour animals, although the RVFW was thinned in the initial 4 to 5 hours of ischemia, by 8 hours RVFW diastolic thickness had increased relative to baseline in 4 of 6 animals and for the group was significantly thicker compared with 1-hour animals (Figs 1, 2, and 6).

**Effects of Reperfusion After 1-Hour Occlusions**

After balloon deflation, the RCA was widely patent by angiography, and perfusion was restored throughout the RVFW (Fig 8). Restoration of flow resulted in prompt improvement in RVFW systolic thickening and motion and consequently enhanced global RV performance despite reduction in the magnitude of compensatory paradoxical septal motion (Fig 1 and Figs 4 through 8). Parameters of RV diastolic function also recovered, RA and LV filling pressures decreased, septal curvature nearly normalized, and the ratio of RV/LV diastolic areas was reduced, as was intrapericardial area. There was prompt resolution of the pattern of equalized diastolic filling pressures and a less prominent RV dip and plateau pattern (Fig 4). Enhanced RV performance led to increments in LV diastolic volume, systolic pressure, global performance, and stroke volume (Fig 1 and Figs 4 through 8). At 4 days and 2 weeks, there was progressive improvement in both RVFW function and global RV performance and decreased RV but increased LV diastolic size (Fig 1 and Figs 6 through 8). At 4 weeks, the RCA was patent, RVFW perfusion was restored to baseline levels, and there was complete normalization of RVFW motion, diastolic area, and FAC (Fig 1 and Figs 6 through 8). Hemodynamic indexes of RV systolic and diastolic function also had recovered (Figs 4 and 5). For the group, gross planimetry documented infarction in <1.0% of the total RVFW. In 4 of the 9 animals, there was no fibrosis (Fig 9). Scar, when present, was confined to the middle segments of the midpapillary muscle level slice (Fig 8).

**Effects of Reperfusion After 4-Hour Occlusions**

Reperfusion after 4-hour occlusions also resulted in a widely patent RCA and restoration of flow throughout the RVFW (Fig 8). However, in contrast to the 1-hour group, there was comparatively minimal recovery of RVFW contraction (Fig 2 and Figs 5 through 8). Nevertheless, global RV performance improved in as-
Sociation with reduction in the extent of RVFW dyskinesis that appeared to be mediated by acute increments in RVFW end-diastolic thickness. These increases in wall thickness (not seen after 1-hour occlusions) occurred early after reperfusion, progressed to a maximum over 30 minutes, and were paralleled by proportionate reductions in the extent of RVFW dyskinesis, which improved global RV performance despite reduced compensatory paradoxical septal motion. Hemodynamic indexes of RV systolic function also recovered although less so than after release of 1-hour occlusions (Fig 5). RV diastolic function improved to a lesser extent than systolic function, as indicated by depressed RV maximum (−)dP/dt and persistently elevated RV filling pressures. However, RV dilation and reversed septal curvature were diminished, LV diastolic size increased, and total intrapericardial area decreased (Fig 2 and Figs 5 through 8). Reperfusion resulted in prompt resolution of equalized diastolic filling pressures as well as a diminished RV dip and plateau pattern.

At 4 days, RVFW thickness was diminished and RVFW had recovered substantially, contributing to further improvement in global RV function (Fig 2 and Figs 6 through 8). RV dilation and reversed septal curvature were decreased, LV diastolic size had increased, and total intrapericardial area was reduced. Over the next several weeks, there was dramatic further improvement in both RVFW function and global RV performance. However, compared with 1-hour animals, the pace of recovery of RVFW function was slower and the magnitude less complete. At 4 weeks, the RCA was patent, RVFW perfusion had returned to baseline levels, and RVFW function and global performance had returned to near baseline levels (Fig 2 and Figs 5 through 8). Measures of RV diastolic function were similarly improved. Although 5 of 6 animals had gross evidence of RVFW infarction, only 2% of the total RVFW was fibrosed, with patchy nontransmural scar confined almost exclusively to the middle segments of the RVFW slice at the midpapillary muscle level (Figs 8 and 9).

**Effects of Reperfusion After 8-Hour Occlusions**

By the completion of 8 hours of coronary occlusion, 3 of 6 animals had developed hemodynamically stable ventricular tachycardia similar to that described previously in

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**Fig 3.** Echocardiographic images in an animal subjected to 8-hour occlusion. At baseline, RV and LV chamber size and function were normal. After 8 hours of occlusion, the RVFW was dyskinetic (solid arrows) and RVFAC depressed; the septum bulged paradoxically (open arrow) into the RV cavity. At ED, the right ventricle was dilated, the septum flattened (arrow), and LV size was reduced. After acute reperfusion, slow ventricular tachycardia developed. The previously dyskinetic RVFW became akinetic in association with increased RVFW diastolic thickness (solid arrows). Despite lack of RVFW contraction, RVFAC increased and RVEDA decreased. At 5 days, sinus rhythm had resumed and the increased RVFW diastolic thickness was diminished. RVFW function improved despite diminished paradoxical septal motion, and RVFAC was increased. Over 4 weeks, RVFW contraction and RVFAC recovered substantially. See Fig 1 for definitions of abbreviations.
Simultaneous superimposed hemodynamic tracings in an animal subjected to 1-hour occlusion. At baseline, right atrial (RA) and right ventricular (RV) diastolic pressures are lower than left ventricular (LV) filling pressure. During occlusion, RA and RV diastolic pressures increased, LV filling pressure decreased, there was equalization of diastolic filling pressures (open arrow), and the RV waveform developed a "dip and plateau" pattern. Acute reperfusion resulted in prompt reductions in RA and RV diastolic pressures, resolution of the equalized filling pressures, and a less prominent RV dip and plateau. By 4 weeks, RA and RV diastolic pressures had decreased further.

Within 15 minutes after reperfusion, the remaining 3 animals previously in sinus rhythm also developed ventricular tachycardia. All animals tolerated this arrhythmia without hemodynamic compromise. In all animals, angiography documented the RCA to be patent with normal angiographic flow. In 1 animal, a small nonocclusive distal intracoronary thrombus was successfully resolved by mechanical disruption with a guide wire. Reperfusion resulted in marked hyperemic flow throughout the RVFW in all animals (Fig 8). Although analysis of regional wall motion during ventricular arrhythmias has limitations, as in the response to acute reperfusion in animals subjected to 4-hour occlusions, there was little improvement in RVFW contraction (Figs 3 and 6). Nevertheless, similar to the 4-hour group, global RV performance improved in association with...
Fig 6. Bar graphs comparing changes over time in RVFW end-diastolic thickness (A), motion score (B), systolic thickening (C), and RV fractional area change (D). *P<.05 with respect to significant changes over time within each group; significant differences between groups at any given time point are indicated (+ vs 1-hour group; +8-hour vs 4-hour group). See Figs 1 and 5 for definitions of abbreviations.

Reduced RVFW dyskinesis mediated by striking reperfusion-induced increments of RVFW diastolic thickness (Figs 3 and 6).

One animal died suddenly at 4 days and was excluded from analysis. In all other animals, by 4 days sinus rhythm had resumed, RVFW end-diastolic thickness had decreased, and RVFW function was improved, as was global RV performance (Fig 3 and Figs 6 through 8). Reversed septal curvature was diminished and LV diastolic size increased. Over 4 weeks, RVFW function and global RV performance improved further; however, at all time points recovery was slower compared with both 1-hour and 4-hour animals (Fig 3 and Figs 6 through 8). At 4 weeks, the RCA was patent and RVFW perfusion was restored to near baseline levels (Fig 8). RVFW contraction and global RV performance had recovered, though less completely than 1- and 4-hour animals. As in 4-hour animals, recovery of RV diastolic function lagged compared with improvement in hemodynamic parameters of RV systolic performance (Figs 5 and 7). Gross infarction was evident in all animals, with fibrosis in a mean of 7% of the total RVFW. Scar was patchy and localized predominantly to the middle segments of the RVFW slice at the midpapillary muscle level (Figs 8 and 9); however, in some animals, there was minimal extension into adjacent anterior and posterior segments. Although total RVFW scar and that in the middle segment were significantly greater compared with both 1- and 4-hour animals, the magnitude of fibrosis was minimal relative to the RVFW area in greatest jeopardy, as judged by the extent of myocardial hypoperfusion, wall motion abnormalities, and reperfusion-induced increments in wall thickness (Fig 3 and Figs 6 through 9).

Fig 7. Bar graphs comparing changes over time in RV (A), LV (B), and intrapericardial (C) end-diastolic areas (expressed as percent change relative to baseline=100%). *P<.05 with respect to significant changes over time within each group; significant differences between groups at any given time point are indicated (+ vs 1-hour group; +8-hour vs 4-hour group). See Figs 1 and 5 for definitions of abbreviations.
Results of Acute Open Chest Studies of 4-Hour Occlusions

Three animals developed refractory ventricular arrhythmias, died early during occlusion, and were excluded from analysis. In the surviving 6 animals, the hemodynamic and echocardiographic changes (Fig 10) at 4 hours of occlusion and during 1 hour of reperfusion were similar in pattern and magnitude to those observed in closed chest animals subjected to 4-hour occlusions (Fig 2). After 1 hour of reperfusion, these animals were killed, and gross inspection of the RVFW slice at the midpapillary muscle level demonstrated increased thickness but no visible hemorrhage. Histopathological examination revealed marked interstitial edema, prominent contraction band necrosis, mild interstitial hemorrhage, and scanty neutrophil infiltration (Fig 11). These changes were most prominent in the middle segment of the RVFW slice at the midpapillary muscle level, that shown by gross inspection and ultrasound to exhibit the greatest increase in thickness after reperfusion and that documented in closed chest animals subjected to a similar duration of occlusion to exhibit not only the most striking reperfusion-induced increments in thickness but the most severe and persistent wall motion abnormalities as well. Although there

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Fig 9. Gross pathological specimens at 4 weeks in animals subjected to 1-, 4-, and 8-hour occlusions. In each animal, all four transverse slices of the right ventricular free wall (RVFW) are illustrated (upper panels) with the slice demonstrating the most extensive scar enlarged (lower panels). Specimens from the animal subjected to 1-hour occlusion reveal no gross scar. In the animal subjected to 4 hours of occlusion, the RVFW scar was localized predominantly to the middle segment of the midpapillary muscle slice; areas of patchy fibrosis (small solid arrows) were interposed between discrete regions of more dense nontransmural scar (open arrows). In the animal subjected to 8-hour occlusion, the scar was similarly patchy and although more extensive than 1- and 4-hour animals, involved a minimal area of the total RVFW. LV indicates left ventricle.
were zones of edema without other abnormalities, contraction bands were evident only in areas of moderate or severe edema. Hemorrhage was seen almost exclusively in zones with moderate to severe edema and contraction bands. Myocyte swelling was apparent in some areas with severe edema and contraction bands. Although these histopathological alterations were evident to a similar degree in all animals within the group, changes within individual animals were quite heterogenous, not only with respect to spatial distribution throughout the RVFW segment but variable as well in severity of involvement within zones manifesting these histological derangements. For the group overall, there was interstitial edema in 77±6% of the RVFW segment area (moderate or worse in 37±8% of the area), contraction band necrosis in 40±5% of the segment area (moderate or worse in 29±9%), hemorrhage involving 27±6% of this RVFW segment (moderate or worse in 1.8±1%), and neutrophil infiltration in 21±7% of the segment area (moderate or worse in 4±2%).

**Discussion**

Observations from the present study emphasize the deleterious impact of ischemia on RV function and demonstrate the beneficial effects of reperfusion on recovery of RV performance. They illustrate also that the responses of the ischemic right ventricle to reperfusion are complex, with disparate effects according to the duration of preceding ischemia. The present findings are consistent with and extend those of prior studies characterizing the acute effects of RVFW ischemia on global RV performance. Central to these observations is the fact that ischemia results in RVFW dyskinesia and depressed global RV function. Under these conditions, global RV performance is dependent on LV-septal contractile contributions. Appreciation of the mechanically deleterious effects of RVFW dyskinesia is a concept essential to an understanding of the complex effects of reperfusion. Analogous to the behavior of dysynergic segments in the left ventricle, the dyskinetic RVFW must be stretched to the maximum extent of its systolic lengthening through septal-mediated systolic ventricular interactions that diminish the effectiveness of LV-septal contributions to both global RV and LV performance. Factors that diminish the magnitude of regional dyssynergy such as volume loading, augmented atrial contraction, and fibrotic stiffening enhance global ventricular performance.

**Acute Effects of Reperfusion: Disparate Responses Related to Occlusion Duration**

In the present study, RCA occlusion resulted in equivalent depression of RVFW function and global RV performance irrespective of occlusion duration. However, the responses to reperfusion were markedly different. After 1 hour of occlusion, reperfusion led to immediate improvement in RVFW function and consequently global RV performance. Of note, reperfusion
resulted in prompt resolution of the pattern of equalized diastolic filling pressures and lesser reversed septal curvature, indicating diminished effects of hemodynamically adverse diastolic ventricular interactions. Improvement in RV function obviated the need for compensatory systolic interactions. These effects contributed to enhanced LV filling and performance. Reperfusion after 4 and 8 hours of ischemia also resulted in acute improvement in global RV performance but to a lesser extent and by different mechanisms, since RVFW contraction remained markedly impaired. This disproportionate improvement in global RV function was predominantly attributable to diminished RVFW dyskinesia associated with reperfusion-induced increments in RVFW diastolic thickness. This abrupt and striking swelling of the RVFW appeared to reduce the distensibility of the dyssynergetic RVFW and thus make more effective the contributions of systolic interactions to global RV performance.

Reperfusion of ischemic LV segments induces analogous increments of wall thickness that are not only associated with impaired recovery of regional contractile function but similarly increase regional passive stiffness, reduce segmental distensibility, and thereby mediate a mechanically beneficial transition from dyskinesis to akinesia. In keeping with present observations, such increments in LV wall thickness are characterized histopathologically by interstitial edema, myocardial cell swelling, contraction band necrosis, and hemorrhage. These structural derangements are thought to reflect altered vascular permeability and loss of myocyte volume regulation attributable not only to the adverse effects of ischemia but to reperfusion injury as well. That reperfusion-induced regional stiffening alone can substantially improve global performance is a concept that has previously been shown with acute antegrade reperfusion in the left ventricle and with slower collateral reperfusion of the ischemic RVFW in models of chronic RCA occlusion. The increased diastolic thickness observed at peak occlusion during prolonged occlusions in the present study may reflect in part similar collateral reperfusion effects whereby promotion of collateral channels over several hours results in reperfusion to the ischemic bed that, although insufficient to restore contractile function, may initiate reperfusion alterations manifest as increments in wall thickness.

**Late Recovery of RVFW Function Irrespective of Occlusion Duration**

In animals subjected to 1-hour occlusions, RVFW function and global RV performance recovered rapidly and completely over 4 weeks, with trivial or no RVFW scar. Although reperfusion after 4- and 8-hour occlusions resulted in little initial recovery of RVFW contraction, there was striking improvement in function over time. However, more prolonged ischemia was associated with slower and less complete recovery of RVFW function and greater infarction. Yet, despite these differences, there was minimal scar relative to the area of jeopardized myocardium. Furthermore, compared with the pace and extent of recovery of RV function after experimental chronic RCA occlusion, even late reperfusion appears to facilitate recovery of RVFW function and global RV performance and minimize RV infarction.

The striking recovery of RVFW function and minimal extent of infarction observed are in marked contrast to the response of the left ventricle to equivalent ischemic insults. Furthermore, reperfusion-induced acute increments in LV wall thickness characterized by similar histopathological derangements have been considered indicative of predominantly irreversible injury. The mechanisms underlying these disparate responses to ischemia and reperfusion are beyond the scope of the present study. We can only speculate as to the contributions of differences between the ventricles with respect to oxygen supply and demand, intramyocardial mechanical forces, responses to injury, remodeling processes, and other factors. However, observations from this and prior experimental studies support the concept that the relative resistance of the right ventricle to infarction is predominantly attributable to more favorable oxygen supply-demand characteristics in general and a superior capacity for acute development of functional collateral vascular supply in particular. Unfortunately, in prior studies of RCA occlusion and
reperfusion, the potential development of collaterals has been limited by ligation, resulting in more extensive RVFW necrosis in a temporal pattern similar to that seen in the left ventricle.\textsuperscript{18,49} No previous reperfusion study has assessed the effects of prolonged RCA occlusion or documented the echocardiographic, hemodynamic, myocardial blood flow responses, or effects on morphology of the right ventricle over time.

**Clinical Implications**

Patients with acute ischemic RV dysfunction typically manifest spontaneous improvement in clinical hemodynamics and recovery of global RV performance over time. However, ischemic depression of RV function is associated with increased early morbidity and mortality.\textsuperscript{1-8} Therefore, if, as in these experimental studies, reperfusion even late after the onset of occlusion facilitates recovery of RV performance, the benefits to patients could be substantial. Unfortunately, there are scant and conflicting clinical data regarding the effects on ischemic RV myocardium of interventions designed to achieve reperfusion.\textsuperscript{12-14} Although the present observations support the concept that an aggressive approach toward coronary recanalization can be of benefit in patients with acute ischemic RV dysfunction, given that the canine coronary circulation is characterized by a nondominant RCA and rich collaterals,\textsuperscript{19} caution should be used when extrapolating the present experimental findings to patients. Whether diminished RVFW dyskinesis associated with increased wall thickness induced by acute antegrade reperfusion in the present study or associated with slow collateral reperfusion in models of chronic occlusion\textsuperscript{10} contributes to the clinical hemodynamic improvement typically seen at 3 to 10 days in patients\textsuperscript{3-7} requires further investigation. Whether reperfusion interventions (early or late) facilitate recovery of RV performance and favorably alter the natural history of patients with RV ischemia requires validation in clinical studies.

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