Enhancement of Regional Myocardial Efficiency and Persistence of Perfusion, Oxidative, and Functional Reserve With Paired Pacing of Stunned Myocardium

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Background Stunned myocardium reflects postreperfusion dysfunction in myocardium that is destined to ultimately fully recover. Most investigators attribute postreperfusion stunning to a primary defect in excitation-contraction coupling or to an altered sensitivity of the myofilaments to calcium. The aim of the present study was to evaluate the interrelation between myocardial perfusion, oxidative metabolism, and function in an effort to better characterize the phenomenon of myocardial stunning, to define the regional efficiency of stunned myocardium, and to characterize its reserve capacity.

Methods and Results Regional myocardial perfusion (measured with radiolabeled microspheres), myocardial oxygen consumption (MV\textsubscript{O2}) (quantified with positron emission tomography using \textsuperscript{1-13}C-acetate), and myocardial function (assessed with two-dimensional echocardiography) were evaluated in 12 anesthetized, closed-chest dogs subjected to 15 minutes of left anterior descending coronary artery occlusion followed by reperfusion. To evaluate flow, oxidative, and functional reserve after measurements were obtained 1 hour after reperfusion, dogs were subjected to paired pacing (an inotropic stimulus that does not alter systemic hemodynamics), and measurements were repeated. One hour after reperfusion, stunned myocardium was characterized by near-normal levels of myocardial perfusion (0.57±0.13 mL/g per minute, 81±13% of that in remote, normal regions) but severe dyskinesis (echo score, 2.6±0.7; percent wall thickening, 14±20%). Despite the low level of contractile function, MV\textsubscript{O2} averaged 1.72±0.7 \textmu mol/g per minute, 71±27% of that observed in remote myocardium. Regional myocardial efficiency (systolic wall thickening divided by MV\textsubscript{O2}) was markedly diminished. With paired pacing, myocardial perfusion increased proportional to that in remote myocardium, systolic function improved (echo score, 1.4±0.7; percent wall thickening, 30±15%), and regional MV\textsubscript{O2} nearly doubled (to 3.41±1.82 \textmu mol/g per minute, \textit{P}<.05 for each paired measurement). Importantly, with paired pacing, regional myocardial efficiency nearly normalized in reperfused myocardium.

Conclusions Stunned myocardium is characterized by near-normal levels of perfusion and oxygen consumption despite marked dyskinesis. Myocardial efficiency is poor. With inotropic stimulation (in the present study, paired pacing), reperfused myocardium demonstrated considerable perfusion, oxidative, and functional reserve and a dramatic improvement in myocardial efficiency. These results may have implications for the treatment of postreperfusion pump failure. (\textit{Circulation.} 1994;89:2290-2296.)

Key Words • metabolism, myocardial • ischemia • tomography

Even after a single, brief period of coronary artery occlusion followed by complete reperfusion, mechanical dysfunction occurs.\textsuperscript{1-4} This dysfunction, which has been termed myocardial stunning,\textsuperscript{5} can compromise cardiac output. Clinically, pump function is the single most important predictor of morbidity and mortality after myocardial infarction.\textsuperscript{6} Myocardial revascularization elicited early after acute ischemia has been shown to favorably decrease infarct size and, in some cases, improve regional function.\textsuperscript{7,8} Nonetheless, reperfused, viable myocardium does not recover functionally for some time.\textsuperscript{1-8}

Although the underlying cause of postischemic ventricular dysfunction has not been elucidated completely, a number of hypotheses have been proposed, including the harmful effects of calcium overload or altered calcium sensitivity after reperfusion\textsuperscript{9,10}; altered high-energy phosphate synthesis, use, or compartmentalization\textsuperscript{11,12}; effects of oxygen-centered free radicals\textsuperscript{13,14}; effects of accumulation of long-chain fatty acyl intermediates\textsuperscript{15}; and impaired nutritive perfusion even after macrovascular coronary revascularization (the no-reflow phenomenon,\textsuperscript{16} among others\textsuperscript{17,18}).

Three general mechanisms can limit the recovery of reperfused myocardium. These include (1) incomplete restoration of nutritive perfusion and/or the inability of the vasculature to permit increased perfusion in response to increased demands (ie, impaired flow reserve), (2) the inability to use oxygen or other substrate effectively to produce high-energy phosphate necessary to fuel contractile function or defects in transport or compartmentalization of ATP once formed, and/or (3) primary or secondary failure of the contractile machinery.

Most studies have demonstrated that myocardial perfusion to territories reperfused after brief intervals of
occlusion is restored to near-normal levels.19-22 However, the ability of myocardial perfusion to increase in response to increased demands may be more limiting21,22 and may compromise myocardial function in the face of increased needs. These experimental observations have been corroborated recently in clinical studies.23,24

Metabolically, oxygen consumption appears to be high in reperfused myocardium20,22,23,25-28 and out of proportion to the work that the reperfused myocardium is performing. This phenomenon has been termed "oxygen wasting" and refers to the high regional oxidative use, which is decoupled from its normal relation to work. Most studies have suggested that oxygen wasting is not due primarily to decoupling of oxidative phosphorylation but rather that it represents an inefficient transfer of energy from catabolic processes to contractile elements or the inefficient use of high-energy phosphates by the contractile element.12,20,22,25-28 Alternatively, it could represent the use of oxygen-requiring processes for restoration of cell homeostasis or repair of injury induced by the ischemic insult. Our laboratory has exploited the observation of high oxygen utilization in reperfused segments to predict myocardium that will ultimately recover contractile function.20,23,25,29

Recently, a number of studies have demonstrated that stunned myocardium may reflect a primary abnormality in the sensitivity of the myofilaments to calcium.9,10 Enhanced function can be observed by increasing extracellular calcium,30,31 suggesting that the contractile machinery per se is intact but altered in regard to its calcium handling. The ability of stunned myocardium to increase its functional capacity has been used with inotropic stimuli such as paired pacing or β-agonist stimulation as a diagnostic procedure that can identify viable from nonviable myocardium and serves as the basis for the dobutamine stress test, which is used for delineating viable myocardium.21,32-37 The aim of the present study was to further delineate the interrelation between flow, metabolism, and function in stunned myocardium, to evaluate reserve capacity, and to assess regional myocardial efficiency.

**Methods**

**Experimental Protocol**

The protocol was approved by the institutional Animal Studies Committee and conformed to the policies of the American Heart Association. Twelve closed-chest, adult condition dogs weighing between 20 and 30 kg were used for this study. After an overnight fast, dogs were premedicated with 1 mg/kg morphine sulfate subcutaneously and anesthetized 30 to 60 minutes later with 12.5 mg/kg sodium thiopental followed by 72 mg/kg IV α-chloralose. Dogs were intubated and ventilated with room air. Supplemental chloralose was administered to maintain a surgical plane of anesthesia. Catheters were placed in the descending aorta for measurement of blood pressure and in the inferior vena cava for injection of tracers. In addition, a catheter was placed retrogradely into the left atrium for administration of radiolabeled microspheres. Arterial pressure, heart rate, and the ECG were monitored continuously.

To explore the relation between flow, oxidative metabolism, and functional characteristics of stunned myocardium, we evaluated dogs subjected to 15 minutes of coronary artery occlusion followed by reperfusion. This preparation results in consistent ventricular dysfunction without permanent injury1-4 and accordingly provides a useful experimental preparation in which to examine factors associated with myocardial stunning and to test potentially beneficial strategies.19

In all dogs, a coronary artery angioplasty balloon catheter was selectively placed into the left anterior descending coronary artery through a guiding Amplatz catheter inserted via the left carotid artery.19,20 Before occlusion, dogs received 10 000 IU IV heparin and 1 mg/kg lidocaine as an intravenous bolus followed by a continuous infusion of 50 µg/kg per minute.

Ischemia was induced by inflating the balloon to 4 to 5 atm of pressure, and occlusion was documented by arteriography and observation of low intracoronary pressure (typically 10 to 20 mm Hg) measured from the distal port of the balloon catheter. The intracoronary balloon was left inflated for 15 minutes. Radiolabeled microspheres were administered just before reperfusion to assess flow during the occlusion period. After the 15-minute occlusion interval, reperfusion was achieved by a gradual deflation of the balloon over 1 minute, and reperfusion was confirmed by the return of aortic levels of intracoronary pressure.

To delineate the response to an inotropic stimulation, after perfusion, metabolism, and functional analyses were performed 1 hour after reperfusion (see below), hearts were subjected to paired pacing. To accomplish this, a bipolar pacing electrode was placed into the apex of the right ventricle through the external jugular vein and connected to a Grass SD9 stimulator. During paired pacing, stimuli were delivered just above the dogs' intrinsic heart rate using 10-millisecond pulses delivered 10% to 15% above threshold just after the absolute refractory period. This point was selected by a stepwise reduction in the coupling rate until the shortest coupling interval was determined. Paired pacing was chosen for use as the inotropic stimulus rather than pharmacological stimulation because paired pacing induces inotropy without the more complex effects of sympathetic agonists that can induce positive inotropy but alter systemic hemodynamics.

**Positron Emission Tomography**

To evaluate regional myocardial oxygen consumption (MVO₂), positron emission tomography (PET) with 1-13C-acetate was performed in all dogs. We have demonstrated previously that clearance of 13C-radioactivity from the myocardium after administration of 1-13C-acetate reflects oxidation of 1-13C-acetate to 13CO₂ and thus reflects oxidative metabolism.38,39 We have demonstrated further that this relation does not depend on the pattern of substrate use,40 which can change dramatically during ischemia and reperfusion.38,41 It also has been demonstrated that estimates of MVO₂ using 1-13C-acetate are valid during ischemia and reperfusion.42 Since the period of ischemia was so brief, we could not perform tomography during the occlusion period. Tomography commenced 60 minutes after reperfusion, under resting conditions. This time interval was selected to avoid the reactive hyperemia phase that may accompany initial reperfusion.

Dogs were positioned supine in a Plexiglas shell and placed within PET VI, a tomograph that permits a simultaneous acquisition of seven slices of the heart. An attenuation scan was performed with an external ring source of gallium-68-germanium-68. To identify the blood pool and vascular structures, dogs inhaled 30 to 50 mCi of 15O-carbon monoxide (CΟ₂), which labels hemoglobin, and tomographic data were obtained over 5 minutes. After decay of radioactivity from 15O to background levels, 0.8 to 0.9 mCi/kg of 1-13C-acetate (t1/2 of 13C=20.3 minutes) was administered as an intravenous bolus, and serial tomograms were acquired over a 30-minute period in 60- to 90-second frames.

After decay of radioactivity from 1-13C-acetate, dogs were subjected to paired pacing. After the appropriate pacing parameters were obtained, dogs were allowed to equilibrate
for 5 to 10 minutes. The dogs then received a second administration of microspheres and of 1-\(^{13}\)C-acetate.

**Tomographic Analysis**

All transverse tomographic reconstructions containing myocardium were analyzed. Nine to 12 regions of interest were interactively placed on each slice. Three regions were placed in the septum, lateral wall, and anterior wall (within the reperfused region). On the more apical slices, three regions of interest also were placed in inferior/posterior myocardium. A further region of interest was assigned to the center of the left atrial chamber for measurement of arterial blood tracer content (necessary for the quantification of spillover).

Multiexponential curve fitting was used to fit decay-corrected, partial volume-corrected, and spillover-corrected myocardial time-activity curves generated from serial tomographic images obtained after administration of 1-\(^{13}\)C-acetate. Curve fitting commenced from the time of maximal rate of decline of myocardial radioactivity. Clearance of 1-\(^{13}\)C-radioactivity from myocardium was generally biexponential, and biexponential solutions to time-activity curves were attempted in all cases. Clearance from regions subjected to occlusion and reperfusion in some cases could only be fitted with monoexponential solutions. The slope of the rapid phase of acetate clearance \(k_2\) was determined for each region. Myocardial oxygen consumption was estimated based on a previously validated relation comparing \(k_2\) with direct measurements of MVO\(_{\text{r}}\). For purposes of comparing regions identified by tomography with those identified by both echocardiography and postmortem analysis of radiolabeled microspheres, large anatomic (ie, anterior, lateral, posterior, and septal) regions of interest were identified by tomography that could be readily compared with other measurements based on known anatomic landmarks.

**Echocardiography**

Two-dimensional echocardiography was performed using a Hewlett-Packard Sonos 500 echocardiography unit and a 64-channel phased-array transducer operating at 3.5 MHz. Short-axis views of the left ventricle were obtained with the dogs positioned on their right side and a transducer applied to the chest wall from below the imaging table. Images were recorded on a Panasonic MV8200 video recorder, and images were analyzed using a Microsonix DataVue system. Short-axis views at the midpapillary muscle level were used to define the anterior wall, and views of the heart corresponded to those interrogated with PET. Echocardiograms were interpreted by two observers blinded to the status of the myocardium being evaluated. For semiquantitative assessment, regional motion for each wall (anterior, septal, lateral, and posterior) was graded from a cine loop digital display based on a 0 to 4 scale, with a grade of 0 reflecting hyperkinetic myocardium, 1 reflecting normal myocardium, and 4 representing dyskinetic myocardium. An overall average regional wall motion score was obtained during reperfusion and paired pacing.

In addition, quantitative analysis of wall motion was made from each measurement.\(^\text{20,44}\) For this, endocardial and epicardial borders were manually traced for three consecutive sinus beats from end-diastolic (largest cavity area) and end-systolic (smallest cavity area) digital frames. Sixty-four radial chords connecting epicardium and endocardium were generated perpendicular to the epicardial border, and wall thickening of eight circumferential regions was defined from the mean values from groups of eight adjacent chords. Percent wall thickening was then calculated for each region as systolic minus diastolic thickness divided by diastolic thickness.

**Calculation of Blood Flow With Microspheres**

Radiolabeled microspheres (15 \(\mu\)m labeled with chromium-51, scandium-46, strontium-85, or cerium-141) were injected into the left atrium immediately before each administration of 1-\(^{13}\)C-acetate. Starting 15 seconds before microsphere administration and for 2 minutes afterward, arterial blood was withdrawn at a flow rate of 10 mL/min from the femoral artery with a constant withdrawal pump. Left ventricular slices obtained postmortem at the midpapillary level and a more apical level were sectioned into eight circumferential samples. Each segment then was divided into endocardial and epicardial samples, and regional myocardial blood flow for each sample was calculated using the standard reference technique.

**Statistics**

All data are presented as mean\(\pm\)1 SD. Differences between reperfused and remote myocardium were compared using a paired \(t\) test, as were comparisons between estimates obtained at rest and during paired pacing. A value of \(P<.05\) was considered to indicate statistical significance.

**Results**

**Hemodynamics**

Heart rate averaged 96\(\pm\)29 beats per minute when dogs were studied 1 hour after reperfusion and tended to be slightly higher (116\(\pm\)27 beats per minute) during paired pacing \((P=NS)\) because of the requirement to override the animals' intrinsic rate, which increased slightly with time after reperfusion. Systolic pressure was not altered by paired pacing (150\(\pm\)26 mm Hg at rest compared with 158\(\pm\)19 mm Hg with paired pacing, \(P=NS\)) (Fig 1).

**Myocardial Blood Flow**

Myocardial blood flow was quantified with radiolabeled microspheres. During ischemia, transmural myocardial perfusion was 32\(\pm\)17% of flow in remote, unaffected zones and averaged 0.23\(\pm\)0.11 mL/g per minute...
Fig 2. Bar graphs: Summary of transmural myocardial blood flow estimated with radiolabeled microspheres during ischemia, after ischemia 1 hour after reperfusion under baseline conditions, and with paired pacing in absolute terms (mL/g per minute) (top) and expressed as a proportion of reperfusion to remote myocardium (bottom). Myocardium subjected to reperfusion regained more than 80% of normal flow by 1 hour of reperfusion. With paired pacing, absolute flow increased, and flow in the reperfused region remained at >80% of flow in the remote regions. Open bars represent reperfused myocardium; closed bars represent remote, normal myocardium. Asterisks represent significance of paired comparisons at each time interval. Values are mean ± 1 SD.

(Fig 2). At the time of the initial PET scan, approximately 1 hour after reperfusion, flow recovered to 81 ± 13% of that in remote, normal regions and averaged 0.57 ± 0.13 mL/g per minute. Flow in remote regions averaged 0.78 ± 0.25 mL/g per minute during occlusion and did not change with reperfusion (0.72 ± 0.20 mL/g per minute). With paired pacing, flow in both the reperfused and remote regions increased by ≈70% above values obtained at rest. Flow in the reperfused region during pacing remained 85 ± 19% of that observed in normal, remote myocardium (0.97 ± 0.27 and 1.15 ± 0.30 mL/g per minute, respectively) (Fig 2). These observations indicate that flow was nearly completely restored in reperfused zones (ie, little no-reflow), and increases in flow induced by inotropic stimulation were matched in reperfused zones compared with responses observed in remote regions.

Oxidative Metabolism

Regional MVO2 was estimated by analysis of clearance of 11C-radioactivity after administration of 1-11C-acetate. One hour after reperfusion, MVO2 in reperfused zones averaged 1.72 ± 0.87 μmol/g per minute, 71 ± 27% of that observed in remote myocardium (Fig 3). With paired pacing, oxidative metabolism nearly doubled in reperfused myocardium (to 3.41 ± 1.82 μmol/g per minute) and averaged 61 ± 27% of that observed in remote myocardium. Although MVO2 was high in reperfused myocardium at rest compared with the amount of systolic work performed (see below), these observations suggest that the capacity to increase oxidative metabolism in stunned myocardium was preserved.

Segmental Function

Evaluation of two-dimensional echocardiograms documented severe hypokinesis or akinesis during the early reperfusion period. The average echo score of reperfused myocardium was 2.6 ± 0.7 compared with a score of 1.6 ± 0.7 (P < .01) in remote, normal regions (Fig 4). During paired pacing, there was substantial improvement in wall motion, with an average echo score of
1.4±0.7 in reperfused zones. Function of remote myocardium was enhanced with paired pacing and became hyperkinetic (echo score, 0.7±0.7) (Fig 4).

Quantitative analysis of two-dimensional echocardiograms was used independently to assess active systolic thickening. It was observed that reperfused myocardium actively thickened only minimally at rest (percent wall thickening averaged 14±20% compared with 36±15% for remote myocardium, \( P < .05 \)). During paired pacing, reperfused regions actively shortened to a greater extent (30±15%, \( P < .05 \) compared with rest), and remote myocardium thickened to an even greater extent (60±23%) (Fig 5).

**Index of Myocardial Efficiency**

An index of regional myocardial efficiency was determined by calculating the average unit of wall thickening generated (estimated from quantitative echocardiography) per unit of oxygen consumed (estimated by PET). At rest, reperfused regions operated inefficiently—that is, these regions used considerable oxygen for relatively little mechanical work (Fig 6). With paired pacing, the efficiency of reperfused myocardium improved to nearly that observed in normal myocardium. Note that the efficiency of normal, remote myocardium was similar under resting conditions and with pacing, reflecting the close physiological coupling of myocardial work and oxygen use.

**Discussion**

Coronary artery reperfusion after acute occlusion has been demonstrated to reduce infarct size, improve regional function, and decrease mortality. However, reperfusion does not benefit cardiac function immediately, and the delay in recovery of ventricular performance after reperfusion (which can be observed in experimental animals after periods of as little as 15 minutes of occlusion) is not well understood. Mechanisms invoked to explain the prolonged contractile dysfunction after transient occlusion include blockage of flow by plugging of capillary and arteriolar vessels by activated vascular elements, effects of oxygen-centered free radicals, effects of long-chain fatty acyl intermediates, altered calcium homeostasis, and decreased high-energy phosphate levels or compartmentation.\(^5,9-18\) Antagonism of each of these proposed mechanisms has been shown to improve regional function after reperfusion. Although the cellular mechanisms of stunning have not been unequivocally defined, it has been suggested that recovery of the ability to oxidatively metabolize substrate is a determinant for ultimate recovery of the myocyte.\(^12,20,25,29\) Use of this observation is compromised by the finding that oxygen use in reperfused myocardium is out of proportion to work (normally the major determinant of oxidative use), a phenomenon termed oxygen wasting. It has been proposed that oxygen is being used to make energy that is needed for recovery of cellular homeostasis and repair but is not being used for contractile function.\(^22,26,28\) It is possible, however, that high-energy phosphates are being used by the hypercontractile myofibrils but that their contractile performance is decreased as a result of alterations in the sensitivity to calcium.

The present study corroborates previous findings\(^1-4\) that myocardium reperfused after a relatively brief interval (15 minutes) of occlusion is dysfunctional at rest despite successful recanalization with restoration of myocardial perfusion to >80% of normal. Although inotropic stimulation may have a deleterious effect on ischemic myocardium, it can increase the contractile performance of reperfused but stunned myocardium.\(^21,30-37\) Although it might be anticipated that such inotropic stimulation of reperfused myocardium might induce additional damage, this has not been observed.\(^21,30,34\) In the present study, with paired pacing used as an inotropic stimulus, myocardial perfusion, oxidative metabolism, and function all showed substantial increases, indicating considerable reserve in stunned, reperfused myocardium.

Under baseline, reperfused conditions, stunned myocardium operated inefficiently, defined by significant oxygen usage with little regional systolic function. During paired pacing, the efficiency of reperfused myocardium improved significantly. Although the measurement of myocardial efficiency is controversial and a number of varied schemata have been proposed for its measurement, the regional approach reported here, although simple, appears to be reasonable since myocardial efficiency did not change in remote, normal myocardium (ie, \( \text{MVO}_2 \) increased proportionately to the increase in regional systolic function; see Fig 6).

The results indicate that myocardial stunning is not attributable to primary defects limiting augmentation of perfusion, oxidative metabolism, or function but rather is due to a primary defect in contractile function (ie, sensitivity to calcium) or excitation-contraction coupling. In addition, stunned myocardium is characterized by a dissociation of the normally tightly coupled relation between myocardial oxygen demands and use but can be made to use oxygen more efficiently with paired pacing. Whether this improved myocardial efficiency would be maintained with more prolonged periods of inotropic stimulation or after longer periods of ischemia is not known. As mentioned above, no deleterious effects of inotropic stimulation on jeopardized myocardium have been observed in a limited number of experimental studies.\(^21,30,34\)

**Technical Limitations**

The inotropic stimulation chosen for this study was paired pacing. This stimulus maintained overall heart...
rate just slightly above the intrinsic sinus rate and was not associated with an alteration in systemic pressures. Systolic function increased both in reperfused and remote, normal myocardium. Paired pacing resulted in a near doubling of myocardial perfusion and regional oxidative metabolism. Whether more profound inotropic stimulation would have resulted in a functional impairment or in a failure of myocardial perfusion and oxidative metabolism to increase proportionately (and thus result in a deterioration of the increased efficiency observed) is not known.

Recovery of contractile function can be nonuniform.45 However, because of the spatial resolution of the current generation of tomographs and echocardiography, only transmural assessments of oxidative metabolism can be made. Accordingly, the results of this study cannot exclude differences in transmural function or oxidative metabolism. The results of microsphere assessments showed uniform endocardial and epicardial increases in perfusion with inotropic stimulation (data not shown); thus, it is unlikely that transmural gradients in the response to reperfusion or in the response to paired pacing were operant.

There are intrinsic difficulties in correlating two-dimensional echocardiograms with PET tomograms. Care was taken to delineate anatomic landmarks (ie, papillary muscles, mitral valve plane, etc) to enable correlation of echocardiograms with PET images and with the postmortem samples. Lumping myocardium into anatomic distributions was viewed to be the most objective approach in correlating the two modalities. Similarly, the assessment of regional efficiency did not incorporate more complex models of wall stress but only wall thickening. As indicated above, the measure appears reasonable, based on the coupling observed in remote regions.

Clinical Considerations

The results of this study indicate that PET may be a useful tool to delineate the metabolic responses to reperfusion. In addition, it may help to define the etiology of stunned myocardium in patients after recanalization and provide a noninvasive means to assess the efficacy and physiological effects of therapeutic interventions designed to augment metabolism and function. Although reperfused, stunned myocardium that is viable is characterized by a dissociation of the normally tightly coupled relation between oxygen use and function, the efficiency of oxygen use can be improved by inotropic stimulation. Whether this increase in efficacy can be sustained or whether prolonged inotropic stimulation may result ultimately in deleterious effects will require additional study, but the approach may improve the contractile function of reperfused myocardium with increased efficacy.

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