Assessment of ischemic regional myocardial dysfunction and its reversibility

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BY ITS very nature, significant disease of the coronary arteries results in regional ischemia or infarction, with sparing of other areas of the heart. Therefore, it is intuitively reasonable that assessment of the consequences of ischemic events on cardiac contraction would be best reflected in regional myocardial performance. On the other hand, if a regional contractile abnormality is sufficiently severe or extensive it can impair global ventricular function, so that a fall in the ejection fraction also can be a useful marker of regional ischemic events. Although other measures of ischemia or infarction are available, including electrocardiographic events, metabolic abnormalities, and reduced coronary perfusion, the generally close coupling between contractile performance and ischemia or ischemic damage frequently has led to its use for the study of changes in regional myocardial function. Nevertheless, dissociations can occur between regional contraction and tissue metabolism or viability, as in delayed but reversible postreperfusion dysfunction. Also, when acute infarction develops into regional scar, when abnormal loading conditions exist, or when compensatory hypertrophy produces hyperfunction of nonischemic zones, measurements of regional contraction are often needed to understand the net effect of an ischemic event on global ventricular function.

It will be the purpose of this brief analysis to examine the characteristics of regional contraction, its usefulness and limitations in relation to global left ventricular function for the detection of myocardial ischemia and infarction, and its role in assessing responses to experimental reperfusion and clinical thrombolytic therapy. Although diastolic abnormalities can be important as well, the brevity of the review will limit discussion to that of systolic function.

Characteristics of regional myocardial dysfunction during ischemia. Regional myocardial shortening or regional wall thickening can be measured in experimental animals by implanted sonomicrometers during the development of ischemia after acute coronary occlusion (figure 1). At each time point, the wall motion abnormalities observed can resemble those during various degrees of steady-state mild-to-severe acute coronary stenosis. Likewise, they can be related to wall motion abnormalities in man, as measured by ventriculographic or echocardiographic methods. It is useful to define the phases of such regional contraction abnormalities into three time periods: the preejction, ejection, and postejction phases. Relatively early during the development of full ischemia, or with sustained mild coronary stenosis, the preejction phase may show mild elongation of segment length and slight thinning of the wall (figure 1), whereas during ejection there is a decreased extent of shortening and diminished systolic wall thickening (hypokinesia) (figure 1), reflected as decreased inward endocardial motion on the angiogram together with decreased velocity of wall motion. Immediately after the end of ejection during mild-to-moderate degrees of ischemia, postejction segment shortening may be seen with increased velocity of shortening (corresponding to late inward wall motion) and late systolic wall thickening (figure 1, 25 sec), which, of course, do not contribute to ventricular ejection. As regional ischemia becomes more severe these changes become more marked, with akinesia during the ejection phase, and during full ischemia segment elongation occurs during the preejction and ejection phases (with holosystolic wall thinning), followed by marked postejction shortening and wall thickening (figure 1).

It is important to recognize that during mild ischemia, postejction shortening may lead to a normal extent of overall or maximum wall motion (often measured clinically at minimum ventricular volume), even though distinct abnormalities of regional contraction are present. To detect such an abnormality, it is necessary to analyze shortening in inward wall motion at the...
end of ventricular ejection, or to use phase analysis to detect the abnormal synergy or timing of regional contractile events. The mechanism for delayed postejection shortening may relate to passive recoil in the ischemic region, or to continued ability to develop tension after ejection, which is manifest only at a reduced tension level, so that shortening occurs only when ventricular pressure (and hence the systolic load on the involved region) has fallen to a relatively low level.

Accompanying these changes in the ischemic zone are alterations in the contraction pattern in normal regions. Early after complete coronary occlusion the extent of segment shortening is increased, due primarily to postejection shortening in the normal region (figure 1, 5 sec). Later, as full ischemia develops, increased resting fiber length in the normal zone may be associated with increased shortening in that region (compensatory hyperfunction with use of the Frank-Starling mechanism) (figure 1). Such compensatory hyperfunction may become even more marked in the days and weeks after acute myocardial infarction, as hypertrophy occurs in normal zones. These compensatory effects in normal regions can limit the sensitivity of the ejection fraction for detecting regional ischemic heart disease, since a normal global ejection fraction can be produced despite the presence of regional dysfunction.

Sensitivity of regional wall motion for the detection of ischemic heart disease. Studies at rest in which progressive coronary stenosis is produced in the conscious resting dog have shown a nearly linear correlation between regional wall motion and subendocardial blood flow over a wide range (whereas a poor correlation exists with subepicardial blood flow), and small decrease in blood flow of about 20% produces a correspondingly small reduction in systolic wall thickening. This close coupling between the level of ischemia (marked by low regional blood flow) and regional contraction suggests that regional wall motion should be a sensitive marker of acute ischemic events.

Recent experimental studies indicate that regional wall motion during exercise also has good sensitivity for detecting relatively mild coronary stenosis that is associated with significant vasodilator reserve. In those studies, failure of regional myocardial contraction to increase normally during exercise did not consistently detect ischemia, but a fall in regional contrac-

![FIGURE 1](image-url)

**FIGURE 1.** Progressive changes in regional wall motion in a conscious dog before (control) and after coronary occlusion. Left ventricular pressure (LVP) and its first derivative (dP/dt) were measured with a high-fidelity micromanometer. Regional function was measured with ultrasonic dimension gauges placed near the subendocardial region to measure segment function and those placed across the wall to measure wall thickness in a control (anterior region) and an ischemic (posterior lateral) region in the area served by the occluded circumflex coronary artery. Vertical lines mark the onset and end of ejection. The segment and wall thickness crystals are implanted in closely adjacent regions. For further discussion see text. Reproduced, by permission, from Sasakiya S, Franklin D, Ross Jr, Kemper WS, McKown D: Dynamic changes in left ventricular wall thickness and their use in analyzing cardiac function in the conscious dog. Am J Cardiol 38: 870, 1976.
tion of greater than 10% always reflected a defect in subendocardial perfusion. As noninvasive echocardiographic, radionuclide, and digital intravenous angiographic methods continue to improve, it may be expected that detection of regional contraction abnormalities induced by severe exercise may prove to be a sensitive and relatively specific approach for the detection of latent or “silent” coronary heart disease.

In chronic coronary heart disease, regional wall motion abnormalities have been shown to be more sensitive than the ejection fraction for identifying subtle evidence of coronary artery disease. For example, in the patient with a completely occluded coronary artery and a normal ejection fraction, asynergy may be detected by phase analysis of regional wall motion by cineangiography.

Determinants of regional myocardial dysfunction. A variety of factors can influence the characteristics of regional contraction and the degree of regional myocardial dysfunction (table 1). As mentioned above, the degree of subendocardial ischemia relates closely to the severity of dysfunction, and with chronic infarction the percentage of transmural scar correlates with the degree of regional wall motion abnormality. Positive or negative inotropic stimulation, perhaps in part through augmentation of contraction in a normal outer wall when the ischemia or scar is nontransmural, can alter contraction in regionally dysfunctional areas. Abnormal electrical activation of normal myocardium, as produced by premature ventricular activations or by ventricular pacing, can also produce contraction patterns near the region of abnormal stimulation that resemble those caused by ischemia.

Extrinsic factors can affect regional dysfunction as well (table 1). Altered loading conditions on the left ventricle caused by changes in arterial pressure, by altering the afterload, can change the degree of regional dysfunction due to acute ischemia or chronic scar without necessarily affecting the degree of ischemia.

Also, an “autoloading” phenomenon occurs, whereby the inability of an ischemic region to generate normal wall thickening (or to even maintain the resting wall thickness) during systole results in a progressively higher regional wall stress during contraction, thereby contributing to diminished function through increased regional afterload. Even though the outer half of the wall may be well perfused during partial ischemia, the outer fibers appear to contribute little to overall regional function (although they may participate in active tension development), a phenomenon that suggests that tethering exists across the wall.

Finally, the mechanical effects of an ischemic region may extend beyond the borders of the region in which blood flow is reduced (table 1). It has been suggested by results of several echocardiographic studies that there may be a fairly broad area in which hypokinesia is manifest in normally perfused areas, leading to overestimation of the extent of ischemia. However, recent experimental studies indicate that dysfunction is produced only in regions immediately adjacent to an ischemic zone, a zone of mild hypofunction that extends less than 1 cm from the ischemic border, with hyperfunction beyond that region. It should also be noted that when an area of ischemia is particularly large, it is likely that acute dilation of the entire left ventricle increases afterloading conditions on normal regions, so that compensatory hyperfunction may be prevented.

Reversibility of experimental regional dysfunction. As mentioned previously, a dissociation can occur between the occurrence of regional wall motion abnormalities and the presence of ischemia (low blood flow) or permanent ischemic damage. In the conscious dog, when a 2 hr period of coronary occlusion is followed by reperfusion, postischemic dysfunction in hypokinetic regions improves or resolves over a 2 to 3 week period, with small improvement in dyskinetic regions. A number of studies have shown that postschismic dysfunction (or “stunning”) occurs after release of a 15 min coronary occlusion and that recovery requires many hours or days. In dogs undergoing reperfusion after 5 hr of partial circumflex coronary arterial stenosis that produces moderate regional hypokinesia, a gradual return of function to normal occurs over several days in the left ventricular free wall without associated necrosis (although infarction may occur in the posterior papillary muscle). The latter study supports the idea that chronic partial ischemia can exist and may lead to chronic wall motion abnormalities, and all of these experimental studies illustrate that dysfunction caused by ischemia can be prolonged yet still reversible.

Effects of thrombolytic treatment on myocardial function. Proof of the sustained effects on cardiac function of thrombolytic therapy in acute myocardial infarction

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has been difficult to obtain. It was demonstrated a number of years ago that coronary arterial reperfusion after 3 hr of coronary occlusion in dogs reduces myocardial damage 1 week later, and recently several large randomized clinical studies in which reperfusion was produced by thrombolysis, including the Italian (GISSI) study with nearly 12,000 patients, have shown that mortality after acute myocardial infarction can be reduced, but whether or not left ventricular function is favorably affected has been controversial. Efforts to document improved function have been extensive, since most investigators have considered that improvement in myocardial contraction, as reflected in the ejection fraction or regional wall motion, constitutes a satisfactory marker of myocardial tissue salvage. Analysis of published results of thrombolysis is complicated by several issues, including true variability in the amount of tissue salvaged depending on the time when thrombolysis was instituted, delayed recovery of function with variations in the time at which postreperfusion studies were performed, variability in the degree of residual coronary stenosis, and differences in the methods used to assess recovery of contractile function. Moreover, most studies have not documented changes in regional and global myocardial function over time in large randomized (and complete) groups of treated and control patients. Adding to the analytic difficulties is the finding in a number of ventriculographic and echocardiographic studies that even the normal left ventricle exhibits a considerable degree of inhomogeneity of function around its perimeter, so that careful comparisons with normal subjects are required to clearly define abnormalities in regional contraction.

Whereas several uncontrolled studies have suggested improved ventricular function after thrombolysis, some controlled investigations have failed to show significant improvements in the left ventricular ejection function or wall motion immediately or late after intravenous or intracoronary thrombolysis. For example, the Western Washington Streptokinase Randomized Trial, which reported a decreased mortality after thrombolysis, did not demonstrate improvement in the global or regional ejection fraction as assessed by radionuclide ventriculographic techniques in 207 patients at an average of 62 days after treatment. In that study, the mean time when therapy with intracoronary streptokinase was commenced was nearly 5 hr after onset of symptoms, and it seems likely that the findings relative to cardiac function reflect relatively delayed treatment. However, possible insensitivity of the radionuclide regional wall motion analysis technique is suggested by the failure to show improved function in those patients randomized in less than 3 hr.

Additional insight into the factors affecting ventricular function after thrombolysis is provided in recent nonrandomized observational studies in 52 patients by Dodge et al., in which a contrast ventriculographic method involving a centerline with 100 chords was developed, and regional wall motion defects were analyzed in terms of standard deviations from data in a group of normal subjects; quantitative analysis of coronary arterial diameter was also performed. These investigators compared angiographic data at the time of treatment with findings from a later study and were able to show significantly improved regional function at an average of 45 days after intracoronary thrombolysis with streptokinase or urokinase (often associated with coronary bypass surgery), provided that treatment was carried out within 3 hr of onset of symptoms. The greatest improvement in regional wall motion was seen in patients treated within 2 hr (71% of patients improved), and in patients with a minimum residual coronary arterial diameter larger than 0.4 mm. On the other hand, the global ejection fraction showed no change. Thus, hyperkinesia in normal regions compensated for hypokinetic zones in studies early after thrombolysis, and as regional hypokinesia later improved, compensatory regional hyperkinesia diminished so that reciprocal changes precluded significant alterations in the global ejection fraction. Therefore, only analysis of regional wall motion was capable of detecting the modest improvements in regional function produced by thrombolysis in these studies.

In a recent study by the Working Group of the Netherlands Interuniversity Cardiology Institute in 533 randomized patients, early mortality was reduced from 10% to 5% after streptokinase was given by the intracoronary route or by intravenous followed by intracoronary administration (40% of patients), with additional acute percutaneous transluminal coronary angioplasty being performed in 18% of patients, and vessel patency was documented in 85% of the individuals at a median time of 3.3 hr from onset of symptoms. In a subset (67%) of patients radionuclide angiography showed a small increase in ejection fraction between days 2 and 4 and a second study at days 10 to 20. In an associated study by this group, left ventriculograms were also available in 52% of the 533 patients at a median of 11 days after admission. Global ejection fraction was measured and regional ejection fractions were calculated with a series of 20 coordinates with which the regional contributions to the global ejection fraction were compared with those in normal
left ventricles. In this subset of patients, the global ejection fraction was considerably and significantly higher in treated patients (52%) than in control subjects (47%), and in those with anterior and inferior infarctions the improvement was shown to be caused by improved function in the ischemic region. Whether this subset of patients was entirely representative of the whole group cannot be established with certainty, but these favorable results on both global and regional function after combined modes of reperfusion seem likely to relate primarily to the relatively early intervention achieved.

Implications. Measurements of regional and global left ventricular dysfunction in ischemic heart disease are finding increasing application as markers of the severity and extent of acute ischemia or of changes due to acute and chronic myocardial damage. Whether global function, as reflected by the ejection fraction, or regional contraction should be assessed must depend to a considerable degree on the nature of the problem under study.

Of course, when regional ischemia or ischemic damage is moderate to severe, the ejection fraction will adequately reflect the reduction in regional performance. Moreover, many studies have shown the ejection fraction to be an independent predictor of mortality after acute myocardial infarction. In addition, the exercise ejection fraction is useful for determination of long-term prognosis in patients with chronic coronary heart disease. Therefore, in the determination of the overall effect of a therapeutic intervention on early and late events, ejection fraction provides a valuable marker of the net effect of acute and chronic regional ischemic damage on cardiac function and hence on morbidity and mortality. Indeed, it might be argued that unless a detectable change in the ejection fraction is produced by an intervention having long-term effects, such as thrombolysis, it is unlikely to have a major impact on mortality (a seeming paradox in the Western Washington study results). In addition, the ejection fraction is easier to measure in a reliable manner than regional wall motion. However, it reflects the net effect of areas of regional contraction that can range from dyskinetic, to hypokinetic, to hyperkinetic within a given ventricle, and the usefulness of the ejection fraction is limited when the extent of myocardial ischemia or damage, or responses to treatment, are modest.

It seems clear from current evidence that, provided it can be measured reliably, regional myocardial dysfunction is more sensitive than the ejection fraction for assessing ischemic events and responses to therapy. However, such regional analyses are more difficult than assessment of global function, in part because of the normal inhomogeneity of regional wall motion. Moreover, as discussed earlier, regional wall motion can be affected by a number of factors in addition to ischemia or scar. It seems likely that use of regional wall motion analyses for demonstrating changes in myocardial contraction after various forms of treatment for ischemic heart disease, or for detecting mild stress-induced abnormalities in subclinical coronary heart disease, will continue to widen as methods for identifying regional abnormalities during the various phases of contraction and diastole are further developed and the resolution of minimally invasive imaging techniques continues to improve.

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_Circulation_. 1986;74:1186-1190
doi: 10.1161/01.CIR.74.6.1186
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1986 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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