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EDITORIAL REVIEWS

Heterogeneous Fate of the Left Ventricle After Acute Myocardial Infarction*

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What happens to the left ventricle after an acute myocardial infarction? The sequence of events at a microscopic level has been known for some time; these include edema an infiltration of polymorphonuclear leukocytes within several hours. After 24 hours, cellular destruction with accumulation of leukocytes is clearly seen. After several days, removal of necrotic tissue begins, followed by fibroblast infiltration and, by 10 days, the formation of granulation tissue. The necrotic tissue continues to be removed, and by 6 weeks a firm scar has formed. This brief sketch of the major events does not reflect the multiple dynamic changes to the left ventricle that may take place as it seeks to maintain cardiac output.

Global Left Ventricular Function After Myocardial Infarction

Several clinical (1–3) and experimental (4,5) studies have demonstrated that improvement in global left ventricular function is common in the days and weeks after myocardial infarction, suggesting that early functional impairment is disproportionate to the true extent of tissue necrosis and the ultimate loss of left ventricular pump function. Other studies have suggested that improvement in global function is limited to particular patient subgroups. Kupper et al. (6) found that only patients with a pulmonary artery end-diastolic pressure greater than 12 mm Hg during acute infarction had improved left ventricular pump function 4 to 6 weeks after infarction, while Borer et al. (7) found that only patients with a submaximal exercise left ventricular ejection fraction greater than 40% before hospital discharge had improved rest and exercise ejection fractions 6 to 14 months after infarction. Although these observations may be somewhat disparate, it is in fact unclear why patients with either mild or more significant functional impairment in the acute stage should preferentially show improvement over time. Lastly, Reduto et al. (8) were unable to demonstrate improvement in left ventricular performance in humans. It is thus probable that at the level of global left ventricular function, change is heterogeneous. In addition, the determinants of such change have not been completely characterized and may interact in complex ways. An examination of the various factors that may be responsible for global functional improvement or deterioration in the days or weeks after infarction may provide avenues for further investigation.

Limitations of measurements of left ventricular function. To meaningfully assess changes in left ventricular function after infarction, the limitations of standard measurements should be recognized. Although there is a very strong relation between ejection fraction and the histologic extent of fibrotic tissue (9), neither ejection fraction nor any other overall index adequately characterizes performance. The ejection fraction is dependent on regional contractility as well as on loading conditions (10). Contractile state may vary with hormonal and metabolic factors and, although measures of contractile state such as the end-systolic pressure-volume index are more independent of loading (11), their use may be criticized in the regionally asynergic ventricle because there is no one contractile state to characterize the entire left ventricle (10). Thus, abnormalities in regional function may not be adequately accounted for by global indexes of function, although there is a general correlation (12). Studies of left ventricular performance must be interpreted regionally as well as globally, with consideration of loading and contractile state, to optimize a full understanding of function after infarction.

Factors Affecting Left Ventricular Function After Infarction (Table 1)

Role of spontaneous reperfusion and collateral flow. In the setting of acute ischemia the subendocardium will undergo infarction sooner than the subepicardium (13,14).

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Table 1. Factors Affecting Left Ventricular Function After Infarction

Improved global function
1) Improved function in surviving epicardium
a) Through collaterals
b) Through spontaneous reperfusion
2) Decreased circumferential extent of dysfunction
a) Through tissue salvage at the lateral border
b) By scarring and "shrinkage" of the ischemic zone
3) Increased function ("hyperfunction") in the remote normal zone
a) Increased contractility
b) Variation in loading
4) Resolution of "ischemia at a distance"
5) Decreased compliance as the ischemic zone scars
a) Decreased paradoxic motion
b) Increased passive tethering to the normal tissue
6) Beneficial change in loading or metabolic factors
Decreased global function
1) Loss of epicardial function
a) With further tissue necrosis
b) Tethering to the subendocardium
2) Ischemia at a distance
3) Infarct expansion
4) Deleterious change in loading or metabolic factors

Thus, with spontaneous or therapeutic reperfusion or collateral flow the subepicardium may be partially or totally spared. The tissue in this epicardial "border zone" would fit the situation termed "stunned myocardium" by Braunwald and Kloner (15). There may then be partial return of function or at least less paradoxic motion even in the center of the ischemic zone (16,17). Conversely, further loss of tissue with epicardial extension or "tethering" of the epicardium to the subendocardium or both, with restriction of subepicardial function (18) may result in subsequent decreased function in the ischemic zone. There is evidence that collateral flow will decrease the transmural extent of and may even prevent acute infarction (19–22), and there is also experimental evidence that collateral flow will shift to a surviving epicardial rim over 24 hours after infarction (23). That reperfusion within several hours limits infarct size, at least in certain subgroups, is established. The role of spontaneous reperfusion is somewhat more uncertain. That spontaneous partial reperfusion occurs, perhaps in as many as a third of patients by 1 day, is clear (24).Rentrop et al. (25) showed that patients with spontaneous recanalization at a chronic stage of infarction have little change in ejection fraction from the acute to the chronic stage, whereas patients without recanalization have a decrease in ejection fraction. There was evidence in that study of a larger infarct initially in the group with permanent occlusion. Thus, both collateral flow and spontaneous reperfusion may result in infarcts with a lesser transmural extent. That patients in these groups are more likely to have, in addition to the initial sparing of the epicardium, spontaneous improvement or no deterioration seems probable because subendocardial infarcts are less apt to undergo expansion and aneurysm formation. If the infact is ultimately affected at least in its epicardial extent by "spontaneous" reperfusion or collateral flow, efforts to improve collateral flow and, more directly, to augment reperfusion could be useful.

Role of variation in loading. In addition, the influence of loading on ultimate infarct extent is uncertain. While decreasing left ventricular pressure will reduce the pressure at the collateral head, it may have less effect on collateral flow because a lower intraventricular pressure will lower intramyocardial resistance to collateral flow. Of potential importance, by reducing wall tension in the infarct zone, a decreased load may thereby decrease paradoxic bulging and infarct expansion. The functional loss of a surviving epicardial rim could also be prevented by reducing myocardial oxygen demand. If this rim then becomes more functional, what appears to be "shrinking" could result.

Tissue salvage in border zone. Assessment of the lateral or circumferential border zone poses a unique problem. Recent studies (26–28) have suggested that the lateral border for function and blood flow is an admixture of normal and ischemic tissue with a remarkably discrete interface between the two, perhaps with dysfunction extending into the normally perfused zone (29). Echocardiographic data (30) have suggested that there may actually be return of segment function at the lateral border in dogs after infarction, although there is a changing anatomic reference base as the infarcted area contracts with scar formation (31). Thus, improvement in function at the lateral border noted by any technique that does not necessarily image the same tissue in any one location over time may reflect the abnormal area being a smaller part of the left ventricle. Thus, apparent improvement in function at the lateral border may simply indicate return of function to normal tissue or be an artifact of imaging as the infaracted area scars. However, the possibility that the infarct is susceptible to "shrinkage" at its lateral borders requires further careful evaluation. It is entirely possible that the "geometry" of the normal and abnormal tissue admixture or the amount of distribution of normally perfused myocardium in this zone, or both, is an important determinant of the outcome of this zone.

Increased function in remote, uninfarcted myocardium. Several studies (32–34) in anesthetized animals have suggested that variations in loading could account for increased function in the remote myocardium after infarction. However, because anesthesia may depress autonomic responses, these studies cannot easily be extended to conscious humans. During the healing phase of myocardial infarction several mechanisms for increased function of noninfarcted myocardium have been postulated. Hood (35) suggested either increased contractility of the noninfarcted myocardium or the rapid development of myocardial cell

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hypertrophy. Although rapid myocardial hypertrophy is an attractive hypothesis, Sasayama et al. (36) were unable to demonstrate increased muscle mass in the nonischemic zone over a 3 week period, although it was noted in one dog studied over a longer time interval. Recent biochemical evidence for cellular hypertrophy has been presented (37). Thus, while the noninfarct zone might develop increased function, separating this effect from loading variations may be difficult.

Ischemia at a distance. The concept that an infarct in one vascular zone may adversely affect another zone was first postulated by Blumgart et al. (38) and reintroduced by Schuster and Bulkley (39). Recent studies (40–42) have shown that the interactions between vascular zones can be quite complex, with occlusion in one zone leading to ischemia in the other. These studies highlight the complex series of pathophysiologic events that may occur after infarction. Clearly, resolution of "ischemia at a distance" may result in improved function, whereas the development of or worsening of ischemia at a distance may adversely effect function. It will be important to determine how best to recognize ischemia at a distance using indexes in addition to postinfarction angina or a positive stress test, or both. Less clear is the possible relation between the fate of the infarct zone and that of the noninfarct zone. If "ischemia at a distance" or, conversely, "hyperfunction" affects ultimate infarct size, methods to decrease ischemia, augment comtraction or even stimulate hypertrophy should be explored early during infarction.

Changes in myocardial compliance as ischemic zone scars. Such changes over time after an infarction may explain improvement in function (43). Initially the length of the ischemic segment becomes greater at all levels of tension (a process called "creep" [44]). However, the relation between length of the ischemic segment and transmural pressure (or tension) is exponential rather than linear (45,46), so that compliance (change in length/change in tension) increases only at lower tension (46). If ischemic segment length is plotted against tension, this would appear as a shift to the right of the tension-length loop (46,47). Decreased compliance, or at least a shift to the left of the loop with scar formation over a period of weeks could account for less paradoxic bulging of the ischemic segment and, thus, improved left ventricular function (16,43). However, the issue of improvement in function due to decreased compliance of the ischemic zone over time may be complicated by hemodynamic variation because the amount of bulge may vary with loading state due to the exponential nature of the tension-length curve (46). In addition, scar formation alone may increase the ejection fraction if the ischemic zone becomes a smaller part of the left ventricle (16).

Infarct expansion. Infarcted areas, however, may also expand to form an aneurysm, that would lead to decreased global ejection fraction (48,49). If the infarcted zone expands, global function could worsen even if there was decreased compliance of the scar itself. Infarct expansion has been associated with transmurality of infarction, anterior infarction and infarct size (50). The influence of loading on expansion is much less certain. As noted, decreased load may decrease the transmural extent of the infarct and thereby decrease the potential for infarct expansion. Decreased load may also lessen the potential for expansion by decreasing the tension and stretch on the myocardium directly. How best to set load to prevent expansion is, however, conjectural and careful study is warranted.

Conclusion. Thus, it is not currently possible to reliably predict either how left ventricular function will change after acute infarction or which of many factors is of greatest importance. The interaction of these variables is also unclear and, furthermore, still other factors such as the location and size of the infarct (51), the presence of previous scar, left ventricular hypertrophy, the age of the patient and the presence of other disease processes may play a role. It is not surprising then that the observed temporal changes have been heterogeneous. Whether measures can be taken to preserve function, *in addition* to limiting infarct size in the acute stage with reperfusion, and in which patients, this would be possible, is a matter of speculation deserving increased study. Given the tremendous importance of preserving left ventricular function after myocardial infarction, further characterization of these issues is essential.

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