Remodeling and recovery following myocardial infarction

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Following a myocardial infarction (MI), changes in the size and shape of the ventricle occur almost immediately, as the region of myocardium supplied by the occluded vessel, no longer able to contract normally, becomes subjected to the forces generated by the remaining viable myocardium. These early morphologic changes in the infarcted heart are reversible, and the myocardium remains relatively plastic during this initial period following coronary occlusion. Similar temporary conformational changes can be seen during inflation of an angioplasty balloon. Whether these changes become permanent and progressive, or whether the myocardium recovers is dependent on a number of factors, including the promptness of reperfusion therapy, the size of the infarct, and the post-infarct therapy offered. If reperfusion of the affected region does not occur, or occurs too late, there will be long-term changes in the size, shape and function of the heart. This latter process, typically referred to as post-infarction ventricular remodeling, accompanies the loss of contractile function[1,2].

The extent of contractile loss, and the extent of ventricular remodeling, following infarction is directly related to the degree of myocardial necrosis[3,4]. Short of preventing the initial infarct, the best way to prevent ventricular remodeling is to decrease the overall infarct burden and reduce the extent of irreversible myocardial damage with prompt reperfusion therapy[5,6]. Enlargement following infarction likely occurs as an adaptation to the loss of stroke volume secondary to the loss of contractile function. Indeed, the increase in stroke volume observed in the weeks after infarction directly correlates with the extent of enlargement[7]. Nevertheless, ventricular dilation following MI has been associated with increased risk of death and other adverse events[8,9]. Whether this increased risk is secondary to the ventricular remodeling or to the increased infarct size associated with remodeling remains unclear.

Remodeling is not inevitable following infarction, and the aggressive approaches to the acute coronary syndromes that have become the standard of cardiac care in the past decade have led to the emergence of a relatively new phenomenon in a large number of patients – recovery of ventricular function[10]. The incidence and extent of post-MI recovery is probably greater than previously appreciated. In a study of 286 patients following Q-wave anterior MI[11], 24% of patients demonstrated complete recovery of ventricular function 2 weeks post-MI, as evidenced by ejection fraction returning to the normal range and absence of regional wall motion abnormalities[10]. The likelihood of recovery, like remodeling, was dependent on the extent of the initial myocardial insult and was inversely related to measures of infarct size.

Recovery and remodeling are interrelated but independent phenomena. While the extent of remodeling and recovery appear to be inversely related in general, it is not uncommon for patients to demonstrate both remodeling and recovery of function. In the HEART study, 32% of patients demonstrated ventricular enlargement despite significant recovery of ventricular function[10]. This paradoxical *dissociation* between remodeling and function is not surprising in light of the fact that remodeling itself is an adaptation to the loss of stroke volume, and that restoration of stroke volume and even improvement in ejection fraction can occur in association with, and perhaps due to, ventricular dilation.

Predictors of remodeling and recovery

How can we predict which patients will recover function and which patients will remodel following MI? Since both recovery and remodeling are related to infarct size, any reliable estimator of the extent of myocardial necrosis will predict the likelihood of both remodeling and recovery[4]. Echocardiographic estimates of infarct size have been shown to predict remodeling and recovery[10,12]. However, it is important to recognize that estimates of infarct size based on imaging techniques that assess the degree of ventricular dysfunction, such as echocardiography, may, in the early post-MI period, overestimate the extent of myocardial necrosis. This is especially true in the setting of reperfusion therapy in which much of the dysfunctional region of myocardium may ultimately recover function. In HEART, 24% of patients who had akinetic or dyskinetic myocardial regions on the first day following infarction ultimately demonstrated complete recovery function by day 14. The degree of dysfunction that occurs early after infarction must not be interpreted as an indicator of the extent of myocardial necrosis or of the extent of future myocardial dysfunction. This reversible myocardial dysfunction is most likely due to myocardial stunning – dysfunction in the setting of normal perfusion – that appears to result from the initial insult[13,14]. Standard imaging techniques may not distinguish between stunned myocardium and permanent myocardial dysfunction in the early stages following infarction. Newer imaging methods such as magnetic resonance imaging may be capable of identifying the extent of myocardial necrosis early following infarct. The presence of delayed hyper-enhancement on magnetic resonance imaging has been proposed as a reliable indicator of true infarction[15], although recent studies have suggested that even this measure may not accurately assess the extent of permanent myocardial necrosis when used in the early infarct period[16].

In contrast, biochemical markers of myocardial necrosis correlate well with the degree of ultimate remodeling or recovery of function, even in the setting of reperfusion therapy[17]. Peak creatine kinase has been related to the degree of myocardial necrosis in a number of experimental and human studies[3]. In HEART, each 100 unit increase in creatine kinase levels was associated with a 4.3% decreased odds of full recovery of function[10].

Because recovery of function following infarction begins to occur soon after reperfusion, assessment of ventricular function within a few days following infarction, perhaps even prior to hospital discharge, may represent a reasonable alternative to early evaluation. Ventricular function 1 or 2 weeks following infarction will correlate better with eventual ventricular function[10]. Electrocardiography may also be useful in predicting the degree of eventual recovery of function and remodeling. In a recent study, Manes et al.[18] showed that the extent of ST-segment elevation 1 week following infarction was a powerful and independent predictor of recovery of function and ventricular remodeling.

Modifiers of remodeling and recovery

While the most important modifier of ventricular remodeling is the extent of myocardial necrosis, a number of other preexisting factors may influence ventricular remodeling following MI. Patients who have left ventricular hypertrophy, or a history of hypertension, prior to MI appeared to be at increased risk of ventricular remodeling[19]. Patients with left ventricular hypertrophy may be at greater risk for subendocardial ischemia. Alternatively, the fibrosis that accompanies left ventricular hypertrophy might alter ventricular compliance, which in turn may predispose towards increased left ventricular remodeling.

Ischemic preconditioning that occurs prior to the infarct may also modify the extent of ventricular remodeling following infarction. Patients who experience angina prior to MI have improved in-hospital outcome, and smaller infarcts[20]. Likewise, patients with angina prior to infarction appear to be at decreased risk for left ventricular remodeling[21], a finding that appears to be primarily due to reduced overall infarct size. The extent to which this finding is due to recruitment of collateral's prior to infarction or true ischemic preconditioning at the cellular level remains unknown.

Diabetes may also modify the risk of subsequent left ventricular remodeling following MI[22]. While diabetics develop heart failure following infarction twice as frequently as patients without diabetes, even with similarly sized infarcts, the diabetic heart appears to remodel less than the nondiabetic heart. While remodeling appears to be an intermediate in the development of heart failure in nondiabetics, this relationship is much less clear in the diabetic. It is possible that the increased risk of heart failure in the diabetic patient may occur, in part, due to the inability of the diabetic heart to remodel. The interaction between diabetes and remodeling underscores the complexity of the relationship between infarct size, remodeling and development of heart failure following infarction.

New therapeutic approaches to remodeling/recovery

While remodeling is not inevitable, at least 30 to 50% of patients will show some degree of left ventricular dilation even following a small MI. A variety of approaches have been considered to limit directly the extent of post-MI remodeling. While pharmacologic therapy with ACE-inhibition attenuates ventricular remodeling, the extent of this attenuation is relatively small[9]. In the SAVE trial, ventricular sizes were decreased by only 3% in patients who received captopril compared

with placebo. It is now clear that the mortality benefit seen with ACE-inhibitors following MI is due not primarily to attenuation of remodeling, but to a variety of other factors, including reduction of new vascular events[23]. The utility of other inhibitors of the renin-angiotensin system in attenuation of post-infarct remodeling is currently being investigated, as are other pharmacologic approaches. A number of experimental studies in animals have shown that matrix metalloproteinase inhibition may profoundly attenuate the remodeling process[24,25]. These experiments not only demonstrate an important role of the matrix metalloproteinases in the remodeling process, but also suggest a potential novel pharmacologic approach to post-MI therapy.

In addition to pharmacologic therapies, physical or conformational therapies have emerged which might also affect the remodeling process. A surgical approach to remodeling will be evaluated in a National Institute of Health-sponsored trial in which patients will be randomized to a ventriculotomy procedure aimed at optimizing ventricular mechanics by decreasing the size of the ventricle. Another approach utilizes a restraining net that fits over the left ventricle like a stocking and physically inhibits the ventricle from expanding[26]. In considering approaches that limit ventricular dilation in the early post-MI period, it will be important to be vigilant about the possibility that inhibiting the adaptive process may increase the short-term risk of developing heart failure.

Finally, novel cell-therapy approaches to ventricular remodeling are currently being investigated in clinical trials in United States and Europe[27,28]. One such trial, MAGIC, will assess whether autologous skeletal myoblasts grown in culture and implanted into scarred myocardium will improve ventricular function and reduce ventricular remodeling. Other approaches, utilizing bone marrow or cardiac stem cells are also being considered.

Conclusions

Despite the enormous advances in the care of patients with MI over the past decade, most survivors of infarction are left with some degree of myocardial dysfunction. The extent of this dysfunction, and the risk that these patients will develop congestive heart failure subsequently, is dependent on the degree of myocardial damage, and the therapies offered in the immediate post-infarct period. Ventricular remodeling, once thought to be inevitable following infarction, is directly related to the extent of myocardial damage. While ventricular recovery is becoming much more common in the setting of prompt reperfusion therapy, remodeling occurs even in patients with substantial recovery of ventricular function. Recovery and remodeling are related but independent phenomena, and while remodeling is clearly associated with adverse outcome following infarction, we must be cognizant of the risk of interfering with this adaptive mechanism. Finally, while aggressive peri-infarct therapies have led to substantive recovery of function and have minimized ventricular remodeling following infarction, few effective therapies have emerged for patients who have suffered an MI in the past, and are left with enlarged and dysfunctional ventricles. For these patients, therapies that improve the contractile function of the ventricle or optimize the mechanical properties of the ventricle may represent the best long-term hope.

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