Cardiac Regeneration

Materials Can Improve the Passive Properties of Myocardium, but Cell Therapy Must Do More

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ellular therapy to replace lost myocardial mass with new, contractile myocardium has the potential to revolutionize the treatment of myocardial infarction and heart failure. Studies have shown small but consistent improvements in mechanical function, largely independent of the cell type chosen. The reasons for this lack of specificity are presently unknown. In the current issue of Circulation, Wall et al1 present computational models that suggest that the injection of passive materials alone may improve ejection fraction and reduce wall stress in the ventricle. The present study raises the possibility that some cellular therapies contribute to increased heart function purely through a passive mechanism rather than through active contraction associated with the addition of new myocytes. Because materials lack many of the uncertainties associated with cellular therapies (eg, mode of delivery, homing, immune rejection, arrhythmias), and because they can be engineered to have a number of inherent advantages (eg, uniformity, reliability, greater safety, reduced cost), one conclusion of the current finding is that biomaterials alone may be important for future cardiac therapy.

Given the results of this study by Wall and colleagues,1 it is also clear that passive contribution must be separated from active contribution to evaluate the efficacy of any cell therapy approach. Passive contribution can result from replacing a stiff material, such as an infarct, with a more compliant material. Completely replacing the infarcted tissue with a compliant scaffold can accomplish this task. Matsubayashi and colleagues2 demonstrated that passive properties can improve global heart function by seeding a synthetic scaffold with smooth-muscle cells before implantation in a full-thickness ventricular defect model. The smooth-muscle cells, which are unlikely to contribute contractile function, increased elastic tissue formation and likely increased the compliance of the scaffold. Skeletal myoblasts, which have been employed in clinical trials, are also unlikely to contract in synchrony with the normal myocardium. These cells do not make connexins, the building blocks of gap junctions, and are therefore unlikely to make electrical connections with the native myocardium.3 Several reports, however, have documented improved mechanical function with these cells.4 Such improvement is likely the result of improved passive function and not the addition of contractile mass. The present study suggests that this improvement could also result from the addition of an inert biomaterial to the infarcted region. Whereas skeletal myoblasts leave the heart susceptible to arrhythmias,5 a biomaterial can be chosen to provide electrical stability while adding passive mechanical function to the heart.

Ultimately, the goal of cell therapy extends beyond the improved passive function of biomaterials. It must also produce active mechanical function, which can only be accomplished by increasing the number of contractile cells (Figure). This can be achieved in 2 fundamental ways: (1) endogenously, by enhancing the likelihood of myocyte cell division or stem cells differentiating into myocytes; or (2) exogenously, by delivering cells that can actively contract and integrate into the cardiac syncytium.

In terms of endogenous repair, the adult mammalian heart has been perceived as a postmitotic organ with little ability to regenerate itself once damaged. Recently, others have questioned this view and have suggested a new paradigm in which the mammalian heart has the inherent ability to continuously replace its parenchymal cells.6 Mature myocyte proliferation is possible in amphibians,7 and recent work has shown that the zebrafish has the ability to regenerate as much as 20% of its myocardium in response to injury.8 It has been suggested that release of paracrine factors from endogenous or delivered stem cells simulates the signaling environment of the fetal mammalian heart and may enhance the ability of native myocytes to divide.9 Endogenous cardiac stem cells (c-kit+, islet1+ and sca1+) that can be isolated from the adult mammalian heart can be made to proliferate in vitro. Many research groups believe that an understanding of the biology of these stem cells can enhance their proliferation in response to cellular injury in vivo.

If it is necessary to generate active function in the injured heart from exogenous cells, then the likely candidates include embryonic stem cells, mesenchymal stem cells, and cardiac stem cells. Each of these cell types can be made to differentiate in vitro by physical or chemical manipulations to express cardiac proteins and to generate cardiac electrical activity, and each of these cell types is capable of active contraction.10–12

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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There is more to producing useful mechanical work in the heart than just having contractile cells, however. These cells must (1) be excited in synchrony with the spared myocardium, (2) have longitudinal shortening capabilities, (3) line up with the appropriate geometry, and (4) achieve this mechanical function without electrical consequences (ie, arrhythmias). To be excited in synchrony with the neighboring myocardium requires integration via gap junctions. All 3 proposed cell types make connexins and can form functional gap junctions. To have longitudinal shortening capabilities, sarcomeres must be present in the delivered cells. Although sarcomeric actinin is expressed by each of these cell types in vivo, its organization into functional sarcomeres, with the exception of embryonic stem cells, remains elusive. In addition, evidence is lacking for a normal geometry in which the delivered cells are oriented in a manner consistent with the native myocardium. Perhaps most disturbing is the question of electrical concordance. Embryonic cells give rise to a heterogeneous population of myocytes that lead to arrhythmogenic consequences, which are likely attributable to electrical dispersion of repolarization.

Assuming that these very significant remaining problems of cell therapy are overcome how does one determine whether a cellular therapy improves active mechanical function? Generally, global heart function cannot distinguish contributions from new myocytes compared with the salvaged myocytes. This is of particular interest in stem cell therapy because these cells are likely to play a role in angiogenesis. As Wall and colleagues demonstrate, passive function can alter measurements such as ejection fraction and end diastolic volume. Animal studies have also correlated increased global function with increased compliance. Regional function measurements can be more specific if the region of interest can be clearly delineated. This is not always possible, especially in the case of intravenous injection of cells. To initially determine whether a cell therapy is actively contributing to ventricular contraction, a clearly defined region in which the cells are delivered should be studied. One way to accomplish this is by delivering cells on a scaffold to replace a full-thickness ventricular defect. This allows for analysis in a well-defined region that initially contains only the scaffold, the delivered material, and any tissue trapped from the neighboring borders. In such circumstances, improvements in regional measurements such as regional stroke work, systolic shortening, or systolic wall thickening can be used to determine whether active contraction has been increased in the area of interest. To confirm whether the region is contracting in synchrony with the rest of the ventricle, systole and diastole must be clearly defined to ensure that the material is not passively elongating with increased intracavitary pressure. After functional measurements, the tissue can be easily isolated, and immunohistochemistry can be used to distinguish delivered cells or proliferating native cells from mature myocytes that may have migrated in from neighboring borders.

Once it has been determined whether a given cell type can produce active contraction when administered to the heart, further experiments should be undertaken to determine whether these cell types can restore contractile function in more clinically relevant models. Some cell therapies such as mesenchymal or hematopoietic stem cells contribute to angiogenesis and may produce paracrine factors that lead to increased native cell survival. Although this mechanism may lead to a reduction of infarcted myocardial mass, attenuating the reduction in regional mechanical function, new myocytes are not produced, and thus angiogenesis by itself cannot restore active contraction to the ventricle.

The significant contributions of increased passive function alone should not be dismissed. An increase in global function, whether passive or active, is still likely to be beneficial to patients. In addition, the data published by Wall and colleagues suggest a relationship between passive function and
decreased ventricular wall stress. Returning wall stress to closer to its normal value may result in restoring mechanotransduction signals to more normal levels. This normalized signaling environment is likely to reduce apoptosis, and it might improve the stress-induced changes to the electrical and mechanical properties of myocytes (eg, restore sarcomere overlap, avoid calcium overload).

Biomaterials also may have a use in a combination treatment with partially differentiated cells. If stem cell differentiation occurs in vivo, normalizing the signaling environment might help encourage differentiation to a phenotypically accurate outcome as opposed to a hypertrophic outcome. Normalizing the signaling environment may also allow para- crine effects of delivered cells to induce myocyte proliferation or cardiac stem cell transdifferentiation. The materials may also allow myocytes teetering on the brink to survive by reducing strain and energy consumption.

Thus, although the future is still bright for cellular therapies designed to restore (or generate) contractile myocardium, any resulting improvements in active function from these therapies must be determined. This information will help optimize cell therapy while minimizing risk and is likely to have a significant clinical impact in the treatment of myocardial infarction. It must be emphasized, however, that the advantage of cellular therapies over a pure biomaterial approach, which is likely to improve the passive function of the ventricle, must be in the ability of such therapies to regenerate active mechanical function.

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