Hearth failure is a major worldwide health problem that is growing in prevalence despite recent treatment advances. Patients with heart failure ultimately die from either pump failure or cardiac arrhythmia, and there is a link between the degree of contractile dysfunction and arrhythmic risk. Since the 1960s, the definitive therapy for heart failure has been cardiac transplantation, but the limited supply of organs has restricted the impact of this therapy. Starting in the mid-1990s, a series of observations has led to the concept that cells might be used to repair myocardial damage. Subsequently, this therapy has shown promise in ischemic and nonischemic forms of myocardial injury.

What Is the Right Cell for the Job?
The increased availability of cells as compared with organs has driven an exuberant search for the right replacement cells. Nevertheless, after intense study, there is no obvious frontrunner. The concept driving the cell selection process has been the need for a sufficient number of immune compatible, contractile cells. Proposed cell sources have included skeletal myoblasts, bone marrow–derived progenitor cells, and embryonic stem cells. These 3 cell types have been shown to improve myocardial function in animal models, and the first 2 have shown promise in human clinical trials. Generally, the effects of these 2 cell types on myocardial function have been similar.

Cell Replacement Therapy and Arrhythmogenesis
If they are to fulfill their promise as replacement myocytes, it is important that the implanted cells functionally couple with the endogenous myocytes to permit coordinated excitation contraction coupling. If replacement cells integrated heterogeneously, have abnormal cellular electrophysiology, or show spontaneous activity, they could act as a source of arrhythmias that might offset any benefits related to contractile function improvement. Arrhythmic risk potentially represents a fundamental limitation of cell replacement therapy.

There are several lines of evidence suggesting that cell replacement therapy may be accompanied by an increased arrhythmic risk. Based on the cellular electrophysiology of derived myocytes, Zhang et al proposed that embryonic stem cells may be arrhythmogenic when used as replacement therapy because they differentiated heterogeneously, were spontaneously active, had abnormal action potentials, and showed a high proclivity toward triggered arrhythmias. The possibility of arrhythmic risk is supported by observations of: (1) arrhythmias in human stem cells; (2) abnormal behavior of derived cardiac myocytes in syncytia; (3) slow syncytial conduction velocity of human- or mouse-derived cardiomyocytes; and (4) increased incidence of arrhythmias in cell-treated animal models.

Arrhythmic risk has also been observed in human clinical trials. Although the baseline arrhythmic risk in these patients is high, potentially obscuring any effect of replacement cells, trials involving skeletal myoblasts show increased risk of malignant ventricular arrhythmias. The risk seems highest early after transplantation. Less arrhythmic risk has been seen in trials involving bone marrow–derived cells.

In this issue of Circulation Research, Marbán and colleagues offer important new observations regarding the arrhythmic risk associated with skeletal myoblast transplantation. These observations likely have profound implications for the future of myocardial cell replacement. Using a unique, state-of-the-art optical mapping system, the group examined the electrophysiological effects of skeletal myoblast integration within a 2D array of cardiac myocytes. They demonstrated that: (1) skeletal myoblasts do not communicate electrically with cardiac myocytes; (2) the presence of skeletal myoblasts increases the inducibility of reentrant arrhythmia in these 2D cultures; and (3) induced expression of connexin (Cx) 43 in the skeletal myoblast can reduce arrhythmic risk. Experiments with HeLa cells, which do not express the major cardiac connexin (Cx43), suggest that any electrically isolated cell introduced into the myocardium may increase arrhythmic risk.

Future Directions for Prevention of Arrhythmias During Cell Replacement Therapy
Does this mean that we abandon skeletal myoblast cell replacement therapy because of the arrhythmic risk, use only cells engineered to express cardiac-compatible connexins, or place an implantable defibrillator in every patient prophylactically? One implication of these results from Abraham et al is that skeletal myoblasts are unlikely to improve function by forming a contractile syncytium with the remaining myocytes. The alteration of the cardiac myocyte action poten-
trials observed in the presence of skeletal myoblasts hints that the effect of the myoblasts may involve paracrine factors. Perhaps efforts could focus on defining the factors involved, allowing omission of cells altogether. As Abraham et al rightly point out, the alternative they suggested to use skeletal myoblasts genetically altered to express Cx43 will need further exploration. In addition to the unknown consequences of electrically coupling cells with different action potential properties, connexin expression may alter the differentiation process.25,26 Nevertheless, the combination of gene- and cell-based therapies looks promising.27

It will be interesting to test the effect of bone marrow–derived progenitor cells in the system used by Abraham et al. These cells have shown less arrhythmic risk in clinical trials. Because bone marrow–derived cells integrate in the infarct zone, this suggests that arrhythmic risk is not just a function of cell integration. Could the reduced risk in these cells be attributable to enhanced connexin expression or limited durability of engraftment? It has been suggested that the main effect of these cells is also paracrine. Alternatively, it has been proposed that these cells contribute to myocardial angiogenesis.28 Again, enhancement of these effects may be a way to achieve myocardial repair with reduced arrhythmic risk.

Another way to avoid arrhythmias is by returning to the original concept underlying cell replacement therapy, to regenerate fully the myocardium. Given the limited differentiation potential of bone marrow–derived progenitors and the electrical isolation of skeletal myoblasts, embryonic stem cell–derived cardiac myocytes might likely be the most promising cell source to achieve this goal.29 Still, it remains to be seen whether directed differentiation can be refined to provide enough cells with adult electrophysiological characteristics and whether these cells can be introduced in a sufficiently homogeneous manner. The delivery of cells by tissue-engineered approaches looks promising to address the latter issue.30,31

Laboratory studies are always hard to translate to the clinic. These data strengthen the idea that patients should be protected with implantable defibrillator implantation in any future trials involving genetically unaltered skeletal myoblasts. Future larger controlled trials will help correct for baseline arrhythmic risk and identify risk attributable to cell replacement. One important consideration is that arrhythmic risk and myocardial function are linked. Because of this, it will be necessary to correct for any offsetting contractile improvement as a result of cell replacement to accurately assess arrhythmic risk. The precise mechanism whereby contractile function affects arrhythmic risk remains undefined, however. Cell replacement therapy might improve function to such an extent that any induced arrhythmic risk will prove clinically unimportant. Nevertheless, the manuscript by Abraham et al importantly focuses our thinking on both the benefits and risks associated with cell replacement therapy and/or possible corrective strategies.

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