Is stem cell therapy proarrhythmic?

Stem Cell Therapy Is Proarrhythmic

Ester Macia, MD; Penelope A. Boyden, PhD

Stem cell therapy appears to be a promising modality for myocardial repair of both hearts that are post myocardial infarction (MI) and those with other forms of structural cardiac disease (eg, congestive heart failure). In fact, recent experimental and clinical work has suggested that stem cell therapy contributes to cardiac regeneration. Unfortunately at this time, we contend that stem cell therapy is proarrhythmic. Accordingly, in this review we will approach this subject by restating this potential in the framework of traditional mechanisms of arrhythmias (automaticity and reentry). Lastly, we will address recent clinical work with stem cells, commenting on the proarrhythmic outcomes.

The Players

Before assessing the proarrhythmic potential of stem cells, we think it important to first address the nature of the players. After all, these “players” are the cells selected for use in trials.

Embryonic Stem Cells

Obviously, because this cell population has the capacity to develop into differentiated cardiac cells, these cells have been phenotyped in terms of ionic current makeup, intracellular Ca\(^{2+}\) handling, and connexin expression.\(^1\) Embryonic Stem Cells (ESCs) have been shown to have at least fast sodium current, L-type Ca\(^{2+}\) current, \(I_f\), \(I_{Kt}\),\(^2,3\) and immature excitation-contraction (EC) coupling.\(^4\) Thus, implanting them into damaged myocardium would mean implanting areas of additional excitable cells that presumably would form gap junctions not only with fellow ESCs but also with surviving myocytes of the damaged substrate. Evidence for resident cardiac stem cells\(^5,6\) has surfaced, and these excitable cells could show promise for use in stem cell therapy. For example, c-Kit\(^+\) cardiac-derived cells isolated from a normal rat heart when delivered via the aortic root seem to invade the infarcted myocardium and regenerate muscle to improve left ventricular (LV) function.\(^7\) Unfortunately, no mention was made of rhythm instability (or stability) of the injected hearts in this study. Some have suggested that Kit\(^+\)-expressing cells are actually not heart cells but bone marrow cells (BMCs) out of place. Importantly, human ESCs (hESCs) can be cultured as 3-dimensional differentiating cell aggregates called embryoid bodies (Figure 1).\(^8\)

Skeletal Myoblasts

Perhaps one of the first classes of cell types used for replacement therapy was the autologous skeletal myoblast (SkM)–derived cell. Although these cells are able to contract and show some excitability, the phenotype of EC coupling in these cells differs completely from that of normal cardiac cells.\(^9\) Importantly, undifferentiated myoblasts can express connexins and form gap junctions. However, after time in the new substrate, the myoblast tends to lose this capacity.\(^10\) Thus, myoblasts may survive where replacement tissue is needed but could then lack both mechanical synchronization and electrical integration–forming islands of tissue.

BMCs and Mesenchymal Stem Cells

Various types of BMCs can differentiate into important stem cells. One population is the mesenchymal stem cell (MSC). These cells can be differentiated into neuronal type cells and...
Factors That Would Lead to Enhanced Automaticity

If stem cells are implanted into myocardium for replacement or to become the pacemaker of the heart, they should functionally couple with remaining myocytes of the substrate to allow for a more homogeneous myocardium. As we know from numerous years of study of the pacemaker cells of the normal sinus node, if implanted cells have intrinsic abnormal electrophysiology or show spontaneous electrical activity (or both), they can become the source of electrical excitation. Cell electrophysiology studies of ESCs have shown slow upstroke action potentials and triggered activity (Figure 1).8,17-19 This inherent pacemaking activity is thought to be due to high input resistance and high sodium current density.3 In culture studies of both neonatal rat and hESCs as the implanted cells, intrinsic pacemaker activity of the implanted cells cannot overcome normal rhythm because they were only located in a small area (eg, 200 by 20 μm).8 In contrast, larger denser areas of cell implantation can cause pacemaker potentials derived from the hESCs, a strategy often used for biopacemaker treatment of bradyarrhythmias.20-22 Interestingly, in a rather exhaustive study using mouse hearts after MI,23 no mention was made of enhanced, spontaneous, automatic rhythms after in vivo engraftment of ESCs, fibroblasts, or SkMs alone. Perhaps these events may have occurred but were not reported. Only inducible rhythms were reported.

Experimental work with SkMs has reported that grafted myoblasts differentiate into peculiar hyperexcitable cells24 with EC coupling independent of the host cardiac cells. Experimental work with inexcitable MSCs has not led to increased automaticity of implanted cultures but did alter conduction.25 However, if MSCs are made to express hyperpolarization-activated cyclic nucleotide–gated (HCN) channels and show pacemaker function, then good escape rhythms exist in the injected hearts.21,22 When transplanted in AV-blocked animals, hESCs also show the potential for pacemaker activity. Interestingly, these experiments required only hundreds of hESCs for an effect.20 Thus, depending on your outlook, implanted cells can show enhanced automaticity and be arrhythmic or can show enhanced automaticity and be antiarrhythmic.

Factors That Could Lead to Reentry

Stem cells could lead to an increase in the area of conduction block in the damaged heart if and only if the stem cells do not electrically couple to surviving myocytes. So, does evidence exist that stem cells electrically couple to myocytes?

Most in vitro experimental work has been done using neonatal myocytes and implanted stem cells. These cells couple differently than the typical adult cell surviving in a host myocardium. In fact, hESC cells did show positive staining for Cx43 but no functional electrical coupling (note here: it was presumed on the basis of “normal mechanical contractions”).8 Furthermore, when bone marrow–derived cells were efficiently grafted into the ischemic region of the adult heart, they were located in clusters within the infarct scar or border zone but showed no electronically evoked Ca2+ transients.16 Staining for gap junction proteins was absent in these studies.

The efficacy and arrhythmia occurrence of stem cell therapy depends on the cell number as well as on the delivery route of the cells. An intramyocardial route tends to cause cell clusters embedded in nonmyocardium10,24 leading to heterogeneity in conduction and perhaps conduction block. The intracoronary route could provide more homogeneous delivery, but hopefully cells will aggregate in sufficient quantity at the correct anatomical locale. In fact, in rat hearts after MI,26 intramyocardial BMC injections, although improving cardiac function, increased the risk of ventricular premature complexes for 28 days post injection. When the intracoronary route was used in these studies, ventricular premature complex occurrence was markedly decreased. Importantly, these animal studies were done in the absence of antiarrhythmic drugs, which is often not the case for patients in clinical trials (see below).

Stem cells could promote slowed conduction between substrate myocytes. What is the nature of propagation between “normal” myocardium and stem cells if they are coupled? Is there I_{Na}, and gap conductance?

Theoretical Considerations

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Stem cells could promote slowed conduction between substrate myocytes. What is the nature of propagation between “normal” myocardium and stem cells if they are coupled? Is there I_{Na}, and gap conductance?
Some implanted cells have intrinsic I_{Na} function (e.g., ESCs^2,3) and when implanted could provide reasonably fast sodium-dependent conduction between host myocardium and stem cell areas. On the other hand, if propagation is only Ca^{2+} dependent (so-called slow-response conduction^27) or purely electronic, it may be that the implanted stem cells would provide areas of slowed conduction, setting the stage for reentry.

Even though experimental work has shown a temporal increase in conduction velocity over a combined culture of human MSCs (hMSCs) and neonatal host cells,^28 the actual values of conduction velocity measured are quite slow, ranging from 4 to 17 cm/sec. Furthermore, a 4-fold difference was still found in conduction velocity between the graft and host sites even at the longest time period after culture (14 days). Presumably, cells under these conditions have reduced and differing resting potentials (MSCs ~40 mV versus host ~67 mV), suggesting that this preparation is potentially arrhythmogenic.

Direct calculation of conduction paths and velocities of excitatory waves over integrated hMSCs with rat cell cultures again suggest that hMSCs, which show Cx43-positive staining, do indeed provide conduction between 2 channels of neonatal cells, therefore relieving conduction block. However, propagation is extremely slow (0.9 cm/s) and perhaps electronic,^29 and the hMSCs in the conducting channel show reduced resting potentials and action potential amplitude. As above, the implanted stem cells seem to provide areas of slowed conduction, setting the stage for reentry. When others have transplanted SkMs into adult canine myocardium with and without MI and then mapped conduction,^30 they have also found clear conduction slowing, particularly in the epicardium of the SkM-transplanted wedge sections.

Is refractoriness or action potential duration dispersion promoted with stem cell replacement? Although repair of conduction between the disparate areas of host myocardium by the implanted stem cells has been emphasized, there has been little appraisal of the changes in refractoriness or action potential duration dispersion of substrate with the grafted cells on board. Experimental work has suggested action potential durations differ considerably between host and graft cells,^28,29 and other important work has shown that the increase in tissue heterogeneities of host/graft (MSCs) cell cultures do not align with altered action potential duration restitution curves but with reduced conduction velocity and easily inducible spiral wave reentry (Figure 2).^25 In these MSC/neonatal cocultures, MSCs expressed Cx43 and were coupled to the host cells. However, in cocultures containing >10% MSCs, transplanted cells became areas of inexcitable sinks and delayed activation and repolarization, which led to a proarrhythmogenic substrate.

**Clinical Experience**

Cell-based therapy for cardiac regeneration has been evaluated in the clinic in 3 distinct clinical scenarios: (1) recent acute MI, (2) chronic myocardial ischemia in no-option revascularization patients, and (3) chronic infarct-related heart failure. Cell types that have been transplanted in these clinical settings include SkMs and BMCs (mononuclear stem cells, hematopoietic stem cells, MSCs, endothelial progenitor cells, and circulating progenitor cells). Two cell delivery methods have been used: intracoronary and intramyocardial injections (transendocardial during cardiac catheterization and transepicardial during open-chest surgery). The quantity of injected cells also varies among studies. Thus, a wide range of clinical situations, cell preparations, routes, and doses employed make it difficult to completely interpret and compare the results from human trials. However, in this next
section we will evaluate the consequences of stem cell transplantation and arrhythmia occurrence.

**Skeletal Myoblasts**

A number of features make myoblasts an attractive cell type for cardiac cell transplantation. They can be obtained in sufficient quantity directly from the patient and are resistant to ischemia, making it possible for them to survive in the low-capillary environment of the infarcted myocardium. SkMs can differentiate into myotubes in vivo but do not integrate with surviving cardiomyocytes. In addition, evidence supporting their effectiveness in improving cardiac function is lacking.31

Several small trials investigating the safety and feasibility of myoblast transplantation in patients with ischemic cardiomyopathy have been published (Table 1).32–41 It is known that patients with LV dysfunction and heart failure after MI have a favorable substrate for ventricular arrhythmias. However, these initial experiences suggested a proarrhythmic effect of SkM-cell therapy. In the first phase I clinical trial with SkMs, Menasché et al reported sustained monomorphic ventricular tachycardia in 4 of 10 patients (1 of them syncopal) early after the operation (11 to 22 days) that was not related to myocardial ischemia.32 The 4 patients had each had an implanted cardioverter-defibrillator (ICD) implanted after the ventricular tachycardia episode. At follow-up visits, 2 of these patients still experienced ventricular arrhythmias despite antiarrhythmic drug therapy with β-blockers and amiodarone. Indeed, because of the major concern about the potential arrhythmogenic effect of the new therapy, amiodarone was prophylactically instituted in the last 3 patients included in this study. Despite this, at a median follow-up of 52 months after prophylactically instituted in the last 3 patients included in this study. Despite this, at a median follow-up of 52 months after transendocardial injection of SkMs for the treatment of ischemic heart failure.34 Subsequently, these same investigators have described an unpublished experience of 2 sudden cardiac deaths and 3 serious ventricular arrhythmias in 8 additional patients.

**Table 1. Arrhythmias After SkMs Transplantation in Nonrandomized Studies**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Design</th>
<th>Cell Route</th>
<th>N</th>
<th>f/u, y</th>
<th>Pre tx AAD/ICD</th>
<th>Rhythm Monitoring</th>
<th>Pts With Arrhythmias at Baseline</th>
<th>Pts With Arrhythmias Post tx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menasché et al32 and Hagège et al33</td>
<td>Previous MI, Adjunct to CABG, EF ≥35%</td>
<td>Epicardial</td>
<td>10</td>
<td>4</td>
<td>BB, 3 amio</td>
<td>Holter at baseline, ICD interrogation every 3 m</td>
<td>No mention</td>
<td>1 NSVT, 4 SVT (50%), 5 ICD implants</td>
</tr>
<tr>
<td>Smits et al34</td>
<td>Previous MI, EF 20–45%</td>
<td>Endocardial</td>
<td>5</td>
<td>0.5</td>
<td>Optimal medical therapy</td>
<td>Holter at baseline, 1, 3, and 6 m</td>
<td>SVT, VF, and syncope excluded</td>
<td>1 NSVT runs (ICD implant), 1 SCD (40%)</td>
</tr>
<tr>
<td>Herreros et al35 and Gavira et al36</td>
<td>Previous MI, Adjunct to CABG, EF &gt;25%</td>
<td>Epicardial</td>
<td>10</td>
<td>1</td>
<td>All amio</td>
<td>In-hospital monitoring Holter at baseline, 40 days, and 3 and 6 m</td>
<td>Malignant arrhythmias exclusion criteria</td>
<td>1 NSVT (10%)</td>
</tr>
<tr>
<td>Pagani et al37</td>
<td>Heart transplantation candidates. Adjunct to LVAD</td>
<td>Epicardial</td>
<td>5</td>
<td>2</td>
<td>2 ICD</td>
<td>Holter at baseline</td>
<td>1 AF, 4 NSVT (3 pts, 60%)</td>
<td>2 AF, 3 VT (4 pts, 80%)</td>
</tr>
<tr>
<td>Dib et al38</td>
<td>Previous MI, Adjunct to CABG, EF &lt;40%</td>
<td>Epicardial</td>
<td>24</td>
<td>2.25</td>
<td>2 ICD</td>
<td>Holter at baseline and 1, 3, 6, 12, and 24 w</td>
<td>4 AF, 2 SVT, 14 NSVT</td>
<td>1 AF, 1 VT, 8 NSVT, 1 ICD activation, 5 ICD implant</td>
</tr>
<tr>
<td>Siminiak et al39</td>
<td>Previous MI, Adjunct to CABG, EF 25%–40%</td>
<td>Epicardial</td>
<td>10</td>
<td>1</td>
<td>8 amio</td>
<td>Holter at 1, 2, 3, and 4 w and at 12 m</td>
<td>No mention</td>
<td>4 SVT</td>
</tr>
<tr>
<td>Siminiak et al40</td>
<td>Previous MI, EF 25–40%</td>
<td>Percut transcoronary-venous</td>
<td>9</td>
<td>0.5</td>
<td>All BB, 8 amio ≥2 ICD</td>
<td>10–16 days of Holter monitoring, Holter every w</td>
<td>No mention</td>
<td>1 VT and ICD intervention. No more SVT in f/u</td>
</tr>
<tr>
<td>Veitman et al41</td>
<td>Previous MI, EF 20%–45%</td>
<td>Endocardial</td>
<td>14 treated, 28 control</td>
<td>4</td>
<td>All BB, ICD: 9 treated, 8 control</td>
<td>ICD monitoring, Holter at end of f/u</td>
<td>No mention</td>
<td>ICD intervention 7 treated and 1 control, 2 ARD treated and 1 control. No difference in NSVT in Holter.</td>
</tr>
</tbody>
</table>

f/u indicates follow-up; EF, ejection fraction; AAD, antiarrhythmic drugs; Pts, patients; tx, transplantation; amio, amiodarone; BB, β-blockers; Holter, 24-hour ECG monitoring; NSVT and SVT, nonsustained and sustained ventricular tachycardia; LVAD, left ventricular assist device; AF, atrial fibrillation; VT, ventricular tachycardia; SCD, sudden cardiac death; VF, ventricular fibrillation; AF, atrial fibrillation; and ARD, arrhythmia-related death.
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In other studies, arrhythmias after myoblast transplantation have been reported. Siminiak et al gave prophylactic amiodarone to prevent ventricular arrhythmias to the last 8 patients included in their study of epicardial SkM transplantation during coronary artery bypass grafting (CABG), after the first 2 had ventricular tachycardias in the early postoperative period.49 Two other studies also included prophylactic amiodarone as a standard pretransplantation therapy.35,40 In fact, in a different study by Siminiak et al, the only patient not receiving amiodarone developed episodes of ventricular tachycardia and experienced 2 interventions from its ICD at day 8 after the procedure.40 This outcome strongly suggests that the proarrhythmic effect of SkM transplantation might be prevented by amiodarone, even though it is not known how amiodarone may exert this effect.

To date, the only placebo-controlled randomized study evaluating the efficacy of SkMs has been the MAGIC (Myoblast Autologous Grafting in Ischemic Cardiomyopathy) II trial. Here, the efficacy of this cell-based therapy in patients with a history of MI, LV dysfunction and indication for coronary surgery was evaluated.31 Investigators tested 2 different doses of transendocardial injected SkMs versus placebo during CABG. An ICD and antiarrhythmic therapy were used in all patients. Even though the patients included in the trial are among those at the highest risk for ventricular arrhythmias, it seems that the investigators had significant concerns about the safety of the new procedure because they not only implanted an ICD, but they also recommended antiarrhythmic drugs. This trial failed to detect an incremental improvement in regional or global LV function over that provided by CABG alone. However, at the 6 month follow-up, the number of ventricular arrhythmias was 2 times greater in patients of the treated groups. Notably, these investigators called attention to the proarrhythmic risk of myoblast transplantation (Table 2). It is important to mention that the MAGIC II trial was the first large study providing exhaustive rhythm monitoring to the entire population. In sum, small trials using SkMs have shown the treatment to be proarrhythmic.

Bone Marrow–Derived Stem Cells
The effects of adult bone marrow–derived progenitor cells have been investigated in patients with recent acute MI after successful primary percutaneous coronary intervention. Other studies have also been performed in chronic MI and heart failure patients. Intracoronary, transendocardial, and transepidermal administration routes have been used. Initially, the several small and nonrandomized clinical trials that evaluated both safety and feasibility of BMCs in these situations reported no obvious evidence of arrhythmic risk associated with the procedure or during follow-up care.42–49 Perin et al reported 1 sudden cardiac death in a patient 14 weeks after transendocardial autologous BMC transplantation for chronic severe heart failure.50 When direct intramyocardial percutaneous delivery of autologous BMCs in 10 patients with refractory myocardial angina was used, one patient experienced acute heart failure 7 days after the procedure due to acute atrial fibrillation.48 In another study, 4 of 12 patients developed transient atrial fibrillation after transendocardial injection of BMCs during CABG.49 Interestingly, no other arrhythmic episodes were described in these phase I safety studies. It is important to mention that arrhythmia monitoring was not continuous in any of these studies except during the periprocedural time. Only occasional 24-hour Holter ECGs and clinical evaluations were carried out and the follow-up period was no more than a few months.

So far, few of the randomized clinical BMC therapy studies suggest either no or a small benefit in patients with ischemic heart disease.51,52 From the published data of these randomized placebo-controlled trials, there does not seem to be an enhanced risk of clinical arrhythmias related to this type of cell transplantation, but again, the method of evaluating the arrhythmic risk is generally not exhaustive (Table 3).53–67 Only Wollert et al tested arrhythmia inducibility with programmed ventricular stimulation 6 months after intracoronary BMC in 30 cell-treated and 30 control patients.66 Most groups never report any specific rhythm monitoring during follow-up after transplantation. Thus, arrhythmia occurrence is unknown.56,59–67 On the other hand, most of the patients included in these few clinical trials were taking β-blocker agents because they are indicated for ischemic heart disease. Treatment with β blockers might mask a potential proarrhythmic effect of the transplanted cells in humans.

Two other nonrandomized studies have specifically evaluated the electrophysiological and arrhythmogenic effects of transplantation of autologous bone marrow–derived progenitor cells.68,69 The study by Beeres et al was carried out in 20 patients with drug-refractory angina and myocardial ische-

### Table 2. Ventricular Arrhythmias at 6-Months Follow-Up in the MAGIC II Study

<table>
<thead>
<tr>
<th>Outcome Description</th>
<th>Placebo (n=34)</th>
<th>Low Dose (n=33)</th>
<th>High Dose (n=30)</th>
<th>HR (95% CI)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total ventricular arrhythmias, n (%)</td>
<td>2 (6)</td>
<td>4 (12)</td>
<td>5 (17)</td>
<td>2.7 (0.6; 12.6)</td>
<td>0.18</td>
</tr>
<tr>
<td>Sustained VF or polymorphic VT, n</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Sustained monomorphic VT, n</td>
<td>1</td>
<td>2</td>
<td>4</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Sustained monomorphic VT and sustained VF or polymorphic VT, n</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

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HR indicates hazard ratio of pooled treatment groups vs placebo; CI, confidence interval; VF, ventricular fibrillation; and VT, ventricular tachycardia.

*Log-rank test comparing pooled treatment groups vs placebo group.
Table 3. Arrhythmias in Randomized-Design Clinical Trials of BMC

<table>
<thead>
<tr>
<th>Reference</th>
<th>Design</th>
<th>Pts and Treatment</th>
<th>Cell Route</th>
<th>t/u, y</th>
<th>Rhythm Monitoring</th>
<th>Arrhythmias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen et al63</td>
<td>Rand placebo-controlled, 18 days after PCI for AMI</td>
<td>34 MSC, 35 placebo</td>
<td>IC</td>
<td>0.5</td>
<td>Holter at 3 m</td>
<td>No arrhythmias</td>
</tr>
<tr>
<td>Kang et al64,65</td>
<td>Rand controlled, 3–270 d after AMI</td>
<td>10 G-CSF+PBSC, 10 G-CSF, 7 control</td>
<td>IC</td>
<td>2</td>
<td>Clinical assessment and treadmill test at 1, 2, 4, and 6 m</td>
<td>No substantial arrhythmias</td>
</tr>
<tr>
<td>Erbs et al66</td>
<td>Rand placebo-controlled, 10 d after opening of a chronic total occlusion</td>
<td>12 G-CSF+PBPC, 11 G-CSF+placebo</td>
<td>IC</td>
<td>0.25</td>
<td>Clinical assessment once per week. No specific monitoring</td>
<td>No mention</td>
</tr>
<tr>
<td>Schächinger et al67</td>
<td>Rand placebo-controlled, 3–6 d after reperfusion for AMI</td>
<td>101 BMC, 103 placebo</td>
<td>IC</td>
<td>1</td>
<td>Holter at 4 m and 1 y</td>
<td>Treatment group: 5 VT, 1 SCD; control group: 4 VT, 1 syncope, 1 SCD</td>
</tr>
<tr>
<td>Janssens et al68</td>
<td>Rand placebo-controlled, 24 h after PCI for AMI</td>
<td>33 BMC, 34 placebo</td>
<td>IC</td>
<td>0.33</td>
<td>In-hospital Holter monitoring</td>
<td>Treatment group: 5 SVA; control group: 6 SVA, 3 NSVT. No late potentials</td>
</tr>
<tr>
<td>Assmus et al69</td>
<td>Rand controlled, crossover 3 m after AMI</td>
<td>24 PBSC, 28 BMC, 23 control</td>
<td>IC</td>
<td>0.25</td>
<td>Holter after procedure</td>
<td>In-hospital VT: 1 PBSC, 0 BMC, 1 control. No VT after discharge</td>
</tr>
<tr>
<td>Meluzin et al70,71</td>
<td>Rand controlled, 3–9 d after PCI for AMI</td>
<td>20 low-dose BMC, 20 high-dose BMC, 20 control</td>
<td>IC</td>
<td>1</td>
<td>No mention</td>
<td>No mention</td>
</tr>
<tr>
<td>Kang et al72</td>
<td>Rand controlled after PCI for AMI (7 d) or OMI (517 d)</td>
<td>AMI: 25 G-CSF+PBSC, 26 control; OMI: 16 G-CSF+PBPC, 16 control</td>
<td>IC</td>
<td>0.5</td>
<td>No mention</td>
<td>No mention</td>
</tr>
<tr>
<td>Lunde et al73,74</td>
<td>Rand controlled, 4–6 d after PCI for AMI</td>
<td>47 BMC, 50 control</td>
<td>IC</td>
<td>1</td>
<td>Signal-averaged ECG at baseline and 3 m Holter at baseline and 6 m</td>
<td>BMC: 2 SVA, 3 syncope. Control: 1 SVA. No differences in NSVT, PVC, and signal-averaged ECG in f/u</td>
</tr>
<tr>
<td>Wollert et al75 and Meyer et al76</td>
<td>Rand controlled, 5 d after PCI for AMI</td>
<td>30 BMC, 30 control</td>
<td>IC</td>
<td>1.5</td>
<td>Holter before discharge, at 6 w and 3 and 6 m ProgVS at 6 m. Clinical evaluation at 18 m</td>
<td>No dif in PVC or NSVT. ProgVS: 1 NSVT treatment; 1 NSVT, and 1 VF control</td>
</tr>
</tbody>
</table>

Rand indicates random; MSC, mesenchymal stem cells; IC, intracoronary; PCI, percutaneous coronary intervention; AMI, acute myocardial infarction; G-CSF, granulocyte-colony stimulating factor; BMC, bone marrow stem cell; PBSC, peripheral blood stem cell; SCD, sudden cardiac death; VT, ventricular tachycardia; SVA, supraventricular arrhythmias; NSVT, nonsustained ventricular tachycardia; ProgVS, programmed ventricular stimulation; OMI, old myocardial infarction; PVC, premature ventricular complex; and VF, ventricular fibrillation.

Mia. Immediately before intramyocardial BMC injection, 3-dimensional electroanatomical LV mapping was performed to evaluate the local bipolar electrogram characteristics of the myocardial region with ischemia in which BMCS were to be injected. Three months later, mapping was repeated in the same area, and electrograms showed no prolongation and no decrease in amplitude or increase in fragmentation, suggesting conduction was not affected. Twenty-four-hour Holter monitoring was performed at baseline and 3 and 6 months later. The total number of ventricular premature beats remained unchanged. However, this was a nonrandomized study, without a control group and with no programmed ventricular stimulation protocol to evaluate the inducibility of ventricular tachycardia. Also, the authors state that the measurement of electrogram duration by electrophysiological mapping is influenced by the direction of the wave front in relation to the bipolar, which could limit the interpretation of the results. In the second study, Katritsis et al followed-up on patients with a history of MI and ICD for ventricular arrhythmias in whom intracoronary transplantation of MSCs and endothelial progenitor cells was performed. Before stem cell transplantation, clinical nonsustained ventricular tachycardia and inducible monomorphic ventricular tachycardia or ventricular flutter were demonstrated in all 5 patients. At 16 to 36 months follow-up, the interrogation of the ICD failed to detect sustained or nonsustained ventricular arrhythmias in any patient, and a repeated electrophysiological study induced sustained ventricular arrhythmias in only 2 patients. This small and nonrandomized study should be regarded as a preliminary experience and not as proof of an antiarrhythmic potential of this type of stem cell.

The exact mechanism of “electrical” action after BMC transplantation is unknown. With intracoronary administration, <5% of cells are retained in the infarcted myocardium.
If the cells do not remain in the areas of interest, neither important long-lasting effects nor arrhythmic potential might be expected. In fact, a lack of sustained long-term beneficial effects of BMC has recently been reported.55,65,67 Further clinical experience and more exhaustive studies are necessary before reaching valid conclusions about the electrical safety of BMCs or MSCs.

Other Stem Cells and Future Clinical Directions

SKMs and BMCs might have some beneficial indirect effects on the myocardium (paracrine mechanisms, potential to induce angiogenesis),37 but they do not differentiate into cardiomyocytes.70 Finally, the suppressive therapy might be needed. Second, they have the use of hESC. First, these cells are allogeneic, and immunosuppressive therapy might be needed. Second, they have the potential to form teratomas when injected in vivo, an issue that will probably be solved with technical advances to lead their differentiation only into cardiomyocytes.70 Finally, the use of hESC is still surrounded by ethical problems.

Conclusions

In conclusion, given both the experimental and clinical data available so far we contend that stem cell therapy is arrhythmogenic. Experimental studies have provided some electrical basis for such a contention, in that stem cells can show intrinsic pacemaker function and provide for areas of slowed conduction. These latter changes in the substrate could set the stage for arrhythmias. Clinical studies so far are not exhaustive in their rhythm monitoring and usually have some type of antiarrhythmic therapy accompanying the treatment. This is a wise idea because stem cell therapy can be proarrhythmic.

Note Added in Proof

Many studies that pertain to the opinions expressed here have been published since the acceptance of this article. We apologize for not including any reference to them. However, this does show how rapidly this field is morphing.

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Disclosures

None.

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Perin EC, Dohmann HF, Borovec R, Silva SA, Sousa AL, Mesquita CT, Rossi MI, Carvalho AC, Dutra HS, Dohmann HJ, Silva GV, Belém L,


Response to Macia and Boyden

Hung Q. Ly, MD, MSc; Stanley Nattel, MD

Macia and Boyden provide a careful review of basic mechanisms underlying stem cell arrhythmogenesis, which they accompany with clinical evidence. However, we differ radically with their conclusion that “stem cell therapy is arrhythmogenic.” Most breakthrough therapies require honing before becoming perfected. Implanted stem cells can affect electrical activity: The fact that they can lead to arrhythmogenesis should surprise no one. The issue is rather whether their effects on cardiac bioelectricity can be manipulated to avoid arrhythmogenesis. We show in our article that this is indeed the case: Recent developments such as better cell type selection, improved injection methods, superior growth media, and short-term antiarrhythmic therapy make stem cell proarrhythmia an avoidable complication. Furthermore, we discuss evidence that stem cell therapy can promote cardiac rhythmicity by positively affecting remodeling, providing biological pacemakers in patients with bradyarrhythmias, electrically reengineering tachyarrhythmic substrates, and favoring synchronous cardiac activation. Thus, stem cell therapy is no more intrinsically “proarrhythmic” than antiarrhythmic drug therapy is intrinsically “antiarrhythmic.” Either can suppress arrhythmias or promote arrhythmias. Only careful use and development can optimize antiarrhythmic actions and avoid proarrhythmia. Clinical medicine is filled with examples of beneficial therapies that required refinement through research from bench to bedside and back. We contend that stem cell therapy is a good example, and that with further refinement it will prove to be a highly useful clinical intervention that, properly applied, will carry no excessive proarrhythmic risk and can produce important antiarrhythmic consequences. Indeed, stem cell–based therapeutics may one day be more effectively antiarrhythmic than presently available antiarrhythmic drug therapy. Thus, we maintain that stem cell therapy is not inherently proarrhythmic.
Stem Cell Therapy Is Proarrhythmic
Ester Macia and Penelope A. Boyden

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