Cell Therapy for Rate Control in Atrial Fibrillation

A New Approach to an Old Problem

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Physicians and patients alike have long sought ways by which to tame the rapid and irregular heartbeats that typically accompany atrial fibrillation (AF). In addition to offering symptomatic relief from palpitations, this goal has gained further importance since the recognition that sustained rapid, and perhaps also irregular, ventricular rates can lead to adverse structural cardiac remodeling and the development of a tachycardia-induced cardiomyopathy.1 In many instances, maintenance of sinus rhythm is either impractical or unachievable, and in addition to therapeutic anticoagulation, most patients will require some strategy to control their ventricular rate during AF.

The mainstays of pharmacological rate control for AF have remained unchanged for decades and consist of digoxin, β-blockers, and the nondihydropyridine calcium channel antagonists verapamil and diltiazem alone or in combination.2,3 However, medical treatment often is limited by a lack of efficacy or intolerance of side effects. Research involving novel agents such as selective A1 adenosine agonists4,5 remains in early stages and is unlikely to overcome the drawbacks of currently available drugs.

A nearly 100% efficacious approach to ventricular rate control in AF is catheter-based radiofrequency ablation of the AV junction (AVJ).6-7 Experimentally, the same result is achievable with cryoablation,8 laser energy,9 or ethanol infusion into the AV nodal artery.10 Although appropriate in selected patients,6,11-13 radiofrequency AVJ ablation has the distinct disadvantage of rendering them permanently pacemaker dependent. An increased risk of tachyarrhythmic sudden death after AVJ ablation may be countered by pacing at higher rates early after the procedure; however, concerns exist over the potential long-term hemodynamic consequences of obligate right ventricular pacing, particularly in the presence of preexisting heart failure.14-17 A notionally more appealing procedure is catheter-based radiofrequency AVJ modification18; however, a high rate of unintended AVJ modification limits the procedure to those patients in whom a pacemaker would be acceptable.7

Thus, limitations of current pharmacological and catheter ablation options to achieve rate control in AF have motivated investigators to develop novel, more biologically based strategies for nonpharmacological rate control without producing high-grade AV block. Donahue et al19 used adenoviral transfer of the gene encoding for the inhibitory G-protein subunit Goi2, delivered via selective catheterization of the AV nodal artery, to achieve a 500% overexpression of Goi2, in the porcine AV node. Seven days after gene transfer, this resulted in prolongation of the AH interval and AV nodal effective refractory period during sinus rhythm and slowed the rate of the ventricular response to acutely induced AF by 20% compared with control (16% after 1 mg epinephrine IV). A pioneering proof of concept, this study was the first to apply a purely biological strategy (gene therapy) toward rate control in AF, although its practical translation is limited by unsustained transgene expression and safety concerns associated with viral infection. Zhang and colleagues20 recently demonstrated the feasibility of selective vagal stimulation of the epicardial AV nodal fat pad to achieve sustained (up to 6 weeks) and reversible lowering of the ventricular response in a chronic, ambulatory canine model of AF. Although this approach circumvents the need for chronic ventricular pacing and theoretically may offer the potential to “titrate” the level of rate control, it requires permanent surgical implantation of a nerve stimulator.

In this issue of Circulation, Bunch and colleagues21 report on a novel, nonpharmacological, non–device-based, targeted cell injection therapy to achieve control of the ventricular rate during AF in a canine model. Briefly, fibroblasts were isolated from skin biopsies, cultured, labeled with the fluorescent marker CM-DiI, and subsequently suspended in normal saline (10⁶ cells/mL) with or without transforming growth factor-β1 (TGF-β1) before the experiments. Using the CARTO electroanatomic mapping system and NOGA mapping and injection catheter ( Biosense Webster, Inc, Diamond Bar, Calif) supplemented with intracardiac echocardiography, the investigators injected hundreds of 0.25-mL aliquots of suspended fibroblasts into the anterior and posterior atrial approaches to the AV node, regions referred to clinically as the fast and slow AV nodal pathways, respectively. Control animals received either saline or TGF-β1 without fibroblasts. AV nodal conduction was assessed by intracardiac recordings of the AH interval (the time between atrial and His bundle activation electrograms) during sinus rhythm, high right atrial pacing, left atrial pacing (via the coronary sinus), and pacing-induced atrial fibrillation immediately before and after injections and at the repeated study 4
weeks later. Acute injury and chronic regional injury were assessed in vivo with intracardiac echocardiography, and the targeted regions were structurally characterized postmortem through the use of standard histology and immunofluorescence techniques to identify surviving injected fibroblasts.

The principal results were that untreated fibroblast injections resulted in statistically significant prolongation of the AH intervals during sinus rhythm and right atrial pacing (but not left atrial pacing) after 4 weeks compared with saline-injected dogs. The ventricular interbeat (RR) intervals during pacing-induced AF also were prolonged by cell therapy. Although this did not reach statistical significance (probably because of the large variance in RR intervals in AF), the difference in mean rates would be considered clinically significant: −54 bpm in cell-treated animals versus 25 bpm in saline controls.

The impact of cell injection was potentiated when the fibroblasts were treated with TGF-β1: AH intervals were more prolonged with both right and left atrial pacing, and the mean ventricular rates in AF were reduced by 103 bpm, a highly clinically (but not statistically) significant decrease. Two dogs receiving TGF-β1–treated fibroblasts developed transient heart block requiring temporary pacing during the experiment, but none demonstrated chronic or late-occurring heart block. Injection of TGF-β1 without cells had no effect. On histological examination, animals that received cells showed evidence of subendocardial fibroblastic proliferative scar and CM-diI–positive fluorescence. TGF-β1–treated fibroblast recipients also showed evidence of a persistent mononuclear inflammatory response.

Although the present study by Bunch et al represents promising novel proof of concept, more work remains to test both the robustness and safety of this approach over the long term. Animals used in this study were fully anesthetized and not subject to adrenergic challenge such as with intravenous isoproterenol. Future studies will need to test the ability of the procedure to maintain rate control in the face of β-adrenergic stimulation and vagal withdrawal, ideally with physiological exercise in awake and ambulatory subjects. Many patients with atrial fibrillation will also at times have atrial flutter, especially in the presence of antiarrhythmic drug therapy. Because the ventricular response to atrial flutter can be even more difficult to control than AF, how well cell therapy will perform during this rhythm is not known. Validated animal models of atrial flutter exist in which this can be tested. Drug-refractory or drug-intolerant patients whom this procedure might benefit are likely to be older. Might early heart block be more likely in older subjects because of preexisting fibrosis? Does fibroblast injection increase the risk of developing heart block as subjects age? Or conversely, does the node heal or develop reconnections, leading to waning of the rate-controlling effect over time? What is the meaning of the inflammatory response in the group receiving TGF-β1–treated cells? Was the enhanced negative dromotropic effect the result of a more vigorous fibrotic response or inflammation? Obviously, the equivalent of “dose-finding” studies are needed to establish the optimal fibroblast and TGF-β1 concentrations, as well as the number and location of injections. Also, might this strategy come with proarrhythmic potential?

Fibroblast injection and proliferation within the triangle of Koch presumably increase anisotropy and more discontinuous conduction in an already highly anisotropic region. This could predispose to reentrant arrhythmias in the region if AF is not permanent. Finally, a more complete understanding of the functional impact of cell therapy on the AV node requires still more detailed electrophysiological studies. These should include atrial and ventricular programmed electrical stimulation to directly assess effects on AV nodal refractory periods, dual-pathway AV nodal physiology, VA conduction, and the patterns of atrial breakthroughs when VA conduction is present.

Although a number of issues remain to be addressed experimentally, several aspects of this type of cell-based therapy support its prospects for translation to the clinical arena in the future. From a safety standpoint, the autologous cellular nature of the therapy assuages concerns of rejection, infection, and transformation associated with other biological approaches. Practically, the endocardial catheter-based techniques will be familiar to clinical electrophysiologists. Even if only partially efficacious in achieving rate control, fibroblast therapy could carve a niche as an adjunct to pharmacological therapy, improving the efficacy of drugs and permitting the use of fewer concomitant drugs at lower, more tolerable doses. On the other hand, even a low rate of heart block requiring pacemaker implantation attributable to this procedure would relegate it to the status of radiofrequency AVJ modification or ablation—a last resort that should be considered only when the prospect of a pacemaker is acceptable.

Disclosures

None.

References


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