Autologous Dermal Fibroblast Injections Slow Atrioventricular Conduction and Ventricular Rate in Atrial Fibrillation in Swine

Fernando Tondato, MD, PhD; Hong Zeng, MD; Traci Goodchild, PhD; Fu Siong Ng, MD, PhD; Nicolas Chronos, MD; Nicholas S. Peters, MD

Background—Nonpharmacological ventricular rate control in atrial fibrillation (AF) without producing atrioventricular (AV) block remains a clinical challenge. We investigated the hypothesis that autologous dermal fibroblast (ADF) injection into the AV nodal area would reduce ventricular response during AF without causing AV block.

Methods and Results—Fourteen pigs underwent electrophysiology study before, immediately, and 28 days after ≈200 million cultured ADFs (n=8) or saline (n=6) were injected under electroanatomical guidance in the AV nodal area, with continuous 28-day ECG recording. In the ADF group at 28 days postinjection, there were prolongations of PR interval (after versus before: 130±13 versus 113±14 ms, P=0.04), of AH interval during both sinus rhythm (92±13 versus 76.8±8 ms, P<0.01) and atrial pacing at 400 ms (102±13 versus 91±9 ms, P<0.01), and of AV node Wenckebach cycle length (230±19 versus 213±24 ms, P<0.01), with no changes in the control group. The RR interval during induced AF 28 days after injections was 24% longer in ADF-treated group compared with controls (488±120 versus 386±116 ms, P<0.001). Histological analysis revealed presence of ADF-labeled cells in the AV nodal area at 28 days. Transient accelerated junctional rhythm during injections, and transient nocturnal Mobitz I AV conduction occurred early postinjection in both groups.

Conclusions—Cells survived for 4 weeks and significantly slowed AV conduction and ventricular rate in acutely induced AF. Critically, despite a large number of injections in the AV nodal area and marked effects on AV conduction, AV block did not occur. Further studies are necessary to determine the clinical feasibility and safety of this strategy for ventricular rate control in AF. (Circ Arrhythm Electrophysiol. 2015;8:439–446. DOI: 10.1161/CIRCEP.114.001536.)

Key Words: atrioventricular node • cell transplantation • fibroblasts

Drug treatment to maintain long-term sinus rhythm or achieve ventricular rate control in atrial fibrillation (AF) is limited by lack of efficacy or intolerance of side effects.1,2 Nonpharmacological approaches3,4 such as pulmonary vein isolation are effective, but this is not practicable or appropriate for all patients. Several randomized controlled clinical trials5–7 have shown that ventricular rate control in patients with AF can be an effective therapeutic approach, with outcomes in some patient groups that are comparable to strategies for maintenance of sinus rhythm. Rate control in AF, therefore, remains an appropriate and common palliative strategy, and for symptomatic patients when all pharmacological and other nonpharmacological approaches have failed, atrioventricular node (AVN) ablation is a well-established and widely practiced technique,8 achieving control of symptoms in the majority of patients, but requires permanent pacemaker implantation. Previously, various strategic approaches to attempt AVN modification to control rather than abolish atrioventricular (AV) conduction have all been shown to have prohibitive risk of complete AV block9,10 and are therefore rarely attempted in current clinical practice.

Among the advances in the area of cell therapy,11–14 multiple cell types have been used for myocardial repair and regeneration,15–18 including restoration of conduction in experimental models.19,20 Cellular therapies have the potential to either enhance or block electric conduction of the heart,21,22 and although dermal fibroblasts injected in the AVN area have been shown to modify conduction velocity,21 the clinical therapeutic goal in AF is not that of slowing AV nodal conduction, but of controlling ventricular response rate. The aim of this study was to address the hypothesis that injections of adult autologous dermal fibroblasts (ADF) in the AVN area would inhibit AVN conduction, resulting in control of ventricular response during AF without inducing complete AV block or evidence of fibrotic changes in the lung.

Methods

Animal Preparation

The protocol was consistent with federal guidelines for the care and use of laboratory animals and was approved by the Institutional Animal Care and Use Committee of the Saint Joseph’s Translational Research Institute/Saint Joseph’s Hospital of Atlanta, GA (F.T., H.Z., T.G., F.S.N., N.C.).

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WHAT IS KNOWN

- Ventricular rate control remains a common and appropriate goal in managing atrial fibrillation.
- Currently, the options include drugs to control the atrioventricular (AV) node or AV node ablation followed by pacemaker implantation.
- All previous interventional strategies for AV node modification, including by nonselective and subsequently slow- or fast-pathway selective radiofrequency ablation, have been unsuccessful because of the prohibitively high risk of complete AV block.

WHAT THE STUDY ADDS

- The present study proved the concept that autologous dermal fibroblasts can safely be injected in the AV node area, resulting in persistent modification of atrioventricular conduction in the absence of complete AV block, despite a large number of injections and volume of injectate.
- The current study demonstrated survival of dermal fibroblasts injected in the AV node area, with sustained biological effect of slowing AV conduction.
- If reproduced clinically, this would be the first approach to controlling ventricular rate in atrial fibrillation that preserves intrinsic AV conduction, therefore safely obviating the need for AV nodal controlling drugs or pacing.

Research Institute. Fourteen juvenile farm pigs weighing 48.7±10.1 kg were enrolled into the study. Anesthesia was induced by an intramuscular injection of a combination of 2 to 4 mg/kg of telazol, 4 mg/kg of ketamine, and 2 mg/kg of xylazine, followed by intubation and general anesthesia induced and maintained using inhalant isoflurane (≈1.5%–2.5% in O₂).

ADF Preparation

The groin regions were shaved, scrubbed, and draped. A 6×2 cm sample of skin was harvested. The tissue was minced and digested in 0.25% Trypsin-EDTA for 1 hour at 37°C. DMEM containing 15% fetal bovine serum was added, and then digest was filtered through 100-μm strainer. Cells were washed twice with PBS, and the final cell pellet was resuspended in DMEM with 10% fetal bovine serum. The cell suspension was filtered through a 100-μm strainer. Cells were washed twice with PBS, and the final cell pellet was resuspended in DMEM with 10% fetal bovine serum.

Electrophysiological Study

Standard quadripolar electrophysiology (EP) catheters (Cordis, 6F) were inserted through the right and left femoral veins and advanced to the right atrial (RA), right ventricular apex, coronary sinus, and His bundle positions under fluoroscopic guidance. The electrodes were connected to an EP-3 WorkMatesystem (EP MedSystems, Inc., Mount Arlington, NJ), and standard electrophysiological study with programmed stimulation was performed to determine PR, AH, and HV intervals, AVN Wenckebach, and RR intervals during AF induced by rapid RA pacing. PR interval was determined as the time interval between the P wave onset and QRS onset on the surface ECG. AH interval was determined as the time interval between the initial atrial deflection to the initial H deflection recorded in the His bundle electromgram and was measured during sinus rhythm and atrial pacing at 400, 500, and 600 ms drive cycle length by using 2.0 ms square pulses at twice diastolic pacing threshold. HV interval was determined as the time interval between the initial H deflection recorded in the His bundle electromgram and the earliest deflection of the QRS complex on the surface ECG. The AVN Wenckebach cycle length was determined by decremental pacing from RA (progressive reduction of pacing cycle length, translating into faster pacing rates) at twice the diastolic pacing threshold until anterograde type I second-degree AV block (Wenckebach) occurred. The above EP measurements were performed before injections, immediately after injections, and at postinjection time point of 28 days. AF was induced at follow-up (28 days) by RA pacing at a cycle length of 100 ms at 2.0 ms square pulses and current 10.0 mA, and sustained for a variable period after cessation of pacing, during which 10 consecutive RR intervals during AF were used to calculate ventricular rate.

ADF Injections

Eight pigs received cell injections and 6 pigs received saline solution as a control. An RA geometry was made with a 4-mm tip electroanatomical mapping catheter (Biosense Webster, Diamond Bar, CA) with a filling threshold of 15 mm, marking the positions of the His bundle and the ostium of coronary sinus (CARTO 4.0 system, Biosense, Diamond Bar, CA). A Myostar catheter (Biosense Webster, Diamond Bar, CA)—a deflectable CARTO-compatible injection catheter—was then used for marking the locations of the multiple injections on the RA geometry. The Myostar catheter has an adjustable needle depth. Preliminary bench testing had determined the ideal cell concentration to maximize viability and the optimal volume of each injection that could be retained in an ex vivo myocardial preparation. Based on these preliminary studies (data not shown), the yield from the fibroblast cell cultures was diluted to a

Figure 1. Three-dimensional mapping of right atrium with CARTO 4.0 mapping system. His bundle (orange dot) and coronary sinus ostium (pink dot) were marked on the map. Injections were performed along the slow and fast pathways around perinodal region (red dots). IVC indicates inferior vena cava; and SVC, superior vena cava.
volume of 50 mL for an injection volume of 0.8 mL delivered by indeflator pressurized to 20 atm, resulting in $\approx 60$ injections per case. The Myostar is deflectable and designed to provide support for needle penetration on deployment, and preliminary in vivo studies using radiopaque contrast in the injectate confirmed tissue penetration and contrast retention, and 2 mm as being an optimal needle-depth setting for the purposes of injection in the region of the triangle of Koch in this study (data not shown).

Guided by the RA geometry, multiple 0.8 mL injections of a total of 50 mL of ADF or saline were delivered along the slow and fast pathway regions around the AVN. Although initial injections focused on the inputs to AVN, the large number of injections extended to the region of confluence of slow and fast pathways, and therefore the region of the compact AVN, which was not deliberately avoided. In each position, the needle was deployed, and the interval between each indeflator injection was $\approx 60$ seconds. The sites of injections were tagged on the CARTO map (Figure 1). After injections, a transesophageal echocardiogram (Acuson, Siemens, Mountain view, CA) was performed to exclude complications and evaluate atrial and ventricular form and function.

Preliminary bench testing had determined the ideal cell concentration to maximize viability and the optimal volume of each injection that could be retained in an ex vivo myocardial preparation. Based on these preliminary studies (data not shown), the yield from the fibroblast cell cultures was diluted to a volume of 50 mL for an injection volume of 0.8 mL delivered by indeflator pressurized to 20 atm, resulting in $\approx 60$ injections per case. The Myostar is deflectable and designed to provide support for needle penetration on deployment, and preliminary in vivo studies using radiopaque contrast in the injectate confirmed tissue penetration and contrast retention, and 2 mm as being an optimal needle-depth setting for the purposes of injection in the region of the triangle of Koch in this study (data not shown).

Transmitter Implant and ECG Monitoring

After completing injections and EP evaluation, animals underwent implantation of a telemetry transmitter (TA10CTA-D70, DSI Systems, Data Sciences International Inc, St. Paul, MN) in the subcutaneous space of the abdomen for continuous telemetry ECG monitoring and recording over the ensuing 4 weeks. On full disclosure and examination of all ECG recording, the PR interval at its longest and any changes indicative of AV block or other cardiac arrhythmia during each period of 24 hours were reported.

Restudy and Histology

At 28 days after injections, CARTO mapping and EP studies were repeated. Animals were euthanized; the heart and the lungs were harvested, and the injected area corresponding to Koch’s triangle encompassing the AVN region was dissected for histological analysis (Figure 2). Samples were divided into 3 pieces, and each piece was further divided into 3 sections where 1 was fixed in 10% buffered formalin, embedded in paraffin, 5-μm sections cut, and stained with hematoxylin and eosin for assessment of overall cellularity and Verhoeff–Masson for collagen deposition. The other 2 sections were processed for frozen sectioning to identify CM-DiI positively labeled ADF. Frozen sections were cut and counterstained with 4′, 6-diamidino-2-phenylindole (Sigma, St. Louis, MO) to highlight cell nuclei. Images were acquired using epifluorescence microscopy (Nikon Eclipse E400, Japan).

Data Analysis

Data are expressed as mean±SD. Student $t$-tests were performed to compare continuous variables with normal distribution. Paired $t$-tests were used to compare repeated measurements in the same group. The nonparametric test of Mann–Whitney was used for comparison between those samples without a normal distribution. A $P<0.05$ was considered significant. For multiple repeated-measures comparisons, 2-way ANOVA was used, using significant $P<0.05$.

Results

Cell Culture and Injection

A total of 1.9±0.6×10⁸ cells were obtained from each culture (Figure 3). The average culture time was 27±10 days. The cell viability after CM-DiI labeling and immediately before injection was 96±5%.

Figure 2. Right atrial septum visualization during necropsy in one animal. The dotted lines represent the histological sections—A1, A2, and A3 were submitted to formalin fixation for 24 hours before embedding in paraffin; sections A2, B2, and C2 were frozen after use of fixation, and sections A3, B3, and C3 were frozen without fixative. C.S. ostium indicates coronary sinus ostium; and F. Ovalis, fossa ovalis.

Figure 3. Pig autologous skin fibroblasts in culture. A, Pig autologous dermal fibroblast (ADF) culture at 2 days, ×100 magnification. B, Pig ADF culture at 28 days, ×100 magnification.
Injections were performed without apparent adverse effect. The number of injections was comparable between both groups (cell group [n=8]; 66±20; control group [n=6]; 59±17; P=0.52).

Electrophysiological Study
Brief episodes of junctional rhythm with normal QRS morphology during and immediately after injections were common in both groups and resolved with return to sinus rhythm in the first few hours postprocedure. For this reason, PR and AH interval measurements could not be consistently or reliably measured immediately after injections. PR and AH intervals in sinus rhythm were comparable between groups at baseline. A summary of measured intervals is shown in Table 1.

During sinus rhythm at 28 days after injection, there was significant prolongation of both the PR (130±13 versus 113±14 ms, P=0.04) and AH (92±13 versus 80±7 ms, P=0.016) intervals compared with baseline in the ADF-treated group but not in the control group (Table 1). The analysis of PR and AH intervals was limited to comparison between baseline and 28 days follow-up (Student t) because of frequent episodes of junctional rhythm immediately after injections.

During fixed atrial pacing at 600, 500, and 400 ms at 28 days, AH intervals were significantly increased at all cycle lengths in the ADF group compared with baseline in the ADF-treated group but not in the control group. These findings translated into significant differences in AH interval between ADF-treated and control groups at all paced cycle lengths (Table 2).

The ANOVA analysis showed that there were no significant variations in the measured HV interval at baseline, immediately after injection and at follow-up (Table 1), neither in the cell group (P=0.37) nor in the control group (P=0.47).

The AVN Wenckebach cycle length showed no difference between groups either at baseline (210±32 ms in control group, and 213±24 ms in cell group, P=0.87) and prolonged significantly at 28 days only in the ADF-treated group compared with baseline (230±19 versus 213±24 ms, P=0.009).

Ventricular Rate During AF
At 28 days after injection, the mean RR interval during acutely induced AF was ≈100 ms longer in the ADF-treated group compared with controls (488±120 versus 386±116 ms, P<0.001).

Continuous ECG Telemetry
Real-time ECG monitoring during the 28 days of observation showed PR interval prolongation during the first 5 to 7 days after injection in both groups and then progressively returning to baseline levels in the control group. The ADF group, however, presented a partial return of PR interval but not back to baseline levels and remained steadily elevated for the ensuing period of observation (Figure 4). In 1 animal in ADF-treated group, 2 transient episodes of isolated nonconducted P waves during nocturnal second-degree AV block occurred on the second and third days of observation (Figure 5). Neither late AV block nor change in HV intervals occurred in either group.

Necropsy and Histological Findings
No evidence of perforation, thrombosis, or pericarditis was noted during macroscopic analysis. Under light microscope, small isolated concentrations of scant mononuclear cells were found in the perinodal myocardium in the ADF-treated group, probably representing mild localized inflammation (Figure 6), with no evidence of any major inflammatory response. Under epifluorescent microscopy, only in the ADF group, CM-DiI-labeled cells were identified (Figure 7). The presence of CM-DiI at the membrane surface concordant with the 4′, 6-diamidino-2-phenylindole counterstaining in the nuclei confirms cell viability at the time of euthanasia. Extensive examination of the lungs showed no macroscopic or microscopic abnormalities.

Discussion
The findings of this study are that ADFs can be safely injected into the AV nodal region, resulting in slowing of AV nodal

Table 1. Basic Interval Measurements at Baseline, After Injection and at Follow-Up, Expressed in Milliseconds

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Postinjection</th>
<th>28 Day</th>
<th>P Value</th>
<th>Baseline</th>
<th>Postinjection</th>
<th>28 Day</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR</td>
<td>113±14</td>
<td>163±17</td>
<td>130±13</td>
<td>0.044*</td>
<td>113±14</td>
<td>146</td>
<td>124±12</td>
<td>0.161*</td>
</tr>
<tr>
<td>AH</td>
<td>80±7</td>
<td>113±18</td>
<td>92±13</td>
<td>0.021*</td>
<td>75±9</td>
<td>100±25</td>
<td>76±8</td>
<td>0.832*</td>
</tr>
<tr>
<td>HV</td>
<td>34±3</td>
<td>33±2</td>
<td>33±1</td>
<td>0.372†</td>
<td>31±4</td>
<td>32±2</td>
<td>32±4</td>
<td>0.471†</td>
</tr>
</tbody>
</table>

ADF indicates autologous dermal fibroblast.

*Statistical comparison between 28 day and baseline.
†ANOVA analysis comparing baseline, immediately after injection and at follow-up.

Table 2. AH Interval Measurements, Expressed in Milliseconds at Pacing Cycle Length of 400, 500, and 600 ms

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>28 Day</th>
<th>P Value</th>
<th>Baseline</th>
<th>28 Day</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>400 ms</td>
<td>91±9</td>
<td>102±13</td>
<td>&lt;0.01</td>
<td>87±14</td>
<td>88±12</td>
<td>0.47</td>
</tr>
<tr>
<td>500 ms</td>
<td>84±9</td>
<td>96±15</td>
<td>0.02</td>
<td>85±15</td>
<td>82±9</td>
<td>0.83</td>
</tr>
<tr>
<td>600 ms</td>
<td>82±8</td>
<td>93±16</td>
<td>0.04</td>
<td>81±15</td>
<td>78±10</td>
<td>0.61</td>
</tr>
</tbody>
</table>

ADF indicates autologous dermal fibroblast.
conduction and of the ventricular response rate in acutely induced AF in pigs. Importantly, despite a deliberately large number of injections, no animal developed complete AV block in the first 28 days, and only 1 animal had 2 brief episodes of transient nocturnal second-degree AV block (narrow QRS) during the first 2 days after injection. No attempt was made to avoid the compact AVN, and that some of the injections will have been directly in to this region was evident from the acute detectable effects on AV nodal function (prolongation of AH and PR intervals) in the absence of AV block ≤28 days, suggests a margin of safety that is unique among all previous attempted strategies for AV nodal modification and a highly promising proof of concept.

Transient junctional rhythm and prolongation of the PR interval during injections were both observed but always settled with return to sinus rhythm and normalization of the PR interval within a few hours after completion of the injections. The frequency, timing, and consistency of these transient changes in rhythm in both groups would implicate mechanical trauma of the injection procedure and not the later biological response to ADF transplantation.

Although the initial changes can be explained by a simple mechanical effect, the late changes seen only in the ADF group, the prolongation of the AH interval, the Wenckebach cycle length and, most importantly with respect to potential clinical applicability, prolongation of the mean RR interval in acutely induced AF, result from the late biological effect of the injected ADF cells.

Dermal fibroblasts are mesenchymal cells that are readily isolated and cultured in the laboratory and play an important role in tissue engineering and regeneration, including the treatment of burns, chronic venous ulcers, and several other

Figure 4. PR interval on real-time ECG during 28 days of observation period.

Figure 5. Presence of second-degree atrioventricular block during real-time ECG monitoring in 1 animal at 2 days after autologous dermal fibroblast injections.
clinical applications in dermatology and plastic surgery.

Although previous studies have reported the effects of ADF on myocardial conduction, including the AVN and focusing principally on conduction velocity, no previous studies have addressed the critical safety concern of high-grade AV block excluded by the extended and continuous rhythm monitoring in the present study. The putative mechanisms for the effect of the transplanted ADFs in retarding AV conduction include collagenous interruption of the myocardial syncytium and cell separation, and myocyte–fibroblast gap-junctional coupling providing an alternative sink for charge transfer between cardiac myocytes. We have shown previously that injection of ADFs in chronic myocardial infarction can potentially lead to stabilization of arrhythmogenic burden in a swine model, preventing development of both induced and spontaneous ventricular arrhythmias. Kizana et al reported that fibroblasts can be genetically modified to produce excitable cells capable of electric coupling, with additional potential for treating cardiac conduction defects.

In the present study, histological examination showed that after 4 weeks, there was no significant inflammatory or major fibrotic response in either the perinodal myocardium or the lungs, which will have received significant ADF overspill from injections, indicating that despite a different tissue of origin, autologous cells for ventricular rate control in AF remains a realistic proposition requiring further investigation.

Clinical Application

Clinical trials continue to address the question of rate versus rhythm control in AF, and some studies indicate that in certain populations of patients, a rate control strategy may be preferable. Although the strategy of rhythm control has benefited from ablation and novel antiarrhythmic drugs, therapeutic options in rate control have remained largely unchanged for decades and expose patients to drugs frequently with limited efficacy and side effects or the need for permanent ventricular pacing after AVN ablation.

Specifically, attempts at AV nodal modification, such as with selective radiofrequency, cryo ablation, or other

Figure 6. Right atrium histology. A, Site of injection stained with hematoxylin and eosin. Arrows show sites of injection (×4); B, Section shown in A under ×10 magnification; C, Site of injection stained with Masson–Verhoeff. Arrows show the clusters of cells, and D shows the same area as C under ×10 magnification.

Figure 7. Identification of autologous dermal fibroblast labeled with CM-Dil (A) and nuclei counter-staining with 4′, 6-diamidino-2-phenylindole (B) 28 days after injection. The white arrows represent the edge of a site of the exact same field.
detrimental ablation with the intent to avoid complete abolition of AV nodal conduction and retain normal ventricular activation sequence, have proven unsuccessful because of an unacceptable incidence of AV block. Although of limited clinical utility as a measure of efficacy, when assessing safety the PR and AH intervals were important to measure at the time of injection because this study was designed specifically to give a large number of injections in and around the AVN in an attempt to cause AV block—failure to achieve which, coupled with the early modest changes in AH and PR, is reassuring of a much wider margin of safety of critical importance to this proof of concept compared with previous interventions to modify AVN, including radiofrequency and cryo. Autologous fibroblast injection that can safely be delivered transvenously to slow ventricular rate in AF as an alternative to long-term drug treatment is a compelling treatment strategy of potential high impact requiring further investigation.

Before progressing to clinical use in humans, further studies will be necessary to determine the ideal cell concentration, volume, and total number of cells or injections per patient to achieve maximum efficacy, without compromising the safety of the procedure.

Limitations
Despite the small numbers of animals, the lasting and beneficial effects on AV conduction indicate a robust treatment effect for the 4 weeks of follow-up. Further studies will be required to investigate more long-term effects in progressing toward clinical application and to better clarify the specific mechanism involved in the AV conduction delay induced by ADF. The AF in this study was acutely induced episodes and may differ from more naturally occurring AF. The present study did not evaluate the effect of isoproterenol challenge acutely after injections because the expected effects of this intervention on AVN conduction, as proved to be correct, took days to evolve, and procedural testing would not therefore have been informative. In fact, acutely the main question was that of safety (AV block) rather than efficacy, and to have given isoproterenol may potentially have masked this. In follow-up, we considered the telemetered ventricular rate monitoring that was performed in this study to be the most informative measure.

Conclusions
Transplantation of ADFs in the AVN area in pigs is feasible, safe, and slows ventricular rate in acutely induced AF. Despite a large number of injections, complete AV block did not occur. These results encourage further investigation of a novel strategy for controlling ventricular rate in AF.

Acknowledgments
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Disclosures
None.

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