Selective Molecular Potassium Channel Blockade Prevents Atrial Fibrillation

Guy Amit, MD, MPH; Kan Kikuchi, MD; Ian D. Greener, PhD; Lizhu Yang, BS; Victor Novack, MD, PhD; J. Kevin Donahue, MD

Background—Safety and efficacy limit currently available atrial fibrillation (AF) therapies. We hypothesized that atrial gene transfer would allow focal manipulation of atrial electrophysiology and, by eliminating reentry, would prevent AF.

Methods and Results—In a porcine AF model, we compared control animals to animals receiving adenovirus that encoded KCNH2-G628S, a dominant negative mutant of the \( I_{Kr} \) potassium channel \(-H9251\)-subunit (G628S animals). After epicardial atrial gene transfer and pacemaker implantation for burst atrial pacing, animals were evaluated daily for cardiac rhythm. Electrophysiological and molecular studies were performed at baseline and when animals were euthanized on either postoperative day 7 or 21. By day 10, none of the control animals and all of the G628S animals were in sinus rhythm. After day 10, the percentage of G628S animals in sinus rhythm gradually declined until all animals were in AF by day 21. The relative risk of AF throughout the study was 0.44 (95% confidence interval 0.33 to 0.59, \( P<0.01 \)) among the G628S group versus controls. Atrial monophasic action potential was considerably longer in G628S animals than in controls at day 7, and KCNH2 protein levels were 61% higher in the G628S group than in control animals (\( P<0.01 \)). Loss of gene expression at day 21 correlated with loss of action potential prolongation and therapeutic efficacy.

Conclusions—Gene therapy with KCNH2-G628S eliminated AF by prolonging atrial action potential duration. The effect duration correlated with transgene expression. (Circulation. 2010;121:2263-2270.)

Key Words: atrial fibrillation | gene therapy | ion channels | electrophysiology | arrhythmia

Atrial fibrillation (AF) is the most common sustained arrhythmia, affecting 2 to 5 million people in the United States and several million more worldwide.\(^1\) The presence of AF increases mortality risk 1.9-fold and stroke risk 5-fold. AF has a complex interaction with heart failure, with each increasing the probability and severity of the other.\(^2\) Safety and efficacy limit currently available AF therapies. The best antiarrhythmic drugs allow AF recurrence in \( >50\% \) of patients within 1 year of therapy initiation.\(^3\) Toxicities frequently limit antiarrhythmic use, most notably ventricular arrhythmias in up to 5% of patients.\(^4\) Percutaneous endocardial radiofrequency ablation can eliminate AF in a limited subset of patients, but recurrences are frequent, and the procedure is highly complex and time intensive and carries substantial risk for complications, including pulmonary vein stenosis, atrial-esophageal fistula, cardiac tamponade, stroke, and death.\(^5\) The Cox-Maze procedure is a curative but extremely invasive surgical option.\(^6\) Epicardial approaches using radiofrequency or ultrasound ablation to reduce the invasive nature of the Cox procedure are under development, but there is limited experience with safety and long-term results for these techniques.\(^7\) Therefore, molecular therapies for AF that could overcome the limitations of current treatment options may be highly desirable.

Clinical Perspective on p 2270

An important first step for developing AF therapies is consideration of the arrhythmia mechanism. Extensive investigation in a number of laboratories has shown that the underlying mechanism for AF includes triggering events that start the arrhythmia and maintenance conditions that sustain the rhythm (for a more thorough review, see Nattel\(^9\)). Triggers generally are single or repetitive atrial premature beats that occur after depolarizations in individual cells spread throughout the atria. A variety of mechanisms can sustain AF, including continuation of the triggering afterdepolarizations and either focal or broad reentrant electric circuits. Conditions that allow electric reentry in the myocardium are essentially conditions that

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allow the cells within the circuit to recover in the interval between 1 beat and the next, e.g., a short cellular refractory period, slow conduction velocity, or focal conduction block.

We hypothesized that lengthening the atrial action potential duration (APD) would disrupt intra-atrial reentry and thereby terminate fibrillation. We addressed this hypothesis in a porcine model of burst-pacing–induced AF with gene transfer of KCNH2-G628S, a dominant negative mutant of the $I_{Kr}$ $\alpha$-subunit, using our previously reported atrial painting method that allows 100% transmural gene transfer.10,11 Zhou et al12 showed that gene transfer with this mutant causes normal expression, posttranslational processing, and membrane localization of the ion channel and that it disrupts $I_{Kr}$ by blocking the channel pore. Here, we test the ability of gene transfer with this mutation to prolong atrial APD and prevent AF.

**Methods**

**Adenovirus Vectors**

Ad$\beta$gal contained the _Escherichia coli_ lacZ gene driven by the human cytomegalovirus immediate/early promoter. AdG628S contained the KCNH2-G628S gene driven by the human cytomegalovirus immediate/early promoter. Virus construction, expansion, and molecular properties at peak gene effect, 5 more animals that received AdG628S and 5 more control animals were studied in a 7-day protocol.

The animals for the present study were maintained in accordance with the policy on humane care and use of laboratory animals from the Office of Laboratory Animal Welfare, National Institutes of Health. The experimental protocol was approved by the institutional Animal Care and Use Committee.

**EP Studies and Rhythm Evaluation at Follow-Up**

Immediately before and 7 or 21 days after gene transfer, the animals underwent open-chest EP study. Animals in AF were cardioverted to sinus rhythm (SR) for EP study. A conventional 12-lead ECG was recorded with standard lead positions. Monophasic action potential (MAP) recordings were assessed from the epicardial wall under direct visualization to reproduce the locations. MAPs were acquired in digital format (EP Medical Systems, New Berlin, NJ) and animals that underwent the same painting protocol without virus (no virus control, n = 5). To assess electrophysiological and molecular properties at peak gene effect, 5 more animals that received AdG628S and 5 more control animals were studied in a 7-day protocol.

Animals received AdG628S ($n = 7$) were compared with animals that received Ad$\beta$gal (virus control, $n = 5$) and animals that underwent the same painting protocol without virus (no virus control, $n = 5$). To assess electrophysiological and molecular properties at peak gene effect, 5 more animals that received AdG628S and 5 more control animals were studied in a 7-day protocol.

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Western Blot
The animals were euthanized after the follow-up EP study. The atria were dissected free from the ventricles and frozen in liquid nitrogen for later analysis. To quantify protein content of tissue extracts, Western blot analysis was performed on proteins extracted from the frozen tissue samples. The concentrations of proteins were determined by the BCA method (Pierce Chemical, Rockford, Ill). Proteins were fractionated by 4% to 12% SDS-PAGE and transferred to a nitrocellulose membrane. After they were blocked with 5% nonfat dry milk, membranes were blotted with anti-KCNH2 C-20 (polyclonal goat IgG diluted 1:200, Santa Cruz Biotechnology, Santa Cruz, Calif) and anti-GAPDH (polyclonal goat IgG diluted 1:100, Santa Cruz Biotechnology) and a secondary antibody directed against the primary antibody and conjugated with horseradish peroxidase (donkey anti-Goat IgG, Santa Cruz Biotechnology). Bands were detected with an enhanced chemiluminescence assay (GE Healthcare, Piscataway, NJ) and quantified with the ImageQuant software package (National Institutes of Health, Bethesda, Md).

Statistical Analysis
Given our previous demonstration that lacZ gene transfer causes no electrophysiological effects,13–15 we prospectively combined the 2 control groups for statistical analysis. Owing to the sample size, continuous parameters were compared with the Mann-Whitney U nonparametric test, with P<0.05 considered significant. Data are presented as medians with minimum and maximum observed values. Because each animal was assessed more than once, to compensate for repeated measurements, the risk of AF over time was assessed with a generalized estimating equations model (Poisson distribution) to address animal-level clustering, with a dependent variable of having AF on any given day.

Results
Rhythm Analysis
We compared response to therapy between 7 AdG628S animals and 10 control animals (5 that received no virus and 5 that received Adfgal, which encodes lacZ, a protein that we have previously shown to have no detectible electrophysiological effects13–15). At baseline, all animals underwent open-chest EP study, atrial pacemaker insertion, and atrial painting of a gel that contained 20% poloxamer, 0.5% trypsin, and 1×10⁶ pfu/mL of the indicated virus. In the case of the no-virus controls, the painting solution contained only poloxamer and trypsin. Immediately after closing the chest in each animal, we activated the burst protocol to pace the atria at 42-Hz frequency for 2-second increments alternating with 2-second no-pacing increments. Follow-up consisted of daily telemetry recordings that were performed with animals in the unsedated, normally active state. Burst pacing was continued throughout the telemetry recordings, and we analyzed the 2-second no-pacing increments for rhythm analysis.

Immediately after initiation of the pacing protocol (days 1 to 3), the control and G628S groups had a similar percentage of animals in SR (Figure 1). Among the controls, the proportion of animals in SR decreased progressively until none had SR on or after day 10 (all animals were in AF at that point). In contrast, the number of animals in SR increased abruptly on day 4 for the G628S animals, and all G628S animals were in SR for days 4 to 10, except 1 G628S animal was in AF on day 8. That animal returned to SR on day 9. After day 10, the number of G628S animals in SR gradually declined until all animals were in AF by day 21.

Statistical analysis by use of a generalized estimating equation model showed that the G628 group had significantly less risk of AF (relative risk of AF=0.44, 95% confidence interval 0.33 to 0.59, P<0.01). Interestingly, the median time from onset of burst pacing to persistent AF for the control group in the present study (5 days) was the same as our previously published result with the model,15 and the time from gene transfer to therapeutic effect in the treatment group was similar to previous observations for atrioventricular nodal gene therapy with this model.14

Effect on Atrial Action Potential
To understand the mechanism underlying this successful intervention, an invasive EP study was performed at termination of the in-life phase of the experiments. Animals in AF were cardioverted to SR for the EP study. Compared with baseline measurements, atrial MAPD₉₀ was increased in all animals after either 7 or 21 days of burst pacing; however, the atrial MAPD₉₀ increase was considerably longer at day 7 in G628S animals than in controls (Figure 2). The differences in right and left atrial MAPD₉₀ between G628S animals and controls were attenuated on day 21. The left atrial MAPD₉₀ in G628S animals was not significantly different from controls at the later time point.

At the 1-week time point in the G628S animals, there appeared to be a more pronounced effect on the right than the left atria. This finding was not anticipated, so it was not part of our prospective analysis plans. Post hoc analysis showed that this difference was not statistically significant (P=0.3 by Wilcoxon signed rank test), although we cannot rule out the possibility that the present study was underpowered to distinguish interatrial differences in therapeutic effect.

Protein Expression
The observed physiological effects were compared with Western blot–determined KCNH2 expression levels. The median expression level of KCNH2 normalized to GAPDH was 1.12 (0.84, 1.37) among the G628 group compared with 0.62 (0.46, 0.72) among controls (P=0.003), which represented 79% higher KCNH2 levels in the G628S group compared with 0.62 (0.46, 0.72) among controls (P=0.003), which represented 79% higher KCNH2 levels in the G628S group at 1 week than in control animals (Figure 3). At 3 weeks, there were no statistically significant differences in KCNH2 expression between G628S animals and controls.

Effect on Conduction Time
Looking for alternative explanations for AF termination, we evaluated measures of atrial conduction while the animals were in SR during the invasive EP study. P-wave duration on the surface ECG is a global assessment of the time required to activate the atria. P-wave duration increased in all burst-paced animals compared with the pre-AF baseline, but there were no differences between G628S animals and controls at either the 7- or 21-day time point. With the 7-day animals, we also assessed conduction times between the sinus node and
the left and right atrial appendages. None of these measurements differed between groups (Table).

Safety
Several measures of safety were evaluated. Atrial proarhythmia was evaluated by looking for early afterdepolarizations in the day 7 peak-effect animals. There were no early afterdepolarizations at baseline heart rate. The heart rate in 2 animals was then slowed by localized cooling of the sinus node, and MAPD\(_{90}\) recordings were repeated in left and right atrial areas away from the cooling site. Still, no early afterdepolarizations were observed. The ventricles were assessed for any electrophysiological changes. When controls were compared with G628S animals, no change was noted in QRS duration or QT interval on the surface ECG or in MAPD\(_{90}\) on MAP recordings (Figure 2; Table). There were also no ventricular arrhythmias noted during the daily ECG recordings.

Discussion
Overall, we found that KCNH2-G628S gene transfer successfully prevented sustained AF, even with the very aggressive and persistent AF trigger of rapid burst pacing. The therapeutic effect correlated to APD prolongation. We saw no suggestion that alternative mechanisms of reentry disruption played a role; several measures of intra-atrial conduction were unchanged between groups. We also saw a direct correlation between therapeutic effect and the timing of transgene expression, starting shortly after gene transfer at a time when we and others have observed expression onset\(^{14}\) and lapsing after a few weeks as adenovirus-mediated gene expression waned.\(^{16}\) We observed repeated termination of AF with daily ECG recordings, albeit over limited time periods each day. Within the constraints of that limit, we saw in the G628S animals the reproducible onset of fibrillatory conduction with burst pacing and repeated termination of fibrillation a few beats after conclusion of the burst-pacing episode. The present results are the first documentation of a molecular therapy to disrupt this pervasive and debilitating arrhythmia.

Mechanism of AF Maintenance
The present data have implications for the continuing debate on the mechanism of AF. Our study was not equipped to answer the question of the triggering mechanism, because we used an artificial trigger (the electronic pacemaker). The present data do provide insight into the mechanism of AF maintenance. Suggested mechanisms have included the possibility that the triggering stimulus continues, with the macroscopic appearance of AF coming from a breakdown in uniform conduction away from the trigger (so-called fibrillatory conduction), or that the trigger initiates persistent reentrant wavelets.\(^{9}\) In the present model, the G628S animals continued to show evidence of fibrillatory conduction during the burst-pacing episodes,
with loss of organized atrial electric activation and rapid, irregular activation of the atria, so our effective therapy affected neither trigger nor fibrillatory conduction. The disruption of AF in the G628S animals correlated with APD prolongation. If AF is sustained by a triggered mechanism, as some postulate, then APD prolongation should have worsened the situation by provoking more triggered activity. If reentry maintains AF, as others have argued, then APD prolongation should have terminated the arrhythmia by causing the electric activation wave front to meet still-depolarized and therefore refractory cells. Because the episodes of AF reproducibly terminated in the G628S animals, the present data support the hypothesis that AF is sustained by a reentrant mechanism, at least in this model.

Translation of Findings to the Prevention or Treatment of AF

The present data suggest the viability of KCNH2-G628S gene transfer for treatment of sustained AF. Current

| Table. EP Study Results for Control and G628S Animals |
|------------------|------------------|------------------|
|                  | 7 Days           | 21 Days          |
|                  | Control          | G628S            | Control          | G628S            |
| 12-Lead ECG      |                  |                  |
| P-wave duration  | 92 (86, 92)      | 91 (71, 96)      | 95 (85, 120)     | 85 (75, 100)     |
| PR interval      | 120 (117, 124)   | 119 (117, 121)   | 120 (120, 130)   | 130 (117, 138)   |
| QRS interval     | 70 (69, 78)      | 66 (59, 78)      | 75 (64, 80)      | 70 (60, 70)      |
| QTc              | 392 (384, 402)   | 395 (392, 401)   | 411 (368, 412)   | 394 (375, 425)   |
| Heart rate, bpm  | 106 (105, 114)   | 105 (108, 129)   | 100 (75, 130)    | 93 (93, 115)     |

Intra-atrial conduction time (pacing 400-ms cycle length)

|                  |                  |                  |
| SN→RAA           | 54 (51, 55)      | 43 (42, 47)      | NP               | NP               |
| SN→LAA           | 90 (69, 108)     | 96 (86, 105)     | NP               | NP               |
| RAA→LAA          | 101 (92, 101)    | 103 (89, 117)    | NP               | NP               |

QTc indicates QT interval corrected for heart rate by use of Bazett’s formula; SN→RAA, pacing at sinus node and measurement of conduction time at right atrial appendage; SN→LAA, pacing at sinus node and measurement of conduction time at left atrial appendage; RAA→LAA, pacing at right atrial appendage and measurement of conduction time at left atrial appendage; bpm, beats per minute; and NP, test not performed in that group.

Data are reported as median (interquartile range). Time unit for all measures (except heart rate) is milliseconds. *P<0.01, ‡P=NS for all between-group comparisons.
pharmaceutical options are limited by efficacy and safety concerns. Approximately half of all patients who begin therapy with an antiarrhythmic drug today will be back in AF within 1 year, and 10% to 30% will have therapy-limiting side effects.\(^4,5\) Compared with pharmacotherapy, gene therapy has the advantages of more robust ionic current block and localized effect, which allows more aggressive action in the atria without danger of ventricular effects. Pharmacological block of an ion channel is controlled by drug biodistribution, affinity for the target channel, and the need to bind the channel in a particular physiological state. Gene transfer with a dominant negative mutant circumvents these limitations by infiltrating and polluting individual channel function as channels are formed inside the cell.

The differences between drug and gene therapy become apparent when the present results are compared with those of Blaauw et al,\(^17\) who investigated \(I_{Kr}\)-blocking drugs in the goat burst-pacing AF model. At baseline, ibutilide and dofetilide increased the atrial effective refractory period by \(\approx 20\%\). After 48 hours of burst pacing and AF, the effective refractory period–prolonging effects of the drugs were almost completely lost, and the drugs had no preventative effect against AF. Unfortunately, the QT-prolonging effect of the \(I_{Kr}\)-blocking drugs was not lost, so drug dosing was limited by ventricular effects. In contrast, we saw that \(I_{Kr}\) disruption by gene therapy was durable throughout the time of gene expression, and there were no ventricular effects that would limit dose.

Broad translation to the treatment of AF will require a less invasive delivery method and stable long-term gene expression. Percutaneous access to the pericardial space has already been described for minimally invasive cardiac surgery and arrhythmia ablation.\(^18,19\) Development of similar tool sets for gene painting should solve that problem. The 3-week limitation to gene expression in the present study is a well-reported characteristic of adenovirus vectors.\(^16\) This constraint would be unacceptable in patients who would need permanent therapy. Adeno-associated virus and lentivirus vectors have achieved long-lasting, stable gene expression in other applications,\(^20,21\) and they should work similarly for atrial gene painting. Of course, long-term testing with an appropriate AF model and preferably continuous telemetry with a system that can reliably distinguish AF from burst pacing would be required to establish efficacy and stable expression before translation to the much more complex environment of permanent AF.

One potential concern is the utility of this approach in situations in which atrial APD is already prolonged. Kirchoff et al\(^22\) noted atrial APD prolongation and arrhythmia vulnerability in congenital long-QT syndrome patients with a variety of genotypes, and Johnson et al\(^23\) found an association between early-onset AF and KCNQ1 mutations in patients with long-QT syndrome. A dog model of ventricular tachypacing–induced heart failure found that atrial APD increased with the occurrence of heart failure and that increased atrial APD correlated with vulnerability for AF induction.\(^24\) Although a recent study showed that AF in human heart failure was actually associated with shortened atrial APD,\(^25\) the number of subjects in both studies was small, which raises the possibility that both mechanisms may be relevant to different situations. These findings raise the question of whether further APD prolongation might be helpful or harmful. For the most part, these are observational reports in very small numbers of patients, and clinical trials with pharmacological block of \(I_{Kr}\) have been associated with AF termination, not AF induction.\(^26\)

Of even greater interest is a recent study of the KCNH2 polymorphism K897T. The common allele K897 is associated with an average QT interval and an odds ratio of 1.25 for development of AF relative to the rare T897 allele, which increases \(I_{Kr}\) and shortens ventricular repolarization times.\(^27\) Ultimately, more research is required to address the question of possible interactions of atrium-specific G628S gene therapy in heart failure or other situations in which atrial APD might be long at baseline.

**Specific Application to Postoperative AF**

Application to the problem of post–cardiac surgery AF is a natural extension of our data. With the chest already opened for the surgical procedure, access to the cardiac atria for gene painting is straightforward. The timing of therapeutic effect in the present experiments corresponds to the observed time of AF vulnerability after cardiac surgery, with peak AF risk 3 days after the surgical procedure, which corresponds to the time of gene expression. For the most part, resolution of AF risk occurs 1 to 2 weeks after surgery, which is shortly before loss of expression occurs with the adenovirus vector.\(^28\)

Postoperative AF affects 30% to 50% of the several hundred thousand patients undergoing cardiac procedures each year, lengthening hospital and intensive care unit stay and increasing risk for stroke and in-hospital and long-term mortality.\(^29\) The mechanism of postoperative AF remains controversial. Prior studies have implicated a variety of factors, including preexisting atrial fibrosis, expression levels of various ion channels, metabolic or oxidative stress on myocytes, alterations in connexin expression, and adrenergic, purinergic, and/or cholinergic stimulation.\(^30,36\) The model used in the present study would appear to be ideally suited to test efficacy in the postoperative setting. Just as in the human cardiac surgical situation, we opened the chest, manipulated the heart, and saw postoperative inflammation and adhesions (in all animals, including no-painting control animals). In spite of this extensive manipulation, we saw the efficacy of G628S gene painting in the postoperative setting. These findings suggest that our intervention could have enormous impact on this pervasive problem.

**Summary**

Here, we have shown that atrial gene painting with KCNH2-G628S lengthens atrial APD and disrupts AF. The duration of these effects correlated to the time of gene expression, which suggests that longer-lasting effects should be possible with expression vectors that allow long-term, possibly permanent gene expression. An important consistent
finding with our method was the absence of ventricular effects from atrial painting. This localization of therapy distinguishes gene-transfer approaches from conventional drug therapy. Not only does it increase the safety of the method, but it also potentially improves efficacy by allowing higher-intensity atrial therapy without the limitation of concomitant ventricular adverse effects. Future studies could include investigation of long-term efficacy with a permanently expressing gene-transfer vector, investigation of efficacy in other AF models (eg, old age or preexisting heart failure), and dissection of gene-transfer effects on the target ion channel and other channels that participate in the repolarization process. Taken together, the present efficacy and safety data suggest that atrial gene painting with KCNH2-G628S could become an effective and safe therapy for the prevention or termination of AF.

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Disclosures
Dr Donahue has an ownership interest in Excigen Inc, an arrhythmia gene therapy company. The remaining authors report no conflicts.

References
CLINICAL PERSPECTIVE

Atrial fibrillation is the most common arrhythmia found in clinical practice, affecting 2 to 5 million people in the United States and several million more worldwide. The presence of atrial fibrillation substantially increases individual risk of stroke, heart failure, and death. A principal limitation to clinical practice is the lack of safe, effective therapies for this pervasive arrhythmia. We previously reported a gene-painting method capable of 100% transmural gene transfer to all parts of the atria accessible from an open-chest pericardium approach. In the present report, we used this method to transduce the atria with KCNH2-G628S, a mutation that blocks the rapid component of the delayed rectifier potassium current. This current is also blocked by class III antiarrhythmic drugs, but those drugs affect atrial and ventricular myocytes alike. The painting method is specific to atrial myocytes. We found that KCNH2-G628S gene transfer prolonged atrial action potential and prevented atrial fibrillation. This effect correlated with the time course of transgene expression. The method should be directly applicable to the problem of postoperative atrial fibrillation. With modifications to increase duration of gene expression and to reduce the invasive nature of delivery, the method should also be applicable to general atrial fibrillation. Formal preclinical testing is required before clinical investigation.
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