Focal Pharmacological Modulation of Atrioventricular Nodal Conduction via Implantable Catheter

A Novel Therapy for Atrial Fibrillation?

Daniel C. Sigg, MD, PhD; Prasanga Hiniduma-Lokuge, MS; James A. Coles, Jr, PhD; Phillip Falkner, DVM; Rebecca Rose, DVM, PhD; Jon F. Urban, PhD; Michael R. Ujhelyi, PharmD

Background—Pharmacological ventricular rate control is an acceptable atrial fibrillation (AF) therapy limited by systemic toxicity. We postulate that focal catheter-based drug delivery into the atrioventricular nodal (AVN) region may effectively control ventricular rate during AF without systemic toxicity. This study evaluated the effects of focally administered acetylcholine on AVN conduction and refractoriness during sinus rhythm and AF.

Methods and Results—Canines (n=7) were anesthetized and instrumented to assess cardiac electrophysiology and blood pressure. A custom drug delivery catheter was implanted in the AVN region. Incremental doses of acetylcholine starting at 10 μg/min were infused until complete AV block was achieved. Acetylcholine induced dose-dependent AV block. AF induction and electrophysiology measurements were performed during baseline and acetylcholine-induced first-degree and third-degree AV block. During AF, infusion of acetylcholine decreased ventricular rates from 182±32 to 77±28 and 28±8 bpm (first-degree and third-degree AV block, respectively; P<0.05). At the first-degree AV block dose, AVN effective refractory period increased from 186±37 to 282±33 ms, and Wenckebach cycle length increased from 271±29 to 378±58 ms (P<0.05). The first-degree AV block dose prolonged AV and AH intervals by 26% and 23% (P<0.05), whereas AA intervals and blood pressure remained unchanged, demonstrating a local effect. All effects were reversed 20 minutes after infusion was stopped.

Conclusions—Focal acetylcholine delivery into the AVN increased AVN refractoriness and significantly decreased ventricular rate response during induced AF in a dose-related, reversible manner without systemic side effects. This may represent a novel therapy for AF whereby ventricular rate is controlled with the use of an implantable drug delivery system. (Circulation. 2006;113:2383-2390.)

Key Words: acetylcholine • catheters • conduction • pharmacology • tachyarrhythmias
profound electrophysiological (EP) changes within the AVN region that would slow the depolarization waveform from the atria to the ventricles in a dose-dependent fashion.

The goal of this study was to prove the concept that AVN conduction and refractoriness can be modulated pharmacologically via focal perfusion of pharmacological agents at subsystemic dosages in an intact animal. More specifically, the dose-response effects of a continuous infusion of acetylcholine to the AVN with particular focus on AVN refractoriness were evaluated. After identifying an optimal dose, we tested the hypothesis that low-dose acetylcholine infusion would prevent rapid ventricular response during electrically induced AF.

Methods

Animal Preparation and Surgical Instrumentation
All procedures were reviewed and approved by an internal independent animal review committee. All procedures conformed to the Guide for the Care and Use of Laboratory Animals (Department of Health, Education, and Welfare [Department of Health and Human Services] publication (National Institutes of Health) No. 85-23, revised 1996). Dogs (n = 7) (Twin Valley Kennel, Spring Green, Wis, and Covance, Kalamazoo, Mich) of random sex were anesthetized and induced AF. 

Continuous Delivery of Acetylcholine: Identification of Maximum Dose

After washout and return of EPCP and AVN ERP to baseline, 1 mg/mL acetylcholine was continuously delivered at increasing infusion rates for 10 minutes at each rate. This was accomplished by connecting the proximal Luer end of the catheter to a programmable syringe pump (Harvard Apparatus PHD 22/2000, Holliston, Mass). The specific infusion rates tested were 10, 20,
40, 80, 100, 120, 150, and 200 μg/min. At each dose, EPCP were assessed. The dose that produced complete heart block (third-degree AV block) was noted (maximum dose). Subsequently, AF was electrically induced during continuous infusion at this dose, and EPCP and RR intervals were recorded. A washout period of at least 20 minutes followed the initial dose-response studies, and EPCP were recorded in all animals to ensure full recovery of AV block. In several animals, data for AVN ERP, Wenckebach cycle lengths, and RR intervals during electrically induced AF were collected to further verify the reversibility of pharmacological third-degree AV block.

### Continuous Delivery of Acetylcholine: Identification of Minimum (First-Degree AV Block) Dose and Final Washout
Because of the steep dose-response curve in combination with a lengthy experimental protocol, it was necessary to adjust the initial target dosage in several animals to establish a stable first-degree AV block. First-degree AV block was defined by a consistent PR prolongation from baseline without occurrence of second-degree AV block. Once this dose was identified (minimum dose) and administered, EPCP, AVN ERP, Wenckebach cycle length, and RR intervals during electrically induced AF were assessed at the end of the dosage interval.

The drug was allowed to wash out again over at least a 20-minute period, and data for final EPCP, AVN ERP, Wenckebach cycle length, and RR intervals during electrically induced AF were collected to verify the reversibility of pharmacological first-degree AV block. Blood pressures and AA intervals are summarized in the online-only Data Supplement (Figure IIIC).

### Evaluating Systemic Effects
In selected animals (n=5), the pharmacodynamic effects of intravenous bolus administration of acetylcholine were studied for comparison with the effects observed during direct AVN bolus administration. In these animals, acetylcholine was administered intravenously at a dosage of 1 mg (in 1 mL) over a peripheral venous catheter and immediately flushed with saline 0.9%, and electrophysiological EPCP data and blood pressures were recorded.

### EP Measurements
#### AVN Effective Refractory Period
To determine the AVN ERP, a stimulus (S1) train of 10 beats with an S1-S1 interval of 400 was delivered via the right atrial appendage EP catheter. The eleventh stimulus (S2) was delivered at an interval (S1-S2) of 350 ms. The sequence was repeated by decreasing the S1-S2 interval by 10 ms until no ventricular response was observed. The longest S1-S2 interval that failed to produce a stimulus (conduit through the AVN) was the AVN ERP.

#### Wenckebach Cycle Lengths
AVN refractoriness was also determined by noting Wenckebach-type behavior (eg, 5:4, 4:3) at increasing atrial pacing rates. The AA interval at which AV block was observed was defined as Wenckebach cycle length.

#### RR Intervals During Electrically Induced AF
AF was induced via a quadripolar EP catheter located in the right atrial appendage. The atrium was paced at 10 mA with the use of a 300-ms cycle length for 10 beats followed by a 50-ms pause and a 20-Hz pulse train (10-ms pulse width) lasting 500 ms (10 pulses). If AF was not induced, the pacing stimuli were repeated, and the pulse train length was increased to 750 ms until the induction of nonsustained AF episodes lasting at least 15 seconds. The RR intervals of 3 AF episodes were averaged.

### Data Collection and Analysis
EP data and blood pressures were recorded digitally with the use of a Windows-based PC and the Prucka CardioLab Software (version 5.1D) on the Prucka CardioLab EP System (GE Healthcare). Statistical analysis was done with the use of the Wilcoxon signed-rank test with the exception of the 2-sample t test, which was applied for the comparison of intravenous and direct AVN bolus data. Statistical significance was inferred if the probability value was <0.05.

### Pathology and Histopathology
After termination, animals were subjected to a partial necropsy; hearts were opened, and the location of the implant site was determined either by direct visualization of an implanted lead or by assessment of disturbed endocardium. Histopathology was performed on each of the 7 animals to determine proximity of the implant site to the AVN. Tissue between the ostium of the coronary sinus and the membranous septum was cut into 3-mm slices, with each slice running perpendicular to the annulus of the tricuspid valve. Slices were fixed in 10% neutral-buffered formalin, embedded in paraffin, and cut into 3-μm sections. Duplicate sections were stained with hematoxylin and eosin and with Masson’s trichrome. For each animal, the location of the implant site was determined by a combination of the following factors: degeneration or necrosis of cardiac myofibers, a breach in the endocardium, mural thrombus, hemorrhage, and disruption of the myocardium. The location of the AVN was determined by the typical size, appearance, and location of the AVN myofibers.

The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.

### Results
#### Bolus Injection of Acetylcholine
Correct location of the AVN catheter was verified initially by a prolonged AV block after focal acetylcholine administration. We were able to elicit prolonged third-degree AV block in all 7 animals. To ensure that the observed effect was not systemic, an identical dose of acetylcholine was administered intravenously. Direct AVN injection was associated with a mean third-degree AV block duration of 10.61±6.22 minutes (n=7), whereas intravenous administration showed no occurrence of third-degree AV block (Table). The occurrence and prolonged duration of third-degree AVN block observed after focal AVN injection of acetylcholine strongly suggest a local effect. To further rule out any systemic effects of focally delivered acetylcholine, we also measured blood pressures as well as AA intervals to investigate any negative chronotropic effects mediated via binding of acetylcholine to the sinus node or to peripheral vascular receptors. AVN and intravenous bolus injection of 1 mg acetylcholine induced no statistically significant effects on AA intervals, whereas both delivery methods induced a very transient hypotensive effect (online-only Data Supplement, Figures IIIA and IIIB). These data demonstrate a local effect with minimal spillover even though systemic doses were delivered into the AVN region.

### Third-Degree AV Block Duration and Overall AV Block Duration for Direct AVN Bolus Injection vs Intravenous Bolus Injection

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<tr>
<td>Overall AV block duration, min</td>
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<tr>
<td>Third-degree AV block duration, min</td>
<td>10.61±6.22</td>
<td>0.00±0.00</td>
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</table>

*Duration of first-, second-, and third-degree AV block.
Continuous Delivery of Acetylcholine: Identification of Maximum Dose

The EPCP during incremental acetylcholine infusion are summarized in Table I of the online-only Data Supplement. These data show a dose-response increase in PR and AH intervals without any effect on HV, QRS, and QT intervals, demonstrating a specific local effect on AVN conduction. A stable fixation of the His catheter for continuous recording of His signals throughout the study protocol was attempted in all animals but was only achieved in n=10 animals throughout the study protocol. Interestingly, but not surprisingly, there was variability in the onset of AV block in the dose-response studies (see online-only Data Supplement, Figure IV); the mean (±SD) dosage to induce third-degree AV block was 90±66 μg/min.

Continuous Delivery of Acetylcholine: Identification of Minimum (First-Degree AV Block) Dose and Final Washout

After another washout phase, the dose that induced first-degree AV block (minimum dose) was established. The mean (±SD) dosage to accomplish a stable first-degree AV block was 36±32 μg/min. During the administration of the minimum dose, a reversible increase in AH, AV, and PR intervals by 23%, 26%, and 27%, respectively, was observed (Figure 2).

During administration of the minimum dosage, there was a reversible increase of AVN refractoriness. More specifically, AVN ERP and Wenckebach cycle length increased by 51% and 39%, respectively, compared with baseline and by 71% and 49% compared with maximum dose washout, respectively (P<0.05; Figure 3A and 3B). These effects were fully reversible after drug washout. In 1 animal, AVN ERP could not be tested at minimum dosage because the Wenckebach cycle length was >400 ms during minimum dosage.

RR Intervals During Electrically Induced AF

Finally, the ability of acetylcholine to modulate ventricular rate during induced AF was assessed at the first- and third-degree AV block doses. At the first-degree AV block dosage, RR intervals during AF were reduced from 182±32 to 77±28 bpm (P<0.05). At the third-degree AV block infusion dose, AF induction had no effect on RR intervals. The heart rate was dependent on the ventricular escape interval, and there was complete AV dissociation. These data are summarized in Figure 4A and 4B.

Gross Pathological and Histopathological Analysis

All 7 AVN catheter implant sites were either within the triangle of Koch or at its edge (Figure 5). Histopathological analysis of the AVN region showed that the implant sites were either in the same section as the AVN (n=2), in a
section 3 mm from the AVN (n=2), or in a section 3 to 6 mm from the AVN (n=2) (Figure 6A and 6B). The implant site in 1 animal could not be identified histologically. Generally, histopathological changes in the tissues were those expected from careful placement of a catheter with a helical fixation mechanism.

Discussion

In the present study it was demonstrated that AVN refractoriness can be modulated by focal pharmacological delivery of the muscarinic agonist acetylcholine. In all animals, AVN refractoriness increased, even at the minimum dosage (eg, first-degree AV block dosage) tested. More importantly, the ventricular rate response during electrically induced AF was reduced to physiological levels during the minimum dosage: average heart rates of 182 bpm during AF without drug decreased to 77 bpm during the first-degree AV block dosage. This represents an average decrease of 58%, and all observed electrophysiological changes were completely reversible. Therefore, we demonstrated, on a proof of concept level, that focal catheter-based drug delivery directed to the AVN region may be a feasible approach to treat AF. Because we observed consistent and reversible increases in PR, AV, and AH intervals with no systemic effects (eg, changes in sinoatrial rate or blood pressures), a specific local effect of acetylcholine has been demonstrated in this study. In support of a specific local effect is the observation that in 5 of the 7 study animals, the AVN catheter needed to be initially repositioned because of lack of third-degree AV block occurrence after 1 mg acetylcholine was delivered as a bolus after successful catheter fixation in the atrial tissue.
After repositioning of the catheter, prolonged third-degree AV block was observed in all 5 animals, further confirming a highly specific location-dependent effect. Moreover, administration of 1 mg acetylcholine intravenously did not result in any occurrence of third-degree AVN block, further supporting a local effect.

AF remains a significant problem in Western society, and its socioeconomic impact is likely to continue to increase. Treatment approaches include ablation, pharmacotherapy, and device-based therapies. Rate-control approaches have shown at least equivalent overall mortality, AF-related symptoms, and quality of life compared with rhythm-control approaches in several clinical trials.1,2,4–6 However, a combination of numerous drugs is often necessary to effectively control ventricular rate, leading to significant side effects. In the present report we propose a novel method of treating AF, namely, focal drug therapy. The advantage of this method is that subsystemic doses of drugs (eg, <10% of the intravenous dose) can be delivered to the target site, thereby avoiding systemic side effects. For example, in the present study, focal bolus administration of 1 mg acetylcholine to the AVN was associated with a prolonged third-degree AV block, whereas administration of the same dose intravenously did not induce third-degree AV block at all. During continuous administration, the average dose of acetylcholine that effectively controlled ventricular rate response during induced AF was 35 µg/min, and at these dosages, no systemic side effects were observed (eg, negative chronotropic effects or hypotension).

Focal administration of acetylcholine to the AVN has been accomplished in dogs via the AVN artery, and an increase in AVN refractoriness was reported.7 The mechanisms of action of acetylcholine on the AVN have been described elsewhere.8,9

Limitations

Although a short-acting muscarinic agonist was clearly a suitable drug for proof of concept for many reasons, this particular drug would be unsuitable for a long-term (pump-based) clinical application. Acetylcholine is not very stable in solution, and the observed dose-response curves in the present study may be too steep (eg, the therapeutic window is too small). Because of these potential limitations, we tested a clinically more relevant drug, the calcium antagonist verapamil, in pilot studies and observed promising effects with a much wider therapeutic window, as well as successful control...
of ventricular rate during electrically induced AF (data not shown).

Another concern is that long-term application of cholinergic drugs such as methacholine could maintain paroxysmal AF. In our study there was no evidence that AVN acetylcholine infusion would maintain AF because almost all electrically induced AF episodes ended spontaneously and were nonsustained.

One of the challenges of this particular study was to establish a dosage that could induce a sustained first-degree AV block. The dose-response curves were very steep, and first-degree AV block was often observed only transiently before the animals went relatively quickly into second- or third-degree AV block (see online-only Data Supplement, Figure IV). In several animals, a number of dose adjustments were necessary to ultimately identify a dosage that induced a sustained first-degree AV block (minimum dosage). It is possible that isoflurane or otherwise induced changes of autonomic tone during the lengthy experimental protocol (up to 9 hours) may be partially responsible for this phenomenon.

Although the amount of variability in the dose-response curves between animals was significant, this was not necessarily unexpected. This could be explained by the location of the AVN catheter tip relative to the AVN. The variability may certainly be dependent on the diffusion distance and overall diffusion characteristics and diffusion pathways of the catheter tip relative to the AVN, a very complex structure. Although theoretically it would be desirable to keep the effective volume administered constant and change the drug concentration for the dose-response studies, for practical reasons we needed to operate with a constant concentration and changed the infusion volume to adjust the effective dosages. In addition, this is the typical dosing strategy that would be used in a clinical application. To better correlate anatomic data (catheter location and fluid delivery paths) with physiological function, additional studies with the use of marker dyes delivered to the AVN in conjunction with acetylcholine may be required.

In a long-term application, it is possible that a helical drug delivery catheter could potentially lead to fibrotic changes subsequent to the initial tissue injury evolving from the implant site. This might have an impact on the effect of catheter-delivered drug over time, and this potential limitation would need to be addressed in long-term studies.

One could envision that an implantable AVN drug delivery catheter could be connected to an implantable pump containing verapamil or similar drugs. The drug pump device could be a hybrid device also containing an internal electronic pacemaker connected to a ventricular sensing/pacing lead. This system could work in an open-loop (physician-controlled) or closed-loop (sensor-driven) feedback fashion and deliver therapeutic dosages of an agent to the AVN and/or pace on the basis of RR and PR intervals. In particular, the AVN catheter used in this study has sensing as well as pacing features and hence could be used to detect and record the atrial electrogram and pace the atria as well.

The ultimate clinical application could involve focal drug delivery regulated via a closed-loop feedback sensing system whereby the drug delivery is titrated to achieve a desirable ventricular rate for supraventricular tachyarrhythmia therapies to regulate AVN refractoriness into a physiological range that averts the need for ventricular pacing. Importantly, managing supraventricular tachyarrhythmias with this approach would not only have the advantage of closed-loop feedback, physiological conduction, and backup ventricular pacing but would also be associated with extremely low or immeasurable systemic drug levels, and therefore no systemic side effects. In addition, unlike biological therapies, the achieved therapeutic effects are highly controllable and fully reversible. This novel therapy would be associated with highly effective, therapeutic local drug levels and consequently virtually no systemic side effects. Finally, this technology may be advantageous not only for patients with chronic AF but also for those suffering from paroxysmal AF. In these patients, drug delivery could be initiated “on demand” by sensing AF and ventricular rate response and titrated to effect. This would be a key differentiator of this novel concept from current therapies, including pharmacotherapy for rate control or ablate and pace.

In summary, we have provided proof of concept that focal AVN drug delivery can be used successfully to modulate AVN refractoriness at subsystemic dosages. During electrically induced AF, AVN conduction was maintained, but ventricular heart rate was slowed down from pathological to physiological and clinically relevant levels. Long-term preclinical studies need to be conducted as a next step to address the long-term efficacy and safety of this interesting and novel concept for the treatment of chronic AF.

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Disclosures

All of the authors are employed by and have an ownership interest in Medtronic, Inc.

References


**CLINICAL PERSPECTIVE**

Local drug delivery to the atrioventricular nodal (AVN) region may offer a unique solution for atrial fibrillation (AF) management. The advantages of local drug delivery include increased effectiveness and decreased systemic toxicity. The local dose can be 10-fold lower than systemic doses, thereby minimizing systemic exposure with similar effectiveness. Indeed, the present study proved that local AVN drug delivery can control ventricular rate during AF without having a systemic effect. Given the above, it is reasonable to believe that this therapy may offer distinct benefits over pace and ablate therapy. The greatest advantage is that local drug delivery is reversible, and therefore if the patient received a curative therapy the system could be turned off and perhaps removed. Reversibility is not the case for pace and ablate therapy. Although not yet ready for clinical use, the next step for this research is to develop the drug delivery system and perform long-term testing. It is envisioned that this system would be implanted like a pacemaker and would contain a drug pump and pacemaker. Leads would be implanted into the atrium, AVN, and ventricle. The system would continuously monitor for AF and rapid ventricular response. Drug therapy would be regulated when AF and a high ventricular rate are detected. The system would continuously titrate drug dose to a desired ventricular rate and employ pacemaker therapy if the ventricular rate became too slow.
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Figure I. Data Supplement: Panel A: Fluoroscopic Image taken after injection of 100µL Isovue™ confirming intramyocardial location of AVN drug delivery catheter (A), and also showing the Medtronic Attain™ delivery catheter (B). Panel B: Custom Medtronic Attain™ catheter used for delivery of AVN catheter.
**Figure II.** Data Supplement: Procedural flowchart describing the procedure of delivering the AVN catheter step by step.

1. Obtain biplane fluoroscopic images of the heart and import into GUI of the Cardiac Navigation system
2. Map and Store His-points and points at the CS Os on biplane virtual fluoroscopic GUI using a custom Medtronic EP Navigation Catheter
4. Navigate ATTAIN™ Catheter Model 6226DEF with 10158 Navigation Insert to stored points using the GUI
5. Remove 10158 Navigation Catheter Insert
6. Deliver AVN catheter via ATTAIN™ Catheter Model 6226DEF to AVN and fixate under fluoroscopic control
Figure IIIA. Data Supplement: Mean (± SD) AA intervals (AA) and blood pressures (BP) at baseline and after bolus administration of 1 mg acetylcholine directly into the AVN.
Figure IIIIB. Data Supplement: Mean (± SD) AA intervals (AA) and blood pressures (BP) at baseline and after intravenous bolus administration of 1 mg acetylcholine.
Figure III C. Data Supplement: Average Blood Pressure (Panel A) and AA interval (Panel B) before, during and after washout of minimum dosage of Acetylcholine (dosage inducing first-degree AVN block). No statistical differences were detected.
**Figure IV.** Data Supplement: Individual Dose-Response Curves. The AV Block Category is shown on the Y-axis, while the continuous infusion rate is shown on the X-axis. Because of the steep dose-response curves in combination with a lengthy experimental protocol, it was necessary to adjust the initial target dosage (minimum dosage) in several animals in order to establish a stable first-degree AV block.
Supplemental Data

Table I. Mean EP Intervals for dose response. All values are in msec.

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