Nonpharmacologic Control of Postoperative Supraventricular Arrhythmias Using AV Nodal Fat Pad Stimulation in a Young Animal Open Heart Surgical Model

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Background—Supraventricular arrhythmias (junctional ectopic tachycardia [JET] and atrial tachyarrhythmias) frequently complicate recovery from open heart surgery in children and can be difficult to manage. Medical treatment of JET can result in significant morbidity. Our goal was to develop a nonpharmacological approach using autonomic stimulation of selective fat pad (FP) regions of the heart in a young canine model of open heart surgery to control 2 common postoperative supraventricular arrhythmias.

Methods and Results—Eight mongrel dogs, varying in age from 5 to 8 months and weighting 22±4 kg, underwent open heart surgery replicating a nontransannular approach to tetralogy of Fallot repair. Neural stimulation of the right inferior FP was used to control the ventricular response to supraventricular arrhythmias. Right inferior FP stimulation decreased baseline AV nodal conduction without altering sinus cycle length. AV node Wenckebach cycle length prolonged from 270±33 to 352±89 ms, P<0.001. Atrial fibrillation occurred in 7 animals, simulating a rapid atrial tachyarrhythmias. FP stimulation slowed the ventricular response rate from 166±58 to 63±29 beats per minute, P<0.001. Postoperative JET occurred in 7 dogs. FP stimulation slowed the ventricular rate during postoperative JET from 148±31 to 106±32 beats per minute, P<0.001, and restored sinus rhythm in 7/7 dogs.

Conclusions—Right inferior FP stimulation had a selective effect on the AV node, and slowed the ventricular rate during postoperative JET and atrial tachyarrhythmias in our young canine open heart surgery model. FP stimulation may be a useful new technique for managing children with JET and atrial tachyarrhythmias. (Circ Arrhythm Electrophysiol. 2013;6:641-647.)

Key Words: animal model surgery □ atrial tachycardia □ atrioventricular node □ autonomic nervous system □ fat pad stimulation □ junctional ectopic tachycardia □ pediatric

Supraventricular arrhythmias frequently complicate the postoperative recovery from open heart surgery (OHS) in children. In 2011, Smith et al reported their institutional experience evaluating the frequency of postoperative arrhythmias in 724 children undergoing OHS. In reviewing their experience, the authors noted that junctional ectopic tachycardia (JET) and accelerated junctional rhythm occurred in 18% of their population, and atrial tachyarrhythmias (AT) occurred in 8%. JET and AT can be difficult to medically manage. Pharmacological treatment of JET can result in significant morbidity, such as excessive bradycardia and hypotension.2 Prolonged intubation with neuromuscular paralysis is required if hypothermia and cooling are used.3

Previous research has shown the presence in the heart of localized concentrations of parasympathetic nerve cell bodies in fat pads (FPs).4,5 Using a chronic canine model of atrial fibrillation, Wallick et al6 were able to perform FP stimulation to achieve well-tolerated rate control in this animal model. FP stimulation may be a useful new clinical technique for managing children with postoperative atrial arrhythmias that occur after OHS. We hypothesized that the right inferior AV nodal FP has a selective parasympathetic effect on the AV node that may be exploited to help in the control of supraventricular arrhythmias, specifically junctional ectopic tachycardia. Our goal was to develop a nonpharmacological approach using autonomic stimulation of the right inferior FP region of the heart to control 2 common postoperative supraventricular arrhythmias, specifically JET and AT.

Clinical Perspective on p 647

Experimental Preparation

The research protocol was approved by the Animal Care and Use Committee of The George Washington School of Medicine and Children’s National Medical Center. All animals received humane...
Atrial Fibrillation and JET Induction
Atrial fibrillation frequently occurred spontaneous during surgical manipulation of the heart. If not spontaneous, sustained atrial fibrillation was induced using rapid atrial stimulation.

After completion of the baseline atrial stimulation protocol, cardiopulmonary bypass was instituted to allow induction of JET. Heparin (200 U/kg) was administered for a goal ACT above 400 s. The superior and inferior vena cavae were cannulated using a 20 to 32 Fr right-angled, wire reinforced venous return cannulae (Terumo Cardiovascular Systems Corporation, Ann Arbor, MI) after ligating and dividing the ayzygous vein. The aorta was cannulated using a 10 to 16 Fr straight Bio-Medicus arterial cannula (Medtronic, Minneapolis, MN).

Cardiopulmonary bypass was initiated using a Sarns 8000 roller pump (Terumo Cardiovascular Systems Corporation, Ann Arbor, MI) and membrane oxygenator (Terumo CAPIOX oxygenator [Terumo Cardiovascular Systems Corporation, Ann Arbor, MI] and Dideco D733 arterial filter [Sorin Group USA, Inc, Arvada, CO]). The circuit was primed with Plasma-Lyte A to a goal hematocrit >25%. After institution of cardiopulmonary bypass, core temperature was cooled to 30 to 32°C because it is used in surgical repair of infants with congenital heart disease. Once on stable cardiopulmonary bypass, replication of a nontransannular approach to tetralogy of Fallot repair was performed after cardioplegia administration and induction of hypothermia. These steps involved (1) surgical exploration of the right atrium and right ventricle, (2) stretch of the tricuspid valve, (3) suturing a Gortex patch in the perimembranous region of the right ventricle using pledgeted sutures, and (4) performing a nontransanular right ventricular outflow patch in half of the animals. Aortic cross clamp duration varied between 30 and 60 minutes, and cardiopulmonary bypass time exceeded 120 minutes.

The dog was subsequently weaned from cardiopulmonary bypass after rewarmon on dopamine and isoproterenol. If JET did not spontaneously happen, the sinus node region was crush with a clamp to produce mild sinus node dysfunction. If JET still was not observed after crush of the sinus node, digoxin was administered in small incremental doses (250 μg) until the desired effect was achieved (ie, the development of JET). We demonstrated our findings after weaning the experiment subjects from cardiopulmonary bypass and observed the animals for periods ≤5 to 5 hours postoperatively.

FP Neural Stimulation
Neural stimulation of the right inferior FP was performed using a Grass Telefactor model SD9 neurostimulator (West Warwick, RI) outputting a square wave pulse at a stimulation frequency between 20 and 30 Hz. The pulse amplitude varied between 8 and 15 V at a pulse width of 0.15 ms. Stimulation was performed continuously for a defined time interval of 15 to 30 s.

Statistical Analysis
Descriptive statistics were reported as the mean±SD. For cardiac parameters, 3 repeated measurements of the response before (pre) and after (post) AV nodal FP stimulation for each of the study outcomes were collected and used in the analysis. After first checking the normality assumption, we implemented random effect longitudinal linear models in STATA 11.2 (Statacorp, College Station, TX) to compare the pre versus post time-averaged estimates of basal sinus heart rate and AV node Wenckebach cycle length. The model corrected variance estimates for the correlation between repeat assessments on the same animal. We used the Swamy-Arora estimator and
the robust option to improve the estimation of individual variance in this small sample. The coefficient for the variable time was used to test whether the pre versus post means were statistically different with a 2-tailed, type 1 error of 0.05.

Results

Effect of FP Stimulation on the Sinus Node
Right inferior FP stimulation decreased AV nodal conduction without altering sinus cycle length. No change, specifically slowing of the heart rate was noted after the onset of FP stimulation. The mean heart rate in the baseline state was not altered after FP stimulation (96±23 versus 97±23 beats per minute [N=8; P=0.70]).

Effect of FP Stimulation on AV Node Conduction During Atrial Fibrillation
As demonstrated in Figure 2, AV nodal FP stimulation diminished AV nodal conduction. On average, the AV node Wenckebach cycle length significantly prolonged from 270±33 to 352±89 ms after FP stimulation (N=6; P=0.02).

Effect of FP Stimulation on AV Node Conduction During JET
We next studied the effect of AV nodal FP stimulation during JET (Figure 4). On the left-hand side of the atrial electrogram channel (Figure 4A), evident was the simultaneous occurrence of the atrial and ventricular electrograms, consistent with JET. After the onset of FP stimulation, the ventricular rate slowed, and the atrial and ventricular electrograms separated, with the atrial electrogram preceding the ventricular electrogram, indicating the development of sinus rhythm. These observations were confirmed on the surface ECG. An increase in the systolic blood pressure accompanied the development of sinus rhythm. When AV nodal FP stimulation was terminated (Figure 4B), indicated by the cessation of activity on the FP stimulation channel, sinus rhythm graduated transitioned back to JET and was accompanied by an increase in the ventricular rate and a decline in the systolic blood pressure. As demonstrated in Figure 4A and 4B, AV nodal FP stimulation diminished the ventricular rate during JET. On average, AV nodal FP stimulation significantly slowed the average ventricular rate during JET from 148±31 to 106±32 beats per minute (N=7; P<0.001). Sinus rhythm occurred in 7 of 7 experiments. Sinus rhythm developed during the period of FP stimulation. When FP stimulation was terminated, the rate of JET gradually increased back to the baseline rate.

Discussion
In our canine experiments, we observed that right inferior AV node FP stimulation had a selective effect on the AV node, decreasing AV nodal conduction. No significant change in the sinus cycle length was observed. Using our animal model, we were able to create sustained episodes of atrial fibrillation and postoperative JET. Right inferior AV node FP stimulation slowed the ventricular rate during postoperative JET and atrial fibrillation in our young canine OHS model. These results demonstrate the ability of right inferior AV node FP stimulation to not only decrease AV nodal conduction but also peri-AV nodal automaticity, demonstrated in these experiments for the first time.

Postoperative atrial arrhythmias are common in children after OHS. Grosse-Wortmann et al studied the prevalence of arrhythmias in children undergoing OHS. Using serial 24-hour Holter ECG, these investigators found a high incidence of atrial arrhythmias in the first 24 hours after OHS (supraventricular tachycardia, 7%; accelerated junctional
rhythm, 14%; JET, 9%). In newborns and infants, the prevalence of supraventricular arrhythmias was similar (supraventricular tachycardia, 12.7%; accelerated junctional rhythm, 16.7%; JET, 5.4%). Medical treatment of these atrial arrhythmias can result in significant morbidity, such as excessive bradycardia and hypotension, and require prolonged intubation with neuromuscular paralysis if cooling is used, therefore, the need to develop alternative nonpharmacological therapies. Management of intractable arrhythmias may require the use of emergent extracorporeal membrane oxygenation support or need catheter-based ablation.

The selective autonomic effect of differential FP structures in the mammalian heart was first recognized by Lazzara et al. The authors used subthreshold nerve stimulation at 2 separate epicardial sites in the dog heart to have differential effects on the sinus and AV nodes. The cardiac rhythm effects of nerve stimulation were blocked by atropine and lidocaine. Histological evaluation at the sites of successful parasympathetic nerve stimulation revealed neuronal elements—ganglion cells and myelinated nerve fibers. Randall et al. extended these observations, demonstrating that dissection of the sinus or AV node FPs resulted in parasympathetic denervation with abolition of the response to cervical vagal nerve stimulation.

Pauza et al. explored histologically the complexity of the intrinsic cardiac nervous system of the canine heart. Depending on the age of the animal, the number of intrinsic ganglia per heart ranged from 400 to 1500, with younger animals having more ganglia per heart. The canine right atrium was innervated by 2 subplexuses and the wall of the left atrium by 3 subplexuses. The structural organization of the neural subplexuses varied among hearts within an age group and between age groups.

Improvement in hemodynamics and slowing of the ventricular rate during atrial fibrillation using selective AV nodal vagal stimulation was initially demonstrated by Wallick et al. The authors showed that selective right inferior AV node FP stimulation slowed the ventricular rate and improved hemodynamics during atrial fibrillation. Right inferior FP stimulation helped reverse the detrimental effects of atrial fibrillation on stroke volume, cardiac output, peak left ventricular systolic pressure, left ventricular end diastolic pressure. In a similar animal model of sustained atrial fibrillation, Schauerte et al. demonstrated using an endocardial approach to AV nodal FP stimulation that the parasympathetic effects were sustained for at least a period of 20 hours and were related to the intensity of nerve stimulation. Rossi et al. demonstrated that right inferior FP stimulation...
stimulation could slow the ventricular rate during postoperative atrial fibrillation in human patients during simulation periods of ≤2 hours.

The use of this technique for control of postoperative atrial fibrillation and atrial tachycardias and its applicability to a younger age group is a logical extension of the studies reported to date. However, no previous data existed on the effects of right inferior FP stimulation on postoperative JET. Our experiments demonstrate for the first time the effects of right inferior AV node FP stimulation on postoperative JET.

The site of origin of postoperative JET is unclear. Possible sites of origin include the slow AV nodal pathway, the proximal AV node itself or the proximal His bundle region. Two lines of evidence suggest that right inferior FP stimulation has a broader effect, extending until 10 to 20 mm from the coronary sinus os. After RF ablation either around the fast AV nodal pathway or coronary sinus os, there was a graded impairment of the efferent vagal effects from FP stimulation ≤10 mm from the coronary sinus os. When RF ablation was performed at distances >10 mm from the coronary sinus os, no impairment of AV nodal conduction followed FP stimulation.

Quan et al\textsuperscript{13} noted a graded change in shortening of the atrial refractory period after FP stimulation up to distances of 20 mm from the AV node FP. The shortening of the atrial refractory period that accompanied FP stimulation became less with increasing distance from the AV node FP. No effect was observed at distances >20 mm.

How might FP stimulation affect AV nodal conduction and automaticity? Mazgalev et al\textsuperscript{16,17} showed in an in vitro rabbit AV nodal preparation that postganglionic parasympathetic stimulation resulted in reproducible disorganization of the prevailing excitation front, manifested as local nonuniform depression of conduction, hump formations in the action potentials, and alteration in the sequence of depolarization. Acetylcholine results in membrane hyperpolarization and depression of action potential amplitude in the N region of the AV node, thereby slowing or blocking conduction. Multiple hump potentials recorded from N region cells suggested 2 different mechanisms for slowing of AV nodal conduction—concealed conduction or localized reentry. Parasympathetic slowing of the rapid ventricular rate response during atrial fibrillation is a consequence of acetylcholine-induced depression of AV nodal conduction.
We previously reported using a porcine animal model of postoperative JET that the underlying arrhythmia mechanism was consistent with triggered activity.17 Catecholamines are known to increase cyclic-AMP. In turn cyclic-AMP has been demonstrated to induce delayed after-depolarizations and triggered activity in vitro and in vivo. Acetylcholine can block catecholamine-mediated increases in intracellular cyclic-AMP and has also been shown to terminate catecholamine-induced triggered activity in isolated in vitro cardiac atrial preparations.18 Adenosine usually slows or terminates cyclic-AMP–dependent ventricular tachycardia.19 In 1 patient with adenosine insensitive ventricular tachycardia, Lerman et al20 noted a mutation in the G alpha2 gene sequence that was shown to increase intracellular cyclic-AMP concentration and inhibit suppression of cyclic-AMP by adenosine; thereby further supporting the importance of G-protein–mediated changes in cyclic-AMP in arrhythmia initiation or termination. In our animal model of postoperative JET, we hypothesize that FP stimulation through parasympathetic stimulation and acetylcholine release alters G protein activity, decreasing cyclic-AMP levels; thereby slowing or terminating triggered activity in the peri-AV nodal region.

Study Limitations
Our research studies were done in a canine animal model, and, therefore, have unknown applicability to human patients. Previous human studies that have tested sinus and AV node FP stimulation in adult human patients have observed correspondingly similar findings to the canine studies. For example, stimulation through epicardial electrodes placed in the human sinus node FP can prolong sinus cycle length by 50%, and shorten atrial refractoriness.21 Stimulation of epicardial and endocardial electrodes placed in the AV nodal FP region can cause complete AV block, or markedly slow the ventricular rate response during atrial fibrillation.13,14,21,22 Therefore, we do not anticipate too discrepant observations once tested in children undergoing OHS.

Clinical Implications
In our canine animal model of OHS, right inferior FP stimulation had a selective effect decreasing AV nodal conduction and peri-AV nodal automaticity. No significant change in the sinus cycle length was observed. FP stimulation slowed the ventricular rate during postoperative JET and atrial fibrillation. We speculate that FP stimulation may be a useful new technique for managing children with postoperative atrial arrhythmias, specifically JET and AT that occur after OHS. We hope to begin translating our animal data to human trials in the near future.

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Disclosures
Dr Bornzin is employed by St Jude Medical CRMD, Sylmar, CA. The other authors have no conflict to report.

References


**CLINICAL PERSPECTIVES**

Supraventricular arrhythmias (junctional ectopic tachycardia [JET] and atrial tachyarrhythmias) frequently complicate recovery from open heart surgery in children and can be difficult to manage. Medical treatment and systemic hypothermia are the 2 most common treatment modalities used to treat postoperative patients with JET. These arrhythmias along with the demonstrated adverse effects associated with treatment can result in significant morbidity and on rare occasion mortality. Our goal was to develop a nonpharmacological approach using autonomic stimulation of selective fat pad (FP) regions of the heart in a young canine model of open heart surgery to control these 2 common postoperative supraventricular arrhythmias. Neural stimulation of the right inferior FP was used to control the ventricular response to supraventricular arrhythmias. Right inferior FP stimulation decreased baseline AV nodal conduction without altering sinus cycle length. FP stimulation slowed the ventricular response rate during atrial fibrillation (used to simulate atrial tachycardia). FP stimulation slowed the ventricular rate during postoperative JET and restored sinus rhythm. We found that right inferior FP stimulation had a selective effect on the AV node, and slowed the ventricular rate during postoperative JET and atrial tachyarrhythmias in our young canine open heart surgery model. We, therefore, suggest that FP stimulation may be a useful new technique for managing children with postoperative JET and atrial tachyarrhythmias. Clinical investigation of these techniques in human subjects should be considered.
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