Non-Pharmacologic Control of Post-Operative Supraventricular Arrhythmias
Using AV Nodal Fat Pad Stimulation in a Young Animal
Open Heart Surgical Model

Running title: Moak et al.; Post-operative Atrial Arrhythmias

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Abstract:

**Background** - Supraventricular arrhythmias (junctional ectopic tachycardia (JET) and atrial tachyarrhythmias (AT)) frequently complicate recovery from open heart surgery (OHS) in children and can be difficult to manage. Medical treatment of JET can result in significant morbidity. Our goal was to develop a non-pharmacologic approach using autonomic stimulation of selective fat pad (FP) regions of the heart in a young canine model of OHS to control two common post-operative supraventricular arrhythmias.

**Methods and Results** - Eight mongrel dogs, varying in age from 5-8 months and weighting 22 ± 4 kg, underwent OHS replicating a non-transannular 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. AVN Wenckebach cycle length prolonged from 270 ± 33 to 352 ± 89 msec, p=0.02. Atrial fibrillation occurred in 7 animals, simulating a rapid AT. FP stimulation slowed the ventricular response rate from 166 ± 58 to 63 ± 29 bpm, p<0.001. Post-operative JET occurred in 7 dogs. FP stimulation slowed the ventricular rate during post-operative JET from 148 ± 31 to 106 ± 32 bpm, p < 0.001, and restored sinus rhythm in 7/7 dogs.

**Conclusions** - Right inferior FP stimulation had a selective effect on the AVN, and slowed the ventricular rate during post-operative JET and AT in our young canine OHS model. FP stimulation may be a useful new technique for managing children with JET and AT.

**Key words:** animal model surgery, autonomic nervous system, pediatric, atrial tachycardia, atroventricular node, junctional ectopic tachycardia, fat pad stimulation
Introduction

Supraventricular arrhythmias frequently complicate the post-operative recovery from open heart surgery in children. In 2011, Smith et al. reported their institutional experience evaluating the frequency of post-operative arrhythmias in 724 children undergoing open heart surgery. 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 occurred (AT) in 8%. JET and AT can be difficult to medically manage. Pharmacologic treatment of JET can result in significant morbidity, such as excessive bradycardia, and hypotension. Prolonged intubation with neuromuscular paralysis is required if hypothermia and cooling are used.

Previous research has shown the presence in the heart of localized concentrations of parasympathetic nerve cell bodies in Fat Pads (FP). 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. Using a chronic canine model of atrial fibrillation, Wallick et al. were able to perform FP stimulation to achieve well tolerated rate control in this animal model.

FP stimulation may be a useful new technique for managing children with post-operative atrial arrhythmias that occur following OHS. Our goal was to develop a non-pharmacologic approach using autonomic stimulation of the right inferior AV nodal FP region of the heart to control two common post-operative supraventricular arrhythmias, specifically junctional ectopic tachycardia and atrial tachyarrhythmias.

Methods:

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 care in compliance with the Guide for the Care and Use of Laboratory Animals. Eight mongrel dogs weighing 22 ± 4 kg (range 16.5 – 28 kg) and varying in age from 5-8 months old were used for this study. Three animals were males and 5 were female. The dogs were brought to the WISE surgical laboratory after fasting for 24 hours. Anesthetic induction followed pre-medication with a combination of Telazol (4.4 mg/kg) + Xylazine (2.2 mg/kg). The dogs were then intubated, and ventilated with room air supplemented with oxygen to maintain normal oxygen saturation by a respirator. Throughout the experiment, oxygen saturation was kept above 95%. Body temperature was monitored with a rectal probe and kept at 38 ± 1°C using a temperature controlled heated water blanket.

Anesthesia was maintained with 1-3 % isoflurane, supplemented with midazolam (0.05-0.1 mg/kg) and sufentanil (load = 1 mcg/kg/min, and continuous drip = 1 to 2 mcg/kg/hr.) throughout the experiment. Normal saline at 100-200 ml/hr. was infused to replace spontaneous fluid and blood losses. Arterial blood gases and electrolytes were monitored using an I-STAT analyzer and EG7+ test cartridges (Abbott Laboratories. Abbott Park, IL).

Using clean surgical practice, femoral artery and venous catheterization was performed using a combined cut down and Seldinger technique for monitoring arterial blood pressure and gases; and central venous pressure, respectively. Two body surface ECG leads (II, and III) were monitored for heart rate and cardiac rhythm assessment. Signals were amplified, digitized and displayed on a PC using an AD Instruments (Colorado Springs, Co) PowerLab 8 data acquisition system with LabChart Pro 7.1.

Following a midline sternotomy incision, the pericardium was opened, and a cradle formed. Two bipolar pair of pacing wires was sewn to the left atrium to allow atrial pacing and
recording from separate electrodes. One bipolar pair of pacing wires was sewn to the right ventricle for either recording or pacing the ventricle. A custom electrode for neural stimulation of the right inferior AV nodal fat pad was sutured to the IVC – right lower pulmonary vein region of the atrium, figure 1.

**Assessment of AV Nodal Function:** AV nodal function was assessed in the baseline state prior to CPB, and during neural stimulation of the right inferior AV nodal fat pad. The AV node Wenckebach cycle length was determined using a Medtronic (Minneapolis, MN) model 5328 programmable stimulator and rapid atrial pacing.

**Definition of Atrial fibrillation and JET:** Atrial fibrillation was characterized by rapid and irregular atrial activation with inter-atrial electrograms less than 160 msec, and no discrete surface ECG P waves. While there is no uniformly accepted definition of post-operative JET, we defined JET for the purposes of this study as a supraventricular arrhythmia (same QRS morphology as in sinus rhythm) with no preceding P wave at a rate that exceeded the normal junctional escape rate for age. The pattern of VA conduction could be either 1:1 VA conduction, VA Wenckebach or dissociated. JET usually exhibited variability in rate at onset or termination - warm up or cool down; and did not demonstrate sudden onset or termination. The ventricular rate had to be greater than 120 beats/min in order to be considered JET. The normal junctional escape rate after creation of sinus node dysfunction in our studied animals was usually less than 90/min.

**Atrial Fibrillation and Junctional Ectopic Tachycardia 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 units/kg) was administered for a goal ACT above 400 secs. The superior and inferior vena cavae were cannulated using a 20-32 Fr. right angled, wire reinforced venous return cannulae (Terumo Cardiovascular Systems Corporation, Ann Arbor MI) after ligating and dividing the azygous vein. The aorta was cannulated using a 10-14 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 greater than 25%. After institution of cardiopulmonary bypass, core temperature was cooled to 30-32°C, as is used in surgical repair of infants with congenital heart disease. Once on stable cardiopulmonary bypass, replication of a non-transannular approach to tetralogy of Fallot repair was performed following 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 Gore-Tex patch in the peri-membranous region of the right ventricle using pledgeded sutures, and 4) performing a non-transannular right ventricular outflow patch in half of the animals. Aortic cross clamp duration varied between 30-60 minutes, and cardiopulmonary bypass time exceeded 120 minutes.

The dog was subsequently weaned from cardiopulmonary bypass after rewarming 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 mcg) until the desired effect was achieved, i.e. the development of JET. 7 We demonstrated our findings after
weaning the experiment subjects from cardiopulmonary bypass, and observed the animals for periods up to 4-5 hours post-operatively.

**Fat Pad Neural Stimulation:** Neural Stimulation of the right inferior AV nodal FP was performed using a GrassTelefactor model SD9 neurostimulator (West Warwick, RI) outputting a square wave pulse at a stimulation frequency between 20-30 Hz. The pulse amplitude varied between 8 and 15 volts at a pulse width of 0.15 msec. Stimulation was performed continuously for a defined time interval of 15-30 secs.

**Statistical analysis:** Descriptive statistics were reported as the mean ± standard deviation. For cardiac parameters, three repeated measurements of the response before (pre) and after (post) AV nodal fat pad 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, Texas) to compare the pre vs. 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 as well as 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 vs. post means were statistically significantly different with a 2-tailed, type 1 error of 0.05.

**Results:**

**Effect of FP Stimulation on the Sinus Node:** Right inferior AV nodal FP stimulation decreased AV nodal conduction without altering sinus cycle length. No change, specifically slowing of the heart rate was noted following the onset of FP stimulation. The mean heart rate in the baseline
state was not altered following FP stimulation (96 ± 23 beats per minute vs. 97 ± 23 beats per min, \(N=8\), \(p=0.70\)).

**Effect of FP Stimulation on AV Node Conduction:** 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 msec following FP stimulation, \(N=6\), \(p=0.02\).

**Effect of FP Stimulation on AV Node Conduction during Atrial Fibrillation:** Illustrated in Figure 3, is a representative example of the effect of AV node FP stimulation during atrial fibrillation. Following AV nodal FP stimulation, the ventricular rate significantly slowed from approximately 200 to 75 beats/min. Accompanying electrical slowing of the ventricular rate was correction of the electrical-mechanical pulse deficit. When FP stimulation was terminated, as indicated by the absence of activity on the FP stimulation channel, the ventricular rate increased back to baseline, and there was redevelopment of an electrical-mechanical pulse deficit. As illustrated in figure 3A and 3B, AV nodal FP stimulation diminished the ventricular rate response during atrial fibrillation. AV nodal fat pad stimulation significantly slowed the average ventricular response from 166 ± 58 to 63 ± 29 beats per minute, \(N=7\), \(p<0.001\).

**Effect of FP Stimulation on AV Node Conduction during Junctional Ectopic Tachycardia:** We next studied the effect of AV nodal fat pad 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. Following 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 electrocardiogram. An increase
in the systolic blood pressure accompanied the development of sinus rhythm. When AV nodal FP stimulation was terminated (Figure 4 B), indicated by the cessation of activity on the FP stimulation channel, sinus rhythm gradual 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 fat pad 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/min, (N =7, p< 0.001). Sinus rhythm occurred in 7 of 7 experiments. Sinus rhythm developed during the period of fat pad stimulation. When fat pad 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 post-operative junctional ectopic tachycardia. Right inferior AV node FP stimulation slowed the ventricular rate during post-operative 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.

Post-operative atrial arrhythmias are common in children following open heart surgery. Grosse-Wortmann et al. studied the prevalence of arrhythmias in children undergoing OHS.9 Using serial 24 hour Holter electrocardiograms, these investigators found a high incidence of atrial arrhythmias in the first 24 hours after OHS (supraventricular tachycardia – 7%, accelerated junctional rhythm – 14% and JET – 9%). In newborn and infants, the prevalence of
supraventricular arrhythmias was similar (supraventricular tachycardia – 12.7%, accelerated junctional rhythm – 16.7 % and 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 non-pharmacologic 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 fat pad structures in the mammalian heart was first recognized by Lazzara et al. The authors used subthreshold nerve stimulation at two 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. Histologic 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 fat pads 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 up to 1500, with younger animals having more ganglia per heart. The canine right atrium was innervated by two subplexuses, and the wall of the left atrium by three subplexuses. The structural organization of the neural subplexuses varied among hearts within an age group as well as 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
The authors showed that selective right inferior AV node fat pad stimulation slowed the ventricular rate, and improved hemodynamics during atrial fibrillation. Right inferior fat pad stimulation helped reverse the detrimental effects of atrial fibrillation on stroke volume, cardiac output, peak left ventricular systolic pressure, left ventricular dP/dT, and 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 fat pad 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 could slow the ventricular rate during post-operative atrial fibrillation in human patients during simulation periods of up to 2 hours.

The use of this technique for control of post-operative 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 AV nodal fat pad stimulation on post-operative JET. Our experiments demonstrate for the first time the effects of right inferior AV node fat pad stimulation on post-operative JET.

The site of origin of post-operative 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 AV nodal fat pad stimulation has a “broader” effect, extending until 10 - 20 mm from the coronary sinus (CS) os. Following RF ablation either around the fast AV nodal pathway or CS os, there was a graded impairment of the efferent vagal effects from fat pad stimulation up to 10 mm from the CS os. When RF ablation was performed at distances greater than 10 mm from the CS os, no impairment of AV nodal conduction followed fat pad stimulation. Quan et al noted a graded change in shortening of the atrial
refractory period following fat pad stimulation up to distances of 20 mm from the AV node fat pad. The shortening of the atrial refractory period that accompanied fat pad stimulation became less with increasing distance from the AV node fat pad. No effect was observed at distances over 20 mm.

How might fat pad stimulation affect AV nodal conduction and automaticity? Mazgelev et al showed in an in vitro rabbit AV nodal preparation that post-ganglionic parasympathetic stimulation resulted in reproducible disorganization of the prevailing excitation front, manifested as local non-uniform 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 two 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 post-operative JET that the underlying arrhythmia mechanism was consistent with triggered activity. 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. Adenosine usually slows or terminates cyclic-AMP dependent ventricular tachycardia. In one patient with adenosine insensitive ventricular tachycardia, Lerman et al.
noted a mutation in the G alpha12 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.20 In our animal model of post-operative JET, we hypothesize that fat pad 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 fat pad stimulation in adult human patients have observed correspondingly similar findings to the canine studies. For example, stimulation through epicardial placed electrodes in the human sinus node fat pad can prolong sinus cycle length by 50%, and shorten atrial refractoriness. 21 Stimulation of epicardial and endocardial electrodes placed in the AV nodal fat pad 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 open heart surgery.

**Clinical Implications:** In our canine animal model of open heart surgery, right inferior fat pad stimulation had a selective effect decreasing AV nodal conduction and peri-AV nodal automaticity. No significant change in the sinus cycle length was observed. Fat pad stimulation slowed the ventricular rate during post-operative JET and atrial fibrillation. We speculate that fat pad stimulation may be a useful new technique for managing children with post-operative atrial arrhythmias, specifically JET and atrial tachyarrhythmias that occur following OHS. We hope to begin translating our animal data to human trials in the near future.
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Conflict of Interest Disclosures: Gene Bornzin is employed by St Jude Medical CRMD, Sylmar CA. No direct financial benefit from participation in this study. All others have nothing to disclose.

References:


**Figure Legends:**

**Figure 1:** Right Inferior AV Node Fat Pad. Shown in figure one is the posterior wall of the heart from a post-mortem dog. Illustrated and labeled in the center of the image is the right inferior AV node fat pad, which is located at the junction of the inferior vena cava, coronary sinus and right lower pulmonary vein. Our neural stimulating electrode was sewn to this region of the atrium. CS = coronary sinus.

**Figure 2:** Development of AV Nodal Block during FP Stimulation. From top to bottom, the following parameters were monitored: femoral artery blood pressure, ECG lead 2, ECG lead 3, a left atrial electrogram, a right ventricular electrogram, the fat pad stimulation channel, atrial stimulation channel and a graph of the ventricular rate. Prior to FP stimulation, the dog was in an atrial paced rhythm at 400 msec with 1:1 AV conduction. Following the onset of fat pad stimulation, the cardiac rhythm transitioned to second degree AV block, and the arterial blood pressure increased. BP = blood pressure, EGM = electrogram, Vent = ventricular.
**Figure 3:** Effect of FP Stimulation during Atrial Fibrillation on the Ventricular Rate Response. (A) Onset of FP Stimulation. The atrial electrogram revealed continuous and fragmented electrical activity consistent with persistent atrial fibrillation. Evident on review of ECG lead II and III was a rapid and irregular ventricular response to the atrial fibrillation. Following AV nodal fat pad stimulation, the ventricular rate significantly slowed from approximately 200 to 75 beats/min. Accompanying electrical slowing of the ventricular rate was correction of the electrical-mechanical pulse deficit. (B) Termination of FP Stimulation. Following termination of Fat Pad stimulation, as indicated by the absence of activity on the Fat Pad stimulation channel, the ventricular rate increased back to baseline.

**Figure 4:** Effect of FP Stimulation during Junctional Ectopic Tachycardia. (A) Onset of FP Stimulation. JET was present prior to the onset of FP stimulation and was evident on the left hand side of the figure. No P waves are observed preceding the QRS and there was simultaneous occurrence of the atrial and ventricular electrograms. Following the onset of fat pad 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. An increase in the systolic blood pressure accompanied the development of sinus rhythm. (B) Termination of FP Stimulation. When AV node fat pad stimulation was terminated, indicated by the cessation of activity on the Fat Pad stimulation channel, sinus rhythm gradual transitioned back to JET and was accompanied by an increase in the ventricular rate and a decline in the systolic blood pressure.
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