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CASE REPORT

Ventricular rate control using a novel vagus nerve stimulating system in a dog with chronic atrial fibrillation

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Abstract A 4-year-old, intact male Dogue de Bordeaux dog with congenital valvular pulmonic stenosis, tricuspid valve dysplasia, and chronic atrial fibrillation underwent ultrasound-guided balloon valvuloplasty in addition to pharmacological treatment. Owner compliance to prescribed pharmacotherapy proved very poor, and concerns developed regarding the ability to successfully control heart rate and symptoms using drug therapy alone. These concerns were addressed by the implantation of a novel vagal stimulation system that was programmed to prevent a ventricular rate of >145 bpm. Consequently, post-operative ventricular response rate decreased from up to 250 to 140 bpm. Successful ventricular rate control was maintained for 291 days post-operatively, following which euthanasia was elected by the owner due to persistent right-sided congestive heart failure. To the authors' knowledge, this is the first report of successful continuous rate control using a vagal stimulating system in a closed-chest, client-owned dog with chronic atrial fibrillation secondary to spontaneously occurring organic heart disease.

Chronic, primary or secondary supra-ventricular tachy-arrhythmias (SVTs) are frequently identified in canines and are typically documented in large

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and giant breed dogs.[1,2] Of these rhythms, chronic atrial fibrillation and/or flutter are among the most common tachy-arrhythmia entities requiring therapy.[3] Although only seldom life threatening in the short-term, the hemodynamic impact of chronic SVT such as atrial fibrillation (AF) or flutter can dramatically compromise quality of life and exacerbate morbidity, eventually triggering or aggravating congestive heart failure, leading to a shorter life expectancy.[4,5] Moreover, sustained, rapid, and irregular ventricular rates secondary to AF can lead to adverse structural cardiac remodeling and to the development of tachycardia-induced cardiomyopathy.[6]

Frequently, AF recognition occurs too late to enable conversion to sustained, normal sinus rhythm (NSR). While reported in canines, most successful cardioversion procedures are in equine patients when they do not suffer from an underlying heart disease.[7,8] However, recurrent AF often does occur following successful cardioversion, especially if chronic organic heart disease is involved.[2] Traditionally, chronic and sustained AF is pharmacologically treated in order to achieve rate control rather than rhythm control.[9] Commonly used agents include digitalis glycosides, calcium channel or beta-adrenergic receptor blocking agents, amiodarone and, under certain circumstances, lidocaine.[10,11] Drugs such as selective A1 adenosine agonists are also being investigated in human patients.[12] Use of any of these agents, however, may fail to provide hemodynamically optimal or even adequate rate control.[13] Moreover, their use may also be associated with intolerable adverse effects or toxicity,[14] or be relatively contraindicated. For example, negative inotropic agents such as calcium channel or beta-adrenergic receptor blocking agents may exacerbate on-going congestive heart failure (CHF) by aggravating myocardial failure in severely sick cardiac patients. Conversely, positive inotropic agents such as digitalis glycosides may be contra-indicated due to potentially hazardous drug interactions. Digoxin may be harmful in some CHF patients, such as those with any degree of heart block, renal failure, hypokalemia, hypomagnesemia, hypertrophic obstructive cardiomyopathy, the Wolff—Parkinson—White syndrome with atrial fibrillation, or (shown in human beings) diastolic dysfunction due to concentric ventricular hypertrophy.[15—17] In addition, some patients with severe, chronic tachy-arrhythmia depend on non-pharmacological therapy if their owners are not committed to life-long drug therapy. When pharmacotherapy is limited by such circumstances, alternatives can be sought such as radiofrequency ablation of the origin of the arrhythmias or of the atrioventricular node, followed by chronic pacemaker therapy.[18,19] Such measures, however, are largely unavailable to many veterinary clinicians.

The objective of this communication is to describe the use of a novel, non-pharmacological approach for reliable rate control in a veterinary patient with chronic AF associated with a rapid ventricular response rate. Rate control was achieved by implementing a vagus nerve stimulating system to chronically prolong the atrioventricular refractory period. Although successful chronic rate control could, theoretically, supplement chronic pharmacotherapy in improving quality of life, there was no ethical or practical means by which to quantify such an effect in a controlled manner when applied in a single client-owned patient. This, therefore, was not included in our defined goals.

Case report

A 4-year-old, 38.6 kg intact male Dogue de Bordeaux dog referred for lethargy, ascites, and anorexia of several days duration had been treated for right-sided congestive heart failure with enalapril[d] (0.5 mg/kg PO BID), digoxin[e] (0.0065 mg/kg PO BID), and furosemide[f] (0.8 mg/kg SQ TID). Two and a half liters of modified transudate had been drained from his abdominal cavity over the previous 24 h. The dog was normokalemic and no azotemia was present. Pleural effusion and atrial fibrillation were detected with a ventricular response rate of 200—250 bpm, as recorded electrocardiographically. Following thoracocentesis, echocardiography confirmed suspected valvular pulmonic stenosis, and also demonstrated tricuspid valve insufficiency, attributable to congenital tricuspid valve dysplasia. A peak systolic pressure gradient of 86 mmHg was measured between the right ventricle (RV) and pulmonary artery (PA) using spectral Doppler.[g] Tricuspid regurgitation with a peak systolic pressure gradient of 41 mmHg was demonstrated between the RV and the right atrium (RA). Atenolol[h] at 0.65 mg/kg PO BID was added to the on-going therapy for its negative

[d] Vivid 3 General Electric Ultrasound Israel Ltd, Einstein Building, 7 Etgar Street, Tirat Hacarmel 39120, Israel.
[e] Balt, Cristal pediatric valvuloplasty balloon catheter, 18 mm in diameter; 10 Rue, Croix-Vigneron 95160, Montmorency, France.
[f] Enaladex®; Dexcel Ltd., Hadera 38100, Israel.
[g] Fusid®; Teva Pharmaceutical Industries Ltd., Petah-Tiqva 3190, Israel.
[h] Digoxin-Zori®, Teva Pharmaceutical Industries Ltd., Petah-Tiqva 3190, Israel.

inotropic effect, while furosemide dose was slightly increased to 1.0 mg/kg PO TID and the administration route was switched to oral.

One week following diagnosis, when the non-anesthetized electrocardiographic (ECG) ventricular response rate was 156 bpm, an ultrasound-guided balloon valvuloplasty[i] was performed under general isoflurane anesthesia. The maximal trans-pulmonic systolic pressure gradient decreased by 58% to 36 mmHg, when the dog was awake. The post-operative peak systolic pressure gradient across the tricuspid valve was 36 mmHg as well. The dog was discharged with enalapril (0.5 mg/kg PO BID), furosemide (1.0 mg/kg PO TID), digoxin (0.0065 mg/kg PO BID) and, given the valvuloplasty results, a slightly reduced daily dose of atenolol (0.65 mg/kg PO in the morning, and 0.3 mg/kg PO in the evening). Three months later, right CHF was present and the dog's ECG-recorded ventricular response rate rose to 200 bpm (averaged over 30 s under physical restraint), along with recurrent severe ascites. Careful anamnesis revealed that owner compliance was both at fault and unlikely to improve. It was felt that the chances for long-term success of rate control and maintenance of reasonable life-quality were minimal if on-going management would solely depend on oral drug therapy. It was therefore decided, in addition to prescribed oral medications and client-education and consent to implant a medical device presently under development: a vagus nerve stimulator.[j]

Device description

This device is designed to potentially contribute to hemodynamic stabilization by pacing the vagus nerve so as to control the rate of ventricular response to sustained supra-ventricular tachyarrhythmia. The system (Fig. 1) consists of:

1. A nerve stimulator (NS)[k] ($70 \times 48 \times 11$ mm) placed intra-operatively under cervical muscles to serve as an electrical power source. A processing unit adjusts the impulse rate and intensity to keep the heart rate within a desired range. Maximal stimulation current, pulse width and operation algorithm are controlled both intra- and post-operatively by a programmer.
2. A standard pacemaker unipolar intra-ventricular electrode, placed intravenously, is utilized as an intra-cardiac rate-sensing electrode, and is attached to the nerve stimulator. Intra-cardiac ventricular depolarization fronts detected are termed ''V'' waves, and each V-to-V interval serves for continuous rate-sensing by this electrode.
3. A multiple contact cuff electrode[l] is secured around the left cervical vagus nerve and is used as a stimulation lead, when connected to the nerve stimulator.

Figure 1 The CardioFit™ system, consisting of 3 components: a nerve stimulator (at the top right), a standard pacemaker unipolar intra-ventricular electrode (at the top left), and a multiple contact cuff electrode (at the bottom left).

To achieve safe and optimal rate control, an intra- and post-operative rate control set point can be programmed non-invasively. A programmer[m] is used in conjunction with the nerve stimulator to adjust the stimulation algorithm and settings for optimal therapy. Adjustments are made through a programming wand placed over the nerve stimulator while information is sent and received via wireless communication. Stimulus intensity, rate, and duration (as dictated by the desired ventricular response rate) are all programmable non-invasively.

Turning the nerve stimulator on or off can be done non-invasively using a portable safety-magnet[n] at the discretion of either the attending clinician or the owner, whenever adverse effects

[i] Normalol 25®, Dexxon Ltd. Or-Akiva, P.O. Box, Hadera 38100, Israel.
[j] CardioFit™, Model 500, BioControl Medical Ltd, Yehud 56100, Israel.
[k] Model 5000, Electrostimulator, BioControl Medical Ltd, Yehud 56100, Israel.
[l] Model 5100, BioControl Medical Ltd, Yehud 56100, Israel.
[m] Model 5300, BioControl Medical Ltd, Yehud 56100, Israel.
[n] Model 5400, BioControl Ltd, Yehud 56100, Israel.

are suspected or whenever testing the need and/or impact of stimulation.

Electrical nerve stimulation

The NS electrically stimulates the vagus nerve via the stimulation electrode with varying duration, intensity and frequency according to the heart rate detected as compared to a preset target heart rate adjusted via a programmed stimulation algorithm, as follows: stimulation intensity is set in the range of 1—10 mA, with a pulse width of 1 ms. Average stimulation frequency ranges from 0 to 15/s (15 Hz). The amount of stimulations per any given burst (or ''trigger'') is set at 1—8 as needed, based on previously sensed, V-to-V intervals. By default and as a safety feature protecting from erroneous detection leading to under- or over-stimulation, operation is automatically stopped if sensing identifies a heart rate lower or higher than 60 or 240 bpm, respectively. This default can be changed at the clinician's discretion as deemed necessary according to confirmed heart rate data.

Implantation procedure and disease course

A complete physical examination, blood count, biochemistry, chest radiographs and echocardiography preceded implantation. Following surgical exposure and dissection of a 2-cm long section of the left vagal sheath between the sternocephalic and brachiocephalic muscles at the caudal third of the cervical region, the multiple contact cuff electrode was wrapped and ''locked'' around the left cervical vagus nerve. It was then passed subcutaneously and tunneled to the right cervical region, where it was connected to the nerve stimulator. The latter was then connected to an intra-cardiac sensing electrode[o] that was placed under fluoroscopic guidance through the right jugular vein in the right ventricular apex. Next, the stimulator was implanted in a pocket deep to the right brachiocephalic muscle, which was created by blunt dissection. Prior to final transfixation, the system was tested for proper communication, acceptable ECG signaling, stimulating electrode impedance, and heart rate reduction in response to transient stimulation. The stimulator was then set to ''quiet'' mode (zero stimulation) for the duration of the anticipated healing period.

Eight days post-operatively, the ventricular response rate was programmed at a set point of 140 bpm, i.e. the vagus nerve being stimulated when the spontaneous ventricular response rate reaches levels above 140 bpm. This target heart rate was empirically selected so as to maintain ventricular response rate close to the higher end of traditionally recognized normal heart rate range during resting sinus rhythm. This was done to potentially compensate for the lack of atrial contribution to ventricular stroke volume and overall cardiac output. At this point, digoxin therapy was discontinued.

Device-documented heart rate data, 1 month post-operatively, revealed failure of the device to sense spontaneous heart beats due to a supra-optimal programmed device ''refractory period'' (i.e. charging and blanking period) of 300 ms that followed each detected ventricular impulse. This led to under-sensing of short V-to-V coupling intervals and, therefore, decreased the stimulation frequency to actually less than what was needed. This was corrected and optimized by an elevation of the battery-supplied current from 5.4 to 6.7 mA, and by an abbreviation of the charging and blanking period to 150 ms. Average heart rate was 145 ± 3 bpm from the time of correction (day 30) until day 195 (Table 1).

Stimulator set point testing, adjustment, and response rate interrogation were performed twice during the first week, once during the second, 3 times during the fourth and twice during the fifth post-operative week, while a 24-h Holter's monitor[p] was applied on weeks 1, 4 and 5 post-operatively, until stability could be documented on day 35 (Table 1). From that point on, device interrogation was performed 11 more times, every 1—10 weeks, while the Holter data were collected 3 more times, every 3—6 weeks (Table 1). The only adverse effect during the first post-operative day was a minor, self-limiting cough, speculatively attributable to irritation secondary to endo-tracheal intubation, or to artificial electrical stimulation of the recurrent laryngeal nerve, one of the vagal branches. No other adverse effects could be documented at any later time point.

Sixty-three days post-operatively a heart rate of 140 bpm was documented and the systolic pressure gradient across the pulmonic valve was 49 mmHg. A modified transudate (5.5 L) was drained from the abdominal cavity via abdominocentesis. Despite the controlled heart rate and although pulmonic

[o] Model PY-R 67 Unipolar, Dr. Osypka GMBH Medizintechnik, Earl-H. Wood Strasse, 1 D-79618 Rheinfelden Herten, Germany.

[p] LifeCard CF, Del Mar Reynolds Medical Ltd., Hertford, UK.

Table 1 Data collected by the vagal stimulating device and by a Holter monitor between stimulation days −8 and 265. Q5

Day	Interrogation-to-interrogation interval (days)	Pulse Current (mAmp)	Target HR (bpm)	Device Averaged HR (bpm)[a]	Holter's Averaged HR (bpm)	Stim:V[b]	Average PPT[c]	Battery Voltage[d]
−8	NA	NA	NA	NA	156	NA	NA	NA
8	16	5.5	140	128	103	53	6.5	2.86
9	1	5.5	140	113	—	9	1.6	2.89
14	5	5.5	140	126	—	22	1.6	2.89
27	13	5.3	140	149	131	33	2.3	2.89
28	1	**5.4**	140	**178**	—	35	2.7	2.84
30	2	**6.7**	140	**178**	—	44	3.8	2.86
35	5	6.7	140	142	138	75	4.3	2.89
36	1	6.6	140	143	—	71	3.3	2.87
57	21	6.5	140	149	130	92	6.7	2.85
59	2	6.5	140	144	—	93	5.7	2.82
62	3	6.4	140	147	—	98	6.8	2.82
78	16	6.5	**145**	141	—	73	4.2	2.8
83	5	6.6	145	147	136	81	4.3	2.83
128	45	6.5	145	143	144	60	3.6	2.84
129	1	6.3	145	150	—	98	6.2	2.83
148	19	6.5	145	144	—	60	3.9	2.76
195	47	6.2	145	144	—	64	5.2	2.84
265	70	5.8	145	NA	—	63	5.1	**2.75**

Note that while the average heart rate (HR) throughout the entire period of time was 145 ± 17 bpm, it was 145 ± 3 following elevation of battery-supplied current and abbreviation of the charging and blanking period, between days 35 and 195.
NA — not applicable. ''Bold numbers in the table legend are used to indicate where transition is made in a relevant column between two sets of data of which difference is meaningful: an increase in pulse current, an elevation in target heart rate, an elevation in device averaged heart rate, or a significant decrease in battery voltage''.

[a] Heart rate as averaged by the stimulating device's sensing electrode between consecutive series of 10-min-long increments as continuously collected between 2 consecutive interrogations, starting at the previously and ending at the currently recorded date. Note that averages of several (e.g. 5—45) consecutive days as calculated by the stimulating device are mostly higher than those documented by the Holter monitor when applied for only 20—45 h at a time, on respective days. Heart rate data from days 8 to 265 are not applicable as, while values in this column are averaged from a time-interval that has an onset and an offset, the former has no onset and the latter has no offset.

[b] The percent of cardiac cycles (based on V-to-V intervals on sensed electrograms) that were followed by burst stimulation (or ''triggers'') during the period of time between 2 consecutive interrogations, starting at the previously and ending at the currently recorded date.

[c] PPT = ''pulses per trigger''; the amount of pulses per burst (or ''trigger''), averaged only from those sensed V-waves that were followed by burst stimulation over the period of time between 2 consecutive interrogations, starting at the previously and ending at the currently recorded date. Each burst (or ''trigger'') of stimulations consisted of 0—8 pulses, as deemed needed by a programmed algorithm. The algorithm is based on a ''rolling'' average (updated every time a new V-wave is identified) consisting of the 8 cardiac cycles just previous to those V-to-V intervals that were followed by burst stimulation.

[d] The optimal battery voltage range is considered to be 2.86—2.92 V. Note that from day 57 on, despite the fact that the battery voltage was less than optimal it did not compromise device performance. The system is designed to last for 8 years as it is originally intended for use in CHF rather than in AF patients, where the current battery life expectancy is ~2 years due to larger voltage/current consumption during the same amount of time. Future prototypes are expected to last much longer when used for this specific indication.

stenosis at this point could be considered as moderate in severity, atenolol dose was now increased back to its pre-valvuloplasty level at 0.65 mg/kg BID, with hopes of further reducing the RV-to-PA systolic pressure gradient. Furosemide dose was increased to 2 mg/kg PO in the morning and 1 mg/kg PO in the afternoon. Enalapril was maintained at 0.5 mg/kg PO BID.

Despite stabilization of the dog's quality of life for several months (improved appetite and activity levels) and despite an elevated furosemide dose (2.0 mg/kg PO TID), symptoms of right CHF persisted and necessitated periodical abdominocentesis. On post-operative day 78, the target heart rate was empirically elevated to 145 bpm with hopes to slightly increase the cardiac output so that signs of congestive failure could be better controlled. On post-operative day 196, furosemide dose was reduced to 2.0 mg/kg PO in the morning and the afternoon, and 1.0 mg/kg PO in the

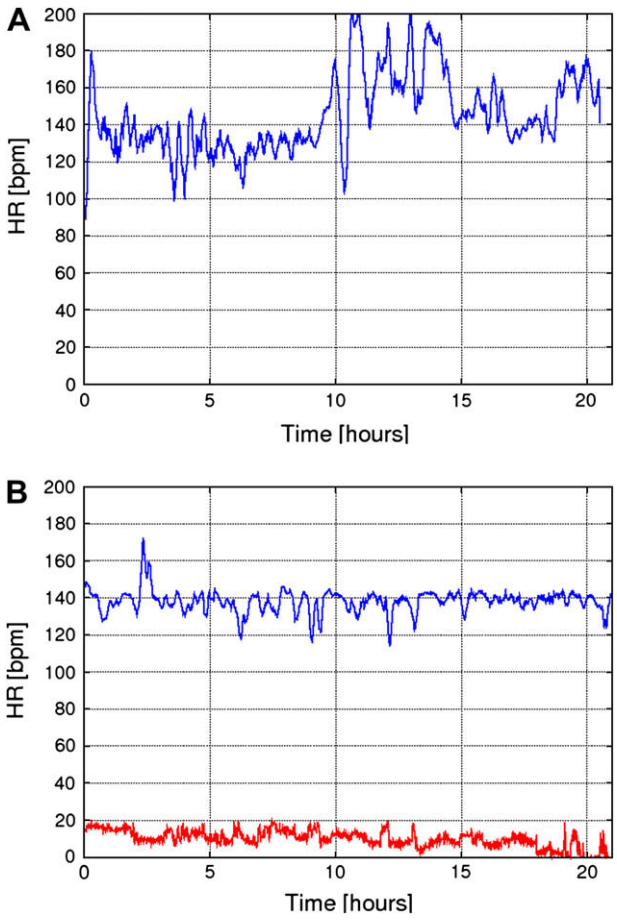

Figure 2 Twenty-h-long Holter's monitor data recorded from a 4-year-old, intact male Dogue de Bordeaux dog with chronic atrial fibrillation, prior to (A) and 36 days (B) following implantation and activation of a vagal stimulating device. The blue trend line consists of consecutive averages, each reflecting a 10-min-long period. Note the decreased variability and the increased proximity of recorded heart rates to the 140 bpm target rate, following activation of the stimulating device as opposed to baseline data. (A) Pre-implantation baseline (day −8). (B) Day 36 following activation. The red line reflects pulses per trigger (PPT) data (see Table 1 for explanation).

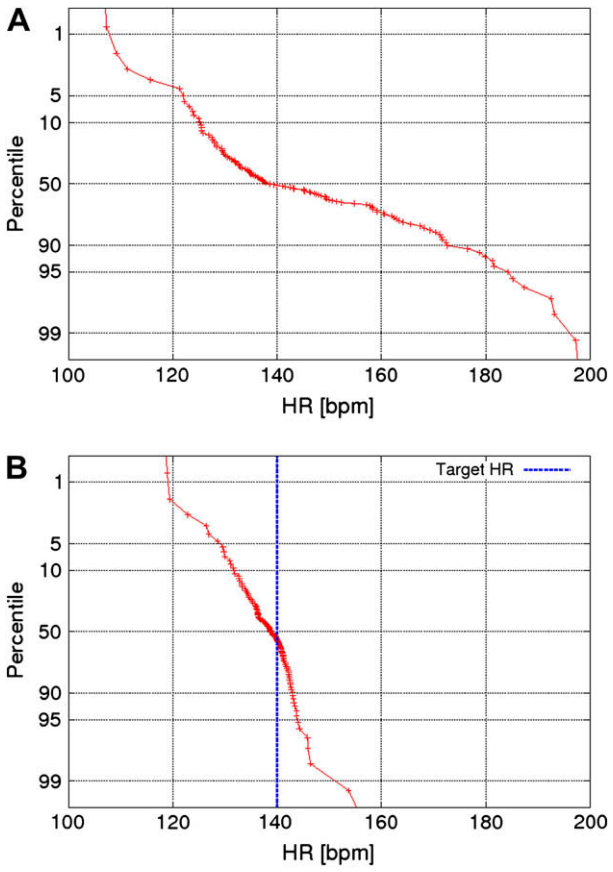

Figure 3 Distribution of heart rates as recorded by a Holter monitor from the same patient as in Fig. 2, prior to and following implantation and activation of a vagal stimulating device. Holter's data are divided into consecutive, non-overlapping 10-min-long segments. For each of these segments the average heart rate is depicted as an X. Each X represents one of 122 such segments, reflecting 20.3 consecutive hours. These averages, however, are not displayed in a chronological order but rather are rank-ordered according to their respective percentiles. For example, when an X is located at the 5th percentile showing a heart rate of 123 bpm, this means that 95% of all depicted X values reflect averaged heart rates of >123/min. Note that when successful stimulation takes place, the percentile rank-order pattern changes its course acutely and displays most of its data closer to the target heart rate, when compared to baseline. (A) Pre-implantation baseline (day −8). (B) Day 36, following implantation and activation, when the target heart rate was programmed at 140 bpm.

evening, and spironolactone[q] (0.65 mg/kg PO BID) and hydrochlorothiazide[r] (1.0 mg/kg PO BID) were added to the diuretic regimen.

The dog's appetite and activity levels remained satisfactory but progressive ascites led the owner to elect euthanasia 291 days following device implantation. Consent was, unfortunately, not given for necropsy or histopathology. A retrospective analysis of recorded device-calculated heart rate data averaged from the first 195 days, revealed that the mean heart rate throughout this period of time was 145 ± 17 bpm (ranging from 83 to 178 bpm), the standard deviation of 17 being different by ±12% from the programmed target heart rate of 145 bpm throughout this period of time (Figs. 2 and 3, Table 1). While no attempt

[q] Aldactone®, Pharmacia Ltd (Formerly Searle Ltd), Morpeth, Northumberland, UK.
[r] Disothiazide 25®, Dexxon Ltd. Or-Akiva, P.O. Box, Hadera 38100, Israel.

could be made to interpret the heart rate data in terms of their impact on clinical outcome, their distribution around the mean was subjectively regarded as adequately low.

Discussion

To the best of the authors' knowledge, this is the first attempted clinical use of a minimally invasive device to chronically control the ventricular response rate to spontaneously occurring AF in a client-owned dog. Although no long-term clinical benefit could be tested in the absence of a comparative study design, stimulating device and the Holter monitor data repeatedly demonstrated ventricular response rates being maintained within the pre-programmed range. The device was well-tolerated throughout the time period following implantation.

Non-pharmacological AF treatment reported in the human and veterinary cardiology literature includes injection of manipulated autologous fibroblasts into the atrioventricular node,[20] and radiofrequency ablation or modification of the septal right atrium or the atrioventricular node, followed by right ventricular pacemaker implantation when needed.[18–23] Other than the potentially problematic irreversibility of this strategy, reported risks of chronic right ventricular pacing in this setting include the development of left ventricular remodeling and myocardial failure, or producing a non-physiological and reportedly inferior retrograde activation sequence of the ventricular myocardium.[24] The presently described technique may help avoid such consequences.

A more important advantage of direct vagal stimulation is its ability to reduce excessive atrial rate swings during permanent AF, which is also considered a worthy goal of therapy for AF.[25] Correspondingly, the single most important achievement, in the authors' opinion, of the device reported here is its proven ability to tightly control the ventricular response rate in this patient over 291 days.

Retrograde vagal stimulation has been described in both human beings and canines for non-cardiac indications such as control of depression and of seizure activity.[26–32] Possible complications are attributed to stimulation of the recurrent and superior laryngeal nerves (that branch off the vagus nerve) and include vocal stridor, cough, hoarseness, voice alteration, and bronchoconstriction.[27–29] The risk of complications is low and should these develop, they are expected to be mild, self-limiting, and reversible once stimulation is discontinued. A year-long vagal stimulation in human patients with epilepsy had no significant effects on heart rate variability indices.[30] This may be an encouraging finding suggesting that retrograde and antegrade vagal stimulation are not necessarily interdependent or mutually influential during artificial stimulation of the cervical vagus nerve.

A clinical study of retrograde vagal stimulation in 10 epileptic client-owned dogs revealed no stimulation-related side effects over 13 consecutive weeks, although transient Horner's syndrome occurred during the first 2 post-operative weeks.[32] Other than a mild, transient cough, no adverse effects were observed in the presently reported patient. Whether similar risks are relevant to veterinary patients receiving antegrade vagal stimulation for ventricular rate control, remains to be investigated.

Similarly, the long-term efficacy of this novel strategy for both rate control and symptomatic improvement in dogs with AF has yet to be established in a controlled fashion and in a patient population. If proven safe and effective, antegrade vagus nerve stimulation may become beneficial to veterinary patients with symptomatic supraventricular tachy-arrhythmia where negatively chronotropic pharmacological therapy is intolerable, ineffective, impractical, or contraindicated.

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