Supraventricular Arrhythmias and Treatment

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Abstract
The objective of this article is to review supraventricular arrhythmias emphasized the importance of atrial fibrillation (AF) and its novel therapeutic approach in dogs. Supraventricular arrhythmias include disturbances of impulse formation at sinus node, atria and junctional area or alterations of impulse conduction within the chamber above ventricles. Among those supraventricular arrhythmias, AF is the most commonly seen supraventricular arrhythmias in veterinary practice. While APC, AT, atrial flutter, re-entrant supraventricular tachycardia, and atrial standstill are relatively uncommon in veterinary patients. AF contributes to increase mortality through its association with cardiomyopathy or valvular heart disease. Current therapies of canine AF are limited by their efficacy and adverse effects, including proarrhythmic effects or by their adverse effects to other organs. These limitations are necessary to select novel pharmacological therapy to expand the treatment options in AF dogs. Dronedarone is a benzofuran derivative that was synthetized based on amiodarone, but has some structural changes to avoid adverse effects. Recent studies showed that oral dronedarone (20 mg/kg BID, 7 days) can attenuate the duration of sustained AF in canine AF model without effect on cardiac inotropy or lusitropy. Clinical trials of dronedarone in clinical AF dogs are challenges for the future.

Introduction
Supraventricular arrhythmias are defined as one of the rhythm disturbances that originate in the upper chambers of the heart. Supraventricular arrhythmias include sinus rhythm disturbances (i.e. sinus tachycardia, sinus bradycardia, sick sinus syndrome, sinus arrest and sino-atrial exit block), atrial rhythm disturbances (i.e. atrial fluster, atrial fibrillation, atrial premature complex) and junctional rhythm disturbances (i.e. premature junctional complexes). Atrial premature complexes (APC), atrial tachycardia (AT), atrial flutter, atrial fibrillation (AF), re-entrant supraventricular tachycardia, and atrial standstill are atrial rhythm disturbances. These arrhythmias can be transient, recurrent, or permanent. In most cases recurrent or permanent arrhythmias are associated with structural heart diseases such as chronic valvular disease or cardiomyopathy.

Atrial premature complexes and atrial tachycardia
The SA node is normally the dominant, driving pacemaker for the heart. When impulses arise prematurely from the atrial tissues, instead of the SA node, resulting in early relative to the dominant P-wave to P-wave cycle, the resultant complexes are called atrial premature complexes. The impulse then carries on to the AV node and into ventricles by normal conduction pathway. Characteristics of P waves from electrocardiogram (ECG) are observed including haphazard distribution, atrial bigeminy and runs of atrial premature complexes or atrial tachycardia. Atrial tachycardia is a rapid sustained atrial ectopic rhythm caused by abnormal atrial automatic activity or localized atrial reentry. The rhythm may occur in bursts called paroxysmal atrial tachycardia or develop into a sustained rhythm. The resultant P waves typically occur at a faster rate than the normal sinus rate (more than 300 per minute). Furthermore, the morphology of ectopic P waves are generally different from during sinus rhythm (4).

Atrial flutter
Atrial flutter is sustained atrial arrhythmias. The rhythm is generated by a circuit movement from abnormal re-entrant electrical activity activated around atria associated with atrial enlargement from valvular insufficiency or cardiomyopathy. The resultant ECG shows the atrial activation in the form of regular, saw-tooth waves instead of regular P wave. The atrial rate is more than 300 per minute and may exceed 400 per minute. Atrial flutter typically spontaneously reverts to sinus rhythm or develops to AF (4).

Atrial fibrillation
Atrial fibrillation (AF) is the most common supraventricular tachyarrhythmias characterized by irregularly rapid atrial electrical activity. Consequently, this arrhythmia may lead to decrease cardiac output and impair mechanical function of the heart and quality of life due to inadequate ventricular filling and the accelerated rate of ventricular response. In addition, AF may develop or worsen clinical signs of heart failure resulted in a higher risk of mortality (14, 24). AF is associated with the clinical course of cardiomyopathy, advanced atroventricular valvular disease, and untreated congenital heart disease. AF is caused by either disordered re-entry in the atria or fibrillatory conduction of a rapidly discharging atrial or pulmonary venous electrical focus. The resultant ECG shows fibrillatory waves instead of regular P wave in ECG with atrial rate more than 400-600 per minute. Irregular ventricular rate response and relatively normal appearing QRS complexes are presented (Figure 1).
Canine Atrial fibrillation

AF. The purpose of rhythm control is to convert AF to continuing sinus rhythm while the aim of rate control is to optimize ventricular response though AF still goes on. Anticoagulation is aimed to prevent thromboembolism that may cause a risk of stroke. Therefore, therapeutic strategies of AF can be divided into two categories, non-pharmacotherapy and pharmacotherapy. Electrical cardioversion, surgical ablation, catheter ablation, pacemakers and internal defibrillators have been used for treatment of AF. Several reports demonstrated that some AF patients gained advantage from these non-pharmacotherapies, although there had distinctively different of successful rate and adverse effects (12, 17, 18).

The most common medications that can all be effective in managing ventricular rate are beta-adrenergic blockers, L-type calcium channel blockers, and digitalis glycosides (36).

General antiarrhythmic drugs have been used for rhythm control are class I and III antiarrhythmic drugs (sodium channel blockers and potassium channel blockers, respectively). Class I acts by slow conduction and suppress ectopic activity. Class III prolongs refractory periods resulted in suppression of re-entry, but this can enhance early afterdepolarizations that causes proarrrhythmia (13). In addition, drugs that act as multichannel blockers have been used in converting AF to sinus rhythm, but there still have reports of developed adverse effects (23).

Many new compounds have been tested and clinical trials have been launched for patients with AF. Atrial selective compounds are novel strategy for the management of AF since these compounds possess inhibitory effect on ultrarapid delayed rectified potassium current (I_{Kur}), acetylcholine-activated inward rectifier potassium current (I_{KACH}), or connexin-40 (15). In addition, atrial selective compounds may include agents that use-dependent block sodium current (I_{Na}) and agents that rapidly dissociate from sodium channel (8).

Vernakalant was developed as an atrial selective antiarrhythmic compound. It acts as sodium channel blocker and potassium channel blocker (16). From clinical trials in human, intravenous vernakalant terminated acute onset of AF (3-72 hours), and it restored sinus rhythm in short AF (3-7 days) but vernakalant was ineffective to restored sinus rhythm in long-lasting AF (8-45 days) (27, 28). Until now no publication of oral treatment of this drug was found.

Furthermore, drugs that possess sodium channel blocker may terminate AF by increasing post-repolarization refractoriness (PRR) at the atria. PRR is the extending of effective refractory period (ERP) beyond the action potential duration at 90% of repolarization (APD_{90}).
Flecainide (class Ic antiarrhythmic drug), ranolazine (antianginal drug), amiodarone (class III antiarrhythmic drug), and dronedarone (class III antiarrhythmic drug) which all exert sodium channel blocker effect increased PRR in experimental studies (in vitro), leading to effective suppression AF under the studied conditions (1, 9, 10).

The main purpose of AF therapy in dogs is to manage clinical signs that may affect quality of life. After AF is diagnosed, the start of treatment relies on the present of underlying cardiac diseases and clinical signs and the hemodynamic conditions. Dogs with acute and severe hemodynamic problems, such as weakness, collapse, and systemic hypotension are required acute intravenous antiarrhythmic medications. On the other hand, oral medications are adequate for general cases.

AF in dogs can be restored to sinus rhythm by synchronized electrical cardioversion. In two retrospective reports, the success rate of biphasic transthoracic cardioversion was achieved in 92.3% (36/39) and 93.2% (41/44) (5, 6). Conversion AF to sinus rhythm succeeds in acute AF and lone AF (or without underlying cardiac diseases) human patients; however, those are uncommon in dogs (32, 40). Although several antiarrhythmic drugs have been used to restore sinus rhythm in human patients, only amiodarone, diltiazem, quinidine, and verapamil have been reported to convert AF to sinus rhythm in a small number of dogs. Only one and two cases of AF dogs were converted to sinus rhythm by verapamil and quinidine respectively. In a retrospective study of using amiodarone to manage AF in dogs, only 6 AF dogs were converted to sinus rhythm (25, 33).

According to Vaughan Williams classification, amiodarone is a class III antiarrhythmic drug and assists with effects of class I (sodium channel blocker), class II (beta-adrenergic blocker), and class IV (calcium channel blockers). Amiodarone has efficiency for managing AF in both of human patients and dogs (33). In the retrospective study of 17 dogs with AF that were treated with amiodarone, 35% of dogs were successfully converted sinus rhythm. Amiodarone has complicated pharmacokinetic and adverse effects that restrict widespread usage. Adverse effects in dogs mostly are extracardiac effects including increasing of hepatic enzyme activity, decreasing of neutrophil, decreasing of platelets, agglutination, corneal deposits, and GI disorders (2, 3, 33). Recently a novel antiarrhythmic drug, dronedarone, that uses amiodarone as a prototype has been developed into clinical use.

**Novel pharmacological therapy for canine AF**

Dronedarone is a benzofuran derivative that was synthetized based on amiodarone molecule, but has some structural changes. In order to avoid adverse effects of amiodarone, iodine molecules were removed to get rid of iodine-related organ toxicity, especially thyroid gland. Furthermore, a methane-sulphonyl group was added to reduce lipophilicity resulted in decreasing drug accumulated in tissue (39). Furthermore, dronedarone has shown an improvement of safety profile and advantages on the considerable clinical endpoints, such as cardiovascular hospitalization and mortality in AF patients in clinical trials (20). From the results of several large clinical trials, dronedarone was approved to manage AF patients that absent severe heart failure by the U.S. Food and Drug Administration (20, 21, 26, 34, 37). In humans, dronedarone has the elimination half-life approximately 24 hours. As the result of high first-past hepatic metabolism of dronedarone, its bioavailability is only about 15%. In addition, to reach sufficient steady-state plasma concentration dronedarone has to give two times a day. Therapeutic dose recently administered in human is 800 mg/day (26, 39, 41).

In anesthetized dogs, electrophysiological of intravenous dronedarone was similar to amiodarone (22). Although the heterogeneity of drug response among left ventricle, right ventricle, and Purkinje fibers are different, dronedarone caused no change in action potential duration (APD) in most of those regions. However, APD at right ventricle was slightly increased in the isolated canine heart (38). Dronedarone had slightly effectiveness to prevent the induction and the termination of persistent Ach-mediated AF in canine coronary-perfused right atrial preparations (10).

Recently, saengklub et al (29) showed that intravenous dronedarone at 2.5 mg/kg significantly reduced heart rate and lengthened PQ interval (P<0.01) in anesthetized dogs. Intravenous dronedarone impaired systolic function by significantly decreased end-systolic pressure-volume relationship, preload recruitable stroke work, contractility index and dP/dt max. It also impaired diastolic function by increased end-diastolic pressure-volume relationship, tau and dP/dt max. While the study in conscious dogs instrumented with telemetry units showed that oral dronedarone (20 mg/kg, BID) significantly prolonged PQ interval (P<0.001) without effects on cardiac contractility and relaxation (30). Furthermore, the study of efficacy of dronedarone to attenuate the duration of AF in dog model of sustained AF revealed that oral dronedarone (20 mg/kg, BID, for 7 days) significantly attenuated the duration of sustained AF (p<0.05). The atrial APD was significantly lengthened and atrial ERP was significantly prolonged (p<0.05). These results indicated that oral dronedarone attenuates duration of sustained AF in dog model of AF by extended the atrial ERP more than atrial APD causing post-repolarization refractoriness, suggesting that dronedarone blocks fast sodium channels in a state-dependent manner. Furthermore, oral dronedarone at a dose of 20 mg/kg (BID) had no effect on cardiac inotropy and lusitropy same as previous study (31).

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In most cases, dogs with atrial fibrillation almost always have underlying heart diseases. Therefore, care should be taken when prescribed dronedarone to dogs especially when the dogs have impaired cardiac function. When compared with amiodarone, dronedarone has been proved in human medicine to possess an excellent safety profile with no pulmonary or thyroid toxicity. However, there is no chronic test in veterinary medicine. In case of the price, dronedarone is more expensive than amiodarone approximately 2.5 times. In case of efficacy, dronedarone has been demonstrated to be 100 times more potent than amiodarone for inhibition of I_{K,ACh}. However, some investigators have shown that efficacy of dronedarone for antiarrhythmic is inferior to amiodarone when tested in vivo. All in all, with consideration of safety profile and its efficacy dronedarone should be first-line prescribed to patients instead of amiodarone especially atrial fibrillation patient with minimal heart disease.

**Future direction**

Limitations in the current therapies for canine AF have increased awareness of its therapeutic improvement. Further data from clinical trials investigating dronedarone as routine AF therapy will yield useful information regarding the use of this agents for treatment or prevention of canine AF.

**References**