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# Pharmacological Treatment for Atrial Fibrillation

## —Modalities in Equines and Companion Animals

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## Abstract

Cardiac arrhythmias are probably more common in horses than in any other domestic animal species where poor performance and exercise intolerance is the most frequent clinical complaint. Atrial fibrillation is a type of cardiac arrhythmia that appears as a common finding during medical examinations in humans, large breed dogs and horses. Clinical presentations are of a particular value in racehorses in high performing activities. Atrial fibrillation is characterized by an irregular heart rhythm, secondary to a primary disease or without any sign of comorbidity. The generation and maintenance of Atrial Fibrillation requires a substrate. Some breeds have a genetic predisposition to developing Atrial Fibrillation. Most cases of Atrial Fibrillation are of the paroxysmal type and self-regulate within a few hours to days without the need for treatment. The focus of this study is on the arrhythmic agents that are used for the treatment of Atrial Fibrillation, therefore other arrhythmic agents may not be included, or are included to demonstrate their effect on increasing, inhibiting or decreasing efficacy when used together with medications for the treatment of Atrial Fibrillation. The "working horse" for the pharmacological treatment of Atrial Fibrillation is Quinidine.

## Keywords

Atrial Fibrillation, Arrythmia, Equine Cardiology, Poor Performance, Pharmacological Treatment, Quinidine, Genetic Predisposition, Sinus Rhythm

## 1. Introduction

Atrial fibrillation is a type of cardiac arrhythmia that presents as a common

finding during medical examinations in humans, dogs and horses [1]. In cats not in physical activity, *i.e.* at rest [2] [3], a degree of arrhythmia is evident in indoor environmental conditions, but if the physical examination indicates atrial fibrillation, this is always accompanied by pathological findings.

Atrial fibrillation is of a special medical value in racehorses as it is the most common arrhythmia in this species that causes poor performance [4]-[9]. Atrial Fibrillation impairs ventricular filling and Cardiac Output resulting in poor peripheric oxygenation [10] [11]. The first report of Atrial Fibrillation in horses dates back to the 1950s [12] [13]. Cases have been diagnosed in post-race medical checks of horses that were slowing down or failed to finish the race [14]-[16] or have been submitted for medical examination related to complaints of reduced performance [5] [17].

Atrial Fibrillation may go undetected or occur intermittently and present in different frequencies or/and vary in duration, but still result in poor performance in racehorses. This review aims to investigate the current literature going through interspecies differences on atrial fibrillation and actual treatments and future pharmacological modalities are discussed in horses and large breed dogs.

The focus of this study is on the arrhythmic agents that are used for the treatment of Atrial Fibrillation, therefore other arrhythmic agents may not be included, or are included to demonstrate their effect on increasing, inhibiting or decreasing efficacy when used together with medications for the treatment of Atrial Fibrillation.

## 2. Materials and Methods

This review is based on a course of clinical trials developed by several authors on the atrial fibrilation and clinical trial treatment regiemens and is supplemented by several animal cardiology books and PubMed search using the keywords "clinical research in treatment of atrial fibrillation", "Antiarrhythmic investigations in large animal with atrial fibrillation", "current therapies in atrial fibrillation", "pharmacologic cardioversion of atrial fibrillation in large animals", "treatment of atrial fibrillation", "pathophysiology of atrial fibrillation", "atrial fibrillation in the racehorse", "cases of paroxysmal atrial fibrillation racehorse", "mechanisms of cardiac arrhythmia", "RyR2-related disease", "arrhythmias in domestic animals", "funny channels", "feline arrhythmias", "canine and feline cardiology", 'equine cardiology", "canine atrial fibrillation", "lone atrial fibrillation", "recurrence of atrial fibrillation in horses", "Clinical significance of atrial fibrillation in horses", "pathological changes in atrial fibrillation in the horse", "drugs in the treatment of cardiac disease in the horse", "classification system of atrial fibrillation".

This review provides an overview of previous studies based on Case series, Case report, Retrospective studies, Cross-sectional, Case control study, Clinical study, Retrospective study and Prospective study in clinical research for the treatment of atrial fibrillation.

Atrial Fibrillation is reviewed based on classification of the duration, the types,

the mechanism and the cause of atrial fibrillation in horses and large breed dogs and actual treatment antiarrhythmic agent treatment considering their mechanism of action and the effect on *ion currents* on each drug proven safety and efficacy in treating/preventing the clinic of atrial fibrillation on horses, dogs, and cats.

## 3. Limitations of the Study

In the last decades, numerous studies have been conducted regarding the mechanism of Atrial Fibrillation in horses along with different treatment options and their effect on performance [3] [18]-[25].

More knowledge is needed about Atrial Fibrillation, and studies on Atrial Fibrillation use different methodologies and refer to different populations, but agree that poor performance in horses with no other clinical signs is an indicator for the clinical presentation of cardiac arrhythmias [26]; some of them are listed below.

Sudden decline in performance is a indicative sign of Atrial fibrillation (AF) as the most common [5] [7] [26] [27] arrhythmia in poorly performing horses; But reported incidence and prevalence vary widely; from an estimated prevalence of 0.29% (or 1 case in every 341 starts) in racing horses, with 90% of cases recovering naturally without treatment within 24 hours [16]; in an estimated incidence of 4.9% of Thoroughbreds with reduced racing performance [14] [28]-[30] in an overall prevalence of Atrial Fibrillation in Standardbred of 0.11% [31]; to the report of patients in a hospital for horses of mixed breeds (3434 horses), where the incidence of Atrial Fibrillation recorded an average of 2.3% - 6.2% [32]; and Great Britain, during and immediately after the race, where paroxysmal atrial fibrillation was identified with a prevalence of 0.2% per 1000 starts [33].

Likewise, in a similar article with a mixed population of 2477 horses consisting of racing horse patients (n = 389, AF prevalence 6.2%), military and racing horses (n = 496, 0.8%) and horses examined in one slaughterhouse (n = 1592, 2.2%) the incidence of Atrial Fibrillation was reported to be 2.5% [29].

Veterinarians who work with racehorses understand that it is common for horses to return from racing with an arrhythmia, with no identifiable abnormalities the next day, despite medical investigations. In equine medicine, the challenge is early identification of the arrythmia and identification of horses at risk for this type of arrhythmia [5] [24] [34]-[37].

## 4. Automaticity of the SAN

A property of cardiac cells is that of automaticity to generate spontaneous action potentials. Spontaneous activity is the result of diastolic depolarization driven by a net inward current during the 4-thirds phase of the action potential, which progressively leads to a change in membrane potential [34] [38]-[41].

The automaticity property allows cardiac cells to generate action potentials spontaneously through diastolic depolarization (phase 4), where the net inward current progressively drives the membrane to threshold potential. All myocytes have excitatory, refractory, and conducting properties [40]-[43].

All kind of changes in the cell membrane affect the electrophysiology of the cell [25] [43]-[46] by reducing the negative resting potential, slow phase "0" depolarization and reduction of the plateau phase [39] [47].

The type of cell affected, medications or electrolyte imbalances, including the autonomic nervous system, have their own effects on the rhythm [42]. Sinus arrhythmias are not present when the animal is at rest, but they are most evident in post-exercise periods when there is a transition from sympathetic to vagal tone [48]. The clinical presentation may be caused by primary diseases that affect heart function, such as respiratory disease, where the right atrium is enlarged in response to reduced right ventricular function [14].

The property of myocytes is like neurons; once the threshold is reached, they are fully activated by an action potential [41]. Therefore, cells can be described as excitable. Upon reaching the excitability phase, they cannot be depolarized without reaching the resting potential (refraction) that is followed by repolarization, a period where no stimulus can give an excitability potential (*avoiding tetanic spasms*). The period of refractoriness after each wave of depolarization prevents the wave from traveling back to the Sino Atrial node (SAN), by forcing it to travel in only one direction, to the Atrio Ventricular node (AVN) [39] [42] [49].

The current is then passed from cell to neighboring cell; from the Atria to the Ventricles to forms two syncytia where the excitability passes from cell to cell through intercalated discs. The specialized cells of the conducting network do not have contractile proteins [39]. The sinoatrial node (SAN) normally has the highest intrinsic rate. All other pacemakers are called latent pacemakers because they take over the function of initiating stimulation only when the SA node is unable to generate impulses or when these impulses fail to conduct.

## "Funny" Channels in the Automaticity of the Sinoatrial Node

Cardiac automaticity is a field in which there has been a lot of interest from researchers, but some questions about how the heart rhythm is generated and controlled in physiological and pathological conditions are still the subject of study. One study showed that "funny" current disorder is associated with atrial tachyarrhythmia. The authors suggested that "$l_f$" current disorders may be the basis of the mechanisms of tachyarrhythmia and bradyarrhythmia syndrome [50]-[52].

To explain ($l_f$) currents, it is worth mentioning the term sarcolemma voltage or Ca Clock terms that are used from [40] [53] to describe the mechanism of automaticity of the sinoatrial node (SAN) [50] [52] [54] [55].

A voltage clock refers to a membrane that is sensitive to currents, such as the "*hyperpolarization-activated pacemaker current*" for short ($I_f$) regulated by cyclic adenosine monophosphate (cAMP) [50] [54].

This current is also called the "funny" current because, unlike most voltage-sensitive currents, it is activated by hyperpolarization rather than depolarization. At the end of the action potential, ($I_f$) is activated and depolarizes the sarcolemmal

membrane [50].

"$I_f$" channels are encoded by the "hyperpolarization-activated, cyclic nucleotide-gated" gene family) or HCN for short. Of the four known HCN subunits, HCN4 is the most highly expressed in the mammalian sinoatrial node (SAN). The central role of "If" is reinforced by the fact that mutations in the "If" channel are associated with reduced heart rate [56], and medications that block "If" (*such as ivabradine which will be discussed in the paragraphs of pharmacological treatment modalities of Atrial Fibrillation*) have the same function [50] [55].

In patients who have a genomic exon deletion in RyR2 [49] [57] the mutation predisposes in the dysfunction of the $Ca^{2+}$ clock and to atrial fibrillation, among others rhythm disturbances. But the functioning of the "$I_f$" current membrane is not the only one involved in the mechanism of automaticity in the Sino Atrial node; this especially noted during sympathetic activation [52]. Even if $HCN_4$ point mutations result in sinus bradycardia, the maximum heart rate achieved during exercise is normal.

In addition to the "$I_f$" membrane, time and voltage dependent ionic currents have been identified in cardiac pacemaker cells, which contribute to diastolic depolarization. Some of these currents are ICa-L, ICa-T, and variants of $K^+$ currents [53] [58]. Many of these membrane currents are known to respond to $\beta$-adrenergic stimulation. All these membrane ionic currents contribute to the regulation of the automaticity of the SinoAtrial node by changing the membrane potential.

These studies suggest that sympathetic stimulation accelerates heart rate by phosphorylating proteins that regulate Calcium balance and spontaneous calcium cycling (SR Ca). These proteins include phospholamban (PLB, an SR membrane protein regulator of SERCA2a), L-type Ca channels, and RyR2. Phosphorylation of these proteins controls the phase and extent of subsarcolemmal SR Ca release [35] [49] [59].

The above play an important role in the initiation and maintenance of Atrial Fibrillation and may provide both the substrate and the trigger (the involvement of which will be discussed below) of Atrial Fibrillation.

## 5. Arrhythmia in a-FIB

Atrial fibrillation is defined as a supraventricular tachyarrhythmia characterized by uncoordinated atrial depolarization due to multiple chaotic reentrant waves, rendering the atrial contraction mechanism nonfunctional. Horses are presumably predisposed to atrial fibrillation (AF) primarily due to their high vagal tone and large atrial mass which combine to promote the maintenance of multiple reentrant circuits, or spiral waves, within the atria of affected individuals [4] [7] [18] [19] [24] [25] [45] [46] [60]-[64]. While the behavior of the spiral waves is subject of considerable research and debate, it is generally accepted that they are responsible for the rapid, irregular atrial depolarizations forming the characteristic of atrial fibrillation (AF).

Atrial fibrillation is characterized by an irregular heart rhythm [65]-[67] which

can occur or be secondary to a primary disease (for example myocardial diseases, mitral regurgitation or pulmonary diseases) [26] [68]-[70] or without any identifiable disease.

Atrial fibrillation as the most frequently reported cardiac arrhythmia in horses [30] [71] reported to adversely affect peak performance, but return to normal sinus rhythm has a good prognosis if no other primary heart disease is present [4] [66] [72] [73] Reversion to the previous level of performance is common in such cases [71].

Heart size is a predisposing factor for experiencing atrial fibrillation (AF); When it comes to large breed horses and dogs, studies have shown that their hearts easily develop the "lone" type of atrial fibrillation (AF), due to the size of the atria and the ability for reentry [10] [14] [26] [38] [46] [47] [68] [74] [75]. In horses, "lone"AF, or as it is known in human medicine, Idiopathic Atrial Fibrillation, is the most frequently encountered arrhythmia in cardiac clinical presentations [47].

There are many factors that lead to the development of cardiac arrhythmias. Deviations from normal cardiac cell action potentials involving Trigering (*early or late afterdepolarizations during the 3rd phase of the action potential, with high amplitude, stimulate $Na^+$ channels, giving another action potential again*) [47], refractarity, conduction or automaticity during stage 4 (*abnormal membrane potentials approximately -55 mV which often has metabolic, ischemic, hypoxemia or high sympathetic tone*) causes, predispose to arrhythmia [19] [42].

The loss of effective atrial contraction, which occurs in the case of Atrial Fibrillation, reduces the maximum volume of the diastole phase of the ventricle (Preload). Atrial contraction can contribute up to 30% (or more) of total ventricular diastolic volume when the heart rate is high, and the resulting effect is a decrease in Cardiac Output (CO) [39] [42] [49].

### 5.1. Classification by Duration of a-FIB

Arrythmias are classified according to the cardiac structure from which they originate, their rhythm, and the mechanism responsible for their production [24] [49]. The generation of arhythmias can come as abnormal generation of impulses, or anormal impulse conduction from the sino strial (SAN); damage to some localized cells that give abnormal depolarization, or that affect the conduction network, and most myocytes [20] [39] [47] [66].

Most studies are based on human studies and reports related to the clinical presentation of the disease, where Atrial Fibrillation can be categorized depending on the duration of the arrhythmia as: paroxysmal or sporadic forms paroxysmal atrial fibrillation (pAF) where: *Atrial fibrillation ends spontaneously within hours or days [5]* [11] [65] [75] persistent (*a longer period or requiring pharmacological or electrical treatment*) [11] [76]-[80] or permanent (*continues even if untreated, but also if treated pharmacologically*) *[75]* [78] [81] [82].

This terminology has been associated with clinical use in veterinary medicine

as well [83]. In contrast with humans, Atrial Fibrillation in Horses has no clear correlation with age.

Atrial fibrillation in its sporadic form is defined as coming into sinus rhythm spontaneously within 24 - 48 hours [15] [84], This can be seen in racehorses, during intense exercise in which Atrial Fibrillation is recorded [16] [30]; within 72 hours [10] [11] or within 5 days [30] [31].

While in human medicine, sporadic or "paroxysmal" Atrial Fibrillation (pAF), by definition, reverses to sinus rhythm spontaneously within 7 days, in animals it is a more variable period [76] [79] [85] [86].

An accurate determination for the reversion period of this cardiac phenomenon is necessary for comparison and reference in future studies, but also to provide clinicians with information about prognosis and possible treatment. This paper, for pharmacological treatment and control modalities, also includes continuous and permanent Atrial Fibrillation.

In most horses which are active in sporting activities, Atrial Fibrillation is common finding and horses are hospitalized for arrhythmia that requires treatment to switch to sinus rhythm. In some horses, although being treated, atrial fibrillation fails to return to sinus rhythm, and these horses develop permanent atrial fibrillation [87].

### 5.2. Classification by the Cause of a-FIB

Atrial fibrillation can also be classified according to its cause. A form called 'lone AF', is a form in which during clinical checks using routine diagnostic tests, no disease can be identified as the possible cause [21] [63] [71] [88] although mild valvular regurgitation without atrial dilatation is occasionally found in these animals [70] [83] [89].

The terms "Idiopathic Atrial Fibrillation" or "lone AF" have been used to emphasize the absence of primary cardiac disease but subclinical pathophysiological changes in the atrium are considered by some researchers to be the "primary" causes [26] [49] [90]; therefore, it is recommended that the terminology 'lone AF should be avoided as these patients may have atrial microstructural abnormalities of the myocardium, such as fibrosis [91] [92].

As a cause for the clinical presentation of Atrial Fibrillation, genetic predisposition is seen, for example in the Standardbred race horses [5] [8] [31] [57] [90] [93] but Atrial Fibrillation can be caused by a primary heart disease [9] [26] [94]. Horses may be predisposed to develop Atrial Fibrillation following structural heart disease such as valvular insufficiency or congenital defects that cause atrial enlargement [70].

These horses are prone to re-present to the clinic for treatment, if treatment is attempted, after the first incidence [95].

## 6. Effects of Atrial Fibrillation in Animals

The first step in learning about equine health is determining what the normal

signs are in a healthy horse. Values for horses vary from the conformation of the horse, the normal use of the horse and its general condition; this also applies to other animals. The use of treatments for Atrial Fibrillation in animals with primary heart problems (e.g. quinidine in horses) is contraindicated [71].

The resting heart of adult horses is reported between 32 and 38 but these can rise to around 240 bpm at high exercise intensity rate [41].

In horses, the rate of atrial activation during Atrial Fibrillation is about 250 - 450/min, and <200 - 400/min in dogs. However, because of the high vagal tone, in horses, the atrioventricular node (AVN) blocks most of these pulses. As a result, the final ventricular rate while the patient during resting periods is normal, at least if there is no other clinically significant cardiac disease. Since the normal heart rate allows sufficient passive ventricular filling and thus shows sufficient cardiac function [15] [36] [41] [83] [96] and this is the reason why the horse does not show symptoms when it is not performing activity or is at rest.

In dogs, chronic rapid atrial activation (400 bpm) reduces atrial conduction velocity [83], contributing to the development of a substrate supporting sustained atrial fibrillation (AF) in >80% of the animals; relevant to the way in which sustained atrial fibrillation (AF) alters atrial properties to promote its own maintenance, known as "AF begets AF" [97].

During the exercise period, sympathetic tone replaces vagal tone, where conduction through the Atrioventricular node is facilitated resulting in a disproportionate tachycardia [30] [38].

Both the loss of atrial contractility and the extreme increase in heart rate during exercise result in reduced cardiac function and exercise intolerance. However, this exercise intolerance is mainly seen at higher performance levels of this species, as compensatory mechanisms for self-regulation are sufficient during non-intense physical activity. It happens that during exercise, the heart rate reaches about 250 - 280 beats per minute; this is a common finding in elite equine athletes considered, otherwise, healthy [6] [30] [98] [99].

There are some properties of cardiac arrhythmias which are presented due to vagal tone like sinus arrhythmia or sinus block, sinus arrest, sinus bradycardia, wandering pacemaker, first-degree AV block, and second-degree AV block which are found in resting horses to be generally considered as normal findings and generally do not require therapy [41]. Sinus arrhythmia (*abnormally low sinus rhythm*) goes back to regular sinus rhythm when sympathetic tone increases and vagal tone decreases; this usually happens at Heart Rates above 50 beats/minute in horses and 150 beats/minute in dogs.

## 7. Pathophysiology

A cardiac arrhythmia is a variation from the normal heart rate and/or rhythm that cannot be physiologically explained. A heart rate that is high, abnormal, or rapid for the clinical context sinus rates exceeding 50 beats/minute in horses, 180 beats/minute in dogs, and 240 beats/minute in cats during a resting ECG may be

caused by sinus tachycardia or an ectopic or reentrant tachyarrhythmia [2] [4] [5] [13] [20] [24] [25] [39] [45] [60]-[62] [64] [68] [74].

Loss of atrial contractile function, irregular cardiac cycles from Atrial Fibrillation, or premature beats can worsen diastolic dysfunction [18] [19] [27] [81] [92] [99].

Information available regarding the pathophysiology (see **Figure 1**) and underlying mechanisms of Atrial Fibrillation in horses are not well explained, and most of the knowledge is being derived from experimental studies in various animal models and clinical studies in human patients [18] [19] [25] [49] [63] [64] [91] [92].

The electrophysiological basis of Atrial Fibrillation is defined as an interaction between electrical triggers and a reentrant-sensitive substrate [19] [73] [92].

### 7.1. Mechanism of Atrial Fibrillation

The mechanisms responsible for cardiac arrhythmias are generally divided into 2 main categories: 1) increased or abnormal impulse formation (*i.e. ectopic activity*) originating from cells that do not normally demonstrate automaticity; cause profound bradycardia when conduction through the AV node fails and 2) electrical conduction abnormalities (*i.e.* re-entry) which can be the basis for the cycle of a tachycardia through a *reentry mechanism*; *impulse conduction disorders* (see **Figure 2** and **Figure 3**), or a *combinations of both* [4] [19] [22] [25] [47] [49] [60] [64] [74] [91] [92] [100].

Genesis of Atrial Fibrillation [40] [59] [62] [64] it is thought to start from one or more premature beats coming from an ectopic focus, but the exact location of the ectopy has not been well documented [30] [101] in horses for localization of premature depolarizations or prediction of the associated risk of arrhythmias using although when well positioned a 12-lead ECG is and adding value to the diagnosis [12] [39] [102] [103]. It is also not known whether the mechanism of Atrial Fibrillation in animals an ectopy, reentry or rotor is, as defined in their human counterpart [72] [74] [92] [104].

The complex pathophysiological mechanisms of atrial fibrillation (AF) have been investigated mainly in human clinical cases, and in vivo animal models including dogs, rodents, goats, pigs and horses [1] [49] [105] also in vitro experiments at the cellular and molecular levels [24] [47] [74] [106].

The repetitive fluctuation in rhythm and P wave morphology in sinoatrial node (SAN) arrythmia is a normal rhythm variation which happens to be a common finding in dogs (over one month of age) and horses. No significant correlation between Heart Rate and body weight is evident in clinically determined healthy dogs [107].

The electrophysiological properties of myocytes derive from the cell membrane. Inside the cell the charge is negative (with a high concentration of $K^+$, and small amounts of $Na^+$ and $Ca^{2+}$) compared to that outside it (difference −90 mV), and membrane pores/channels, characteristic of cardiac cells, that works on

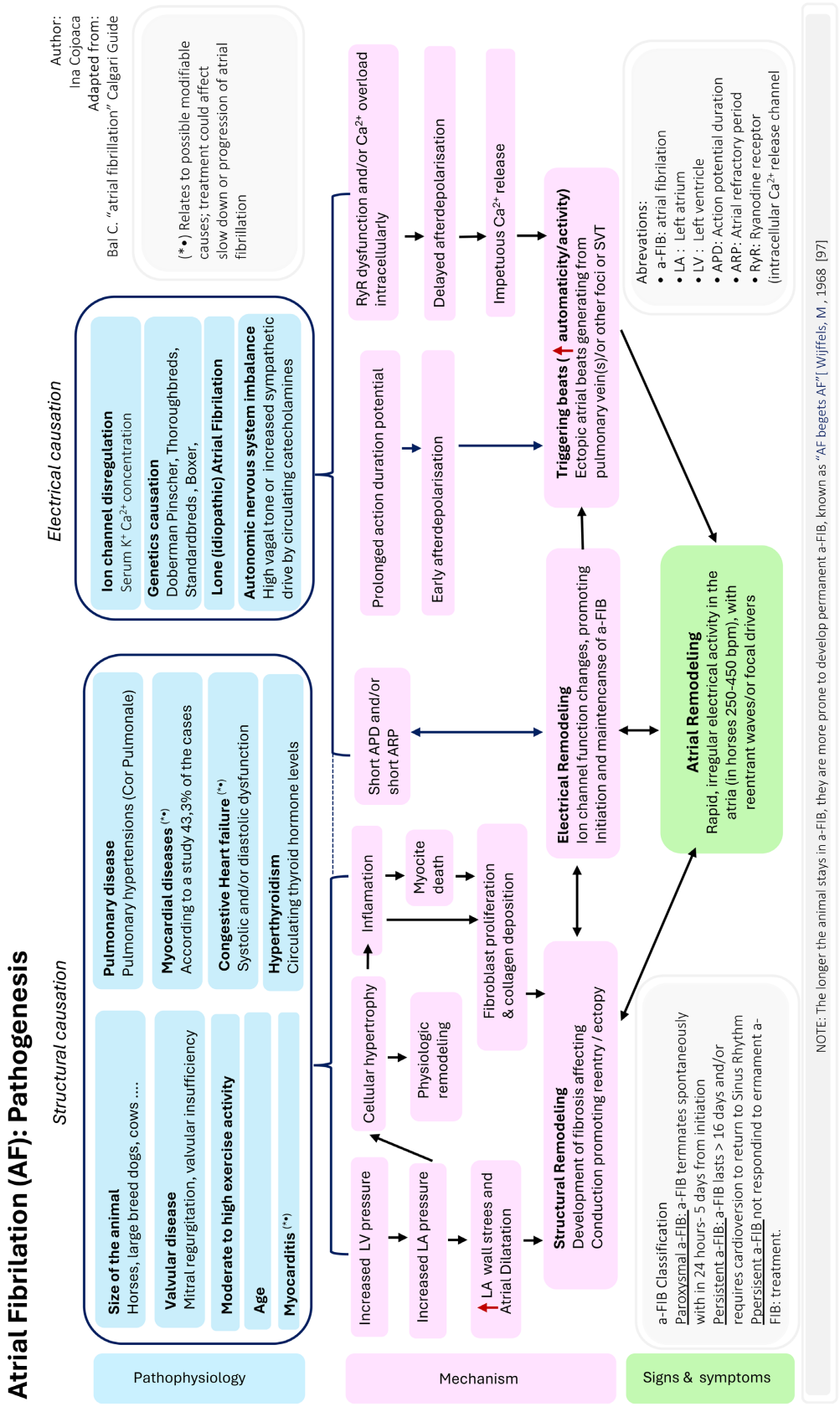


**Figure 1.** Atrial fibrillation (AF) Pathogenesis, adapted from Bal C. Calagri Guide.

opening/closing with the movement of ions, give a transmembrane potential resultant of +20 mV in depolarization and again −90 mV in repolarization [53].

Action potential is divided into 5 stages (0 - 4) but for simplicity is usually considered in three phases depolarization, repolarization and the resting phase [43] [100].

### 7.1.1. Triggers

Triggers are considered premature atrial depolarizations due to altered automaticity or incited activity, or by local (micro) reentrants. Arrhythmias are driven by changes in atrial myocardial ion channels, changes in $Ca^{2+}$ exchange, structural abnormalities, and autonomic nervous system imbalance [6] [18] [47] [60].

Ectopic triggers result from several dispersed foci in the atrium and may produce a premature atrial complex (PAC), if this occurs earlier than predicted in the cycle; these premature complexes when they are several in number, within a short interval of time, are estimated to be capable of producing Atrial Fibrillation in horses [61] [92] [95] [104].

Their development is influenced by drug therapy, dominant autonomic tone, baroreceptor reflexes and variations in Heart Rate, as well as major diseases [108].

Ectopic activity (focal spontaneous) results in Atrial Fibrillation. When there are many foci of ectopic excitability (see **Figure 2**), the result is the induction of Atrial Fibrillation, and a single focal point is seen to be needing a substrate for it to generate Atrial Fibrillation. The excitability itself results from: increased cellular automaticity and abnormal automaticity from ectopic regions caused by $Ca^{2+}$ circulation abnormalities [53] [81].

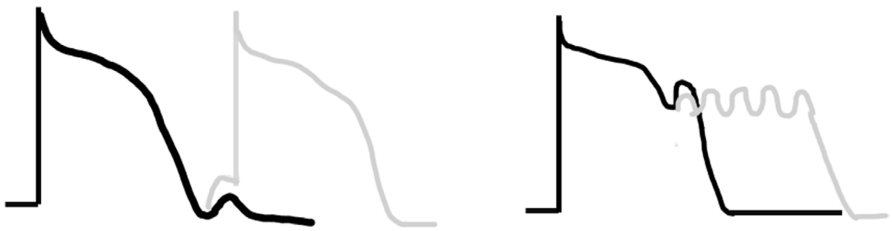

**Figure 2.** Abnormal flow of + ions in cardiac cells, creating a bump in the activation potential, which is called after-depolarization, in phases 2, 3, 4; of with sufficient magnitude can trigger premature action potential (graphic adapted from Cardiology—Coronel R, 2013 Electrophysiological changes in heart failure pp. 31-36).

These triggers can be stimulated or depressed by altered neurological stimulation either sympathetic or parasympathetic tone but can also be triggered from type B receptors sensible to the stretch of Atria that affects Atrial Fibrillation [25] [108]-[110].

The SinoAtrial node is influenced by a variety of *autonomic* and *metabolic factors* and participates in numerous Cardiovascular and Respiratory reflexes. For example, changes in body temperature, circulating thyroid hormone levels, and serum kalium ($K^+$) concentration directly affect SinoAtrial node discharge (see **Figure 3**). And the autonomic effect in the control the rate of sinus node consists

on activity of the sympathetic and vagal nerve, as well as circulating catecholamines [38] [62] [102].

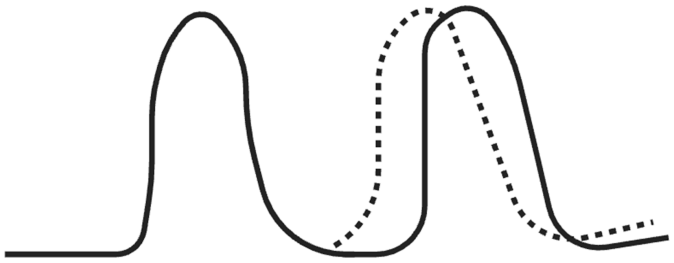

**Figure 3.** Cell membrane become abnormally permeable to $Na^+$ during phase 4, which result in early depolarization. This can cause other cells to accelerate their automaticity and generate impulses faster than SAN (graphic adapted from Cardiology—Coronel R, 2013 Electrophysiological changes in heart failure pp. 31-36).

Sometimes the trigger comes from some cells with membrane potential similar to cardiac pacemaker cells, of the same origin as embryonic cells in myocardial conduction network tissues which are to be found near the pulmonary veins (PV) in humans [61] [69] [82] [108] [111] and when they are stimulated they cause Paroxysmal Atrial Fibrillation.

The role of cells with membrane potential in the Pulmonary Veins has also been found in horses, [96], according to a study in a horse, which underwent atrial mapping, provided evidence that spontaneous atrial stimulation can originate from the area of the pulmonary veins [61] [96] [111] reinforcing the idea that the activity of these cells in the pulmonary veins play a role in Atrial Fibrillation in horses.

Molecular changes in the movement of $Ca^{2+}$ and disorders of the ryanodine receptor (RyR2), which can cause leakage of $Ca^{2+}$ from the sarcoplasmic reticulum gives after-depolarization delays, resulting in Atrial Fibrillation [49] [57].

### 7.1.2. Substrate

If a focal point exists, it's spontaneous termination will depend on the substrate, (*so from Atria and the size of the created circle*); the given possibilities are that atrial fibrillation ends naturally or with the help of medical treatments. But when prolonged and in turn induces atrial remodeling [22] [23] [46] [58] [105] the latter can degenerate into permanent Atrial Fibrillation [25] [92] [97].

These horses may have ion channel dysfunction or undiagnosed (micro)structural changes of the myocardium. On the other hand, atrial fibrillation itself results in electrical, contractile and structural remodeling, leading to prolonged atrial fibrillation that does not respond to medication [18] [21]-[23] [57] [58] [70] [83] [91] [105] [112].

From the information recorded from clinical data, the increase in the number of foci induced in horses is related to the increase in the incidence of Atrial Fibrillation. In small animals (mentioning here goats,') also in dogs as a species under study but also in ponies', but also in humans, studies have shown that the shortening of the atrial refractory period takes place within the first days of Atrial

Fibrillation [64] [72] [83] [92] [112] [113].

### 7.2. Types Atrial Fibrillation Remodeling

An important factor in the development of Atrial Fibrillation is the *arrhythmogenic remodeling* of atrial function or structure, which triggers Atrial Fibrillation. Electrical remodeling [19] [23] [78] [91] [105] leads to shortening of the effective atrial refractory period, promoting reentry [39] [74] Contractile remodeling [24] [105] consists in reducing the contraction of the myocardium. Whereas Structural remodeling consist in the development of interstitial fibrosis and atrial enlargement [23] [57] [105] [83] [92] [112].

Histological changes that appear because of Atrial Fibrillation include cellular hypertrophy, increased interstitial fibrosis, glycogen accumulation, gap junction redistribution, sarcoplasmic reticulum disruption, and apoptosis [27] [59].

Reverse remodeling [23] [58] [69] occurs after returning to sinus rhythm, but full recovery may take weeks to months depending on the duration of the Atrial Fibrillation.

In Horses Remodeling of Contraction and Electrical Impulses during an Induced Protocol of Chronic Atrial Fibrillation in Ponies showed a rapid electrical remodeling mechanism and contractile remodeling but also a slower left atrial dilatation [114]. In horses, due to the high vagal tone (parasympathetic system), some arrhythmias are considered "physiological" arrhythmias.

Physiological remodeling (see **Figure 1**) is associated with an increase in mitochondria synthesis, an increase in contractile proteins and an increase in cardiac function, but without an increase in collagen content in the myocardium [1] [58] [61] [73] [83].

This type of hypertrophy differs from pathological hypertrophy in terms of signaling pathways and vascular dynamics [22] [67] During physiological hypertrophy in Horses, an expansion (dilation) of the chamber and an increase in wall thickness and lumen diameter is observed [39]. This form of cardiac chamber expansion can be reversible, non-pathogenic and results in improved heart function by reducing vascular resistance.

In humans and dogs, Atrial Fibrillation is associated with reduced quality of life and increased morbidity and mortality from atrioventricular dis-synchrony, hemodynamic changes, and progressive cardiac dysfunction [18] [115] also including the increased possibility of thrombus formation due to reduced systole and increased atrial stasis [110], where Atrial Fibrillation begins in the early stages of *hypercoagulability* [76] [116].

Even the prolongation of Atrial Fibrillation indicates a pathological change in the heart muscle (*Myo lysis*), in dogs and humans which further reduces atrial contractile function. Atrial contraction dysfunction contributes to the impairment of atrial transport function and the occurrence of atrial thrombi [116].

While in Horses with Atrial Fibrillation, the same findings are not reported [117]-[119]. According to the study, horses with atrial fibrillation did not have

clinical evidence of a hypercoagulable state; in a greater number of patients included into the study with Atrial Fibrillation compared to the control group of horses, it was possible to be demonstrated clinically a subclinical coagulation activation by standard coagulation tests. The use of anticoagulants is therefore not suggested as part of the management of AF in horses.

Increased heart wall thickness without an increase in lumen diameter is an unusual finding in horses and is commonly seen in human hypertensive patients, but can also occur in animals with aortic stenosis [47] [70] [109].

## 8. Predisposition to Atrial Fibrillation

In predisposing factors to developing the clinical presentation of Atrial Fibrillation in many studies, the size of the body of the animal has been considered, with special reference to the size of the Atria and the valvular function [46] [47] [79] [92] [120].

In the analyses for clinical presentations, attention has been paid to possible factors determined from birth triggering Atrial Fibrillation, such as race, gender and age as predisposing factors. The results are non-deterministic; some of them are presented below.

### 8.1. Race and Genetic Predisposition

Cases of Atrial Fibrillation have been shown to be genetically predisposed in Thoroughbreds [28] [29] [88] [121] and Standardbreds [5] [8] [31] [90] [93] where the arrhythmia was found to be quite common in offspring within the same family [23] [122], but not only [105].

Paroxysmal Atrial Fibrillation has been found in racing horses especially in Thoroughbreds and has been associated with a sudden drop in performance [5] [11] [30] [65] [123].

In patients (or races) who have genomic deletions of the 3d exon RyR2 [49] [57], the mutation predisposes to $Ca^{2+}$ clock dysfunction and Atrial Fibrillation, among others other rhythm disturbances.

Genetic predisposition of Dilated Cardiomyopathy in Doberman Pinscher breeds, in dogs, that present with this genetic primary disease are a high risk of death from arrhythmia [21]. The same goes for Boxer dog breeds, where the risk of high mortality from arrhythmia increases with the presence of arrhythmogenic cardiomyopathy (of the right ventricle) hereditary for the type [24].

### 8.2. Gender Predisposition

Most cases hospitalized and treated for Atrial Fibrillation are male horses. This statistic must also be related to the participation of the male gender, in competitions and not those of the female gender [11] [16] [29] [65].

### 8.3. Age Predisposition

Whether or not the incidence of Atrial Fibrillation in horses increases with age, is

not conclusive, and it still needs to be determined. According to a study, atrial fibrillation is more common in adult horses compared to ponies [17]. And in another study, comparing horses in a hospital facility aged 4 with horses of 5 years or older [7] no significant difference was found in the prevalence of Atrial Fibrillation.

However, another study in racehorses that were 4 years of age or older found that the incidence of Atrial Fibrillation increased with age [16]. This conclusion also arises in a study where age appears as a risk factor in Standardbreds [31].

Cases of Atrial Fibrillation have also been reported in three newborn foals [28] presented with a different triggering mechanism from adult horses, by the onset of breathing, which triggered an increased pulmonary blood flow and by that ab increased left atrial pressure, resulting in atrial stretch which itself triggers atrial fibrillation (AF) [109].

### 8.4. The Size of the Animal

According to related studies, animals with larger bodies such as horses, large breed dogs and even cows with large atrial size tend to develop Atrial Fibrillation in the absence of other diseases [1] [21] [89] compared to smaller size animals (like other dog breeds, pigs and goats); because larger animals have a larger atrial mass, allowing more re-entry circuits to coexist at the same time predisposing to Atrial Fibrillation [4] [46] [124].

Also, another study conducted in dogs, failed to establish a substantial correlation between heart rate and body weight [107].

### 8.5. Valvular Diseases

Valvular regurgitation, which is common in horses, predisposes to Atrial Fibrillation, but not in the early stages [70] [71].

But moderate mitral regurgitation leading to atrial volume overload and therefore an increase in atrial pressure and myocardial dilatation [109], can cause Atrial Fibrillation in horses.

Aortic regurgitation occurs most often in older horses due to calcification or noninflammatory degeneration of the aortic valve. It may also develop secondary to aortic endocarditis (infection of the valve leaflets), most often in large-breed dogs [125].

### 8.6. Heart Related Diseases

Symptoms depend on the degree of primary heart disease and the exercise required to be performed by the patient, if animals are being kept for breeding or companion animal. Atrial Fibrillation is usually an incidental finding, unless congestive heart failure (CHF) is present. Intolerance and problems are always evident in racehorses when performance is at its peak [5] [35] [36] [71] [99] [115].

Initially, according to studies [72] [67] myocardial diseases were thought to be the suspected cause of Atrial Fibrillation. But in a later study [71] it was reported

that 56.7% of horses with Atrial Fibrillation did not present with cardiac disease. In the same study the remaining 43,3% of the patient's Mitral regurgitation was the most common underlying cardiac disease followed by Tricuspid regurgitation, aortic regurgitation, myocardial dysfunction and atrial septal defect. Congestive heart failure was common in this group of horses with underlying cardiac disease.

Pulmonary hypertension leading to Cor Pulmonale causing increased right atrial pressure and volume expansion, which promotes atrial remodeling, acts *as a substrate* for Atrial Fibrillation and is seen in both horses and humans [82] [110] [126].

The affected horse with cor pulmonale developed even Paroxysmal Atrial Fibrillation for 2 days and self-healed with treatment of the primary disease [69].

## 9. Clinical Signs

All for the purpose of defining the righteous treatment, the patient must first be clearly diagnosed as atrial fibrillation (AF) one, and the next question is whether it is a lone atrial fibrillation (lone AF) [26] [30] [75] or not; and if there are indications for primary, structural heart disease(s).

The most frequent clinical complaint associated with cardiac arrhythmias is exercise intolerance. Patients that have abnormal heart rates will undergo a thorough check-up [36] [99] [123] [124] including a physical exam, blood work, electrocardiogram (ECG), and echocardiogram to diagnose atrial fibrillation (AF) and rule out any other primary conditions [10] [65] [88]. But the techniques and modality of examinations are not the subject of this study.

The clinical signs of Atrial Fibrillation therefore depend on the aerobic demands during exercise, the response of the ventricular rhythm and the presence or not of primary heart diseases. atrial fibrillation (AF) is suspected by an irregularly irregular rhythm during auscultation at rest and should be confirmed by electrocardiography [5] [33] [36] [48] [62] [123].

The electrocardiogram is used to make a definitive diagnosis of the dysrhythmia; heart rate monitoring for atrial fibrillation (AF) detection by horse owners, based on the disproportionally high heart rate during exercise or increased heart rate variability. Echocardiography and laboratory analysis are useful to identify the etiology and to assess the significance of the arrhythmia and underlying cardiac disease, if are present. During physical examination the auscultation for abnormalities such as fast or slow heart rate, irregular rhythm, extra sounds, long pauses, or abnormal heart sounds are being evaluated [35] [124] [127].

In horses with so-called "lone AF", clinical signs are usually absent during periods of rest, but during physical activity the horse will present with poor performance, exercise-induced pulmonary hemorrhage, respiratory distress, weakness or, less commonly, collapse of the animal may provide information [5] [10] [14] [123].

Discoordination and collapse are an after effect of decreased cardiac pumping function and an increase in atrial pressure with a reduction in pulmonary

circulation, as identifiable cause [65] [67] [122], but there may also be no sign at all, and the horse still be in fibrillation [100].

The presented arrhythmia initial might present as a need for correction of electrolyte abnormalities and the need for anti-inflammatory medications, the recurrent nature tends to lead to inconsistent performance [62].

Atrial Fibrillation (AF) may also be present in horses with marked cardiac abnormalities, and in these horses is the clinical presentation considered to be a secondary development, because of atrial dilatation. Some horses with secondary atrial fibrillation (AF) are limited more due to the primary condition than due to the atrial fibrillation (AF).

The differences in clinical presentation for lone AF are considered to relate to the performance demands placed upon the horses. Racing horses that are exercising near maximal cardiovascular demands are more likely to show evidence of poor performance. Other horses that are low to moderate into physical activity, the finding is usually incidental.

## 10. Treatment for Atrial Fibrillation

Treatment of atrial fibrillation, although often successful, requires thorough pretreatment and evaluation for the use of therapeutic medications. Due to the narrow therapeutic window of the drugs administered [6] [9] [35] [62] [76] [87] [95] [128]-[133] careful monitoring of the patient is necessary.

The two modalities of therapies consist of pharmacologic treatment, usually involving pharmacological or electrical cardioversion, which are recommended if the episode lasts for more than 48 h in equine patients [1] [6] [17] [84] [125] [133] both have potentially harmful effects, and the choice of the most appropriate therapy is based primarily on the predicted efficacy for the specific case.

Antiarrhythmic therapy is given when clinical signs specifically related to the arrhythmia are present, when hemodynamic parameters are compromised by the arrhythmia, or when the ECG reveals abnormalities that put the patient at risk for development of more severe arrhythmias.

### 10.1. Arrhythmic Agents

Three classes of pharmacologic medications are used to control heart rhythm. But only a few medications are commonly used to treat horses that have atrial fibrillation (see **Table 1**).

#### Classification of Arrhythmic Agents

The Vaughan-Williams classification is one of the most widely used classifications for antiarrhythmic agents. Although many antiarrhythmic drugs have multiple mechanisms of action, they are classified based on the primary mechanism of antiarrhythmic effect and the effect at different stages during the cardiac action potential [134] [135].

The most used medications are Class I, Class II b-blockers, Class III C2+ channel blockers, Digoxin, and HCN. The most used medication for returning to

**Table 1.** Indications for treatment and doses* of antidysrhythmic drugs used in equines and small companion animals.

| Mechanism | Class | Medication | Indication for treatment | Dose* | Study Author | Ref. |
|---|---|---|---|---|---|---|
| Moderately slows conduction, increases action potential duration | Ia | Quinidine Gluconate < 2 weeks | AF, AV | 0.5 - 1.5 mg/kg IV every 5 - 10min IV to a total 6.2 mg/kg in **horses**, 6 - 20 mg/kg, IM, every 6 hours, or 6 - 20 mg/kg, PO, every 6 - 8 hours in **dogs** | Gordon SG, 2023; Gerber H, 1971; Muir WW, 1990; McGuirk SM, 1981 | [125] [129] [143] [144] |
| | | Quinidine Sulphate | AF | 5 - 10 mg/kg, IV, every 6 hours and 6 - 20 mg/kg, PO, every 6 - 8 hours in **dogs**, 22 mg/kg, PO, every 2 hours and 10 mg/kg/2h PO in **horses** | Marr CM, 2010; Morris DD, 1982; Reef VB, 1999; Gordon SG, 2023; Gerber H, 1971; Amada A, 1978; McGuirk SM, 1981 | [41] [95] [97] [125] [129] [136] [144] |
| | | Procainamide | AF | 1 mg/kg/min IV to total 20 mg/kg and 25 - 25 mg/kg/8h PO in **horses**, 25 mg/kg over 10 - 15 min, 25 - 40 mcg/kg/min CRI or 10 - 20 mg/kg, PO, every 8 hours IM/Sc; 4 - 6 mg/kg, PO, every 2 - 4 hours or in **dogs** | Reef VB, 1999; Gordon SG, 2023; Bertone JJ, 1987; Ellis EJ, 1994 | [97] [125] [137] [149] |
| Little change in conductivity, decreases action potential duration | I | Ib | Lidocaine | AF, SVT, VT | 1.3 mg/kg, IV, ~5 minutes, followed by 0.05 mg/kg/min CRI. Otherwise 0.25 - 0.5 mg/kg, slow IV, 5 – 10 minute intervals in **horses**, 2 mg/kg, IV ~1 minute, cumulative dose of 8 mg/kg over ~30 minutes. 25 - 75 mcg/kg/min CRI for maintainance in **dogs**, 0.1 - 0.4 mg/kg, IV ~1 minute ta a total dose of 0.25 - 1 mg/kg, slow IV, if no response and/or 10 - 20 mcg/kg/min CRI in **cats** | Reef VB, 2014; Moïse NS, 2005; Wright KN, 2019; Pariaut R, 2008; Dickey EJ, 2008 | [84] [150]-[152] |
| | | | Mexiletine | SVT | 4 - 6 mg/kg, PO every 8 hours or 8 mg/kg PO in **dogs** | Gordon SG, 2023; Gelzer AR, 2010 | [125] [153] |
| Slows conduction without change in action potential duration | | Ic | Flecainide | SVT, AF | 4.1 mg/kg, per os (PO), with a total dose 2.2 g treatment intervals 2 hours for a maximum of 4 - 6 doses in **horses**, 2 mg/kg, 1% solution slow IV bolus; 0.2 mg/kg/min infusion If not converted: additional 1 mg/kg/total dose, IV as 1% solution at rate of 0.05 - 0.10 mg/kg/min | Takahashi Y, 2018; Risberg AI, 2006 | [148] [157] |
| | | | Propafenone | AF | 0.5 - 1 mg/kg in 5% dextrose IV over 5 - 8 minutes in **horses** or 2 mg/kg PO every 8 hours in **horses** | Marr CM, 2010; Reef VB, 2014; De Clercq D, 2009; Puigdemont A, 1990 | [41] [84] [159] [160] |
| Beta-adrenergic | II | Propanolol | SVT, VT | 0.03 - 0.1 mg/kg IV in **horses**, 0.2 - 1 mg/kg, PO, every 8 hours | Marr CM, 2010; Gordon SG, 2023; van Loon G., | [41] [125] [133] [135] |

| | | | | | |
|---|---|---|---|---|---|
| blockade, reduces effects of sympathetic stimulation | | | (titrate dose to effect) in **dogs**, 0.4 - 1.2 mg/kg (2.5 - 5 mg/cat), PO, every 8 hours in **cats** | 2003; Muir WM, 1985; Romito G, 2024 | [162] |
| | | Esmolol | SVT, VT | 0.05 - 0.5 mg/kg i.v. bolus over 5 min; 25 - 200 µg (micrograms)/kg/min CRI in **dogs** and **cats** | Romito G, 2024; Verschoor-Kirss M, 2022 | [162] [163] |
| | | Atenolol | Rate control AF | 0.2 - 1 mg/kg PO every 12 hours in **dogs**, 0.2 - 1 mg/kg, PO, every 12 hours in **dogs**, 1 - 2.5 mg/kg, PO, every 12 hours, or 6.25 - 12.5 mg/kg PO, every 12 to 24 hours in **cats** | Gordon SG, 2023; Meurs KM, 2002; Romito G, 2024; Pariaut R, 2017 | [125] [132] [162] [175] |
| Selectively prolongs action potential duration and refractory period; antiadrenergic effects | III | Sotalol | AF | 2 mg/kg PO every 12 hours in **horse**, 1 - 3 mg/kg PO every 12 hours dogs and **cats**, 2 2 mg/kg q 12 h (1 - 2.8 mg/kg every 12 h) in **dogs** | Gordon SG, 2023; Gelzer AR, 2010; Romito G, 2024; Pariaut R, 2014; Broux B, 2018; Decloedt A, 2018 | [125] [153] [162] [164] [172] [173] |
| | | Amiodarone | AF, VT | 1.9 mg/kg/h for 30 hr in **horses**, 15 mg/kg every 12 - 24 hr Intravenous (new formulation) in **dogs**, 2mg/kg IV/10 min, 8 - 10 mg/kg/12 - 24 hr PO for 7 - 10 days; 4 - 6 mg/kg/24 hr for longterm treatment; 0.8 mg/kg/hr CRI for 6 hours in **dogs** | Cushing DJ, 2009; Romito G, 2024; Pariaut R, 2014; De Clercq D, 2006; Clercq D, 2007; Imhasly A, 2008; Levy NA, 2016; Pedro B, 2012; Saunders AB, 2006 | [44] [162] [164]-[169] [171] |
| | | Dronaderone | AF | 20 mg/kg in **dogs** | Saengklub N, 2017 | [174] |
| Decreases slow inward Ca++ current (greatest effect on SA and AV nodes) | IV | Diltiazem | AF, SVT | 0.125 to 1.125 mg/kg IV over 2 minutes repeated every 12 minutes to effect in **horses**, 0.05 - 0.2 mg/kg, IV, over 5 min, in dogs; repeated to a cumulative dose of 0.3 mg/kg;2 - 6 µg/kg/min CRI in **dogs**, 0.5 - 2 mg/kg, PO, every 8 hours in **dogs**, 2 - 4 mg/kg PO every 12 hours PO in **dogs**, 7.5 mg/kg, PO, every 8 hours and of the sustained - release formulation 30 - 60 mg/kg PO, every 12 - 24 hours in **cat** | Pedro B, 2020; Gordon SG Wall M, 2005; Romito G, 2024; Schwarzwald CC, 2005; Schwarzwald CC, 2007; Miyamoto M, 2000 | [37] [125] [127] [162] [176]-[178] |
| | | Verapamil | SVT | 0.025 - 0.05 mg/kg, IV (every 30 min; can repeat to 0,15 - 0.2 mg/kg total dose) in **horse**, 0.5 - 3 mg/kg PO every 8 h or 0.025 - 0.05 mg/kg slowly IV over 5 min in **dogs**, 0.5 - 1 mg/kg PO every 8 h or 0.025 | Marr CM, 2010; Kittleson M, 1988 | [41] [182] |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | mg/kg IV over 5 min to a total 3 doses if necessary in **dogs**, 1.1 to 2.9mg/kg three times daily (mean dose: 1.75 mg/kg TID) in **cats** | | |
| Antiarrhythmic; increased vagal tone, as well as some direct effects | Other | Digoxine | rate control AF, SVT, CHF | 0.022 mg/kg IV or 0.011 mg/kg PO, in 12 hours or 6 - 7 mcg/kg, IV, every 24 hours maintenance dose or 11 - 17.5 mcg/kg, PO, every 12 hours maintenance dose for **horses**, 0.003 - 0.011 mg/kg, PO, every 12 h, maintenance dose for **dogs**, 0.005 - 0.01 mg/kg, PO, every 24 - 48 h maintenance dose for **cats** | Reef VB, 2014; Lotstra RJ, 2015; Gordon SG, 2023; Parraga ME, 1995 | [84] [122] [125] [183] |
| Inhibits the If to reduce sinus node rate | | Ivabradine | AF | 0.1 - 0.3 mg/kg PO, 12 h in **cats**, 4 mg/kg/d PO in **dogs** | Riesen SC, 2012; Li YD, 2015 | [184] [185] |

*There is limited data to suppot the dose protocols and the reader is reccommended to consult recent literature for modicication and recomandation after the time of publication of this text. AF, Atrial Fibrilation; SVT, Supraventricular tachycardia; VT, ventrichular tachicardia; CHF, congestive heart failure; PO, per os or oral dose; CRI, constant rate infusion; IV, intravenous.

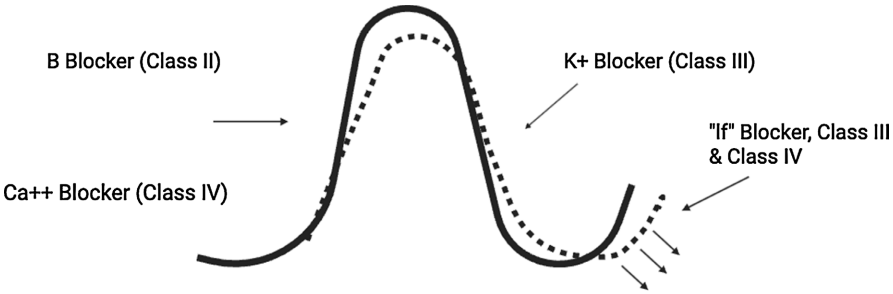


**Figure 4.** Illustration of antiarrhythmics medication major effects on the slow response (pacemaker) action potential (depolarization) (graphic made in Adobe Photoshop, based on Klabunde RE. Cardiovascular Physiology Concepts, 3rd edition.

sinus rhythm is Quinidine [74] [124] [129] [136]-[140].

Below is the classification and agents used to treat Atrial Fibrillation.

The focus of this study is on the arrhythmic agents that are used for the treatment of Atrial Fibrillation, therefore other arrhythmic agents may not be included, or are included to demonstrate their effect on increasing, inhibiting or decreasing efficacy when used together with medications for the treatment of Atrial Fibrillation.

**1) Vaughan-Williams classification**

There are five main classes in the Vaughan-Williams classification. Class I with 3 subclassifications where a-b-c; Class II (blocks b-adrenergic, reduces effects of sympathetic stimulation) Class III, (Prolongs selectively the action potential duration and refractory period Other Medications: *Digoxin,* (Increases sinus node activation and Atrioventricular conduction). *Ivabradine* blocks "If" to reduce sinus rhythm [13] [52] [131] [134] (see **Figure 4** and **Figure 5**).

**2) Classification "Gambit Sicilian"**

A second classification scheme (gambit sicilian) [134] [141] is listing antiarrhythmic drugs according to their actions of the underlying mechanisms of arrhythmia, with an emphasis on how they affect *ion currents*, *membrane pumps* and *receptor*. This does not help the clinical aspect of arrhythmia in veterinary medicine, since electrophysiological studies are done less often in veterinary practice.

**3) A combination of both**

This new classification also includes class 0 in the system (for drugs that block hyperpolarization-activated, cyclic nucleotide-gated channels—HCN), including "pacemaker" or "funny" current, "$I_f$" [50] [54] [55] [134].

## 10.2. Class I Agents

These antiarrhythmic agents interfere with $Na^+$ channel function. Class I agents are divided into class $I_a$, $I_b$, and $I_c$ based on their effect on the cardiac action potential. These agents have membrane-stabilizing effects that tend to slow conduction, as well as decrease automaticity and increase refractoriness (decrease excitability). They depend on the concentration of K+ in the serum, hypokalemia makes the drugs ineffective [4] [87] [95] [115] [125] [135].

### Class $I_a$ Agents

The main property of a Class $I_a$ agent is to block the $Na^+$ channel and multiple $K^+$ currents, reducing the automaticity of Purkinje fibers and pacemakers by lowering the phase 4 curve of the cardiac action potential by driving the voltage threshold towards zero (see **Figure 5**). Extending the refractory period is estimated to have the effect of calming atrial fibrillation and other reentrant arrhythmias [142].

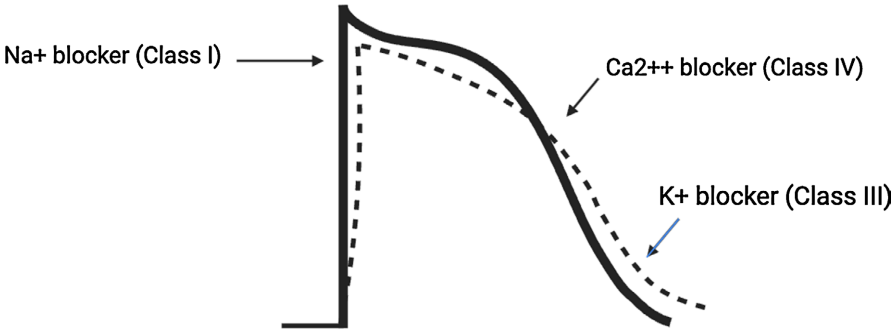


**Figure 5.** Illustration of antiarrhythmics medication major effects on the fast response action potential(depolarization) (graphic designed in Adobe Photoshop based on Klabunde RE. Cardiovascular Physiology Concepts, 3rd edition.

Referring the action of atrial fibrillation as a spiral pattern, which re-enters and maintains the rhythm of atrial fibrillation, with the administration of the first class of antiarrhythmics, the circulation of these spiral waves is diminished to zero [5] [77].

Studies done in sheep, suggest for small and single reentrant circuits or spiral

waves, or an ectopic focal point, mainly in the left atrium; that are important in causing and maintaining Atrial Fibrillation [74].

Ectopic waves resulting from a *trigger* are different from those generated by *abnormal automaticity* (metabolic causes), due to the fact that ectopic waves are often aggravated by a *rapid heartbeat* (*i.e.* they do not suppress overloads) and can result in irregularities and therefore lead to the development of "torsade's de pointes" with fatal outcomes for the patient's life [71].

The most used for the treatment of Atrial Fibrillation are: *quinidine, procainamide.*

**1) Quinidine**

Quinidine sulfate was first used to treat AF in the horse by Roos in 1924 [94]. For the treatment of Atrial Fibrillation, Quinidine Sulfate has been used for decades [7] [21] [62] [71] [136] [139] [143]; the main veterinary indication for the usage of quinidine is the conversion of "lone AF" to sinus rhythm in horses, and rarely, in large breed dogs. Quinidine typically decreases automaticity and conduction velocity and prolongs the effective refractory period [63] [143].

Some horses with acute onset of atrial fibrillation may spontaneously transition to sinus rhythm 24 to 48 hours after the disturbance [84] [143] after this waiting time the treatment of choice is Quinidine, a class Ia antiarrhythmic agent that primarily blocks $Na^+$ channels and prolongs action potential duration and the refractory period of atrial cardiomyocytes [95].

Horses with heart rate greater than 60 beats/min had a poor prognosis for life with 7.7% survived rate in the study [70]. and a poor conversion to normal sinus rhythm about 23.1%.

Quinidine is effective for the treatment of atrial fibrillation by its vagolytic action and by increasing the atrial fibrillation threshold, conduction through the atrioventricular node (AVN), and the effective refractory period of the atrial myocardium. For Atrial Fibrillation that is recent (less than 2 weeks) IV/PO administration of quinidine gluconate is recommended [95] [129] at a dose of 6.2 mg/kg or as an IV bolus at a dose of 0.5 to 1.5 mg/kg administered every 10 to 15 minutes [41]. A total dose of quinidine gluconate greater than 10 to 12 mg/kg is reported to cause a significant decrease in mean arterial pressure [74] [129] [131] [137] IV administration is contraindicated in small companion animals.

Quinidine sulphate as antiarrhythmic agent is administered P/O at a dose of 22 mg/kg every 2 hours, up to a total dose of 88 - 132 mg/kg over a 24-hour period (a total of 4 to 6 doses). Unless mild signs of quinidine toxicity presents or plasma quinidine levels are above 5 μg/ml, therapy can be successfully continued using 6-hour treatment intervals [95] [124].

The success rate of pharmacological treatment after oral administration of quinidine sulfate is up to 89%, in horses with an Atrial Fibrillation (AF) duration of less than 1-2 month, resting heart rate of fewer than 60 bpm [71] [84] [95] [144] with no identifiable cardiac disease, the prognosis for cardioversion is good, although systemic and cardiovascular side effects are common [7] [93] [95] [145].

The prognosis for horses with minimal heart disease is quite good, provided the duration of atrial fibrillation is short enough (about a month), but side effects become more common in horses that have experienced prolonged atrial fibrillation [71].

Blocking $Na^+$ channels produces myocardial depression by decreasing inotropy [146]. Approximately 80% of plasma quinidine is bound to proteins, particularly to *α1-ac. glycoprotein* whose presence is abundant in heart failure. It is metabolized by the cytochrome P450 system. Species deficient in *P-glycoprotein* may have adverse reactions to quinidine.

Biotransformation occurs by hydroxylation. Urinary elimination depends on increasing pH, and there is greater urinary elimination for higher urine pH [41] [77].

It is suggested to rest horses with suspected acute myocarditis for 1 to 2 months before treating for arrhythmias [147]. Horses with congestive heart failure (CHF) and atrial fibrillation should not receive quinidine sulfate but should be treated for congestive heart failure (CHF) with positive inotropic agents, diuretics, and other medications necessary for heart health stabilization [35] [71].

*Side effects:* Individualized treatment is needed because of pharmacodynamic variation among animals and the potential for toxic effects. Cardiotoxicity can manifest in the form of ventricular arrhythmias; increased impulse conduction via the atrioventricular node (AV) to the ventricles and paradoxical acceleration in ventricular response in animals with atrial fibrillation. There are some toxicity effects recorded form Quinidine administration that extends from the electrophysiological, hemodynamic and nervous effects, to the negative effects of the function of the Intestinal Tract; up to 76% of treated horses may experience adverse effects including urticaria, nasal edema, colic, diarrhea, laminitis, anaphylactic shock, hypotension, decreased cardiac contractility, ECG abnormalities, tachycardia, ventricular arrhythmia, stridor of the upper respiratory tract, syncope, widening or increasing the amplitude of the QRS complex, increased ventricular rate and reversed T wave including sudden death [71] [145]. This α-adrenergic antagonist can significantly decrease vascular tone and mean arterial pressure. It has a negative inotropic effect on the myocardium and a positive chronotropic effect that can lead to *supraventricular tachycardia* [68] [124] [15] [140] [145] [148].

Despite the high success rate, the toxicity of quinidine and the difficulty in obtaining the drug have stimulated attention to alternative therapies. These alternative medical treatment options for Atrial Fibrillation have also side effects, and are resulting to be somehow expensive, and yet, there is little evidence that they are effective. They are listed as follows.

**2) Procainamide**

Procainamide has efficacy against ventricular and supraventricular arrhythmias and has been used for both indications in dogs. The parenteral formulation has also been used to treat supraventricular arrhythmias, including conversion of

recent onset atrial fibrillation [125]. Intravenous procainamide has successfully converted one newborn foal with atrial fibrillation (AF) [28].

Procainamide is less effective for the treatment of atrial fibrillation (AF) due to reduced vagolytic activity when compared to quinidine; it is less effective for atrial tachyarrhythmias [62] [149]. It has also less anti-cholinergic effects and no a-blocking, compared to Quinidine.

In a study with six horses the dose used for treatment was 15 or 20 mg/kg body weight procainamide as an intravenous (IV) dose over 10 min [149]. Procainamide is proved to increase the ventricular response rate to AF (because of its vagolytic effect) when used without beta or calcium channel blocker or digoxin (*unlike Quinidine, has no interaction with digoxin*) [80].

In dogs, Procainamide is used as a treatment for atrial fibrillation at a dose 2 mg/kg, slow IV bolus, till a maximum dose of 25 mg/kg over 10 - 15 minutes. If the there are clinical indications the treatment might continue as a constant-rate infusion (CRI) at 25 - 40 mcg/kg/min or at 10 - 20 mg/kg, every 6 - 8 hours, IM or SC. The oral dose formulation is 4 - 6 mg/kg, PO, every 2 - 4 hours (and as maintenance dose every 4 hours), and the sustained-release formulation at 10 - 20 mg/kg, PO, every 8 hours [125].

*Side effects:* Procainamide administration causes a vasodilation effect due to sympatholytic effects on the brain and spinal cord [80]. It can also be pro-arrhythmic.

### 10.3. Class $I_b$ Agents

Class $I_b$ agents include Lidokaine HCl and Mexiletine. These drugs have little effect on the "0" phase of depolarization as they do minimal blockade of $Na^+$ channels. These drugs shorten repolarization by blocking $Na^+$ channels during the second phase of the activation potential. This causes a reduced duration of the activation potential as well as a short refractory period. It inhibits the activity of the sympathetic nervous system. This class of antiarrhythmic has not shown effectiveness for arrhythmias of Atrial origin [135].

The most used for the treatment of Atrial Fibrillation are: *lidocaine, mexiletine.*

#### 10.3.1. Class $I_b$ Agents—Lidocaine

This medicine is used in dogs but also in cats and horses. But clinical treatment in atrial fibrilation (AF) is suggested for vagally mediated atrial fibrillation (AF) or supraventricular tachycardia (SVT) in some dogs [150] [151] and quinidine-induced ventricular tachycardia to control heart rate in horses at a dose of 20 - 50 μg/kg/min or 0.25 - 0.5 mg/kg very slowly IV [41] [84] [95] [145].

Lidocaine has proven effective as a tretment for orthodromic atrioventricular tachycardia in a study for twenty seven dogs which experienced successfull cardioversion marking a 84.4% succes rate; Median total lidocaine dose for cardioversion was 2 mg/kg administered intraveniously (IV) (interquartile range, 2 - 5.5 mg/kg). Patients with right free wall atrioventricular accessory pathway had a

significantly higher rate of cardioversion than did patients with right posteroseptal atrioventricular accessory pathway [151]. In another study, 2 mg/kg lidocaine administered IV converted atrail fibrilation (AF) to sinus rhythm (SN) in all dogs and all episodes (n = 19) with a onversion time for 27 - 87 seconds in German Shepherd dogs [152].

Persistent ventricular arrhythmias can be treated with IV lidocaine at 20 to 50 μg/kg/min. Antiarrhythmic effects occur within 2 minutes after an IV bolus and lessen within 10 - 20 minutes in dogs. A dose of 0.5 mg/kg/10min constant rate infusion (CRI) in cats helps minimize toxicity. Serum concentration rises rapidly after IV bolus in horses under anesthetisia, and declines quickly after infusion is stopped [41] [125] [152].

In cats, which are more susceptible to toxic effects, cardiac suppression and central nervious system (CNS) excitation may be seen.

#### 10.3.2. Mexiletine

Used for its ability to suppress arrhythmias associated with repolarization abnormalities by decreasing late $Na^+$ influx during repolarization and thereby decreasing early afterdepolarizations (EADs); Mexiletine is an oral analogue of lidocaine that has been proven successful in treating chronic reentrant supra ventricular tachycardia (SVT) associated with an accessory pathway in dogs [153]. Common adverse effects include anorexia, vomiting, tremors, and hepatotoxicity.

The dosage in dogs is 4 - 6 mg/kg, PO, every 8 hours; with unknown effect in Cats and toxicity effects similar to those of lidocaine. In dogs, adverse effects have included sinus bradycardia, and thrombocytopenia among others [153].

### 10.4. Class $I_c$ Agents

Class $I_c$ antiarrhythmic drugs strongly depress $V_{max}$ and thus phase 0. After administration is observed a decrease in cardiac cell conductivity and excitability, but minimal effects on action potential duration. Class $I_c$ agents have the most potent $Na^+$ channel blocking effects. Drugs in this class are considered mainly for the management of difficult atrial arrhythmias, including suppression and cardioversion of AF [154].

Class $I_c$ drugs that have been used in protocols for the treatment of Atrial Fibrillation in animals are *propafenone, flecainide, cibenzoline.*

#### 10.4.1. Flecainide

Flecainide is a $Na^+$ channel blocker that prolongs the action potential, by suppressing phase zero upstroke of Purkinjean and myocardial fibers (*slowing conduction on all cardiac tissues*), with minor effects on refractoriness duration and action potential duration. Flecainide does not have the extracardiac alpha-adrenergic blocking effect of quinidine [155].

Intravenous flecainide acetate 1 - 2 mg/ kg at 0.2 mg/kg/min, was reported to be clinically effective in horses with induced experimental atrial fibrilation (AF) [1] [148] [154]-[157] but failed to convert horses with naturally-occurring chronic

AF [128] [154].

Horses from the latter group even developed potentially dangerous ventricular dysrhythmias [154]-[156] [158] This medication has proven also ineffective when used IV in chronic atrial fibrillation [128] [154].

Also, is important in the research of dose and clincal presentation of atrial fibrilation to point out that single study, using an oral dose 4.1 mg/kg, per os (PO), with a total dose 2.2 g treatment intervals every 2 h for a maximum of 4 - 6 doses, has successfully converted a horse into normal sinus in 17 hours [157]. And according to a study of 107 cases was shown successful only in 41% of the time converting horses with acute atrial fibrillaition (AF) [148].

Thus more research and clinical studies and in a larger natural ocurring atrial fibrilation (AF) population would be needed, to result in more conclusive in dose efficacy.

#### 10.4.2. Propafenone

Propafenone is a class $I_C$, $Na^+$ channel blocker. Propafenone decreases excitability and suppresses spontaneous automaticity and triggered activity. Effects on action potential vary with the species; it suppresses sinus nodal automaticity [145].

The dose of 2 mg/kg propafenone bolus IV over 15 minutes in a study on horses with naturally-occurring chronic atrail fibrilliation (AF) the treatment resulted in therapeutic propafenone concentrations without significant side effects, but the medication failed to restore sinus rhythm in any horse with chronic atrial fibrillation (AF) [159].

In comparative study of propafenone kinetics after intravenous (IV) administration showed was concluded that the medication was largely distributed and having a high clearance. The plasma concentrations were very low, under 1 microgram/mL, in most cases; after 30 min these concentrations can be considered as nonefficient for the treatment of arrhythmia [160].

The treatment regimen in horse for quinidine-induced ventricular dysrhythmia for intravenous and oral use were derived from human dosages are 0.5 - 1 mg/kg in 5% dextrose slowly IV over 5 - 8 minutes and 2 mg/kg every 8 hours of oral administration [41] [16].

However, the author successfully converted one horse with AF and VT with intravenous propafenone.

#### 10.4.3. Cibenzoline

In alternative therapies we also mention intravenous Cibenzoline (0.1 mg/kg/min), a class $I_c$ drug (with added properties of class III and IV), was shown unsuccessful when used in a horse with atrial fibrillation (AF) and was associated with severe ventricular pro-arrhythmia [133].

### 10.5. Class II Agents

Class II agents consist of drugs that block the binding of catecholamines to $\beta$-adrenergic receptors ($\beta$1—heart and $\beta$2—bronchi/blood vessels), which act by

inhibiting the effects of catecholamines on the heart by reducing the effects of sympathetic stimulation (see **Figure 4**). At high doses, selective $\beta$1 blockers also block $\beta$2 receptors. [125] [134].

As a class II antiarrhythmic drugs which are beta-adrenergic receptor antagonists they are classified as nonselective (antagonize both beta1 and beta2 receptors) or selective (antagonize predominantly beta1 receptors). The earliest generation of this class was nonselective, antagonizing both $beta_1$ and $beta_2$ receptors (*like propranolol*).

### 10.5.1. Propranolol

Propranolol is rapidly metabolized by the liver and oral bioavailability is low due to the first pass effect in horses. In this animal, the propranolol is added as part of a protocol for the treatment of Atrial Fibrillation in the form of Intravenous Propranolol 0.03 mg/kg IV (13.5 mg/450kg) to slow heart rate for quinidine-induced supraventricular or ventricular tachycardia to control heart rate [41] [145] [133].

The suggested doses for intravenous use of propranolol is advised not exceed 0.1 mg/kg in slow flow given over 1 minute. Hypotension, bradycardia and muscular weakness is reported in single IV doses more than 0.3 mg/kg in horses with heart disease [135].

There is not enough evidence supporting benefits and side effects of propranolol in veterinary medicine in cats and dogs although the specification of usage is for sinus tachycardia and supraventricular arrhythmias among others. But being a initiating beta-adrenergic receptor antagonist, propranolol should be avoided in animals with indication of evidence of primary respiratory disease or heart failure. The dosage for propranolol in dogs is 0.2 - 1 mg/kg, PO, every 8 hours (titrate dose to effect) and in cats is 0.4 -1.2 mg/kg (2.5 -5 mg/cat), PO, every 8 hours [125] [161] [162].

### 10.5.2. Esmolol

An ultra-short-acting beta-blocker. Esmolol is a selective $\beta$1-adrenoceptor antagonist with its effect primarily in the myocytes. It has an antiarrhythmic effect through its blockade of adrenergic stimulation of the heart.

It is shown to be clinical successful in a retrospective case series of 17 years, in the treatment of supraventricular or sinus tachycardia in dogs and cats by administration of Esmolol at continuous rate infusion in 46% of the cases at a median dose of 50 μg(micrograms)/kg/min. The recommended doses in Dogs, Cats: 0.05 -0.5 mg/kg i.v. bolus over 5 min; 25 -200 μg (micrograms)/kg/min constant rate infusion [162] [163].

### 10.5.3. Atenolol

Atenolol is a beta1-adrenergic receptor antagonist used to control rhythm and rate during atrial fibrillation in dogs, the most used beta-adrenergic receptor antagonist in veterinary medicine because of its properties in saving bronchospasm [125] [162] [164].

Atenolol dose of administration to treat atrial fibrillation in dogs is 0.2 - 1

mg/kg, PO, every 12 hours, and in cats 1 - 2.5 mg/kg, PO, every 12 hours, or 6.25 -12.5 mg/cat, PO, every 12 hours. Some references suggest cats can be dosed every 24 hours; however, most cardiologists believe that continuous beta-blockade (the clinical target) is not possible with daily dosing [125] [132] [162].

### 10.6. Class III Agents

Class III agents selectively prolong action potential duration and refractory period; are $K^+$ channel blockers (non-specific channels) that prolong the effective refractory period of cardiac action potentials without reducing conduction velocity (see **Figure 4** and **Figure 5**); these agents are effective in depressing reentrant arrhythmias or preventing fibrillation (atrial and ventricular).

Class III antiarrhythmic drugs primarily block $K^+$ channels resulting in a prolongation of the action potential. These agents have less effect on $Na^+$ channels, so conduction velocity does not change.

The most used for the treatment of Atrial Fibrillation in animals are: *Amiodarone*, *Sotalol, Dronedarone.*

#### 10.6.1. Amiodarone

Amiodarone HCl is a unique class III antiarrhythmic agent; an iodine-containing benzofuran compound that has effects on $Na^+$, $K^+$, and $Ca^{2+}$ channels. It also has non-competitive properties for α1- and $\beta$-blockers. Amiodarone has had results in the treatment of Atrial Fibrillation, after quinidine, in occurring under natural conditions, not induced atrial fibrillations (AF) in 50% - 67% of the cases [165].

Therapeutic doses intravenous amiodarone treatment of 5 mg/kg/h for 1 h followed by 0.83 mg/kg/h for 23 h and subsequently 1.9 mg/kg/h for 30 h in horses has shown to slow down sinus velocity, decrease atrioventricular conduction velocity, and decrease myocardial contractility and blood pressure [165]-[167].

Reasons for starting a treatment with amiodarone include refractory tachyarrhythmias of atrial and ventricular origin, especially *reentrant arrhythmias* using an accessory pathway.

Amiodarone has shown variable effectiveness in converting Atrial Fibrillation to sinus rhythm in dogs with doses 2 mg/kg IV/10min, preventing Atrial Fibrillation after surgery with tricuspid dysplasia [44] [164] [168]-[171] and this medicaition is not sufficiently described in cats.

*Side effects*: According to studies, Amiodarone has shown side effects: diarrhea, weakness of the hind limbs [165]. Deficiency of *P-glikoproteine*, may make some animals very sensitive to amiodarone.

#### 10.6.2. Sotalol

A class III agent, sotalol has also be used to slow the heart rate in horses with AF slowing rate and suppressing ventricular ectopy in AF horses with ventricular ectopy having though some efficacy in treatment of atrial fibrillation (rate control) [125].

Sotalol has been seen to be more effective in preventing Atrial Fibrillation

rather than terminating it, due to its effect in the prolonging the refractory period. Sotalol decreases the ventricular response rate of heart rate and increases the duration of the QT interval in horses with Atrial Fibrillation. But it has not been very successful in preventing recurrence of Atrial Fibrillation in horses treated with Sotalol after electro cardioversion [172] [173].

At a dose of treatetment with 2 mg/kg sotalol PO every 12 hours for 3 days for several days prior to electrical cardioversion, fewer shocks and lower energy were required for conversion [173]. The dose of treatment of 0.75 - 1.25 mg/kg IV over 15 minutes and was not associated with adverse effects, but was inefective to restore sinus rhythm to normal [133].

$\beta$-blockers and potassium channel blockers are generally not first-line drugs for rate control in dogs with secondary atrial fibrillation, especially when used as monotherapy. Sotalol dose for dogs and cats use for oral administration is 1 - 3 mg/kg every 12 hours [125] [153] [170].

#### 10.6.3. Dronedarone

Dronedarone has an atrial-selective property, but limited information is available in dogs.. In an animal induce atrial fibrilation (AF) the dose of treatment 20 mg/kg, BID, orally for 7 days, suggested that oral dronedarone attenuates the duration of sustained atrial fibrilation (AF) and may be useful for management of AF in dogs [174].

### 10.7. Class IV Agents

Class IV agents contain drugs that block $Ca^{2+}$ entry (see **Figure 4** and **Figure 5**). These are most useful for supraventricular tachyarrhythmias; ventricular arrhythmias that are usually unresponsive to other medications.

The most used for the treatment of Atrial Fibrillation in animals are: *Diltiazem, Verapamil.*

#### 10.7.1. Diltiazem

Diltiazem HCl is a benzothiazepine, a non-dihydropyridine calcium channel blocker that has primarily negative chronotropic and dromotropic effects [175]. Depending on the dose, it causes slowing of the activity of the sinus node, increases the refractory period of the AtrioVentricular nodes and can block some arrhythmias caused by abnormal automaticity, triggers and reentrants of the arrhythmia.

Diltiazem effectively controls heart rate response to atrial fibrilation (AF) in other species like dogs and cats [125], but there ares also studies suggesting its safety use for horses that show quinidine-induced supraventricular tachycardia with the use of diltiazem dose of 0.125 - 1.125 mg/kg over 2 minutes [41] [176].

The bioavailability of PO diltiazem in horses is unclear, but intravenous diltiazem administered IV every 30 minutes to achieve cumulative dose 1, 1.5, and 2 mg/kg appears relatively safe in healthy horses, but dosage may be limited by hypotension from vasodilatation and direct suppression of sinus node discharge.

Because of its inhibitory effects on AV nodal conduction, diltiazem may prove useful for heart rate control in horses with AF [176] [177].

In a study with some horses the effective doses of diltiazem ranged from 0.125 to 1.125 mg/kg IV over 2 minutes repeated every 12 minutes to effect, in coadministration with quinidine gluconate at dose 10 mg/kg IV over 30 minutes; and 12 mg/kg IV over 5 minutes followed by 5 mg/kg/h constant rate infusion for the remaining duration of the study [177].

Diltiazem is indicated for supraventricular tachyarrhythmia in dogs. It is usually used in combination with digoxin [178] [179] to further slow the rate of ventricular response to atrial fibrillation in dogs; with an IV dose at 0.4 - 0.9 mg/kg in an experimentally induced Atrial Fibrillation it was attained plasma concentrations 68 to 117 ng/mL and heart rate (HR) closer to normal sinus rhythm for the animal [125] [162] [178].

In cats, the dosage of the standard oral formulation is 7.5 mg/kg, PO, every 8 hours, and of the sustained-release formulation 30 - 60 mg/cat, PO, every 12 - 24 hours. Initial doses should be at the lower end of the dose range and titrated up to a clinically effective dose [125]. The 60-mg dosage (9.3 to 14.8 mg/kg) was associated with lethargy, gastrointestinal disturbances, and weight loss in nine (36%) of 25 client-owned cats [127].

*Side effects:* Side effects may be more common in cats, including anorexia with weight loss, vomiting, lethargy, hepatopathy, personality changes when treated with diltiazem. [178] significant hypotension (*slight impairment of systolic and diastolic function with a decrease in systemic vascular resistance*) and nodal depression is reported in studies conducted in horses [176] [177].

### 10.7.2. Verapamil

Verapamil is phenylalkylamine, used to control supraventricular tachyarrhythmias, such as accessory pathway-mediated SVT, atrial tachycardia and flutter, with potent cardiac effects, that generally is avoided in companion animals. Verapamil works by prolonging nodal tissue refractoriness it can abolish reentrant supraventricular tachicardia (SVT) and slow the ventricular response rate to atrial fibrillation (AF). Verapamil is a second-choice calcium-channel blocker behind diltiazem as it has a more pronounced negative inotropic effect [180].

There is limited number of studies done in equines for this medicament but the given doses for treatement of quinidine-induced supraventricular dysrhythmia is 0.025 - 0.05 mg/kg, IV (every 30 min; can repeat to 0.15 - 0.2 mg/kg total dose [41].

Verapamil regimen in dogs is 0.5 - 3 mg/kg PO every 8 hours or 0.05 mg/kg slowly IV over 5 minutes (with ECG monitoring). Up to 4 repeat IV administrations at a reduced dose of 0.025 mg/kg q5min if necessary [180] [181].

In cats Verapamil is dosed at 0.5 - 1.0 mg/kg oraly (PO) every 8 h or 0.025 mg/kg slowly intravenous (IV) over 5 minutes (with ECG monitoring). It can repeat up to 3 intravenous (IV) administrations every 5 min if necessary [180].

In a study were 14 dogs were administered a titrated dose of 0.05 mg/kg every 5 to 30 minutes and when was needed an additional injections of 0.025 mg/kg can be given at 5-minute intervals to effect with a maximum cumulative dose of 0.15 mg/kg; Verapamil terminated the arrhythmia in 12 dogs and was concluded as an effective treatment for acutely converting supraventricular tachycardia to sinus rhythm in these dogs [182]. The recommended oral dosage in the dog of the study is also 0.5 - 1.0 mg/kg, approximately 10 times the IV dosage [182].

## 10.8. Other Medications

Other medications that antagonize vagal effects on the SA and AV nodes are those that increase sinus node activation and Atrio Ventricular conduction. They inhibit the "$I_f$" currents that help reduce the rhythm of the sinus node like Ivabradine. And with antiarrhythmic action resulting mainly from indirect autonomic effects, especially from increased vagal tone like Digoxin.

### Digoxin

Digoxin has a narrow therapeutic window and the risk-benefit ratios with respect to toxicity has dramatically decreased the clinical use of this medicament. Digoxin changes in conduction can lead to AV nodal blockade and reductions in heart rate (ventricular response rate) it has been found useful to treat supraventricular arrhythmias (SVT), including atrial fibrillation (AF) [41] [122].

Caution is indicated in this combination because quinidine can increase plasma digoxin concentrations [43] [125] [183].

Rarely efficacious as a single agent for this indication it is used combination and as part of the protocol of treatmen with Quinidine-induced tachycardias caused by increased conduction through the atrio ventricular node (AVN) node in horses where sustained supraventricular or ventricular tachycardia (<100 beats/min) is generally treated with digoxin (0.0022 mg/kg) [84] [95] [122] [125].

If conversion has not occurred in 24 - 48 hours by quinidine alone, the use of digoxin can be added to the therapeutic regimen in horses and cattle with atrial fibrillation [84] [95] The dose for Digoxin is 0.022 mg/kg IV or 0.011 mg/kg PO, in 12 h in horse [36] [84] [95] [125].

The use of digoxin with quinidine is considered a good combination, resulting in the successful conversion of horses with Atrial Fibrillation as the combination therapy of digoxin with quinidine sulfate gives success in converting 85% of treated horses on the second day, after 24 hours; the combination came to use after quinidine's sulfate alone usage was resulting unsuccessful [95] [135]; an IV loading dose of 12 - 14 mcg/kg can be considered but should be divided into three administrations. Maintenance dosages are 6 - 7 mcg/kg, IV, every 24 hours or 11 - 17.5 mcg/kg, PO, every 12 hours for horses [125].

Digoxin in dogs is used as an adjunctive (in combination with another antiarrhythmic) treatment of supraventricular arrhythmias such as atrial fibrillation with a maintenance dose is 0.003 - 0.011 mg/kg, PO, every 12 hours [125]

[162] [179].

Digoxin is rarely if ever administered to cats for any clinical indication; the maintenance dose is suggested 0.005 - 0.01 mg/kg, PO, every 24 - 48 hours for cats [125] [180].

*Side Effects:* Digoxin toxicity can cause anorexia, nausea, sialorrhea, diarrhea, abdominal pain, neurological signs. Digoxin-induced cardiac toxicity includes ***premature beats***, excessive slowing of AV conduction, AV block, AV dissociation, sinus bradycardia, disturbances in ECG measurements [125].

## 10.9. Class 0 Agents

Class 0 agents include HCN channel blockers, "If" (see **Figure 4**). The sino atrial node cells exibit automaticity under normal physiological conditions, under the mechanism of the "membrane clock" which helps in the process of diastolic depolarization described as the pacemaker potential. The process is followed by a net inward current, to which the most important contribution is evaluated to be the "funny current" (If) carried by hyperpolarization-activated cyclic nucleotide-gated channels, particularly during the initial phase of the diastolic depolarization [13] [50] [55] [53] [134].

Inhibition of funny current ($I_f$) reducing SAN phase 4 pacemaker depolarization rate, thereby reducing heart rate; possible decreased AVN and Purkinje cell automaticity; increase in RR intervals [40] [52].

The most used medication for the treatment of Atrial Fibrillation is ***Ivabradine***.

### Ivabradine

Ivabradine has a selective inhibitory effect on the "Funny current" (If), of HCN channels; its action is held in the diastolic depolarization of cells of the sinus node. This current is particularly active when the diastolic potential is hyperpolarized by sympathetic tone and b-receptor activation. The decrease in the rate of diastolic depolarization leads to a decrease in the Heart Rate, along the sinus rhythm observed in a small study of anesthetized cats with hypertrophic cardiomyopathy [54] [184].

In a induced age-related atrial fibrilation (AF) model of study of dogs, was admnistered Ivabradine capsule (4 mg/kg/d) orally. The results of the study showed that Ivabradine prolonged the effective refractory period in several regions of the left atrium, reduced susceptibility to induction of Atrial Fibrillation and shortened the duration of Atrial Fibrillation; suggesting that ivabradine could effectively reduce the inducing rate of atrial fibrilation AF, and thus be used as an upstream drug for the prevention of age-related atrial fibrilation (AF) in dogs [185].

Ivabradine undergoes hepatic metabolism via P450 enzyme. The plasma 1/2-life is ~2 h in dogs and ~3.5 h in cats. Recommended dose 0.1 - 0.3 mg/kg PO, 12 h is suggested for cats without clinical heart disease [184] [185].

*Side effects:* it should not be administered to animals with diseases of the sick sinus of the heart.

## 11. Performance in Horses with Atrial Fibrillation

Horses with atrial fibrillation that are not converted will have a poorer overall prognosis. If conversion is not attempted or achieved, it is advised to inform the owner for possible sudden collapse of their horses, if the horse is used beyond for athletic ability. Horses successfully converted to sinus rhythm can be returned to light exercise ~3 days after conversion [147].

Full training resumes 7 to 10 days after conversion. Horses that do not have significant heart disease but perform in competitions that require submaximal exercise of short duration or that are in the breeding process may be able to perform successfully without treatment for atrial fibrillation (AF) [30] [147].

The prognosis for quality of life is very good to excellent if there is no other cardiac disease. Horses with "lone AF" for less than 2 months duration generally respond well to treatment in more than 85% of cases and even return to their previous athletic performance [7] [71] [95] However, the recurrence rate of atrial fibrillation (AF) in these horses ranges from 15 to 30% [29] [47] [109],and horses with longer atrial fibrillation (AF) are more difficult to treat [7] [72] [97].

### Atrial Fibrillation Relapse

According to a study extended in several medical centers regarding the recurrence of atrial fibrillation pharmacological or electrical cardioversion, the results were of 39% relapse within one year in horses treated for the first time; but most horses return to their previous level of performance. The relapse results have been related to previous unsuccessful treatment attempts, valvular regurgitation and the presence of atrial premature depolarizations or low atrial contractile function after cardioversion. Large atrial size and long AF duration have also been suggested as risk factors [137]. A history of previous atrial fibrillation and changes in the atrial apex as predictors of many recurrences of incidence [109].

Relapses of Atrial Fibrillation in horses have been noted about 34 - 1060 days after the first episode [29].

The relapse rate of Atrial Fibrillation was 25.1% in 4684 horses from 2007 to 2017 measurement study period. Recurrence was seen in 64% of horses previously treated for persistent AF, which was higher than recurrence in horses with paroxysmal AF with only 23% [29].

## 12. Conclusions and Future Research

While the fibrillary condition cannot be prevented, it is important to identify it as early as possible so that early treatment can be obtained to ensure satisfactory results.

Horses at submaximal and maximal physical activity with sudden loss of speed are seen as the most common clinical signs.

The longer the horse stays in atrial fibrillation, the less likely it is to successfully return him into normal sinus rhythm. Pretherapeutic assessment and monitoring maximizes the chances of successful cardioversion and minimizes clinical signs of drug-related toxicity.

Successful conversion to sinus rhythm and rate of relapse to atrial fibrillation are inversely related to duration of arrhythmia and primary heart disease(s). Different approaches for preventing recurrence have been described but large clinical studies have not been published.

The main veterinary indication for the usage of quinidine is the conversion of lone atrial fibrillation (AF) to sinus rhythm in horses, and rarely, in large breed dogs. Amiodarone is the second drug of treatment for atrial fibrillation (AF), after quinidine, occurring under natural conditions, not induced experimentally in 66% of the cases.

Other medications are showing success in a few numbers of clinical cases, but not successful in others. There is a need for more clinical data to prove efficacy.

Determining treatment for a patient with atrial fibrillation should be based on the proposed activity of the animal. Successfully converted horses without any heart pathology can return to their previous level of racing and competitions.

More information about pathophysiology of the remodeling process can be of help in identifying possible targets for future treatments. There is a need to unify the method and determine the prevalence and incidence related to cases of Atrial Fibrillation to help improve the most appropriate management of treatment and provide additional prognostic information.

## Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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## Abbreviations

| | |
|---|---|
| AF | atrial fibrillation |
| AVN | atrio-ventricular node |
| SAN | sinoatrial node |
| SVT | supraventricular tachycardia |
| pAF | paroxysmal atrial fibrillation |
| PAC | premature atrial complex |
| PV | the pulmonary veins |
| CHF | congestive heart failure |
| SN | sinus rhythm |
| CRI | constant rate infusion |
| CNS | central nervous system |
| EAD | early afterdepolarizations |
| DAD | delayed afterdepolarizations |
| HR | heart rate |
| "If" | hyperpolarization-activated pacemaker current |
| HCN | hyperpolarization-activated, cyclic nucleotide-gated |
| ICa-L | L-type calcium current |
| ICa-T | T-type calcium current |
| SERCA2a | arcoendoplasmic Reticulum Calcium ATPase |
| SR | sarcoplasmic reticulum |
| cAMP | cyclic adenosine monophosphate |
| ECG | electrocardiogram |
| RyR2 | Ryanodine receptors |
| ECG | Electrocardiogram |
| mV | millivolt distribution of charge across the cell membrane |
| IV | intravenous administration |
| PO | oral administration |
| pH | potential of hydrogen |