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Paroxysmal atrial fibrillation in seven dogs with presumed neurally-mediated syncope

D.M. Porteiro Vázquez, Dr Med Vet [a], M. Perego, Dr Med Vet [a], L. Santos, MScb [b], M. Gerou-Ferriani, Dr Med Vet [a], M.W.S. Martin, MVBc [c], R.A. Santilli, Dr Med Vet, PhD [a,*]

[a] *Clinica Veterinaria Malpensa, Viale Marconi 27, 21017, Samarate, Varese, Italy*
[b] *Federal University of São Paulo, São Paulo, Brazil*
[c] *The Veterinary Cardiorespiratory Centre, Thera House, Kenilworth, Warwickshire, UK*

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KEYWORDS
Arrhythmias;
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Abstract *Objectives:* To document the electrocardiographic findings of vagally-induced paroxysmal atrial fibrillation following a presumed reflex syncopal episode in the dog.
Animals: Seven dogs with a syncopal episode followed by a paroxysm of atrial fibrillation recorded on a 24-hour Holter.
Methods: Twenty-four hour Holter monitors were retrospectively reviewed, analysing the cardiac rhythm associated with syncopal events. Each recording was analysed from 10 min before the syncopal episode to until 10 min after a normal sinus rhythm had returned.
Results: Nine episodes were recorded in seven dogs, with one patient experiencing three events during one Holter recording. Five of the seven dogs presented with underlying structural heart disease. In two the syncopal episodes occurred following exercise, two associated with coughing and three were during a period of rest. All dogs had documented on the Holter recording a rhythm abnormality during syncope. The most common finding leading up to the syncopal event was development of a progressive sinus bradycardia, followed by sinus arrest interrupted by a ventricular escape rhythm and then ventricular arrest. This was then followed by an atrial fibrillation. The atrial fibrillation was paroxysmal in seven recordings and persistent in two. In two dogs, the atrial fibrillation reorganised into self-limiting runs of atypical atrial flutter.

* Corresponding author.
E-mail address: rasantil@alice.it (R.A. Santilli).

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Conclusions: This combination of electrocardiographic arrhythmias are probably caused by an inappropriate parasympathetic stimulation initiating a reflex or neurally-mediated syncope, with abnormal automaticity of the sinus node and of the subsidiary pacemaker cells and changes in the electrophysiological properties of the atrial muscle, which promoted the paroxysmal atrial fibrillation.

Introduction

Syncope is defined as a transient loss of consciousness due to global cerebral hypoperfusion and it is characterized by rapid onset, short duration, with a spontaneous and complete recovery.[1] In humans syncope is divided into reflex (vasovagal, situational or carotid sinus syndrome), cardiac (arrhythmias and structural heart disease) and orthostatic (autonomic failure, volume depletion or hypotensive drugs).[1] Reflex syncope is an inappropriate and intermittent neural response to a trigger and is classified based on the efferent autonomic nervous pathway involved. The response is the combination of a cardioinhibitory mechanism (predominance of parasympathetic tone) and/or vasodepressor mechanism (loss of sympathetic tone) that results in a fall in systemic blood pressure and cerebral hypoperfusion.[1] The vagal cardiac activity during the cardioinhibitory mechanism determines the genesis of different arrhythmogenic patterns.[2] The vagal activity inhibits impulse generation in the sinoatrial node generating bradycardia or sinus arrest,[3] slows conduction through the atrioventricular node, generating atrioventricular block[4] and alters the electrophysiological properties of atrial and pulmonary veins cells.[5] Vagal stimulation shortens the effective refractory period and action potential in the atrial tissue, favouring the formation of re-entry circuits, dispersion of repolarisation and the development of atrial fibrillation.[6] In a similar way, acetylcholine shortens the action potential duration of the sleeves of the pulmonary veins enhancing calcium transient and Na—Ca exchange current, and when acting in conjunction with high sympathetic tone this facilitates the development of early afterdepolarisation in the pulmonary veins that enable ectopic foci.[7] These electrophysiological alterations create the substrate for the genesis of the vagal atrial paroxysmal atrial fibrillation. Furthermore, the autonomic nervous system can modulate the initiation, maintenance and termination of a functional atrial flutter (Well's type II), characterised by very rapid rhythm originating under vagal stimulation with no excitable gap in the circuit and cannot be entrained.[8,9] Atrial fibrillation and atrial flutter are re-entrant arrhythmias and there is an interrelationship between them.[10] The conversion from atrial flutter to atrial fibrillation is due to an acceleration of atrial rate due to the disappearance of areas of slow conduction, decrease in the length of functional block and occurrence of unstable re-entrant circuits of very short cycle lengths with various locations and shape, which disappear and reformed.[11] The peculiar combination of neurally-mediated syncope and development of atrial fibrillation has been previously described in human.[12]

The aim of this study was to determine the arrhythmia and mechanism that led to the development of atrial fibrillation, associated with an episode of syncope and to ascertain if such a rhythm was consistent with a neurally-mediated mechanism for the loss of consciousness.

Materials and methods

Patients

Case records were retrospectively searched for syncope that had been documented on Holter and associated with a bradyarrhythmia followed by atrial fibrillation. Seven cases were found; these included: three Boxers, one Beagle, one Pug and two mixed breed dogs. Five dogs were male and two female. Age ranged from 5 to 12 years (median: 9.3 years). Body weight ranged from 10 to 40 kg (median: 20.8 kg). Five dogs had underlying structural heart disease including degenerative mitral valve disease (n = 3), dilated cardiomyopathy (n = 1) and aortic stenosis with 'afterload mismatch' (n = 1). Four dogs were in well-controlled heart failure, being medicated with furosemide, pimobendan and an angiotensin converting enzyme inhibitor. The Holter recordings were collected from two referral centres, Clinica Veterinaria Malpensa (Cube Holter Cardioline;

n = 6) and Veterinary Cardiorespiratory Centre (Lifecard; Spacelabs; n = 1). All dogs experienced one syncopal episode during the Holter monitoring, except one dog that had three syncopal episodes. Two dogs had syncope associated with exercise, two associated with cough and three at rest. A total of nine electrocardiographic tracings recorded during syncope were analysed.

Analysis

All Holter recordings were manually edited and analysed by one operator (RAS) starting 10 min before the syncopal episodes reported in the diary until 10 min after sinus rhythm was restored.

The electrocardiographic features during the syncopal episodes were analysed and classified. The electrocardiographic patterns considered were: the presence of bradycardia, sinus arrest, ventricular arrest, atrial flutter and atrial fibrillation. Bradycardia was defined as a reduction in ventricular rate more than 30% or less than 60 bpm, sinus arrest as the absence of P waves with or without a junctional or ventricular escape rhythm, ventricular arrest as the absence of a junctional or ventricular escape rhythm for at least 3 s during sinus arrest.[1] The presence of fibrillatory waves or flutter waves was classified respectively as atrial fibrillation or atrial flutter. The following electrocardiographic parameters were assessed: (1) sinus bradycardia, rate and duration, (2) sinus arrest duration, (3) type of escape rhythm, rate and duration, (4) ventricular arrest duration, (5) atrial fibrillation, ventricular rate and duration and (6) atrial flutter, atrial rate and duration. All rates are reported as the median rates in bpm (and the range) and all durations as the median time in seconds (and the range).

Results

A total of nine Holter recordings documenting syncopal events were analysed. In all these dogs there was a period of sinus arrest followed by atrial fibrillation. Six electrocardiograms were characterized by an initial progressive sinus bradycardia with a median duration of 6.6 s (range 4.9—15 s) and median ventricular rate of 60 bpm (range 31—86 bpm), followed by sinus arrest with a median duration of 8.8 s (range 2.2—20.8 s). The other three electrocardiograms showed a sinus rhythm with a median ventricular rate of 117 bpm (range 116—119 bpm), followed by sinus arrest with a median duration of 8.4 s (range 2.8—18.3 s). The median duration of ventricular arrest was of 13.5 s (range 3.9—20.8 s). In three tracings an escape ventricular rhythm occurred with a median heart rate of 27 bpm (range 18—55 bpm) and a median duration of 27 s (range 19—41 s; Fig. 1A—H). Finally, in all electrocardiographic tracings there was atrial fibrillation following the period of sinus arrest. Atrial fibrillation was paroxysmal in seven recordings and persistent in two. The median duration of paroxysmal atrial fibrillation before restoring sinus rhythm was 87 s (range 4.4—161.4 s) and with an average ventricular heart rate of 131 bpm (range 102—174 bpm; Fig. 2). Persistent atrial fibrillation showed an average ventricular rate of 223 bpm. In two dogs atrial fibrillation reorganised into six episodes of paroxysmal atrial flutter (two in one dog and four in another dog). Atrial flutter showed a median duration of 5 s (range 2—30 s), with a median atrial rate of 600 bpm (range 461—600 bpm). The median ventricular rate was slower (300 bpm, range 110—300 bpm) because of the presence of different degree of atrioventricular block (Fig. 3).

Discussion

Moya et al. [1] proposed a classification of different electrocardiographic findings obtained during syncope. This classification system divided these into four main rhythm disorders observed to explain the possible mechanism of syncope: asystole, bradycardia, no or slight rhythm variation and tachycardia. The characteristic findings of the initial progressive sinus bradycardia, leading to sinus arrest or atrioventricular block followed by ventricular arrest suggest that the syncope is probably neurally-mediated.[1,2,4,13] Six electrocardiographic tracings in this study showed a progressive sinus bradycardia with a median heart rate of 60 bpm. All tracings during syncope showed periods of prolonged sinus arrest with ventricular arrest of variable duration. Our findings therefore suggest that the underlining mechanism of the syncopal episodes was a reflex syncope.

Reflex or neurally-mediated syncope is a heterogeneous group of conditions in which the cardiovascular reflexes, that normally maintain homoeostasis, do not respond appropriately to trigger stimuli, such as emotion, orthostatic stress, cough, exercise or mechanical manipulation of the carotid sinuses.[1] Neurally-mediated syncope can be classified based on the efferent pathway most involved, i.e. sympathetic or parasympathetic and

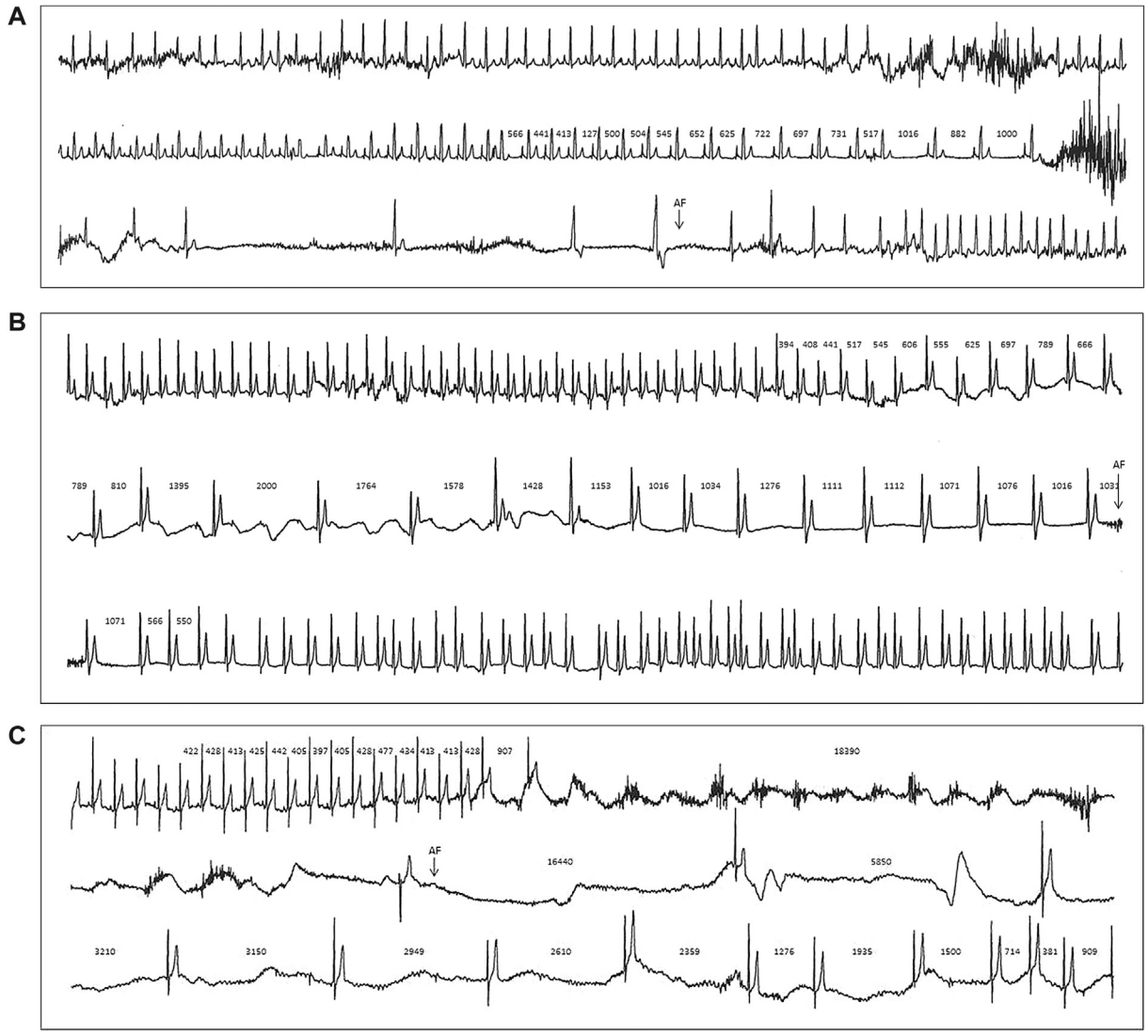
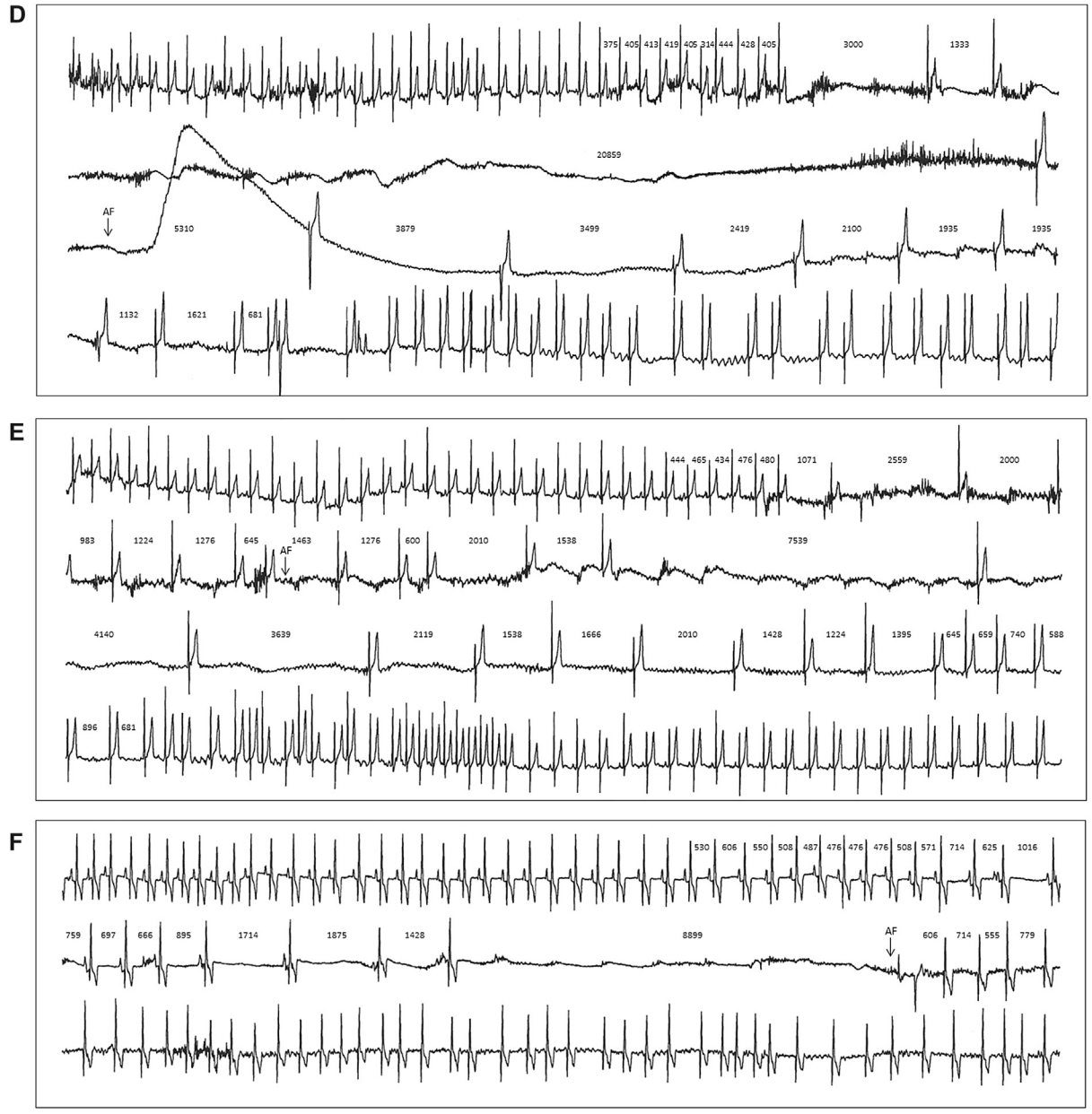


Fig. 1 A) Electrocardiogram recorded during a syncopal episode in an 8 year old male Boxer. The first part of the tracing reveals a sinus rhythm with an average ventricular rate of 114 bpm, followed by a progressive sinus bradycardia (duration of 6.8 s with an average ventricular rate of 75 bpm), sinus arrest (duration of 8.7 s) and ventricular arrest (duration of 3.9 s) interrupted by an escape ventricular rhythm (average ventricular rate of 27 bpm). After sinus arrest a persistent atrial fibrillation (AF: arrow) with an average ventricular heart rate of 194 bpm occurs. Paper speed 7.5 mm/s. Calibration is 2 mm/mV. (B) Electrocardiogram recorded during a syncopal episode in a 9 year old male Boxer. The first part of the tracing reveals a sinus rhythm with an average ventricular rate of 153 bpm, followed by a progressive sinus bradycardia (duration of 6.4 s with an average ventricular rate of 86 bpm), sinus arrest of 16.1 s and an escape ventricular rhythm (average ventricular rate of 55 bpm). After sinus arrest a paroxysmal atrial fibrillation (AF: arrow) with an average ventricular heart rate of 166 bpm occurs, which lasted 161.4 s. Paper speed 7.5 mm/s. Calibration is 2 mm/mV. (C—E) Electrocardiograms recorded during three syncopal episodes in a 7 year mixed breed dog. (C) The first part of the tracing reveals a sinus rhythm with an average ventricular rate of 119 bpm followed by sinus arrest (duration of 18.3 s) and ventricular arrest (duration of 18.3 s) interrupted by an escape ventricular rhythm (average ventricular rate of 18 bpm). After the sinus arrest a paroxysmal atrial fibrillation (AF: arrow) with an average ventricular heart rate of 120 bpm occurs, which lasted 137.4 s. (D) The first part of the tracing reveals a sinus rhythm with an average ventricular rate of 122 bpm, followed by a progressive sinus bradycardia (duration of 5 s with an average ventricular rate of 31 bpm), sinus arrest (duration of 20.8 s) and ventricular arrest (duration 20.8 s) interrupted by an escape ventricular rhythm (average ventricular rate of 19 bpm). After sinus arrest a paroxysmal atrial fibrillation (AF: arrow) with an average ventricular rate of 102 bpm occurs, which lasted 114.6 s. (E) The first part of the tracing reveals a sinus rhythm with an average ventricular rate of 116 bpm followed by a sinus arrest (duration of 8.4 s) interrupted by an irregular escape ventricular rhythm (average ventricular rate of 50 bpm). After sinus arrest a paroxysmal atrial fibrillation (AF: arrow) with an average ventricular heart rate of 131 bpm occurs, which lasted 12 s.

Paper speed 7.5 mm/s. Calibration is 2 mm/mV. (F) Electrocardiogram recorded during a syncopal episode in a 14 year old female Beagle. The first part of the tracing reveals a sinus rhythm with an average ventricular rate of 150 bpm, followed by a progressive sinus bradycardia (duration of 9.1 s with an average ventricular rate of 69 bpm) and by sinus and ventricular arrest (duration of 8.8 s) interrupted by a ventricular escape beat. After ventricular arrest a paroxysmal atrial fibrillation with an average ventricular heart rate of 147 bpm occurs, which lasted 87 s. Paper speed 7.50 mm/s. Calibration is 2 mm/mV. (G) Electrocardiogram recorded during a syncopal episode in a 12 year old male mixed breed dog. The first part of the tracing reveals a sinus rhythm with an average ventricular rate of 117 bpm followed by a sinus arrest with a duration of 2.8 s. After sinus arrest a paroxysmal atrial fibrillation (AF: arrow) with an average ventricular heart rate of 174 bpm occurs, which lasted 4.4 s. Paper speed 7.5 mm/s. Calibration is 2 mm/mV. (H) Electrocardiogram recorded during a syncopal episode in an 11 year old male Boxer dog. The first part of the tracing reveals a sinus rhythm conducted with intraventricular conduction delay with an average ventricular rate of 142 bpm, followed by a progressive sinus bradycardia (duration of 15 s with an average ventricular rate of 52 bpm) and by sinus arrest with a duration of 2.2 s. After sinus and ventricular arrest a persistent atrial fibrillation with an average ventricular heart rate of 220 bpm occurs. Paper speed 7.5 mm/s. Calibration is 2 mm/mV.



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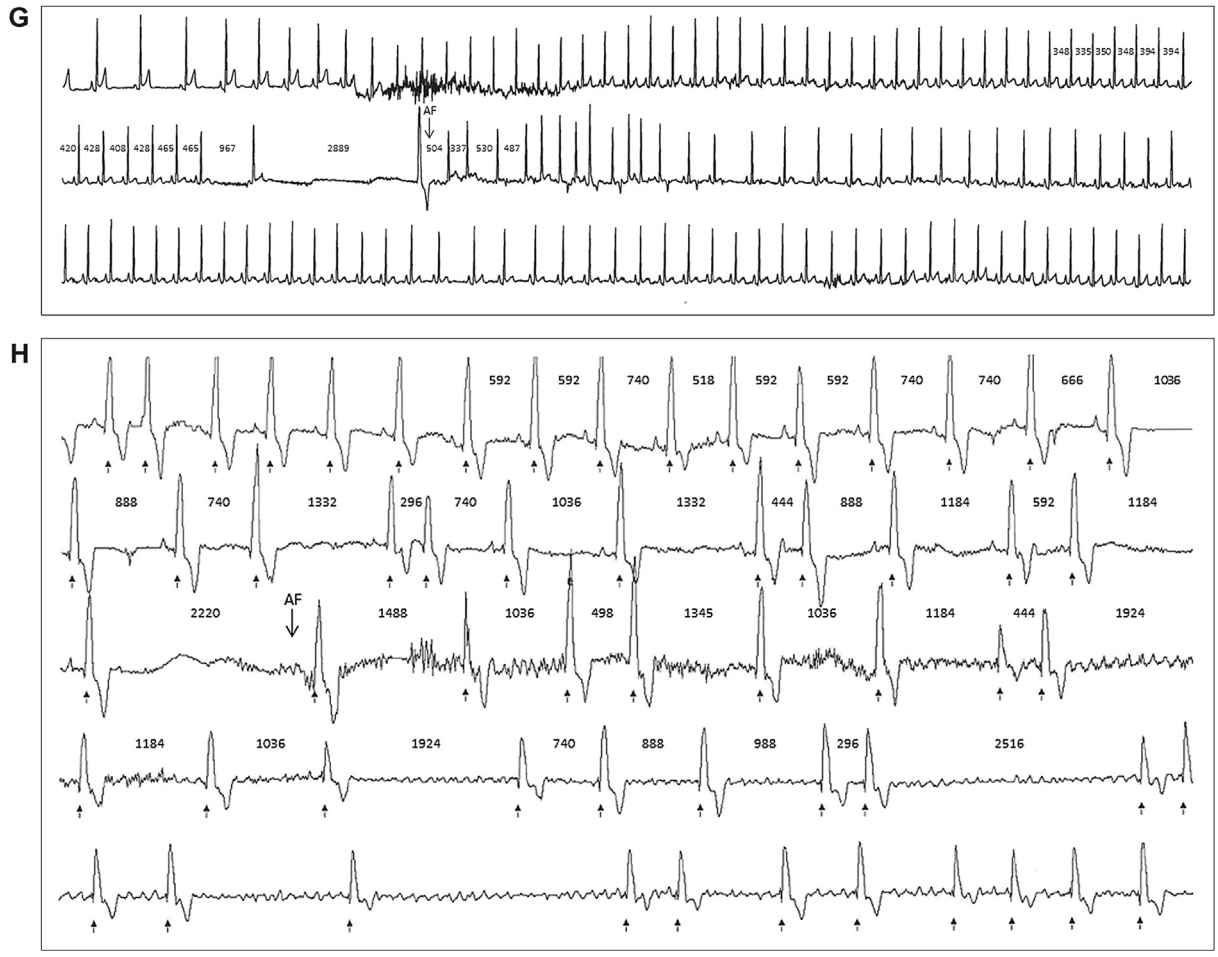

Fig. 1 (*Continued*)

on its trigger (afferent pathway).[1] The increased vagal tone generates a cardioinhibitory action that causes bradycardia and asystole, that in combination with sympathetic tone withdrawal producing a loss in vasopressor tone, this results in a profound hypotension. The combination of both factors is responsible for the fall in cardiac output and decreased peripheral resistance, and hence of cerebral hypoperfusion.[1] The triggering situations are variable and therefore reflex syncope is classified into vasovagal (emotional or orthostatic stress), situational (vomit, cough, after exercise) and carotid sinus (mechanical manipulation of carotid sinuses).[1] In four of the Holter recordings in this study, cardio-inhibition was the dominant component during loss of consciousness, while in five cases the duration of asystole was less than 3 s suggesting that loss of consciousness was probably due by the concomitant presence of a vasodepressor component.[1,13]

In this study, the development of atrial fibrillation was documented in all Holter recordings after a reflex or neurally-mediated syncope. A vagal-associated paroxysmal atrial fibrillation has been reported in approximately one quarter of human patients with no structural heart disease and typically follows a vagal stimulus such as sleep, postprandial or other vagal triggers. Paroxysmal atrial fibrillation secondary to a reflex syncope has been anecdotally described.[12,14] Vagal atrial fibrillation results from an interplay between a trigger for initiation and a vulnerable substrate for maintanence.[14] The autonomic nervous system plays a major role facilitating the initiation and maintenance of atrial fibrillation triggering pulmonary vein ectopies and changing atrial refractory period.[15–17] Experimentally, the use of

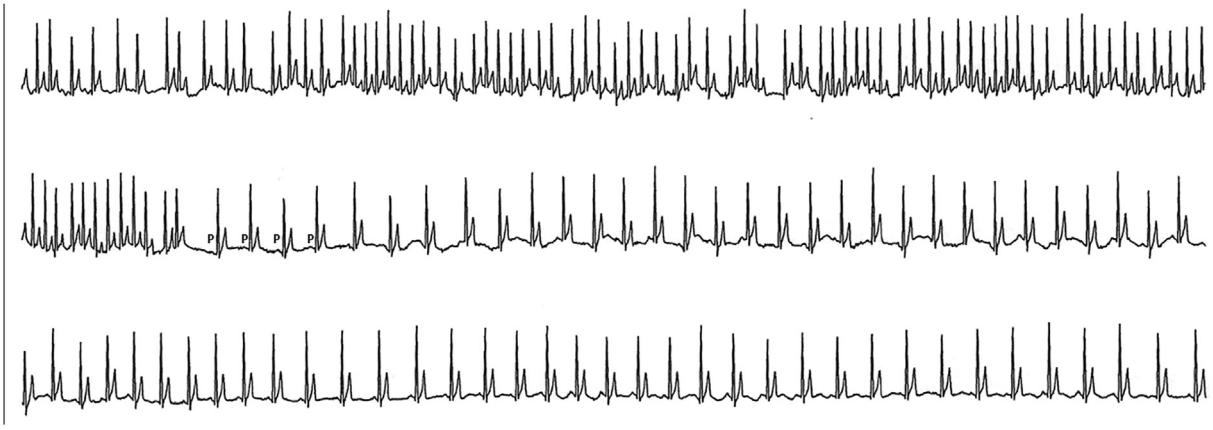

Fig. 2 Electrocardiogram recorded after a syncopal episode in a 9 year old male Boxer. The tracing reveals an initial paroxysmal atrial fibrillation with an average ventricular rate of 165 bpm with a sudden end and restoration of sinus rhythm. Speed of the recording is 7.50 mm/s. Calibration is 2 mm/mV.

cholinergic agonists[18] or the presence of conditions of increased parasympathetic tone[19] favour the induction of atrial fibrillation in dogs without structural cardiac disease. The parasympathetic tone favours the formation of re-entrant wavelets[20] or multiple atrial ectopic foci.[21] Cholinergic stimulation shortens the effective refractory period (ERP) and action potential duration (APD) non-uniformly, mainly through the activation of the acetylcholine dependent K^+ current (IKACh).[22] Experimental studies also showed that vagal stimulation increases the spatial dispersion in atrial refractoriness, inducing and maintaining atrial fibrillation. Both absolute APD/ERP shortening and increased APD/ERP dispersion facilitate the formation of re-entrant circuits.[6] Furthermore, cholinergic stimulation shortens the action potential duration of the pulmonary veins, promoting early afterdepolarisation.[7] Also the sympathetic nervous system has an important effect on initiation, maintenance and termination of atrial fibrillation.[23–25] Sympathetic stimuli shorten the atrial refractory period and increase the vulnerability to atrial fibrillation.[23–25] An interplay that unbalances the sympathovagal discharge is profibrillatory and enhances the firing from the pulmonary veins.[23–25] The cessation of vagal stimulation contributes to the elimination of predisposing factors for paroxysmal atrial fibrillation.[25]

In the Holter recordings, the atrial fibrillation was paroxysmal in seven of the nine electrocardiograms and remained incessant in another two. The paroxysmal character of this arrhythmia may be related to the cessation of vagal stimulation after the end of syncope. In the two dogs with incessant atrial fibrillation, the sustained presence of this arrhythmia could be secondary to the existence of a large mass of atrial myocardium associated with concomitant structural heart disease and a raised sympathetic tone that promoted the maintenance of atrial fibrillation.[14–17]

Another type of arrhythmia documented in three electrocardiograms in this study following the episode of reflex syncope was atrial flutter. Atrial flutter is a macroreentrant atrial tachycardia, in which the re-entrant circuit depends upon the existence of anatomic or functional barriers within the left or the right atrium.[26] Wells et al.[9] classified atrial flutter in two main forms: type I or anatomical atrial flutter ('typical atrial flutter') and the type II or functional atrial flutter ('atypical atrial flutter'). Morphology, polarity and amplitude of atrial electrocardiograms are uniform in both types of atrial flutters. Type II atrial flutter presents a shorter atrial cycle length, and it is usually more unstable; it can revert spontaneously to type I atrial flutter or degenerate into atrial fibrillation. As for atrial fibrillation, autonomic nervous system modulates the initiation of this type of atrial flutter. Allesie et al.[8] described the existence of an atrial re-entrant circuit without an anatomic barrier during acetylcholine infusion and rapid pacing in the dog. The termination of the atrial flutter and transition to sinus rhythm can occur because of decreased vagal stimulation. The cessation of vagal stimulation causes the prolongation of atrial cycle length and slows conduction velocity leading to a functional block.[8] However, when the line of functional block is not sufficiently long, the cycle length of the re-entrant circuit shortens and the re-entrant circuit becomes

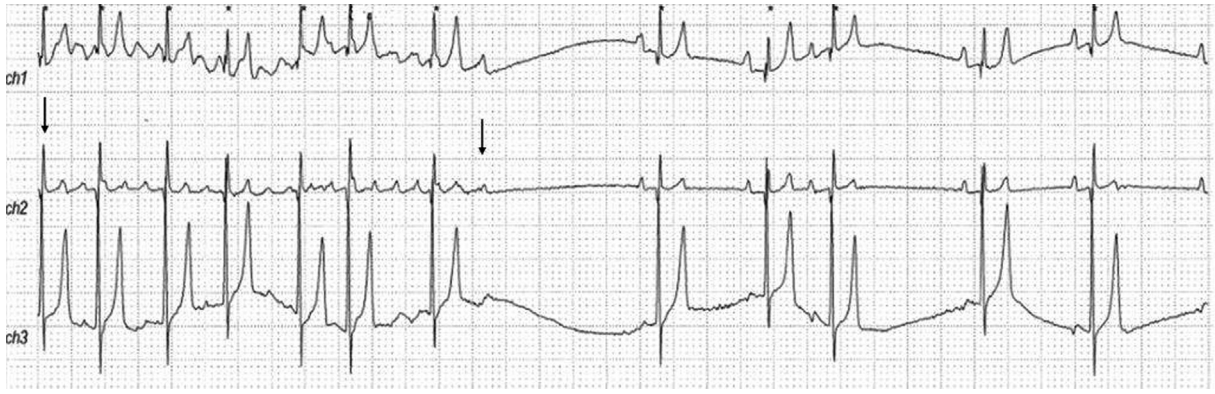

Fig. 3 Electrocardiogram recorded after a syncopal episode in a 7 year old male mixed breed. The tracing reveals the reorganization of a paroxysmal atrial fibrillation into paroxysmal atrial flutter (duration of 2 s) at the beginning of the rhythm strip (arrows) followed by restoration of the normal sinus rhythm. The rate of atrial flutter waves was 460 bpm with variable atrioventricular conduction. Speed of the recording is 25 mm/s. Calibration 10 mm/mV.

unstable causing fibrillation.[11] In this study, one dog showed atrial fibrillation interrupted by four paroxysms of unstable atypical atrial flutter with a rapid atrial rate (600 bpm) a duration of 6.5 s. In another dog, atrial fibrillation re-organised into two episodes of atrial flutter with an atrial rate of 461 bpm and a duration of 3 s before sinus rhythm spontaneously restored. This suggests that the underlining electrogenic mechanism could be a Wells type II atrial flutter, an unstable functional re-entry that easily deteriorates into AF.

The main limitations of this study include the low number of dogs and the characteristics of the population. The diagnosis of reflex syncope was based on the electrocardiographic findings reported in humans and in experimental models in dogs. The actual mechanism of reflex or neuromediated syncope could not be determined in the absence of tilt-table testing.[1] Other causes of cardioinhibition could not be completely ruled out. Some of the dogs reported here had concurrent cardiac diseases and were being treated with pharmacological medications. In such cases the vagal reflex could have been multifactorial, influenced by drugs and probably different from that documented in dogs with no structural heart disease. Finally, because some cases had a short-term follow-up, recurrence of vagal atrial fibrillation and data regarding the trigger of persistent atrial fibrillation by vagal paroxysm of the arrhythmia could not be analysed.

In conclusion, changes of autonomic nervous balance during presumed reflex syncope can induce paroxysmal atrial fibrillation and atypical Wells type II atrial flutter in the dog. Further studies are needed to define the duration of this arrhythmia and their possible role in the development of persistent or permanent atrial fibrillation in dogs with or without cardiostructural heart diseases.

Conflict of interest statement

The authors do not have any conflicts of interest to disclose.

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