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Review

Vagal atrial fibrillation: What is it and should we treat it?☆

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ABSTRACT

Vagal atrial fibrillation (AF) remains an under-recognised entity, affecting younger patients often with structurally normal hearts. Although there remains no universal definition or diagnostic criteria, in this review we describe recognised triggers and associated features, including a well-established association with athletic training. We explore potential mechanisms, including the role of the autonomic nervous system and ganglionated plexi in initiating and maintaining arrhythmia. We discuss the limited evidence base addressing the question of progression to persistent AF, and debate the merits of anti-arrhythmic treatment, as well as uncertainty regarding the risk of stroke. Differences in suggested pharmacological therapy are highlighted and as is the emerging promise of radiofrequency catheter ablation as a therapeutic option. As we recognise the emerging burden of vagal AF, we hope to explore the important similarities and differences crucial to developing our understanding of the disorder, and highlight some significant questions which remain unanswered.

1. Introduction

Atrial fibrillation (AF) is a globally important cause of death and disability, with numerous complications including thromboembolic stroke [1], heart failure [2], cognitive impairment [3] and is a risk factor for mortality independent of cardiovascular disease, potentially increasing an individual's risk of death by 50–90% [4]. It is the most common sustained arrhythmia worldwide, with estimates that at least 1% of the general population are affected at any one time [5] and this is predicted to increase [6]. This problem is not limited to developed nations, with an increasing burden having been demonstrated within developing countries [7]. AF is estimated to increase stroke risk 5-fold [8] and accounts for 15% of all strokes worldwide [9], accounting for 1% of healthcare expenditure in the United Kingdom [10], with much of the cost related to the treatment of thromboembolic stroke [11].

Atrial fibrillation is most commonly divided into separate clinical entities and these are dependent on the timescale of the disorder. A single episode resolving within 48 h is referred to simply as the first symptomatic or first detected episode [12]. If further spontaneously resolving episodes occur, it is termed paroxysmal AF. If these episodes require a medical intervention such as electrical or pharmacological cardioversion and are persisting beyond 7 days, we move from paroxysmal to 'persistent AF'. If over 12 months it is termed 'long standing persistent AF'. Episodes of persistent AF may then be terminated with pharmacological or electrical cardioversion. If attempts at cardioversion have been unsuccessful or are no longer pursued, this describes a state of 'permanent AF' [13].

Many triggers are involved in initiating AF. Haissaguerre et al. [14] were the first to demonstrate that the pulmonary veins were the origin for the majority of these triggers. Subsequently triggers have been identified in other thoracic veins such as the superior vena cava [15,16] and coronary sinus [17,18]. Since 2009 increasing attention has moved to target the ganglionated plexi (GP) which are important in regulating autonomic tone, and play a role in the modulation and initiation of AF [19,20].

2. Role of the autonomic nervous system in AF

The autonomic nervous system (ANS) plays an important role in the initiation and maintenance of AF [21–25]. In patients with established atrial fibrillation or structurally abnormal hearts, sympathetic stimulation may be a driver for AF [26]. In isolated canine models, rapid atrial rates seem to sensitise intrinsic cardiac nerves to catecholamines, stimulating adrenergic activity and potentially triggering local ectopy [27]. In patients undergoing coronary artery bypass grafting (CABG), a decrease in heart rate variability postoperatively was associated with increased postoperative AF, postulated – as a result of increased circulating noradrenaline levels and higher resting heart rates – to be due to increased sympathetic tone [28]. This theory is supported by the finding that post-operative AF may be partially suppressed by peri-operative beta-blockade [29].

However, Dimmer et al. commented on the difficulty of isolating the individual role of the sympathetic versus parasympathetic influence, noting that the late-onset of parasympathetic tone, as well as fluctuations in autonomic tone, may be key triggers [28]. Within the cardiac autonomic ganglia the co-localisation and complex inter-relation between sympathetic and parasympathetic innervation has made it difficult to

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assess the relative contribution to arrhythmogenesis. In most cases of AF both sympathetic and parasympathetic autonomic stimulation likely play contributory roles [22,28].

Work by Nattel and colleagues suggested that vagal stimulation had a profound effect on AF induction and duration, with an observed prolonging of the atrial effective refractory period (ERP) which was not seen during sympathetic stimulation [30]. Subsequent work by Olgin and colleagues found that sympathetic denervation alone, of dog hearts, encouraged AF [31]. More recently, intrinsic cardiac nerves (ICNs) and their associated GP have emerged as potential anatomical sites for the initiation and maintenance of AF by the parasympathetic nervous system. Stimulation of these areas can trigger AF [19,20] in humans and high frequency stimulation of GP at the pulmonary vein, can induce ectopy and AF [32]. Other studies in human subjects have too implicated shifts in autonomic tone towards vagal predominance in the initiation of paroxysmal AF (potentially following an initial sympathetic surge), enhancing ectopy occurring at the site of the pulmonary veins [22].

Coumel was the first to hypothesise vagal overactivity as a causative mechanism [33], suggesting that "shortening the wavelength of the atrial impulse" [26] triggered macro-reentrant circuit formation. This was further supported in experiments by Liu and Nattel which demonstrated a shortening of the action potential and refractory period creating heterogeneity across the atrial wall and a substrate for re-entrant arrhythmogenesis [34]. Subsequent work has further shown that vagal stimulation causes potent increases in the heterogeneity of the atrial ERP, far in excess of that caused by sympathetic stimulation [30]. Associated increases in variability of local activation frequency reflect increased dispersion of atrial refractoriness, regional variations of which demonstrate increased propensity to AF in animal models [35,36]. Indeed, the duration of vagally-stimulated AF seems to correlate with the standard deviation of atrial refractoriness, rather than absolute values [37].

Acetylcholine (ACh) has been implicated in the pathogenesis of AF: vagal stimulation causes release of ACh, which acts predominantly on M2 receptors, activating the G-protein activated potassium current (I_{KACh}) [38] producing shortening of action potential duration (APD) and ERP [39]. The non-uniform distribution of nerve endings, which, under vagal stimulation release ACh, has been proposed as a mechanism for generation of APD heterogeneity [40], with anatomical mapping within the sheep heart suggesting a decreasing gradient of density of ACh concentration from the left to right atria [41]. Kneller and colleagues [42] used computer modelling based on the canine atrium to explore mechanisms underlying the initiation maintenance of AF. They found that heterogenous distribution of ACh concentrations within the model created repolarization gradients which promoted the disintegration of re-entrant circuits into AF while maintaining the primary organised spiral wave.

Vagal stimuli such as eating, sleeping, relaxation following stress or exercise and alcohol consumption have been implicated [26,43]. When alcohol, usually beer, is a trigger for paroxysmal atrial fibrillation (PAF), it is seen to be preceded by vagal activity, tending to more greatly affect those of a younger age or with a family history of AF [43]. Indeed the observation that vagal AF tends to affect those with structurally normal hearts has been supported with evidence that these patients have a much more normal atrial electrical substrate, with normal intra-atrial conduction, compared with patients experiencing non-vagal AF [44].

3. Whose AF is vagal?

Currently, there is no universal definition of vagal AF [45]. Experimental studies involving the stimulation of autonomic ganglia have used several criteria to label AF as vagal, including the observation of atrioventricular block, asystolic periods, sinus bradycardia and an increase in heart rate variability — defined as >50% in one study [46,47]. Indeed, one group found that up to 38% of patients suffering with PAF report vagal activities as triggers [48], while the large Euro Heart Survey found that of 1517 patients with PAF, 33% had autonomic triggers with vagal stimuli accounting for 91 (6%) of these patients [49] Vagal triggers for AF in this study were defined as AF occurring after eating, present solely at night and without presence of adrenergic triggers (exercise, emotion and presence mainly during daytime). However, a significant proportion of clinicians may not even check for the presence of such triggers [49].

Alternating AF and atrial flutter has been described as common [26] as are slow ventricular rates during AF episodes [23]. While a predilection to younger individuals and males has been described [26], there have been no large-scale epidemiological studies to support this. The concept of nocturnal onset as a marker of vagal AF deserves attention. The relationship between obstructive sleep apnoea (OSA) and AF is now well recognised [50,51], and a link between OSA and alterations in autonomic tone has been hypothesised [52]. While the complex interplay between autonomic tone and AF induction remains elusive, it may be too soon to attribute all cases of nocturnal-onset AF to vagal causes, especially in those with risk factors for OSA such as male sex, obesity and hypertension [53,54].

Interestingly, an association between AF triggering and gastrointestinal disorders has been identified. A case–control study found that AF catheter ablation patients who had gastro-oesophageal reflux disease or irritable bowel syndrome were more likely to have vagal triggers, often related to their gastrointestinal disease, for AF episodes and were less likely to demonstrate a left atrial scar [55], suggesting the fluctuations in vagal tone may be triggering factors. Radiofrequency ablation was equally successful in the GI and non-GI AF groups. There have been suggestions that reflux-mediated inflammation may be a causative factor [56].

4. AF in athletes

In athletes, particularly endurance athletes, the prevalence of AF as a whole has been reported to be up to 10 times greater [57], with the finding that a great proportion of episodes may be vagally driven — in one study, a cohort of cross-country endurance runners were found to be five times more likely to develop vagal AF [58], possibly due to vagal hyperactivity observed in athletes. Numerous other studies have established a strong link between atrial flutter and fibrillation and endurance sports [59–63], although the majority of study subjects were males. There is a suggestion that risk may increase with frequency of exercise [61,64], with one study reporting frequency above 5 episodes per week conferring additional risk [65]. It should be borne in mind that vagal AF is not a contra-indication to participation in sporting activities, although symptom burden and medication side-effects may affect performance. If asymptomatic and without structural heart disease, appropriate rate control [66] and consideration as to appropriateness of anticoagulation are warranted. In those who are symptomatic, reduction of sporting activity [67], pharmacological management [68] or ablation [69] are possibilities, although these therapeutic options pertain to the spectrum of athletic atrial fibrillation as a whole, as opposed to the vagal subtype.

Several hypotheses have been proposed to explain the mechanism of AF with exercise. It is postulated that a complex interaction among sympathetic–parasympathetic tone [64,70–73], inflammation [56,74,75], metabolic alterations resulting in electrical and structural remodelling of both atria with progressive fibrosis [73,76,77] of the myocardium contributing to the development of AF. Increases in atrial pressure and subsequent atrial remodelling increases dispersion of atrial refractoriness, predisposing to AF [72,78,79]. Potent vagal overactivity remains for many years in former athletes manifesting as persistently low heart rates many years after cessation of training [80], although the mechanism for these low heart rates remains controversial [81]. This potential vagal overactivity, coupled with withdrawal of sympathetic tone, results in an imbalance between sympathetic and parasympathetic autonomic stimulation with increased atrial ectopy and modification of atrial