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Review

Role of autonomic nervous system in atrial fibrillation

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ABSTRACT

Atrial fibrillation is the most common sustained arrhythmia and is associated with significant morbidity and mortality. The autonomic nervous system has a significant role in the milieu predisposing to the triggers, perpetuators and substrate for atrial fibrillation. It has direct electrophysiological effects and causes alterations in atrial structure. In a significant portion of patients with atrial fibrillation, the autonomic nervous system activity is likely a composite of reflex excitation due to atrial fibrillation itself and contribution of concomitant risk factors such as hypertension, obesity and sleep-disordered breathing.

We review the role of autonomic nervous system activation, with focus on changes in reflex control during atrial fibrillation and the role of combined sympatho-vagal activation for atrial fibrillation initiation, maintenance and progression. Finally, we discuss the potential impact of combined aggressive risk factor management as a strategy to modify the autonomic nervous system in patients with atrial fibrillation and to reverse the arrhythmogenic substrate.

1. Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia and is associated with significant morbidity and mortality [1]. Several clinical and experimental observations suggest that the progression of AF is promoted by the presence of modifiable concomitant cardiovascular risk factors such as hypertension, obesity, and sleep-disordered breathing [1]. These risk factors are associated with atrial stretch and cardiac volume- and pressure-overload, which create an arrhythmogenic substrate characterized by atrial dilation and subsequent atrial extracellular matrix remodeling [2,3]. Importantly, many of the risk factors for AF are associated with activation of the autonomic nervous system (ANS), potentially altering atrial electrophysiology and increasing susceptibility to atrial arrhythmias. Additionally, AF itself results in substantial shifts in ANS activation that may further promote the maintenance and progression of AF [4].

Recent review articles mainly addressed the effect of the ANS on atrial cellular electrophysiology and on the role of the ANS on the development of substrates for AF [2–6]. In this review, we update and focus on changes in reflex control during AF, the role of combined sympatho-vagal activation for atrial fibrillation initiation, maintenance and progression and the impact of concomitant cardiovascular risk factors (with focus on hypertension, obesity and sleep-disordered breathing) on ANS activation in patients with AF. Finally, we explore the potential antiarrhythmic effects of modulation of the ANS by risk factor modification and pharmacological or device-based interventions.

2. Efferent autonomic innervation of the atria

The cellular effects of adrenergic and cholinergic activation as components of the atrial efferent autonomic innervation on AF arrhythmogenic mechanisms are summarized in Fig. 1.

2.1. Atrial sympathetic innervation

Sympathetic innervation to the heart originates inside the vertebral column (levels C7 to T7) and reaches the stellate ganglion located in front of the neck of the first rib and just below the subclavian artery. At the synapses within the stellate ganglion, preganglionic neurons release acetylcholine which activates postganglionic nicotinic acetylcholine receptors. In response to sympathetic stimuli, postganglionic neurons release norepinephrine, activating β-adrenoceptors (β-ARs).

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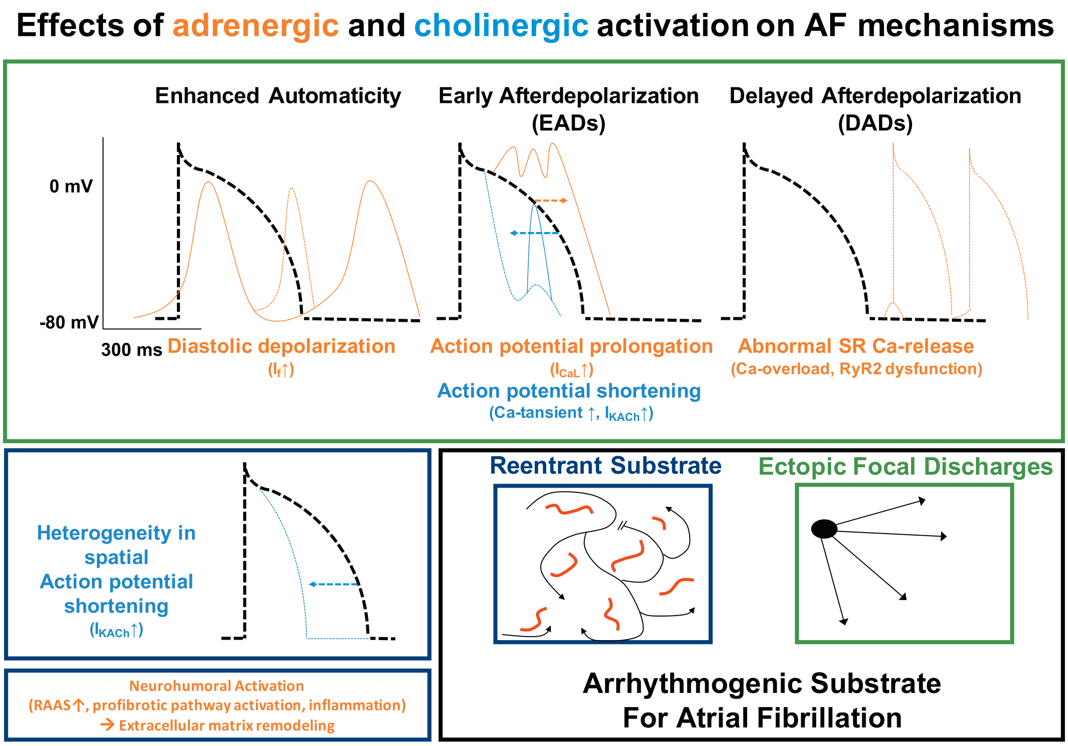

Fig. 1. Effects of adrenergic and cholinergic activation on atrial fibrillation (AF) arrhythmogenic mechanisms. Green boxes: AF–inducing ectopic firing (enhanced automaticity, early afterdepolarizations (EADs) and delayed afterdepolarizations (DADs)). Dark blue boxes: AF reentrant substrates. Black dotted action potential, reference action potential. Orange action potential: result of adrenergic activation. Light blue action potential: result of cholinergic activation. RyR2, ryanodine receptor type-2. I_f, "funny" current. I_{KACh}, acetylcholine-gated potassium current.

The β-adrenergic response is mediated via stimulatory G proteins, the activation of which leads to stimulation of adenylyl cyclase with subsequent protein kinase A–mediated phosphorylation of L-type calcium channels (increasing calcium influx), troponin I (enhancing myofilament relaxation), and phospholamban (disinhibiting the sarcoplasmic reticulum (SR) calcium ATPase type-2 and increasing SR calcium uptake). SR calcium release channels (ryanodine type-2 receptors, RyR2) release calcium in response to transmembrane calcium entry. RyR2 are normally closed during diastole but can open if they are dysfunctional or if the SR is calcium-overloaded [7,8]. Excess calcium is extruded to the extracellular space by the sodium/calcium exchanger (NCX). Due to the 3:1 stoichiometry (3 sodium ions are exchanged for 1 calcium ion), the NCX is electrogenic and produces an inward current that underlies delayed afterdepolarizations–related ectopic firing. Changes in ion channel activation during adrenergic stimulation also contribute to enhanced automaticity (Fig. 1). Additionally, α-AR stimulation inhibits the cardiac transient outward potassium current I_{to}. Activation of β-ARs increases ultra-rapid delayed rectified potassium current I_{Kur}, slow delayed rectified potassium current I_{Ks}, and acetylcholine-gated potassium current I_{KACh} [3]. As a net result of sympathetic stimulation, the total action potential duration is either unaffected or slightly abbreviated [9].

Enhanced automaticity and triggered activity do not only occur in atrial tissue but also in pulmonary veins which represent a common arrhythmia trigger in patients with paroxysmal AF [5,10].

2.2. Atrial parasympathetic innervation

The parasympathetic nervous system originates from the medulla with vagal efferents extending to postganglionic nerves that innervate the atria. At the cellular level, cholinergic muscarinergic receptors (M2Rs) are the primary mediators of parasympathetic control of cardiac function. M2R stimulation effects are opposite to those of β-adrenergic stimulation. M2R stimulation by acetylcholine inhibits adenylyl cyclase and reduces cyclic adenosine monophosphate via pertussis toxin-sensitive inhibitory G-proteins (Gi), which can inhibit I_{CaL} and hyperpolarization-activated ("funny") current I_f. M2R-stimulated Gi also directly activates I_{KACh}, leading to effective refractory period shortening in the atrium [3]. The effect of vagal stimulation on atrial refractoriness is heterogeneous because of the spatial distribution of parasympathetic nerve endings and/or M2Rs (Fig. 1) [11]. Additionally, preganglionic neurons synapse on postganglionic neurons at the level of the heart within ganglia (ganglionated plexi) as part of the intrinsic cardiac nervous system [5,6].

2.3. Role of combined sympatho-vagal activation for the onset of AF

It has been widely accepted that AF patients with structurally normal hearts tend to show a vagal pattern of AF onset (nocturnal, postprandial or postexercise AF), while patients with structural heart disease tend to display a sympathetic pattern (AF during daytime or exercise) [12]. Studies in both lone AF patients and animal models of intermittent rapid atrial pacing and heart failure have indicated that AF onset is associated with combined sympatho-vagal activation rather than alterations in vagal or sympathetic drive alone [13–15]. Using direct nerve recordings from the stellate ganglia and vagal nerves, Ogawa et al. demonstrated increased sympathetic and vagal nerve discharges before the onset of atrial arrhythmias in dogs with pacing-induced congestive heart failure [16]. In animal models and humans, M2R (acetylcholine or carbachol) and β-AR (isoproterenol and epinephrine) agonists can induce AF [9,10,17]. However, rather than exclusively sympathetic or parasympathetic stimulation, sequential combined sympathetic and vagal activation appears to create a more pronounced AF substrate for AF induction [9,10,17]. Adrenergic, cholinergic, or combined sympatho-vagal activation can cause triggered activity-promoting early after depolarisations (Fig. 1). Although both branches of the ANS contribute to the initiation of AF, cholinergic stimulation is often the main factor for spontaneous AF initiation in animal models whilst adrenergic tone modulates the initiation and maintenance of cholinergically mediated AF [17].

3. Afferent regulatory signaling in AF

3.1. Extracardiac centers

3.1.1. Arterial baroreceptor reflex

Baroreceptors located in the carotid sinus at the bifurcation of the external and internal carotids and the aortic arch [18] provide the main input for the arterial baroreceptor reflex, which buffers acute changes in arterial blood pressure through modulation of both parasympathetic and sympathetic ANS. Long coupling intervals between ventricular activations during AF have been postulated to lead to beat-to-beat variability in pulse pressure and pulse loss, subsequently unloading the arterial baroreceptors which may contribute to increased sympathetic nerve activity [19]. However, several studies have demonstrated that sympathoexcitation during induced AF or irregular pacing occurs in the absence of significant fluctuation in systemic blood pressure [20]. Despite these findings, baroreflex sensitivity has been shown to be impaired amongst patients with AF [21] and improved as a result of sinus rhythm restoration [22]. However, other studies have shown similar baroreflex sensitivity in AF patients versus controls [23]. The main challenge in assessing baroreflex sensitivity, and particularly the reflex control of heart rate, is the difficulty in its assessment amongst patients with persistent AF or pacemakers. Additionally, alterations in arterial baroreceptor gain and in reflex control of heart rate are commonly observed with concomitant risk factors such as aging, obesity, hypertension and sleep apnea [18], thus making it difficult to attribute differences to AF itself or to underlying comorbidities.

3.1.2. Chemoreceptors

Carotid bodies are chemoreceptors located on the external carotid arteries close to the bifurcation with the internal carotids. Stimulation of the carotid bodies, e.g. in sleep apnea, drives sympathetic tone through direct signaling to the nucleus tractus solitarius and medulla increasing blood pressure and minute ventilation [18]. Moreover, chemoreceptor hypersensitivity has been described in heart failure patients, leading to sympathetic overactivity and a strong association with increased mortality [18].

3.1.3. Renal nerves

The renal nerves are major regulators of kidney function, volume homeostasis, and blood pressure control [24]. Additionally, afferent unmyelinated fibers transmit important sensory information from renal chemo- and mechanoreceptors to brainstem regions involved in cardiovascular control. Renal sympathetic nerve activity is increased in hypertension, obesity, chronic kidney disease and heart failure [24] and regulates left stellate ganglion neuronal activity [25]. Additionally, renal sympathetic denervation has been shown to prevent the development of an atrial arrhythmogenic substrate in different AF animal models [24,26].

3.2. Intracardiac centers and neural remodeling

3.2.1. Intracardiac centers

As a sensing organ, the atria are populated by both mechanically (volume-sensitive reflex) and chemically (chemo-sensitive reflex) sensitive nerve endings informing both non-myelinated and myelinated afferent fibers [27]. The efferent responses they elicit are heterogeneous and organ-specific. Complex unencapsulated endings of myelinated nerves, whose density is greatest at veno-atrial convergence, discharge in response to two stimuli: atrial filling and atrial contraction. They are perceived, classically, to represent the afferent limb of a reflex that when stimulated evokes cardiac and peripheral sympathoinhibition. Unmyelinated nerves are generally dormant at normal atrial pressures but are also activated by both atrial filling and atrial systole, but at higher atrial pressures. Central venous pressure and atrial filling pressures increase with both the progression of cardiac structural remodeling [3,18] and the irregular sequence of ventricular activation intervals with the induction of AF [28]. One acute autonomic consequence of AF would be loss of the normal restraint of atrial systole and reduced inhibition of central sympathetic outflow. In heart failure patients, baroreceptor unloading by passive head up tilt reduced filling pressures similarly in patients in sinus rhythm and AF, but cardiac sympathetic response, assessed by transcardiac norepinephrine gradients, was impaired in AF [29]. This impaired response to baroreceptor unloading could be attributed to decreased compliance of the remodeled atria in patients with AF [3], which may translate into altered volume-sensitive reflex activity, and hence sympathetic activation [30,31]. Although specific data in AF patients is lacking, recent studies in heart failure patients have provided evidence for a paradoxical sympathoexcitatory response to skeletal muscle in response to increased cardiac filling pressure [32].

3.2.2. Ganglionated plexi

Additionally, the heart's intrinsic nervous system consists of additional ganglia (ganglionated plexi), which contain local circuit neurons of several types and chemo- and mechanosensory neurons, which are distributed throughout the heart [3]. Ganglionated plexi are innervated with both adrenergic and vagal nerve endings and mainly housed in fat pads located around the pulmonary vein ostia. Ganglionated plexi may modulate the interactions and balance between extrinsic and intrinsic cardiac ANS and contain efferent cholinergic and adrenergic neurons [33]. Stochastic interactions in intrinsic cardiac local circuit neurons control regional cardiac function and excessive activation of these neurons precedes and persists throughout episodes of AF in dog models [4,33].

3.2.3. AF-induced neural remodeling

Atrial sympathetic hyperinnervation is reported in patients with persistent AF and in animal models with pacing induced AF or heart failure [34,35]. In dogs with pacing-induced heart failure, increased sympathetic and parasympathetic nerve growth could be demonstrated in the pulmonary veins and the posterior wall of the left atrium [35]. Whereas nerve growth factor (NGF) stimulates axon growth, its precursor, proNGF, triggers axon degeneration and may be involved in regional denervation. Both sympathetic hyperinnervation and denervation may lead to heterogeneous β-AR activation, either through spatial heterogeneity, localized catecholamine release or localized β-AR supersensitivity [36]. This non-uniform sympathetic activation increases the risk of focal triggers and creates gradients of repolarization, increasing the susceptibility to reentry [3]. In patients undergoing AF ablation, excessive cardiac sympathetic nervous activation, assessed by MIBG scintigraphy, has been associated with increased AF recurrence [37]. Similarly, there is also evidence for remodeling related to parasympathetic activation. Although M2Rs are the primary receptors activating I_{KACh} and subsequently shortening the effective atrial refractory period, the relative contribution of non-M2R subtypes to overall I_{KACh} activation has been shown to be increased in patients with chronic AF compared to patients with sinus rhythm [38]. Additionally, I_{KACh} underlies a remodeling process during the progression of AF and can be constitutively active in patients with chronic AF, even without vagal stimulation [38].

3.3. A bidirectional relationship between ANS and AF

The ANS is controlled by several regulatory mechanisms, particularly by afferent signals arising from extracardiac centers (renal nerves, baroreceptors, carotid bodies) and intracardiac centers (ganglionated plexi). Although most studies evaluated the role of the ANS for the progression of AF ("ANS begets AF"), a growing body of literature has sought to describe the effects of AF on ANS activity, atrial neural remodeling and reflex function ("AF begets ANS"). A bidirectional relationship whereby ANS activation contributes to the pathogenesis of AF and AF itself promotes ANS activation may further perpetuate the progression of the arrhythmia.

In patients with heart failure and concomitant AF, single-unit muscle sympathetic nerve activity was significantly higher than in heart failure patients with sinus rhythm [39]. This indicates recruitment of previously silent neurons, possibly due to higher atrial filling pressures, a greater number of cardiac cycles during AF in which multiple single neuron discharges develop and unloading of arterial baroreceptors by pulse loss during AF. This may result in the following functional consequences: Multiple firing of single units and unloading of arterial baroreceptors during AF evoke greater norepinephrine release; more norepinephrine release results in greater vasoconstriction; greater vasoconstriction increases afterload; increased afterload results in higher left atrial pressure; higher left atrial pressure in addition to ANS activation can contribute to more sustained AF.

4. Contribution of concomitant modifiable risk factors to ANS activity in AF

In a significant portion of patients with AF, ANS activity is likely a composite of reflex excitation due to AF itself and of concomitant risk factors such as hypertension, obesity and sleep-disordered breathing [2].

Long-term exposure to hypertension, obesity and sleep-disordered breathing is associated with a progressive arrhythmogenic structural substrate and electroanatomical changes characterized by low voltage areas, fractionated electrograms and scar as well as to a persistent increase in ANS activation, mainly characterized by sympathetic overactivation [1,3]. In addition, long-term vigorous endurance exercise training [40] can contribute to atrial structural maladaptive remodeling and may increase the risk of incident AF by increased vagal activity (Table 1) (Fig. 2A).

Transient exposure to occasional intensive exercise sessions in athletes or episodic nocturnal apneas in patients with sleep-disordered breathing may result in dynamic changes in hemodynamic status and ANS activation (Fig. 2B). During exercise, parasympathetic withdrawal and progressive sympathetic activation contributes to increased cardiac output. Upon cessation of exercise, sustained sympathetic activation accompanied by rapid parasympathetic reactivation results in a transient state of combined sympatho-vagal activation, which may increase AF susceptibility [40]. Similarly, in patients with sleep apnea, ineffective breathing attempts against the occluded upper airways [41] are associated with pronounced intra-thoracic pressure swings (often 50 mm Hg or greater), which increases transmural pressure gradients in the atria. This mechanical impact can contribute to atrial structural maladaptive remodeling and lead to parasympathetic activation through the diving reflex [41] followed shortly by a sympathetic surge which arises from inhibition of pulmonary stretch, hypoxia and arousal [41]. This profound peri-apneic vagal activation followed by combined sympathetic activation at the end of the apnea may trigger and maintain AF.

Therefore, the extent of structural remodeling as well as persistent ANS activation may occur in proportion to the number of long-term concomitant risk factors (risk factor burden). Additionally, exposure to

Table 1
Risk factors, atrial fibrillation (AF) substrates and autonomic nervous system (ANS). Electroanatomical substrate, ANS activation and the effect of intervention on ANS in patients with obesity/metabolic syndrome, hypertension and sleep apnea.

	Patient's characteristics		Effects of intervention	
	Electroanatomical substrate	ANS activation	Effect of intervention on ANS	Effect of intervention on AF and ablation outcome
Obesity/metabolic syndrome	Atrial remodeling: Increased low voltage areas. (Refs.: S1)	Sympathetic activation ↑ (Refs.: S2–S4)	Intervention: Diet and exercise-based weight loss. Effect: ANS-activation ↓ (Refs.: S5–S9)	Weight loss in severely obese patients with long standing persistent AF improved quality of life but had NO impact on symptom severity and long-term ablation outcome. ➔ No effect on ablation outcome (Refs.: S10)
Hypertension	Atrial remodeling: Global conduction slowing, regional conduction delay, increased AF inducibility. (Refs.: S11)	Sympathetic activation ↑ (Refs.: S12–S15)	Intervention: pharmacological antihypertensive treatment Effects: differential effects Renal denervation Effects: ANS-activation ↓ (Refs.: S16,S17)	Aggressive pharmacological blood pressure treatment in AF patients with minimal hypertension did NOT improve ablation outcome (SMAC-AF). ➔ No effect on ablation outcome Renal denervation reduced blood pressure in AF patients with drug resistant hypertension and reduces AF recurrence when combined with AF ablation. ➔ Improvement of ablation outcome (Refs.: S18–S23)
Sleep apnea	Atrial remodeling: Atrial enlargement, larger low voltage areas, widespread conduction abnormalities, and longer sinus noderecovery. (Refs.: S24,25)	Sympathetic activation ↑ (Refs.: S26–S30)	Intervention: Chronic positive airway pressure. Effects: ANS-activation ↓ (Refs.: S31–S36)	Chronic positive airway pressure improved ablation outcome in AF patients with sleep apnea. ➔ Improvement of ablation outcome (Refs.: S37)
Combined risk factor management (RFM)			Unclear	Aggressive RFM improved the long-term success of AF ablation (ARREST/LEGACY). ➔ Improvement of ablation outcome (Refs.: S38–S40)

References: see online supplement

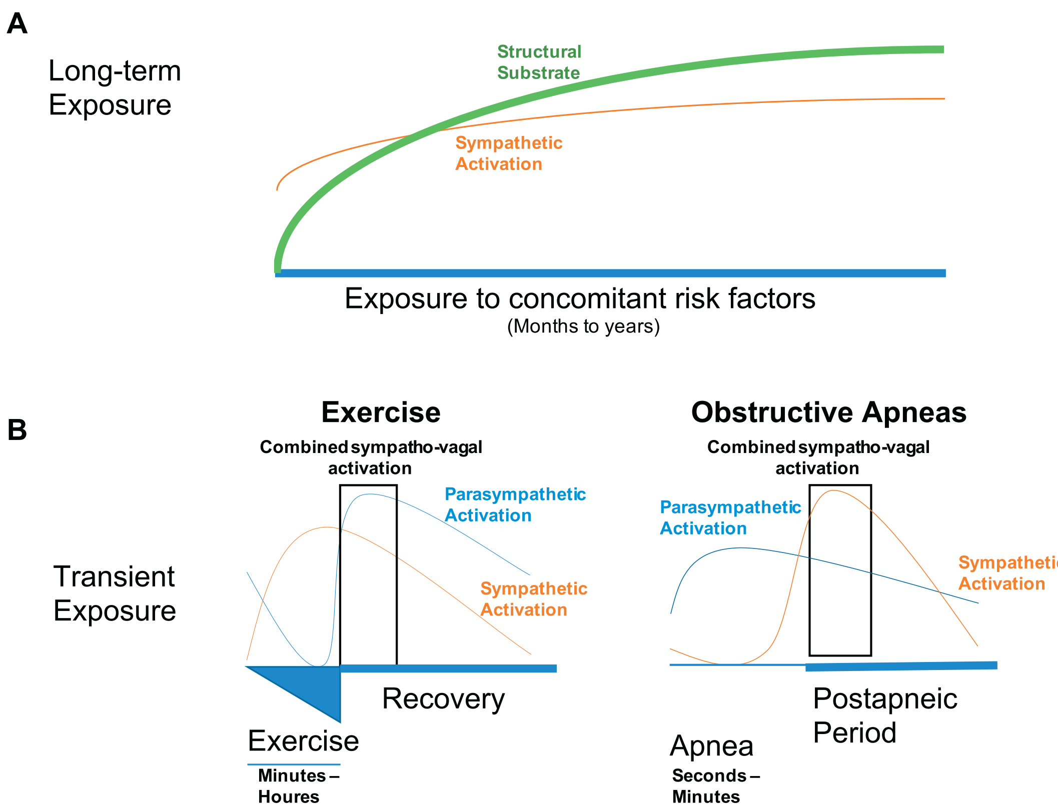

Fig. 2. (**A**) Long-term exposure to concomitant risk factors such as hypertension, obesity and sleep apnea is associated with a persistent progression of a structural substrate and increase in sympathetic activation. (**B**) Acute exposure to conditions such as vigorous exercise in athletes or nocturnal apneas in patients with sleep-disordered breathing may result in differential activation of the autonomic nervous system contributing to a state of transient combined sympatho-vagal activation. This may create a dynamic arrhythmogenic substrate for atrial fibrillation.

acute conditions associated with transient increases in ANS activation may contribute to a dynamic arrhythmogenic substrate for AF.

5. Targeted ANS modulation to manage AF

Modulation of the ANS might be an effective strategy to protect the atrial myocardium from proarrhythmic autonomic influences and the development of electrical, structural and neural atrial remodeling [4]. In patients with AF, sympathetic excitation may be mainly driven by other coexisting clinical characteristics such as obesity, hypertension or sleep-disordered breathing, and this notion has implications for the clinical evaluation of patients, application of current treatment, and development of new therapies. Additional references concerning clinical studies are provided in the *online supplement* and summarized in Table 1.

5.1. Risk factor modification

AF is a progressive disease, and the formation of proarrhythmic substrates is promoted by inadequately treated or unrecognized cardiovascular risk factors involving hypertension, obesity and sleep-disordered breathing. This atrial remodeling as well as accompanied ANS activation is partially reversible when the underlying disease is treated. Aggressive combined risk factor management (treatment of hypertension, sleep apnea, metabolic syndrome) plus exercise and diet-based weight management reduce AF symptoms, improve AF ablation outcomes and promotes long-term rhythm control (see Table 1) [1]. It has been shown that weight loss in obese patients leads to a significant reduction in sympathetic activation. Additionally, exercise training, sleep apnea treatment and anti-hypertensive therapy have been shown to reduce sympathetic activity, potentially reversing changes in ANS activity and subsequently reducing AF burden. Critically, treating just one risk factor in a patient with multiple concomitant risk factors might be not sufficient to prevent substrate development and ANS activation. In contrast, combined risk factor management represents a potent strategy to modulate the ANS, reverse structural remodeling and to modify the progression of AF (see Table 1). This concept may be relevant for primary as well as for secondary prevention of AF. The potential impact of combined aggressive risk factor management on the interaction between risk factors, ANS and AF is summarized in Fig. 3.

5.2. Pharmacological ANS modulation

Although current evidence indicates that a combined sympatho-vagal activation is most commonly responsible for eliciting AF episodes, pharmacological inhibition of one of the ANS arms has been shown to improve sinus rhythm maintenance. Blockade of β-ARs with metoprolol can be effective in preventing recurrence of AF after successful cardioversion [42]. Additionally, central sympathetic inhibition by moxonidine reduced postablation AF recurrences in hypertensive patients in a randomized, controlled study [43]. The observed antiarrhythmic effects with metoprolol and moxonidine do not appear to depend on their antihypertensive action. Theoretically, pharmacological inhibition of $I_{K,ACh}$ may also display antiarrhythmic effects, but clinical and preclinical data with selective $I_{K,ACh}$ inhibition have been rather not effective.

5.3. Interventional ANS modulation

Several interventional strategies have been investigated for their antiarrhythmic effects in the atrium.

5.3.1. Renal denervation

Renal denervation reduces renal norepinephrine spillover as well as total sympathetic activity. Catheter-based renal sympathetic denervation

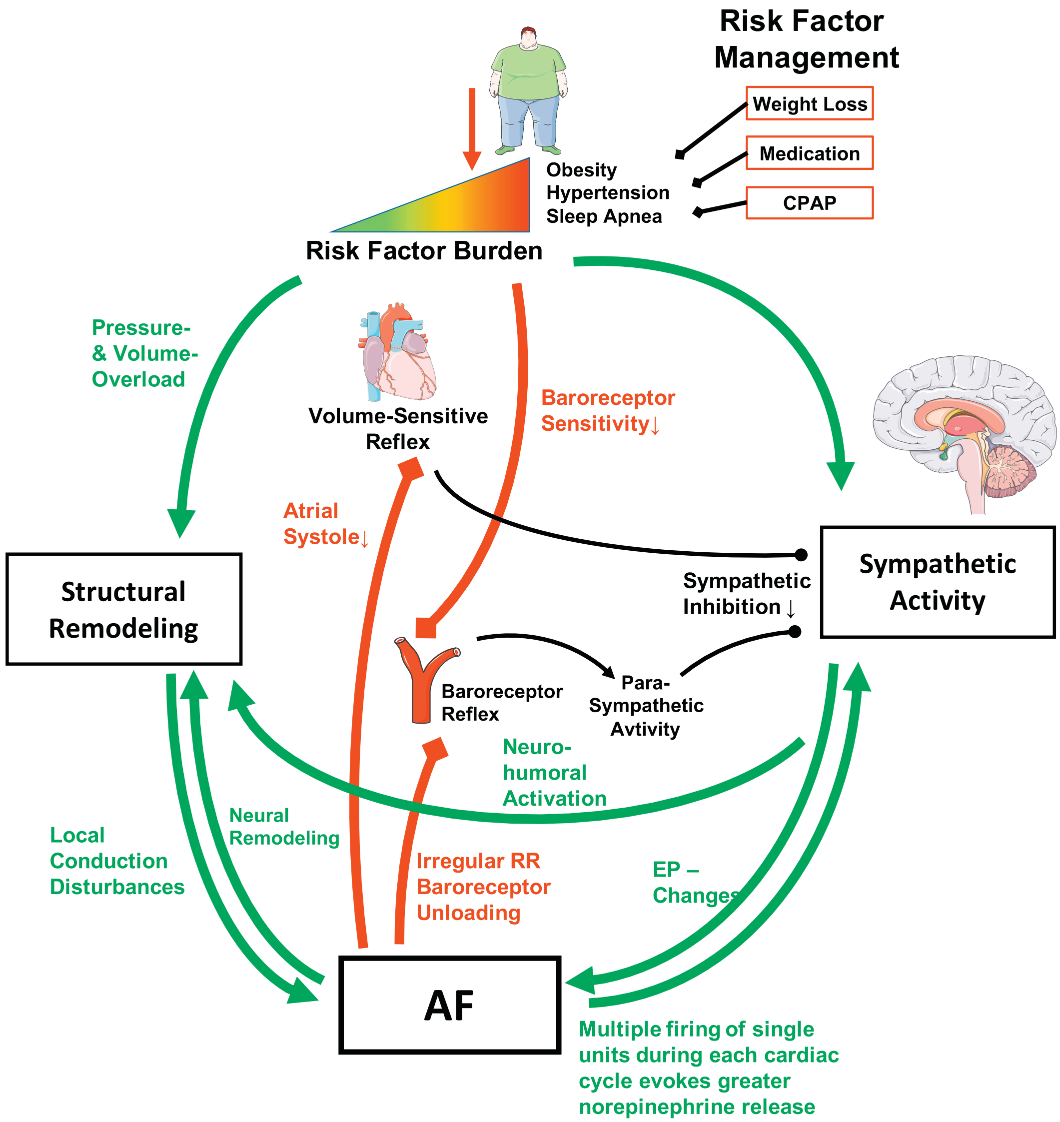

Fig. 3. Interaction between risk factors, autonomic nervous system (ANS) and atrial fibrillation (AF). Exposure to risk factors such as obesity, hypertension and sleep apnea (risk factor burden) is associated with (i) pressure and volume overload, (ii) reduced baroreceptor sensitivity and (iii) increased sympathetic activation and subsequent neurohumoral activation which contribute to the development of an arrhythmogenic structural remodeling process. Atrial structural remodeling results in atrial local conduction disturbances. AF is associated with (i) atrial electrophysiological changes (EP-changes) (ii) neural atrial remodeling, (iii) baroreflex unloading due to irregular RR intervals, (iv) multiple firing of single units during each cardiac cycle evoking greater norepinephrine release during fast AF and (v) loss in atrial systole lowers volume-sensitive reflex activity reducing sympatho-inhibition. Therefore, a bidirectional relationship whereby ANS activation contributes to the pathogenesis of AF and AF itself promotes ANS activation may further perpetuate the progression of the arrhythmia. The potential impact of risk factor management by weight loss, medication and chronic positive airway pressure (CPAP) is indicated. Green: Activation. Red: Inhibition. Thickness of the lines indicate the intensity of activation or inhibition.

lowers blood pressure and improved left atrial and left ventricular structure and function in selected patients with therapy-resistant hypertension [24]. In preclinical AF models, renal denervation attenuated atrial structural changes and reduced AF susceptibility [24,26]. Similarly, adjunct renal denervation improved outcome of catheter ablation in AF patients with drug resistant hypertension in small non-randomized clinical trials (see Table 1).

5.3.2. Ganglionated plexi ablation

Ablation of the ganglionated plexi at the ostium of the pulmonary veins has been shown to reduce AF susceptibility in several large-animal studies [4]. In humans, addition of ganglionated plexi ablation to pulmonary vein isolation conferred a significantly higher success rate compared with either pulmonary vein isolation of ganglionated plexi ablation alone in patients with paroxysmal AF [44–46]. Success rates appear to be better in patients with paroxysmal than persistent AF.

5.3.3. Sympathetic denervation

In patients with paroxysmal AF, unilateral temporary stellate ganglion blockade acutely reduced AF inducibility and decreased AF duration [47].

5.3.4. Vagal nerve stimulation

Vagal nerve stimulation shortens atrial refractoriness and promotes AF [3]. However, low-level vagal nerve stimulation at an intensity which does not reduce heart rate and atrioventricular conduction velocity resulted in a suppression of pulmonary vein firing and AF [4]. Similarly, transcutaneous low-level tragus electrical stimulation suppresses AF and decreases inflammatory cytokines in patients with paroxysmal AF [48].

5.3.5. Baroreceptor stimulation

Carotid baroreceptor stimulation by implantable devices can reduce peripheral sympathetic nervous system activity and arterial pressure [4]. In pigs, baroreceptor stimulation at an intensity used in hypertensive patients resulted in a vagally-mediated shortening in atrial refractoriness and increased AF inducibility. However, low-level BRS reduced AF-inducibility in a pig model of sleep apnea [49].

Sympathetic denervation, vagal nerve stimulation and baroreceptor stimulation are currently largely investigational and randomized controlled clinical studies are warranted to determine the antiarrhythmic effects of these techniques in AF patients.

6. Clinical implications and perspectives

The ANS plays a central pathophysiological role in the initiation and progression of AF. In addition to promoting AF-progression, ANS activation might also determine the presence and severity of AF-related symptoms. For example, impaired baroreflex or carotid sinus sensitivity may explain neurological symptoms such as dizziness, presyncope, or syncope. In support of this hypothesis, amongst patients with paroxysmal AF, impaired baroreflex sensitivity was found to be predictive of quality of life [21]. Additionally, AF patients with syncope show an abnormal neural response whereby the onset of AF may trigger vasovagal syncope [50]. ANS modulation, whether through risk factor management or by interventional strategies, may improve symptom control in addition to maintenance of sinus rhythm.

Despite the evidence presented, there remains uncertainty regarding whether ANS activation in AF patients is just a bystander of more advanced disease or whether it actually represents a modifiable risk factor and viable treatment target. Critically, it is unclear how assessment of the ANS can be optimized in AF patients. Heart rate variability analysis and beat-by-beat analysis of ventricular repolarization (QT interval variability) may allow an estimate of ANS regulation and repolarization lability, although such techniques can be impacted by the presence of AF during the recordings. Additionally, more accurate measures such as transcardiac norepinephrine spillover, muscle sympathetic nerve activity, subcutaneous nerve activity, skin sympathetic activity, and circulating catecholamine levels can provide precise estimates of ANS activation that warrant further investigation. Whether the routine assessment of these parameters results in improved phenotyping or guidance of treatment is currently unknown.

7. Conclusions

Combined sympathetic and vagal activation creates a more pronounced AF substrate than sympathetic or parasympathetic stimulation alone. A bidirectional relationship exists between ANS activation and AF that may further perpetuate the progression of the arrhythmia. In most patients with AF, ANS activity is also contributed by common concomitant risk factors such as hypertension, obesity and sleep-disordered breathing and may depend directly on the number of risk factors and the duration of exposure (risk factor burden). Acute conditions associated with transient increases in ANS activation may contribute to a dynamic arrhythmogenic substrate and provide the trigger and initiator for AF. Combined aggressive risk factor management together with adjunct pharmacological or interventional strategies may provide a strategy to modify the ANS and to reverse the substrate for AF.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.11.091.

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