Atrial fibrillation (AF) is the most common sustained arrhythmia and is associated with significant morbidity and mortality (1). Besides several other mechanisms, such as atrial stretch and atrial structural alterations (2–6), the autonomic nervous system has been considered to contribute to the creation of AF substrates (7). The autonomic nervous system of the heart consists of extrinsic and intrinsic ganglia (8). The parasympathetic components of the extrinsic cardiac nervous system originate in the vagus nerve. The sympathetic components originate primarily in the cervical spinal cord and in the vagus nerve, which contains both sympathetic and parasympathetic fibers (9). Mechanical stress receptors, baroreceptors, and chemoreceptors located in the heart and great vessels modulate autonomic tone (8). Additionally, groups of intrinsic ganglia form a complex neural network composed of ganglionated plexi, which are located in the atria in multiple locations and modulate the interactions between the extrinsic and intrinsic nervous systems (10).

In this review, we discuss the role of the autonomic nervous system on the development of substrates for AF and explore the potential antiarrhythmic effect of modulation of the autonomic nervous system by different approaches.

### Physiology of Afferent Signaling Regulating Autonomic Innervation

The autonomic nervous system is regulated by several mechanisms particularly by afferent signals arising from the kidney, baroreceptors, carotid bodies (CB), and intracardiac ganglionated plexi (GP).

**Renal nerves.** The renal nerves are major regulators of kidney function, volume homeostasis, cardiac output, and blood pressure control (11). Increased efferent nerve activity mediates changes in renal function through innervations of all essential renal structures including the renal vasculature, the tubules, and the juxtaglomerular apparatus resulting in volume retention, sodium reabsorption, reduction of blood flow, and renin-angiotensin-aldosterone system activation (11). The kidney, however, also has an extensive network of afferent unmyelinated fibers that transmit important sensory information to the central nervous system (11). Afferent fibers from the kidney have been shown to travel along with the sympathetic nerves at the level of the kidney and then enter the dorsal roots and project to neurons at both spinal and supraspinal levels. Most of the brainstem regions involved in cardiovascular control including the hypothalamus receive inputs from the renal afferents, which carry information to the central nervous system from renal chemo- and mechanoreceptors (11). Renal afferent nerve activity directly influences sympathetic outflow to the kidneys and to other highly innervated organs involved in cardiovascular control such as the heart and peripheral blood vessels, predominantly by modulating posterior hypothalamic activity (11).

**Carotid baroreflex.** The carotid baroreflex originates mainly from a type of mechanoreceptor (baroreceptors) located in
Carotid bodies. CB are chemoreceptors located on the internal carotids. Afferent nerve external carotid arteries close to the bifurcation with the pressure (13). CB are chemoreceptors located on the internal carotids. Afferent nerve external carotid arteries close to the bifurcation with the pressure (13). A compensating decrease in sympathetic activity and blood by the brain as blood pressure increases, resulting in a compensating decrease in sympathetic activity and blood pressure (13).

Ganglionated plexi. The heart’s intrinsic nervous system consists of ganglia (ganglionated plexi), which contain local circuit neurons of several types and chemo- and mechano-sensory neurons, which are distributed throughout the heart (5). GP are particularly well innervated with both adrenergic and vagal nerve endings and are housed in so-called fat pads, which are mainly located around the pulmonary vein ostia. GP may modulate the interactions and balance between extrinsic and intrinsic cardiac autonomic nervous systems (10) and contain efferent cholinergic and adrenergic neurons influencing the atrial myocardium. Different neuro-modulations (e.g., by spinal cord stimulation) can stabilize local circuit neurons of the intrinsic cardiac system attenuating neuronally mediated atrial arrhythmias (15). Stochastic interactions in intrinsic cardiac local circuit neurons control regional cardiac function and excessive activation of these neurons precedes and persists throughout episodes of atrial fibrillation in dog models (16). Additionally, high-frequency electrical stimulation of autonomic ganglia in the pulmonary vein area led to episodes of AF and atrial tachycardia that could be inhibited by both sympathetic and vagal pharmacological blockade in dogs (17).

Efferent Autonomic Innervation of the Atria

Atrial sympathetic innervation. Sympathetic nerves originate inside the vertebral column, toward the middle of the spinal cord in the lateral horn, beginning at the thoracolumbar region of the spinal cord (levels T1 to L3, specifically), and reach the stellate ganglion (or cervicothoracic ganglion or inferior cervical ganglion) located in front of the neck of the first rib and just below the subclavian artery. At the synapses within the ganglia, preganglionic neurons release acetylcholine, a neurotransmitter that activates nicotinic acetylcholine receptors on postganglionic neurons. In response to sympathetic stimuli, postganglionic neurons release norepinephrine, activating beta-receptors.

Beta-1-receptors compose 70% to 80% of all beta-receptors in the normal atrium. The stimulatory beta-adrenergic response is initiated via G protein subunit alpha complexes (Gα), leading to the activation of adenylyl cyclase and subsequent protein kinase A–mediated phosphorylation of L-type calcium channels, troponin I, and phospholamban, resulting in increased calcium influx. Sarcoplasmic reticulum calcium channels (called ryanodine receptors), release calcium in response to transmembrane calcium entry. Ryanodine receptors are normally closed during diastole but can open if they are functionally defective or if the sarcoplasmic reticulum is calcium-overloaded (5,6,18). Excess calcium is extruded to the extracellular space by the Na+/calcium exchanger. Due to the 3:1 stoichiometry (3 Na⁺ ions are exchanged for 1 Ca²⁺ ion), the Na+/calcium exchanger is electrogenic and produces an inward current that underlies delayed afterdepolarizations–related ectopic firing. Additionally, alpha-adrenergic stimulation inhibits the cardiac transient outward potassium current (Iₒ). On the other hand, beta-adrenergic receptor activation increases L-type calcium current (Iₘ), ultra-rapid delayed rectified potassium current (I₉α), slow delayed rectified potassium current (I₉β) and acetycholine-dependent potassium current (I₉αCh) (5). As a net result of sympathetic stimulation, the plateau potential of the action potential is increased (19,20), while the total action potential duration is unaffected or even decreased (21).

Atrial parasympathetic innervation. The parasympathetic nervous system originates from medial medullary sites (nucleus ambiguous, nucleus tractus solitarius, and dorsal motor nucleus) and is modulated by the hypothalamus. Vagal efferents extend from the medulla to postganglionic nerves that innervate the atria with a neurotransmission that is modulated via nicotinic receptors.
On the cellular level, cholinergic muscarinic receptors (M2R) are the primary mediators of parasympathetic control of heart function. M2R stimulation effects are opposite to those of beta-adrenergic stimulation. M2R stimulation by acetylcholine causes inhibition of adenyl cyclase and reduces cyclic adenosine monophosphate via pertussis toxin-sensitive Gαo proteins, which leads to an attenuated ICaL and hyperpolarization-activated current (Ih). M2R-stimulated Gα also directly activates IKACH, leading to an effective refractory period shortening in the atrium (2–6). The effect of vagal stimulation on atrial refractoriness is homogeneous because of the heterogeneity in the distribution of parasympathetic nerve endings and/or M2R (22). In contrast, the effect of sympathetic stimulation on refractoriness is more homogeneous (22).

**Autonomic Nervous System and Atrial Fibrillation**

Exercise-induced AF may be sympathetically driven; in contrast, the parasympathetic nervous system may contribute to AF in young patients without structural heart disease (23). Several observations suggest that the autonomic nervous system plays an important role in the initiation and the maintenance of AF. Studies in lone AF patients and in animal models of intermittent rapid atrial pacing and congestive heart failure have indicated that AF onset is associated with simultaneous sympathovagal activation rather than with an increase in vagal or sympathetic drive alone (24–28). In animal models and humans, beta-adrenergic agonists (isoproterenol and epinephrine) can induce AF (29,30). Increased AF susceptibility in rats with chronic endurance exercise is caused by vagal promotion and occurs via augmented baroreflex responsiveness and increased cardiomyocyte sensitivity to cholinergic stimulation (31). Interestingly, it has been shown that postoperative AF is more common in patients after lung transplantation than in heart transplant recipients, who have functional pulmonary vein isolation (PVI). Cardiac autonomic denervation, which just occurs in heart transplant patients, might explain reduced post-operative AF (32). Additionally, in a large series of patients after orthotopic heart transplantation, the majority of supraventricular arrhythmias in stable patients can be attributed to macro-re-entrant tachycardias (flutter and scar re-entry). Catheter ablation is effective in management of these arrhythmias. By contrast, AF was never encountered in stable patients in this series (33). Beta-receptor blockade by metoprolol was effective in preventing recurrence of AF after successful cardioversion (34,35).

**Autonomic, Electrical, and Structural Atrial Remodeling**

Figure 1 summarizes the complex interaction between electrophysiological changes induced by autonomic activation, autonomic remodeling, and other AF mechanisms: for example, AF-induced electrical remodeling (electrical loop); triggered activity (trigger loop); and structural changes, such as those due to fibrosis (structural loop).

**Autonomic remodeling.** Sympathetic hyperinnervation is reported in patients with persistent AF (26). A heterogeneous increase in sympathetic innervation in the atria of dogs subjected to rapid atrial pacing for prolonged periods might lead to increased AF susceptibility (25). Ogawa et al. (36) have shown increased sympathetic and vagal nerve discharges before the onset of atrial arrhythmias in dogs with pacing-induced congestive heart failure by direct nerve recordings from the stellate ganglia and vagal nerves. Indeed, the atrial tachyarrhythmias in dogs with pacing-induced congestive heart failure were prevented by prophylactic ablation of the stellate ganglion and the T2 to T4 thoracic sympathetic ganglia (36). In the same model of pacing-induced congestive heart failure, Ng et al. (24) recently demonstrated increased sympathetic and parasympathetic nerve growth in the left atrium; nerve growth was most pronounced in the pulmonary veins and the posterior wall of the left atrium.

**Electrical remodeling.** AF itself causes shortening of atrial refractoriness, thereby contributing to the progression from paroxysmal to more persistent forms of AF (AF begets AF), early AF recurrence after cardioversion, and progressive drug resistance of longer-lasting AF (2–6). Calcium enters atrial cells with each action potential. During rapid atrial rates, increased calcium loading initiates autoregulatory mechanisms that reduce calcium entry by calcium current inactivation and L-type calcium current down-regulation. This results in decreased calcium loading and a shortening of the action potential duration leading to a stabilization of re-entry circuits perpetuating AF (2–6) (electrical remodeling). Additionally, the high calcium load in the atrial cardiomyocytes results in an increased spontaneous release of calcium from the sarcoplasmic reticulum leading to atrial ectopies (trigger loop), potentially initiating and perpetuating AF (2–6).

Interestingly, the cardiac autonomic system plays a role for the acute atrial electrical remodeling during atrial tachypacing as shortening in the atrial effective refractory period (AERP) could be inhibited by GP ablation (37). Electrophysiological changes induced by autonomic activation might also occur during several pathophysiological conditions. Simulated obstructive apneas in a pig model led to pronounced shortening of atrial refractoriness and increased AF inducibility, which was mainly mediated by combined sympathovagal activation (38,39). Additionally, forced inspiration–induced acute atrial distension causes an arrhythmogenic atrial electrical remodeling in a rat model for obstructive sleep apnea (OSA), which was partly prevented by combined autonomic blockade (40). In a dog model for central sleep apnea, GP-ablation inhibited AF inducibility (41).

**Structural remodeling.** Structural remodeling is characterized by increased atrial fibrosis formation and cardiomyocyte hypertrophy. Atrial tissue fibrosis impairs electrophysiological cell-to-cell coupling and conduction...
Long-term AF leads to myocyte hypertrophy and increased endomysial fibrosis associated with dissociated conduction and electrical dissociation between the epicardial layer and the endocardial bundle network that contributes to the development of permanent forms of AF (42,43). Besides AF itself, other conditions can cause structural alterations in the atrium. Long-term hypertension leads to electro-structural changes characterized by conduction abnormalities, atrial inflammation and fibrosis, and increased AF inducibility (44). Congestive heart failure is associated with the development of structural remodeling characterized by increased fibrosis formation and alterations in gap junction expression promoting heterogeneity of conduction and pathways, facilitating micro-re-entry and macro-re-entry (45). Long-term OSA is associated with significant atrial remodeling characterized by atrial enlargement, site-specific and widespread conduction abnormalities, and longer sinus node recovery in humans (46).

Taken together, atrial structural changes with autonomic remodeling and acute electrophysiological changes induced by autonomic activation may play a significant role in the creation of AF substrates.

**Different Modalities to Influence the Autonomic Nervous System**

Modulation of the autonomic nervous system might be a promising strategy to protect the myocardium from proarrhythmic autonomic influences and the development of electrical, autonomic, and structural atrial remodeling. Possible targets are summarized in Figure 2.

**Renal sympathetic denervation.** Catheter-based renal sympathetic denervation (RDN) significantly lowers blood pressure in patients with therapy-resistant hypertension (47,48). Mechanistically, it has been observed that the procedure resulted in a 47% reduction of renal norepinephrine spillover measured with a radiochemical tracer methodology using 3H-norepinephrine (47,48), as well as in a 37% reduction in firing of single sympathetic vasoconstrictor fibers, measured by single-muscle sympathetic nerve
activity (49). These findings indicate a combined modulation of efferent and afferent signaling at the kidney by RDN.

Effects of RDN on cardiac electrophysiology have already been shown in animal models and humans. RDN results in a reduction in heart rate and atrioventricular-conduction velocity in humans (50). The effect of RDN on atrial electrophysiology was investigated in chloralose/urethane anesthetized pigs. Neither AERP nor P-wave duration were influenced by RDN excluding relevant changes in atrial refractoriness and atrial conduction (51). Additionally, sensitivity of GP (38) was not modulated by RDN. In a pig model for obstructive sleep apnea, shortening in AERP (38), acutely induced by applied negative thoracic pressure, was mainly mediated by combined sympathovagal activation, because it could be influenced by atropine, bilateral vagotomy, or beta-receptor blockade (38,39). Compared with beta-blocker treatment, RDN resulted in an even more pronounced attenuation of AERP shortening during negative thoracic pressure, which might explain the superior antiarrhythmic effect of RDN compared with beta-blocker therapy in this animal model (39) (Fig. 3). Importantly, clinically used antiarrhythmic drugs such as amiodarone or sotalol displayed a considerably less-pronounced antiarrhythmic effect than did RDN in the same pig model for OSA (52). Additionally, in an AF pig model with rapid atrial pacing, RDN also showed antiarrhythmic effects. RDN reduced duration of pacing-induced AF. However, AF-induced electrical remodeling was not attenuated (51). Interestingly, in humans with AF as well as in anesthetized pigs with AF induced by rapid atrial pacing, RDN reduces heart rate during AF, which might reduce clinical symptoms in patients with AF (51) (Fig. 4). In a small study in humans, the atrial antiarrhythmic effects of circumferential PVI combined with RDN were investigated (53) (Fig. 5). Patients who received both procedures showed significant reductions in average systolic and diastolic blood pressure, whereas those in the PVI-only group did not show any significant improvement in blood pressure (53). At the 1-year follow-up, 69% of patients who received both procedures no longer had AF recurrences, compared with 29% of those in the PVI-only group (53). In a case report, even RDN without PVI reduced blood pressure and attenuated paroxysmal AF episodes, which were symptomatic and drug-resistant before RDN (54).

Potentially, RDN might display antiremodeling effects by a variety of mechanisms. Hypertension, diabetes, and OSA are associated with early and progressive changes in atrial remodeling characterized by structural and electrophysiological remodeling (55). Modulation of autonomic nervous system by RDN has been shown to reduce blood pressure (47,48), which was associated with reduction of left ventricular mass (56) and improvement of arterial stiffness.

**Figure 2** Complex Neural Interaction Between Central Nervous System and Peripheral Organs

The efferent sympathetic fibers (blue), afferent sympathetic fibers (red), nervus vagus (yellow), and afferent parasympathetic fibers (green) are shown. Different strategies to modulate the autonomic nervous system are depicted (stimulation, inhibition; AP = action potential) (for a further explanation, see text). Figure by Craig Skaggs.
and central hemodynamics (57) in patients with resistant hypertension. That regression of electrocardiographic left ventricular hypertrophy is associated with decreased incidence of new-onset AF in patients with hypertension, which has already been shown in a recent study (58). Additionally, RDN has been shown to reduce sleep apnea severity (59) and improve glucose metabolism and insulin sensitivity (60) in patients with drug-resistant hypertension. Therefore, RDN might reduce arrhythmogenic atrial autonomic signaling and structural alterations. However, whether RDN has an antiarrhythmic effect beyond normalization of blood pressure remains to be determined. In ongoing studies on RDN, the development of AF and of atrial structural remodeling should be closely monitored.

Ganglionated plexi ablation. GP may modulate the interactions between the systemic and intrinsic cardiac autonomic nervous systems and contain efferent cholinergic and adrenergic neurons. In large-animal studies, ablation of the autonomic ganglia at the base of the pulmonary veins has been shown to contribute to the effectiveness of PVI in vagally induced AF and has also been shown to eliminate rapid pulmonary vein firing in response to GP high-frequency stimulation (61). In a dog model for central sleep apnea, GP ablation inhibited AF inducibility (41). GP ablation, alone or with PVI, has been used in patients with both paroxysmal and persistent AF with variable success, although success rates appear to be better in patients with paroxysmal than persistent AF (62–64). The comparison of GP ablation plus PVI versus PVI alone was investigated by Katritsis et al. (64) in a randomized controlled trial. They demonstrated that GP ablation significantly improved success rates after PVI compared to PVI alone. Although autonomic denervation of the atria by GP ablation may lower recurrence rates, particularly after PVI, recent studies in dogs suggest that GP ablation after acute myocardial infarction increases the risk of ventricular arrhythmias compared with GP ablation of the normal heart (65). This potential ventricular arrhythmogenic effect of GP ablation under certain conditions needs to be evaluated in future studies in more detail.

Ganglion stellatum ablation. The stellate ganglion (or cervicothoracic ganglion) is a sympathetic ganglion formed by the fusion of the inferior cervical ganglion and the first thoracic ganglion. Myocardial infarction results in persistent increase in synaptic density of bilateral stellate ganglia and is associated with increased stellate ganglionic nerve activity indicating remodeling of the extracardiac autonomic nerve activity and structure (66). Left cardiac sympathetic denervation (surgical excision of stellate ganglion, together with the second and third thoracic ganglia) reduces arrhythmia in high-risk patients and dogs following myocardial infarction (67,68), patients with long-QT syndrome (69), and patients
with catecholaminergic polymorphic ventricular tachycardia (69). Cryoablation of bilateral stellate and T2 to T4 thoracic ganglia reduced paroxysmal AF induced by sympathetic discharges in dogs with pacing-induced congestive heart failure (70). Despite potential antiarrhythmic effects by left cardiac sympathetic denervation, incidence of procedure-associated complications such as Horner syndrome is <1% and usually temporary if only the lower half of the stellate ganglion is removed. Furthermore, sympathectomy has been a treatment option for refractory angina.

**High thoracic epidural anesthesia.** High thoracic epidural anesthesia reduced afferent and efferent sympathetic nerve impulses to the heart. The overall reduction of sympathetic tone and block of the cardiac fibers by high thoracic epidural anesthesia was observed in patients during cardiac surgery and cardiopulmonary bypass (71,72). In patients with refractory electrical storm, initiation of high thoracic epidural anesthesia was associated with a subsequent decrease in arrhythmia burden (73). In a dog model with rapid atrial pacing, high thoracic epidural anesthesia prevented sustained AF. This was associated with inhibition of atrial autonomic nerve sprouting (74). A meta-analysis showed that the use of high thoracic epidural anesthesia in patients undergoing cardiac surgery reduces the risk of post-operative supraventricular arrhythmias (75). However, at least 2 trials were not able to show decreased incidence of post-operative sustained AF despite a significant reduction in sympathetic activity (76,77). The definite effect of high thoracic epidural anesthesia on atrial electrophysiology and arrhythmogenesis needs to be determined in future studies.

**Low-level vagal nerve stimulation.** Vagal stimulation leads to M2R-mediated activation of atrial IKACh, leading to a potent effective refractory period shortening that promotes atrial arrhythmias (2–6). However, low-level vagal nerve stimulation not resulting in reduction of heart rate and atrioventricular conduction has been shown to result in antiarrhythmic effects. The initial observation was that intravenous phenylephrine increased blood pressure and initiated a baroreflex independent of heart rate reduction. This resulted in a suppression of pulmonary vein firing in patients (78) and resulted in a reduction of rapid atrial firing and AF (79). The antiarrhythmic effects have been shown to involve nitric oxide signaling pathways (80) and vasostatin-1 signaling (81).

**Baroreflex stimulation.** Implantable devices for carotid baroreceptor stimulation (BRS) produce an electric field stimulation of the carotid sinus wall (82) resulting in a sustained reduction in peripheral sympathetic nervous system activity and blood pressure (83,84). Significant improvements were observed in left atrial and left ventricular structure and function after chronic BRS in patients with resistant hypertension (85). However, BRS modulates autonomic balance not just by sympathetic withdrawal, but also by increased vagal activation, finally resulting in reduced total body sympathetic drive (86,87). Reduced sympathetic drive is generally considered to result in an atrial antiarrhythmic effect. In contrast, it could be speculated that increased vagal tone, as associated with BRS, could potentially shorten atrial refractoriness, thereby increasing the vulnerable phase, resulting in stabilization of re-entry circuits perpetuating AF (2–7). This is in contrast to the ventricle, where the parasympathetic nervous system appears to be protective against arrhythmias (88). In normotensive

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![Figure 4 Effect of RDN on Atrial and Ventricular CL After RDN or Sham Procedures](Image)

Rapid pacing induced AF without changing the atrial cycle length (CL) (A), but significantly prolonging the ventricular CL (B). This provides evidence for improved rate control after induction of AF. Abbreviations as in Figures 1 and 3. Modified with permission from Linz et al. (51).

![Figure 5 Incidence of AF Recurrences in Patients With and Without Renal Denervation](Image)

The group that underwent both pulmonary vein isolation (PVI) and renal denervation has a significantly reduced atrial fibrillation (AF) recurrence rate over time compared with the control PVI-only group. AT = atrial tachyarrhythmia. Modified with permission from Pokushalov et al. (53).
anesthetized pigs, electrical BRS at an intensity used in hypertensive patients resulted in a pronounced shortening in atrial refractoriness that was associated with a pronounced increase in AF inducibility (89). Interestingly, low-level BRS atropine (Fig. 6B). Whether chronic low-level BRS results in antirhythmic effects, as shown for low-level vagal nerve stimulation, needs to be investigated in future studies. In ongoing studies on BRS, development of AF should be closely monitored, especially in patients with structurally remodeled atria.

**Carotid body ablation.** In rats with intermittent hypoxia, surgical denervation of peripheral chemoreceptors prevented the hypertensive response to hypoxic stimuli (90). Carotid sinus denervation (denervation of both carotid body and carotid sinus baroreceptors) prevented the development of hypertension in young pre-hypertensive spontaneously hypertensive rats and significantly decreased arterial pressure in adult hypertensive spontaneously hypertensive rats (91) and hypertensive humans (92). Chemoreflex sensitivity is enhanced in rabbits with pacing-induced congestive heart failure (93), potentially increasing central sympathetic drive.

Up to now, there are no studies characterizing the effects of CB denervation on atrial electrophysiology and the occurrence of atrial arrhythmia. However, reduction in systemic autonomic tone and blood pressure might reduce arrhythmogenic atrial autonomic signaling and attenuate atrial structural alterations.

**Conclusions and Perspectives**

Available data indicate that autonomic influences contribute to the creation of AF. Therefore, modulation of the autonomic nervous system is a promising strategy for antiarrhythmic treatment. However, different modalities approach the problem differently, making the prediction of arrhythmogenic and/or antiarrhythmic effects difficult. Autonomic denervation of the atria by GP ablation might lower recurrence rates, particularly after circumferential PVI in patients with AF. High thoracic epidural anesthesia may play a role in post-surgery AF management. The antiarrhythmic effects of CB denervation and BRS are unknown and need to be investigated in future studies. Modulation of the autonomic system by RDN already showed promising results in animal models and humans. Randomized trials are required to investigate the definite effect of the different strategies on atrial arrhythmogenesis.

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