Autonomic and surgical substrate modulation of atrial fibrillation

Krul, Sébastien

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Chapter 2

Treatment of atrial and ventricular arrhythmias through autonomic modulation

SPJ Krul, WR Berger, MW Veldkamp, AHG Driessen, AAM Wilde, T Deneke, JMT de Bakker, R Coronel and JR de Groot

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ABSTRACT

This paper reviews the contribution of autonomic nervous system (ANS) modulation in the treatment of arrhythmias. Both the atria and ventricles are innervated by an extensive network of nerve fibers of parasympathetic and sympathetic origin. Both the parasympathetic and sympathetic nervous system exert arrhythmogenic electrophysiological effects on atrial and pulmonary vein myocardium, while in the ventricle the sympathetic nervous system plays a more dominant role in arrhythmogenesis. Identification of ANS activity is possible with nuclear imaging. This technique may provide further insight in mechanisms and treatment targets. Additionally, the myocardial effects of the intrinsic ANS can be identified through stimulation of the ganglionic plexuses. These can be ablated for the treatment of atrial fibrillation. New (non-) invasive treatment options targeting the extrinsic cardiac ANS, such as low-level tragus stimulation and renal denervation, provide interesting future treatment possibilities both for atrial fibrillation and ventricular arrhythmias. However, the first randomized trials have yet to be performed. Future clinical studies on modifying the ANS may not only improve the outcome of ablation therapy but may also advance our understanding of the manner in which the ANS interacts with the myocardium to modify arrhythmogenic triggers and substrate.
The atria and ventricles are innervated by an intricate network of autonomic nerves.\(^{1,2}\) The role of the sympathetic and parasympathetic nervous system in the pathophysiology of cardiac arrhythmias is complex. Parasympathetic and sympathetic activation influence atrial and ventricular electrophysiology and these changes can initiate, facilitate, or counteract cardiac arrhythmias depending on the presence of a suitable substrate.\(^{3,4}\) By selectively ablating or stimulating the different components of the autonomic nervous system (ANS), such as ganglionic plexuses (GPs) or the vagal nerve, the net activity of the ANS can be modulated and arrhythmias treated.\(^{5,6}\) Here, we briefly review the role of the ANS as trigger and modulator of cardiac arrhythmias. Notably, we focus on novel methods to clinically identify the cardiac ANS and we discuss autonomic modulation as treatment for cardiac arrhythmias.

**ANATOMY OF THE CARDIAC ANS**

In the human heart, the extrinsic sympathetic innervation is mediated via the cervical, stellate (cervicothoracic), and thoracic ganglia. Parasympathetic extrinsic innervation is routed via the vagus nerve, although sympathetic fibers are found in vagal nerves and parasympathetic fibers in sympathetic nerves as well.\(^{7,8}\) The extrinsic nerves pass through the hilum of the heart along the great cardiac vessels and branch into 7 epicardial subplexuses, the intrinsic neural pathways of the ANS.\(^{1}\) Small nerve fibers form an extensive neural network of small interconnecting efferent and afferent sympathetic, parasympathetic, and mixed nerve fibers, that contain the neurotransmitters noradrenaline and acetylcholine, respectively, but some also contain neuropeptide Y, somatostatin, vasoactive intestinal polypeptide, and substance P.\(^{2,9–12}\) The density of small fibers and ganglia is highest in the posterior part of the left atrium and around the antrum of the (left) pulmonary veins (PVs).\(^{11,13}\) The atria are predominantly parasympathetically innervated, while in the ventricles (where only 16% of total cardiac ganglia reside) predominantly sympathetic nerve fibers are found.\(^{1,14,15}\) GPs are conglomerates of ganglia from different subplexuses and function as an integration center of the parasympathetic and sympathetic nerves and interconnect the intrinsic ANS.\(^{9,16,17}\) The atrial GPs are located near the sinus node and PVs and reside in epicardial fat pads as shown in Figure 1. Ventricular GPs are located near the interventricular groove.\(^{9}\) The ligament of Marshall, the embryonic remnant of the left superior caval vein, near the left superior PV is densely innervated with parasympathetic and sympathetic nerves.\(^{18,19}\)
Figure 1. – Anatomy of the intrinsic autonomic nervous system. Pauza et al. have shown an extensive network of epicardial nerves on the atria and ventricles divided in 7 subplexus (A). Right is a posterior and left is an anterior view of the heart. Along these subplexus, ganglia are localized, conglomerated in ganglion plexus (GP) marked in light gray. Armour et al. (B) identified the major atrial and ventricular GP from a posterior view of the heart. A is reprinted with permission from Pauza et al.; B is reprinted with permission from Armour et al.

AUTONOMIC MODULATION IN ATRIAL FIBRILLATION

The atrial susceptibility to autonomic nervous modulation relates to the high density of autonomic nerves and the presence of acetylcholine sensitive potassium channels. The influence of the intrinsic ANS on the atrium was reviewed by Stavrakis et al. recently.

Trigger modulation

In the study of Choi et al., atrial fibrillation (AF) and atrial arrhythmias (induced by rapid atrial pacing) were always preceded by activation of the intrinsic ANS in dogs, but no intracardiac recordings were made to localize the origin of AF. In patients, PV ectopy, most frequently arising in the superior PVs, commonly triggers paroxysmal AF. Animal and human studies have shown that stimulation of the GPs near the PV triggers PV ectopy. Patterson et al. demonstrated that decreased action potential duration was mediated by the parasympathetic system, and that the sympathetic system increased myocardial cytoplasmatic $[Ca^{2+}]$. The combination of both components was required for early afterdepolarizations in the PVs, which in turn triggered AF. In right atrial tissue a similar protocol did not yield arrhythmias. A high degree of autonomic innervation near the PVs and a shorter action potential duration in PV myocytes than in atrial myocytes might underlie these findings. Ectopic activity in other highly innervated structures, such as the ligament of Marshall, may also trigger AF. Stimulation of the ligament of Marshall caused ectopy and triggered AF in 8 AF patients during catheter ablation. However, triggers of AF are not confined to highly innervated tissue. In 27% of 987 patients with repeat ablation after a first PV isolation had been unsuccessful, with predominantly nonparoxysmal AF, ectopic firing from the left atrial appendage was observed. It is unknown whether this trigger mechanism is different from patients with AF not previously treated or whether non-PV triggers remain once PV triggers are excluded after ablation.

Substrate modulation

The perpetuation of AF requires an arrhythmogenic substrate suitable for reentry or the presence of a continuous trigger. A short effective refractory period, heterogeneity in repolarization, or slow conduction constitute the main determinants for reentry. Vagal stimulation shortens the effective refractory period in rapid pacing induced AF models in dogs and creates a functional substrate for AF. In addition, repolarization becomes more heterogeneous, most likely due to the heterogeneous nature of parasympathetic innervation. In canine atria, AF was induced after superfusion with a combination of isoprenaline and acetylcholine. Isoprenaline facilitated initiation and maintenance of acetylcholine induced AF through a decreased AF threshold (lowering the acetylcholine dose required to induce AF). The ANS not only affects repolarization,
but also conduction properties. In patients, GP stimulation has been shown to affect activation time.\textsuperscript{33,34} GP stimulation activates all nerves present in the GP and is therefore not specific for 1 arm of the ANS, but conduction slowing was particularly evident in patients using beta-blockers.\textsuperscript{33} Conduction slowing by acetylcholine could be attributed to a reduced excitability, but a role of noncholinergic neurotransmitters released upon vagal stimulation cannot be excluded.\textsuperscript{35} In dogs, vasoactive intestinal polypeptide induced conduction slowing in a dose-dependent manner.\textsuperscript{36} ANS-mediated conduction changes might cause or increase fractionation in atrial electrograms with or without the presence of a suitable structural substrate such as fibrosis.\textsuperscript{37,38}

**Autonomic Remodeling**

Most of the data on autonomic modulation come from healthy tissue, frequently from animal studies, with only short-term remodeling.\textsuperscript{3,32} In most cardiac patients, the myocardium is electrically, structurally, and autonomically remodeled for a long period. Autonomic remodeling may change the response to ANS stimulation and (the balance of) the para- and sympathetic innervation.\textsuperscript{39-41} Increased sympathetic nerve and beta-adrenergic receptor density was observed in dogs with heart failure together with increased acetylcholinesterase activity and less shortening of effective refractory period on vagal stimulation.\textsuperscript{41} In rapid pacing AF models in dogs, parasympathetic and sympathetic nerve density was increased.\textsuperscript{42} An increase of sympathetic nerve density has been described in human chronic AF patients, but whether this is compensatory to increased vagal stimulation or causal for AF is unknown.\textsuperscript{12,43}

**AUTONOMIC MODULATION IN VENTRICULAR ARRHYTHMIAS**

In acute myocardial infarction, a high heart rate is an important risk factor for arrhythmias.\textsuperscript{44} Not only is it a marker of a high sympathetic tone, but a high heart rate increases ventricular oxygen demand and has important proarrhythmic effects such as a decreased action potential duration and increased myocardial cytoplasmatic [Ca\textsuperscript{2+}].\textsuperscript{45} Heart rate variability has been used as an indirect measure of autonomic balance and is significantly associated with the risk of life threatening arrhythmias.\textsuperscript{46} Additionally, a high sympathetic tone during myocardial infarction leads to vasoconstriction and increased infarct size.\textsuperscript{47} However, the sympathetic nervous system also exerts an arrhythmogenic effect independent of heart rate. Evidently, ventricular arrhythmias in the setting of inherited arrhythmia syndromes such as catecholaminergic polymorphic ventricular tachycardia (VT) are entirely dependent on sympathetic activity.\textsuperscript{48} Furthermore, QT interval and QT dispersion are markedly increased upon infusion of epinephrine (but not phenylephrine)
in patients with Long QT syndrome 1 compared to healthy controls, underscoring the arrhythmogenic potential of the sympathetic ANS.49

**Trigger modulation**

Experimental data suggest a role of triggered activity in ANS-mediated ventricular arrhythmias, although there is limited data from clinical studies. For example, in 20 dogs treated with cesium-chloride to prolong QT time, left stellate ganglion stimulation caused early afterdepolarizations.50 Left stellate ganglion stimulation decreased action potential duration and elicited delayed afterdepolarizations in 10 of 14 cats.51 Early afterdepolarizations were also elicited in isolated ventricular cardiomyocytes from failing human hearts after superfusion with noradrenaline.52 The contribution of triggered activity to ventricular arrhythmias in patients with myocardial infarction is unknown.53

**Substrate modulation**

Sympathetic stimulation either shortens or prolongs the ventricular effective refractory period, depending on species and comorbidities. For instance, in a study on dogs, the ventricular effective refractory period was prolonged after vagal stimulation and shortened after sympathetic stellate ganglion stimulation.4 Indeed, stellate ganglion stimulation reduced ventricular fibrillation (VF) intervals in dogs on cardiopulmonary bypass.54 Interestingly, these effects were heterogeneous, with differences upon right or the left stellate ganglion stimulation, and with marked individual variation. Therefore, sympathetic stimulation can facilitate reentry not only through shortening of effective refractory period but also through increased repolarization heterogeneity.47,54–56 Although parasympathetic nerves are not abundantly present on the ventricle, they may partially and regionally antagonize the effects of the sympathetic nervous system.4,57

**Autonomic remodeling**

In addition to electrical and structural remodeling of the ANS, the sympathetic branch in particular remolds following myocardial infarction.58 The density of synapses and nerves and nerve activity of the left stellate ganglion increased in dogs with myocardial infarction.59 These remote changes preceded increased ventricular myocardial sympathetic innervation.60 In transplanted human hearts an increased density of sympathetic nerves was found in patients with a history of ventricular arrhythmias.61 Heterogeneity in sympathetic innervation due to denervation in infarcted areas induced supersensitivity, resulting in increased shortening of the effective refractory period during sympathetic stimulation.62 This may increase vulnerability to ventricular arrhythmias during ischemia.63
IDENTIFICATION OF ANS ACTIVITY

Noninvasive methods to identify autonomic activity are limited. The exception is heart rate variability, which has been extensively studied as a marker for autonomic activity and balance but this parameter only supplies information on sinus node innervation and does not reflect the extrinsic and intrinsic nerve activity. The activity from the postganglionic nerve fibers in skin and muscle appears to accurately reflect central sympathetic activity more sensitively than heart rate variability in dogs, but this option has to prove its clinical value. Computed tomography and magnetic resonance imaging have been of great value in demonstrating the structural substrate of cardiac arrhythmias, but are of limited value in the identification of the ANS. Currently, only iodine-123 metaiodobenzylguanidine (123I-MIBG) imaging provides information on the sympathetic ANS and has been extensively studied in patients with ventricular arrhythmias.

123I-MIBG Imaging

123I-MIBG imaging assesses sympathetic nerve distribution and quantifies local noradrenaline reuptake and sympathetic activity. A lower heart/mediastinum 123I-MIBG ratio, represents increased sympathetic neurotransmitter reuptake activity. A high sympathetic activity on 123I-MIBG imaging predicted progression to permanent AF during a mean follow-up of 4 years or correlated with increased recurrences of AF after ablation. However, 123I-MIBG imaging lacks the resolution for assessment of local atrial innervation and denervation. Therefore, its application might be limited in unselected populations with atrial arrhythmias. There is an association between increased sympathetic activity on 123I-MIBG imaging and the increased risk of recurrent ventricular arrhythmias in patients with structural heart disease, as in patients with myocardial infarction. Similar observations were made in patients with VT and apparent normal structural hearts. These patients present either a subgroup of patients at high risk or a group of patients with a cardiac disease before it is clinically detectable. Defects in sympathetic innervation can be assessed and neural activity can be compared with perfusion images from single-photon emission computed tomography scanning. Sympathetic denervation on 123I-MIBG scans has a high accuracy in predicting arrhythmic events in implantable cardioverter-defibrillator patients and patients with previous ventricular arrhythmias. In the ADMIRE-HF (AdreView Myocardial Imaging for Risk Evaluation in Heart Failure) trial, a low 123I-MIBG heart/mediastinum ratio (<1.6) was associated with an increased risk for cardiac arrhythmias in patients with heart failure and a left ventricular ejection fraction of ≤35%. However, sympathetic denervation per se did not predict cardiac events, potentially because these patients had no prior ventricular arrhythmias. Therefore, the heart/mediastinum ratio is useful only in selected patient populations to identify risk for future arrhythmic events. Klein et al. investigated the use of 123I-MIBG acquired
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denervation maps in combination with voltage maps for the ablation of ventricular arrhythmias. In this study the denervation maps were larger than the scar areas and VT ablation sites were located in the areas of abnormal innervation. However, the VT recurrence rate of 43% after 6 months was similar to conventional treatment (not guided by $^{123}$I-MIBG- single-photon emission computed tomography). This study is of interest because it looked beyond structural substrate ablation toward autonomic modulators in ablation of ventricular arrhythmias. Thus, clinical validation of $^{123}$I-MIBG single-photon emission computed tomography derived parameters in different patient populations with different risk profiles is needed.

Cardiac ANS localization

GPs may be a target for ablation, and thus it is important to identify their location. Endocardial stimulation of atrial GPs with high frequency stimulation induces a vagal reaction, reflected in a R-R interval prolongation of >50%. Right atrial GP ablation attenuates this vagal response, as it is predominantly mediated by the anterior right GP on the sinus node and by the inferior right GP on the AV node. Thus, absence of an increase in R-R interval of 50%, only proves a loss of innervation of the sinus node or AV-node and not the dysfunction or destruction of the GPs per se. Therefore, absence of increase in R-R interval upon high frequency stimulation is an unreliable endpoint of successful ablation of the GPs. A randomized study in 80 patients showed that an anatomical rather than a functional (eliciting a vagal response) approach toward atrial GP localization and ablation led to more favorable results (77.5% vs. 42.5% absence of AF, 13.1 ± 1.9 months follow-up) (Figure 2). Despite high success rates for GP ablation compared to other studies, the data suggest that anatomical localization and ablation of the GPs might be superior. An anatomical epicardial approach of ablation, as with thoracoscopic surgery allows clear visualization of epicardial fat pad in which the atrial GPs reside. Areas of complex fractionated atrial electrograms, defined as low-voltage multiple potential bipolar atrial electrograms with a high degree of fractionation are found around the anatomical locations of the GPs. They may represent a dynamic substrate driven by both parasympathetic and sympathetic innervation, and are often identified to guide ablation procedures in patients with AF. However, complex fractionated atrial electrograms are not a specific marker of the ANS but an electrophysiological representation of structural, electrical and autonomic remodeling resulting from a variety of pathophysiologic conditions.
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**ThERAPEUTIC MODULATION OF THE INTRINSIC ANS**

**Pharmacological GP modulation**

Direct injection of botulinum toxin, a cholinergic blocker, in epicardial fat pads containing the GPs, temporally suppressed AF inducibility in dogs 87 (Central Illustration). In a small pilot study in patients undergoing coronary artery bypass surgery botulinum toxin injection resulted in less post-operative AF (7% vs. 30%). 88 Larger studies are needed to confirm this finding. Yu et al. 89 delivered a neurotoxin N-isopropyl acrylamide monomer to the GPs using iron-core nanoparticles, both after direct injection and intracoronary infusion. Nanoparticles injected into the anterior right GP resulted in a reduced sinus node response upon GP stimulation and increased AF threshold. The nanoparticles were magnetically directed to the inferior right GP using a large magnet and resulted in a reduced ventricular rate response upon GP stimulation. This proof-of-concept study demonstrates that it is possible to selectively target the intricate neural network, although clinical application has to be awaited.
Central Illustration - Targets of autonomic nervous system modulation for treatment of cardiac arrhythmias. A schematic representation of the extrinsic and intrinsic autonomic nervous system. The different targets for autonomic nervous system modulation in the treatment of cardiac arrhythmias are shown.

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**GP Ablation**

GP ablation additional to PV isolation (PVI) (but not as a stand-alone procedure) appears to improve procedural efficacy (Central Illustration). Combined PVI and GP ablation resulted in a 74% success rate in patients with paroxysmal AF compared to 56% and 48% in GP ablation and PVI alone, respectively, after 2 years of follow-up. The effects may be due to prevention of PV ectopy through GP ablation and PVI, although it cannot be excluded that GP ablation involves more extensive left atrial myocardial ablation. This alone, even without the involvement of ANS modulation, might have contributed to the added effect of GP ablation and makes the potential beneficial effect of GP ablation uncertain. Compared to endocardial ablation, where the delivered energy may not always reach the epicardially located fat pads, the epicardial approach through thoracoscopic surgery allows visualization of GPs and more effective ablation of a larger part of the epicardial neural network. However, regardless of the approach to GP ablation, partial recovery of GPs function has been observed, which may limit the long-term procedural effect. This might be due to reinnervation by efferent nerves or through neural remodeling, leading to increased sensitivity to the remaining neural stimulation or both. Ablation of GP may not be harmless. He et al. reported an increased incidence of myocardial ischemia induced VF after atrial GP ablation in dogs, potentially due to attenuated parasympathetic tone. Few data exist of GP modulation of ventricular arrhythmias. Stimulation of the GPs in dogs has been reported to decrease the incidence of ventricular arrhythmias, which may relate to parasympathetic effects indirectly modifying sympathetic activity. However, selective ablation of ventricular GPs has not been studied.

**THERAPEUTIC MODULATION OF THE EXTRINSIC ANS**

Modulation of the extrinsic ANS, mainly stellate ganglion ablation, has been applied for VF. Recently, there have been a number of studies investigating the extrinsic ANS for the treatment of AF (Central Illustration). However, most data are derived from animal studies and await clinical confirmation of efficacy and safety.

**Stellate ganglion ablation**

Modification of the sympathetic tone through ablation of the stellate ganglion reduces ventricular arrhythmias. In patients with recurrent multiple VF episodes after myocardial infarction sympathetic blockade, either with stellate ganglion ablation or with beta-blockers, increased survival compared to standard antiarrhythmic drugs. Additionally, stellate ganglion ablation has been applied in patients with inherited arrhythmia disorders with drug resistant sympathetically induced arrhythmias, such as long QT
syndrome and catecholaminergic polymorphic VT.\textsuperscript{103,104} Although highly successful, stellate ganglion ablation surgery may lead to surgical complications and denervation is not always complete.\textsuperscript{103,104} There are no reports on stellate ganglion ablation for the treatment of atrial arrhythmias in humans. However, in a study with 6 dogs with pacing-induced heart failure, left and right paravertebral T2 to T4 thoracic sympathetic ganglion ablation reduced the number of atrial tachycardia episodes compared to a control group without stellate ganglia ablation.\textsuperscript{105}

**Spinal cord stimulation**

Spinal cord stimulation (SCS) of T1 to T5 with an external stimulator appears to modulate autonomic activity, possibly via inhibition of the stellate ganglion, but a role for increased vagal activity has been reported as well.\textsuperscript{106,107} This discrepancy may be related to the level (T1 to T5) of SCS. Antiarrhythmic effects in both atrial and ventricular arrhythmias have been described in canine studies. In canine AF tachypacing models SCS was able to reduce AF burden and inducibility.\textsuperscript{108} No effect was observed if SCS was initiated 8 weeks after tachypacing was started. SCS decreased the occurrence of ischemia-induced ventricular arrhythmias via an anti-sympathetic action in dogs with healed myocardial infarctions.\textsuperscript{109,110} Interestingly, in animals using beta-blockers there was an additional antiarrhythmic effect of SCS, which suggests that SCS is not limited to the reported anti-sympathetic effects.\textsuperscript{110} Similarly, SCS led to fewer ventricular arrhythmias and reduced heart rate variability and left stellate ganglion activity in acute myocardial infarction.\textsuperscript{107} In 2 patients with a cardiomyopathy and high burden of ventricular arrhythmias SCS reduced VT and VF episodes up to 75\% to 100\%.\textsuperscript{111} The mechanism of SCS is not completely understood, and long term clinical effects and safety have never been studied in patients with arrhythmias.

**Vagal nerve stimulation**

Stimulation of the cervical vagosympathetic trunks can antagonize the pro-arrhythmic sympathetic surge during acute myocardial infarction. Indeed, high-intensity vagal stimulation during myocardial infarction resulted in 71\% VF free survival versus 40\% with low intensity and 10\% with no vagal stimulation. During ventricular pacing to exclude heart rate effects, less VF occurred, suggesting a protective effect of the vagal stimulation beyond heart rate reduction.\textsuperscript{112} Vagal stimulation shortly after onset of myocardial ischemia also decreased VF incidence (from 92\% to 10\%) in dogs with prior myocardial infarction.\textsuperscript{113} Although vagal stimulation has pro-arrhythmic effects in the atria because of the presence of acetylcholine sensitive ion channels, discrete modulation of vagal tone with low-level vagal stimulation (LLVS) prevents atrial arrhythmias.\textsuperscript{32} LLVS stimulates the vagal nerve below the threshold at which an effect on heart rate is elicited. One week of LLVS reduced sympathetic nerve density in the stellate ganglion, as observed in dogs with
rapid pacing-induced AF, which is associated with fewer paroxysms of AF and decreased AF inducibility. Additionally, LLVS prevented and reversed atrial remodeling induced by rapid atrial pacing. These data have been confirmed in a proof-of-concept study where patients with paroxysmal AF received transcutaneous LLVS to the tracheal nerve, a branch of the vagus nerve. The patients had shorter episodes of pacing induced AF. This study only applied short lasting vagal stimulation, during an ablation procedure. If, however, transcutaneous LLVS proves effective and safe in ambulatory patients with AF, this may pave the way for noninvasive application of this therapy.

**Carotid body stimulation**

No large clinical studies have been performed on electrical carotid body stimulation (CBS) in the treatment of atrial and ventricular arrhythmias. However, high-output CBS induces a vagal response that can be pro-arrhythmic in the atrium. CBS resulted in a shortening of the effective refractory period and increased AF inducibility in pigs. Low-level CBS might prevent excessive vagal activation but still modulate autonomic activity: it prolonged the effective refractory period and prevented rapid atrial pacing–induced remodeling in rabbits. Low-level CBS also prolonged ventricular effective refractory period and reduced ventricular arrhythmias after acute myocardial infarction. However, in light of the recent progress in LLVS, which appears to act in a similar manner, it remains unclear whether CBS will develop as a viable alternative, as the carotid body is a delicate structure, located in a complex anatomical area.

**Renal denervation**

Renal denervation (RDN) caused decreased central sympathetic activity and lowered blood pressure in patients with refractory hypertension in experimental and early clinical studies. However, the SYMPLICITY HTN-III (Renal Denervation in Patients With Uncontrolled Hypertension) trial, a large multicenter trial, showed no benefit of RDN on systolic blood pressure in 535 patients with refractory hypertension compared to control. This could be explained by procedural characteristics, operator experience, placebo effect of the sham procedure, or insufficient selection of patients. However, although no effect on blood pressure was observed, and there is evidence that the effect on blood pressure and sympathetic activity are independent, RDN affects atrial and ventricular electrophysiology, independent of the blood pressure effect as outlined subsequently. Similarly, RDN led to decreased left atrial volume independent of the change in blood pressure in 66 patients with hypertension but without AF. Subjects with a high burden of premature atrial complexes experienced a reduction of these premature complexes, but this was not related to left atrial volume change. The lack of correlation between morphological and electric or autonomic changes might be due to a low sample size and heterogeneity within the group. Nevertheless, these findings suggest that RDN has an
effect beyond blood pressure reduction and appears to influence autonomic activity. In 16 dogs with a hypersympathetic state (induced by rapid atrial pacing and left stellate ganglion stimulation), RDN diminished AF inducibility and reversed the effective refractory period shortening following stimulation of the left stellate ganglion and rapid atrial pacing.\textsuperscript{126} RDN applied before the onset of AF reduced atrial remodeling after 5 weeks of rapid atrial pacing in dogs and after 6 weeks in goats independent of the change in blood pressure.\textsuperscript{122,127} Therefore, RDN may affect extensive remodeling during long-term follow-up. These observations suggest that RDN is effective in patients with sympathetically driven AF. In a small clinical study, 69\% of the 27 paroxysmal or persistent AF patients with refractory hypertension who underwent PVI and RDN were free of AF versus 29\% in the PVI alone group (Figure 3).\textsuperscript{100} A meta-analysis of 80 patients showed similar results, with a more profound effect in a subgroup analysis in patients with severe hypertension.\textsuperscript{128} Although follow-up was performed without continuous monitoring, RDN appears beneficial in patients with AF and moderate or severe hypertension. However, there are no data on RDN in patients with AF without hypertension. RDN also reduced the number of spontaneous ventricular extra systoles and VF in pigs (with acute regional ischemia) in a similar manner as betablockade with atenolol.\textsuperscript{123} Additionally, in 4 patients with (non) ischemic cardiomyopathy and frequent VT despite maximal drug therapy and ablation, RDN reduced the occurrence of VT episodes from 11.0 episodes during the month before

Figure 3. – Incidence of AF recurrences in patients with and without renal artery denervation. The group that underwent both PVI and renal artery ablation has a significantly reduced atrial fibrillation (AF) recurrence rate over time compared with the control pulmonary vein isolation (PVI)–only group. Reprinted with permission from Pokushalov et al.\textsuperscript{100}

AT: atrial tachyarrhythmia.
to 0.3 episodes the month after ablation. However, in light of the SIMPLICITY HTN-III experience, blinded clinical studies with sham interventions should be performed to assess the antiarrhythmic effect of RDN.

CONCLUSIONS

Modulation of the ANS may be used to treat cardiac arrhythmias. Animal and human studies have revealed an intricate network of interconnected nerves of both the parasympathetic and sympathetic nervous system on the atria and ventricle. New functional imaging techniques can help us visualize the ANS in individual patients. Ablation of GPs, the integration centers of the intrinsic ANS, shows promising results for the treatment of AF. However, with current imaging techniques it is difficult to identify or localize the intrinsic ANS. New invasive treatment options aimed at the extrinsic cardiac ANS, such as LLVS and RDN, provide interesting future treatment possibilities both for AF and ventricular arrhythmias, but await thorough clinical testing. Furthermore, targeting these nerve structures is invasive and associated with the risk of complications. Once we are able to reliably identify the intrinsic ANS and define the optimal treatment target of ANS modification, clinical studies on modifying the ANS may open an entirely new stage for treatment of arrhythmias. Such studies may not only improve the outcome of ablation therapy but may also advance our understanding of how the ANS interacts with the myocardium to cause cardiac arrhythmias.
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