

The consequences of cardiac autonomic nervous system modulation during pulmonary vein isolation: A review

Piotr Brzozowski^{1,2,A–F}, Piotr Niewiński^{1,2,A,D–F}, Stanisław Tubek^{1,2,A,E,F}, Krzysztof Nowak^{1,2,A,E,F}, Piotr Ponikowski^{1,2,E,F}

¹ Institute of Heart Diseases, Wrocław Medical University, Poland

² Clinical Cardiology Ward, University Teaching Hospital, Wrocław, Poland

A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation;

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Address for correspondence

Piotr Brzozowski

E-mail: piotr.brzski@gmail.com

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Abstract

Pulmonary vein isolation (PVI) is a well-established treatment modality for atrial fibrillation (AF). Apart from the desired effect regarding the arrhythmic substrate within the left atrium, PVI commonly leads to modulation of the intrinsic cardiac autonomic nervous system (ICANS). Using the available literature, this article presents the anatomy of ICANS and describes methods of assessing its function, mainly focusing on heart rate (HR) variability metrics. Then, we summarize the modern pathophysiological outlooks on the onset and recurrence of AF and explain how the arrhythmia and the activation of ICANS are intertwined. Further, the article discusses the extent, dynamics and persistence of ICANS modulation during PVI, accounting for various modalities and procedural strategies. Both the potential benefits and pitfalls of such modulation are explored, considering AF recurrence, HR and HR variability changes, as well as the unclear effect on ventricular arrhythmias and nerve remodeling. Finally, the article aims to outline further directions of research necessary to improve our understanding of ICANS and its modulation.

Key words: atrial fibrillation, catheter ablation, pulmonary veins, autonomic ganglia, autonomic denervation

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Introduction

Atrial fibrillation (AF) is the most common arrhythmia in adult patients worldwide. Its estimated prevalence is 7.7% among individuals aged 55 and above, with an observed increase in prevalence with age. Projections indicate a potential rise in the number of cases in the near future.^{1,2} Catheter ablation has been established as a reliable method of treatment and prevention of AF recurrence, and it holds a strong position in the European Society of Cardiology (ESC) guidelines.³ Pulmonary vein isolation (PVI) is regarded as a standard in AF catheter ablation, given that the role of the pulmonary veins (PVs) in AF pathophysiology has been widely researched and agreed upon.⁴ Both well-established techniques, radiofrequency ablation (RFA) and cryoballoon ablation (CBA), have similar safety profiles and provide a similar reduction in AF burden and freedom from AF recurrence.⁵ A recently developed method, pulse field ablation (PFA), is showing comparable results as well.⁶

It has been postulated that the intrinsic cardiac autonomic nervous system (ICANS) plays a pivotal role in the triggering and recurrence of AF.⁷ The ICANS is an intricate network of neurons and ganglionated plexi (GP) that regulates electrical and mechanical functioning of the heart. The GPs, which consist of parasympathetic neuronal bodies intertwined with sympathetic neuron axons, are located on the epicardial fat pads, with major GPs placed in close proximity to the PVs, atrioventricular node (AVN) and sinoatrial node (SAN). The intrinsic cardiac autonomic nervous system consists of both sympathetic and parasympathetic neurons, which in healthy patients assure that the heart rate (HR) and blood pressure are adequate to meet the demands of the organism. Several studies have shown that the PVI procedure, whether RFA or CBA, modulates ICANS noticeably, although the extent and permanence of this modulation remain disputed.^{8–10} There is much disagreement regarding many aspects of targeted ICANS modification during PVI, including both efficacy and safety issues.¹¹ Considering that even the anatomical terminology is not uniform, we feel that a comprehensive review of the literature is needed to summarize what we already know and what directions are worth exploring.

Objectives

The aim of this article is to review the physiological, anatomical and procedural background of ICANS modulation during and after PVI, provide insight into its potential benefits and consequences, and indicate areas that need further exploration.

Anatomy of the atrial autonomic nervous system

The adult heart contains an average of 701 ganglia, and up to 84% of them are located on the surface of the atria, with most of them located on the posterior and superior surfaces.¹² While the terminology of ICANS anatomy remains inconsistent and varies between anatomists and electrophysiologists, we adapted the nomenclature of atrial GPs proposed by Aksu et al.,¹³ which is based on older anatomical studies.^{12,14,15} It postulates 5 major atrial GPs: superior right atrial (RSGP) – on the posterosuperior surface of the right atrium (RA) adjacent to the junction of the superior vena cava (SVC) and the RA; inferior right atrial (RIGP) – on the posterior surface of the RA adjacent to the interatrial groove; superior left atrial (LSGP) – on the posterosuperior surface of the left atrium (LA) between the PVs; posteromedial left atrial (PMLGP) – on the posteromedial surface of the LA; and posterolateral inferior left atrial (LIGP) – on the posterior lateral surface of the LA base on the atrial side of the atrioventricular groove (Fig. 1). Of these GPs, the most prominent (RIGP and PMLGP) and their extensions were shown to be merged to form the interatrial septal GP (ISGP), which contains the highest number of ganglia (average of 355) among ICANS.¹⁴ Two vital structures of the heart's conductivity system are innervated by atrial GPs: RSGP extensions reach the SAN, while the AVN is innervated primarily by PMLGP.¹²

While historically it was thought that the intrinsic GPs consisted only of parasympathetic neurons synthesizing acetylcholine (ACh), histological studies proved that ICANS also contains neurons that have the potential to release noradrenaline (NA), although these were significantly more prominent in the ventricular ganglia.¹⁶

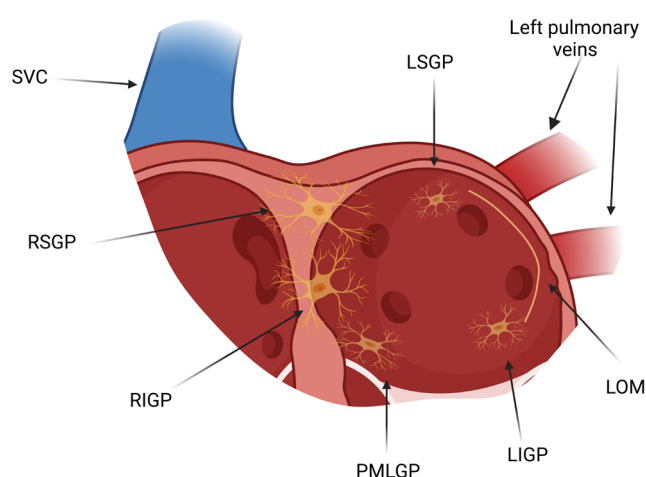


Fig. 1. A simplified overview of intrinsic cardiac autonomic nervous system (ICANS) anatomy in the human atria

SVC – superior vena cava; RSGP – superior right atrial ganglion plexus; RIGP – inferior right atrial ganglion plexus; PMLGP – posteromedial left atrial ganglion plexus; LIGP – inferior left atrial ganglion plexus; LOM – ligament of Marshall; LSGP – superior left atrial ganglion plexus.

In immunohistochemical studies of porcine and mouse hearts, a variety of other potent neurotransmitters, such as vasoactive intestinal peptide, neuropeptide Y, nitric oxide, synaptophysin, and calcitonin gene-related peptide, were found throughout ICANS.^{17,18}

One crucial feature that differentiates sympathetic nerves from parasympathetic nerves is the location of their neural bodies. While the nuclei of parasympathetic neurons are located directly on the surface of the heart, the bodies of sympathetic neurons are located further away in the stellate and caudal cervical ganglia.¹⁹ Thus, given the appropriate penetration of radiofrequency or cryoenergy originating from the intracardiac catheter, the effect toward the parasympathetic arm ought to be more permanent due to the ablation of neural bodies. On the contrary, sympathetic modulation would be transient because of isolated destruction of the long axons with spared sympathetic ganglia.

The autonomic innervation of the heart does not only involve the GPs. Parasympathetic neurons located on the surface of the heart operate under the control of the central nervous system. Said control is exerted through the longest cranial nerve in the human body, the vagus nerve, connecting the lower brainstem (mainly the nucleus ambiguus and the nucleus tractus solitarius) to the GPs of the heart.²⁰ The anatomical proximity of the vagus nerve and the internal jugular vein allows for transvenous stimulation, which is often utilized during cardioneuroablation (CNA) procedures. One cannot ignore the significance of the ligament of Marshall (LOM), which was described in 1850 as “a vestigial fold containing fibrous bands, small blood vessels and nervous filaments”.²¹ It is located above the left atrial appendage and lateral to the left superior PV and runs from the coronary sinus to insert itself into the LA free wall myocardium. The muscular fibers inside the LOM, called Marshall bundles, were shown to merge with the muscle tissue of both the coronary sinus and the LA and have been reported to be a potential source of arrhythmia.²² Today, we also know that the structure contains abundant parasympathetic and sympathetic innervation, with parasympathetic ganglia located in the vicinity of the coronary sinus–LOM junction and sympathetic fibers concentrated in the part closer to the LA–LOM junction.²³

Onset and recurrence of atrial fibrillation: A review of modern pathophysiological outlooks

The pathophysiology of AF is a very complex and still poorly understood matter. Modern hypotheses assume a conjunction of anatomical substrate,²⁴ focal triggers²⁵ and autonomic fluctuations²⁶ in inducing and sustaining AF. Studying each of these components and how they interact with each other is of vital importance in understanding the basis of this arrhythmia and how modern medicine can attempt to treat it.

Atrial fibrosis has been linked to the incidence and recurrence²⁷ of AF; however, there has been a disagreement on whether the extent of fibrosis is correlated to the type (paroxysmal/persistent) of AF.^{27,28} At the same time, the presence of fibrous tissue facilitates arrhythmogenesis through providing a basis for re-entrant circuits that enable the induction of the arrhythmia.²⁹ Atrial fibrillation then propagates electrical and structural remodeling of the atria, which led to the emergence of the concept that “AF begets AF”.³⁰

Anatomical substrate alone would not initiate the arrhythmia on its own. It needs a trigger – a premature, most of the time ectopic beat – that will induce a re-entrant loop. These premature impulses can originate from any part of atria or even the aforementioned LOM,²² but predominantly, up to 94% of the time, their source lies within the PVs.³¹ This knowledge is the rationale behind PVI – isolating the source of the focal trigger from the LA prohibits the initiation of AF and prevents its recurrence.

The 3rd key factor in initiating and sustaining AF is autonomic regulation. Bettoni and Zimmermann²⁶ proved that there are significant variations in HR variability (HRV) parameters before the onset of paroxysmal AF, suggesting increased adrenergic modulation at least 20 min before initiation of the arrhythmia, with a subsequent shift toward parasympathetic dominance in the last minutes before the onset of AF. In a computational simulation study with models based on recordings of human atrial myocytes, Bayer et al.³² showed that parasympathetic activation through heterogeneous ACh release promotes AF by creating unidirectional conduction blocks and re-entry loops, especially in fibrotic atria. Furthermore, in an experimental canine model, simultaneous adrenergic and cholinergic stimulation of the atria through NA and ACh infusions were shown to induce AF.³³ Similar results were obtained by Hou et al.,³⁴ who proposed that both ACh and NA excitatory effects on human atria were stronger when both transmitters acted simultaneously. Interestingly, adrenergic-mediated AF could not be induced if parasympathetic modulation was blocked by atropine. Conversely, cholinergic-mediated AF, while less likely to occur after propranolol infusion, still manifested despite total adrenergic blockade.³³ With that amount of evidence, it is clear that both the parasympathetic and sympathetic nervous systems play significant roles in the propagation of AF, which makes the topic of ICANS modulation even more important in regard to the long-term efficacy of PVI.

Assessment of cardiac autonomic nervous system function

Measurement of the regulatory functions of ICANS can be conducted both during and after the procedure. Intra-operatively, acute vagal responses (VRs), such as deep sinus bradycardia (<40 bpm), asystole or atrioventricular block, can be elicited using all contemporary PVI methods.^{35–37} These responses are triggered by energy applications

at the locations of the GPs and are transient, although sometimes the use of atropine or temporary pacing is necessary. At the same time, after successful ablation, one can sometimes observe the elimination of VRs, which stems from vagal denervation.³⁸

Further assessment of ICANS function is usually done through HR and HRV analyses of Holter recordings. Through the aforementioned vagal denervation, an increase in resting HR can be observed in many patients who underwent PVI.⁹ While the measurement of average HR is a rather trivial task, analyses of HRV are more complex, as we can divide them into time domain analyses and frequency domain analyses.

Time domain analyses provide us with parameters that are derived from beat-to-beat changes in RR intervals. While relatively simple to calculate, they mostly reflect the parasympathetic influence on HRV. Examples of such parameters are as follows:

- SDNN – standard deviation of normal beat to normal beat (NN) interval;
- SDANN – standard deviation of average (taken from 5-min periods) NN intervals;
- RMSSD – root mean square of successive RR interval differences;
- pNN50% – percentage of successive RR intervals that differ by >50 ms.

Frequency domain analyses with the use of more complex calculations based on fast Fourier transform or autoregression modeling measure the power of HR fluctuations within 3 frequency bands:

- Very low frequency (VLF – spectrum between 0.01 and 0.04 Hz);
- Low frequency (LF – spectrum between 0.04 and 0.15 Hz) influenced by both sympathetic and parasympathetic activity;
- High frequency (HF – spectrum between 0.15 and 0.4 Hz) predominantly connected to respiratory arrhythmia and vagal activity.³⁹

The ratio of power within the LF band to the HF band (LF/HF ratio) has been used as a measure of adrenergic tone toward the sinus node in many reports. However, its usefulness for the assessment of the sympathetic system is questionable.⁴⁰ It has to be noted that the aforementioned parameters are by no means the only ones used in HRV analyses. However, they are the most commonly used metrics in the reviewed literature.

The quantitative assessment of autonomic denervation might also be accomplished with atropine administration. When given in a sufficiently high dose (i.e., 0.04 mg/kg), atropine leads to complete vagal blockade.⁴¹ The elimination of parasympathetic input by atropine leads to a situation in which HR is determined by only the 2 following factors: 1) sympathetic input and 2) intrinsic activity of the sinus node. Thus, given the unchanged intrinsic activity of the sinus node, the difference in HR on atropine before and after CNA reflects the change in sympathetic activity

toward the sinus node. Hence, the atropine method gives us the opportunity for a more comprehensive insight into the consequences of CNA.

A method of intraprocedural assessment of parasympathetic denervation using a neurostimulator was developed by Pachon et al.⁴² It involves electrical stimulation of the vagus nerve through a catheter positioned in the internal jugular vein, which results in an acute vagal response (mostly temporary asystole) in patients with unmodified ICANS. Conversely, after ablation of the GPs, vagal responses could not be induced through the identical mode of stimulation. A recent study suggested improved long-term efficacy of CNA procedures with the use of vagus nerve stimulation.⁴³ Another way to assess the extent of parasympathetic injury due to PVI is based on measuring the serum concentration of neuron-specific enolase, an enzyme released from damaged neurons, which was shown to significantly increase after PVI.⁴⁴

Does pulmonary vein isolation modulate the autonomic system of the heart?

The effectiveness of PVI relies predominantly upon thorough isolation of the PVs from the LA myocardium. Ouyang et al.⁴⁵ showed that recovery of conduction in the PVs is found in approx. 80% of patients with AF recurrence. Successful isolation is achieved through applying a continuous line of transmural lesions. Due to the anatomical reasons outlined above, the proximity of ICANS and the PV ostia could lead to inadvertent damage of the autonomic neurons during PVI. Moreover, a strategy of purposeful atrial GP ablation as an addition to standard PVI has also been proposed.

Aksu et al.⁴⁶ conducted an interesting study in patients undergoing targeted CNA. By mapping the LA and presenting an electroanatomical map to a blinded observer, they showed that the designed lines for PVI, especially around the right PVs, exhibit a major overlap with the location of the atrial GPs. In fact, all of the patients in the study had some, although varied, degree of overlap, with approx. 80% of the cases showing overlap in 2 or 3 PVs, which gives us the reasoning for both the occurrence and variance of ICANS modulation throughout the population of patients undergoing PVI.

There is abundant evidence of autonomic modulation related to PVI. Modulation of ICANS can already be seen during the procedure. There are studies that describe coincidental acute VRs during RFA, CBA and PFA alike. These responses manifest as deep sinus bradycardia (<40 bpm), asystole or atrioventricular block.⁴⁷ The first experiments regarding HR changes after interventions within the PV ostia were performed in animal models as early as 1964.⁴⁸ One of the first reports regarding this topic in human study participants was made in 2004 when Pappone et al.³⁸ proved significant alterations in HR (72.4 ± 8.4 bpm baseline vs 80.3 ± 9.1 bpm after 1 week; $p < 0.001$) and HRV

(130.4 $\pm$ 30.5 ms SDNN baseline vs 81.4 $\pm$ 18.8 ms SDNN after 1 week) in patients undergoing radiofrequency PVI. Similarly, in 2006, Bauer et al.⁴⁹ showed significant changes in HR (65 $\pm$ 7 bpm baseline vs 71 $\pm$ 7 bpm after 12 months; $p = 0.01$) and HRV (SDNN 125 $\pm$ 31 ms baseline vs 110 $\pm$ 20 ms after 12 months; $p = 0.01$) after catheter radiofrequency PVI. That study also showed that autonomic modulation after RFA persists after 12 months. Interestingly, similar changes in HRV parameters were shown by Suwalski et al.⁵⁰ in patients after surgical PVI.

Periprocedural changes in HR after PVI are different from patient to patient; however, most of the reviewed literature shows a short-term increase in mean HR ranging from 4 to 12 bpm in PVI patients,^{9,35,51–53} while targeted GP ablation can yield higher periprocedural increases, even up to 27 bpm.⁵⁴ At the same time, no significant changes in maximal HR during exertion have been described in PVI³⁸ and CNA⁵⁵ alike, and maximum metabolic equivalents on exercise treadmill testing remained stable.⁵⁶ Another marker of autonomic modulation – cardiac baroreflex sensitivity – was also significantly reduced in patients after PVI. This reduction, however, was only transient, as in the reviewed study, most metrics apart from Valsalva ratio returned to baseline after 6 months.⁵⁷

Persistence and dynamics of ICANS modification after transcatheter ablation is still not an entirely clear matter. While analyzing the CIRCA-DOSE (Cryoballoon vs Irrigated Radiofrequency Catheter Ablation) study population, Tang et al. showed that HRV parameters change significantly not only right after PVI (both CBA and RFA), but also throughout the following 12 months.⁹ In that study, patients were monitored using implantable loop recorders. Immediately after the procedure, a sizable drop in HRV (mean baseline SDANN 122.26 $\pm$ 1.66 ms decreased by approx. 60 ms) was noted, with a partial reversal during the next 3 months (mean 100-day follow-up SDANN 103.0 $\pm$ 1.7 ms), after which it remained stable throughout 12 months after the procedure (mean Δ SDANN of 2.2 ms, 3.7 ms, 4.7 ms for months 6, 9 and 12 vs month 3). An increase of approx. 5 bpm in daytime HR (from mean baseline DHR of 68.18 $\pm$ 0.57 bpm) after the procedure was also recorded, with further augmentation in the 100-day follow-up (Δ DHR at 100 days post-PVI of 9.6 bpm; range: 7.4–11.8 bpm; $p < 0.0001$) and a slight downward, although statistically insignificant, trend in the following months. A similar trend of a peak and small gradual decline in HR can be observed in other studies regarding PVI; however, the decrease likewise failed to reach statistical significance.^{58,59} In CNA, on the other hand, this trend seems to be exacerbated, with a higher peak and greater drop in HR in the months following the procedure, which suggests a greater degree of acute autonomic modulation.⁶⁰ The aforementioned HR and HRV changes spanning months after both PVI and CNA suggest at least some degree of reinnervation during the first months post-procedure. Pachon et al.⁵⁵ demonstrated that significant

autonomic denervation lasted for at least 24 months (median HR 71.2 $\pm$ 11 bpm at baseline vs 79.6 $\pm$ 12 bpm 2 years after CNA; $p < 0.0001$; SDNN 134.3 $\pm$ 32 ms at baseline vs. 88.3 $\pm$ 30 ms 2 years after CNA; $p < 0.0001$) in patients undergoing targeted CNA. There were no significant differences in HR and HRV parameters comparing 12 to 24 months follow-up, which indicates that most reinnervation concludes in the first few months after the procedure, after which HRV parameters remain stagnant.

The differences in devices used could also potentially influence procedural outcomes regarding autonomic modulation. It is known that second-generation cryoballoons (CBs), compared to first-generation CBs improve procedural efficacy (procedural duration 128 $\pm$ 27 min vs 98 $\pm$ 30 min; $p < 0.001$; fluoroscopy exposure 19.5 $\pm$ 7.4 min vs 13.4 $\pm$ 5.3 min; $p = 0.001$)⁶¹ and clinical outcomes (freedom from AF at 365 days follow-up 63.9% vs 83.6% of patients)⁶² of PVI. It would also seem that second-generation CBs provide more definitive ICANS modulation. In the study conducted by Oswald et al.,¹⁰ HRV metrics were back to baseline 3 months after PVI using first-generation CBs. In contrast, in more recent studies utilizing second-generation CBs, the effects of ICANS modulation were more permanent, lasting over 12 months,^{9,53} which could be explained by the fact that second-generation CBs have a bigger ablation surface, providing a wider and more thorough line of lesions. Yorgun et al.⁸ also hypothesized that the size of the CB might also influence the extent of ICANS modulation (Fig. 2).

However, not all PVI techniques carry the risk of autonomic nervous system neuronal damage. While CBA and RFA use thermal energy, a novel method with a different approach (PFA) has been developed recently and is rising in popularity. Using irreversible electroporation (IRE), PFA targets the myocardium while sparing the surrounding tissues, including nerves, which was confirmed both in preclinical⁶³ and clinical studies.⁶⁴ Considering the tissue specificity of PFA, it was not surprising that Musikantow et al.³⁷ proved that despite eliciting coincidental VRs in some patients, there was no significant change in resting HR after 3 months following PFA. In conclusion, PFA seems to have only minor and insignificant effects on ICANS.

Benefits of cardiac autonomic modulation during PVI

Having established that PVI utilizing CBA and RFA indeed has a significant impact on autonomic regulation of the heart, we have to assess whether such an impact is beneficial or detrimental in the scope of the cardiovascular system.

Importantly, Yorgun et al.⁸ showed that patients developing intraprocedural VRs requiring atropine administration or temporary pacing during CBA had significantly less AF recurrence (16.20% vs 29.00%; $p = 0.009$), and such

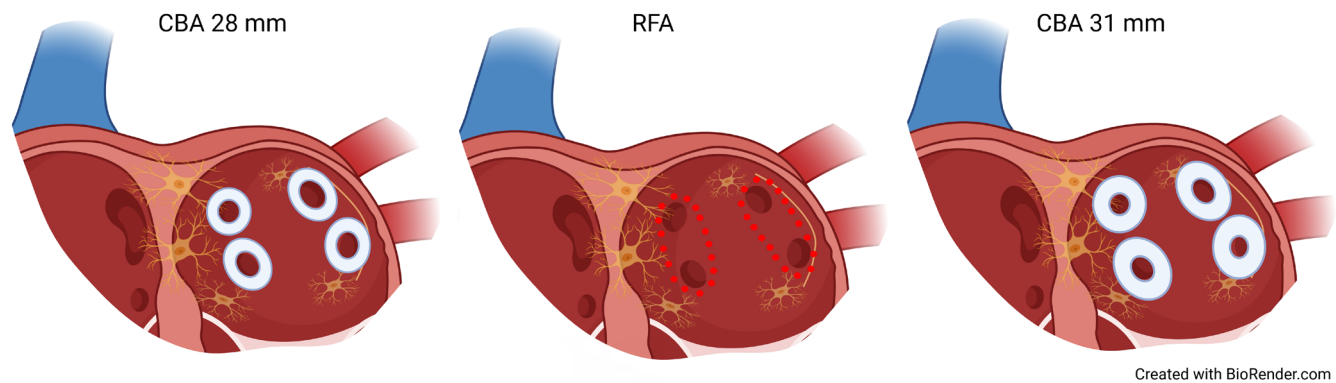


Fig. 2. Schematic view of potential differences in intrinsic cardiac autonomic nervous system (ICANS) modulation related to pulmonary vein isolation modality. RFA – radiofrequency ablation; CBA – cryoballoon ablation.

VRs were associated with decreased arrhythmia recurrence (hazard ratio (HR): 0.550, 95% confidence interval (95% CI): 0.331–0.915; $p = 0.021$). Moreover, Qin et al.⁶⁵ showed that identifying and eliminating those reactions by means of RFA can significantly reduce the recurrence of arrhythmia in comparison to the non-VR group (HR: 0.53, 95% CI: 0.22–0.89; log-rank = 15.3; $p = 0.004$).

In the CIRCA-DOSE⁹ study, patients with no AF recurrence after PVI had a larger relative change in nighttime and daytime HR than those with recurrence (Δ DHR 11 ± 11 bpm vs 8 ± 12 bpm; $p = 0.001$; Δ NHR 8 ± 9 bpm vs 6 ± 8 bpm; $p = 0.049$). However, there was no difference in measured SDNN between the 2 groups. Conversely, the research conducted by Pappone et al.³⁸ showed that vagal denervation occurring at the time of PVI (expressed in transient changes in both HR and HRV parameters) was correlated with longer AF-free survival (adjusted HR: 0.101, 95% CI: 0.014–0.750; $p = 0.025$).

Interestingly, the strategy of anatomic atrial GP ablation in addition to classic PVI was found to yield better results in terms of arrhythmia recurrence than PVI or GP ablation alone in patients with paroxysmal AF.⁶⁶ At 2-year follow-up, patients in the PVI + targeted GP ablation group were significantly more often free from arrhythmia than those in the PVI or GP ablation groups (74% vs 56% vs 48%; $p = 0.0036$).⁶⁷ The aforementioned findings were confirmed in a meta-analysis performed by Yan et al.⁶⁸ that pooled together 5 studies comparing standalone catheter PVI vs PVI + GP ablation. A significant benefit of adjunct GP ablation was demonstrated in terms of freedom from AF (odds ratio (OR) [95% CI]: 1.79 [1.35, 2.37]; $p < 0.001$).

At the same time, while ICANS modulation may not be effective in the treatment of bradycardia–tachycardia syndrome (BTS), as the cause of BTS is often an organic dysfunction of the SAN, it can be beneficial in patients with both AF and vasovagal syncope. Targeted CNA is emerging as an alternative to traditional pacing, especially in young, otherwise healthy patients with vagally-mediated syncope,⁶⁹ and ICANS modulation employing PVI could have a similar therapeutic effect as proposed by Maj et al.⁷⁰

Intrinsic cardiac autonomic nervous system modulation also exerts a significant effect on the physiological properties of the AVN. As reported by Wichterle et al.,⁷¹ after targeted CNA, there was a significant increase in AVN conduction capabilities (shortening of AH interval by 15 ± 31 ms, increase in Wenckebach point by 28 ± 33 bpm). This, in conjunction with increased resting HR, could potentially open up the possibility of β -blocker and antiarrhythmic drug uptitration (if needed) in patients treated with PVI.⁷² Moreover, Aksu et al. showed that CNA can also successfully treat an advanced atrioventricular block.⁷³ Such interventions, however, would only be effective in a case of functional block, rather than organic block, so careful identification of potential responders using pre-procedural atropine challenge is mandatory.

Potential pitfalls of cardiac autonomic modulation during PVI

As discussed above, ICANS modulation during PVI commonly leads to a profound decrease in HRV. It was shown that decreased HRV following myocardial infarction was significantly correlated with mortality rates, as patients with SDNN < 50 ms had a 5.3 times higher chance of death than those with SDNN > 100 ms.⁷⁴ In fact, decreased HRV was the strongest Holter-derived predictor of mortality among patients in that study, even stronger than ventricular arrhythmias (VAs). The Framingham Heart Study analysis also showed that decreased HRV was significantly associated with all-cause mortality,⁷⁵ while the UK-Heart study described a correlation between SDNN < 100 ms and mortality due to progressive heart failure.⁷⁶

While it is true that impaired HRV is correlated with increased mortality throughout multiple studies, we must keep in mind that correlation does not equal causation, and decreased HRV is most probably not the cause of death but merely a marker of potentially lethal coexisting conditions. Thus, HRV-increasing agents, such as scopolamine, failed to provide protection against fatal VAs, even though they significantly improved HRV metrics.⁷⁷ It is highly unlikely

that the iatrogenic HRV decrease caused by PVI increases the risk of death by itself, as there was no significant difference in mortality in studies comparing PVI to optimal medical therapy.⁷⁸

Respiratory sinus arrhythmia (RSA), a phenomenon primarily mediated by cardiac vagal tone and predominantly responsible for HRV in high frequency domains, is an old evolutionary mechanism present not only in humans but also throughout the animal kingdom.⁷⁹ Through ICANS modulation, RSA was observed to be severely diminished in patients undergoing PVI.⁸⁰ Although seemingly unimportant, physiological RSA was shown to improve pulmonary gas exchange efficiency through a reduction in intrapulmonary shunting and pulmonary dead space to tidal volume ratio compared to abolished RSA.⁸¹ Additionally, in a sheep model of heart failure, a special pacing protocol emulating RSA led to an improvement in cardiac output (1.4 ± 0.5 L/min; $p < 0.001$) compared to both traditional pacing and non-paced groups.⁸² Attenuation of RSA after PVI may then have a similar detrimental effect in humans, although studies investigating this matter have not yet been conducted.

The effect of ICANS modulation on VAs is still a matter of debate. In canines after myocardial infarction,⁸³ it was shown that ablation of atrial GPs and LOM caused increased inducibility of VAs, as programmed stimulation (S1S2S3) induced VAs in 30% of study participants in the control group compared to 90% in the post-ablation group ($p = 0.02$). Induced arrhythmias were also significantly faster in the GP ablation group (363 ± 6 bpm vs 274 ± 8 bpm; $p < 0.001$). Susceptibility to VAs was probably related to greater prolongation of the QTc interval at 8 weeks after the procedure compared to the control group (342 ± 14 ms vs 356 ± 12 ms; $p < 0.05$), larger dispersion of the effective refractory period (32 ± 13 ms vs 24 ± 10 ms; $p < 0.05$), and increased density of the immunohistochemical marker of adrenergic neurons (tyrosine hydroxylase) ($582 \pm 301 \mu\text{m}^2/\text{mm}^2$ vs $231 \pm 187 \mu\text{m}^2/\text{mm}^2$; $p = 0.006$) and nerve growth factor ($672 \pm 387 \mu\text{m}^2/\text{mm}^2$ vs $266 \pm 202 \mu\text{m}^2/\text{mm}^2$; $p = 0.009$). This suggests that there was promotion of ventricular sympathetic nerve remodeling. In a porcine model,⁸⁴ CNA was associated with QTc prolongation after sympathetic stimulation ($11.23\% \pm 4.0\%$ vs $1.49\% \pm 4.0\%$; $p < 0.001$), earlier occurrence (61.44 ± 73.7 s vs 245.11 ± 104.0 s; $p = 0.002$) and incidence of VA after left coronary artery ligation. In human studies, however, there is no conclusive evidence of arrhythmia propagation after ICANS modulation. There is a study that reported temporary QTc prolongation after the CNA procedure (QTcHodges 434 ± 24 ms vs 409 ± 23 ms 1 day after procedure; $p < 0.00001$).⁸⁵ However, this was not confirmed in other observations following CNA.^{55,86} A similar discord can be found in studies on PVI and QTc. Chikata et al.⁸⁷ noticed a QTc prolongation after PVI (QTcHodges 400.7 ± 22.8 ms vs 410.6 ± 40.2 ms 1 day after procedure; $p < 0.05$), whereas Hermans et al.⁸⁸ did not produce such findings in their study. At the same time, Styczkiewicz

et al.⁵⁷ observed decreased baroreflex sensitivity in patients after PVI, and research conducted by Garcia et al.⁸⁹ suggests an association between reduced cardiac baroreflex sensitivity and VAs.

One of the common side effects of ICANS modulation is inappropriate sinus tachycardia (IST). Van Deutekom et al.⁹⁰ showed that IST was not uncommon (4.1%) in patients undergoing PVI. In patients undergoing targeted CNA, however, this phenomenon was much more frequent, ranging from 7% to even 27% of patients,⁹¹ which is an important factor to consider when deciding on a procedural strategy. The only identified risk factors for developing IST following CNA are higher baseline and post-atropine HR.⁹² The issue of IST could be especially important in patients in which an increase in HR is known to be detrimental, as in, e.g., heart failure (as shown in the SHIFT trial⁹³) or coronary artery disease (CAD).⁹⁴

Further directions

Considering how important autonomic regulation is in the context of cardiovascular diseases and how complex its mechanisms are, further research on the topic of autonomic modulation is critical for a deeper understanding of this subject and the development of new treatments.

First, to gain certainty in the degree and effectiveness of ICANS modulation, appropriate and validated measurement techniques should be agreed upon. For example, throughout the reviewed literature, many different HRV metrics were used, which are often incomparable to each other and provide different information about the state of ICANS. Also, there is no consensus regarding which of the following modalities ought to be used to establish vagal modulation of the heart and serve as the periprocedural end-point: HR, HRV, intraprocedural VRs, or extracardiac vagal stimulation.⁵⁵

Second, no trials have compared the influence of various sizes of CBs on the autonomic parameters after PVI, given that a greater ablation surface could equal a greater degree of autonomic modulation. The advent of adjustable 28–31 mm CBs⁹⁵ could be a logical starting point for further exploration in this area.

Third, a lack of long-term follow-up of autonomic function metrics after PVI should also be addressed by proper research initiatives to adequately assess the far-reaching implications of the intervention, especially now that operators in some cases can choose the degree of impact on ICANS (PFA vs CBA/RFA vs PVI + CNA). Larger studies, or perhaps thorough meta-analyses of certain issues (QT interval, AVN conduction, VA susceptibility, exercise tolerance, left ventricular contractility, autonomic remodeling, and reinnervation), would be beneficial for understanding the potential consequences of long-standing ICANS modulation.

Another point of consideration is: How should operators decide on the extent of ICANS modulation, taking into

account the availability of different modalities? What criteria should be taken into account to differentiate patients who will benefit from additional autonomic modulation from those who should be treated with myocardium-specific methods? At this point, we can only hypothesize that patients with sinus bradycardia, vasovagal syncope and functional atrioventricular block will benefit from adjunct CNA, while perhaps patients with heart failure or at risk of VAs could gain more by sparing the parasympathetic nerves.

Limitations

This review was limited by the available research. Drawing conclusions from studies with different methodologies, metrics of autonomic modulation or even anatomical nomenclature makes comparing their results challenging. A large share of the cited studies also had relatively small sample sizes, and some concepts were studied only in animal models. Only studies that were published in English were analyzed.

Conclusions

In summary, PVI, as a staple of AF treatment, is a well-studied method with regard to its safety and efficacy. However, the extent of its impact on ICANS remains disputed. While the benefits of ICANS modulation during PVI have been widely reported, the potential disadvantages of vagal denervation also require careful attention (Fig. 3).

We believe that all PVI modalities and adjunct CNA strategies have their place in the clinical setting. Ideally, however, the optimal method should be chosen through an individualized approach to maximize the benefits and avoid the potential pitfalls of autonomic modulation.

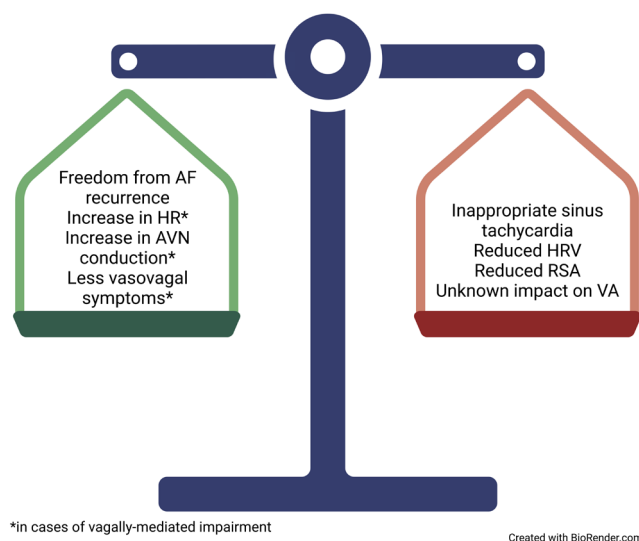


Fig. 3. Advantages and potential disadvantages of pulmonary vein isolation-related intrinsic cardiac autonomic nervous system (ICANS) modulation

Further research on larger groups with long-term follow-up might allow for the identification of the appropriate ablation modality tailored to the clinical and autonomic profile and needs of each patient.

ORCID iDs

Piotr Brzozowski <https://orcid.org/0000-0003-0206-8124>

Piotr Niewiński <https://orcid.org/0000-0001-8148-071X>

Stanisław Tubek <https://orcid.org/0000-0002-0059-5150>

Krzysztof Nowak <https://orcid.org/0000-0001-9078-0087>

Piotr Ponikowski <https://orcid.org/0000-0002-3391-7064>

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