JACC: CLINICAL ELECTROPHYSIOLOGY VOL. ■, NO. ■, 2022

PUBLISHED BY ELSEVIER

Autonomic Changes Are More Durable After Radiofrequency Than Pulsed Electric Field Pulmonary Vein Ablation

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ABSTRACT

OBJECTIVES We investigated whether PVI by a PEF compared with RF energy will result in less prominent alteration of the cardiac autonomic nervous system.

BACKGROUND Pulmonary vein isolation (PVI) by radiofrequency (RF) energy is associated with a collateral ganglionated plexi ablation. Pulsed electric field (PEF) is a nonthermal energy source that preferentially affects the myocardial cells and spares neural tissue.

METHODS A total of 31 patients with atrial fibrillation underwent PVI using a novel lattice-tip catheter and PEF energy (n = 18) or a conventional irrigated-tip catheter and RF energy (n = 13). The response of the sinoatrial node and atrioventricular node to extracardiac high-frequency, high-output, right vagal nerve stimulation was evaluated at baseline and during and at the end of the ablation procedure. Substantial reduction in responsiveness was arbitrarily defined as stimulation-inducible pause <1.5 seconds.

RESULTS Reduced response of the sinoatrial node was documented in 13 of 13 (100%) and 6 of 18 (33%) patients ($P = 0.0001$) in RF and PEF groups, respectively. Reduced response of the atrioventricular node was found in 10 of 11 (93%) and 6 of 18 (33%) patients ($P = 0.002$) in RF and PEF groups, respectively. The major effects were observed predominantly during ablation around the right pulmonary veins. Early recovery of ganglionated plexi function was noticed only in the PEF ablation group. RF ablation resulted in higher acceleration of the sinus rhythm compared with PEF ablation (20 ± 13 beats/min vs 12 ± 10 beats/min; $P = 0.04$).

CONCLUSIONS PEF compared with RF energy used for PVI induces significantly weaker and less durable suppression of cardiac autonomic regulations. (J Am Coll Cardiol EP 2022;■:■-■) © 2022 by the American College of Cardiology Foundation.

Catheter ablation is a well-established treatment modality for rhythm control in patients with drug-refractory atrial fibrillation (AF).[1,2] Contemporary ablative energy sources such as radiofrequency (RF) energy, cryoenergy, and laser energy cause nonselective thermal destruction of the target tissue. Recently, a novel technique of nonthermal energy called a pulsed electric field (PEF) has been introduced.[3-5] This method uses short direct-current electric field pulses to create pores in cardiomyocyte cell membranes resulting in apoptosis (irreversible electroporation). The advantage of this method is a short duration of the energy delivery and low potential for collateral damage caused by the high sensitivity of cardiomyocytes compared with surrounding cells, including the phrenic nerve and esophagus. On the other hand, PEF ablation may not significantly influence autonomic

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received December 28, 2021; revised manuscript received March 28, 2022, accepted April 24, 2022.

ISSN 2405-500X/$36.00 https://doi.org/10.1016/j.jacep.2022.04.017

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

AV = atrioventricular

AVN = atrioventricular node

ECVS = extracardiac vagal stimulation

GPs = ganglionated plexi

HRV = heart rate variability

PEF = pulsed electric field

PV = pulmonary vein

PVI = pulmonary vein isolation

RF = radiofrequency

SAN = sinoatrial node

innervation to the heart that would be comparable to pulmonary vein isolation (PVI) performed by thermal energy. Ablation of ganglionated plexi (GP) by RF energy during PVI is believed by many to contribute to the overall clinical effect of the catheter ablation procedure.[6-9] Whether PEF applications can affect cardiac autonomic ganglia remains unknown. In the present study, we hypothesized that PVI by PEF compared with RF energy will result in less prominent acute alteration of the cardiac autonomic nervous system (ANS).

METHODS

A single-center, prospective, parallel-arm, nonrandomized study was conducted at our institution. A study was approved by the institutional ethical committee and conducted in accordance with the Declaration of Helsinki.

STUDY POPULATION. We enrolled all (n = 18) consecutive patients undergoing point-by-point PEF ablation and a random sample (n = 13) of comparable patients undergoing standard RF ablation. All patients signed informed consent with the study procedures.

CATHETER ABLATION PROCEDURE. Ablation procedures were performed on uninterrupted oral anticoagulation and under general anesthesia. Administration of parasympatholytic drugs was prohibited during the procedure. General anesthesia was induced by sufentanil and propofol and was maintained with volatile agent desflurane. Patients were relaxed using rocuronium bromide when needed. Patients who presented with AF were cardioverted. Unfractionated heparin was administered before transseptal puncture as an initial bolus and continuous infusion was adjusted to maintain the activated clotting time between 300 and 350 seconds. One decapolar catheter was deployed into the coronary sinus. The left atrium was accessed via a single or double transseptal puncture that was facilitated by intracardiac echocardiography (AcuNav, Siemens Medical Solutions). In all patients, left pulmonary veins (PVs) were isolated first.

PULSED ELECTRIC FIELD ABLATION. PVI was performed using a novel 3-dimensional electroanatomical mapping/ablating system that has been described previously (Affera, Inc).[10] The 8-F ablation catheter is equipped with a 9-mm expandable lattice tip that contains 9 microelectrodes and 9 thermocouples, distributed equally on the surface of the lattice-tip (Sphere-9, Affera, Inc).[10,11] PEF is delivered in a point-by-point manner to achieve circumferential ipsilateral PVI. A dedicated PEF generator (HexaPulse, Affera, Inc) was used, and PEF (24-32 Amps, biphasic pulses) was applied in short microsecond-scale pulses over 4 seconds (synchronized to either atrial or ventricular depolarization) between the lattice-tip and a skin patch position on the patient's back during saline irrigation of 15 mL/min. Bidirectional conduction block across the ablation line was confirmed by pacing from the PVs.

RF ABLATION. PVI was navigated using a 3-dimensional electroanatomic mapping system CARTO 3 (Biosense Webster) and guided by intracardiac echocardiography. PVs were isolated using a 3.5-mm irrigated-tip catheter (NaviStar ThermoCool, Biosense Webster). Circumferential lesions were created around PV ostia in a point-by-point fashion. During saline irrigation of 17 mL/min, RF energy was delivered using SmartAblate generator (Biosense Webster) in power-controlled mode with output set at 25-30 W on the anterior wall and 20-25 W at the posterior wall of the left atrium, respectively. Duration of each application at a single spot varied between 25 and 35 seconds. PVI was confirmed by a 10-pole circular Lasso catheter (Biosense Webster) positioned at the ostial level of PVs.

ELECTROPHYSIOLOGICAL STUDY. Twelve-lead surface electrocardiograms and bipolar intracardiac electrograms were recorded on the CardioLab system (GE Healthcare). A programmable cardiac stimulator EPS320 (MicroPace EP Inc) was used to deliver electrical impulses as appropriate. The mean sinus rate (over the 10 consecutive cycles), sinus node recovery time, and Wenckebach point were assessed at baseline and at the end of the procedure. Extracardiac vagal stimulation (ECVS) using the Neurostimulator Pachon was performed as described in detail in the study by Pachon et al.[12] Briefly, the second decapolar catheter (with electrode spacing of 2-5-2 mm) was introduced into the right internal jugular vein to the level of upper wisdom tooth with the posteromedial bend via the 7-F/90-cm Super Arrow-Flex® sheath (Teleflex) from the groin access (Central Illustration). The bipolar stimulation between the distal and third electrode (with mutual distance of 7 mm) was accomplished with a frequency of 50 Hz, a pulse width of 0.05 ms, an output of 1 V/kg (<70 V), and a train duration of 5 seconds. The catheter position was slightly adjusted to maximize the response of the sinus and atrioventricular node (AVN). Once reached, this position was recorded on the x-ray system and used as a reference for repeated stimulation during the study. The response of sinoatrial node (SAN) and

AVN to ECVS were recorded before, immediately after the left and the right PVI and after 20 minutes from the last energy application, and it was quantified by the longest ECVS-induced pause, ie, maximum P-P interval during the sinus rhythm and maximum R-R interval during atrial pacing. Substantial reduction in responsiveness at the end of the procedure was arbitrarily defined as a maximum inducible pause ≤1.5 seconds.

STATISTICAL ANALYSIS. The statistical analyses were conducted using a combination of SPSS (version 23, SPSS Inc) and R (R Foundation). Continuous variables were described as means with SDs and compared with a 2-tailed *t-test* for independent samples. Variables with non-normal distribution were compared by the nonparametric Mann-Whitney test. Categorical variables were compared by Fisher exact test. Within-patient time-dependent data were analyzed using analysis of variance for repeated measures. Post hoc tests were performed using Bonferroni corrections. A P value < 0.05 was considered statistically significant.

RESULTS

PVI was achieved in all PVs in all patients, representing 62 electrically complete circular lesions around ipsilateral veins. No major clinical complications, including cardiac tamponade, stroke, phrenic nerve injury, and esophageal injury, occurred. The baseline clinical characteristics were comparable in both groups (Table 1). However, patients scheduled for ablation using RF energy were more likely to be in sinus rhythm on admission and had lower body mass index.

At baseline, physiological response to ECVS (long sinus arrest and/or atrioventricular [AV] block) was apparent in most of the patients in both groups.

RF ABLATION GROUP. In the RF ablation group, isolation of the left-sided PVs had an inconsistent but, on the average, neutral impact on SAN and AVN response to ECVS. In contrast, isolation of the right-sided PVs abolished the response almost completely, and this effect persisted until the end of the procedure (Figure 1, top).

PEF ABLATION GROUP. In the PEF group, both SAN and AVN responses to ECVS progressively attenuated during the ablation of all PVs with perceptible effects already after the left-sided PVI and additive effect of right-sided PVI. However, the cardiac ANS function markedly recovered during the 20-minute waiting period (Figure 1, bottom).

TABLE 1 Baseline Characteristics

	Radiofrequency Group (n = 13)	Pulsed Electric Field Group (n = 18)	*P* Value
Age, y	53 ± 16	59 ± 10	0.2
Male	7 (54)	15 (83)	0.11
Body mass index, kg/m^2	26 ± 3.6	31 ± 5.3	0.008
Arterial hypertension	8 (62)	11 (61)	1
Diabetes mellitus	1 (8)	2 (11)	1
Coronary artery disease	1 (8)	2 (11)	1
Transient ischemic attack or stroke	0 (0)	2 (11)	1
Left ventricular ejection fraction, %	59 ± 1	57 ± 5	0.07
Left atrium volume index, ml/m^2	34 ± 10	39 ± 9	0.10
Atrial fibrillation duration, months	36 ± 53	28 ± 23	0.60
Beta-blockers	9 (69)	15 (83)	0.41
Antiarrhythmic drugs[a]	8(61)	14 (77)	0.43
Sinus rhythm on admission	12 (92)	9 (50)	0.01

Values are mean ± SD or n (%). [a]Propafenone or amiodarone.

COMPARISON OF PEF VS RF ABLATION GROUPS. Immediately after PVI, the responsiveness of SAN to ECVS was influenced significantly less after PEF compared with RF ablation ($P = 0.001$), whereas the between-group difference in AV node responsiveness was not significant ($P = 0.48$). However, as a result of the rapid recovery of neural tissue during the waiting period, the difference between the RF and PEF ablation groups fully manifested at the end of the procedure (Figure 2).

Final effects on responsiveness in the categorical evaluation were also significantly weaker after PEF vs RF ablation (Figure 3). Substantial reduction in the responsiveness of the SAN was demonstrated in 13 of 13 (100%) and 6 of 18 (33%) patients ($P = 0.0001$) in RF and PEF groups, respectively. Analogically, reduced responsiveness of the AVN was observed in 10 of 11 (93%) and 6 of 18 (33%) patients ($P = 0.002$) in RF and PEF groups, respectively (Figure 3). In the same line, RF ablation was accompanied by significantly higher acceleration of the sinus rhythm (20.3 ± 13.2 vs 12.1 ± 9.9; $P = 0.04$) compared with PEF ablation (Table 2). The durations of the procedures were 170 ± 40 minutes and 152 ± 24 minutes in the RF and PEF groups, respectively ($P = 0.15$).

DISCUSSION

We quantified for the first time the impact of the PEF PVI on the vagal innervation of the SAN and AVN using ECVS. We confirmed that RF PVI alone is highly efficient in eliminating vagal responses at the level of both SAN and AVN and that this effect, which is primarily achieved by ablation around right PVs, is

FIGURE 1 **Time Course of SAN and AVN Responsiveness to ECVS During the RF and PEF Ablation Procedure**

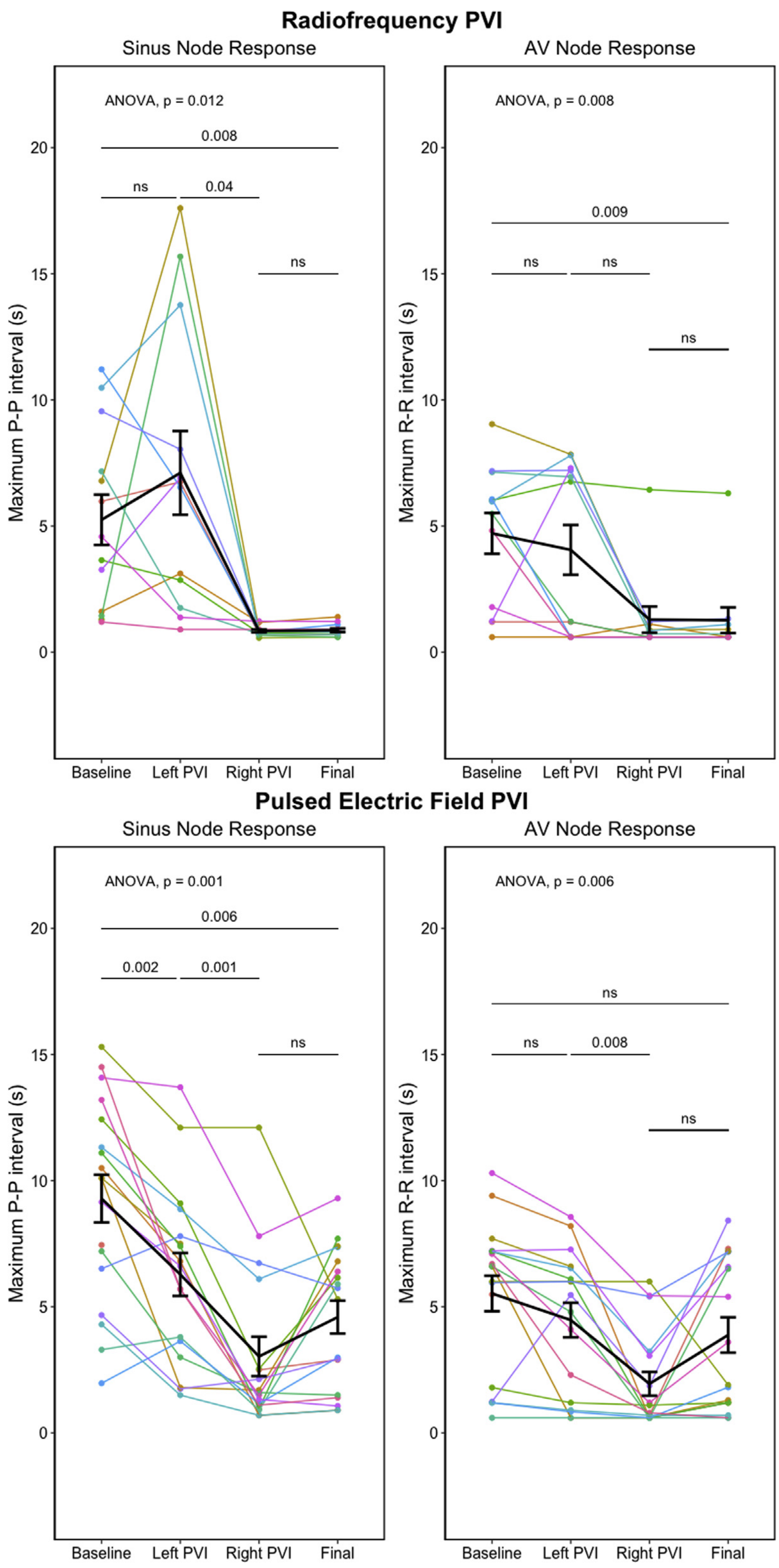

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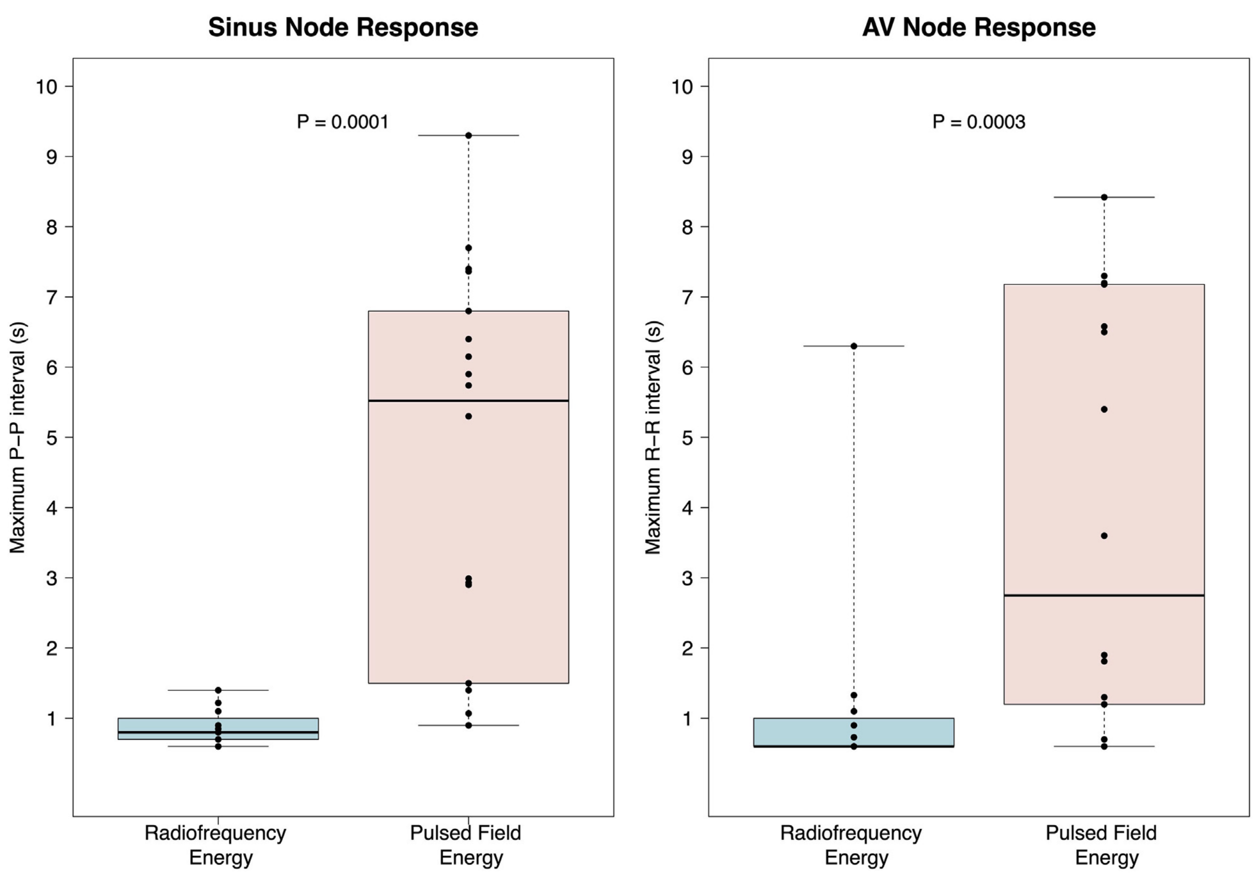
FIGURE 2 **SAN and AVN Responsiveness to ECVS at the End of the Procedure: Continuous Variable Evaluation**



The maximum P-P interval in sinus rhythm **(left)** and R-R interval while atrial pacing **(right)** induced by ECVS is compared between RF **(red)** and PEF **(cyan)** ablation groups. **Boxes** indicate medians and IQR. The **whiskers** indicate the maximum and minimum values. Abbreviations as in Figure 2.

intraprocedurally durable. We newly revealed that the PEF PVI results in significantly weaker abolition of the vagal responses and that early recovery can be observed within the range of a few minutes (Central Illustration).

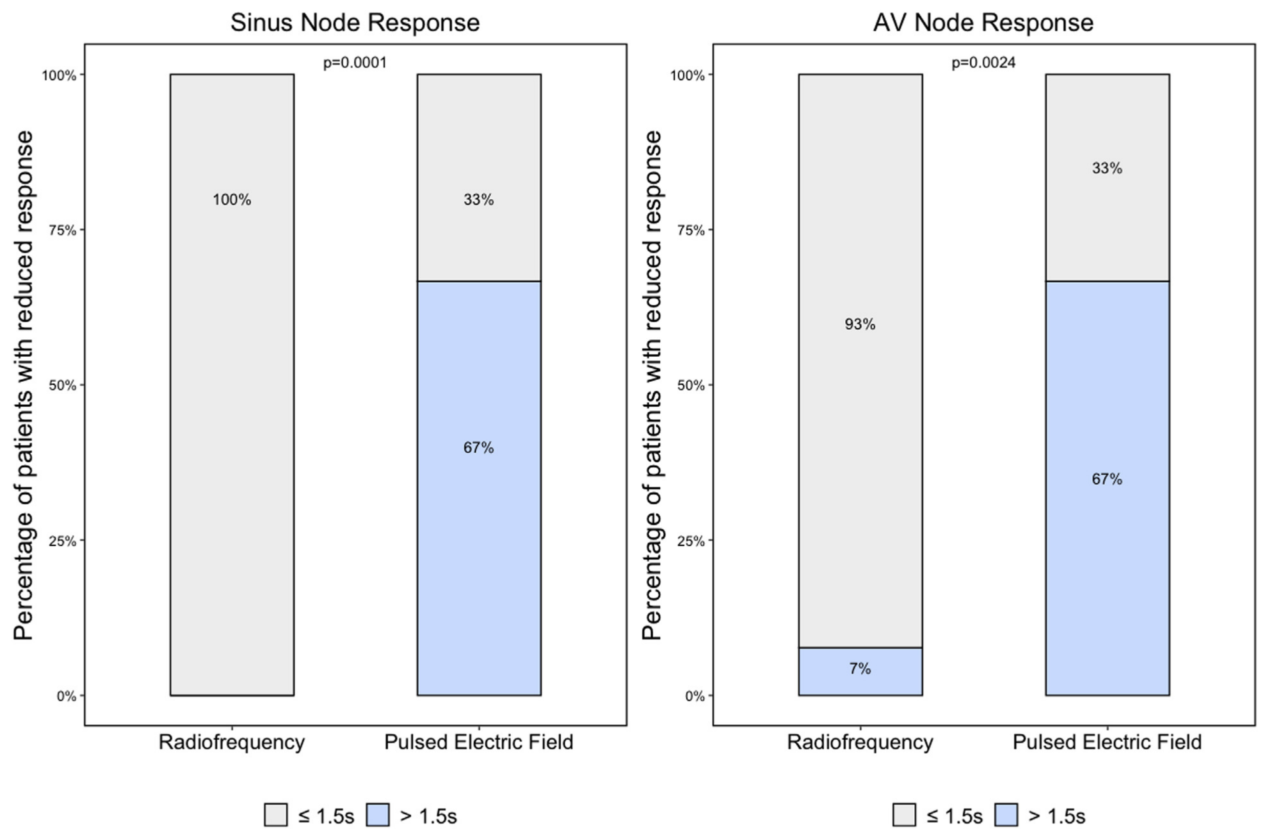
The results must be seen in the context of the potential role of vagal action in the pathogenesis of AF and the efficacy of catheter ablation.

ABLATION OF GPs. ANS plays an important role in regulation of cardiac functions.[13,14] Earlier observations have suggested that parasympathetic attenuation after RF PVI might play a role in preventing late arrhythmia recurrence.[6-9] Ablation of GPs occurs as “collateral damage” during PVI and the effect is more durable after large antral compared with ostial lesions.[15] Although some studies have shown a benefit of adding intrinsic ANS modulation to PVI,[7,8] others have not.[14,16] The ablation of GPs alone has never been superior to PVI.[17-19] Nevertheless, if the thermal ablation of GPs has an adjuvant

FIGURE 1 **Continued**

(Top) RF and **(bottom)** PEF ablation procedure. The maximum induced P-P interval in sinus rhythm **(left)** or R-R interval while atrial pacing **(right)** is plotted at baseline, after left- and right-sided PVI, and after 20 minutes of waiting period (final). The **colored lines** depict the trend in individual patients. **Black lines with error bars** are for group means and SEs. ANOVA = analysis of variance; AV = atrioventricular; AVN = atrioventricular node; ECVS = extracardiac vagal stimulation; PEF = pulsed electric field; PVI = pulmonary vein isolation; RF = radiofrequency; SAN = sinoatrial node.

FIGURE 3 **SAN and AVN Responsiveness to ECVS at the End of the Procedure: Categorical Evaluation**



The maximum P-P interval <1.5 seconds in sinus rhythm **(left)** and maximum R-R interval <1.5 seconds while atrial pacing **(right)** induced by ECVS define substantial reduction of responsiveness to parasympathetic stimuli. RF and PEF ablation groups are compared. Abbreviations as in Figure 1.

effect on suppression of AF, PEF ablation with the limited collateral damage of neural tissue may be theoretically handicapped in terms of efficacy compared to RF ablation.

Ablation of GPs can be targeted anatomically, guided by endocardial high-frequency stimulation[20] or single-photon emission computed tomography imaging.[21] In our study, PV ostia were ablated circumferentially without selective targeting of GPs. It is well known, however, that PV antrum isolation by thermal energy results in a profound reduction of responsiveness of both sinus and AV nodes to vagal stimulation. Therefore, patients undergoing RF energy ablation served as a suitable comparator group for investigating the hypothesis that PEF ablation is associated with a lower effect on parasympathetic innervation of both nodes.

ASSESSMENT OF CARDIAC ANS FUNCTION. Previous studies have shown a significant impact of RF ablation for AF on cardiac ANS function, with an increase of mean heart rate (around 10 beats/min) postablation.[22-24] The increase was found to be positively associated with a significantly lower rate of AF recurrences.[25] However, such an observation may not be causal. A higher elevation of heart rate after PVI because of higher parasympathetic modulation at baseline might be an epiphenomenon of younger age and/or absence of comorbidities in patients who are principally less prone to AF recurrences. We observed a much higher increase in heart rate in our patients after RF ablation (around 20 beats/min) because this change was investigated intraprocedurally when its magnitude is the highest, whereas the effect weakens during the follow-up.

Attenuated heart rate variability (HRV) is another marker of reduced cardiac ANS activity. This was also reported to be associated with a better outcome of AF ablation.[23,24,26] Various HRV measures can be used, including the simple time-domain indexes, advanced frequency domain measures, descriptors of heart rate

TABLE 2 Changes of Electrophysiological Parameters

	Radiofrequency Ablation (n = 13)			Pulsed Electric Field Ablation (n = 18)			
	Before PVI	After PVI[a]	Change	Before PVI	After PVI[a]	Change	*P* Value RF vs PEF
Heart rate, beats/min[b]	60.5 ± 8.7	80.8 ± 8.8	+20.3 ± 13.2[c]	55 ± 11.5	67.1 ± 9.9	+12.1 ± 9.9[c]	0.04
Heart rate, beats/min[d]	55 ± 8.2	73.3 ± 15.5	+18.6 ± 11.9[c]	49.2 ± 9.0	60.7 ± 15.5	+11.5 ± 13.4[c]	0.06
Sinus node recovery time, ms	1,322 ± 301	1,116 ± 309	−205 ± 338[e]	1,794 ± 650	1,500 ± 484	−294 ± 586[e]	0.7
Wenckebach point, beats/min	155 ± 23	156 ± 25	+1.5 ± 12[f]	126 ± 22	132 ± 22	+5.7 ± 21[f]	0.6

Values are mean ± SD. [a]At the end of the procedure (after the waiting period). [b]Mean heart rate from standard surface electrocardiogram recorded at the ward. [c]$P < 0.005$ (for the statistical significance of the change within the study groups). [d]Mean heart rate recorded during the ablation procedure. [e]$P \le 0.05$. [f]$P > 0.05$.
PVI = pulmonary vein isolation.

turbulence, heart rate recovery, or acceleration/deceleration capacity of the heart rate by sophisticated signal-processing technology.[26] The disadvantage of all of these methods is that they require several hours (or at least several minutes) of electrocardiogram recording, so they are not suitable for the assessment of intraprocedural dynamics of HRV.

UTILITY OF THE ECVS. To overcome this, we have used the ECVS technique proposed by Pachon et al,[27] which was already used in previous studies for the quantification of acute reduction of parasympathetic innervation during cryoballoon ablation.[28] The ECVS can be repeatedly assessed during the procedure with almost instant assessment of temporal evolution of cardiac vagal innervation (including trends to recovery during the waiting period). Another advantage of the ECVS is that, unlike HRV, which is limited to analysis of the behavior of SAN, the parasympathetic innervation of AVN can be assessed with the help of atrial pacing. Such a systematic investigation of vagal modulation of both nodes in the setting of PVI was performed for the first time in our study.

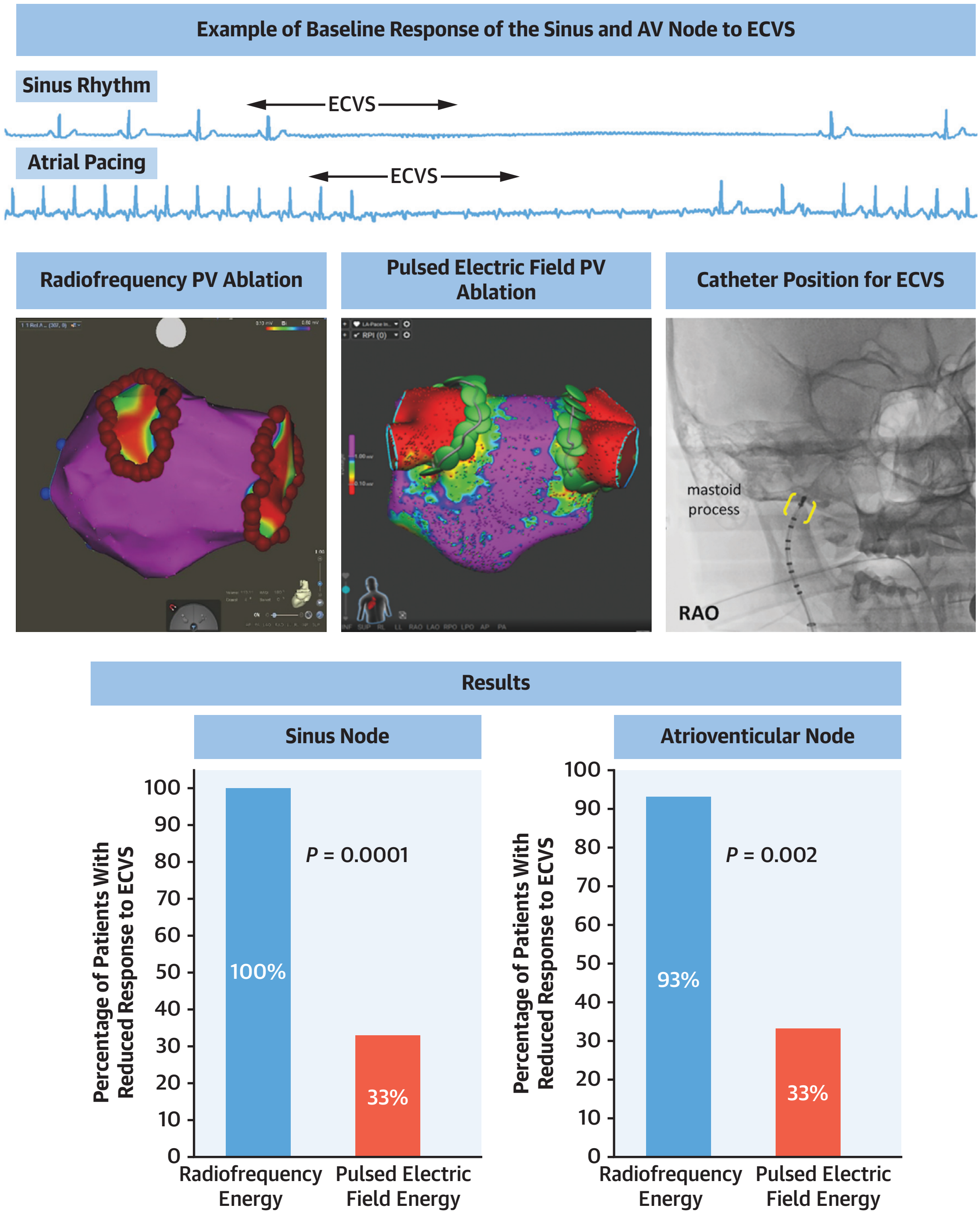
We stimulated the right vagal nerve because access to the right vs left jugular vein is considerably easier. As the right vagal nerve innervates predominantly the SAN, stronger responses of SAN vs AVN were observed at baseline. We do not consider this to be a limitation because we used the right ECVS consistently in all patients and primarily investigated the relative change of vagal responses during the ablation procedure.

COLLATERAL AF ABLATION EFFECTS. Known effects of ablation on cardiac ANS were derived mainly from studies that used RF energy. However, comparable modulation of cardiac ANS was also reported after cryoballoon-based PVI[29,30] and is probably present in all thermal energy ablations. Interestingly, the RF PVI resulted in complete loss of responsiveness of both SAN and AVN to ECVS in all but 1 patient (with persistent AVN innervation only), even if specific sites of GPs were ablated merely because of spatial coincidence within PV antra or were not targeted at all (namely those responsible for AVN innervation). Perhaps, the major attenuation of vagal responses was associated with isolation of right-sided PVs, and this was in agreement with results of previous studies.[22,29] Although the reduction in responsiveness was weaker after PEF ablation, it was rather concordant with RF ablation in terms of the higher impact of right PVI.

Until now, it was not possible to differentiate whether the modulation of cardiac ANS is required for the prevention of AF recurrences or whether it is only a bystander effect.

Given the high selectivity of PEF ablation for cardiomyocytes compared with neural cells, not only is PEF ablation promising in overcoming the drawbacks of RF or cryo-based approaches to PVI, but it may also serve as an investigational tool that yields highly durable PVI with a limited extent of GPs ablation. Our observations confirm for the first time that PEF results in transient abolition of the vagal responses with subsequent early recovery, probably because of the neural stunning effect. Whether this will be reflected by lower efficacy of ablation in the maintenance of sinus rhythm has to be verified. In this respect, a recent study has shown a high clinical success rate of 84% in patients undergoing PEF PVI at 1 year follow-up.[31] In addition, the role of parasympathetic modulation of the heart in the prevention of AF recurrence is not well established. Although attenuation of vagal innervation may have a protective role, the opposite intervention—intermittent low-level transcutaneous stimulation of the auricular branch of the vagal nerve—was shown to lower the median AF burden in a randomized trial.[32] This suggests that elimination of parasympathetic innervation may not be necessary for successful AF elimination. Whether adjuvant modulation of the cardiac ANS may play a role in selective patient subpopulation remains to be elucidated by upcoming studies.

CENTRAL ILLUSTRATION Acute Change of Responsiveness of Sinoatrial Node and Atrioventricular Node to Extracardiac Vagal Stimulation After Pulmonary Vein Isolation



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Example of baseline response to extracardiac vagal stimulation during sinus rhythm and atrial stimulation **(top)**. Voltage remaps after pulmonary vein isolation performed by radiofrequency and pulsed electric field energy and the x-ray of the skull with decapolar catheter position used for extracardiac vagal stimulation **(middle)**. The results are shown on the **bottom**.

STUDY LIMITATIONS. First, only acute effects of PVI were investigated. Even if there was a significant recovery of the parasympathetic branch of cardiac ANS after PEF ablation within the first 20 minutes of the waiting period, we cannot speculate whether this is followed by further restoration, with a theoretical return to preablation level. Second, the small number of patients were allocated to treatment strategies in a nonrandomized fashion, limiting the direct comparison between groups, subgroup analyses, and applicability of results. Third, although the differences between study groups were not significant for the majority of baseline variables (because of the small sample size), the patients in the PEF group had more advanced disease with a higher proportion of patients on beta-blockers and antiarrhythmic therapy, lower proportion of patients in sinus rhythm on admission, and lower baseline sinus rate. All of these factors could contribute to between-group differences in the PVI-induced suppression of cardiac ANS function. Fourth, a longer duration of general anesthesia in the RF group could hypothetically potentiate the gradual suppression of cardiac ANS. However, both sudden change in cardiac ANS function after the right PVI and a trend toward recovery in the waiting period in the PEF group go against this concept. Fifth, we investigated merely the innervation of SAN and AVN, which is not equivalent to overall atrial innervation. In addition, recent studies[33,34] have shown that there is significant discordance between the location of GPs that either cause bradycardia responses or trigger atrial ectopy that may initiate or perpetuate AF. The outcome measure in our study was based on the functional assessment of bradycardia-related GPs. Sixth, the acute effect of ablation on cardiac sympathetic innervation was not assessed because of the absence of a clinically suitable surrogate measure. A certain degree of loss of sympathetic innervation can be expected because previous studies demonstrated that adrenergic and cholinergic nerves are highly colocated close to the PV-LA junction.[35] Finally, the efficacy of PEF ablation is conditioned by ablation catheter type, pulse energy and duration, and many other PEF characteristics. Our data are relevant for a specific mapping and ablating system with a lattice-tip ablation catheter introduced by the Affera company.

CONCLUSIONS

PEF ablation provides a unique opportunity to test in the clinical setting the hypothesis of whether ablation of GPs during PVI contributes to the effectiveness of AF ablation. Our data suggest that cardiac vagal response is preserved in a considerable proportion of AF patients after PEF ablation, which is in contrast to a significantly stronger effect of RF energy. Therefore, it would be important to analyze the freedom from AF during the follow-up in both study groups.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

This work has received institutional support from the project (Ministry of Health, Czech Republic) for development of research organization 00023001 (IKEM, Czech Republic). Dr Peichl has received speaker honoraria from St. Jude Medical (Abbott); and has served as a consultant for Biotronik and Boston Scientific. Dr Nakagawa has served as a consultant of Affera, Inc, Biosense Webster, and Gallaxy Medical, Inc. Dr Kautzner has received personal fees from Bayer, Biosense Webster, Boehringer Ingelheim, Medtronic, and St. Jude Medical (Abbott) for participation in scientific advisory boards; and has received speaker honoraria from Bayer, Biosense Webster, Biotronik, Boehringer Ingelheim, Daiichi Sankyo, Medtronic, Merck Sharp and Dohme, Mylan, Pfizer, ProMed, and St. Jude Medical (Abbott). All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Significant alteration of cardiac ANS functions has been described as a collateral effect of PVI. Previous studies suggested that targeted ablation of GPs on top of PVI may have a beneficial effect in terms of the clinical outcome of the procedure. Our data suggest that cardiac vagal response is preserved in a considerable proportion of AF patients after PEF ablation, which is in contrast to a significantly stronger effect of RF energy ablation.

TRANSLATIONAL OUTLOOK: Further studies are needed to elucidate whether a stronger alteration of cardiac ANS after PVI is associated with a better clinical outcome of the procedure.

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KEY WORDS atrial fibrillation, autonomic regulation, catheter ablation, ganglionated plexi, pulsed electric field