ДРУЖЕСТВО НА КАРДИОЛОЗИТЕ В БЪЛГАРИЯ
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НЕЦЕЛЕНАСОЧЕНА НЕВРОМОДУЛАЦИЯ ПРИ ИЗОЛАЦИЯ НА БЕЛОДРОБНИТЕ ВЕНИ ЗА ПРЕДСЪРДНО МЪЖДЕНЕ – НЕПОСРЕДСТВЕНИ И КРАТКОСРОЧНИ ЕФЕКТИ НА РАДИОФРЕКВЕНТНАТА И КРИОГЕННАТА ЕНЕРГИЯ

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INADVERTENT NEUROMODULATION DURING PULMONARY VEIN ISOLATION FOR ATRIAL FIBRILLATION – IMMEDIATE AND SHORT-TERM EFFECTS OF RADIOFREQUENCY AND CRYOGENIC ENERGY

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Резюме. Нецеленасочената вагусова денервация е докладвана като съпътстващ ефект при изолация на белодробните вени (ИБВ) за предсърдно мъждене (ПМ). Не е известно обаче колко често възниква този ефект и колко траен е при термална аблация. **Материал и методи:** Това е ретроспективно проучване на последователни пациенти с ПМ и първа ИБВ с радиофреквентна или криогенна енергия в синусов ритъм. Изследвахме честотата на трайното ускоряване на сърдечната честота (СЧ) и/или предизвикване и елиминиране на вагусов рефлекс (ВР), както и персистирането на увеличена СЧ на първия месец. **Резултати:** ИБВ беше извършена при 102 пациенти (крио, n = 46). При 60 пациенти (58.8%) настъпи нецеленасочена невромодулация, изразяваща се в предизвикване и елиминиране на ВР (n = 18, 17.6%), а най-често – в увеличаване на СЧ (n=50, 49%). При пациентите със спрямо тези без ускоряване на СЧ, средното увеличение на СЧ в края на процедурата беше 14.2 ± 5.64 уд./min срещу -2.63 ± 5.43 уд./min, а на следващия ден – 10.6 ± 7.53 уд./min срещу 3.68 ± 7.75 (p < 0.001 за всички). Средната СЧ на първия месец беше 74.2 ± 9.91 уд./min срещу 68.9 ± 12 уд./min (p=0.048). Пациентите с трайно увеличаване на СЧ бяха по-млади (медианна възраст 61 срещу 65.5 години, p = 0.016) и по-рядко имаха сърдечна недостатъчност с намалена изтласна фракция (1% срещу 6.9%, p = 0.031). **Заключение:** Нецеленасочена невромодулация възниква при повече от половината пациенти с радиофреквентна или криогенна ИБВ за ПМ. Ефектът е представен предимно от увеличаване на сърдечната честота и персистира поне до края на първия месец след процедурата.

Ключови думи: кардионевроаблация; вагусова денервация; предсърдно мъждене

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Abstract. Inadvertent vagal denervation has been reported as an adjunctive effect during pulmonary vein isolation (PVI) for atrial fibrillation (AF). However, it is not known how frequent and durable this effect is during thermal ablation. **Material and methods:** This is a retrospective study of consecutive patients with AF and first PVI in sinus rhythm using radiofrequency or cryogenic energy. We studied the incidence of non-targeted and non-transient heart rate (HR) acceleration, induction and abolition of vagal reflex (VR), as well as the durability of the HR increase at the end of the first month. **Results:** PVI was carried out in 102 patients (cryo, n = 46). Overall, 60 patients (58.8%) had inadvertent neuromodulation, presented by VR induction and abolition (n = 18, 17.6%) and predominantly by HR increase (n = 50, 49%). In patients with vs those without HR acceleration the mean HR increase at the end of the procedure was 14.2 ± 5.64 bpm vs. -2.63 ± 5.43 bpm, and at the next day – 10.6 ± 7.53 bpm vs. 3.68 ± 7.75 bpm (p < 0.001 for all). The mean HR at 1 month was 74.2 ± 9.91 bpm vs. 68.9 ± 12 bpm (p = 0.048). Patients with a durable HR increase were younger (median age 61 vs. 65.5 years, p = 0.016) and less frequently had heart failure with reduced ejection fraction (1% vs. 6.9%, p = 0.031). **Conclusion:** Inadvertent neuromodulation occurs in more than half of the patients with radiofrequency or cryo PVI for AF. It is mostly represented by a HR increase and persists for up to at least one month post-procedurally.

Key words: cardioneuroablation; vagal denervation; atrial fibrillation

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Introduction

Inadvertent vagal denervation has long been reported as an adjunctive effect during radiofrequency (RF) pulmonary vein isolation (PVI) for atrial fibrillation (AF) [1, 2]. Its occurrence is due to a major overlap of the locations of the epicardial ganglionated plexi and the ablation lines around the PV ostia [3-5]. The abolition or dampening of the vagal tone may exert a favorable effect on decreasing the recurrences of AF by way of lengthening the atrial effective refractory period and decreasing its dispersion, especially in patients with "vagal" AF [1, 5-8]. However, data on how often non-targeted vagal denervation during PVI is achieved and how durable is this effect during cryoballoon ablation for AF is scarce [9].

Our aim was to study the incidence of non-targeted neuromodulation during PVI by means of radiofrequency or cryogenic energy in patients with AF and compare the immediate and short-term durability of the effect.

Material and methods

Patient population

We retrospectively studied consecutive patients with AF and first RF or cryo PVI procedure performed between January 2023 and May 2024. The inclusion criteria were the following: patients with symptomatic paroxysmal or persistent AF, refractory to at least one antiarrhythmic drug, who were in sinus rhythm before the first and after the last delivery of ablation energy and without an indication for cardioneuroablation (CNA). The exclusion criteria were: previous CNA; purposeful CNA within the procedure; previous PVI procedure; non-sinus rhythm before the first and after the last energy delivery (pacemaker; AF; atrial flutter; atrial tachycardia).

Pulmonary vein isolation

All patients underwent a contrast-enhanced multidetector computed tomography scan of the left atrium. The image series were segmented and 3-dimensional reconstruction of the left atrium and the PVs was created prior to the procedure. Oral anticoagulation was not interrupted and non-fractionated heparin was administered immediately after the transseptal puncture and thereafter during the procedure.

Radiofrequency PVI was performed as previously described. [10] The EnSite Precision system (Abbott, MN, USA) was used for electroanatomic mapping in all RF procedures. Briefly, a reference catheter was inserted in the coronary sinus. A steerable 10-polar variable loop circular mapping catheter with 7 mm interelectrode distance and 4 mm tipped irrigated ablation catheter were introduced transseptally in the left atrium. A geometrical reconstruction of the left atrial endocardial shell, the proximal parts of the left atrial appendage and the PVs, together with an automatic bipolar voltage map were created simultaneously using the circular mapping catheter. Then, circumferential ablation was performed until complete electrical isolation of all PVs was achieved as verified by the disappearance or dissociation of the PV potentials on the circular mapping catheter positioned in each vein, and by non-capture of the atrium during pacing with an output > 10 mA in the veins. The order of isolation of the PVs was left at the discretion of the operator.

Cryoablation was done using the SmartFreeze cryoconsole (Boston Scientific, MA, USA) and 28-mm cryoballoon introduced in the left atrium over an 8-polar circular mapping catheter with 6 mm interelectrode distance via a steerable sheath. The inflated cryoballoon was inserted in the PVs until occlusion was achieved. Freezing time was 240 seconds for each of the left-sided PVs and 180 seconds for each of the right-sided PVs. The freezing sequence started always with left superior PV, followed by left inferior, right inferior and right superior PV. High-output pacing was delivered in the superior caval vein to monitor the function of the right phrenic nerve during the cryoablation of the right-sided veins. Electrical isolation of all PVs was verified by disappearance or dissociation of the PV potentials on the circular mapping catheter positioned in each vein, and by non-capture of the atrium during pacing with an output > 10 mA in the veins.

Neuromodulation

All EP records were reviewed for the occurrence of a vagal reflex (VR) or sudden non-transient increase of the sinus heart rate (HR). Neuromodulation was arbitrarily defined as induction and abolition of a VR or as induction of a sudden non-transient increase of the baseline HR by ≥ 10% or shortening of the sinus cycle length ≥ 100 ms during energy delivery (Fig. 1A). Vagal reflex was defined as the sudden occurrence of sinus bradycardia ≤ 40 bpm or a sinus pause > 2 seconds during energy delivery (Fig. 1B).

Data was collected on the demographic and clinical characteristics of the patients, the incidence of neuromodulation, the sites of induction of VR and/or HR acceleration, the HR at baseline, at the end of the procedure, and on the next day on ECG, as well as the mean HR on Holter-ECG at 1-month follow-up. The mean HR acceleration was calculated as the difference between the HR at the end and the HR at the start of the procedure. The mean next day HR acceleration was calculated as the difference between the HR on the day after the procedure and the HR at the start of the procedure.

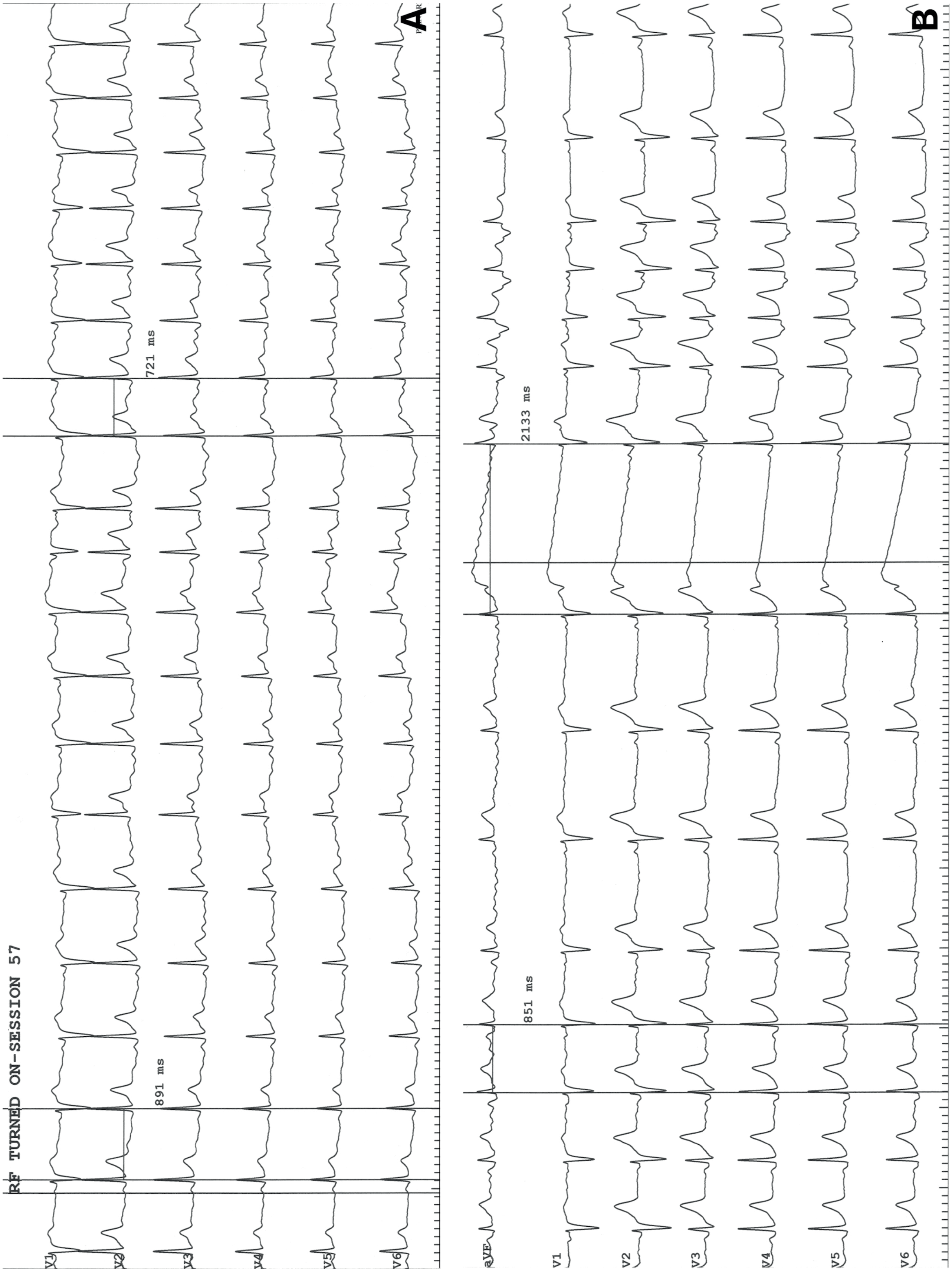

Figure 1. A – sudden heart rate acceleration. Within 9 seconds from the start of RF energy delivery the sinus cycle length shortened from 891 to 721 ms, corresponding to an acceleration of the heart rate from 67 to 83 bpm. **B** – vagal reflex. The initial heart rate of 71 bpm suddenly slowed and a pause of 2133 msec followed. After brief atrial pacing at a rate of 100 bpm a sinus heart rate of 45 bpm was restored, and subsequently increased to normal (not shown)

Statistical analysis

The statistical analysis was carried out with jamovi v.2.6 (The jamovi project 2024) [11, 12]. Distribution of data was assessed by the Shapiro-Wilk test. Continuous data were presented as mean ± standard deviation or median (interquartile range 25%-75%,). Proportions were presented as percentages. Differences between groups were assessed by the chi-squared test for association and the Brunner-Munzel test. Pre- and post-ablation differences in HR overall were assessed by the paired samples T-test. P-value < 0.05 was considered significant.

Results

During the specified time period 102 patients fulfilled the inclusion and exclusion criteria and were included in the analysis. Overall, the HR at baseline was 61.7 ± 9.47 bpm, at the end of the procedure – 67.4 ± 12.1 bpm ($p < 0.001$), and on the next day – 68.9 ± 9.06 bpm ($p < 0.001$, compared to pre-ablation). The baseline characteristics of the patients, split by the ablation energy used, are presented in Table 1. The RF and cryo groups did not differ significantly, except for the induction/abolition of VR. Irrespective of the energy used, non-transient HR acceleration, as defined above, was recorded in 50 patients (49%), equally distributed in both groups (27 vs. 23 patients, p = 0.858). Vagal reflexes were also induced in both groups; however, they were much more frequent in the cryoablation group [4 vs. 14 patients (3.9 vs. 13.7%), p = 0.002].

Vagal reflexes occurred during ablation of the left-sided PVs in 15 patients (left superior PV in 9 patients) and of the right-sided PVs in 2 patients; in 1 patient the site could not specified. All four VRs induced during RF PVI were on the left-sided PVs; 12 out of all 14 VRs recorded during cryoablation were also induced on the left side; in the remaining two patients this happened during isolation of the right superior PV. Vagal reflex alone without concomitant HR acceleration was induced in 10 patients (in 2 patients on the right-sided and in 8 patients on the left-sided PVs).

Heart rate acceleration was induced in 50 patients (in 8 there was also concomitant VR) – in 33 during isolation of the right superior PV; in 12 – the left-sided PVs; in 2 – right inferior PV; in 1 – non-specified right PV; in 1 – both on the left and right side; in 1 – the PV could not be specified. In 29 patients with RF PVI the ablation started on the right side, in which case non-transient HR acceleration was induced in 12 instances.

In the eight patients with HR acceleration and concomitant VR induction, both phenomena happened on the same PV (LSPV) in only one patient. In the remaining patients the VR was induced on the left side, while the HR acceleration ensued during ablation on the right side.

Overall, neuromodulation occurred in 60 patients (58.8%) – in 36 patients during isolation of the right-sided PVs (32 right superior PVs, 2 right inferior PVs, 2 unspecified right PVs), in 19 patients on the left-sided PVs, both on the right and left side in 3 patients, and in 2 patients on an unspecified site.

Table 1. Characteristics of the patients split by ablation energy used

	RF (n = 56)	Cryo (n = 46)	p
Sex, n M:F (% M:F)	36 : 34 (35.3 : 33.3)	20 : 12 (19.6 : 11.8)	0.297
Age (years)	64 (55.8-70)	61.5 (52.5-71)	0.742
BMI (kg/m^2)	28.3 (25.6-33.3)	28.7 (24.8-33)	0.787
Obesity (%)	21.6	15.7	0.541
Arterial hypertension (%)	51	40.2	0.509
Diabetes mellitus (%)	10.8	12.7	0.307
Coronary artery disease (%)	4.9	6.9	0.327
HFrEF (%)	2	5.9	0.077
HFpEF (%)	8.8	9.8	0.464
LVEF (%)	59.3 (55-64.3)	60 (57-64.8)	0.252
LAVI (ml/m^2)	35.7 (29.7-44.8)	39.5 (31.8-49.8)	0.131
Left atrial dilation (%)	39.2	35.3	0.431
eGFR (ml/min/1.74 m^2)	71 ± 20.5	73.4 ± 19.1	0.599
Cr Cl (ml/min/1.74 m^2)	84 (66.5-106)	90 (68.3-105)	0.723
Vagal reflex, n (%)	4 (3.9)	14 (13.7)	**0.002**
HR acceleration, n (%)	27 (26.5)	23 (22.5)	0.858
Baseline HR, bpm	62.4 ± 9.89	60.9 ± 8.96	0.36
End of procedure HR, bpm	68.1 ± 12	66.5 ± 12.2	0.576
Mean HR acceleration, bpm	5.63 ± 9.68	5.65 ± 10.7	0.87
Next day HR, bpm	69.1 ± 8.64	68.6 ± 9.64	0.819
Mean next day HR acceleration, bpm	6.82 ± 8.44	7.56 ± 8.35	0.463
Mean HR at 1 month, bpm	70.4 ± 11.8	71.7 ± 11.2	0.63

The central tendency is presented by median (25-75 percentile) or mean ± standard deviation. Obesity was defined as BMI ≥ 30. Coronary artery disease was defined as previous myocardial infarction and/or previous percutaneous coronary intervention and/or previous coronary artery bypass surgery. **BMI** – body mass index; **HFrEF/HFpEF** – heart failure with reduced/preserved ejection fraction; **LVEF** – left ventricular ejection fraction; **LAVI** – left atrial volume index; **eGFR** – estimated glomerular filtration rate; **Cr Cl** – creatinine clearance; **HR** – heart rate; **RF** – radiofrequency; **bpm** – beats per minute; **ms** – milliseconds

Comparison between RF and cryogenic energy in the 50 patients with non-transient HR acceleration did not demonstrate any significant differences, except for the incidence of VR, which was again more common in the cryoablation group (1 vs. 7 patients) (Table 2).

The differences between patients with non-transient HR acceleration and those without are shown in Table 3.

Discussion

The main finding of this retrospective single-center study is that inadvertent neuromodulation is achieved in more than half of the patients during first PVI for AF. This effect is mostly demonstrated by HR acceleration and is independent of whether RF or cryogenic energy is used for ablation. Although less pronounced, it per-

Table 2. Characteristics of the patients with HR acceleration

	RF (n = 27)	Cryo (n = 23)	p
Sex, n M:F (% M:F)	16 : 11 (32 : 22)	18 : 5 (36 : 10)	0.151
Age (years)	62 (54-69)	58 (46-66)	0.213
BMI (kg/m²)	28.9 (25.7-32.6)	29.2 (24.9-32.8)	0.885
Obesity (%)	25	16.7	0.353
Arterial hypertension (%)	48	40	0.834
Diabetes mellitus (%)	10	8	0.918
Coronary artery disease (%)	2	4	0.459
HFrEF (%)	0	2	0.274
HFpEF (%)	6	8	0.524
LVEF (%)	61 ± 4.88	62 ± 4.96	0.452
LAVI (ml/m²)	35.3 (28.5-40)	37.2 (31.1-44.1)	0.523
Left atrial dilation (%)	36	34	0.577
eGFR (ml/min/1.74 m²)	71.6 ± 22.2	80.3 ± 17.6	0.183
Cr Cl (ml/min/1.74 m²)	75 (66-104)	90 (75.5-108)	0.258
Vagal reflex, n (%)	1 (2)	7 (14)	**0.01**
Baseline HR, bpm	59.8 ± 9.88	60.1 ± 7.64	0.827
End of procedure HR, bpm	73.6 ± 11.8	74.8 ± 8.59	0.544
Mean HR acceleration, bpm	13.8 ± 6.08	14.7 ± 5.18	0.411
Next day HR, bpm	70 ± 8.28	71.2 ± 9.02	0.805
Mean next day HR acceleration, bpm	10.2 ± 8.47	11.1 ± 6.42	0.613
Mean HR at 1 month, bpm	72.9 ± 10.5	75.8 ± 9.4	0.502

The abbreviations are as in Table 1

Table 3. Characteristics of the patients with HR acceleration vs those without

	Acceleration + (n=50)	Acceleration – (n=52)	p
Sex, n M:F (% M:F)	34:16 (33.3:15:7)	36:16 (35.3:15.7)	0.893
Age (years)	61 (48-67.8)	65.5 (58.8-71)	**0.016**
BMI (kg/m²)	29.4±4.92	29.2±4.93	0.902
Obesity (%)	20	18	0.468
Arterial hypertension (%)	43.1	48	0.267
Diabetes mellitus (%)	8.8	14.7	0.197
Coronary artery disease (%)	2.9	8.8	0.076
HFrEF (%)	1	6.9	**0.031**
HFpEF (%)	6.9	11.8	0.239
LVEF (%)	60 (57.3-66)	59 (54-63)	**0.018**
LAVI (ml/m2)	35.7 (30.9-41.4)	40.2 (32.8-52)	0.124
Left atrial dilation (%)	34.3	40.2	0.305
eGFR (ml/min/1.74 m²)	75.6 ± 20.5	68.7 ± 18.8	0.068
Cr Cl (ml/min/1.74 m²)	89 (72-106)	85 (63.5-106)	0.39
Vagal reflex, n (%)	8 (7.8)	10 (9.8)	0.669
Baseline HR, bpm	59.9 ± 8.83	63.5 ± 9.81	0.072
End of procedure HR, bpm	74.2 ± 10.3	60.9 ± 9.82	**< 0.001**
Mean HR acceleration, bpm	14.2 ± 5.64	–2.63 ± 5.43	**< 0.001**
Next day HR, bpm	70.5 ± 8.56	67.2 ± 9.32	0.095
Mean next day HR acceleration, bpm	10.6 ± 7.53	3.68 ± 7.75	**< 0.001**
Mean HR at 1 month, bpm	74.2 ± 9.91	68.9 ± 12	**0.048**

The abbreviations are as in Table 1

sists for one month after the procedure, with a mean HR significantly higher than in patients without neuromodulation.

Although many characteristics were studied and compared, we found only a few differences between the patients with vs those without neuromodulation. Patients with neuromodulation were younger and less frequently had heart failure with reduced ejection fraction. There was also statistically significant difference in the left ventricular ejection fraction, however the absolute difference was so small that we do not believe it to be of any clinical relevance.

We need to emphasize that the criteria for neuromodulation were arbitrarily defined, hence they may not necessarily reflect its real incidence. In fact, it seems that older patients demonstrate a blunted HR response [13] and as such the rate of non-targeted neuromodulation in our study might be even higher.

Not surprisingly, the most common sites of neuromodulation in this study are in line with what is known about the location of the epicardial ganglionated plexi. Heart rate increase was achieved almost exclusively during isolation of the right superior PV where the anterior right ganglionated plexus overlies the anterior aspect of the venous antrum, while VRs were predominant on the left-sided PVs. We have to remind that during RF PVI the order of isolation of PVs was left to the operator's choice. In this way, starting with the right-sided PVs elicited non-transient HR acceleration in 12 patients. This may have rendered induction of VR on the left side impossible. The wider contact area of the cryoballoon front to the venous antrum may be another potential reason for the much more frequent VR induction in the left PVs during cryo PVI. On the contrary, RF PVI on the left side may have been targeted closer to the PV ostia with the purpose to minimize the risk of thermal injury to the oesophagus, hence RF PVI would have been less probable to induce VR.

Although known to electrophysiologists for many years, the incidence of inadvertent neuromodulation during PVI and its mid- and long-term durability is not yet well studied, and the results reported are somewhat divergent. However, this issue might be of importance in patients with tachy-brady syndrome (paroxysmal AF and intermittent or persistent sinus bradycardia/pauses) where PVI could be combined with CNA within a single procedure. This is obviously only attainable when using RF energy [1, 2]. If it is also possible to achieve a durable effect with cryoballoon ablation as well, this would enrich the currently available armamentarium for CNA. Unfortunately, the durability of the non-targeted neuromodulation after the 1st month in our study remained unknown due to the very short follow-up. In a small study of 14 patients Oswald et al. reported induction of VR by 28 mm cryoballoon and a freeze duration of 300 sec in 36%. Acute HR acceleration was not reported, however, one week post ablation there was significant decrease of the heart rate variability indices derived from Holter-ECG recordings, in 86%. This effect was only temporary and disappeared by the end of the third month post ablation. Furthermore, they did not find any influence on the recurrence rate and concluded that neuromodulation is only a bystander phenomenon to PVI [14]. Yorgun et al. reported VR induction by 28 mm cryoballoon in 40.7% of 145 patients. At least 2 consecutive freezing cycles of 300 sec each were applied for each vein. Acute HR acceleration and heart rate variability indices were not reported. The authors found that patients with VR induction and requirement for atropine administration or temporary cardiac pacing during the procedure had significantly less AF recurrences [15]. The rate of VR induction reported in these two publications was much higher than the one found in our study, which may be associated with the very different ablation protocols. In a more recent study of 472 patients Maj et al. found that some grade of HR acceleration on the day after the ablation was achieved in 96.2% using 28 mm cryoballoon and freezing cycle of 180 sec per vein with a bonus freeze only if needed. They also defined an arbitrary cut-off of 15 bpm acute increase of the HR and found it to reflect 17% less AF recurrences during a mean follow-up of 27 months. Induction of VR and longer-term HR dynamic were not reported. Younger age was among the predictors for greater acute HR increase [16]. To some extent, our findings are in line with this publication, however the magnitude and the rate of acute HR increase overall found by Maj were much larger. The reasons for these differences are unknown to us. It is worth to point out that besides the ablation protocols, the markers and time-points for assessing neuromodulation in all cited papers are quite different as well, hence it is hard to compare the results reported. Very recently a small observational study on non-targeted and targeted CNA using cryoballoon reported a durable post-procedural increase of the resting HR by 6-7 bpm for up to 12 months [9]. Another recent study showed that inadvertent cardioneuroablation was achieved during RF PVI with a HR increase of 7-8 bpm that persisted during a 3-month follow-up [2]. The magnitude of the effect in both studies is comparable to the increase of the HR seen in our study at 1 month. This might mean that after a small initial decrease, the HR then stabilizes at a higher level in the longer term. Yet, we have to point out that the durability of RF CNA, even when done purposefully, is not yet known, as most published studies have a follow-up of up to 2 or 3 years [17-19].

Limitations

This is a retrospective study and although every effort was made to review the EP records and the written reports of the procedures, we cannot be certain that some bias was not introduced. Also, it was not possible to define the site of the neuromodulation in 2 cases. As already pointed out, criteria for neuromodulation were arbitrarily defined and may not reflect its real incidence, especially in older patients. The VR induction may have been masked and its incidence underestimated when RF PVI started on the right-sided PVs. The mean HR before the ablation was not routinely assessed and sought on Holter-monitoring and therefore could not be compared to the mean HR at 1 month follow-up.

Conclusion

Inadvertent neuromodulation occurs in more than half of the patients with PVI for AF irrespective of whether RF or cryogenic ablation energy is used. It is represented mostly by an increase of the mean HR and persists up to at least one month post procedurally.

No conflict of interest was declared

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