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BAROREFLEX ACTIVITY CHANGE AFTER PULMONARY VEIN ISOLATION IN PATIENTS WITH ATRIAL FIBRILLATION

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Aim. To study the intraprocedural changes in baroreflex activity after catheter pulmonary vein isolation in paroxysmal atrial fibrillation patients.

Methods. From October 2021 to June 2022, sinus rhythm was registered at the start of procedure in 21 patients with paroxysmal atrial fibrillation admitted for catheter pulmonary vein isolation. Patients before and after procedure were tested with phenylephrine. Pre- and postoperative baroreflex activity and sinus rhythm rate were analyzed.

Results. After catheter pulmonary vein isolation, the baroreflex activity decreased from 5.8 [3.5; 11.3] ms/mmHg to 0.3 [-0.1; 1.8] ms/mmHg, p<0.001, based on systolic arterial pressure, and from 9.5 [5.1; 15.5] ms/mmHg to 0.6 [0; 7.6] ms/mmHg, p=0.033, based on diastolic arterial pressure.

Conclusion. Intraprocedural phenylephrine test allows to study the baroreflex activity changes and to assess the modification of cardiac autonomic innervation.

Key words: pulmonary vein isolation; atrial fibrillation; autonomic nervous system; arterial baroreflex; phenylephrine; catheter ablation; cardioneuroablation

Conflict of Interests: none.

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Catheter pulmonary vein isolation (PVI) is the most effective treatment for atrial fibrillation (AF). During the radiofrequency energy applications in the area of the right upper and left upper pulmonary veins ostia, sinus rhythm acceleration or slowing are observed in some patients [1, 2]. Most likely these changes are caused by parasympathetic denervation of the heart associated with ablation of intramural vegetative fibers and ganglia [3]. These same fibers are the effector link of the arterial baroreflex (BR), which regulates the inverse dependence of the heart rate and blood pressure (BP) [4]. Changes in the BR activity (BRA) in various clinical situations have been well studied [5, 6]. It is also known that a decrease in BRA is associated with a worse prognosis in various groups of patients [7-9]. The "gold standard" for studying BRA is a test with phenylephrine (PhE) [5].

Taking into account the effect of catheter isolation of pulmonary veins on parasympathetic innervation of the heart in patients with atrial fibrillation, we assumed that during this procedure there is a decrease in BRA and studied this parameter using a test with PhE before and after the PVI.

METHODS

Study population

Twenty-one patient who underwent catheter PVI procedures from October 2021 to July 2022 were enrolled to this study. The inclusion criteria were the age from 18 to 70 years and the presence of a sinus rhythm at the beginning of the operation. The exclusion criteria were the patient's history of acute cerebrovascular accident, heart failure, coronary artery disease and other structural heart disease. All patients signed an informed consent to participate in the study. Demographic data of the patients is presented in Table 1.

Catheter PVI

Catheter PVI was performed under total intravenous anesthesia (midazolam, fentanyl, propofol) without ventilation support or under combined anesthesia with ventilation support (midazolam, fentanyl, propofol, sevoflurane, rocuronium). A 10-pole diagnostic electrode was positioned in the coronary sinus through the right internal jugular or right femoral veins, and interatrial septal puncture

was performed under fluoroscopy guidance. For the intraoperative prevention of thromboembolic complications, a bolus of heparin was injected at a dose of 100 units/kg of the patient's body weight, followed by maintenance of activated clotting time at the level of 300-350 s.

During cryoballon ablation, a transeptal introducer (SR0 8F 61 cm, Abbott, USA or Preface 8F 61 cm, Biosense-Webster, USA) was changed to a steerable introducer CryoCath 12F (Medtronic, USA). Then, cryo-applications were performed sequentially in the left upper, left lower, right lower and right upper pulmonary veins with a duration of 240 s. with the control of electrical PVI by the recordings from the Achieve Advance catheter (Medtronic, USA). The applications in the right pulmonary veins were performed while the right phrenic nerve was paced for timely termination of the application in case of weakening of diaphragm movements.

With radiofrequency (RF) ablation, puncture of the atrial septum under X-ray or intracardiac ultrasound control was performed twice separately. A controlled circular diagnostic 20-pole Lasso electrode and a Smart Touch ablation electrode (Biosense-Webster, USA) were inserted into the left atrial cavity. Wide antral catheter ablation was performed starting from the right pulmonary veins, followed by a bidirectional blockade of conduction through the created lines using stimulation from inside the veins with a Lasso catheter and registration of the absence of electrical activity inside the pulmonary veins. If the AF was induced and persisted until the end of the procedure, an electrical cardioversion was performed.

BRA assessment

To assess the BRA in our study, a test with intravenous administration of PhE (Mezaton, Dalkhimpharm, RF) was used according to the standard methodology [5]. The test with PhE was performed in the EP lab. During the test, ECG monitoring was performed in 3 leads, and blood pressure was measured every minute. Since the PhE test was performed as part of the catheter ablation procedure, it was performed under the same anesthetic conditions that was required for surgery. After the initial measurement of heart rate (HR) and blood pressure, the infusion began at an initial rate of 2-3 micrograms/kg/min and lasted for 3-5 minutes with repeated measurements of heart rate and blood pressure every 1-2 minutes. If the criteria for the end of the test were not reached, the infusion rate was consistently increased by 2-3 micrograms/kg/min every 3-5 minutes with heart rate and blood pressure fixed every 1-2 minutes until the criteria for the end of the test were reached. The criteria for the end of the test were the decrease in heart rate below 30 beats/min or an increase in systolic blood pressure (SBP) above 180 mm Hg.

Table 1.

Clinical and demographic data of studied population

Indicator	Value
Male sex, n (%)	12 (57)
Age, yrs, Me (25, 75)	57 (54, 62)
Paroxysmal AF, n (%)	21 (100)
LVEF, %, Me (25, 75)	60 (61, 64)
LA, mm, Me (25, 75)	41 (37, 43)

Note: AF - atrial fibrillation; LVEF - left ventricular ejection fraction; LA - left atrium.

PhE test endpoint

BRA was estimated as the degree of increase in the RR interval (the difference between the maximum value of the duration of RR intervals at the end of the test and the value of RR before the start of the introduction of PhE) per unit of increase in blood pressure (the difference between the maximum value of blood pressure at the end of the test and the value of blood pressure immediately before the start of the introduction of PhE) and was presented in ms/mmHg. Calculation of BRA was performed according to the formula: $BRA = \Delta RR / \Delta BP$

Statistical analysis

Statistical data processing was carried out using the software SPSS Statistics 26.0 (IBM). The analysis for the normality of the distribution was carried out using the Shapiro-Wilk method (for small samples). The distribution deviating from the null hypothesis with a level of statistical significance $p<0.05$ was considered different from normal (null hypothesis - the data are distributed normally). Median and interquartile range [Q1-Q3] were used to describe continuous variables. The description of discrete quantities is presented in absolute values and fractions (%). From the means of comparative analysis, the McNemar test was used for related samples of parameters with a distribution other than normal. The level of statistical significance at which the differences were considered significant was $p<0.05$.

RESULTS

Changes in hemodynamic parameters during the administration of PhE before and after PVI

In 11 patients, PVI procedure was performed using cryoballon ablation, in 10 - using the RF ablation technique under the control of non-fluroscopic navigation (Carto 3, Biosense Webster, USA). On average, the maximum rate of PhE infusion was 2.96±1.3 mg / kg / min and did not differ significantly before and after PVI. During PhE infusion before PVI there was a significant increase in systolic BP, diastolic BP, as well as a decrease in heart rate (an increase in the duration of RR). With the repeated introduction of PhE after PVI, a similar dynamic was ob-

Table 2.

Phenylephrine test results prior to and post pulmonary vein isolation

Indicator		Before PhE	After PhE	p
Prior to PVI	SBP, mmHg	110[99, 117]	166[144, 181]	<0.001
	DBP, mmHg	72[64, 79]	98[88, 108]	<0.001
	RR, ms	953[848, 1071]	1482[1349, 1847]	<0.001
Post PVI	SBP, mmHg	120[106, 126]	190[174, 200]	<0.001
	DBP, mmHg	77[71, 86]	110[104, 119]	<0.001
	RR, ms	882[825, 1031]	870[808, 1165]	0.147

Note: PhE - phenylephrine; PVI - pulmonary vein isolation; SBP and DBP - systolic and diastolic blood pressure.

served in BP, while the heart rate remained almost unchanged (Table 2).

Changes in BRA after PVI

We have compared the BP changes induced by PhE infusion and BRA before and after PVI (Table 3). The heart rate changes assessed by RR intervals were reduced by 96% after PVI in comparison with preoperative numbers empirically from 524 [324; 711] ms to 15 [-9; 119] ms, P<0,001.

The slope of the HR dependency from BP in the majority of patients became flatter after the PVI. Of note, the HR before and after PVI was relatively stable (RR interval duration was 453 [848; 1071] ms before and 882 [825; 1031] ms after PVI, p=0,17) while HR slowing in response to PhE-induced increase in BP became lesser (fig. 1). Also a 96% reduction in BRA calculated using SBP values (5.8[3.5; 11.3] ms/mmHg vs 0.3 [-0.1; 1.8] ms/mmHg, P<0,001) and 80% reduction in BRA calculated using DBP values were noted (9,5 [5,1; 15.5] ms/mmHg vs 0.6 [0; 7.6] ms/mmHg, P=0.033), (fig. 2).

DISCUSSION

Cardiac autonomic innervation changes after PVI

Changes in the heart rate during catheter PVI are a well-known phenomenon. C.Pappone et al. (2004) described the development of sinus bradycardia and even the sinus arrest with prolonged pauses during RF applications at the left superior pulmonary vein ostium. Repeated RF applications in this zone led to the gradual diminishing of the negative chronotropic effect, probably associated with the elimination of parasympathetic innervation of the heart [2]. On the other hand, the phenomena of rhythm acceleration with RF ablation in the right superior pulmonary vein ostium [1] and the elimination of "vagal" sinus node dysfunction in some patients, if it presented prior to the procedure [10, 11] are well known by interventional electrophysiologists. These circumstances led to the correction of the lesions sequence during PVI: firstly, the isolation of the right pulmonary veins is performed, and then the left PVs are isolated. In addition, the elimination of bradyarrhythmias in some patients has been reflected in AF treatment guidelines -in patients with AF-associated bradyarrhythmia catheter PVI is preferable to perform, rather than the pacemaker implantation [12, 13].

The reason for the described phenomena is that ganglion plexuses are located at the area of the LV ostia [3], and lesions in these anatomical zones cause intentional [14-17] or unintentional [10] damage of those ganglia.

The decrease in BRA revealed in our study may also be caused by parasympathetic denervation of the heart, unintentionally occurring with RF effects at the locations of

Table 3.

Arterial baroreflex activity prior to and post pulmonary vein isolation

Indicator	Prior to PVI	Post PVI	p
ΔSBP, mmHg	82 (88, 99)	68 (55, 79)	0.003
ΔDBP, mmHg	56 (50, 63)	34 (22, 41)	<0.001
ΔRR, ms	524 (324, 711)	15 (-9, 119)	<0.001
BRA by SBP, ms/mmHg	5.8 (3.5, 11.3)	0.3 (-0.1, 1.8)	<0.001
BRA by DBP, ms/mmHg	9.5 (5.1, 15.5)	0.6 (0, 7.6)	0.033

Note: BRA -arterial baroreflex activity

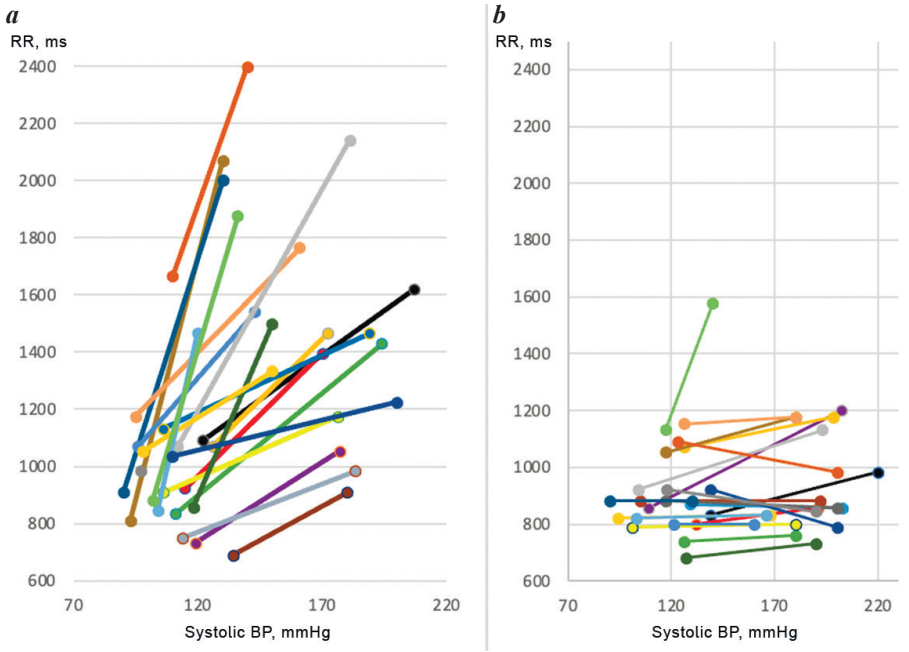

Fig. 1. Sinus RR intervals dependance from BP: a - prior to pulmonary vein isolation (PVI), b - after PVI. In each line the left dot shows RR and BP numbers before PVI and right dot -the same data after PVI.

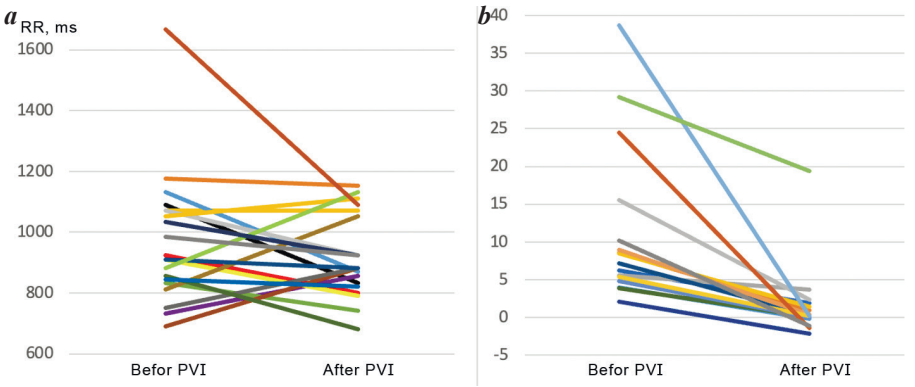

Fig. 2. Sinus RR intervals changes (a) after pulmonary vein isolation (PVI) and decrease in arterial baroreflex activity post PVI (b).

the pericardial ganglion plexuses around the PV ostia. The data obtained by us confirm the results of the studies of M.Miyoshi et al. (2020) and K.Styczkiewicz et al. ((2019) on the reduction of BRA after PVI in patients with paroxysmal and persistent AF [18, 19], but unlike the mentioned studies, our work shows the possibility of intraprocedural evaluation of BRA.

Arterial baroreflex and methods of its activity measurement

For the first time, the measurement of BRA using a pharmacological test with angiotensin [5] and then with PhE [6] was proposed in 1969 by the Oxford group of H.S.Smyth et al. Then in 1992, the "Oxford" technique was modified by T.J.Ebert and A.W.Cowley, who proposed to sequentially inject 100 mcg of nitroprusside (deactivation of baroreceptors) and 150 mcg of PhE (pressor activation of BR), then measure the vagal and sympathetic components of BR by assessing the effect of BP on RR duration and recording the activity of the cutaneous sympathetic nerve, accordingly [20]. The assessment of BR activity is also possible using several other (non-invasive) ways: the method of sequences without [21] or with breath control [22], evaluation of the alpha-index in spectral analysis [23], evaluation of the reaction to a horizontal position with the lowered head end of the tilt-table [24]). Some of the methods turn out to be impracticable, unproven, or contraindicated in some categories of patients (with severe heart failure, with a history of cerebral circulation disorders, etc.) [25], but in different clinical situation it is possible to find an acceptable technique, since the results of the various methods largely correlate with each other [25-29]. In our study, the results of the PhE test were studied, as this BRA assessment method is the most feasible in the EP lab.

BRA assessment perspectives for the interventional electrophysiology

The definition of BRA can be used in an acute assessment of the effectiveness of the treatment of certain diseases developing in the pathology of BR, and requiring the elimination of pathological neurogenic effects on the heart. Such diseases include postural orthostatic sinus tachycardia, vasovagal syncope, carotid hypersensitivity syndrome, sinus node weakness syndrome, paroxysmal disorders of atrioventricular conduction, etc.

In addition, there is clear evidence of a positive correlation between the modification of autonomic (primarily parasympathetic) innervation of the heart and the effectiveness of catheter treatment of AF [18, 30, 31]. In this regard, the reduction of the BRA could be considered as an additional endpoint in the catheter treatment of some patients with AF.

Limitations

The obvious limitations of our study, which could affect the accuracy of its results, include the small volume and non-randomized nature of the sample. Nevertheless, given that the HR slowing caused by PhE-induced BP rise has been found in all patients before PVI and the weakening of these changes were also documented almost in all patients after PVI, it is unlikely that an increase in the sample size and randomization would have greatly changed the results of the study.

Absence of invasive hemodynamic monitoring and continuous beat-to-beat blood pressure measurement (according to E.Vanoli et al. (1994), similar to the invasive one in accuracy [4]) could affect the accuracy of the BRA measurement in our work. Nevertheless, the range of fluctuations in blood pressure and heart rate, which was studied in our study, belonged to the initial (ascending) part of the BR curve. In this segment, the curve is characterized by a direct positive dependence of heart rate on blood pressure. An increase in blood pressure above 200 mmHg when the BR curve reaches a plateau was not part of this study. The object of our work was the slope of the curve which could be measured using any two points on the curve.

Sedation and other methods of general anesthesia can affect the BR sensitivity. In this regard, the different level of sedation at the beginning and at the end of the operation could be a reason for overestimating or underestimating the identified relationships. It would be more objective to judge the same severity of the effect of sedation of consciousness on the BRA before and after ablation if there was intraprocedural monitoring of the electrical activity of the brain using a bispectral index or entropy determination. Since this work is a pilot study, the listed methods of measuring the depth of sedation were not used in it. Their use is planned for further study of the BRA in future works.

Sedation and other methods of general anesthesia may affect the severity of the BR included in our study (age, female gender, hypertension, high blood pressure in the LP are factors associated with a decrease in BRA) or a difference in the method of administration of PE (in studies with bolus administration of PhE, higher doses of PhE were usually used than with intravenous infusions [32, 33]).

Another limitation was the study of only part of the reflex functions - namely, the effect of hypertension on the frequency of the sinus rhythm. In future work, it is planned to take this aspect into account and study how hypotension caused by the introduction of nitrates affects the rhythm before and after catheter ablation.

CONCLUSION

During the catheter ablation for AF, parasympathetic denervation of the heart occurs, which is expressed in a decrease in the BRA and sinus rhythm acceleration. Intraprocedural assessment of these parameters can be used to evaluate the modification of autonomic innervation of the heart during PVI, cardioneuroablation and other procedures.

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