ORIGINAL ARTICLE

Frequency spectra analysis suggests outcomes in patients with paroxysmal atrial fibrillation

Sen Lei, Pihua Fang, Jun Liu, Yu Hou, Xiaofeng Li, Dongfang Cao, Shu Zhang

Fu Wai Hospital, Peking Union Medical College and Chinese Academy of Medical Sciences Centre for Arrhythmia Diagnosis and Treatment, Beijing, China

Abstract

Background and aim: The purpose of this study was to determine the role of dominant frequency (DF) and organised index (OI) in outcomes of pulmonary vein (PV) isolation for paroxysmal atrial fibrillation (AF).

Methods: OI and DF of electrograms in coronary vein (CS) during AF were obtained by frequency spectra analysis in 60 patients with paroxysmal AF who underwent PV isolation. Based on the results of 12 months follow up, 14 patients with recurrent AF were included in group 1 and 46 patients with sinus rhythm were included in group 2.

Results: In group 1, no spectral component was reduced by PV isolation. Spectral components were reduced by PV isolation in 23 patients in group 2. The changes of DF after PV isolation was significantly different between groups 1 and 2 (1.2 ± 1.2 vs. 2.4 ± 1.3, $p = 0.01$); the increment of OI after PV isolation in group 1 was significantly lower than in group 2 (9 ± 13% vs. 22 ± 17%, $p = 0.02$).

Conclusions: A decrease in DF and an increase in OI after PV isolation may suggest a better clinical outcome.

Key words: atrial fibrillation, frequency spectra analysis, dominant frequency, organised index, pulmonary vein isolation

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INTRODUCTION

Recently, it has been reported that spectral analysis and dominant frequency (DF) mapping could identify sites of high-frequency activity during atrial fibrillation (AF) in humans, and ablation at these sites resulted in termination of AF [1, 2]. Furthermore, a critical decrease in DF has proved to be the independent predictor of freedom from recurrent atrial arrhythmias after antral pulmonary vein (PV) isolation and ablation of complex fractionated atrial electrograms for chronic persistent AF [3]. In addition, low organised index (OI) of atrial electrograms in coronary vein (CS) was associated with more multiple driving sources during paroxysmal AF; while a high OI was associated with the presence of limited activity driving the atria [4].

Because atrial electrograms of CS are easily obtained in electrophysiological study, in this study we aimed to investigate whether there was any difference between the changes of DF and OI of electrograms of CS in patients with paroxysmal AF with sinus rhythm (SR) after PV isolation and in patients who had recurrent atrial tachycardia after PV isolation.

METHODS

Patients

All patients provided written informed consent prior to ablation, and the study protocol was approved by the Ethics Committee of the Fuwai Hospital, Peking Union Medical College and Chinese Academy of Medical Sciences.

The study population consisted of 60 consecutive patients (41 men, aged 41 ± 26 years; range 18–71 years) with symptomatic paroxysmal AF who underwent primary PV isolation by a single operator between May 2005 and May 2008. The mean paroxysmal AF history was 4.9 ± 3 (1–12) years. Paroxysmal AF was defined as self-terminating AF episodes lasting < 48 h, alternating with periods of SR. The mean echocardiographic dimension of the left atrium (LA) was 36 ± 5 (25–49) mm and the mean left ventricular ejection fraction was

Address for correspondence:
Dr. Pihua Fang, Centre for Arrhythmia Diagnosis and Treatment, Fu Wai Hospital, Peking Union Medical College and Chinese Academy of Medical Sciences, Beilishi road, 100010 Beijing, China, tel: 13718803615, e-mail: pihuafang@sina.com
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62 ± 7% (45–78%). We included patients with paroxysmal AF who were in AF spontaneously at the beginning of the procedure or those patients whose paroxysmal AF was induced at the beginning of the procedure. The exclusion criteria were patients with SR at the beginning of the procedure, sick sinus syndrome, diabetes mellitus, thyroid dysfunction, myocardial infarction in the previous six months, history of a prior thoracotomy, beta-blocker therapy, and a pacing rhythm. Based on the results of the three year follow-up after ablation, the patients were divided into either an AF recurrence (group 1) or a non-recurrence group (group 2).

Pre-ablation management

A detailed clinical examination, including thyroid function tests, electrocardiogram, chest radiography, 24-h Holter monitoring, transthoracic and transoesophageal echocardiography, and PV and LA multiple-detector row-spiral computed tomography were routinely performed. All patients received a subcutaneous injection with low-molecular-weight heparin sodium for three days after excluding thrombus in LA and left atrial appendage by transoesophageal echocardiography and multiple-detector row-spiral computed tomography scan.

Electrophysiological study and atrial fibrillation ablation

The patients were taken to the electrophysiological laboratory in a fasting state and were given intravenous sedation with propofol and pentazocine. A 7-French decapolar catheter with 1-5-1-mm interelectrode spacing between each electrode pair (St Jude Medical, AF Division, Minnetonka, MN, USA) was deployed into the CS via the right internal jugular vein with the proximal bipole at the CS ostium. A decapolar circular mapping catheter (10-pole 20-mm Lasso, 6-mm bipole spacing, BiosenseWebster) was introduced into the LA via a transseptal approach for sampling at each PV/LA junction. The CARTO-guided PV isolation procedure was performed using a deflectable, circular mapping Lasso catheter (15–20 mm; Biosense Webster Inc.) and a cool-saline irrigated 3.5-mm-tip quadripolar catheter (ThermoCool Navi-Star; Biosense Webster Inc.). Then, PV angiography was performed to verify the ostia of PVs. Subsequently, circular ablation lines were created around the left- and right-sided PVs. The encircling lines were created at a distance of approximately 15 mm from the PV ostia and consisted of consecutive focal lesions. The endpoint of ablation was the amplitude of the local bipolar electrograms reduced to lower than 0.1 mV and electrical isolation of PVs (atrial pacing could not capture the PV potentials). Radiofrequency energy (EP-SHUTTLE; Biosense Webster Inc.) was delivered at a power output of 35 to 40 W and a temperature of 43 to 45°C at each ablation point. After foregoing ablation, drugs and/or direct current cardioversion (300 J) was used to recover SR if AF persisted after PV isolation.

Signal processing and frequency domain analysis

Frequency domain analysis was processed in the MatLab environment (MathWorks, Inc., Natick, MA, USA) using custom software and was performed for one bipolar electrogram positioned in the ostium-proximal CS. We used CS here because activity of CS is the commonest and most useful information in electrophysiological study and to obtain the information including frequency spectrum from CS is the easiest method. We selected the bipolar recording showing no or minimal ventricular potentials (< 10% of atrial signal amplitude). Frequency analysis was performed in successive 5-s segments of electrograms in CS at the beginning of the ablation, after right PV isolation and after left PV isolation [4, 5]. Measurements of DF and OI were performed before and after PV isolation. In patients who converted to SR during ablation, measurements were performed immediately before AF termination. In each patient, two successive 5-s segments with an interval > 5 min before ablation were obtained for evaluation of the temporal stability of DF and OI. Spectral components with peak power > 20% that of the DF were analysed in every frequency spectrum in each patient. Change of spectral components were defined as when the peak power of them was decreased to < 20% that of the DF.

Specifically, at first, intracardiac electrograms were recorded with a filtering from 30 to 500 Hz, which was identical to the one commonly used in electrophysiological study. Preprocessing steps was conducted before a fast Fourier transform was performed. In brief, first digitised bipolar electrograms sampled for 5 s at 1,000 Hz underwent preprocessing steps of bandpass filtering at 40 to 250 Hz, rectification, and low-pass filtering at 20 Hz. A 2,048-point fast Fourier transform was then performed for each successive 5-s segment. The largest peak in the resulted magnitude spectrum was defined as a DF. The power of the DF and its harmonics was estimated by computing the area under the DF and its harmonics. The ratio of this area to the total power was defined as OI [6].

Follow-up

The patients remained hospitalised under continuous rhythm monitoring for at least three days. During the follow-up period, no antiarrhythmic drugs were administered to any patient. The first three months were considered to be a blank period. A clinical follow-up was performed one year after the procedure. A 24-h Holter recording was performed at three months, and every three months thereafter until 12months after the procedure. All patients who reported symptoms were given an event monitor to document the cause of the symptoms.

Statistical analysis

Continuous variables are presented as mean ± SD or proportions. The data distributed normally was analysed by Student's t-test, and the data not distributed normally was analy-

Table 1. Patient characteristics

	Group 1	Group 2	P value
Gender (male/female)	10/4	1/15	0.82
Age [years]	7 ± 9	5 ± 11	0.64
Duration of history [years]	3 ± 4	0 ± 3	0.79
Left atrium size [mm]	35 ± 6	7 ± 4	0.27
Ejection fraction [%]	1 ± 8	63 ± 6	0.32

sed by Mann-Whitney U test or Wilcoxon signed rank test. Categorical variables are presented as number and percentage, and compared by Fisher's exact test. A two-sided $p < 0.05$ was considered statistically significant.

RESULTS

Follow-up results

Based on the 12 month follow-up data (the first three months were considered to be a blank period), 14 patients who complained of palpitation after PV isolation (group 1) were under 24-h Holter recording, and recurrent AF was found in all these 14 patients. Specifically, 13 patients had recurrent AF three months after the procedure, and one patient had recurrent AF six months after the procedure.

Patient characteristics

There were no significant differences in the age, sex, duration of history of paroxysmal AF, LA dimension, or left ventricular ejection fraction between the patients in group 1 and group 2 (Table 1).

Temporal stability of dominant frequency and organised index

Before PV isolation, DF and OI were obtained in all patients at two periods within an interval > 5 min. There was no significant difference in DF (6.4 ± 1.1 vs. 6.4 ± 1.1, p = 0.06) and OI (95 ± 68% vs. 90 ± 68%, p = 0.236) between the first three segments and the second three segments in all these patients. Like the DF, there were no changes of spectral components' peak power > 20% that of the DF in each frequency spectrum in every patient.

Changes of frequency spectrum during atrial fibrillation ablation

Procedure time was 135 ± 10 min in group 1 compared to 135 ± 9 min in group 2 (p = 0.937). In addition to DF, other spectral components have been demonstrated in frequency spectra. Spectral components with peak power > 20% that of the DF were noted in the frequency spectrum in all patients. In group 1, no spectral component was reduced by PV isolation (example in Figures 1A–C); in group 2, after ablation, changes were found in these spectral components in 23 patients. Specifically, in eight patients, changes of spectral

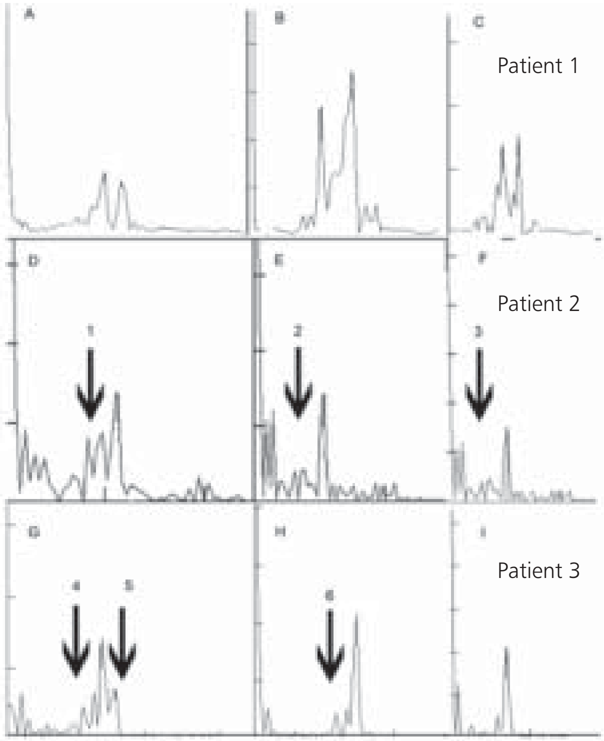

Figure 1. Changes of frequency spectrum in coronary sinus (CS) during pulmonary vein (PV) isolation. The frequency spectrum in CS during PV isolation (**A**, **D**, **G**: at baseline; **B**, **E**, **H**: after right PV ablation; **C**, **F**, **I**: after left PV isolation). In patient 1, no spectral component changed during ablation. In patient 2, spectral components (arrow 1) decreased after right PV isolation (arrow 2) but did not change after left PV isolation (arrow 3). In patient 3, one spectral component (arrow 5) decreased after right PV isolation and another spectral component (arrow 4 or 6) decreased after left PV isolation

components only were observed after right PV isolation (example in Figures 1D–F). Spectral components were reduced by right PV ablation and then were reduced further after left PV ablation in the other 15 patients in group 2, as shown in Figures 1G–I.

Effect of ablation on dominant frequency

There was no significant difference of DF at baseline between group 1 and group 2 (6.2 ± 1.4 Hz vs. 6.5 ± 1.0 Hz, p = 0.513). After PV isolation, DF decreased to 4.9 ± 1.3 Hz in group 1 (p = 0.001), while DF decreased to 4.0 ± 1.0 Hz in group 2 ($p < 0.001$). A significant difference was found in DF after PV isolation between group 1 and group 2 (p = 0.006) and the changes of DF was significantly different between group 1 and group 2 (1.3 ± 1.2 vs. 2.4 ± 1.3, p = 0.006). Specifically, DF was reduced by PV isolation in all patients in group 1; in group 2, DF was reduced by PV isolation in 34 patients, while in the other two patients, DF increased after PV isolation (Fig. 2).

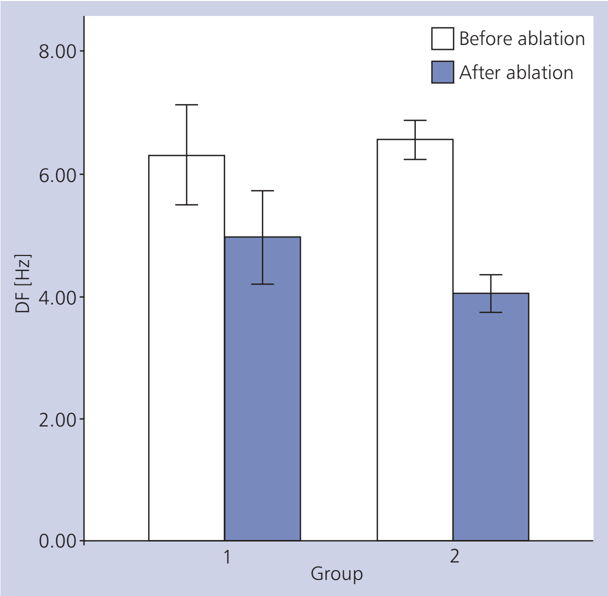

Figure 2. Dominant frequency (DF) before and after ablation in groups 1 and 2. After pulmonary vein isolation, DF decreased in both groups 1 and 2 but the decrement of DF was significantly different in these two groups

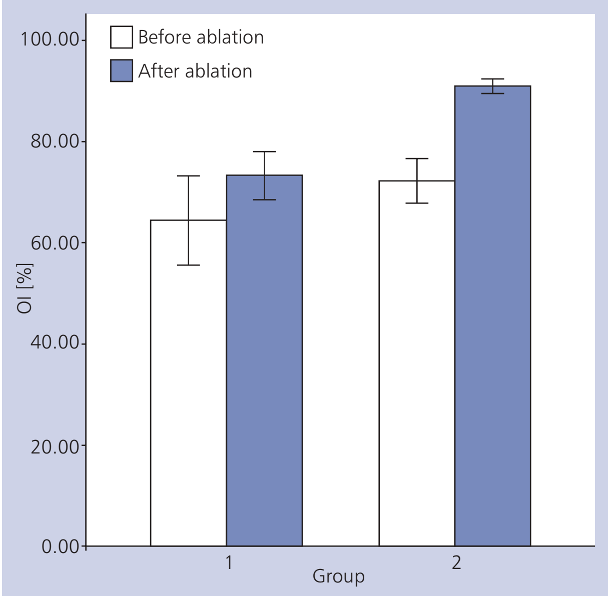

Figure 3. Organised index (OI) before and after ablation in groups 1 and 2. OI increased in groups 1 and 2 after ablation, but the increment of OI after pulmonary vein isolation in group 1 was significantly higher than in group 2

Effect of ablation on organised index

Organised index was calculated at baseline and after PV isolation. OI in group 1 before PV isolation was 64 ± 15%, and was 73 ± 8% after PV isolation ($p = 0.01$). Specifically, OI increased after PV isolation in nine patients; in another three patients, OI did not increase after PV isolation. In group 2, OI was 72 ± 14% before PV isolation and was 90 ± 4% after PV isolation ($p < 0.001$). Specifically, OI decreased in three patients after ablation in group 2; in the other 33 patients, OI increased after PV isolation. There was no significant difference in OI between group 1 and group 2 at baseline ($p = 0.095$); the increment of OI after PV isolation in group 1 was significantly lower than group 2 (8.7 ± 10% vs. 18 ± 15%, $p = 0.034$). After PV isolation, OI was significantly higher in group 2 than in group 1 ($p < 0.001$). In addition, patients in both groups whose OI decreased after ablation were not those patients whose DF increased after ablation (Fig. 3).

DISCUSSION

In a previous study [7], decrease of AF frequency (longer AF cycle length) during ablation, albeit analysed in the time domain, has been demonstrated to be a predictor of short and long term AF ablation success. The main findings of the present study are a decrease in DF and an increase in OI after AF ablation, which may suggest a better clinical outcome in PV isolation for paroxysmal AF. We also indicate in this study that spectral components may reflect the drivers of paroxysmal AF.

Temporal stability of dominant frequency and organised index

In this study, we demonstrated that the DF and OI value of CS activity during AF did not change over time. This indicated the temporal stability of the DF and OI value. The temporal stability of the DF and OI has been demonstrated in previous studies [5, 8]. However, there was evidence of DF variance: an assessment of the stability in the CS over a period of 50 min demonstrated that although there was no trend of acceleration or deceleration of the activation rate, the instantaneous rate fluctuated by approximately 1 Hz [5]. These contradictory results may indicate that the temporal stability of DF and OI may vary in some patients, so it would be always necessary to ascertain the stability of DF and OI before applying them to clinical use.

Effect of pulmonary vein isolation on the frequency spectrum of coronary sinus

In persistent AF, Yoshida et al. [9] reported that spectral components with peak power > 20% that of the DF may reflect site-specific tachycardias that coexist with AF and it may appear to reflect contributors of AF perpetuation. Yokokawa et al. [10] showed that complete conduction block after linear ablation at certain sites led to a significant decrease in the prevalence of these spectral components. In paroxysmal AF, we demonstrated that these spectral components may also reflect the drivers of paroxysmal AF.

In this study, the spectral components were reduced by PV isolation in 23 patients in group 2. In a three-dimensional model constructed by a pectinate muscle and the atrial wall, electrical burst stimulation with a frequency of 8.4 Hz was performed at a site of the pectinate muscle, then a 3:2 pattern of conduction presented from the pacing site of the pectinate muscle to the atrial wall. The frequency spectrum of the electrical activity of the atrial wall comprised the DF with a frequency of 5.7 Hz as well as another spectral component with a frequency of 8.3 Hz [11, 12]. The latter may be related to the frequency of the pacing site. Therefore, some of these spectral components with a second or third peak of power may be directly related to the drivers of AF in PVs. Decrease of these spectral components may indicate the elimination of AF drivers. Indeed, some spectral components were noted to be decreased as PV isolation in group 2. However, in group 1, and even in some patients of group 2, no spectral component with a second or third peak of power was diminished by PV isolation. There may be two reasons for this: firstly, some spectral components that were related to the drivers of AF were not eliminated by PV isolation; in other words, these drivers may not be at PVs but elsewhere. This may be the reason for patients in group 1. Secondly, no spectral component was related to the drivers of AF. This may be caused by too great a distance from the CS to the drivers. This may be the reason for patients in group 2 whose spectral components did not decrease after PV isolation. However, the present study could not elucidate this, and this needs further research.

Dominant frequency and organised index to suggest the outcome of pulmonary vein isolation for paroxysmal atrial fibrillation

Though ablation of paroxysmal AF has a better outcome than ablation of persistent AF, there are also some recurrent cases after PV isolation. Several parameters have been related to a high risk for AF recurrence, such as age, left atrial size, and impaired left ventricular systolic function [13–16]. However, these parameters are not directly associated with electrophysiological information. In this study, we demonstrated that DF and OI may also be useful in suggesting the outcome of AF ablation.

Yoshida et al. [3] demonstrated that patients with persistent AF who have a >11% decrease in the DF during pulmonary isolation complex fractionated atrial electrogram ablation were more likely to remain in SR than patients who remained in AF during radiofrequency ablation, and had a smaller decrease in their DF.

In this study, we also demonstrated that a DF decrease and an OI increase after PV isolation for paroxysmal AF were related to the outcome of the ablation. In the present study, though DF decreased in both groups after PV isolation, the decrement of DF was significantly different between groups 1 and 2, which indicated a sufficient DF decrease was important to the outcome of the ablation. This is also the case when it comes to OI: OI increased after PV isolation in both groups, but the increment of OI was significantly higher in group 2 than that in group 1. It should be noted that in this study, those patients in both groups whose OI decreased after ablation were not those patients whose DF increased after ablation. This suggests that the DF and OI may be two independent factors to suggest the outcome of PV isolation for paroxysmal AF.

As mentioned above, spectral components were reduced by PV isolation in some patients. Because OI was defined as the ratio of the area under the DF and its harmonics to total area in the frequency spectra, this indicated that OI would increase after PV isolation. However, though no spectral component changed in some other patients, OI also increased after ablation; this may indicate that the fibrillatory conduction was reduced by isolation of drivers for AF. Everett et al. [17] showed that higher OI was associated with a lower atrial defibrillation threshold in animal models, leading to the hypothesis that a higher OI is associated with increased organisation of AF or a smaller number of drivers. Takahashi et al. [4] demonstrated that lower OI was associated with more driving sources in paroxysmal AF.

In the present study, the OI at baseline was not different in group 1 and group 2, but after PV isolation, OI showed a greater increase in group 2. These results indicated that higher OI may represent that more drivers were isolated or damaged after PV isolation. Therefore patients with paroxysmal AF whose OI was higher after PV isolation had a better outcome.

Limitations of the study

The limitation of this study was that the recording sites for frequency domain analysis were limited. It may be more accurate to use a high resolution recording. In previous studies, however, AF cycle length from a single site was demonstrated to be related to AF duration or substrate modification by ablation [18, 19]. The CS is the optimal measurement site to allow repeated serial measurements during the procedure because of stability of the catheter. For PV isolation, ablation lesions were deployed remotely from the CS, thus resulting in minimal effects on local electrophysiological properties around the CS. The «recurrence» group is very small and PV exit block after ablation was not confirmed; this may partly affect our results. 24-h Holter ECG may not be enough to determine freedom from arrhythmia, and this is also a limitation of this study.

CONCLUSIONS

A decrease in DF and an increase in OI after PV isolation may suggest a better clinical outcome. DF and OI may independently reflect different properties of atrial electrograms during AF, and both of them may be useful in suggesting the outcome of AF radiofrequency ablation.

Conflict of interest: *none declared*

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Spektralna analiza częstotliwościowa jako metoda o znaczeniu prognostycznym u chorych z napadowym migotaniem przedsionków

Sen Lei, Pihua Fang, Jun Liu, Yu Hou, Xiaofeng Li, Dongfang Cao, Shu Zhang

Fu Wai Hospital, Peking Union Medical College and Chinese Academy of Medical Sciences Center for Arrhythmia Diagnosis and Treatment, Beijing, Chiny

Streszczenie

Wstęp i cel: Celem niniejszego badania było określenie rokowniczego znaczenia częstotliwości dominującej (DF, *dominant frequency*) i współczynnika organizacji (OI, *organisation index*) u chorych z napadowym migotaniem przedsionków (AF, *atrial fibrillation*), u których zastosowano izolację żył szyjnych (PV, *pulmonary vein*).

Materiał i metody: Stosując spektralną analizę częstotliwościową elektrogramu uzyskanego podczas AF z elektrody umieszczonej w żyle wieńcowej, określono OI i DF u 60 chorych z napadowym AF, u których przeprowadzono izolację PV. Na podstawie wyników 12-miesięcznej obserwacji do grupy 1 włączono 14 chorych z nawracającym AF, a do grypy 2 — 46 osób z rytmem zatokowym.

Wyniki: W grupie 1 nie stwierdzono wpływu izolacji PV na zmniejszenie którejkolwiek ze składowych widma. Redukcję tych składowych w wyniku izolacji PV zaobserwowano natomiast u 23 chorych z grupy 2. Zmiany DF po przeprowadzeniu izolacji PV różniły się istotnie między grupami 1 i 2 (1,2 ± 1,2 *v.* 2,4 ± 1,3; p = 0,01); przyrost OI po zabiegu był istotnie mniejszy w grupie 1 niż w grupie 2 (9 ± 13% *v.* 22 ± 17%; p = 0,02).

Wnioski: Zmniejszenie DF i zwiększenie OI po przeprowadzeniu izolacji PV sugeruje lepszy efekt kliniczny.

Słowa kluczowe: migotanie przedsionków, spektralna analiza częstotliwościowa, częstotliwość dominująca, współczynnik organizacji, izolacja żył płucnych

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