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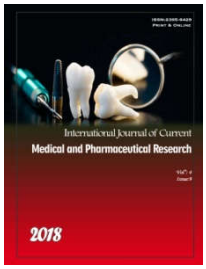

UPSTREAM-THERAPY USING TELMISARTAN AND AMLODIPINE IMPROVES LEFT ATRIAL MECHANICAL FUNCTION AFTER PULMONARY VEIN ANTRUM ISOLATION

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ABSTRACT

The **objective** of the study was to estimate the efficacy of telmisartan and amlodipine combination on the restoration of left atrial (LA) mechanical function after atrial fibrillation (AF) radiofrequency catheter ablation.

Methods: 64 consecutive patients undergoing pulmonary vein isolation (PVI) for treatment of paroxysmal atrial fibrillation were included in the study. Patients were randomly assigned to receive either a telmisartan/amlodipine combination 80/5 mg po daily (group I, n=34) or placebo (group II, n=30) for one week post-ablation. Transthoracic echocardiography (TTE) was performed pre-ablation, immediately post-ablation and after one week of study medication therapy. A six-minute walk test was performed and a standard SF-36 questionnaire was administered the day before the procedure and after a week of medication therapy. LV end-diastolic pressure was measured invasively viatransseptal puncture just prior to the PVI at the time of the transeptal puncture and again after the PVI just before LA sheath removal.

Results: Immediately post-ablation in both groups transmitral and pulmonary vein flow demonstrated a 'pseudo restrictive' pattern on TTE. The LA ejection fraction and LA active emptying fraction decreased by 25% and 40% respectively ($p<0.05$). Mean LA pressure, estimated mean pulmonary artery pressure, and right ventricular systolic pressure increased by 60%, 54%, and 44%, respectively ($p<0.05$). Of note, LV diastolic function did not decline. At the same time, patient-reported quality of life scores and exercise tolerance worsened After one week of therapy with a combination of telmisartan and amlodipine, all hemodynamic parameters, exercise tolerance, and quality of life showed improvement in the therapy group compared to the placebo group.

Conclusion: AF radiofrequency catheter ablation leads to intracardiac hemodynamic deterioration likely by worsening LA elasticity and contractility. This, in turn results in an increase in LA pressure, activation of pulmonary arteriolar spasm reflex, and progression of pulmonary vascular resistance which is seen clinically as a decline in patient exercise tolerance and quality to life. However, the administration of telmisartan and amlodipine pre- and post-ablation appears to improve intracardiac hemodynamics, exercise tolerance and quality of life compared to placebo.

INTRODUCTION

The treatment of atrial fibrillation (AF) with antiarrhythmic therapy is marked by its relatively limited efficacy [1]. Conversely, radiofrequency ablation of pulmonary vein triggers has emerged as an effective alternative therapy. M. Haissaguerre *et al*. demonstrated in 1998 a profound reduction in the frequency of paroxysmal AF after radiofrequency catheter ablation (CA) of pulmonary vein (PV) ectopic foci [2]. Today, the PV and left atrial (LA) antrum are the main targets of radiofrequency ablation of paroxysmal and persistent AF.

The current technique of wide-area antrum isolation requires an extensive ablation across a broad area of the left atrium. If pulmonary vein isolation is combined with substrate modification (linear ablation, CFAE or ganglionic plexi ablation, etc.), the cumulative area of radiofrequency ablation exposure may reach one third of LA myocardium. While this is associated with a reduction of PAF episodes, it also results in impairment of LA mechanical function [3].

Left atrial stunning was first described as a cause of impairment of LA mechanical function following cardioversion in patient with persistent AF [4]. It may last from hours to months and occurs after sinus rhythm restoration, resulting in a significant decrease or absence of LA contraction. LA stunning is manifest as a reduction in peak velocity of thetransmitral A wave and decreased emptying of

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the LA appendage. Later it was determined that stunning is also observed following any method which results in sinus rhythm restoration, including spontaneous cardioversion. The severity and duration of stunning mostly depend on the duration of preceding AF. If AF terminates as a result of ablation, stunning can be significant and prolonged because of trauma to the LA caused by extensive radiofrequency ablation [5].

When PV antrum isolation is performed during sinus rhythm, LA reservoir function deterioration is seen in the postprocedural period as a result of LA myocardial damage and electrical isolation of the PV sleeves [6]. This can be seen echocardiographically as a transformation of transmitral flow into a restrictive filling pattern which can last up to 6 months after the procedure [5].

The LA mechanical function disturbances can adversely affect patients by impairing left atrial emptying, raising the mean left atrial pressure and increasing the risk of thromboembolic events [7]. It is hypothesized that pre-treatment with pharmocologic agents (so called "upstream therapy") which protect the LA myocardium may be useful for improving LA mechanical function post-ablation. Such agents have already been used and appear to be effective in preventing adverse LA myocardial remodeling in patients with AF, especially in those who suffer from hypertension or heart failure. It has been demonstrated that upstream therapy can prevent new-onset AF, decrease recurrent AF or reduce the progression to permanent AF [8]. Several pharmacological groups have been used for this purpose: statins, steroids (after cardiac surgery), ω-3 fatty acids, ACE inhibitors and, especially, angiotensin receptors blockers (ARBs) [9, 10]. The antiarrhythmic effect of ARBs is associated with peripheral vasodilatation, which leads to a decrease in LA preload and after load, and prevention of structural and electrical remodeling. [11]. These data suggest that ARBs may improve LA mechanical function after AF catheter ablation. Telmisartan demonstrates reassuring data as a well-tolerated and effective drug for upstream therapy, which inhibits adverse changes in LA diameter, volume and myocardial mass [12]. Calcium antagonists also show a promising tendency in upstream therapy likely because intracellular calcium overload is one of the mechanisms leading to LA remodeling [13]. In spite of promising data, the efficacy of an ARB and calcium antagonist combination on LA remodeling after atrial fibrillation catheter ablation has not yet been evaluated.

The objective of this study was to estimate the efficacy and safety of a telmisartan and amlodipine combination on the restoration of LA mechanical function after atrial fibrillation catheter ablation.

Material and methods

The study design was approved by the local IRB at our institute in Kemerovo, Russia. All patients provided written informed consent.64 consecutive patients undergoing AF catheter ablation were included in the single-blinded (patient-masked) study in the 2-month period from January 1 to February 28,2016. Clinical and demographic data of the patients are presented in Table 1.

Table 1 Clinical and demographic data of the studied patients

Parameter	Value
Number of patients	64
Males / females	41 / 23
Mean age (years)	53.1±6.7
Paroxysmal AF	64 (100%)
Duration of arrhythmia (months)	16.0±4.8
Heart failure NYHA class	1.84±0.64
Prior AF ablation	4 (6.3%)
Arterial hypertension	50 (78%)
Diabetes mellitus	2 (3.1%)
Stroke / transient ischemic attack in anamnesis	1 (1.6%)
CHA2DS2-VASc score	1.71±0.90
HAS-BLED score	1.99±0.8
LA diameter (cm)	3.85±0.36

As shown in Table 1, all patients had paroxysmal AF, although they had a relatively long duration from the first episode to ablation. Overall, patients had normal LA dimensions, as well as low CHA2DS2-VASc and HAS-BLED scores. Three-quarters of patients were diagnosed with hypertension. The majority of subjects were male.

All patients received warfarin pre- and post-ablation and were maintained in the target range of international normalized ratio (INR) 2.0-3.0. An interrupted anticoagulation protocol before the CA was used with enoxaparin 'bridge therapy', which was started pre-ablation and stopped post-ablation after patients reached an INR level of more than 2.0. During the procedure, anticoagulation was maintained by intravenous heparin infusion to achieve an activated clotting time of >300 seconds. All patients underwent radiofrequency catheter ablation to achieve PV antrum isolation with a goal maximum catheter temperature of 40 °C, 43 W power and irrigation rate set at 17 ml/min. In all cases the predetermined endpoint of entrance and exit block of all PVs without the use of adenosine was achieved.

Before the procedure, patients were randomly assigned to either telmisartan/amlodipine combination in dose 80/5 mg (group I, n=34) or placebo (group II, n=30) taken daily for one week post ablation.

Transthoracic echocardiography was performed using aVivid 7 Dimension (GE, USA) ultrasound machine using a 2.5 MHz sector transducer. The following parameters were evaluated chocardiographically:

- velocity time integral of transmitral flow (TMF) during left ventricle (LV) early filling phase (VTI E, cm), atrial contraction (VTI A, cm), and velocity time integral during the whole LV diastole (VTI TMF, cm);
- peak velocities of E and A phases (peak E and peak A, mm/s), and E/A ratio;
- LV isovolumic relaxation time (IVRT, ms);
- velocity time integral of right superior pulmonary vein flow during LV systole (VTI S, cm/s), LV early filling (VTI D, cm/s), and S/D ratio;
- velocity time integral of right superior pulmonary vein flow during LA systole (VTI Ar, cm/s) and its duration (Ar dur, ms);
- LA emptying fraction by Simpson biplane formula (LAEF, %);
- LA active emptying fraction (LAAEF, %);
- LA diameter (LAD, cm);
- LA volume (LAV, ml);
- mean LA pressure (Mean LAP, mm Hg), mean pulmonary artery pressure (Mean PAP, mm Hg), and right ventricular systolic pressure (RVSP, mm Hg).

The six-minute walk test was used to assess exercise tolerance. The SF-36 questionnaire was used to assess quality of life.
Echocardiography was performed three times: immediately before the CA procedure, immediately after it, and after a week of pharmacologic therapy (either placebo or study drug). The six-minute walk test and SF-36 questionnaire results were administerd twice: one day before the CA procedure and atone week post-ablation. The LV end-diastolic pressure (LVEDP, mm Hg) was measured directly during the CA procedure immediately after transseptal puncture and before LA sheath removal in order to exclude preexisting LV diastolic dysfunction and abnormal intraatrial hemodynamic parameters.

All measured variables appeared to have a normal distribution and are presented as means and standard deviations. The statistical analysis was performed with 'Statistica 12' software package (Stat soft, USA) using the Student's t-test, the paired Student's, and the dispersion analysis of repeated measures ANOVA. $P<0.05$ was considered statistically significant.

RESULTS

Intraprocedural findings are presented in Table 2. There were no statistically significant differences in the intraprocedural characteristics between study drug and placebo groups. Echocardiographic characteristics of transmitral and pulmonary vein flow, LA size and volume, pulmonary circulation pressures during the therapy or placebo administration are presented in Table 3.

Table 2 Intraprocedural characteristics

Parameter	Group I – Therapy (n=34)	Group II – Placebo (n=30)	P
Age (years)	52.3±5.7	54.1±6.2	0.244
Electrophysiological confirmation of PV antrum isolation	34 (100%)	30 (100%)	ns
LA volume measured by 3-D navigation system (ml3)	115.58±20.22	106.28±19.44	0.318
Radiofrequency lesion area to LA area ratio measured by 3-D navigation system (%)	24.67±2.63	25.13±2.82	0.265
Procedure duration (min)	139.58±22.49	142.61±23.78	0.385
Fluoroscopy time (min)	43.24±6.89	42.32±7.06	0.381
Total ablation duration (min)	43.23±7.65	42.63±7.64	0.604

RESULTS INTERPRETATION AND DISCUSSION

The absence of LVEDP changes suggests that PV isolation does not lead to the deterioration of LV diastolic function. Therefore, all observed changes in transmitral, PV and PA flow patterns appear to be due to left atrial changes at the time of PV isolation. These changes are dependent upon LA reservoir and pump function, RV contractility, pulmonary vascular resistance, and mechanical function of the PV sleeves [6].

Immediately after the CA procedure, VTI E increases. This is associated with impaired LA relaxation and increased LA end diastolic pressure, resulting in increased pulmonary vascular resistance. Subsequently, early LV filling increases and a so-called 'pseudo restrictive' pattern of transmitral flow is observed (Fig. 1). During a week of placebo administration, this filling pattern persisted and even increased further, reflecting continuous deterioration of relaxation evidently due to the progression of post ablation myocardial edema.

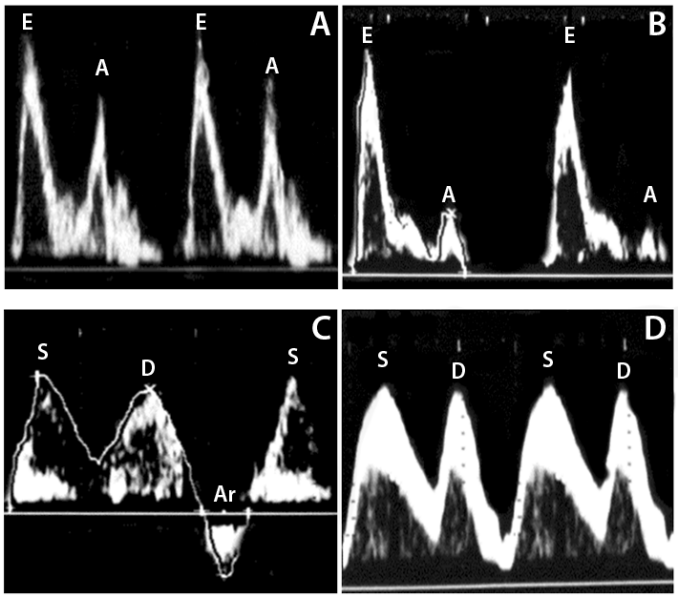


Fig 1 Typical patterns of transmitral (A and B) and PV (C and D) flow in the same patient before (A and C) and immediately after (B and D) PV antrum isolation. Initially post ablation the normal the LV filling pattern transforms into a 'pseudo restrictive' one. This appears as an increase in the transmitral flow velocity during LV passive filling (peak E) and decrease of atrial systole flow velocity (peak A). In this situation the E/A ratio exceeds two. The Ar wave of PV flow disappears simultaneously because of an increase in pulmonary vascular resistance

Table 3 Intracardiac hemodynamic changes during a week of therapy or placebo administrationas measured by transthoracic echocardiography (except LVEDP which was measured directly

Parameter	Group I – Therapy (n=34)			Group II – Placebo (n=30)			P				
	Before the CA (1)	Immediately after the CA (2)	After a week (3)	Before the CA (4)	Immediately after the CA (5)	After a week (6)	1-2-3*	4-5-6*	1-4**	2-5**	3-6**
VTI E (cm)	12.5±3.2	19.7±4	14.7±4.4	11.3±4.2	19.6±4.8	20.9±5.2	0.008	0.003	0.308	0.116	0.040
VTI A (cm)	7.6±2.5	6.9±1.7	7.4±2.6	7.1±2.2	6.4±1.5	5.4±1.3	0.048	0.007	0.634	0.415	0.031
VTI TMF (cm)	20.1±2.8	16.6±2.2	19.1±3.5	18.4±2.9	16.0±2.8	13.3±3.2	0.004	0.002	0.226	0.443	0.008
Peak E (mm/s)	80±10	86±13	84±11	74±11	80±12	87±13	0.546	0.075	0.447	0.227	0.751
Peak A (mm/s)	55±9	40±13	52±11	46±7	38±14	33±15	0.026	0.018	0.604	0.590	0.031
E/A ratio	1.45±0.25	2.15±0.62	1.62±0.35	1.61±0.27	2.11±0.57	2.64±0.63	0.005	0.003	0.081	0.093	0.001
IVRT (ms)	124±22	106±14	117±19	125±18	100±12	98±10	0.015	0.006	0.915	0.475	0.002
VTI S (cm)	11.6±3.1	8.3±1.7	11.2±2.5	10.7±3.3	9.1±3.6	8.3±4.1	0.049	0.032	0.276	0.092	0.001
VTI D (cm)	8.4±1.9	5.1±0.8	8.6±2.1	9.7±2.0	6.1±0.5	5.7±1.7	0.024	0.019	0.183	0.083	0.001
S/D ratio	1.38±0.41	1.63±0.35	1.30±0.39	1.1±0.36	1.49±0.34	1.46±0.37	0.135	0.345	0.743	0.143	0.415
VTI Ar (cm)	3.0±1.1	2.2±1	4.1±1.4	2.8±1.2	2.2±0.9	1.5±0.5	0.046	0.021	0.092	0.077	0.001
Ar dur (ms)	129.4±18.5	115.4±16.8	135±20.1	127.6±17.1	113.5±14.7	110.1±12.2	0.031	0.008	0.733	0.687	0.002
LAEF (%)	52.1±6.5	39.3±4.8	49.1±5.2	49.7±6	37.6±4.3	36.5±4.2	0.044	0.009	0.545	0.183	0.001
LAAEF (%)	45.5±7.2	27.3±6.1	40.0±6.7	44.2±7	25.9±5.7	31.6±6.7	0.010	0.008	0.446	0.108	0.013
LA diameter (cm)	3.8±0.3	4.1±0.4	3.9±0.3	3.9±0.4	4.1±0.5	4.1±0.6	0.208	0.192	0.601	0.737	0.082
LAV (ml)	60.7±10.0	61.7±5.4	60.3±8.0	58.3±9.4	59.0±4.8	59.8±4.4	0.889	0.663	0.390	0.404	0.121
Mean LAP (mm Hg)	8.8±2.1	14.1±2.7	9.0±3.1	9.2±1.6	13.9±3.0	13.8±2.9	0.043	0.018	0.754	0.893	0.027
Mean PAP (mm Hg)	9.1±2.3	14.0±3.1	10.6±2.2	9.4±2.4	14.3±3.3	15.6±3.4	0.011	0.023	0.354	0.326	0.005
RVSP (mm Hg)	19.7±7.5	28.3±12.2	16.7±9.6	21.1±7.9	29.5±13.7	31.6±14.4	0.009	0.003	0.234	0.651	0.001
LVEDP (mm Hg)	8.2±2.3	8.3±2.3	-	8.4±2.2	8.3±2.1	-	0.682	0.813	0.563	0.893	-

In contrast, after a week of study drug administration, VTI E significantly decreased in the treatment group because ofa reduction in LA pressure and pulmonary vascular resistance, though it did not return to baseline values.

Immediately after the CA, VTI A moderately decreased in both groups. It continued to decrease during the week post-ablation in the control group, while it actually increased in the therapy group. Possible explanation for this decline include the one mentioned above and the deterioration of LA contractility. In spite of highly variable LA filling patterns preablation, almost all patients were found to have a pseudorestictive pattern post CA which reflects the development of impaired LA relaxation and elevated pulmonary vascular resistance. A similar pattern of change (decline in both groups with improvement in the therapy group) was seen in the VTI TMF measurements, reflecting the same mechanism. The subsequent improvement in both VTI A and VTI TMF in the treatment group compared to the control group appears to be due to study drug therapy. Of note, approximately one third of all patients had evidence of impaired LV relaxation while the others demonstrated normal diastolic parameters at baseline, yet almost all demonstrated a change in VTI A.

There were no statistically significant differences found in peak E velocity between the two groups. The differences between groups were also not significant at all three control points. This can be explained by 'pseudo restriction' developing in a number of patients with normal LV filling pattern and impaired LV relaxation. In the control group the mean peak E velocity did not change immediately post CA. However, it gradually increased over the course of a week, suggesting a progression in changes resulting in the 'pseudo restriction' pattern. In the study drug group, however, the mean peak E velocity demonstrated only slight variation from initial values. Similar differences in changes between the two groups were observed in the peak A velocity dynamics.

IVRT can increase because of elevated LVEDP or decreased LAP, reflecting the LA after load. Before CA in both groups, mean IVRT slightly exceeded the normal values. This appears to be due to the fact that there were patients in both groups who were initially found to have impaired LV relaxation. Immediately after the CA, LA pressure increased, leading to the elevation of LA/LV diastolic gradient and decrease of IVRT. In the placebo group, this parameter did not improve or worsen within the following week. In the study drug group, IVRT was noted to increase, which was associated with a decrease in LA pressure. Thus, one can presume that treatment with the telmisartan/amlodipine combination resulted in a decrease in LVEDP, but this cannot be validated solely by the use of non-invasive techniques. At the same time, RVSP also decreased in the placebo group leading to a decrease in IVRT.
In the case ofa native mitral valve, VTI S measures LA passive stretch (elastic characteristics). In both groups VTI S decreased after the CA, likely due to LA elasticity loss. In the placebo group, VTI S noteably continued decreasing over time, perhaps because of the progression of LA myocardial edema. In the therapy group, VTI S returned to baseline by one week.

VTI D dynamics and its interpretation were similar to VTI E. It increased after a week in the study drug group compared to preoperative values while it remained depressed in the control group. Likely this is due to the loss of PV sleeve obturative function (PV sleeve contractility during fixed phases of cardiac cycle, preventing regurgitation from LA to PV) after their electrical isolation. The S/D ratio did not exceed the normal values in either group during the follow-up period.

During LA systole, not only LV filling but also PV regurgitation occurs. The majority of LAAEF contributes to LV filling. After CA VTI Ar decreased, and in many patients even disappeared (Fig. 1). Since LVEDP did not change after the CA, simultaneous reduction of VTI Ar and VTI A can be explained by pulmonary arteriolar spasm reflex and subsequent elevation of pulmonary vascular resistance. This condition worsened over a week post-ablation in the placebo group, whereas in study drug group it improved. However, if the administration of the study drugleads to a decrease in the LA pressure, and pulmonary vascular resistance remains the same, VTI Arshould also decrease, but instead it increased. This confirms that the study drug administration results in pulmonary arteriolar dilatation and pulmonary vascular resistance reduction.

Normally, Ar duration is shorter than peak A duration. It becomes longer in the case of elevated LA pressure, but it appears to shortenpost-ablation. The reason for this phenomenon is also increased pulmonary vascular resistance. Ar duration continues to shorten in the control group and becomes longer in the study drug treatment group. This also confirms that pulmonary vascular resistance reduction is due to the administration of the telmisartan/amlodipine combination.

Immediately after the procedure, LAEF decreased due toa reduction in recruitableLA myocardium. The subsequent development of myocardial edema worsened the LA elasticity but apparently did not affect the LA contractility as it was demonstrated in placebo group. In the study drug group LAEF increased due to a decrease in after load. A similar mechanism has been found in LAAEF dynamics.

LA diameter and volume did not change significantly during the short follow-up period in either group. Nevertheless, one can note that the dispersions of both these parameters has narrowed after the procedure. This can be explained by reduced LA passive stretching.

Before the procedure, the mean LAP was almost equal to the mean PAP due to minimal pulmonary vascular resistance. Immediately after the procedure, the mean LAP increased by 1.5 times and exceeded the normal values because of elasticity deterioration. This led to pulmonary arteriolar spasm reflex with subsequent increase in PAP and RVSP. Evidently, high persistent pulmonary vascular resistance increases the RV contractility. During the immediate post-procedure period patients also complained of an increase in exertional dyspnea. However, patients in study drug group demonstrated significantly better exercise tolerance and quality of life after a week of the follow-up (Fig. 2 and 3) than in the placebo group.

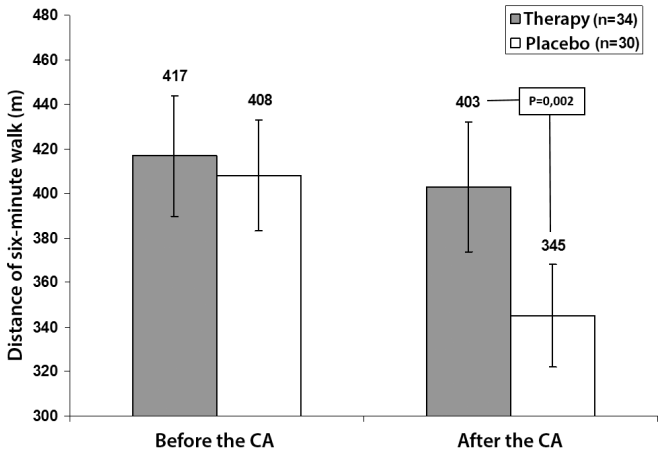
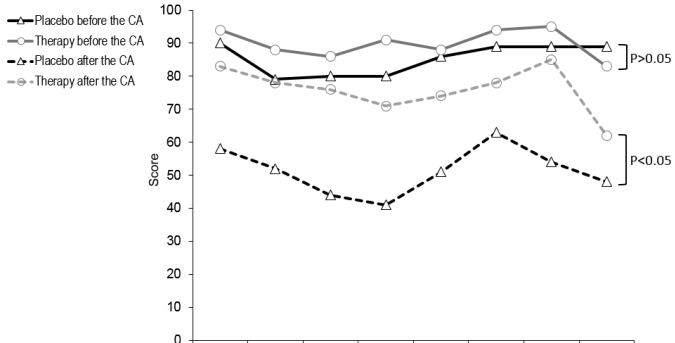


Fig 2 The six-minute walk test dynamics



	PF	RF	BP	GH	VT	SF	RE	MH
Placebo before the CA	90	79	80	80	86	89	89	89
Therapy before the CA	94	88	86	91	88	94	95	83
Placebo after the CA	58	52	44	41	51	63	54	48
Therapy after the CA	83	78	76	71	74	78	85	62

Fig 3 The quality of life dynamics accordingly to SF-36 questionnaire

CONCLUSIONS

PV antrum isolation in patients with paroxysmal AF leads to intracardiac hemodynamics deterioration mostly due to a decline in LA elasticity and contractility. This results in an increase in LA pressure, pulmonary arteriolar spasm reflex activation, and an increase in pulmonary vascular resistance. The administration of a combination of telmisartan and amlodipine in the short-term postprocedural period improves the intracardiac hemodynamics by promoting systemic and pulmonary vasodilatation, which decreaseses LA, PA and RV pressures. This improves exercise tolerance and quality of life.

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