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Research Article

Atrial Fibrillation Recurrence Rate in Different Clinical Groups: Coronary Artery Disease and Age Matter

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BACKGROUND: Catheter ablation (CA) is an established method for atrial fibrillation (AF) treatment. Up to 20% of patients with AF develop coronary artery disease (CAD) as a secondary diagnosis. The data on whether the CAD affects the efficacy of AF ablation is contrary, while arterial hypertension is a known risk factor for AF as well as for AF recurrence after the CA.

AIM: We conducted this research to assess the AF recurrence rate and its risk factors after the primary catheter AF ablation procedure in the different clinical groups including IdiopathicAF, AF concomitant to arterial hypertension (HTN) and AF concomitant to CAD.

MATERIALS AND METHODS: Patients who underwent 451 PVI procedures performed since January 2016 to December 2017 were screened for AH, CAD and other structural heart disease. Among them 153 pts were selected for the subsequent analysis and divided into 3 groups — IdiopathicAF, AF + AH, AF + CAD.

RESULTS: The presence of CAD ($r = 0.313$, $p < 0.001$), age ($r = 0.224$, $p = 0.008$), CHA2DS2-VASc score ($r = 0.279$, $p = 0.001$), history of MI ($r = 0.240$, $p = 0.004$), LA size ($r = 0.204$, $p = 0.018$) were correlated with the recurrence rate. In the AF + CAD group patients older than 65 years demonstrated dramatically lower AF-free survival rate (37.5%) in comparison to younger CAD population (75%, log-rank $p < 0.001$) as well as to younger and older non-CAD patients.

CONCLUSIONS: The presence of CAD should always attract the attention of physicians before considering the AF ablation as an option to treatment. Elderly CAD patients have the lowest ablation efficacy and the best strategy for this group (more extensive primary ablation or conversion to the permanent AF) needs to be studied.

Keywords: atrial fibrillation; catheter ablation; pulmonary vein isolation; arterial hypertension; coronary artery disease.

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Научная статья

Эффективность катетерной аблации фибрилляции предсердий в различных клинических группах: влияние ишемической болезни сердца и возраста

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Обоснование. Катетерная аблация (КА) — распространенный метод лечения фибрилляции предсердий (ФП). До 20 % пациентов с ФП в качестве сопутствующего диагноза имеют ишемическую болезнь сердца (ИБС). Данные о влиянии ИБС на эффективность КА при ФП противоречивы. В то же время артериальная гипертензия (АГ) является известным фактором риска ФП и рецидива ФП после КА.

Цель — оценка вероятности рецидива ФП после первичной КА в разных клинических группах пациентов, включая идиопатическую ФП, ФП на фоне АГ и ФП, сочетающуюся с ИБС.

Материалы и методы. Среди пациентов, которым с января 2016 г. по декабрь 2017 г. были выполнены КА по поводу ФП, был проведен скрининг на предмет АГ, ИБС и другой структурной патологии сердца. Пациенты с ГКМП и клапанной патологией, а также пациенты с повторными КА были исключены. Для последующего анализа были отобраны 153 пациента и разделены на 3 группы — идиопатическая ФП, ФП + АГ, ФП + ИБС.

Результаты. Наличие ИБС (r = 0,313, p < 0,001), возраст (r = 0,224, p = 0,008), риск по CHA2DS2-VASc (r = 0,279, p = 0,001), постинфарктный кардиосклероз (r = 0,240, p = 0,004) и передне-задний размер ЛП (r = 0,204, p = 0,018) коррелировали с риском рецидива ФП. В группе ФП + ИБС пациенты старше 65 лет имели значительно меньшую эффективность КА (37,5 %), чем более молодые пациенты с ИБС (75 %, логарифмический ранг p < 0,001) и пациенты без ИБС.

Заключение. Наличие у пациента ИБС должно учитываться при принятии решения о выполнении КА по поводу ФП. Возрастные пациенты с ИБС имеют наиболее низкую эффективность КА и предпочтительная тактика лечения (более агрессивная КА или перевод в постоянную форму ФП) требует изучения.

Ключевые слова: фибрилляция предсердий; катетерная аблация; изоляция легочных вен; артериальная гипертензия; ишемическая болезнь сердца.

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BACKGROUND

Catheter ablation is an established method for atrial fibrillation (AF) treatment [1]. Despite the fact that it is the most effective approach to maintain sinus rhythm [2, 3], the postprocedural recurrence rate remains high. Better patient selection is one of several directions (as well as durable pulmonary vein isolation (PVI) and looking for additional AF triggers) to improve the AF-free survival after ablation. Up to 20% of patients with AF develop coronary artery disease (CAD) as a secondary diagnosis [4]. The data on whether the CAD affects the efficacy of AF ablation is contrary [6, 7] probably due to the heterogeneity of CAD group (individual coronary anatomy, revascularization status, signs of ischemia, heart failure and other comorbidities, etc.) as well as the number of concomitant risk factors affecting the risk of AF recurrence. We believe that the separation of AF patients into several clinical groups could help describe their profiles better and assess the complex interactions between the AF and CAD in the real-world population.

AIM

This study was aimed to assess the AF recurrence rate and its risk factors after the primary catheter AF ablation procedure in the different clinical groups including IdiopathicAF, AF concomitant to arterial hypertension (HTN) and AF concomitant to CAD.

METHODS

Study design

This study was performed as a single-center retrospective comparison.

Population

Of 451 PVI procedures performed since January 2016 to December 2017, 396 were primary. Two-hundred and forty patients with known coronary anatomy (Coronary angiography (CAG) or computed tomography-angiography (CTA)) were selected for the subsequent analysis. Patients with hypertrophic cardiomyopathy, mitral stenosis (valvular AF) were not included in the study.

After exclusion of the nonqualifying patients, remaining patients (n = 153) were retrospectively enrolled into this study and divided into three groups based on the medical history and CTA data: IdiopathicAF group, AF + HTN group and AF + CAD group (Fig. 1).

IdiopathicAF group (n = 32)

Diagnosis of idiopathicAF was established in AF patients without history of arterial hypertension and coronary atherosclerosis (CCSi = 0).

AF+HTN group (n = 73)

HTN was diagnosed according to guidelines [8]. In all patients' medications were titrated to keep blood pressure at the target level less than 139/89 mmHg.

All patients in this group had no signs of coronary atherosclerosis by CAG or CT-CAG (no stenoses and CCSi = 0).

AF+CAD group (n = 48)

CAD was diagnosed in patients with at least one of the following:

- significant (> 50%) coronary artery stenosis revealed by the CAG or CTA,
- history of percutaneous coronary intervention or coronary bypass surgery before primary ablation.

All patients signed informed consent for the personal data processing during their hospitalization for primary ablation procedure.

Clinical and demographic data are presented in Table 1.

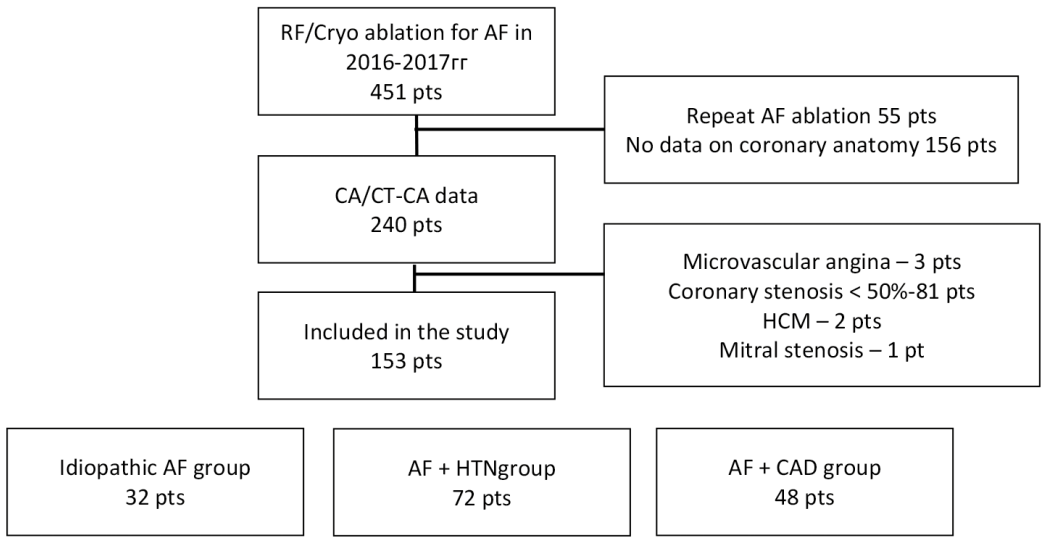


Fig. 1. Study groups selection work-flow

Table 1. Demographic, echocardiography and intraprocedural data

Parameter		IdiopathicAF (*n* = 32)	AF + HTN (*n* = 72)	AF + CAD (*n* = 48)	*p*
Male sex, *n* (%)		22 (68.8)	28 (38.4)	30 (62.5)	1–2 – 0.004 2–3 – 0.009
Age, yrs		48.6 ± 11.9	59.6 ± 9.2	66 ± 6.9	< 0.001
HTN, *n* (%)		0	72 (100%)	48 (100%)	-
DM, *n* (%)		1 (3.1)	5 (6.8)	11 (22.9)	1–3 – 0.005 2–3 – 0.021
MI, *n* (%)		-	-	19 (39.6)	-
Revascularization, *n* (%)		-	-	20 (42)	-
CHA2DS2-VASc score		0.3 ± 0.7	2.3 ± 1.2	3.7 ± 1.3	< 0.001
Anticoagulation	Rivaroxaban, *n* (%)	9(45)	26(60)	18(69)	
	Apixaban, *n* (%)	3(15)	7(16)	0(0)	
	Dabigatran, *n* (%)	6(30)	10(23)	5(19)	
	Warfarin, *n* (%)	2(10)	0(0)	3(12)	
History of stroke, *n* (%)		0	4 (7.1)	9 (22.5)	0.044
Paroxysmal AF, *n* (%)		25 (78.1)	62 (84.9)	44 (91.7)	ns
LV EF, %		64.4 ± 2.3	62.3 ± 4.5	61.2 ± 7.4	1–2 – 0.002 1–3 – 0.008
LA diameter, mm		39.4 ± 4.0	42 ± 4.4	44.3 ± 4.8	1–2 – 0.004 1–3 < 0.001 2-3 – 0.011
Degree of MR		0.8 ± 0.6	1.1 ± 0.6	1.2 ± 0.6	1–2 – 0.013 1–3 – 0.003
CTI ablation, *n* (%)		6 (18.8)	18 (25)	23 (47.9)	1–3 – 0.005 2–3 – 0.01
Energy used for PVI, *n* (%) CBA	RFA	19 (59.4)	55 (76.4)	38 (79.2)	ns
	CBA	13 (40.6)	17 (23.6)	10 (20.8)	

Note: AF — atrial fibrillation, HTN — arterial hypertension, CAD — coronary artery disease, MI — myocardial infarction, LV EF — left ventricular ejection fraction, LA — left atrium, MR — mitral regurgitation, CTI — cava-tricuspid isthmus, RFA — radiofrequency ablation, CBA — cryo-balloon ablation.

Catheter ablation procedure

Left atrial (LA) and pulmonary venous CTA was performed in all patients to assess the individual anatomy and exclude LA thrombosis. In some patients a transesophageal echocardiography was used to exclude LA thrombi (on condition CTA was performed more than 48 hours earlier than ablation procedure) or to assist transseptal puncture. Right femoral and right jugular (or left subclavian) venous access were used to insert diagnostic and ablation catheters. Transseptal access was performed under the fluoroscopy guidance and the direct LA angiography was done while pacing the ventricles at 200 bpm.

Different energy modalities were used to isolate PVs. Radiofrequency ablation (RFA) was used in 112 pts (73.2%) and cryoballoon ablation (CBA) — in 41 pt (26.8%) (Table 1). During RFA procedures a "single puncture – double access" approach was used. Multipolar circular diagnostic catheter Lasso 2515 (Biosense Webster, USA) was introduced into the LA through the transseptal sheath SR0 or SL0 (Abbott, USA). In the majority of cases RFA was performed under the fluoroscopy guidance using an open-irrigated ablation catheter Thermocool EZsteer (Biosense Webster, USA) consecutively in the RSPV, RIPV, LSPV and LIPV. If non-fluoroscopy mapping system Carto 3 (Biosense Webster, USA) was used, the wide antral isolation of the right and then left PVs was performed by Thermocool SF Nav (Biosense Webster, USA) or Thermocool SmartTouch catheters (Biosense Webster, USA). Contact force technology as well as Ablation index and CLOSE protocol, were not routinely used in patients enrolled in this study. Entrance and exit block were checked and achieved at the end of procedure in all patients.

Cryoballoon ablation was performed using Arctic Front Advance (Medtronic, USA) cryoballoon catheters. Single 240 sec application was performed consecutively in LSPV, LIPV, RIPV and RSPV. Entrance and/or exit block were checked after the cryoapplication in each vein using circular multipolar

diagnostic catheter Achieve 20 mm (Medtronic, USA). Phrenic nerve was paced from the SVC at cycle 1000–2000 ms and voltage of 15 V during right PV cryoablation.

If isthmus-dependent atrial flutter was diagnosed prior to or induced during the procedure, the linear RF ablation in the cava-tricuspid isthmus was performed, and bi-directional conduction block was confirmed at the end of procedure.

Follow up

To collect the data on arrhythmia recurrence, patients on antiarrhythmic therapy were interviewed by phone, the query included the following questions:

1. Do you have episodes of palpitations after the ablation procedure?
2. What time after the ablation were you diagnosed with AF recurrence?
3. Has AF transformed to a permanent form?
4. If AF was paroxysmal, how often did the paroxysms happen?
5. How many AF-related admissions did you have after the ablation procedure?
6. What AAD/dosage are you taking now?

Mean follow up duration at the time of the call was similar in the IdiopathicAF group (27.0 mos) and the AF + HTN group (29.1 mos, $p = 0.47$), while in the AF + CAD group it was significantly shorter (23.5 mos, pAF + CADvsIdiopathicAF — 0.011, pAF + CADvs.AF + HTN < 0.001).

AF recurrence definition

Postablation recurrence was diagnosed if sustained AF episode was registered by the standard surface 12-lead ECG tracing or during ECG monitoring.

Antiarrhythmic therapy after ablation

Antiarrhythmic drugs were prescribed to all patients for at least 3 months post ablation period. The decision whether to continue therapy, to change the drug or to discontinue its use after 3 months was made by primary care physician. As shown at the Table 2, at the moment of the phone call 70.5% in IdiopathicAF group, 42.3% in AF + HTN group and 45.4% in AF + CAD group were off Class 1 and 3 antiarrhythmic drugs ($p > 0.05$).

Statistical analysis

Statistical analysis was performed using licensed SPSS Statistics version 26.0 (IBM, USA) software.

Distribution normality test for continuous and categorical parameters was performed using Kolmogorov-Smirnoff test. Descriptive statistics were presented as a mean value and a standard deviation. Nominal variables were described as a number of cases and a valid percent.

Differences between two groups by quantitative parameters were analyzed using Student's *t*-test or Mann – Whitney test depending on the normality of distribution. Three and more groups were compared using Kruscall – Wallis criterion or ANOVA.

Comparison of categorial data was performed using Fisher's exact test or Chi-square criterion. To compare 3 and more groups we performed Pearson's Chi-square Post-Hoc analysis.

Kaplan – Meier analysis was used to compare the efficacy. The difference was assessed by log rank test.

Correlations between the risk factors and recurrence were assessed using Spearmen method.

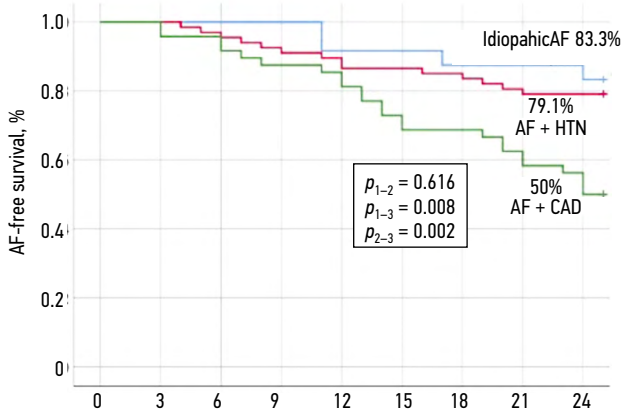
Prognostic model was used to assess the dependence of AF recurrence rate on the studied risk factors. Wald test was used to test the significance of individual coefficients in the model, and the factor with coefficient having the lowest probability of being non-zero is excluded on each step. AF recurrence probability was calculated using formula $p = 1/(1 + e^{-z})$.

The differences in all tests were considered statistically significant when p-value was below 0.05.

Table 2. Antiarrhythmic therapy in 2-years follow up

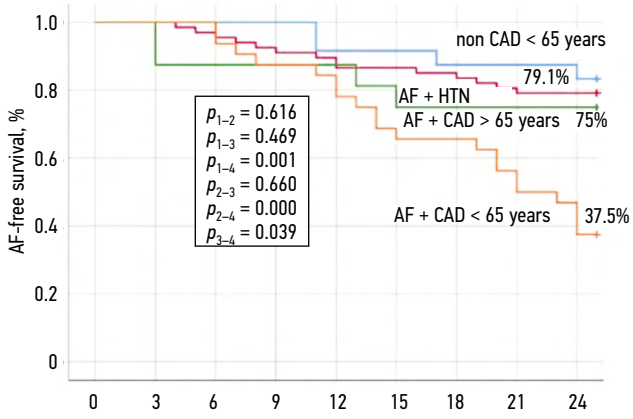
Antiarrhythmic drug	IdiopahicAF	AF + HTN	AF + CAD
Off AAD (none+beta-blocker)	70.5%	42.3%	45.4%
None	47%	23.1%	21.2%
Beta-blocker	23.5%	19.2%	24.2%
Lappaconitine hydrobromide	5.9%	7.7%	9.1%
Propafenone	5.9%	7.7%	0
Flecainide	0	1.9%	0
Sotalol	17.6	32.7%	39.4%
Sotalol + Lappaconitine hydrobromide	0	5.7%	0
Amiodarone	0	1.9%	6.1%

Note: Overall difference between groups was not statistically significant (*p*-value — *ns*)



IdiopahicAF	24	24	24	24	22	22	21	21	21
AF + HTN	67	67	65	62	60	58	57	54	53
AF + CAD	48	48	46	42	41	35	33	30	27

Fig. 2. Caplan – Meyer analysis of the AF recurrence over 2 years after ablation in different clinical groups



IdiopahicAF	24	24	24	24	22	22	21	21	21
AF + HTN	67	67	65	62	60	58	57	54	53
AF + CAD	16	16	14	14	14	13	12	12	12
AF + CAD > 65 years	32	32	32	28	27	22	21	18	15

Fig. 3. Caplan – Meyer analysis of the AF recurrence over 2 years after ablation in different clinical groups depending of age. CAD patients older than 65 years demonstrated worst AF-free survival

RESULTS

Recurrence rate in different clinical groups

As shown at the Figure 2, the patients in AF + CAD group demonstrated significantly lower efficacy than in other clinical groups: 50% vs 83.3% (IdiopathicAF, log-rank p = 0.008) and 79.1% (AF + HTN, log-rank p = 0.002). The recurrence rate in the AF + HTN group did not differ from IdiopathicAF group (log-rank p = 0.616).

Risk factors affecting the recurrence rate

The presence of CAD (r = 0.313, p < 0.001), age (r = 0.224, p = 0.008), CHA2DS2-VASc score (r = 0.279, p = 0.001), history of MI (r = 0.240, p = 0.004), LA size (r = 0.204, p = 0.018) were correlated with the recurrence rate. These weak correlations were confirmed by significant differences which were found during paired comparisons of subgroups of patients with vs without recurrence by these factors.

Table 3. Logistic regression sequence

	Risk factors	*B*-coefficient	*p*-value
Step 1	CAD	0.669	0.234
	Age	0.023	0.442
	CHADS-VASc score	0.184	0.350
	History of MI	0.427	0.500
	LA size	0.057	0.211
	Constant	–5.468	0.037
Step 2	CAD	0.864	0.072
	Age	0.022	0.453
	CHADS-VASc score	0.177	0.368
	LA size	0.054	0.231
	Constant	–5.305	0.042
Step 3	CAD	0.887	0.065
	CHADS-VASc score	0.268	0.087
	LA size	0.051	0.259
	Constant	–4.017	0.034
Step 4	CAD	0.964	0.043
	CHADS-VASc score	0.293	0.059
	Constant	–1.948	0.000

Table 4. Subgroup analysis of AF recurrence risk factors inside the CAD group

Risk factor	Younger 65 years (*n* = 16)	65 years and older (*n* = 32)	*p*-value
Age, years	58.7 ± 4.9	69.7 ± 4.2	< 0.001
Male sex, *n* (%)	14 (87.5)	16 (50)	0.013
LA size, mm	45.6 ± 4.7	43.7 ± 4.7	< 0.001
CHA2DS2-VASc score	2.7 ± 1.1	4.25 ± 1.1	0.01
AF history duration, *Me* (25; 75)	59.4 (14.5; 90)	43.5 (12; 66)	0.001

Note: AF — atrial fibrillation, CAD — coronary artery disease, LA — left atrium

Logistic regression

All factors, correlating with the recurrence rate, showed a low correlation level (less than 0.3) and lost its effects after their inclusion into the regression model. Beta-coefficients and p-values for every separate risk factor at each step of binary regression are presented in the Table 3. At the final step the presence of CAD stayed the only statistically significant risk factor.

The final formula of binary logistic regression model looked like this:

$$p = 1 / (1 + e^{-z}) \cdot 100\%,$$

where $z = -1.948 + 0.964 \cdot \text{CAD}$, p — probability of AF recurrence, CAD — presence of CAD (0 — no CAD, 1 — CAD), were statistically significant (p-0,001) and the model had specificity of 87.1%, sensitivity of 31.7% and diagnostic efficiency of 70.1%.

CAD and age interactions

Then we performed the search on the factors decreasing the AF ablation efficacy in the AF + CAD group. To achieve this goal we consecutively divided AF + CAD group into two subgroups based on different parameters (male *vs* female, paroxysmal AF vs persistent AF, DM vs no DM, LA < 40 mm vs LA > 40 mm, LA < 45 mm vs LA > 45 mm, age < 60 years vs age > 60 years, etc).

The age group over 65 years was the only significant risk factor for AF recurrence.

In the AF + CAD group older patients demonstrated dramatically lower AF-free survival rate (37.5%) in comparison

to younger CAD population (75%, log-rank $p < 0.001$) as well as to younger and older non-CAD patients (Fig. 3).

Risk factors for AF recurrence in CAD patients older than 65 years

Older CAD patients differed from younger CAD population by several significant parameters (Table 4). But none of these factors was an independent predictor of AF recurrence in the regression analysis.

DISCUSSION

Our results support the opinion that in patients with CAD the results of AF ablation are worse than in those without CAD. This could be explained by the effect of CAD itself as well as by the complex action of several risk factors, which are more common in CAD population. All these factors (age, LA size, history of MI, presence of DM and HTN etc.) were found to be insignificant after the adjustment of the presence of CAD.

Data on whether the CAD affects the AF ablation results are contradictory. The retrospective analysis of the Leipzig registry did not find the difference between CAD and non-CAD populations [7]. Similar data are presented by L. Liu at al. in their study [9]. Alternatively in papers by R. Winkle at al. the CAD was described as one of the risk factors for AF recurrence and was used for CAAP-AF score [6; 10]. These discrepancies between studies could be explained by the different inclusion criteria and arrhythmia recurrence definition.

Subsequent analysis of the same risk factors inside the AF + CAD group showed the dramatic decrease in AF-free survival in patients older than 65 years while in IdiopathicAF and AF + HTN groups no correlation between the age and AF recurrence was found.

It is well known that the aging plays an important role in the pathogenesis of AF, as it promotes the atrial fibrosis, dilatation and atrial cardiopathy [11, 12]. In most studies the age serves as a major risk factor for AF development [13] incidence, and morbidity and mortality related to AF (DisModMR software as well as for AF recurrence after ablation [14]. But as these studies were performed on the unselected population it is difficult to understand if worse prognosis in elder patients was affected by age or by higher comorbidity level, including CAD.

LIMITATIONS

Our study presents the retrospective single-center analysis with no investigation of atrial substrate or continuous monitoring of heart rhythm to reveal asymptomatic AF episodes post ablation, however the patients were divided into separate clinical groups and the difference in several demographic and clinical factors was clearly described and accurately analyzed.

Actual recurrence rate (based on the long-term ECG or loop monitoring) would provide more precise results as well as could assess the value of traditional ECG and 24-hour ECG-monitoring in AF detection however, telephone interviews were detailed and all attempts were made to elicit AF recurrence. In the future studies we are going to use subcutaneous loop recorders to assess long term recurrence rate as well as the number of asymptomatic AF paroxysms post catheter ablation in different clinical groups.

CONCLUSION

The presence of CAD should always attract attention of physicians before considering the AF ablation as an option to treat such patient. Elderly CAD patients have the lowest ablation efficacy and the best strategy for this group (more extensive primary ablation or conversion to the permanent AF) needs to be studied

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