ORIGINAL ARTICLE

Cardiac ^{123}I-mIBG scintigraphy for prediction of catheter ablation outcome in patients with atrial fibrillation

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Background. **Previous studies show inconsistent results on the role of innervation imaging (with ^{123}I-mIBG) in predicting late atrial fibrillation (AF) recurrence after catheter ablation (CA). These studies included patients with paroxysmal AF and studied prognostic value of post-CA I-123-mIBG parameters. Current study investigated the ability of pre CA 123-I-mIBG imaging to predict late AF recurrence in patients with persistent AF.**

Methods. **^{123}I-mIBG cardiac imaging was performed before CA in 82 patients with persistent AF. Patient was followed for 12 months.**

Results. **Multivariable analysis demonstrated that late heart-to-mediastinum ratio (H/M_{late}) and washout rate (WR) were independent predictors of AF recurrence. ROC-curve analysis data showed that H/M_{late} <1.6 (sensitivity 73.53%, specificity 81.3%, AUC 0.792, *P* < .001) and WR > 25.11 (sensitivity 70.6%, specificity 70.8.3%, AUC 0.712, *P* < .001) indicate high probability of AF relapses during 12 months after CA.**

Conclusion. **Pre-CA parameters of global cardiac sympathetic activity estimated by ^{123}I-mIBG scintigraphy are associated with late AF relapses in persistent AF patients with normal LVEF and absence of significant CAD. (J Nucl Cardiol 2022;29:2220–31.)**

Key Words: atrial fibrillation • catheter ablation • cardiac innervation • scintigraphy • I-123-mIBG • prognosis

Abbreviations

af	Atrial fibrillation
CA	Catheter ablation
^{123}I-mIBG	Iodine-123 metaiodobenzylguanidine
HF	Heart failure
PVI	Pulmonary vein isolation
H/M	Heart-to-mediastinum ratio
WR	Washout rate

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INTRODUCTION

Atrial fibrillation (AF) is the most common type of arrhythmia and is a challenging problem of modern medicine. The main method offered to relieve AF-related symptoms is catheter ablation (CA), based on evidence illustrating its efficacy compared with antiarrhythmic drug therapy.[1] However, the effectiveness of this approach is not absolute and depends on multiple factors, including left atrium diameter, duration of continuous AF prior to ablation, ventricular rate and others.[1,2] In recent years several predictive scores for rhythm outcome of AF recurrence post CA have been developed and tested, but they need improvement and have limited validation still.[2-5] The current expert opinion is that knowledge on the health modifiers that can cause AF should be incorporated into clinical approach to patients with AF and influence on a choice of therapeutic strategy.[4] One of these modifiers is the autonomic nervous system, which promotes the new onset and progression of AF.[4] Radionuclide cardiac imaging with iodine-123 metaiodobenzylguanidine (^{123}I-mIBG) is the most widely used diagnostic tool for studying cardiac sympathetic nervous system abnormality. To date, there are a lot of studies, showing the possibility of ^{123}I-mIBG scintigraphy to predict mortality in heart failure (HF) patients independently of its cause[6-10] and only few, which demonstrated association of global cardiac sympathetic activity changes with development and recurrence of AF.[11-14] Particularly it was shown that a high global washout rate of ^{123}I-mIBG calculated in a stable sinus rhythm 5 days after pulmonary vein isolation is an independent predictor of AF recurrence in patients with either paroxysmal or persistant AF.[13] However, to date, there are no studies which have investigated the association of pre-procedural cardiac ^{123}I-mIBG uptake with AF relapses after CA. Moreover, there is less evidence supporting AF ablation in persistent and long-standing persistent AF patterns vs paroxysmal AF[1,2] and there is a special need to identify patients who will benefit from ablation.

Thus, the goal of the present study was to estimate the utility of pre-procedural cardiac ^{123}I-mIBG scintigraphy to identify patients at risk for AF recurrence after CA.

METHODS AND MATERIALS

Patients

From October 2012 to October 2019 196 patients with persistent or long-standing persistent AF referred for CA at the Department of Surgical Treatment of Complicated Cardiac Arrhythmias and Pacing, Cardiology Research Institute Tomsk NRMC were considered for inclusion in the study. Among them 12 patients refused to participate, 102 patients met the exclusion criteria. The prospective research included remained 82 (the average age of 58.5±9.7 years) patients with indications for CA of AF.[15] In all patients antiarrhythmic drugs therapy was ineffective to maintain and/ or restore sinus rhythm.

The following inclusion criteria were defined.

Persistent or long-standing persistent AF defined according to appropriate ESC Guidelines for the Management of Atrial Fibrillation,[15] indications for CA of AF,[15] signed informed consent.

Persistent AF was implied as AF that is continuously sustained beyond 7 days, including episodes terminated by cardioversion (drugs or electrical cardioversion) after ≥7 days.[2]

Long-standing persistent AF was implied as continuous AF of >12 months' duration when decided to adopt a rhythm control strategy.[2]

Exclusion criteria were the following: previous CA of AF, age < 18 or > 75 years old, New York Heart Association (NYHA) heart failure functional class III-IV, prior cardiac surgery (all types), hemodynamically significant valvular heart diseases, left ventricular ejection fraction < 50%, severe comorbidity (systemic diseases, pathology of the blood coagulation system, thyrotoxicosis, etc.), renal dysfunction, previous myocardial infarction, percutaneous coronary intervention ≤6 months before ablation, current indications for revascularization, other arrhythmias, myocarditis, presence of left atrium (LA) thrombus, degenerative cerebral disease, history of stroke, dementia, hazardous consuming of alcohol (Alcohol Use Disorders Identification Test score ≥8 for male and ≥7 for female), a refusal to participate in the study.

Pulmonary vein isolation (PVI) was a method of choice of AF ablation for all patients. The antiarrhythmic therapy used at the time of inclusion in the study did not change throughout first 3 month of the follow-up period.

Besides conventional diagnostic procedures all patients underwent myocardium scintigraphy with ^{123}I-mIBG and stress/rest myocardium perfusion scintigraphy with ^{99m}Tc-MIBI at 3-5 days before CA.

Clinical follow-up with 12-lead electrocardiogram (ECG) and twenty-four-hour Holter monitoring was performed for 12 months period after the CA (control visits at 3, 6 and 12 months).

The flow chart of the study is shown on Figure 1.

All procedures performed in the study were in accordance with the ethical standards of the institutional and with the 1964 Helsinki declaration and its later

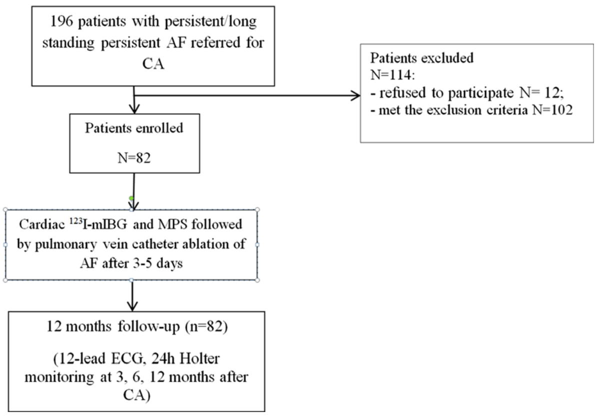


Figure 1. Flow chart of the study. *CA*, catheter ablation; *AF*, atrial fibrillation; *MPS*, myocardial perfusion scintigraphy.

amendments. Informed consent was obtained from all individual participants included in the study.

^{123}I-MIBG IMAGES ACQUISITION AND ANALYSIS

All patients underwent thyroid block by taking a 5% Lugol's solution for 3 days (5 drops of Lugol's solution 3 times a day) before administration of 111-370 MBq ^{123}I-mIBG. Images were acquired in supine position, with a dual-head gamma camera Forte (Philips Healthcare, Amsterdam, the Netherlands) equipped with low-energy general-purpose collimators at fifteen (i.e., early) and 240 (i.e., late) minutes after tracer injection. Planar anterior thoracic images were acquired for 10 minutes with a zoom factor of 1 and stored in a 128 × 128 matrix. SPECT images were acquired over 180° in 64 steps of 30 second per frame in non-gated mode in a 64×64 matrix. For both planar and SPECT, the energy window was symmetrically centered to ±10% of the 159-KeV 123I photopeak. Acquired scintigramms were processed by software application package JetStream Workspace Release 3.0 (Philips Medical Systems, the Netherlands) and reconstructed using AutoSPECT software.

Heart-to-mediastinum (H/M) ratio was calculated from planar imaging using regions of interest placed over the entire heart and upper mediastinum.[16] The myocardial washout rate with background correction (WR) was expressed as a percentage and was calculated using previously proposed formula.[16]

SPECT images were reconstructed into standard long and short-axis, perpendicular to the heart axis. Regional distribution of ^{123}I-mIBG was evaluated with QPS program (Cedars Sinai Medical Center, USA) and a 17 segmental polar map. All 17 segments were visually analyzed using 5-point scale (from 0 to 4) with the calculation of summed ^{123}I-mIBG score early (SMS_e) and summed ^{123}I-mIBG score late (SMS_{late}).[9] Severity of local (in segment) abnormalities in LV sympathetic activity was assessed by scores as follows: 0 = normal uptake, 1 = slight reduction of uptake, 2 = moderate reduction of uptake, 3 = severe reduction of uptake, 4 = absence of radioactive uptake.[16,17]

Myocardial Perfusion Scintigraphy Acquisition and Analysis

Myocardial perfusion scintigraphy (MPS) was performed 48 hours after ^{123}I-mIBG examination using 900 MBq of ^{99m}Tc-Sestamibi (^{99m}Tc-MIBI) according to two-day stress/rest protocol.[18] For stress-testing adenosine infusion at a rate of 140 μg·kg^{-1}·min^{-1} for 4 minutes was used.[18]

Myocardial perfusion scans were acquired using parallel-hole, low-energy, high-resolution collimators. A total of 64 projections (step-and-shoot mode; 25 seconds per projection) were obtained over a 180° circular orbit. Data were stored in a 64x64 matrix. 20% energy window at 140 keV was used. The images were acquired 60 minutes after injection for both the stress and rest studies. All patients were imaged in the supine position with arms placed over their heads.

The raw scintigraphic data were reconstructed with filtered back projection using a Butterworth filter (cut-off frequency of .36 cycles per pixel; order 5). No attenuation correction was used. Processing of the acquired data was performed by the software package Jetstream Workspace Release 3.0 (Philips Medical Systems, Netherlands).

Stress/rest images were reconstructed yielding the standard long- and short-axis projections perpendicular to the heart axis using the AutoSPECT software program (Cedars-Sinai). The analysis of the acquired information was done using QPS/QGS software (Los Angeles, CA, USA). The analysis of the acquired information was done using the specialized program AutoQuant (Cedars-Sinai). The short-axis slices were displayed on normalized polar map format and adjusted for peak myocardial activity (100%). The semiquantitative interpretation of perfusion images was based on analysis of short-axis and vertical long-axis tomograms divided into 17 segments in each patient.[18]

Perfusion in each of 17 segments was visually classified as 0 = normal, 1 = mild reduction, 2 = moderate reduction, 3 = severe reduction or 4 = absent perfusion, and the segmental scores were summed for the stress (SSS) and rest (SRS) images. The difference between SSS and SRS was calculated as the summed difference score (SDS). MPS studies were considered abnormal in the presence of SSS% ≥ 2.[18]

Follow-Up and End-Point

All patients were followed-up prospectively for 12 months after the CA in the outpatient clinic. Holter ECG monitoring was performed at 3, 6 and 12 months. If patient had symptoms suggestive of AF, additional ECGs and Holter ECG recordings were obtained. The criteria of AF recurrence were AF episodes of more than 30 second duration. A blanking period of 3 months was applied and AF recurrence within the first month was considered transient. The primary endpoint of the study was AF recurrence between 3 and 12 months after ablation. Secondary endpoint was major adverse cardiovascular event (MACE).

Statistical Analyses

Continuous data are expressed as mean ± standard deviation (SD), median (interquartile range) or as percentages of patients. Categorical data are presented as absolute values and percentages. The distribution of continuous variables was checked by using the Shapiro-Wilk W-test. Statistical comparisons between two subgroups were performed by the Mann–Whitney U-test. Categorical variables were compared using the Fisher's exact test. A Cox regression analysis was also used to determine the significant predictors of AF recurrences. The receiver-operating-characteristic (ROC) curve analysis was performed to evaluate the sensitivity and specificity of scintigraphic indexes to predict recurrence of AF. A $P < .05$ indicated a statistically significant difference. All statistical analyses were performed using a commercially available software package (SPSS, version 20.0, SPSS Inc., Chicago IL, USA). To evaluate the independent predictors of AF recurrence, forward-stepwise logistic regression analysis was used with an entry criterion of $P < .05$ and a removal criterion of $P < .1$.

The event-free rate was estimated by the Kaplan-Meier method, and the differences were assessed by the log-rank test. We consider significant p values <.05 (Statistica 10.0, StatSoft, USA).

RESULTS

Patient's Characteristics

A total of 82 patients (63 men, mean age 55.71±8.12 years) were enrolled. The baseline characteristics of patients are shown in Table 1.

Table 1. Baseline characteristic, ^{123}I-mIBG and myocardial perfusion scintigraphy results of the study population (N = 82)

Characteristic	Value
Sex, male (%)	63 (76.8%)
Age (M ± SD)	55.71 ± 8.12
Hypertension (%)	51 (62.2%)
Smoker, current, or past (%)	13 (15.85%)
Obesity (%)	41 (50%)
Diabetes mellitus	9 (10.9%)
BMI	31.4 (28.9; 34.7)
Dyslipidemia (%)	40 (48.8%)
CAD (%)	31 (37.8%)
Persistent AF	50 (60.98%)
Long standing persistent AF	32 (39.02%)
AF duration history (years)	4.32 ± 2.86
BNP, pg/mL	73 ± 49
Echocardiography	
LVEF (%)	61.9 ± 3.12
LV EDD (mm)	49.51 ± 4.56
LV EDV (mL)	103.9 ± 21.7
LAD (mm)	42.23 ± 4.56
Therapy	
Beta-blocker (%)	40%
Amiodarone (%)	60%
Statin (%)	40%
Diuretic (%)	25%
ACE-I (%)	53%
Calcium antagonists (%)	27%
DOAC	100%
Scintigraphy	
H/m early	1.7 (1.59; 1.8)
H/m late	1.67 (1.52; 1.8)
WR	23.15 (13.99; 36.46)
SMS_e	4 (2.75; 7)
SMS_{late}	7 (5; 8)
SSS	2 (0.75; 2)
SRS	0.5 (0; 1)
SDS	1 (0; 2)

Data are shown as means ± SD, ratios (%) of patients, median (Me), and lower-upper quartile
BMI, body mass index; *CAD*, coronary artery disease; *NYHA*, New York Heart Association; *BNP*, B-type natriuretic peptide; *LVEF*, left ventricle ejection fraction; *LV EDD*, left ventricle end diastolic diameter; *LV EDV*, left ventricle end diastolic volume; *LAD* left atrium anteroposterior dimension; *ACE-I*, angiotensin-converting enzyme ingibitors; *DOAC*, direct oral anticoagulants; *H/m*, heart-to-mediastinum ratio; *WR*, washout rate; *SMSe*, summed ^{123}I-mIBG score early; SMS_{late}, summed ^{123}I-mIBG score late; *SSS*, summed stress score; *SRS*, summed rest score; *SDS*, summed difference score

Fifty (60.98%) patients had persistent form of AF, and 32 (39.02%) patients long standing persistent AF. Fifty-one (62.2%) patients were diagnosed with hypertension, 31 (37.8%) had coronary artery disease (CAD) (diagnosed in accordance with 2013 ESC Guidelines on the management of stable coronary artery disease[19]) with low risk of adverse outcome, 9 (10.9%) with diabetes mellitus. Heart failure New York Heart Association (NYHA) functional class was I in 65%, II—in 35% of patients, the mean left ventricular ejection fraction (LVEF) was 61.9±3.12. Left atrium diameter calculated from echocardiographic data was enlarged in all patients and averaged 42.23±4.56 mm. Among all of enrolled patients 50% were obese and median body mass index (BMI) was 31.4 (28.9; 34.7). Medication consisted of beta-blockers (40% of patients), amiodarone (60% of patients), angiotensin-converting enzyme inhibitors (53% of patients), diuretics (25% of patients), and calcium antagonists (27%), direct oral anticoagulants (100% of patients).

All acquired scintigraphic images (both ^{123}I-mIBG and ^{99m}Tc-MIBI) were of satisfactory quality. Median for early H/M ratio was 1.7 (1.59; 1.8) with minimum 1.44, for late H/M—1.67 (1.52; 1.8) with minimum 1.3, for WR—23.15 (13.99; 36.46). In most cases regional sympathetic innervation was slightly to moderately impaired (medians for SMS_e and SMS_{late} were 4 (2.75; 7) and 7 (5; 8) respectively), while myocardium perfusion was normal or slightly reduced (medians for SSS and SRS were 2(.75;2) and .5 (0;1)respectively).

Follow-Up Results

The follow-up for 12 month (interquartile range 5.2-12.2) was complete in all 82 patients. According to the ECG Holter monitoring AF recurrence was registered in 34 (41.46%) patients. During the follow-up period neither atrial tachycardia, nor MACE and other potential complications were registered in the study population.

Relationship Between ^{123}I-mIBG, Myocardial Perfusion Results and AF Recurrence

After the end of the follow-up, we divided study population into two subgroups, which included those with (Group 1) and without (Group 2) AF recurrence. Then we have compared there scintigraphic parameters and some clinical characteristics, which are considered as risk factors for AF recurrence after CA (age, duration of AF, LAD, BMI)[2] (Table 2).

According to our results there were no significant differences between Group 1 and Group 2 for patient's age, duration of AF history, LAD, and for all parameters, associated with regional myocardial perfusion and innervation (for SMS_e, SMS_{late}, SRS, SSS,). In the same time parameters of global sympathetic activity (H/Me,

Table 2. Clinical and scintigraphic parameters of patient's groups with or without AF recurrence

Parameter	Group 1 (with AF recurrence) N = 34	Group 2 without AF recurrence N = 48	*P* value
Age (M ± SD)	56.38 ± 7.91	55.23 ± 8.32	.501
Duration of AF history, years	4.23 ± 3.3	4.4 ± 2.41	.740
LAD mm	45.4 ± 6.14	43.2 ± 4.2	.296
BMI	**34.7 (31.6; 36.6)**	**29.25 (26.35; 31.5)**	**.004**
H/m early	**1,65 (1.53;1.76)**	**1.73 (1.62;1.82)**	**.011**
H/m late	**1.53 (1.39;1.67)**	**1.77 (1.62;1.85)**	**<.001**
WR	**34.58 (24.53;41.23)**	**18,83 (9.63;25.16)**	**<.001**
SMS_e	4.5 (3;7.5)	4(2;6.75)	.969
SMS_{late}	8 (5.75;9)	6 (5;8)	.646
SSS	2(0;2)	2(1;2)	.856
SRS	1(0;1.25)	0(0;1)	.501
SDS	1(0;1)	1(0;2)	.104

Significantly different parameters are shown in bold
Data are shown as means ± SD, ratios (%) of patients, median (Me), and lower-upper quartile
BMI, body mass index; *LAD*, left atrium anteroposterior dimension; *H/m*, heart-to-mediastinum ratio; *WR*, washout rate; SMS_e, summed ^{123}I-mIBG score early; SMS_{late}, summed 123I-mIBG score late; *SSS*, summed stress score; *SRS*, summed rest score; *SDS*, summed difference score

H/M_{late}, WR) were significantly different between groups. Moreover, in Group 1 body mass index was significantly higher comparing with Group 2. No correlations between BMI and H/Me, H/M_{late} ($r = .122$, $P = .528$ and $r = -.293$, $P = .139$, respectively) and moderate correlation was between BMI and WR ($r = .448$; $P = .019$) were found.

Univariable logistic analyses demonstrated that BMI, LAD, H/M_{late}, WR and late ^{123}I- mIBG SPECT defect score, were significantly associated with AF recurrence after CA (Table 3). Subsequently, multivariable analysis demonstrated that only LAD, H/M_{late} and WR were independent predictors for AF recurrence.

ROC-curve analysis data (Table 4) showed that H/M_{late} <1.6 (cut-off point) indicates high probability of AF recurrence during 12 months after pulmonary vein ablation (sensitivity 73.53%, specificity 81.3%, AUC .792, $P < .001$). Slightly worse results were obtained for

Table 3. Univariable and multivariable analysis of baseline clinical and scintigraphic parameters

	Univariable analysis		Multivariable analysis	
Parameter	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**
Age	1.038 (.981-1.099)	.199		
Duration of AF history	.994 (.849-1.165)	.945		
AF type (persistent vs longstanding persistent)	1.621 (.661-3.972)	.291		
BMI	1.178(1.045-1.327)	.008*	NS	
LAD	1.131 (1.029-1.242)	.011*	1.139 (1.006-1.291)	.040#
H/Me (per .1 unit increase)	.857 (.687-1.071)	.174		
H/M_{late} (per .1 unit increase)	.546 (.403-.74)	<.001*	.679 (.486-.949)	.023#
WR	1.086 (1.041-1.133)	<.001*	1.058 (1,0038 - 1,1154)	0,036#
SMSe	1.101 (.976-1.242)	.119		
SMS_{late}	1.358 (1.096-1.681)	.005*	NS	
SSS	.862 (.568-1.306)	.483		
SRS	1.366 (.776-2.405)	.279		

*Significant association with AF recurrence at level of $P > 0.05$ in univariate analysis. #Significant association with AF recurrence in multivariate analysis
AF, atrial fibrillation; *BMI*, body mass index; *LAD*, left atrium anteroposterior dimension; *H/M*, heart-to-mediastinum ratio; *WR*, washout rate; *SMS_e*, summed ^{123}I-mIBG score early; *SMS_{late}*, summed 123I-mIBG score late; *SSS*, summed stress score; *SRS*, summed rest score; *SDS*, summed difference score; *NS*, not significant

Table 4. Comparison of receiver-operating curves for the efficacy of LAD and ^{123}I-mIBG cardiac scintigraphy to predict AF recurrence after CA

Parameter	AUC	Cut-off point	Sensitivity %	Specificity %	*P* value
H/M_{late}	.792	<1.60	73.53	81.3	<.001
WR	.712	>25.11	70.6	70.8	<.001
LAD	.637	45 mm	50.0	75.0	.034

AF, atrial fibrillation; *CA*, catheter ablation; *LAD*, left atrium anteroposterior dimension; *H/M*, heart-to-mediastinum ratio; *WR*, washout rate; *AUC*, area under the curve

Table 5. Pairwise comparison of receiver-operating curves for the efficacy of LAD and ^{123}I-mIBG cardiac scintigraphy to predict AF recurrence after CA

	Difference between areas	Standard Error	*P* value
H/M_{late} ~ WR	.025	.058	.672
LAD ~ H/M_{late}	.155	.083	.061
H/M_{late} ~ WR	.08	.051	.115

AF, atrial fibrillation; *CA*, catheter ablation; *LAD*, left atrium anteroposterior dimension; *H/M*, heart-to-mediastinum ratio; *WR*, washout rate

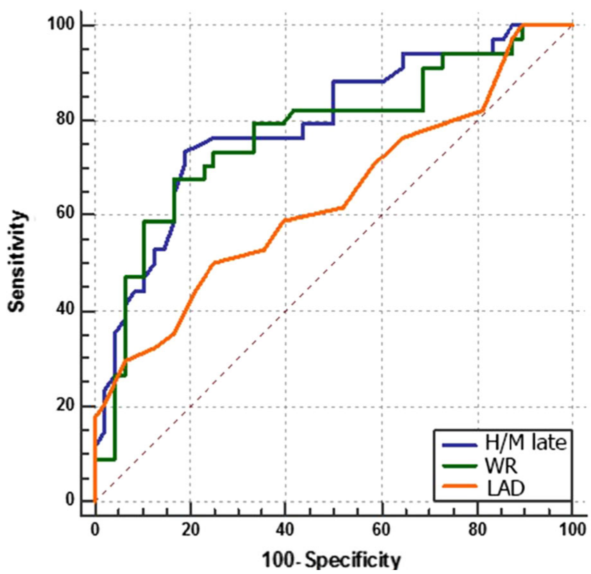


Figure 2. Receiver operating curves for H/M late, WR and LAD in predicting late AF recurrence after CA. *AF*, atrial fibrillation; *CA*, catheter ablation; H/M_{late}, ^{123}I-mIBG late heart-to-mediastinum ratio; ^{123}*I-mIBG WR*, washout rate; *LAD*, left atrium dimension.

WR (cut-off point 25.11, sensitivity 70.6%, specificity 70.8.3%, AUC 0.712, $P < .001$) and the worst—for LAD (cut-off point 45 mm, sensitivity 50.0%, specificity 75.0%, AUC 0.637, $P < .034$). In the same time, no significant differences between AUCs for each parameter were found (Table 5, Figure 2).

Kaplan-Meier analysis showed that the $H/M_{late} < 1.6$, WR > 25.11 and LAD > 45 mm significantly increase the risk of AF recurrence after CA ($P < .001$, $P < .001$, $P < .025$ respectively) (Figure 3.).

Clinical example and scintigraphic images of a patient who had late AF recurrence after CA are presented in Figure 4. An example and images of a patient who did not have late AF recurrence are presented in Figure 5.

DISCUSSION

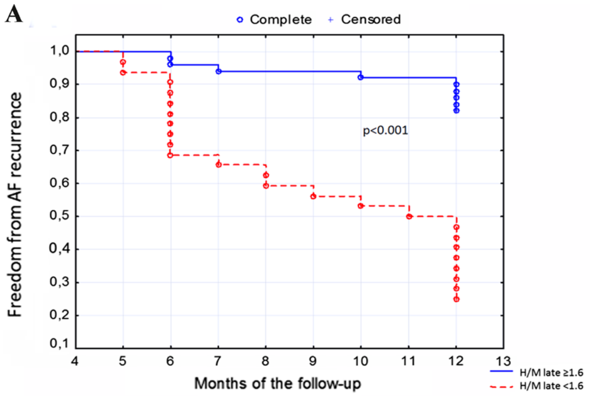
The major finding of the present study is that pre-procedural parameters of global cardiac sympathetic activity determined by ^{123}I-mIBG scintigraphy, particularly H/M_{late} <1.6 and WR>25.11, of patients with persistent/long-standing persistent AF can identify those at risk for AF relapses after pulmonary vein ablation.

Currently there is evidence that the intrinsic cardiac autononomic nervous system (CANS) plays an important role in the initiation and maintenance of AF.[11,20,21] These facts were the background for studying of the mIBG scintigraphy value for predicting late AF relapses after CA. The rationale, mechanisms and goals of using mIBG scintigraphy in patients with AF were discussed in detail in the editorial by Teresińska (2019).[11]

Initially, Akutsu et al. (2011) demonstrated that cardiac sympathetic nervous system abnormality, particularly delayed H/M ratio <2.7, was associated with the occurrence of both heart failure (HF) and permanent AF in idiopathic paroxysmal AF patients.[12] The authors pointed out that high rate of H/M ratio compared to previous studies were obtained due to the use of medium-energy collimators.

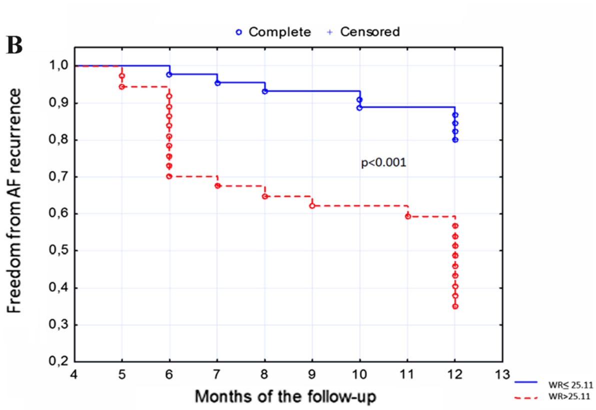
Subsequently Wenning C. et al (2013) performed a prospective series of 16 patients with paroxysmal AF who underwent serial ^{123}I-mIBG/CT imaging before and 4 weeks after PVI and were followed up for AF relapses.[22] In this study, the baseline delayed H/M was also higher comparing with previous and with current study (2.9 ± .5 vs 1.67 (1.52; 1.8)). However, similar to Akutsu Y. et al, a medium-energy collimator was used here for images registration[12,22] and this could affect the appearance of higher H/M values. Also, unlike the current study, global sympathetic activity parameters obtained by Wenning C. et al had no predictive value for AF recurrence, but the presence of regional denervation, defined by SPECT, was indicative for the risk of AF relapses. In our work, the regional defect of mIBG accumulation was significant in univariate analysis and has not showed predictive value in multivariate analysis.

A



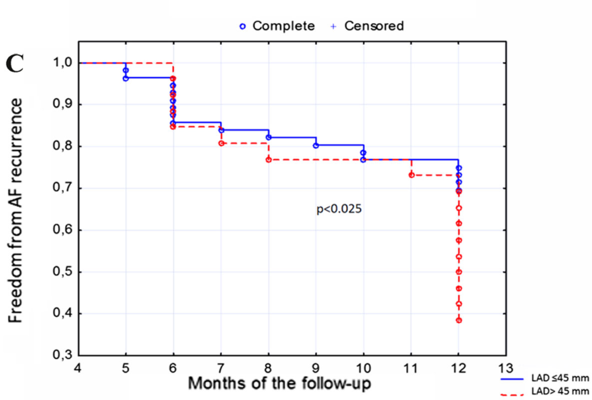
No. of patient at risk													
	Months of the follow-up												
	0	1	2	3	4	5	6	7	8	9	10	11	12
	Blanking period												
^{123}I-mIBG H/M_{late} ≥1.6					50	50	48	47	47	47	46	46	41
^{123}I-mIBG H/M_{late} <1.6					32	30	22	21	19	18	17	16	8

B



No. of patient at risk													
	Months of the follow-up												
	0	1	2	3	4	5	6	7	8	9	10	11	12
	Blanking period												
^{123}I-mIBG WR ≤ 25.11					45	45	44	44	43	43	41	41	37
^{123}I-mIBG WR > 25.11					37	35	26	25	24	23	23	22	13

C



No. of patient at risk													
	Months of the follow-up												
	0	1	2	3	4	5	6	7	8	9	10	11	12
	Blanking period												
LAD ≤ 45 mm					56	54	48	47	46	45	43	43	39
LAD > 45 mm					26	26	22	21	20	20	20	19	10

◀**Figure 3.** Kaplan-Meier AF recurrence-free rate curves. A. AF recurrence-free curves in patients with $H/M_{late}<1.6$. and with $H/M_{late}\geq1.6$. B. AF recurrence-free curves in patients with WR≤25.11 and with WR>25.11. C. AF recurrence-free curves in patients with LAD≤45 mm and with LAD>45 mm. *AF*, atrial fibrillation; *H/M_{late}*, ^{123}I-mIBG late heart-to-mediastinum ratio; *^{123}I-mIBG WR* washout rate; *LAD*, left atrium dimension.

Thus, the effect of CA on regional myocardium innervation remains a subject for further research.

In a recent study published by Kawasaki M. et all (2019), sixty-four paroxysmal AF patients without HF were enrolled and the relationship between the combination of cardiac sympathetic nerve activity, estimated by mIBG, and epicardial adipose tissue, estimated by computer tomography, and AF recurrence following 3 months after CA were investigated.[14] In this study pre-ablation H/M ratio and WR had also no predictive significance for late AF recurrence during 11 ± 4 months follow-up period.[14] Among mIBG parameters only delta WR (≥6.9%) calculated as difference between 1 month pre-ablation and 3 months after ablation parameter was an independent predictor. Thus, so far, no convincing data have been obtained on the possibility of using mIBG indicators to predict AF recurrence in paroxysmal type of this arrhythmia.

At the same time, Arimoto T et al (2011) have demonstrated high predictive value of ^{123}I-mIBG scintigraphy in mixed population of paroxysmal and persistent AF patients.[13] Among others this work is the closest to the current study in terms of enrolled patient's samples and obtained results. In particular, in 88 patients with persistent or paroxysmal AF, it was shown that WR> 25.1 is an independent predictor of late AF recurrence. Noteworthy that WR threshold value completely coincided with obtained in our study, but with somewhat lower sensitivity (64% vs 70.6%) and higher specificity (74% vs 70.8%).

Analysis of several above studies together with the results of our study shows the different prognostic values of ^{123}I-mIBG scintigraphy for CA late outcomes in paroxysmal and persistent subpopulations of AF patients. The likely reason for this discrepancy is the possible association of persistent AF with the presence of latent HF.[13,23-26]

In current study besides scintigraphic parameters, LAD threshold > 45 mm was an independent predictor of AF recurrence. Left atrium dimension is a generally accepted risk factor for AF recurrence, but its significance in our study and others discussed above was inferior to ^{123}I-mIBG.[12-14] This may be due to the fact that the value of LAD varies depending on comorbidity.[27] For example, in the study of Berruezo A. (2007) presence of hypertension further increased the mean predicted proportion of patients with AF recurrence at LAD≥45 mm.[27,28]

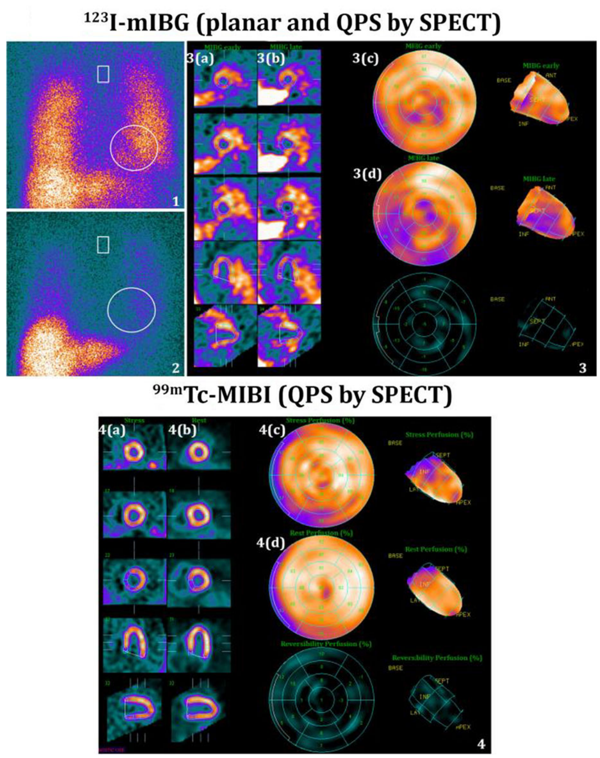


Figure 4. Scintigraphic images of patient with persistent AF, with registered episodes of late AF recurrence after CA. Images acquired at 3 (for ^{123}I-mIBG) and 5 (for ^{99m}Tc-MIBI) days before CA. Patient had hypertension, heart failure NYHA I, LVEF 71%, LAD 38 mm. 1—early planar ^{123}I-mIBG (H/M$_e$ = 1,67); 2—ate planar ^{123}I-mIBG (H/M$_{late}$ = 1,44); 3—^{123}I-mIBG QPS by SPECT: 3(a) early SPECT slices, 3(b) late SPECT slices, 3(c) early polar map (SMSe = 3), 3(d) late polar map (SMS$_{late}$ = 5); 4—^{99m}Tc QPS by SPECT: 4(a) stress SPECT slices, 4(b) rest SPECT slices, 4(c) stress polar map (SRS = 3), 4(d) rest polar map (SDS = 1). This subject had low late ^{123}I-mIBG cardiac uptake on planar images (H/M$_{late}$ = 1.44) and very high WR of ^{123}I-mIBG (49.5%). Patient had nearly normal myocardial perfusion (SSS = 3, SRS = 1). The patient was at high risk according to the value of H/M$_{late}$ and WR. Episodes of AF recurrence were registered on 6 month of the follow-up. *AF*, atrial fibrillation; *CA*, catheter ablation; *NYHA*, New York Heart Association; *LVEF* left ventricle ejection fraction; *LAD*, left atrium dimension; *SMS$_e$*, summed ^{123}I-mIBG score early; *SMS$_{late}$*, summed ^{123}I-mIBG score late; *SSS*, summed stress score; *SRS*, summed rest score.

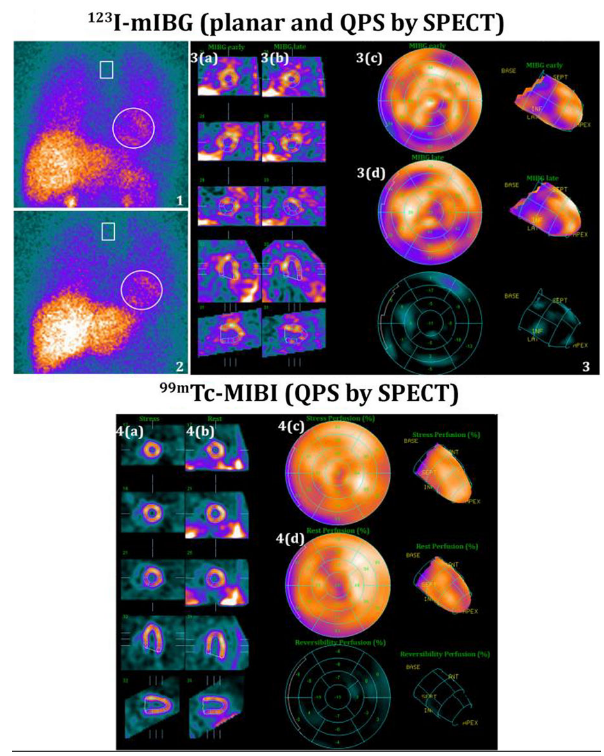


Figure 5. Scintigraphic images of patient with persistent atrial fibrillation, who had no late AF recurrence after CA. Images acquired at 3 (for ^{123}I-mIBG) a 5 (for ^{99m}Tc-MIBI) days before CA. Patient had hypertension, heart failure NYHA I, LVEF 66%, LAD 40 mm. 1—Early planar ^{123}I-mIBG (H/M$_e$ = 1.73); 2—late planar ^{123}I-mIBG (H/M$_{late}$ = 1.85); 3—^{123}I-mIBG QPS by SPECT: 3(a) early SPECT slices, 3(b) late SPECT slices, 3(c) early polar map (SMSe = 0), 3(d) late polar map (SMS$_{late}$ = 5); 4—^{99m}Tc QPS by SPECT: 4(a) stress SPECT slices, 4(b) rest SPECT slices, 4(c) stress polar map (SSS = 0), 4(d) rest polar map (SRS = 0). This subject had high late ^{123}I-mIBG cardiac uptake on planar images (H/M$_{late}$ =1.85) and low WR (8.8%). Myocardium perfusion was normal at stress and rest. The patient was at low risk according to the value of H/M$_{late}$ and WR. During 12 months follow-up after catheter ablation AF recurrence was not registered. *AF*, atrial fibrillation; *CA*, catheter ablation; *NYHA*, New York Heart Association; *LVEF* left ventricle ejection fraction; *LAD*, left atrium dimension; *SMS$_e$*, summed ^{123}I-mIBG score early; *SMS$_{late}$*, summed ^{123}I-mIBG score late; *SSS*, summed stress score; *SRS*, summed rest score.

Notably in the current study BMI also have showed association with post CA AF relapses and this fact is in agreement with numerous studies which previously proved the relationship of BMI with the development, maintenance, and post-ablative recurrences of AF.[2,29] Thus, BMI was significantly increased in patients with post CA AF recurrence comparing with those without, and it was significant in univariate analysis, but has not showed predictive value in multivariate analysis. Interestingly, BMI moderately correlated with WR. Such an association has not been previously studied. Possible explanation for this is influence of increasing of visceral fat amount on the volume and functional activity of epicardial adipose tissue (EAT),[29-33] which, in turn, surrounds the ganglionic nervous plexus of the heart.[11,34] Recent works have observed a causal link between obesity and accumulation and inflammation of EAT, potentially leading to AF[32] through myocardial fatty infiltration and adipokine-induced fibrosis.[29,30,32]

In recent study Kawasaki with coauthors has showed that EAT volumes correlate with H/M and WR in paroxysmal AF patients without HF.[14] The authors suggested that this association is due to the increase in catecholamine content in EAT which results in negative feedback on cardiac sympathetic nerves.[14] Anyway the role of EAT in the pathogenesis of AF is just starting to be explained,[30-33] and these potential mechanisms, particularly influence of EAT on cardiac sympathetic activity, are a promising research subjects and should be evaluated in the future.

It should be noted that other established risk factors for post-CA late AF recurrence, such as age and duration of AF history, were not predictive in either multifactorial or univariate regression analysis. The strongest predictors of late AF relapses by multivariate analysis were *m*IBG parameters.

In our opinion, the pathophysiological link between pre-CA results of ^{123}I-mIBG scintigraphy and late recurrences of AF can be explained as follows:

It is known that AF triggers originate within the pulmonary veins (PV) in majority (80-94%) of AF patients.[35,36] This is because, cardiomyocytes in the PVs, compared to LA myocytes, have a shorter refractoriness and increased triggered activity, which facilitates the initiation of AF.[37] It was also shown, that the main mechanism of late AF recurrence is late pulmonary vein reconnection post PVI.[38,39] However, Scherlag et al.[37,40] demonstrated that stimuli applied to PVs would not induce AF unless there was simultaneous activation of the ganglionated plexi (GP) adjacent to that PV. Since GP are the part and regulating centers of intrinsic CANS, it can be assumed that increased cardiac sympathetic activity is associated with late AF relapses through PVs triggers stimulation. In addition, the global cardiac sympathetic activity, evaluated by ^{123}I-mIBG, is regulated by multiple systemic effects of the body (signals from the brain, carotid arteries and large vessels, etc.)[37] and this influence cannot be interrupted by PVI, therefore continuing to affect the heart after ablation.

The present study has several limitations, the most notable of which are relatively small sample size and short follow-up period. Also, asymptomatic episodes of AF might have gone unrecognized. The images registration was performed in a non-sinus rhythm, which could affect the results, probably.

NEW KNOWLEDGE GAINED

Pre-procedural parameters of global cardiac sympathetic activity estimated by ^{123}I-mIBG scintigraphy are associated with late AF relapses after CA in persistent/longstanding persistent AF patients with normal LVEF and absence of significant CAD.

CONCLUSION

Thus, in the presented study, it was shown that parameters of global cardiac sympathetic activity estimated by ^{123}I-mIBG scintigraphy are associated with late AF relapses after CA in persistent/longstanding persistent AF patients with normal LVEF and absence of significant CAD. Moreover, ^{123}I mIBG parameters were strongest predictors of AF recurrence in multivariate analysis comparing with other established risk factors. One-time evaluation of the cardiac sympathetic activity using ^{123}I-mIBG scintigraphy before the AF ablation may be a promising tool to predict the patient's outcome. Probably, the ^{123}I-mIBG imaging prior to CA could be limited to early and 4 hours delayed planar imaging (with early and late H/M ratio and WR calculation) in relation to the studied population of patients.

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