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Original article

Selection for atrial fibrillation ablation: Importance of diastolic function grading

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ABSTRACT

Background: Pulmonary vein isolation (PVI) has become an accepted therapy for patients with atrial fibrillation (AF) and the indications have widened to include non-paroxysmal AF-patients. Maintenance of sinus rhythm after PVI can be adversely affected by clinical or echocardiographic parameters, which should be clearly identified.

Methods and results: After baseline clinical and echocardiographic evaluations, PVI was performed in patients with paroxysmal or non-paroxysmal AF. The follow-up strategy after PVI included: (1) clinical follow up, 12-lead electrocardiography (ECG) and 24-h ECG every 3 months, (2) trans-telephonic ECGs twice daily and when symptomatic (over 4 weeks) every 3 months, or (3) continuous monitoring via implanted devices. A recurrence was an atrial arrhythmia lasting >30 s. All 340 PVI procedures of 229 patients were analyzed. On average, 1.5 PVI procedures per patient (range, 1–6 PVI) were performed. The mean age was 58 ± 11 years (73% male) with 109 paroxysmal and 120 non-paroxysmal AF cases. Clinical follow-up with 12-lead ECGs, 24-h ECGs, trans-telephonic ECGs, and implanted devices was complete in 100%, 63%, 51%, and 16% of cases, respectively. The overall one-year recurrence rate of 59% (range, 24–82%) was dependent on grades of diastolic function (normal – dysfunction grade III) in a multivariable analysis model. Patients with normal diastolic function had the lowest recurrence rates of 24% and 49% after 1 and 3 years of follow-up, respectively ($p < 0.0001$).

Conclusion: Diastolic function could serve as a simple summary predictor for AF recurrence, and would facilitate clinical decision-making in AF treatment.

Introduction

The prevalence of atrial fibrillation (AF) in the population is increasing [1]. In addition to advanced age, hypertension is a well-known risk factor for AF and has been shown to be predictive for the development of AF in large population studies [2]. But AF is a more complex phenomenon associated with electrical, contractile, and structural changes [3]. The latter can lead to impairment of left ventricular filling, which is often reflected by diastolic dysfunction [4]. Diastolic dysfunction and AF share many common risk factors, including aging and hypertension [5,6]. Hypertension together with the subsequent development of left ventricular hypertrophy is a well-known risk factor for diastolic dysfunction [7]. Diastolic dysfunction and AF increase with age [8] and patients with diastolic dysfunction are more likely to have AF at the time of diagnosis [9]. One short-term study has suggested that the degree of diastolic dysfunction correlates with the development of AF [10].

Pulmonary vein isolation (PVI) has become an accepted therapy for patients with drug-refractory AF and the indications have broadened to include non-paroxysmal AF patients. However, recently published long-term studies showed high recurrence rates up to 70% after a single PVI [11–14]. At present, studies with long-term follow-up examining the relationship between the degree of diastolic dysfunction and AF-recurrences are lacking. For the time being it is unknown whether grading of diastolic function is relevant for therapeutic decision-making in AF patients. Therefore, the aim of our study was to assess whether echocardiographic parameters and clinical parameters such as age, hypertension, or history of AF may predict the outcomes of PVI in a multivariate risk model.

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Methods

Study design and study population

This was a retrospective abstraction of data collected at the Medical University of Vienna, Department of Cardiology, in consecutive patients scheduled to undergo PVI. The diagnosis of paroxysmal, persistent or longstanding persistent AF was established using current guidelines [15]. All patients gave their written permission before PVI after informed consent was obtained. The local ethics committee approved this study. Inclusion criteria: symptomatic or clinically intractable AF refractory or intolerant to at least one Class I or III antiarrhythmic drug. Exclusion criteria: contraindications to anticoagulation, presence of a left atrial (LA) thrombus, life expectancy <1 year, overt thyroid dysfunction. Patients with implanted devices such as pacemakers or defibrillators, and patients with non-normal left ventricular function or valvular heart disease were not excluded from PVI.

Echocardiography

Echocardiographic examinations following a standard protocol [16] were conducted using a Vivid 7 ultrasound machine (GE Healthcare, Milwaukee, WI, USA) or an ACUSON Sequia C256® (Acuson, Mountain View, CA, USA) usually in a 3-month window before PVI. Following the practice at our institution cardioversion was attempted in all patients prior to ablation. This time window, when the patient was in sinus rhythm, was used for echocardiographic examinations. Interventricular septal thickness was obtained at end-diastole from two-dimensional directed M-mode in the parasternal long axis, according to American Society of Echocardiography guidelines [17]. Two-dimensional apical 4- and 2-chamber views were used to calculate left ventricular ejection fraction (LVEF) using the biplane Simpson method. An LVEF <55% was considered abnormal. The severity of mitral regurgitation was evaluated semi-quantitatively from the area of the regurgitant jet by color Doppler. LA antero-posterior diameter in parasternal long-axis view and LA major axis in apical 4-chamber view were used to calculate LA diameters.

Grading of diastolic function

Doppler measures of diastolic function were performed according to recommendations [16] and averaged over three cardiac cycles in sinus rhythm only. Trans-mitral pulsed-wave Doppler velocities were recorded at rest and during Valsalva manoeuver from an apical 4-chamber view with a Doppler sample of 2 mm placed between the tips of the mitral leaflets. Diastolic function was graded blinded to baseline data or outcomes as normal, impaired relaxation (grade I), pseudo-normal pattern (grade II), or as restrictive pattern (grade III), using offline Doppler measurements of the mitral inflow, mitral inflow during Valsalva manoeuver, and tissue Doppler imaging of the mitral annulus. Valsalva manoeuver and E/E' ratio were used to distinguish between normal and pseudo-normal filling pattern. For a normal pattern, the reference ranges used were as follows: ratio of early (E) to late (A) diastolic filling velocities in the mitral inflow recording between 1 and 2; deceleration time (DT) of early filling between 150 ms and 220 ms; ratio of systolic to diastolic peak velocity mitral E/A ratio during Valsalva manoeuver >1 with a reduction compared to baseline of <0.5 of the absolute ratio. Grade I diastolic dysfunction was consistent with an E/A ratio <1, DT >220 ms, and no substantial change in E/A ratio during Valsalva. Grade II diastolic dysfunction resembled the normal configuration with respect to the mitral inflow but with ≥2 of the following features: mitral E/A ratio <1 during Valsalva manoeuver with a reduction of at least 0.5 of the absolute ratio, and E/E' ratio by tissue Doppler imaging of >15 [18]. Grade III diastolic dysfunction was characterized by an E/A ratio of >2, a DT <150, and E/E' >15.

Ablation procedure

All patients underwent either cardiac computer tomography and/or trans-esophageal echocardiography just prior to the procedure to exclude left atrial thrombi and to acquire left atrial anatomy. After obtaining vascular access from the left femoral vein, one decapolar steerable diagnostic catheter was positioned in the coronary sinus (6 Fr, Dynamic Deca, C.R. Bard, Inc., Lowell, MA, USA). Deep sedation was initiated with intravenous midazolam and propofol. Intravenous heparin was administered to maintain an activated clotting time at 300 s. PVI was performed using either conventionally hand-held system or with the use of a magnetic navigation system (MNS) depending on the interventionist's preference. PVI study techniques and system functions have been described in detail elsewhere [19,20] and were adapted based on the operator's decision. Briefly, in MNS patients one fluoroscopically guided transseptal puncture was performed to position one sheath within the left atrium (SRO, 8.5 Fr and BRK™ Transseptal Needle, St. Jude Medical, Inc., St. Paul, MN, USA). In the conventional group two fluoroscopically guided transseptal punctures were performed to position two sheaths within the left atrium. Left atrial mapping was performed with a NAVISTAR® Thermocool™, 3.5 mm, open-irrigated tip (Biosense Webster, Inc., Diamond Bar, CA, USA) or in MNS patients with a NAVISTAR® RMT DS, 8 mm tip or 3.5-mm-tip (the latter is open-irrigated, Biosense Webster). In the conventional group a multipole circular catheter (Lasso 15 or 20 mm, Biosense Webster) was used to guide ablation in order to achieve PVI confirmed by entrance block (coronary sinus pacing for the left-sided PVs). Maps were compared with preprocedure computed tomographic images (Cartomerge™, Biosense Webster). Wide area circumferential ablation was performed and lesions were placed in a point-by-point fashion (MNS group, 40 W, temperature limit 45 °C, 15 s) or linear fashion (conventional group, 40 W, temperature limit 45 °C). After wide area circumferential ablation in the MNS group, the roving catheter was used to guide additional ablation at the tubular portion of each PV to achieve segmental PVI in 10° increments of catheter movement [19]. PV entrance block was confirmed by abolition of PV potentials confirmed with 32-fold threshold amplification on the EP Recording System (coronary sinus pacing for the left-sided PVs). Overall, the procedural end point in both groups was achievement of PV entrance and exit block.

Post-ablation management and monitoring

The recommended initial follow-up was to see all the patients at 1, 3, 6, 9, and 12 months post-ablation at the outpatient department. If patients did not have an implanted device capable of loop monitoring, patients were asked to employ event recorders post PVI at weeks 1–4, 13–16, 25–28, and 37–40 and to send an ECG at least twice a day and additionally when they felt any discomfort. Twenty-four-hour ECG recordings post-PVI at week 5, 17, 29, 41, and 52 were recommended. After 52 weeks, additional ECG recordings at 3-month intervals were requested, if non-sustained AF/flutter/tachycardia had been previously detected or the patient was symptomatic.

Endpoints

Endpoints for both groups were single patient success. Success was defined as freedom from AF/flutter/tachycardia. After the

blanking period of 2 months, a single episode of AF/flutter/tachycardia lasting for 30 s or more was considered a recurrence.

Statistical analysis

Mean ± standard deviation is shown for metric variables and absolute frequencies (relative frequencies within a column) for categorical variables. Mean differences in metric variables between the categories were assessed by one-way ANOVA or, if the assumptions were not met, by the Kruskal–Wallis test. Equality of the distribution of categorical variables between categories was assessed by a Chi-square test of independence or, if any expected number of observations was below 5 and one variable had only two categories assessment would be made using Fisher's exact test. Time-to-event distributions were estimated by the Kaplan–Meier method separately for each instance of recurrence. Kaplan–Meier curves were compared using the log-rank test. To include the time-to-event information from all recurrent events of each patient, conditional gap time models according to Prentice, Williams, and Peterson were calculated [21]. Common effects were assumed, meaning that the effect of a given predictor variable on the hazard rate is identical in each instance of recurrence. This assumption is justified by the observation of highly similar time-to-event distribution estimates for each recurrence. Simple Cox models were calculated initially to regress the time-to-event on each covariate separately. A multiple model was then selected from the scope of variables that were significant on a level of 0.05 in the simple models. A stepwise selection procedure was used with the significance limit to enter the model set to 0.15 and the limit to stay in the model set to 0.05. Software: SAS® Version 9.3 (SAS Inst., Cary, NC, USA).

Results

This study included baseline data of 229 patients with follow-ups of 340 PVI procedures (73% males; median age, 59 years, range, 30–80 years) undergoing radiofrequency ablation for drug-refractory symptomatic paroxysmal (48%), persistent (37%), or longstanding persistent (15%) AF. Patients' clinical characteristics are summarized in Table 1. The most frequent comorbidity was hypertension (81%) followed by hyperlipidemia (23%). Only 2% of patients had more than a mild reduction in left ventricular ejection fraction and 8% had valvular heart disease other than mitral regurgitation. Nineteen percent of all patients had normal left atrial diameters, whereas moderate to severe left atrial enlargement was present in 43% of cases.

PVI and follow-up data

The number of repeated PVIs performed and the rates of procedural success for index and repeated PVIs are shown in Fig. 1. Not all patients with recurrences consented to a "re-do" procedure due to improvement in symptoms. PVI was performed manually and with MNS in 233 (68%) and 107 (32%) cases, respectively. The mean overall follow-up time was 1.7 ± 1.4 years per PVI procedure. Clinical follow-up with 12-lead ECGs, 24-h recordings, trans-telephonic ECGs, and implanted monitoring devices were available in 100%, 63%, 51%, and 16% of cases, respectively.

Table 1
Clinical and echocardiographic data and stratification according to diastolic (dys)function.

No. of patients	Total (n = 229)	Normal (n = 57)	Grade I (n = 87)	Grade II (n = 46)	Grade III (n = 39)	p for trend
Baseline characteristics						
Age (years)	58 ± 11	54 ± 12	59 ± 10	59 ± 12	62 ± 10	0.0013 aov
Male (n)	167 (73%)	35 (61%)	66 (76%)	37 (80%)	29 (74%)	0.1347 *f*
Body mass index	28 ± 5	26 ± 4	28 ± 4	29 ± 5	29 ± 5	0.0039 aov
History of atrial fibrillation						0.0019 chisq
Paroxysmal	109 (48%)	32 (56%)	44 (51%)	16 (35%)	17 (44%)	
Persistent	85 (37%)	23 (40%)	31 (36%)	14 (30%)	17 (44%)	
Long-standing persistent	35 (15%)	2 (4%)	12 (14%)	16 (35%)	5 (13%)	
Comorbidities						
Hypertension	186 (81%)	37 (65%)	75 (86%)	41 (89%)	33 (85%)	0.0036 *f*
Coronary artery disease	26 (11%)	1 (2%)	11 (13%)	4 (9%)	10 (26%)	0.0029 *f*
Diabetes	17 (7%)	2 (4%)	5 (6%)	2 (4%)	8 (21%)	0.0198 *f*
History of ischemic attack	16 (7%)	1 (2%)	7 (8%)	4 (9%)	4 (10%)	0.2636 *f*
COPD	11 (5%)	2 (4%)	6 (7%)	2 (4%)	1 (3%)	0.7795 *f*
Hyperlipidemia	53 (23%)	6 (11%)	25 (29%)	11 (24%)	11 (28%)	0.0656 *f*
Kidney dysfunction	5 (2%)	1 (2%)	1 (1%)	0 (0%)	3 (8%)	0.0967 *f*
Echocardiographic parameters						
Ejection fraction						0.003 *f*
Normal LVEF	203 (89%)	56 (98%)	78 (90%)	39 (85%)	30 (77%)	
Mild LVEF reduction	20 (9%)	1 (2%)	6 (7%)	6 (13%)	7 (18%)	
Moderate LVEF reduction	5 (2%)	0 (0%)	2 (2%)	1 (2%)	2 (5%)	
Severe LVEF reduction	1 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	
Valves						0.0071 *f*
Moderate to severe valve disease	17 (8%)	5 (10%)	3 (4%)	1 (2%)	8 (21%)	
No mitral regurgitation	99 (46%)	32 (64%)	39 (48%)	17 (39%)	11 (28%)	0.0056 chisq
Mild mitral regurgitation	71 (33%)	12 (24%)	26 (32%)	15 (34%)	18 (46%)	
Moderate mitral regurgitation	39 (18%)	6 (12%)	16 (20%)	11 (25%)	6 (15%)	
Severe mitral regurgitation	5 (2%)	0 (0%)	0 (0%)	1 (2%)	4 (10%)	
Left atrium	16 (7%)	1 (2%)	7 (8%)	4 (9%)	4 (10%)	0.2636 *f*
A.p. parasternal long-axis view	45.9 ± 6.3	42.7 ± 5.9	45.6 ± 5.2	46 ± 6.4	49.3 ± 7.3	0.0004 aov
Normal = 28–40 mm	25 (19%)	9 (39%)	6 (11%)	8 (29%)	2 (8%)	
Mild enlarged = 41–46 mm	50 (38%)	8 (35%)	27 (49%)	6 (21%)	9 (36%)	
Moderate enlarged = 47–52 mm	39 (30%)	5 (22%)	17 (31%)	10 (36%)	7 (28%)	
Severe enlarged > 52 mm	17 (13%)	1 (4%)	5 (9%)	4 (14%)	7 (28%)	0.0086 *f*
Interventricular septum (mm)	12.6 ± 1.8	11.3 ± 1.5	12.9 ± 1.8	12.9 ± 1.6	13.5 ± 1.7	<0.0001 aov

aov, one-way ANOVA; chisq, Chi-square test; *f*, Fisher's exact test; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction.

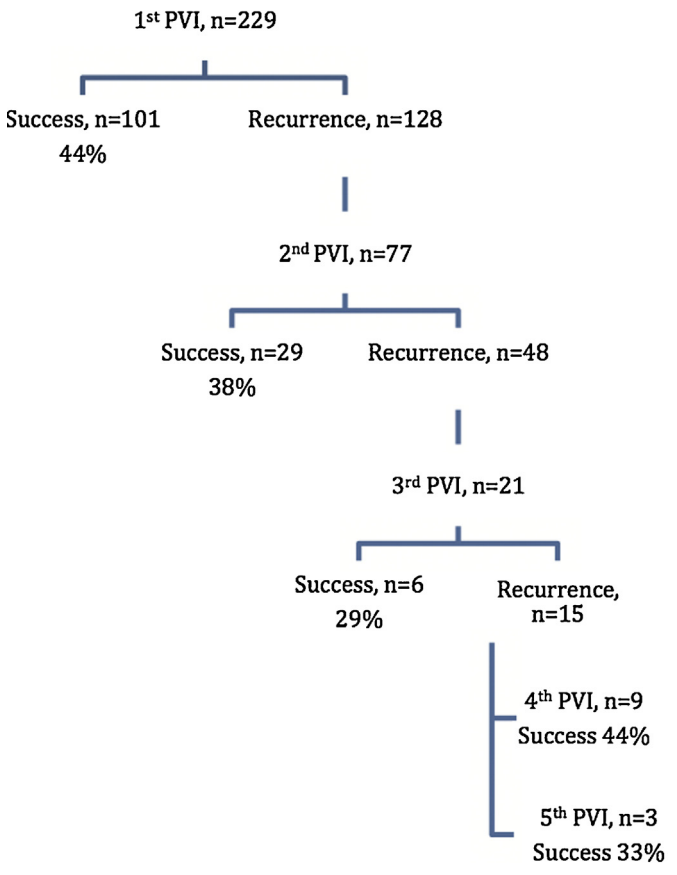

Fig. 1. Procedural flow-chart. Outcomes of 340 PVI procedures in 229 patients. Number of repeated PVIs performed and rates of procedural success for repeated PVIs. The one patient with six PVI procedures is not shown. The mean overall follow-up time with complete follow-up electrocardiograms was 1.7 ± 1.4 years per PVI procedure. PVI, pulmonary vein isolation.

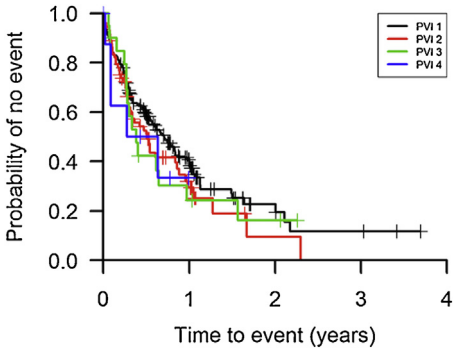

Fig. 2. Time-to-recurrence distribution. Kaplan–Meier estimate for the long-term freedom from recurrence after ablation excluding a 2-month post-procedural blanking window in case the remaining follow-up was event-free. Stratification according to index procedure (PVI 1) and re-do procedures (PVI 2–4). There was no significant difference regarding time-to-recurrence ($p = 0.8236$). PVI, pulmonary vein isolation.

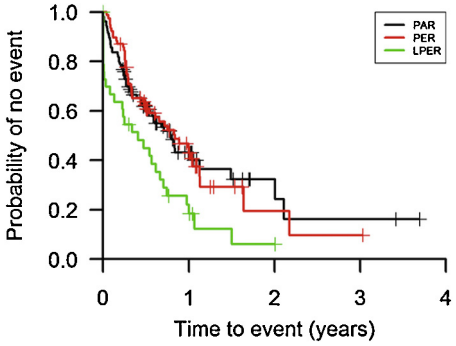

Fig. 3. Sucess rates regarding history of AF. Kaplan–Meier curve of the long-term freedom from recurrence after ablation excluding a 2-month post-procedural blanking window in case the remaining follow-up was event-free. Stratification according to history of atrial fibrillation [0 = paroxysmal (PAR), 1 = persistent (PER), 2 = long-standing persistent (LPER)]: patients with long-standing persistent atrial fibrillation had the highest recurrence rate ($p = 0.0043$).

Details about the use of antiarrhythmic drugs are detailed in Table 2. Fig. 2 demonstrates that the time to a recurrence was not different regarding index or re-do PVI procedures ($p = 0.8236$). PVI success according to AF history is shown in Fig. 3: there was a significantly worse outcome in patients with longstanding persistent AF ($p = 0.0043$).

Simple, univariable and selected, multivariable Cox model for PVI success

The potential baseline predictor variables considered in simple-univariable conditional gap time Cox models are outlined in

Table 2
Medication and PVI outcome data stratification according to diastolic (dys)function.

Nr. of patients	Total ($n = 229$)	Normal ($n = 57$)	Grade I ($n = 87$)	Grade II ($n = 46$)	Grade III ($n = 39$)	p for trend
Medication (index PVI)						
No AA Class I/III	112 (49%)	35 (61%)	45 (52%)	23 (50%)	9 (23%)	0.0026 *f*
AA Class I	25 (11%)	7 (12%)	10 (11%)	3 (7%)	5 (13%)	0.7543 *f*
AA Class II	139 (61%)	37 (65%)	53 (61%)	24 (52%)	25 (64%)	0.5689 *f*
AA Class III	80 (35%)	13 (23%)	29 (33%)	18 (39%)	20 (51%)	0.0331 *f*
AA Class IV	27 (12%)	3 (5%)	11 (13%)	8 (17%)	5 (13%)	0.2517 *f*
Diuretics	49 (21%)	9 (16%)	19 (22%)	7 (15%)	14 (36%)	0.072 *f*
Phenprocoumon	166 (72%)	29 (51%)	63 (72%)	38 (83%)	36 (92%)	<0.0001 *f*
Digitalis	5 (2%)	0 (0%)	1 (1%)	2 (4%)	2 (5%)	0.1656 *f*
Statins	57 (25%)	12 (21%)	23 (26%)	11 (24%)	11 (28%)	0.8463 *f*
ACE	54 (23%)	14 (25%)	19 (21%)	8 (17%)	13 (33%)	0.3599 chisq
ARB	47 (21%)	6 (11%)	20 (23%)	11 (24%)	10 (26%)	0.1897 *f*
PVI outcomes						
PVI procedures/per patient	340/1.5	65/1.1	122/1.4	78/1.7	79/2.0	0.0031 *f*
PVI recurrence rate (1 year)	128 (59%)	12 (24%)	46 (52%)	38 (77%)	32 (82%)	<0.0001 *f*

chisq, Chi-square test; *f*, Fisher's exact test; PVI, pulmonary vein isolation; AA, anti-arrhythmic; ACE, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Table 3a
Simple, univariate Cox model for all PVI procedures regarding recurrence.

Parameter	*p* value	Hazard ratio	95% CI lower	95% CI upper	Global *p*-value
Baseline characteristics					
Age (years)	0.5672	1.004	0.991	1.017	
Gender	0.1541	0.779	0.552	1.098	
Body mass index	0.0711	1.028	0.998	1.060	
Paroxysmal AF		1			0.022
Persistent AF	0.3056	1.180	0.860	1.620	
Long-standing persistent AF	0.0058	1.729	1.172	2.552	
Comorbidities					
Hypertension	0.0188	1.580	1.079	2.314	
Coronary artery disease	0.6541	1.112	0.698	1.773	
Diabetes	0.3208	1.322	0.762	2.292	
History of ischemic attack	0.4738	1.241	0.688	2.240	
COPD	0.7781	1.115	0.522	2.385	
Hyperlipidemia	0.7474	1.059	0.747	1.501	
Kidney dysfunction	0.1586	1.906	0.778	4.671	
Echocardiographic parameters					
LVEF	0.1257	1.270	0.935	1.725	
Moderate to severe valve disease	0.0112	1.788	1.141	2.800	
Mitral regurgitation	0.0427	1.214	1.006	1.466	
Normal diastolic function		1			<0.0001
Diastolic dysfunction I	0.0002	3.088	1.721	5.540	
Diastolic dysfunction II	<0001	5.407	2.958	9.884	
Diastolic dysfunction III	<0001	6.876	3.764	12.560	
Left atrial diameter	0.0062	1.038	1.011	1.067	
Interventricular septum	0.0137	1.102	1.020	1.191	
Non-baseline					
Success and no magnetic navigation system PVI		1			0.157
Magnetic navigation system PVI	0.0722	1.395	0.970	2.006	
Hand-held PVI	0.263	1.241	0.850	1.813	

Table 3b
Selected, multivariate Cox model for all PVI procedures regarding recurrence.

Parameter	Parameter estimates	Std. error	*p* value	Hazard ratio	95% CI lower	95% CI upper
Normal diastolic function	0			1		
Diastolic dysfunction I	0.984	0.300	0.0011	2.675	1.485	4.82
Diastolic dysfunction II	1.597	0.310	<0.0001	4.94	2.692	9.065
Diastolic dysfunction III	1.741	0.308	<0.0001	5.701	3.115	10.436
Moderate to severe valve disease	0.544	0.238	0.0219	1.723	1.082	2.745

PVI, pulmonary vein isolation; AF, atrial fibrillation; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction.

Table 3a. Of these variables, obesity (based on body mass index), non-paroxysmal AF, hypertension, moderate to severe valve disease, mitral regurgitation, diastolic (dys)function, left atrial diameter, and interventricular septum thickness were identified to be significant predictors of recurrences in the simple models, i.e. when no other potential predictors were accounted for (Table 3a). Overall, no significant impact on recurrence was found regarding the method used for PVI (manually vs. MNS, $p = 0.157$) (Table 3a).

In the resulting multivariable model, diastolic dysfunction and moderate to severe valve disease remained significant in predicting recurrences (Table 3b). When compared to normal diastolic function, diastolic dysfunction grade I resulted in a hazard ratio of 2.7 (CI: 1.5–4.8) and diastolic dysfunction grade II and grade III had ratios of 4.9 (CI: 2.7–9.1) and 5.7 (CI: 3.1–10.4), respectively (Table 3b).

The association between the occurrence of PV-reconnections and AF-recurrences was found to be low for the 2nd PVI. In total, 34 patients had one PV, 33 patients had two PVs, eight patients had three PVs, and one patient had all four PVs reconnected. For each PV (left superior PV, left inferior PV, right superior PV, right inferior PV or all PVs), 32 out of 76 patients had re-connections; however, they were not the same patients and no clear correlation between different PVs was observed. There was a borderline significant trend toward an increased risk for an additional (3rd) PVI with right inferior PV ($p = 0.034$). However, when accounting for multiple testing for all PVs, it is not possible to conclude that any of the PV-reconnections has a pronounced effect on the outcome.

Differences based on diastolic function grading

Fifty-seven patients (25%) presented with normal diastolic function, whereas grade I, grade II, and grade III diastolic dysfunction were present in 38%, 20%, and 17%, respectively (Table 1). Echocardiography was done in sinus rhythm in a 3-month interval before PVI. In 5.3%, 4.6%, 4.3%, and 5.1% of cases, respectively, echocardiography was done on the day of electrical cardioversion. In all other patients the median time between cardioversion and echocardiographic investigation in sinus rhythm was 11.7 days (range 3.2–18.4 days). Patients with a higher grade of diastolic dysfunction were older ($p = 0.0013$) and had a higher body mass index ($p = 0.0039$). Comorbidities such as hypertension, coronary artery disease, and diabetes were significant more frequently observed in patients with diastolic dysfunction. Impairment of systolic dysfunction was associated with diastolic dysfunction ($p = 0.003$). The same was true for moderate to severe valvular heart disease. Patients with normal diastolic function had significantly smaller left atrial diameters compared to patients with diastolic dysfunction ($p = 0.0004$) (Table 1). Differences regarding antiarrhythmic drug treatment after index PVI and PVI outcomes are outlined in Table 2: higher rates of PVI

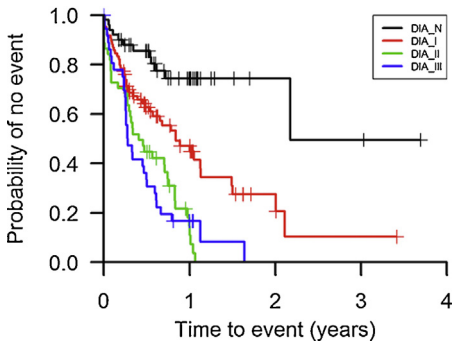

Fig. 4. Sucess rates regarding diastolic function. Kaplan–Meier curve of the long-term freedom from recurrence after ablation excluding a 2-months post-procedural blanking window in case the remaining follow-up was event-free. Stratification according diastolic (dys)function (DIA_N = normal, DIA_I = grade I, DIA_II = grade II, DIA_III = grade III). The patients with normal diastolic function had the best outcome with recurrence rates of 24% and 49% after 1 and 3 years of follow-up, respectively ($p < 0.0001$).

procedures per patient and lower procedural success rates correlated significantly with the presence and severity of diastolic dysfunction. Patients with normal diastolic function had the lowest recurrence rates of 24% after 1 and 2 years of follow-up, respectively ($p < 0.0001$) (Fig. 4).

Discussion

This study population represents a well-characterized sample of real-life patients undergoing PVI for symptomatic, drug refractory, and clinically intractable AF. The major finding of this study is that diastolic function could serve as a simple summary predictor for AF recurrence, and would facilitate clinical decision-making in patients with paroxysmal and non-paroxysmal AF scheduled for PVI.

Identification of baseline clinical and echocardiographic predictors of success in maintaining sinus rhythm after PVI is crucial in contemporary AF treatment [22]. Besides advanced age and hypertension [2] enlarged left atrial diameters are a well-known risk factor for AF [23]. Elderly or hypertensive patients have stiffened left ventricles (LVs) that give rise to elevated LA pressure and LA enlargement, the conditions predisposing to AF [24]. Ventricular diastolic dysfunction might underlie the effect of hypertension on LA dynamics, but this relationship is still speculative, multifactorial, and difficult to reverse [25]. The important role of diastolic function in promoting and perpetuating AF is well established [10]. Current guidelines state that LV systolic and diastolic performance help in decision-making regarding antiarrhythmic and antithrombotic drug therapies only [26]. There are no specific recommendations for the management of invasive catheter procedures in patients stratified according to their diastolic function. The presence and severity of diastolic dysfunction are independently predictive of first documented AF in the elderly [10]; however, there are only limited data [27–33] available demonstrating an association between the presence of diastolic dysfunction and PVI outcomes. To date, it is uncertain whether AF patients with different grades of diastolic dysfunction should be treated the same.

Diastolic dysfunction is reported to be an independent predictor in lone AF, new onset AF, and transition to chronic AF in patients with paroxysmal AF [10]. Li et al. [27] reported the association between diastolic function and AF recurrence after PVI, however, the follow-up period was short (3 months). A study with a longer follow-up period was published by Ejima et al. [28]: only 36% in a sample of 80 patients had diastolic dysfunction, but they had the worst outcome after PVI. Similar to our study LA diameter was not an independent predictor of AF recurrence after PVI. We are in line with others [29–32] who reported that diastolic dysfunction and/or LA stiffness index were independent predictors of recurrence after PVI. To our knowledge, the only available long-term study where a detailed grading of diastolic dysfunction was performed is the study of Cha et al. [33]. Most of their patients had grade II diastolic dysfunction, which is in contrast to our study where most of the patients presented with grade I diastolic dysfunction. We agree with the conclusion of Cha et al., who demonstrated that AF ablation in patients with diastolic dysfunction is not efficacious in the long-term.

This study population represents a selected group of patients compared to data from community-based surveys: our study patients were younger (58 ± 11 years vs. 74.2 ± 11 years) and had a different history of AF (37% persistent, 15% long-standing persistent vs. 7% persistent, 47% long-standing persistent) compared to the Fushimi AF registry [34]. This might explain the clearly demonstrated lower efficiency of ablation in patients with impaired diastolic function. This lower efficiency might become less evident when applying to the older Fushimi AF patients with a mean age of 74.2 years. Otherwise, in the study of Lee et al. [35] a clear relation between LA mechanical function and the degree of LA remodeling and LV diastolic function was found and the contribution of LV diastolic dysfunction to LA electro-anatomical remodeling was especially significant in older patients with large LA diameters.

A better stratification of AF patients who benefit most from PVI should be mandatory since two recent studies report on less favorable PVI results: the FAST-trial showed that the more invasive surgical ablation is superior to catheter ablation in achieving freedom from LA arrhythmias in patients with dilated left atrium and hypertension [36]. In comparing PVI with antiarrhythmic drug therapy as first-line treatment in patients with paroxysmal AF, no difference between the treatment groups was found by Cosedis Nielsen et al. [37]. As a consequence our data support the view that pre-procedural echocardiographic LA and ventricular diastolic parameters should be obtained in patients scheduled for PVI in order to predict outcome.

In AF ablation the reported success rate very much depends upon the monitoring technique applied. Piorkowski et al. [38] reported on success rates after PVI with the use of different monitoring strategies: 70% freedom from AF on a symptom-only-based follow-up, 50% on serial 7-day ECG, and only 45% on trans-telephonic monitoring. Sorgente et al. [13] reported about 2/3 of AF relapses occurring in the first year of follow-up after PVI. In the present study, a close meshed monitoring system with 12-lead ECGs and clinical follow-up, 24-h ECGs, trans-telephonic ECGs and continuous monitoring via implanted devices was completed in 100%, 63%, 51%, and 16% of cases, respectively. In the light of the above-mentioned differences in the success rate depending upon the (monitoring) technique used, our results compare well with those previously reported by others [13].

Limitations

The present single-center, retrospective study had limitations. First, it cannot be ruled out that AF treatment is limited by the ability to record all asymptomatic episodes of AF. Therefore, our findings may have overestimated the efficacy of ablation. Second, diastolic function should be graded in sinus rhythm. The retrospective study design is more a strength than limitation since it guaranteed that grading of diastolic function was not influenced by later PVI outcomes.

Conclusion

The success rate of non-pharmacological interventions to treat AF depends upon the follow-up strategy applied and upon the

presence or absence of structural changes of the heart. In unselected patients PVI may be considered a palliative strategy with high recurrence rates. In this study we could demonstrate that different grades of diastolic (dys)function directly correlate with PVI outcome. Diastolic dysfunction is either the most determining independent risk factor or it efficiently encompasses much of the information contained in well-appreciated risk factors such as hypertension, advanced age, and LA size. In any case, diastolic dysfunction may be considered a useful summary predictor for AF recurrence.

Author contributions

Pezawas, Schmidinger, and Binder were instrumental in study conception and design; also they drafted the article. Stojkovic helped Pezawas in data collection and Binder in Echocardiography works. All the authors have participated equally for data analysis and interpretation works. Ristl and Schneider took care of statistical works. Pezawas, Schmidinger, and Schukro contributed towards PVI. Finally all authors made critical revision of article and approved the final version.

Ethical statement

The study complies with the Declaration of Helsinki, the locally appointed ethics committee has approved the research protocol, and the informed consent of the subjects (or their parents) has been obtained.

Conflict of interest

None declared.

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