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Influence of advancing age on clinical presentation, treatment efficacy and safety, and long-term outcome of pre-excitation syndromes: a retrospective cohort study of 961 patients included over a 25-year period

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ABSTRACT

Objectives: There are very little data on pre-excitation syndrome (PS) in the elderly. We investigated the influence of advancing age on clinical presentation, treatment and long-term outcome of PS.

Setting: Single-centre retrospective study of patient files.

Participants: In all, 961 patients (72 patients ≥60 years (mean 68.5±6), 889 patients <60 years (mean 30.5±14)) referred for overt pre-excitation and indication for electrophysiological study (EPS) were followed for 5.3±5 years. Usual care included 24 h Holter monitoring, echocardiography and EPS. Patients underwent accessory pathway (AP) ablation if necessary.

Primary and secondary outcome measures: Occurrence of atrial fibrillation (AF) or procedure-induced adverse event.

Results: Electrophysiological data and recourse to AP ablation (43% vs 48.5%, p=0.375) did not significantly differ between the groups. Older patients more often had symptomatic forms (81% vs 63%, p=0.003), history of spontaneous AF (8% vs 3%, p=0.01) or adverse presentation (poorly tolerated arrhythmias: 18% vs 7%, p=0.0009). In multivariable analysis, patients ≥60 years had a significantly higher risk of history of AF (OR=4.2, 2.1 to 8.3, p=0.001) and poorly tolerated arrhythmias (OR=3.8, 1.8 to 8.1, p=0.001). Age ≥60 years was associated with an increased major AP ablation complication risk (10% vs 1.9%, p=0.006). During follow-up, occurrence of AF (13.9% vs 3.6%, p<0.001) and incidence of poorly tolerated tachycardia (4.2% vs 0.6%, p=0.001) were more frequent in patients ≥60 years, although frequency of ablation failure or recurrence was similar (20% vs 15.5%, p=0.52). In multivariable analysis, patients ≥60 years had a significantly higher risk of AF (OR=2.9, 1.2 to 6.8, p≤0.01).

Conclusions: In this retrospective monocentre study, patients ≥60 years referred for PS work up appeared at higher risk of AF and adverse presentation, both prior and after the work up. These results suggest that, in elderly patients, the decision for EPS and AP ablation should be discussed in light of their suspected higher risk of events and ablation complications. However, these findings should be further validated in future prospective multicentre studies.

Strengths and limitations of this study

- This large cohort of 900+ patients is sufficiently powered to study the clinical outcome of patients ≥60 years with pre-excitation syndromes (PS).
- We provide evidence for the higher risk of atrial fibrillation and adverse presentation at admission and during follow-up and a higher risk of procedure complications in patients ≥60 years with PS, which has never been reported before in such a large cohort.
- Given its retrospective design, the present study has a noteworthy risk of measurement bias, which would have been much lower in a prospective study.
- Our cohort was not a random sample of patients with PS but, rather, patients referred for a specialised work up including electrophysiological study. As a consequence, the study cannot establish the prevalence of PS in this population of elderly patients.

INTRODUCTION

Severe complications of pre-excitation syndromes (PS) such as ventricular fibrillation[1] have mainly been reported in young patients.[2] Age-related differences have also been previously documented for

pre-excitation patterns as well as changes in electrophysiological data over time. One of the key factors evolving with advancing age is the propensity for atrial fibrillation (AF), which is increased in older patients comparatively to younger patients.[2 3] This is of importance due to the potential poor tolerability of AF episodes in patients with PS.

However, data pertaining to the long-term follow-up of PS in elderly patients remain limited. More importantly, given the widespread use of accessory pathway (AP) ablation, the identification of untreated PS in older patients is now much less common.

In light of the above and given the absence of large-scale data, the present study aimed to assess the influence of age on clinical presentation, treatment and long-term outcome of PS in a large cohort of patients with PS.

METHODS

The population included 961 consecutive patients referred to our centre, from 1990 to December 2014, for overt pre-excitation and indication for electrophysiological study (EPS).

Patients underwent examination for various reasons: (1) 404 patients (42%) had a known history of paroxysmal reciprocal tachycardia; (2) 31 patients (3%) presented with a well-tolerated AF; (3) 342 patients (36.5%) in whom asymptomatic pre-excitation was discovered during the following—systematic assessment prior to anaesthesia, before obtaining a sporting licence, prior to employment in certain at-risk occupations, or during an ECG in the preventive medicine department or in presence of congenital heart disease; (4) 110 patients (11%) presented with unexplained syncope without documentation of any arrhythmic event, which was generally the initial cause leading to the discovery of ventricular pre-excitation and (5) 74 patients (8%) had a spontaneous malignant event associated with ventricular fibrillation (n=7), and a rapid and poorly tolerated AF conducted over the AP. Adverse presentation (poorly tolerated tachycardia) was defined as a documented life-threatening and haemodynamically non-tolerated arrhythmia, with collapses or syncope and requiring emergency treatment.

Prior to EPS and ablation, informed consent was obtained for clinical purposes from all patients and, in the case of children, from the children and their parents.

The protocol included systematic non-invasive as well as invasive studies.

The standard package of non-invasive studies included 24 h Holter monitoring, echocardiography, bicycle exercise testing and head-up tilt test in patients referred for syncope.

EPS was systematically performed either by the transoesophageal route in asymptomatic patients or patients with undocumented tachycardia, or by the conventional intracardiac method. Patients were not sedated. Details of the EPS protocol have been described previously.[4–6]

Briefly, incremental atrial pacing was performed until the highest rate conducted 1/1 through the AP and/or atrioventricular (AV) node. Programmed atrial stimulation was performed at a basic cycle length of 600 and 400 ms with the respective introduction of one and two extrastimuli. For the measurement of the AP effective refractory period (ERP), one atrial extrastimulus was delivered after 7 paced atrial stimuli at a cycle length of 400 ms starting from 390 ms, until reaching the AP refractory pathway or the atrial ERP, with 10 ms decrements. The disappearance of the pre-excitation pattern was indicated on reaching the AP ERP. When a fast AF conducted over AP was induced with this method, the protocol was halted; in the absence of induction of tachycardia conducted over AP at a rate higher than 250 bpm, isoproterenol (0.02–1 µg/min) was infused to increase the sinus rate to at least 130 bpm, after which the pacing protocol was repeated.

Arterial blood pressure was continuously monitored during the study, by an external sphygmomanometer (Baxter, Japan).

Pre-excitation was characterised by the following data:

AP location was determined with a 12-lead ECG recorded in maximal pre-excitation. The diagnosis of multiple APs was retained only if the APs had different locations (left lateral and septal or right lateral and septal, or left lateral and right lateral). In the left free wall location, the ablation potentially required the application of radiofrequency current at two putative sites, although it could represent the same large AP. In the posteroseptal location, left and right septal applications can be required to suppress pre-excitation.

Sustained AF or reciprocating tachycardia was defined as a tachycardia lasting longer than 1 min.

Conduction over the AP was assessed by the maximal rate conducted over AP either in tachycardia or during atrial pacing.

PS was considered as malignant and at risk of sudden death when the following association was observed: when the shortest QRS interval between pre-excited beats was <250 ms in the control state or <200 ms after isoproterenol infusion during induced sustained AF. EPS was considered as negative if no tachycardia was induced and a long refractory period of AP (≥250 ms in control state and ≥200 ms after isoproterenol) was noted.

When ablation was indicated, ablation was performed by the same senior operator, with different assisting clinical fellows.

AP ablation was achieved using a 7F deflectable catheter with a 4 mm electrode by searching the site where AV conduction was the shortest in bipolar and unipolar recordings. Left AP was generally approached by retrograde catheterism. The radiofrequency current was applied with a power output of 40–50 W and at a maximum temperature of 65°C. Exceptionally, an irrigated tip catheter was used to deliver a lower power

output for rare posteroseptal APs identified in the coronary sinus. The disappearance of retrograde conduction over AP was verified by systematic ventricular pacing. Catheters were removed 30 min after the disappearance of the anterograde and retrograde conduction in the AP.

Patients were followed for 5.3±5 years.

Asymptomatic patients in whom there were no electrophysiological criteria for malignancy were not treated and ablation was not indicated. Ablation of AP was proposed in both, symptomatic and asymptomatic patients on detection of a potentially malignant form of the disease. Antiarrhythmic therapy with β-blocker and/or flecainide was the preferred mode of treatment in small children, in patients with an anteroseptal AP and in patients who refused ablation.

Statistical analysis

Data are expressed as means±SD or proportions, as appropriate. Categorical variables were compared using the χ^2 test and continuous variables with the unpaired Student's t test.

Univariable logistic regression was used with the following dependent variables: (1) history of spontaneous AF, (2) history of poorly tolerated tachycardia, (3) AF occurrence during follow-up and (4) haemodynamically poorly tolerated tachycardia occurrence during follow-up. Additionally, in patients who underwent AP ablation, (5) major complications and (6) failure or recurrence were also considered as dependent variables. Variables associated with the considered outcome with a p value <0.10 in univariable analysis were entered in the multivariable models.

A p value <0.05 was considered statistically significant. All statistical analyses were performed using the SPSS package for Windows (V.20, SPSS Inc, Chicago, Illinois, USA).

RESULTS

Baseline characteristics

Of the 961 studied patients, 72 (7.5%) were aged between 60 and 85 years (mean age 68.5±6) (table 1). Only 26 patients were aged >69 years (mean age 75±17, 2.7%), while the remaining 889 patients were <60 years (mean age 30.5±14). Eleven patients evaluated before 50 years were evaluated again after the age of 59 years.

As expected, underlying heart disease was more frequent in patients ≥60 than in patients <60 years (p<0.0001). Posteroseptal (53% vs 46%) and left location (44% vs 35%) of the AP were similarly frequent in patients ≥60 and <60 years. Only one nodoventricular AP was found in a patient aged over 60 years.

Association between age and the risk of AF and adverse events prior to ablation

The occurrence of AF and adverse event prior to admission was more frequent in patients ≥60 years (tables 1 and 2). Patients ≥60 years were more frequently symptomatic and more likely to have a history of AF than patients <60 years. In the multivariable models, patients ≥60 years had a significantly higher risk of history of AF (OR=3.52, 1.92 to 6.45, p<0.001) and history of poorly tolerated tachycardia (OR=2.98, 1.55 to 5.74, p=0.001) prior to the work up (table 2). Importantly, despite the fact that heart disease was more frequent in patients ≥60 years, prior heart disease was not significantly associated with the risk of history of poorly tolerated tachycardia (data not shown, p=0.21).

Electrophysiological data

Electrophysiological data did not differ significantly between patients ≥60 and those <60 years (table 3). Of note, neither induction of AV re-entrant tachycardia (AVRT) nor AF during EPS along with electrophysiological signs of pre-excitation at risk of sudden death differed between patients ≥60 and those <60 years.

Association between age and the risk of ablation failure and complications

The use of AP ablation was similar in patients ≥60 and those <60 years (43% vs 48.5%, p=0.375), as was failure or recurrence requiring a second procedure (table 4). In contrast, a greater risk of complications was observed in patients ≥60 years. Ablation failure and major complications were relatively frequent in the overall population, but tended to decrease during the study period. Failure and/or reappearance of PS was 20.2% before 2005 and 13.9% after 2005 (p=0.08).

AP ablation-related complications were either major (defined as those resulting in permanent injury or death, requiring an interventional procedure, or prolonging hospitalisation, n=11) or minor (n=7). The list of major complications is reported in table 4. These major complications were fivefold more frequent in patients ≥60 than in patients <60 years (10.0% vs 1.9%, p=0.005). Moderate and minor complications were transient and completely amenable to treatment, namely, major sinus bradycardia or second-degree or third-degree AV block (n=5) and bleeding (n=2). Minor complications were 5.5-fold more frequent in patients ≥60 than in patients <60 years (6.6% vs 1.2%, p=0.03).

Association between age and the risk of adverse outcome during follow-up

Follow-up duration varied from 3 months to 17 years (mean 5.3±5 years). The duration was similar for patients ≥60 and those <60 years (5.31±5 vs 5.2±5 years) (table 4).

The risk of AF and poorly tolerated tachycardia during follow-up was as follows:

Occurrence of AF before and after ablation, and poorly tolerated tachycardia before ablation during follow-up, was more frequent in patients ≥60 years (tables 1 and 4).

Table 1 Baseline clinical data in patients ≥60 and those <60 years of age referred for electrophysiological evaluation in the setting of PS

	Patients ≥60 (N=72)	Patients <60 (N=889)	p Value
Age (years)	68.5±6	30.5±14	NA
Age range	5–59 years	60–89 years	
Male gender	37 (51%)	557 (63%)	0.06
Heart disease (total)	14 (19%)	60 (6.7%)	<0.001
Congenital heart disease	0	23 (2.6%)	0.17
Symptoms attributed to the PS	58 (81%)	561 (63%)	0.003
Syncope	12 (17%)	98 (11%)	0.15
History of AVRT	27 (37.5%)	377 (42%)	0.4
History of AF	6 (8%)	25 (3%)	0.01
History of poorly tolerated tachycardia	13 (18%)	63 (7%)	<0.001
AP location			
Left lateral	32 (44%)	315 (35.4%)	0.13
Posteroseptal	38 (53%)	408 (46%)	0.26
Anteroseptal	1 (1.4%)	89 (10%)	0.02
Right lateral	0	49 (5.5%)	0.04
Mahaim	1 (1.4%)	20 (2%)	0.6
Multiple APs	0	7 (0.8%)	0.4
Unapparent PS	9 (12.5%)	88 (9.9%)	0.5

AF, atrial fibrillation; AP, accessory pathway; AVRT, atrioventricular re-entrant tachycardia; NA, not applicable; PS, pre-excitation syndrome.

In both univariable and multivariable regression, patients ≥60 years had a significantly higher risk of occurrence of AF during follow-up (univariable OR=4.32, 2.03 to 9.19, p<0.001; multivariable OR=2.56, 1.12 to 6.04, p=0.03) (table 2). However, AF was not associated with poor tolerance after ablation.

In univariable logistic regression, patients >60 years had a significantly increased risk of occurrence of poorly tolerated tachycardia (OR=7.69, 1.8 to 32.9, p=0.006) during follow-up. However, these events occurred before ablation. Given the low number of adverse events (N=8), multivariable models could not be performed for this outcome (table 2).

DISCUSSION

The major findings of this study show that, in the current population of patients referred for EPS in the setting of PS, the presentation of PS in patients ≥60 years was overall more severe at or prior to admission than in patients <60 years. Specifically, these patients had a higher risk of haemodynamically poorly tolerated tachycardia. In addition, the risk of poorly tolerated tachycardia in patients untreated by ablation was also greater during follow-up. The risk of AF was also increased in patients >60 years. These data thus suggest electrophysiological evaluation of PS without limitation of age. However, a careful evaluation of benefit-to-risk ratio should be performed before AP ablation, given the higher risk of procedural complications observed in elderly patients.

Previous reports have shown that inherent electrophysiological properties of APs are strong predictors of outcomes, as demonstrated in a large study population.[7 8] Indeed, Pappone *et al*[7] reported that a short AP ERP and AVRT triggering sustained pre-excited AF were independent predictors of malignant arrhythmias in

Table 2 Association between age and events prior to work up and during follow-up, using univariable and multivariable logistic regression

	Univariable model			Multivariable model*		
	OR for age ≥60 years	CI	p Value	OR for age ≥60 years	CI	p Value
History of AF	3.12	1.73 to 5.63	<0.001	3.52	1.92 to 6.45	<0.001
History of poorly tolerated tachycardia	2.99	1.55 to 5.75	0.001	2.98	1.55 to 5.74	0.001
Failure or recurrence in patients with ablation	1.39	0.55 to 3.54	0.49	1.35	0.51 to 3.57	0.55
Occurrence of AF during follow-up	4.32	2.03 to 9.19	<0.001	2.56	1.12 to 6.04	0.03
Occurrence of poorly tolerated tachycardia during follow-up in untreated patients	7.69	1.8 to 32.9	0.006	NA	NA	NA

*All multivariable models adjusted at minimum for gender and heart disease. In addition, the model assessing the occurrence of AF during follow-up was further adjusted for history of AF.
AF, atrial fibrillation; NA, multivariable models could not be performed for this outcome due to the limited number of events.

Table 3 Electrophysiological data in patients ≥60 and those <60 years of age

	Patients ≥60 (N=72)	Patients <60 (N=889)	p Value
AVRT during EPS	40 (55.5%)	461 (52%)	0.50
AF during EPS	20 (28%)	209 (23.5%)	0.41
Maximal heart rate over AP in control state (bpm)	182±57	190±65	0.47
Maximal heart rate over AP after isoproterenol (bpm)	230±59	234±69	0.56
AP ERP in control state (ms)	333±100	315±99	0.62
AP ERP after isoproterenol (ms)	282±108	263±90	0.47
Malignant form	9 (8.5%)	71 (8%)	0.18

Malignant form: shortest RR interval between pre-excited beats <250 ms in the control state or <200 ms after isoproterenol infusion during induced sustained AF.
AF, atrial fibrillation; AP, accessory pathway; AVRT, atrioventricular re-entrant tachycardia; EPS, electrophysiological study; ERP, effective refractory period.

initially symptomatic patients with Wolff-Parkinson-White syndrome. These data were recently confirmed in a large cohort study.[8] In the present study, no differences were found in terms of the AP refractory period between patients <60 and those ≥60 years, contrary to previous studies where an increased AP refractory period was reported in old participants,[3 4 9] except for a prior study performed by our group.[10] Differences between young and old patients were also shown by Fan *et al*[3] and Michelucci *et al*.[4] In the latter study, the authors noted a significant direct correlation between age and AP refractory period. Irrespectively of these electrophysiological data, the results of the present study demonstrate that age is an important predictor of poorly tolerated arrhythmias.

Initial clinical presentation of PS in the elderly population has been reported by some authors. Rosenfeld *et al*[11] reported similar data in a small population of 13 patients aged over 50 years: a wide complex tachycardia was the main reason for referral of older patients among whom AF/flutter also tended to be more frequent. Likewise, we found a significantly greater risk for preadmission AF in the current study representing the largest reported sample of older patients to date.

Certain studies[7 8] have also reported a risk of PS-related death or adverse event in patients older than 40 years. Mabo *et al*[12] reported six patients aged from 45 to 74 years who had presented with ventricular fibrillation. The main risk factors identified in their study were age (62±8 years vs 37±15 years in survivors) and associated organic heart disease. Increased risk of AF with age has also been reported in previous studies.[6 11–13]

Procedural complications are occasionally known to be age related. In the present study, minor (6.7% vs 1.2%, p=0.03) and major perprocedural complications (10% vs 1.9%, p=0.005) were more frequent in patients ≥60 than in patients <60 years. However, no differences were observed in terms of procedural failure or recurrence. This safety profile of catheter ablation in elderly and very elderly patients should therefore be considered in the therapeutic decision-making process, as suggested in previous studies.[14 15] Importantly, even if increased, the risk of major complications here remained ≤10% in patients aged over 60 years. Similarly, in a previous study, atrial flutter ablation was also found to be safe and efficient in elderly patients with a <10% procedural risk.[16] These findings are significant since, to the best of our knowledge, this is the largest cohort study investigating the specific impact of age in this setting.

The risk of AF and poorly tolerated arrhythmia during follow-up after AP work up remains high. The present analysis showed a significantly increased risk of AF

Table 4 Procedural data and events during follow-up in patients ≥60 and those <60 years of age

	Patients ≥60 (N=72)	Patients <60 (N=889)	p Value
Accessory pathway ablation	30/72 (41.7%)	431/889 (48.5%)	0.27
Failure or recurrence after ablation	6/30 (20%)	67/431 (15.5%)	0.52
Failure alone	5/30 (17%)	39/431 (11.4%)	0.17
Minor complications of ablation	2/30 (6.7%)	5/431 (1.2%)	0.03
Major complications of ablation	3/30 (10%)	8/431 (1.9%)	0.005
Tamponade	1	3	
Arteriovenous fistula requiring surgery	2	1	
Ventricular fibrillation		1	
Complete AV block		3	
Occurrence of AF	10/72 (13.9%)	32/889 (3.6%)	<0.001
Duration of follow-up	5.21±5	5.2±5	0.156

AF, atrial fibrillation; AV, atrioventricular.

(adjusted OR=2.56, 1.12 to 6.04, p=0.03) in patients ≥60 years compared with that in the younger patients. Indeed, age is the leading cause of AF in numerous settings, including after atrial flutter ablation[17] and AVRT.[18 19] This higher risk of AF with increasing age in patients with PS observed in the present study enhances and strengthens the results of previous reports.[6 9 11 13 20] Accordingly, a large cohort study recently highlighted that AF rates were higher in Wolff-Parkinson-White syndrome patients than in a control population and that this long-term higher risk was not reduced in patients undergoing ablation.[20]

Recurring symptoms are frequent after radiofrequency ablation in several clinical settings.[21] In the present study, the risk of poorly tolerated arrhythmia was also increased in patients ≥60 years (univariable OR=7.69, 1.8 to 32.9, p=0.006). The association of heart disease, increased ventricular stiffness and lower tolerance to high frequency are thought to explain the risk of occurrence of haemodynamically poorly tolerated arrhythmias in elderly patients. Here, a high frequency exceeding the maximal tolerated rate was likely the underlying cause of poor tolerance in the elderly. In the present cohort, although patients ≥60 years presented a higher risk of poorly tolerated arrhythmia prior to ablation (multivariable OR=2.98, 1.55 to 5.74, p=0.001), history of heart disease was not an independent risk factor. Likewise, the risk of poorly tolerated tachycardia during follow-up occurred in patients not treated by ablation and was 7.69-fold higher in patients >60 years.

Clinical implications

Patients with PS are usually young patients. However, in this particular setting and as demonstrated in other fields of medicine,[22] older patients may be under-referred to specialised care. Classical electrophysiological evaluation is mainly recommended in asymptomatic participants before the age of 40 years.[23 24] Notwithstanding the latter, the overall results of the present study would suggest that there is no definitive barrier in referring older patients with PS, and that, consequently, such referral to specialised care may ultimately be favoured.

Limitations of the study

Given its retrospective design, the present study has inherent biases and limitations. All of which have been essentially based on a retrospective analysis of data obtained many decades ago. Specifically, retrospective studies, by nature, have an increased risk of measurement bias, which would have been much lower in a prospective study. In addition, a prospective cohort would have enabled recording of detailed data regarding heart function (diastolic function, left ventricular hypertrophy, etc), greatly contributing to the understanding of the clinical tolerance to arrhythmia recurrences.

In addition, our cohort was not a random sample of patients with PS but, rather, patients referred for a specialised work up including EPS. As a consequence, the study cannot establish the prevalence of PS in this population of elderly patients. Moreover, the present observational cohort was not tailored to assess the treatment effect of ablation. Nonetheless, no major differences were observed in terms of outcome in patients treated with ablation according to age, which may have some clinical value in the absence of clinical trial data.

The high risk of ablation-related complications in patients over 60 years may be amplified by the fact that all left-sided ablations were approached with a retrograde approach, which likely leads to a higher risk of complications, particularly access complications. Higher ablation failure and procedure-related complication rates (about 10%) in older patients could indeed be related to a learning curve of our centre.

As we used data acquired solely during routine clinical care, we had no precise recording of the timing of the events during follow-up. As a consequence, the information was acquired in a way that did not permit performing survival analysis. In addition, we had no precise recording of the procedural times, which could be an important clinical factor associated with complications. Further studies should determine if the significantly higher procedural risk we identified in patients ≥60 years is the consequence of longer procedural times required in these patients.

Finally, the choice of the age of 60 years can be debated and was driven by the fact that PS is rare in elderly patients.

CONCLUSION

In the present retrospective study, patients ≥60 years referred for PS work up appeared at higher risk of events both prior and after the work up. Therefore, we suggest that EPS could be recommended without limitation of age.

However, the major findings of this study are the significantly higher procedural risk associated with AP ablation and the higher post-procedural risk of AF recurrence in the elderly compared with those in the younger group. These results should be further validated in other large cohorts and in prospective studies. Yet, our results may argue for a tempered recommendation for AP ablation in the elderly whereby the risks of ablation should be discussed with the patient prior to intervention. In these patients, a risk-to-benefit ratio evaluation appears of critical importance.

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