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A Stepwise Approach to the Management of Postinfarct Ventricular Tachycardia Using Catheter Ablation as the First-Line Treatment

A Single-Center Experience

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Background—The occurrence of ventricular tachycardia (VT) after myocardial infarction is associated with poorer prognosis. In such patients, implantable cardioverter-defibrillators are recommended. Catheter ablation of VT is currently recommended only as an adjunctive therapy. Whether a successful VT ablation alone might be a viable strategy in some of these patients, however, remains unknown. The aim of the present study was to evaluate this strategy.

Methods and Results—Between January 2002 and December 2011, 189 patients with cardiomyopathy underwent 259 VT ablations in our center. Forty-five patients (mean age, 65.2±9.6 years; 91% men) with a history of myocardial infarction and mean left ventricular ejection fraction of 39.7±9.7% matched the study criteria and were included in this analysis. Acute success was obtained in 40 of 45 patients (88.9%). During a follow-up, on the basis of our stepwise algorithm (using acute success, repeat electrophysiological study, and recurrence of VT), 19 of 45 patients (42.2%) underwent implantable cardioverter-defibrillators implantation. During a median follow-up of 4.5 (interquartile range, 2.1–7.0) years, all-cause mortality occurred in 14 of 45 patients (31.1%). Using multivariate Cox regression analysis, age (hazard ratio, 1.13; 95% confidence interval, 1.03–1.22; *P*=0.007) was the only independent predictor of mortality, whereas implantable cardioverter-defibrillators implantation was not (hazard ratio, 0.54; 95% confidence interval, 0.18–1.64; *P*=0.28)

Conclusions—Our results suggest that a stepwise approach to the management of VT with ablation as a first-line treatment in postinfarct patients presenting with VT might be a reasonable option. Further studies are required to confirm these results. (***Circ Arrhythm Electrophysiol*. 2013;6:351-356.**)

Key Words: catheter ablation ■ implantable cardioverter-defibrillator ■ ischemic cardiomyopathy ■ programmed electric stimulation ■ ventricular tachycardia

In patients with ischemic cardiomyopathy (ICM), ventricular tachycardia (VT) is associated with poor long-term outcomes.[1] Three secondary prevention studies have shown the unequivocal benefit of implantable cardioverter-defibrillators (ICD) in patients with previous myocardial infarction and impaired left ventricular ejection fraction.[2–4] These studies, however, excluded patients with stable VT or with left ventricular ejection fraction >40%. Analysis from the antiarrhythmics versus implantable defibrillators registry,[5] however, suggests that clinically well-tolerated VT carries a poor prognosis as well. ICDs are therefore recommended in patients with previous myocardial infarction and sustained VT.[6] Although ICDs improve overall survival, they do not eliminate the substrate responsible for sustained arrhythmia. ICD without ablation carries a higher risk of shocks,[7,8] and shocks are associated with decreased quality of life and increased mortality.[9] VT ablation, on the contrary, reduces or even abolishes VT episodes in some patients. Currently, guidelines suggest that VT ablation to be used as an adjunct to ICD.[10] It is not known whether some patients presenting with VT can be treated by ablation alone.

Clinical Perspective on p 356

In our center, we have been routinely performing VT ablation as a first-line treatment in patients with ICM presenting with VT. Patients with a successful ablation, defined as the noninducibility of all VTs at the end of the index procedure followed by a negative electrophysiological study (EPS) within 3 months, do not have an ICD implanted. The aim of this study was, therefore, to evaluate this stepwise approach to VT management by comparing the long-term outcomes of those who received an ICD with those who did not.

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Methods

Study Population

Between January 2002 and April 2011, a total of 189 patients with structural heart disease underwent 259 VT ablations in our center: 145 with ischemic cardiomyopathy (ICM), 17 with dilated cardiomyopathy, and 18 with arrythmogenic right ventricular dysplasia. In this study, we included patients with the following criteria: (1) previous history of myocardial infarct, (2) documented monomorphic VT, (3) no prior ICD, (4) repeat or planned EPS after first procedure, and (5) follow-up of at least 1 year after ablation or until censoring at the time of death. Patients were excluded if initial presentation was cardiac arrest, or patients with severe comorbidities where a clinical decision was made not to implant an ICD. Of the 145 patients with ICM, 74 did not have an ICD before VT ablation, and 45 fulfilled the criteria for the study. All patients provided informed consent, and all procedures were conformed to the CHU-Nancy guidelines.

EPS, Mapping, and Ablation

EPS, mapping, and catheter ablation were performed as previously described.[11] Briefly, a bipolar catheter was inserted via the femoral vein and positioned at the right ventricular apex and used primarily for VT induction with the application of up to 3 extrastimuli during spontaneous rhythm and then during paced rhythm (600-ms and then 400-ms basic cycle length). This programmed electric stimulation protocol was delivered through an external stimulator (Biotronik UHS 20, Biotronik Inc) with a 2-ms pulse width at twice the diastolic threshold. Failure to induce a sustained VT promoted the same protocol in the right ventricular outflow tract.

An 8F or 7F, 8 mm-tip or 3.5 mm-irrigated tip catheter (NAVISTAR or THERMOCOOL, Biosense-Webster, Johnson & Johnson) was used for mapping and ablation of VT circuits. Access to the left ventricle was achieved retrogradely across the aortic valve or through transatrial septal puncture.

The electric reference was chosen as a morphologically stable and regular ventricular electrogram that was obtained from either an endocardial or surface lead, with the choice determined by a QRS complex with a sharp apex and a strong positive (or negative) deflection during VT. The width of the window of interest varied from 1 VT map to another, inasmuch as it was correlated with the VT cycle length with the following formula: window of interest width = VT cycle length−20 ms. The middle of the window of interest was selected to coincide with the electric reference. The local activation time for each endocardial position under the mapping catheter was calculated as the interval between the electric reference and the peak deflection of the mapping bipolar electrogram. In case of double potentials, the earliest peak deflection of the doublet was used. Long-duration fractionated electrograms were marked to the highest peaklet.

The left ventricle was plotted during the induced clinical VT by dragging the catheter over the endocardium. In case of a VT with a right ventricular septal exit, the right ventricle was mapped as well to check whether the VT isthmus, or a part of it, was located in the right ventricle. Infarct regions were sought first, and more data points (target filling threshold set to 10) were acquired in and around these areas. Refining the area under investigation relied on the usual clinical indicators, such as sinus rhythm analysis, echocardiography, and VT morphology, on the 12-lead ECG. More data points were acquired in the zones defined as scarified, with low-amplitude potentials, with diastolic electrograms, or with double potentials. These areas were probed because they are important for the identification of the reentrant circuit. The mapping procedure was terminated when a density of points was achieved that was sufficient enough to allow an understanding of the VT circuit. The resulting reentrant circuit was considered to be the spatially shortest route of unidirectional activation encompassing a full range of mapped activation times (>90% of the tachycardia cycle length) and returning to the site of earliest activation. Conventional mapping, including pace mapping during sinus rhythm, entrainment maneuvers, and postpacing interval analysis[12] during VT, were not performed routinely because VT isthmus definition was based on VT activation time mapping. Once defined, linear radiofrequency (RF) lesions were placed so as to transect the VT isthmus in case of mappable VTs. For unmappable VTs, ablation sites were required to have abnormal low-amplitude electrograms, electrograms with double potentials, wide fractionated potentials, or isolated late potentials during sinus or paced rhythm. Pacemapping during sinus rhythm and measurement of the stimulus-to-QRS interval were then used to unmask VT isthmuses and determine ablation sites[13] of unmappable VTs.

Systemic anticoagulation was achieved with heparin (initial bolus of 50 U/kg IV followed by 1000–2000 U/h) throughout the procedure. Sedation was obtained with 10 mg IV nalbuphine, with incremental doses at 5 mg as necessary.

RF Ablation and End Point

Identification of the ablation site was based on analysis of the 3D map. The anode was a 575-cm^2 back plate placed under the patient's left shoulder. RF ablation was performed with a 550-kHz RF Stockert–Cordis generator. The RF energy was delivered in a temperature-controlled mode for 60 to 120 seconds at each ablation site with a maximal temperature/power target of 45°C/40 W for 3.5-mm tips (55°C/75 W for 8-mm tips). Acute success was defined as a negative EPS at the end of the procedure. Successful VT ablation was defined as acute success and a negative repeat EPS at 2 to 3 months. Negative EPS was defined as absence of inducibility of any sustained monomorphic VT with a rate <270/min. Induction of monomorphic very fast VT (rate ≥270/min) as well as polymorphic VT or ventricular fibrillation were not defined as positive EPS.

Management After Ablation

After ablation, patients were monitored for 72 hours by telemetry. Transthoracic echocardiography was performed within 2 days after ablation. Patients were then discharged and followed on an outpatient basis, with clinical evaluation and 24-hour Holter recordings performed regularly.

All patients were evaluated routinely at 6 to 8 weeks postprocedure and at 3- to 6-month intervals. Patients with ICD underwent interrogation every 6 months, and all recorded arrhythmic episodes were collected and analyzed. Follow-up data, including mortality, were available on all patients.

Stepwise Approach Algorithm

All patients underwent VT ablation with the primary aim of complete abolition of all VTs. After a successful procedure, an EPS was performed at 3 months and further ablation was carried on if VT was induced. Before this repeat EPS, antiarrhythmic drugs were withdrawn for at least 5 half-lives in all patients, except amiodarone which was stopped at least 1 month before. Repeat EPS was continued after a successful ablation until the study was negative or an ICD was implanted. The stepwise algorithm is shown in Figure 1. ICD was implanted if any of the following criteria was present:

1. Ejection fraction ≤35% in patients who underwent VT ablation after the publication of the European Society of Cardiology Guidelines[6] for ICD implantation (ie, patients with ejection fraction <35% who underwent VT ablation before this publication did not receive an ICD if they had successful ablation).
2. A fast VT (VT with a shorter cycle length than the clinical VT) was inducible at the end of the procedure.

Statistical Analysis

All variables were tested for normal distribution based on the visual inspection of the frequency histogram and Shapiro–Wilk test. Normal data are presented as mean±SD, and categorical variables are expressed as percentages. Non-Gaussian data are presented as median (interquartile range). For qualitative data, absolute and relative frequencies are shown. Comparisons between groups were made by χ^2 test or Fisher exact test for categorical variables, and unpaired *t* test for normally distributed variables. Survival analysis was performed using the nonparametric Kaplan–Meier curve, and differences between survival curves were analyzed using the log rank test. Multivariate Cox regression analysis was performed to provide adjusted hazard

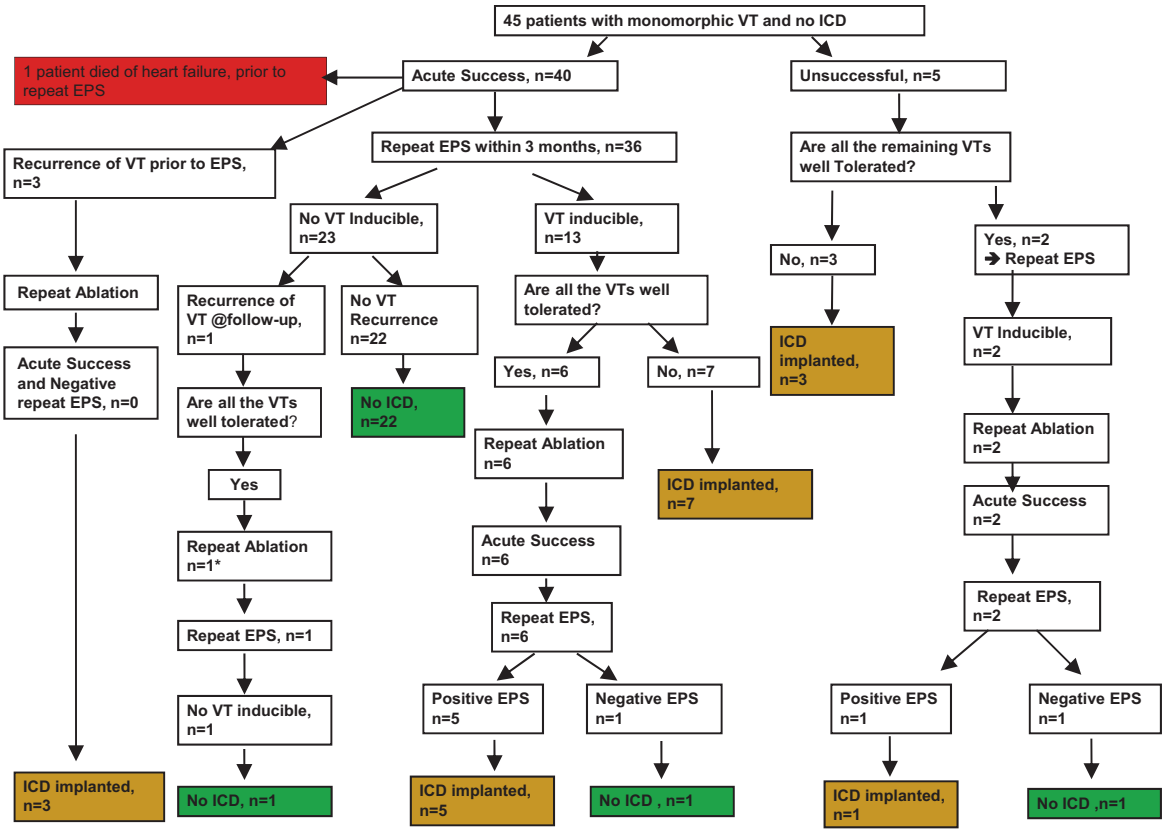

Figure 1. Stepwise approach to the management of patients with ischemic cardiomyopathy and ventricular tachycardia (VT). Well-tolerated VT was defined as VT without cardiovascular compromise (ie, presyncope, pulmonary edema, or cardiogenic shock) and with no requirement of an immediate DC cardioversion. EPS indicates electrophysiology study; and ICD, implantable cardioverter-defibrillator.

ratio. All *P* values are presented as 2 tailed, with statistical significance inferred at $P<0.05$. Analyses were performed using SPSS for windows version 17.0 (SPSS Inc, Chicago, IL).

Results

Patient Characteristics

The study population consists of 45 patients (mean age, 65.2±9.6 years; 91% men) with a previous history of myocardial infarction (Table 1). Thirty-two patients (71.1%) had a previous inferior myocardial infarction and the left ventricular ejection fraction was 40% (interquartile range, 30%–50%). Twenty-seven patients (60%) presented with a combination of shortness of breath or palpitations, 6 (13.3%) with chest pain, 5 (11.1%) with syncope, 1 (2.2%) with cardiogenic shock, and the rest with a combination of these. The median VT cycle length was 370 ms at presentation and varied from 240 to 664 ms. Table 2 shows the characteristics of the different VTs during ablation.

Ablation Results

Success was obtained in 40 patients (88.9%) after first ablation. Of the remaining 5 patients, 3 patients had fast VT at the end of the procedure and had an ICD implanted, and the other 2 patients had repeat EPS (Figure 1).

At follow-up and before repeat EPS, 1 patient died of heart failure, and there was VT recurrence in 3 patients(7.5%). Repeat EPS was performed in 36 patients, and VT was inducible in 13 patients (36.1%). For patients with a negative EPS, 1 (4.5%) had recurrent VT. On the basis of our algorithm, ICD was implanted in 19 patients (42.2%). Complications occurred in 4 patients, including 2 cerebrovascular accidents, 1 femoral hematoma, and 1 complete heart block.

ICD Therapies and Mortality

During a median follow-up of 4.5 years (interquartile range, 2.1–7.0), there were 5 deaths in the group without an ICD and 9 in the ICD group. Patients with an ICD had a lower median survival as compared to patients without an ICD, although the results were not statistically significant (log rank test, $P=0.11$; Figure 2). The mean age in the ICD versus no ICD group were 63.4±10.4 years versus 67.2±8.6 years, $P=0.18$, and median left ventricular ejection fraction (%) was 40 (30–44) versus 45 (30–50), $P=0.21$. ICD implantation was not associated with improved survival (unadjusted hazard ratio, 0.42 [0.14–1.25]; $P=0.11$). Using Cox regression analysis with age and ICD implantation as covariates, only age was an independent predictor of mortality (hazard ratio, 1.13; 95% confidence interval, 1.03–1.22; $P=0.007$), whereas ICD implantation was not (hazard ratio, 0.54; 95% confidence interval, 0.18–1.64; $P=0.28$). A similar trend was obtained when cardiovascular (CV) mortality (4 CV deaths in the group without an ICD and 6 in the ICD group) was compared (Figure 3) between patients with and those without an ICD. The causes of CV deaths were as follows: (1) heart failure (3 in the no ICD group and 3 in the ICD group), (2) intractable VT or ventricular fibrillation (2 in the ICD group), (3) sudden death (1 in the no ICD group), and (4) cardiac tamponade after ICD implantation in 1 patient.

Table 1. Clinical Characteristics

	ICD Group (n=19)	No ICD Group (n=26)	*P* Value
Age, y	63.4±10.4	67.2±8.6	0.18
Sex (% male)	16 (84.2)	25 (96.2)	0.2
Ejection fraction, %	40 (30–44)	45 (30–50)	0.24
History of AF, %	4 (21.0)	3 (11.5)	0.43
History of CABG, %	6 (31.5)	8 (30.8)	0.95
History of PTCA/stenting, %	4 (21.0)	9 (34.6)	0.51
Chronic renal failure, %	2 (10.5)	3 (11.5)	0.92
NYHA, %			0.32
I	1 (5.3)	4 (15.4)	
II	17 (89.4)	18 (69.2)	
III	1 (5.3)	4 (15.4)	
Location of infarct, %			0.19
Anterior	3 (15.8)	9 (34.6)	
Inferior/posterior	16 (84.2)	17 (65.4)	
VT tolerance, %			0.31
Fair	14 (73.7)	21 (80.8)	
Poor	4 (21.1)	1 (3.8)	
Syncope	1 (5.3)	4 (15.4)	
Amiodarone before ablation, %	11 (57.9)	12 (46.2)	0.55
Amiodarone post ablation, % *	10 (52.6)	7 (26.9)	0.07

VT tolerance: Fair, VT without cardiovascular compromise; Poor, VT and cardiovascular compromise (ie, presyncope, pulmonary edema, or cardiogenic shock). AF indicates atrial fibrillation; CABG, coronary artery bypass grafting; ICD, intracardiac defibrillator; NYHA, New York Heart association; PTCA, percutaneous transluminal coronary angioplasty; and VT, ventricular tachycardia.

*Treatment at hospital discharge after the first procedure.

VT With Syncope or CV Compromise

A subgroup of patients (10/45) presented with VT with syncope or significant CV compromise (presyncope, pulmonary edema, or cardiogenic shock). They all underwent the same protocol of VT ablation and ablation-guided ICD implantation. The results of these patients are shown in Table 3.

Arrhythmic Death

Two patients in the ICD group died as a result of intractable VT or ventricular fibrillation, and 1 patient in the group without ICD had a sudden death. He was a 76-year-old man, with a left ventricular ejection fraction of 50%, who initially presented with a VT cycle length of 353 ms and had an acutely successful ablation.

ICD Therapies

In patients with an ICD, therapy for VT was delivered in 8 of 19 patients (42.1%), with 7 patients having had ≥2 therapies.

Discussion

The aim of this study was to look at the results of a stepwise approach for the management of patients with ICM presenting with VT, with ablation as an initial treatment strategy. ICD was implanted based on a predefined decision tree taking into consideration acute success, inducibility at repeat EPS, and recurrence. To our knowledge, this is the first study to look at such an approach. This study has several interesting findings.

Table 2. Ablation and Ventricular Tachycardia Characteristics

	ICD Group (n=19)	No ICD Group (n=26)	*P* Value
No. of ablation procedures	1 (IQR, 1–2)	1 (IQR, 1–2)	0.22
No. of different VTs at first ablation	1 (IQR, 1–2)	1 (IQR, 1–3)	0.57
Epicardial ablation	0 (0.0)	0 (0.0)	NA
Entrainment[12] (% yes)*	0 (0)	3 (11.5)	0.25
Pacemapping (% yes)*	10 (52.6)	20 (76.9)	0.16
VT termination during RF application, %	5 (26.3)	8 (30.8)	0.51
Abolition of post systolic potentials (% yes)†	3 (15.8)	8 (30.8)	0.32
Procedure duration, min	221±76	242±61	0.73

ICD indicates intracardiac defibrillator; IQR, interquartile range; NA, nonapplicable; RF, radiofrequency; and VT, ventricular tachycardia.

*Percentage of patients in whom VT entrainment and pacemapping during sinus rhythm were used to help unmask the VT isthmus.

†Percentage of patients in whom abolition of postsystolic potentials (recorded on sinus rhythm EGM) was performed in addition to VT isthmus transection.

First, it suggests that a strategy of successful VT ablation, defined as noninducibility of all VTs followed by a negative EPS, in patients with postinfarct VT is safe, feasible, and can be used as a means to risk stratify patients as to the implantation of ICD. Second, the mortality rate in the successful ablation group was not higher than the ICD group. Although the numbers are limited, this strategy does not seem harmful even in patients presenting with hemodynamically unstable VT.

In patients with ICM, VT carries a poor prognosis.[1,2,5] Various studies have shown the superiority of ICD therapy compared with medical therapy on long-term outcomes in such patients.[2–4] Devices, however, do not take away the arrhythmic substrate capable of sustaining a VT circuit. They merely provide therapy for fast heart rates, which the ICD recognizes as

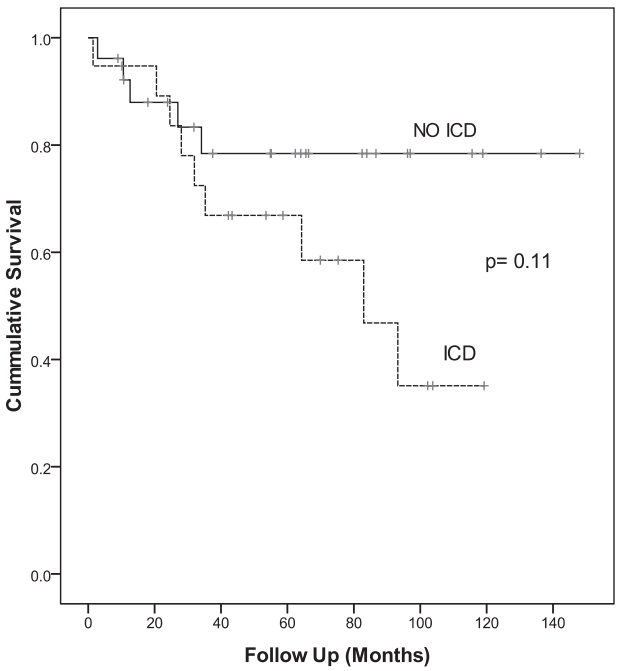

Figure 2. Kaplan–Meier survival curves for patients with and without implantable cardioverter-defibrillator (ICD).

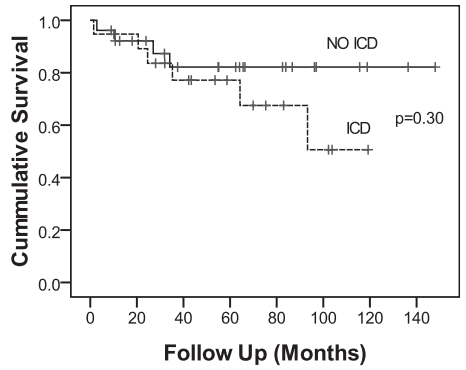

Figure 3. Kaplan–Meier survival-free from cardiovascular death in patients with and without implantable cardioverter-defibrillator (ICD).

VT or ventricular fibrillation based on predefined algorithms. VT ablation, on the contrary, targets the substrate responsible for the arrhythmia mechanism. Two randomized control trials have shown that catheter ablation reduces ICD therapies, including shocks,[7,8] in patients with ICM and VT. The question that arises therefore is whether a successful ablation is enough, at least in a subgroup of patients. One problem with successful VT ablation is the high rate of recurrence varying between 20% and 44%.[14–18] In a group of patients with ischemic heart disease and hemodynamically well-tolerated VT, Della Bella et al[14] showed that VT ablation resulted in the abolition of the targeted VT in 73% of patients. Although the recurrence rate was substantial (27%), only 3 patients (2.5%) died suddenly. Our study is similar to the study by Della Bella et al[14] in that we looked at a similar cohort of patients. However, in the above study, repeat VT stimulation study was not performed. Moreover, ICD was implanted in 11% in the study population before VT ablation. The same group[19] showed that a negative EPS after VT ablation for VT storm was a predictor of absence of VT recurrence over a long period of time. It is possible that incomplete ablation or edema might limit the predictive value of EPS immediately after ablation, and therefore it is possible that an EPS remote from the ablation time provide a better answer. In patients with a structural heart disease, Frankel et al[20] showed that a negative EPS performed 3.1±2.1 days after ablation predicted >80% VT-free survival over 1-year follow-up. We arbitrarily chose a 3-month period to allow the scar to mature. Our study therefore adds further to the current understanding. However, given the high-recurrence rates, additional substrate-based ablation might provide even better results.

There was a trend toward a survival benefit in the successful VT ablation group compared with the group with ICD, although the results were not statistically significant. Several trials have shown that ICD therapies are associated with mortality and morbidity, and therefore it is conceivable that successful ablation and abolition of substrate for sustained VT might lower mortality.

In addition, there is also an economic argument in favor of the stepwise approach to VT ablation. ICDs are costly, and therefore this strategy might allow us to use limited resources in a more cost-effective way.

Limitations

This study is not a randomized controlled trial, and therefore the inherent limitations of observational studies apply. Patient groups are not homogeneous. Decision on whether patients had an ICD was not random but based on a decision tree. It is therefore conceivable that the patient group without an ICD represented a less healthy cohort. However, the mortality difference demonstrated would argue against this. It can be argued that physicians may have felt more comfortable not implanting an ICD in certain patients and this would have created an inherent bias. However, this is unlikely, in our opinion, given that this decision was made on a predefined algorithm.

Second, it is a small study, and analysis of subgroups inherently makes the groups smaller.

Third, the exact timing of a repeat VT stimulation study to confirm noninducibility is unknown. We used a 3-month window based on experience.

Fourth, the only end point of the study was prevention of VT inducibility. Whether modification of the arrhythmia substrate was achieved cannot be proven.

Finally, the results of this observational study need to be verified in a randomized controlled trial. We appreciate that it may take a long time for such a randomized controlled trial to be performed, mainly because of the current guidelines.

Table 3. Clinical Characteristics and Outcomes in Patients Presenting With VT and Cardiovascular Compromise Before Ablation

Sex	Age	LVEF	VT Tolerance	NYHA	ICD Implanted	Death	Death Cause
Male	63	42	POOR	2	YES	YES	Bladder cancer
Male	64	46	POOR	2	YES	YES	Unknown
Male	80	40	POOR	2	YES	YES	Heart failure
Male	75	30	POOR	3	NO	YES	Heart failure
Male	71	30	POOR	2	YES	YES	Untractable VT/VF
Male	78	20	SYNCOPE	3	YES	YES	Heart failure
Male	51	60	SYNCOPE	2	NO	NO	NA
Male	68	30	SYNCOPE	2	NO	YES	Heart failure
Male	68	45	SYNCOPE	2	NO	NO	NA
Female	74	30	SYNCOPE	2	NO	NO	NA

POOR denotes patients presenting with VT and cardiovascular compromise (ie, presyncope, pulmonary edema, or cardiogenic shock). ICD indicates implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; NA, nonapplicable (patient alive); NYHA, New York Heart Association; VF, ventricular fibrillation; and VT, ventricular tachycardia.

Conclusions

The results of this observational study suggest that a strategy of VT ablation and ablation-guided ICD implantation might be a reasonable option in selected patients with previous myocardial infarction.

Disclosures

Drs de Chillou, Andronache, and Aliot have received lectures fees from Biosense-Webster for <10 000 annual USD.

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CLINICAL PERSPECTIVE

Implantable cardioverter-defibrillators (ICD) are recommended in patients with ventricular tachycardia (VT) late after myocardial infarction, and catheter ablation of VT is currently considered only as adjunctive therapy to decrease recurrent VT. Whether a successful VT ablation alone (without ICD implantation) might be a viable strategy for some patients is not known. We evaluated a stepwise approach for VT management in 45 postinfarct patients in whom catheter ablation was offered as a first-line therapy between 2002 and 2011. After acutely successful ablation, defined as absence of any inducible VT, repeat stimulation was performed 2 to 3 months later with further ablation for inducible VT. An ICD was implanted in 19 of 45 patients (42%) for whom VT inducible could not be abolished, or who were studied after 2006 and had left ventricular ejection fraction ≤35%. During a median follow-up of 4.5 years, mortality occurred in 14 of 45 patients (31.1%) and was not statistically different between the ICD and no ICD groups. There was 1 sudden death in the no ICD group. Our results suggest that a stepwise approach to the management of VT, with ablation as a first-line treatment in postinfarct patients presenting with VT, might be a reasonable option.

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A Stepwise Approach to the Management of Postinfarct Ventricular Tachycardia Using Catheter Ablation as the First-Line Treatment: A Single-Center Experience

Maheshwar Pauriah, Gabriel Cismaru, Isabelle Magnin-Poull, Marius Andronache, Jean-Marc Sellal, Jérôme Schwartz, Béatrice Brembilla-Perrot, Nicolas Sadoul, Etienne Aliot and Christian de Chillou

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Review Article

Recommendations for the use of electrophysiological study: Update 2018

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ABSTRACT

The field of cardiac electrophysiology has greatly developed during the past decades. Consequently, the use of electrophysiological studies (EPSs) in clinical practice has also significantly augmented, with a progressively increasing number of certified electrophysiology centers and specialists. Since Zipes et al published the Guidelines for Clinical Intracardiac Electrophysiology and Catheter Ablation Procedures in 1995, no official document summarizing current EPS indications has been published.

The current paper focuses on summarizing all relevant data of the role of EPS in patients with different types of cardiac pathologies and provides up-to-date recommendations on this topic.

For this purpose, the PubMed database was screened for relevant articles in English up to December 2018 and ESC and ACC/AHA Clinical Practice Guidelines, and EHRA/HRS/APHRS position statements related to the current topic were analyzed.

Current recommendations for the use of EPS in clinical practice are discussed and presented in 17 distinct cardiac pathologies. A short rationale, evidence, and indications are provided for each cardiac disease/group of diseases.

In conclusion, because of its capability to establish a diagnosis in patients with a variety of cardiac pathologies, the EPS remains a useful tool in the evaluation of patients with cardiac arrhythmias and conduction disorders and is capable of establishing indications for cardiac device implantation and guide catheter ablation procedures.

1. Role of electrophysiological study in patients with sinus node dysfunction

The prevalence of sinus node dysfunction (SND) is higher in older individuals than in younger individuals, and its incidence is estimated at 1 in 600 patients older than 65 years of age (1) or 0.8 cases per 1000 person-years (2). Men and women are equally affected, with a mean age between 73 and 76 years. Risk factors associated with the development of SND include a history of a cardiovascular event, arterial hypertension, a higher body mass index, and, most importantly, advanced age (hazard ratio [HR] = 1.73 for every additional 5 years of age) (2).

Types of SND include (a) sinus bradycardia, (b) sinus arrest, (c) sinoatrial block, (d) sinus pause, and (e) chronotropic incompetence.

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Clinical symptoms caused by SND are bradycardia related and include dyspnea, chest pain, fatigue, lightheadedness, presyncope, and syncope.

It is important to differentiate intrinsic sinus node disease (SND) from extrinsic (functional) SND (due to increased vagal tone, medication, toxin, electrolyte imbalance, endocrine and metabolic diseases, etc.) because the management of SND varies according to its etiology.

Rationale: To identify patients who are eligible for pacemaker (PM) implantation. Several studies have established the role of PM implantation in reducing symptoms in patients with SND (3–9). In this subgroup of patients, despite the reduced occurrence of bradycardia-related symptoms following PM implantation, it is not known whether a definitive pacing system increases the survival rate (10) (11) (12).

Evidence: Despite a desirable specificity of 75–95% (13, 14), the current role of electrophysiological study (EPS) in evaluating sinus node function is limited for the following reasons: 1) its low sensitivity, of approximately 50% in symptomatic patients (14–16), with an even lower sensitivity in asymptomatic patients. Its sensitivity can, however, be increased by drug-induced autonomic blockade (0.0175 mg/kg i.v. metoprolol or 0.02 mg/kg i.v. propranolol + 0.04 mg/kg i.v. atropine) (17–19); 2) a low predictive value concerning the occurrence of symptoms in asymptomatic patients (20); 3) difficulty in interpreting the clinical significance of isolated abnormal findings; 4) its invasive nature compared to other existing diagnostic methods, mainly autonomic blockade (21) and exercise stress test; and 5) more accurate existing diagnostic alternatives such as implantable loop recorders (ILRs) (22, 23).

The main parameters used to characterize sinus node function during an EPS are sinus node recovery time (SNRT) (normal values < 1500 ms), corrected sinus node recovery time (cSNRT) (normal values < 500–550 ms (24)) and sinoatrial conduction time (SACT) (normal values < 120 ms (25)) by the Strauss and Narula method (25–32).

Despite the fact that a few small studies suggest that a prolonged SNRT (>3 s) and cSNRT ≥ 800 ms in patients with syncope are in favor of a bradyarrhythmic mechanism (32–34), the role of EPS in guiding PM implantation has never been established (10), and an EPS is currently performed only in isolated cases.

1.1. Indications

1.1.1. Class I

(1) To assess the relation between clinical symptoms and SND in symptomatic patients with documented sinus bradyarrhythmias in whom a direct relation between bradycardia and clinical symptoms could not be established by noninvasive methods (35).

1.1.2. Class II

(1) To determine whether abnormalities are due to intrinsic disease, autonomic nervous system dysfunction, or the effects of drugs to help select therapeutic options in patients with electrocardiographically documented sinus bradyarrhythmias (35).
(2) To assess inducibility of other arrhythmias as the potential cause of clinical symptoms in patients with documented SND (35).

1.1.3. Class III

(1) Routine use before PM implantation in symptomatic patients (syncope) and documented asystole ≥3 s in whom an association between symptoms and a documented bradyarrhythmia has been established (10, 36).
(2) Routine use before PM implantation in asymptomatic patients and documented asystole ≥6 s (10, 36).
(3) Asymptomatic patients with sinus bradyarrhythmias or sinus pauses observed only during sleep, including sleep apnea (35).

Conclusion: Given its desirable specificity, the EPS may be used to support the clinical suspicion of SND if abnormalities are found but cannot be used to exclude it owing to its low sensitivity.

2. Role of electrophysiological study in patients with acquired atrioventricular block

Rationale: Unlike in SND, where PM implantation did not reduce the overall mortality (7, 10, 11, 37), PM implantation in patients with a complete atrioventricular (AV) block reduces mortality and alleviates symptoms (38–42)**.** The role of EPS in this population of patients is therefore to identify those patients who will benefit from PM implantation.

Evidence: EPS is not routinely required in patients with AV block (AVB). Patients with minor AV conduction disorders (isolated mild first-degree AVB) are often asymptomatic and do not need a PM. Patients with a more advanced AV conduction disorder (second-degree Mobitz II AVB, high-degree AV block, and complete AVB) have an indication for PM implantation without requiring a prior EPS (10). In the remaining cases, when noninvasive maneuvers fail to localize the site of the block (43), an EPS may be justified. Intrahisian and infrahisian blocks usually progress toward a complete AVB (44). Nodal AVB progression is rarely reported. Type I second-degree AVB can be infranodal even when the QRS is narrow (45).

An EPS is not justified in patients with an AVB due to reversible situations (such as electrolyte disorders: hyperkalemia and hypercalcemia; administration of negative dromotropic drugs: beta-blockers, non-dihydropyridine calcium channel blockers such as verapamil or diltiazem, digoxine, and amiodarone; hypothyroidism; increased vagal tone), which cause an “extrinsic” AVB (10).

However, in doubtful cases, the EPS may unmask an intrinsic conduction disorder requiring PM implantation. Usually, an infrahisian block is triggered by premature atrial or ventricular beats, increased heart rate (phase 3 AVB), or decreased heart rate (phase 4 AVB). These phenomena are typically associated with an “intrinsic” AVB.

According to the 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy, an EPS has a role in identifying patients with an AVB who are eligible for PM implantations when a bradycardia episode is suspected but not documented (transient bradycardia). However, the role of the EPS in evaluating patients with a suspected paroxysmal AVB is limited owing to its low sensitivity. According to Fujimura et al (16), an EPS identified anomalies and suggested the correct diagnosis in only 15.4% of patients with symptomatic documented intermittent AV conduction disorders. Currently, ILRs have a much more important role in identifying paroxysmal conduction disorders (46–53).

2.1. Indications

2.1.1. Class I

None.

2.1.2. Class II

1. In patients with a second-degree Mobitz I AV block (Luciani–Wenckebach) and in patients with a second-degree Mobitz

2:1 AV block, an EPS may be justified to determine the site of the block (above or below the His level) (54).
2. In patients with a suspected paroxysmal AVB, an EPS may be considered in selected patients (55).
3. Patients with premature, concealed junctional depolarizations suspected as a cause of a second- or third-degree AVB pattern (pseudo AVB) (35).

2.1.3. Class III

1. Before PM implantation in patients with a complete AVB, high-degree AVB, and second-degree Mobitz II AVB (10).
2. Isolated first-degree AVB (in the absence of a bundle branch block (BBB)).
3. Asymptomatic patients with an AVB associated with increased vagal tone (e.g., nocturnal type I second-degree AVB) (35).

3. Role of electrophysiological study in patients with bundle branch block (BBB)/intraventricular conduction disease (IVCD)

The normal His-Purkinje system comprises the bundle of His and two branches: the right bundle and the left bundle, the latter dividing itself into the anterior fascicle and the posterior fascicle. Before the widespread use of cardiac electrophysiology in clinical practice, evaluation of conduction through the His-Purkinje system was according to the 12-lead ECG; therefore, the terms characterizing intraventricular conduction delays are derived from the interpretation of the surface ECG. The term "bundle branch block" refers to a prolongation of the QRS duration >120 ms caused by the absence of conduction through either the right or the left bundle branch, with sequential activation of the two ventricles. "Complete BBB" implies a QRS duration >120 ms, whereas "incomplete BBB" implies a QRS duration between 100 and 120 ms. The term "bifascicular block" refers to a combination of the right bundle branch block (RBBB) and the left anterior hemiblock (LAHB) or the left posterior hemiblock (LPHB). A complete left bundle branch block (LBBB) can also be considered as a type of bifascicular block. "Trifascicular block" refers to a combination of RBBB and LAHB alternating with LPHB or LBBB alternating with RBBB. The presence of a bifascicular block and AV conduction delays (e.g., RBBB + LAHB + BAV I type) can be classified as a trifascicular block only with AVB located at the infrahisian site (to the remaining conducting fiber). The term "nonspecific intraventricular conduction disorder" refers to a prolongation of the QRS duration on the surface ECG, which does not comply with the morphological ECG criteria for defining either LBBB or RBBB.

Rationale: Patients with a diseased His-Purkinje conduction system might progress to a more advanced conduction disorder, specifically a complete AVB. The role of EPS in patients with BBB is to identify patients at a higher risk of progression to a complete AVB who are eligible for PM implantation.

Evidence: The most important aspect of EPS in patients with BBB is the evaluation of conduction in the remaining functional fibers, expressed by the HV interval. In patients with a bifascicular block, a normal HV interval (33–55 ms) implies normal conduction through the remaining fascicle, whereas a prolonged HV interval (>55 ms) implies a conduction-diseased remaining fascicle. The natural history of such patients was initially described by Scheinman et al (56), who showed that the progression rate to a complete AVB at 4 years was ≤4% in patients with an HV interval of <70 ms, 12% in those with an HV interval of 70–100 ms, and 24% in those with an HV interval of >100 ms. However, a recent study did not replicate these observations (57). Nevertheless, PM implantation is currently indicated in patients with syncope, BBB, and an HV interval of ≥70 ms.

In addition to measuring the baseline HV interval, other important maneuvers performed during the EPS are incremental atrial pacing and pharmacological provocation (with class IA antiarrhythmic drugs: ajmaline, disopyramide, or procainamide, or class IC drugs: flecainide).

The development of an intrahisian or an infrahisian block during incremental atrial pacing is highly predictive for the development of a complete AVB and justifies PM implantation (58). However, such a finding is rare and has a low sensitivity. An increase in the HV interval >10 ms during incremental atrial pacing or development of a second-degree AVB can be observed in 6% and 5% of patients, respectively. A complete AVB was reported to occur in 40% of such patients during a mean follow-up period of 42 months (59).

Significant prolongation of the HV interval or development of a high-degree AVB during pharmacological provocation is also predictive of complete AVB development, thus justifying PM implantation (59–62). No study directly compared the diagnostic value of pharmacological provocation with different drugs. This test is usually performed in patients with syncope and BBB when the baseline HV interval is nondiagnostic (<70 ms) and a paroxysmal high-degree/complete AVB is suspected as the mechanism of syncope (63–71).

Recently, a group of authors demonstrated the utility of performing pharmacological provocation with ajmaline in patients with recurrent unexplained syncope and preserved ejection fraction (EF), even without conduction abnormalities on surface ECG, thus suggesting a potential role for ajmaline in identifying patients who are prone to higher degree AVB development (72).

As previously reported (10), in studies evaluating the diagnostic value of pharmacological stress testing for a total of 333 patients (59–62), a high-degree AVB was induced in 15% of the patients (n = 50). During the follow-up period of 24–63 months, 68% (range 43–100) of these patients developed spontaneous AVB, thus consolidating the utility of pharmacological testing in identifying potential candidates for PM implantation.

The positive predictive value of a complete EPS (including pharmacological challenge) to correctly identify patients who will require PM implantation for an AVB is ≥ 80% (10). However, a negative EPS does not rule out a paroxysmal AVB as a possible underlying mechanism for syncope, and a false-negative EPS is not uncommon. If clinical suspicion for such a mechanism is high, an ILR may be indicated thereafter (73, 74).

Paroxysmal AVB is not the only syncope mechanism in patients with a BBB. As shown previously, Horwich et al reported a ventricular arrhythmia inducibility rate of 49% in patients with QRS ≥120 ms in their cohort (75). Other studies confirm such findings (76–78).

Using standard evaluation, EPS, and ILRs, Moya et al. (79) showed that among 303 patients with BBB and syncope, this was due to bradyarrhythmias (202), carotid sinus syndrome (20), ventricular tachycardia (VT) (18), neurally mediated (9), orthostatic hypotension (4), drug induced (3), secondary to cardiopulmonary disease (2), supraventricular tachycardia (SVT) (1), bradycardia–tachycardia (1), and nonarrhythmic causes (7).

In patients with syncope, BBB, and reduced LVEF (<45%), VT may be induced during EPS in up to 42% of cases (77). Therefore, a complete EPS (including sinus node function evaluation and programmed atrial and ventricular stimulation) remains necessary to correctly identify the cause of syncope in patients with BBB.

3.1. Indications

3.1.1. Class I

(1) Patients with unexplained syncope and bifascicular block (10, 80).

3.1.2. Class II

(1) Asymptomatic patients with BBB in whom pharmacological therapy that could increase conduction delay or produce heart block is contemplated (35).
(2) A complete EPS (including sinus node function evaluation and programmed atrial and ventricular stimulation) remains necessary to correctly identify the cause of syncope in patients with BBB (76–79).

3.1.3. Class III

(1) Asymptomatic patients with intraventricular conduction delay [35)
(2) Symptomatic patients whose symptoms can be correlated with or excluded by ECG events
(3) Patients with isolated incomplete BBB or nonspecific IVCD with QRS <120 ms.

3.2. Indications for pharmacological challenge during EP study in patients with BBB

I. Symptomatic patients (syncope present)
   a. HV = 35–55 ms → pharmacological provocation may be useful (72)
   b. HV = 55–69 ms → pharmacological provocation may be useful (72)
   c. HV ≥ 70 ms → PM implantation (56)
II. Asymptomatic patients (syncope absent, EPS performed for other reasons):
   a. HV = 35–55 ms → no further test
   b. HV = 55–69 ms → no further test
   c. HV = 70–100 ms → follow-up (56)
   d. HV > 100 ms → PM implantation (56)

4. Role of electrophysiological study in diagnosis of patients with narrow QRS complex tachycardias

The term “narrow QRS complex tachycardia” is a general term comprising several types of SVTs (heart rate > 100 bpm): sinus tachycardia, focal/multifocal atrial tachycardia (AT), atrioventricular nodal re-entry tachycardia (AVNRT), orthodromic atrioventricular re-entry tachycardia (AVRT), atrial flutter (AFl), and focal junctional tachycardia (FJT). The term supraventricular tachycardia does not include atrial fibrillation (AF), which is considered as a distinct entity (81, 82). VT originating from the His-Purkinje conduction system (fascicular tachycardia) can also have narrow QRS complexes on the 12-lead ECG.

Rationale: Although all the above-mentioned SVTs have certain characteristics on the 12-lead ECG, their differential diagnosis is not always possible by standard noninvasive methods. The role of EPS in patients with SVT is to 1) identify the tachycardia mechanism and 2) to guide catheter ablation.

Evidence: The prevalence of SVT in the general population is reported as 2.25 per 1,000 individuals (83). Men and women are equally affected. After a first initial event, recurrences are common. Diagnostic work-up includes ECG during tachycardia and sinus rhythm, cardiac rhythm monitoring (telemetry, Holter ECG, external loop-recorders, and internal loop recorders) and may also include exercise stress test and echocardiography. The use of smartphone devices for the diagnosis of paroxysmal palpitations has lately been proposed as a useful diagnostic method (84–87), and several studies aimed at its validation in these clinical scenarios are ongoing (such as the IPED trial, ClinicalTrials.gov Identifier: NCT027838980).

The treatment goal in the acute phase is to terminate tachycardia and on the long term to prevent recurrences. Treatment options include vagal maneuvers (carotid sinus massage and Valsalva maneuver), antiarrhythmic medication, and catheter ablation (88, 89). Catheter ablation has widely developed during the past 20 years, and three-dimensional electroanatomical mapping systems, which allow a better arrhythmia substrate characterization and understanding of the tachycardia mechanism, are currently available on a large scale. These systems also allow for an important reduction in the radiation dose during the procedure. Data from a recent randomized controlled trial have finally confirmed that catheter ablation is the treatment of choice for AVNRT compared to antiarrhythmic drugs, which are less effective and less well tolerated (90).

An EPS precedes each catheter ablation procedure and has the following goals: 1) baseline characterization of the normal His-Purkinje conduction system; 2) determination of the presence of an arrhythmia substrate such as abnormal AV connections (accessory pathways)/dual AV nodal physiology, zones of conduction block (such as an atrial scar in congenital heart disease (CHD) or postsurgery); 3) initiation of tachycardia for determining its underlying mechanism, with or without pharmacological provocation (isoprenaline (91–94), atropine (95–97), and adrenaline (98)); 4) applying electrophysiological maneuvers for the differential diagnosis; and 5) establishing the correct diagnosis. Several electrophysiological maneuvers are also made after catheter ablation to confirm acute success, assess the integrity of the His-Purkinje conduction system, and confirm the presence or absence of additional tachycardia substrates.

4.1. Indications

4.1.1. Class I

(1) Patients with frequent or poorly tolerated episodes of tachycardia that do not adequately respond to drug therapy and for whom information about the site of origin, mechanism, and electrophysiological properties of the pathways of the tachycardia is essential for choosing appropriate therapy (drugs, catheter ablation, pacing, or surgery) (35)
(2) Patients who prefer ablative therapy compared to pharmacological treatment (35, 88, 89)

4.1.2. Class II

(1) Patients with frequent episodes of tachycardia requiring drug treatment for whom there is concern about proarrhythmic effects of the antiarrhythmic drug (35)

4.1.3. Class III

(1) Patients with tachycardias easily controlled by vagal maneuvers and/or well-tolerated drug therapy who are not candidates for nonpharmacological therapy (35)

5. Role of electrophysiological study in diagnosis of patients with wide QRS complex tachycardias

Wide QRS complex tachycardias are characterized by a QRS width of >120 ms in the presence of a heart rate of >100 bpm. Depending on the underlying mechanism, there are three possible entities: 1) VT, 2) SVT with pre-existing or functional BBB, and 3) ventricular preexcitation. It should be mentioned that up to 80% of times, a wide QRS complex tachycardia is ventricular in nature; SVT with BBB account for 15–25% of cases (99–102).

Several ECG algorithms have been developed to make a positive diagnosis (103–116), but all these algorithms have limitations, and a correct diagnosis using only surface ECG is not always possible, particularly when trying to differentiate some forms of VT from ventricular pre-excitation. The doubtful cases can be approached by EPS.

Rationale: The purpose of EPS in patients with wide QRS complex tachycardia is to 1) establish the underlying mechanism (differential diagnosis between VT/SVT with BBB/Ventricular Pre-excitation); 2) identify patients at risk of SCD (VT); 3) identify patients eligible for ICD implantation (VT); and 4) guide catheter ablation.

Evidence: Several entities may manifest as wide QRS complexes on surface ECG, for which the clinician might wonder whether an EPS should be performed. These entities are 1) isolated premature ventricular contractions (PVCs), 2) ventricular couplets, 3) non-sustained VT, 4) sustained monomorphic VT, 5) polymorphic VT, and 6) preexcitation pattern (WPW).

For patients with ventricular arrhythmias, the prognosis depends on the presence or absence of an underlying structural heart disease. In the former case, the risk of sudden death seems to be related to the frequency and complexity of the PVCs.

1. Isolated premature ventricular contractions (PVCs)

Isolated PVCs are not uncommon findings even in the absence of structural heart disease, with a prevalence varying according to age. According to one study performed on military subjects (117), the prevalence of PVC was 4.6% in the patient group aged 16–19 years, 6.2% in the patient group aged 20–24 years, 5.7% in the patient group aged 25–29 years, 8.3% in the patient group aged 30–34 years, and reaching 21.7% in the patient group aged >50 years.

It is currently considered that in the absence of an underlying heart disease, isolated PVCs are benign (118). However, in the presence of an underlying heart disease, especially postmyocardial infarction (MI), complex (defined as Lown class 4 or 5) and frequent (defined as >10 PVCs/h (119) or >30 PVCs/h (120)) represent an increased risk factor for mortality (119, 121, 122). Nevertheless, no association was found between isolated PVCs (<10 PVCs/h) and increased mortality, even in this context. Therefore, isolated rare PVCs per se do not justify the performance of an EPS for risk stratification. However, in the case of a high arrhythmic burden or tachycardiomyopathy linked to frequent monomorphic PVCs, the EPS can be performed with the goal of localizing the origin of the PVCs, provided catheter ablation is offered in the same procedure (123–125).

2. Ventricular couplets

Ventricular couplets are present in both patients with and without structural heart disease. However, it seems that there is a significant difference in prognosis between these two groups, and patients without an underlying heart disease have a benign prognosis (118, 126). In patients with an underlying heart disease, especially post -MI, ventricular couplets as well as nonsustained VT and “R on T” PVC were determined as independent risk factors for sudden cardiac death (121).

3. Nonsustained ventricular tachycardia

In the absence of an underlying heart disease, NSVT is not considered as a risk factor for sudden death (118, 127–130). However, with underlying heart disease, it represents a negative prognostic marker. This is particularly true for patients with post-MI (120, 131) but not for patients with idiopathic dilated cardiomyopathy (DCM) (132) nor for causes of heart failure other than ischemic heart disease (133).

Several studies have documented the negative impact of NSVT in patients with post-MI (121, 122, 131). The MUSTT trial (131) showed that in patients with a prior MI, low LVEF% (<40%), and nonsustained VT, an EPS successfully guided therapeutic strategy, thus identifying candidates for ICD implantation. This strategy resulted in a reduction in mortality of 31%.

5.1. Indications for EP study in patients with PVC, Couplets, and NSVT

5.1.1. Class I

None.

5.1.2. Class II

(1) Patients with other risk factors for future arrhythmic events, such as a low EF, positive signal-averaged ECG, and non-sustained VT on ambulatory ECG recordings in whom EPSs will be used for further risk assessment and for guiding therapy in patients with inducible VT (35).
(2) Patients with highly symptomatic, monomorphic premature ventricular complexes (PVCs), couplets, and NSVT who are considered as potential candidates for catheter ablation (35).
(3) In patients with a prior MI, LVEF < 40%, and nonsustained VT, performance of an EPS with programmed ventricular stimulation is indicated for selecting suitable candidates for ICD implantation (134).

5.1.3. Class III

Asymptomatic or mildly symptomatic patients with PVCs, couplets, and nonsustained VT without other risk factors for sustained arrhythmias (35).

4. Sustained monomorphic ventricular tachycardia

a) VT in structurally normal hearts

There are currently several documents that provide an indication for catheter ablation for symptomatic sustained monomorphic VT in patients with a structurally normal heart (135–142). The use of EPS is justified in this scenario before the catheter ablation procedure.

5.2. Indications

5.2.1. Class I

(1) Before catheter ablation, an EPS should be offered to symptomatic patients with surface ECGs highly suggestive of RVOT tachyarrhythmia (135).

5.2.2. Class II

(1) Before catheter ablation of LVOT/aortic cusp/epicardial VT/PVC by experienced operators after failure of one or more sodium channel blockers (class IC agents) or in patients who do not want long-term antiarrhythmic drug therapy should be considered in symptomatic patients (135).

b) VT in patients with structural heart disease

In the presence of structural heart disease, the presence of documented sustained monomorphic VT represents an indication for ICD implantation. Doubtful cases should be managed with EPS. Additionally, in the case of sustained monomorphic VT, if a catheter ablation of VT is planned, an EPS with programmed electrical stimulation precedes the procedure. This is particularly of interest in patients with prior MI, arrhythmogenic right ventricular cardiomyopathy (ARVC) and in patients who develop VT post valvular surgery. In up to 30% of patients who undergo valve surgery, VT occurs mostly within 1 month of surgery and can due to bundle branch re-entry, which is potentially curable by catheter ablation.

5.3. Indication

5.3.1. Class I

(1) An EPS should be performed preceding catheter ablation in patients with monomorphic sustained VT in candidates suitable for catheter ablation, desirably in the same procedure (143).
(2) Patients with wide QRS complex tachycardia in whom correct diagnosis is unclear after analysis of available ECG tracings and for whom knowledge of the correct diagnosis is necessary for patient care (35).

5.3.2. Class II

(1) An EPS with standby catheter ablation should be considered in patients who develop VT following valvular surgery to identify and cure bundle branch re-entry VT (class IIa, level of evidence (LOE) C). (135)

5.3.3. Class III

(1) Patients with VT or SVT with aberrant conduction or pre-excitation syndromes diagnosed with certainty by ECG criteria and for whom invasive electrophysiological data would not influence therapy. However, data obtained at baseline EPS in these patients might be appropriate as a guide for subsequent therapy (35).

5) **Polymorphic ventricular tachycardia**

When present, polymorphic VT is usually in the context of acute myocardial ischemia (144) but can also be present in other situations such as electrolyte imbalance, sinus bradycardia, preceding sinus pauses, or a prolonged QT interval. Catecholaminergic polymorphic VT (CPVT) is an inherited primary arrhythmia manifested with polymorphic VT during exercise or intense emotion.

The EPS has currently no role in the evaluation of these patients.
Indication: none.

6) **Ventricular pre-excitation**

Clinical and therapeutic approach for patients with WPW syndrome may vary according to the presence of WPW-related symptoms.

a) Symptomatic patients (WPW Syndrome)

Typical WPW-related symptoms are palpitations, dyspnea, chest pain, presyncope, syncope, or sudden cardiac death. Patients with resuscitated SCD due to VF secondary to AF with rapid conduction over the accessory pathway have a recommendation for EPS and catheter ablation (35, 88, 89). The same is also true for patients with syncope or palpitations, especially with accessory pathway with the refractory period of $\leq$240 ms, where catheter ablation is a first-line therapeutic option (88, 89). The EPS should target the anterograde and retrograde effective refractory period of the accessory pathway and the shortest R–R interval between two pre-excited QRS complex during induced AF. EPS should also rule out multiple accessory pathways.

5.4. Indication

5.4.1. Class I

1. Patients with ventricular pre-excitation who have survived cardiac arrest (CA) or who have unexplained syncope (35).
2. EPS with the option of ablation is useful for the diagnosis and potential treatment of SVT (89) (class I, LEO B-BR), (88) (class I, LEO B).

5.4.2. Class II
None.

5.4.3. Class III
None.

b) Asymptomatic patients (WPW pattern present on the ECG in the absence of symptoms)

Many studies have provided important data during the last few years, thus helping to solve the controversy related to the performance of the EPS in asymptomatic patients with WPW syndrome. This was mainly because asymptomatic individuals have a low risk of sudden cardiac death and that the EPS may have rare but potentially serious complications.

It is currently known that SCD may be the first presentation of patients with asymptomatic WPW ECG pattern or undiagnosed patients with WPW. The risk of SCD is associated with a history of symptomatic tachycardia, the presence of multiple accessory pathways, and a shortest pre-excited R–R interval of $\leq$240 ms during AF. The risk of SCD is the highest in the first two decades of life, being estimated as 1.3%–1.6% in children (145–149). Even though the risk of SCD is small when this occurs, this has major consequences on the patient and his family; this is the reason why the performance of an EPS is considered as appropriate even in asymptomatic patients with WPW (145). A PACES/HRS official document dedicated to the management of patients with asymptomatic WPW has been published, and it addresses this topic in detail (150).

5.5. Indications (89)

5.5.1. Class I

None.

5.5.2. Class II

2. An EPS is reasonable in asymptomatic patients with pre-excitation to risk-stratify for arrhythmic events. (class IIa, LOE B).
3. Catheter ablation of the accessory pathway is reasonable in asymptomatic patients with pre-excitation if an EPS identifies a high risk of arrhythmic events, including rapidly conducting pre-excited AF (class IIa, LOE B).
4. Catheter ablation of the accessory pathway is reasonable in asymptomatic patients if the presence of pre-excitation precludes specific employment (such as with pilots) (55, 165, 187–193, 207–209) (class IIa, LOE B).
5. Observation, without further evaluation or treatment, is reasonable in asymptomatic patients with pre-excitation (class IIa, LOE B).

6. Role of electrophysiological study in patients with inherited primary arrhythmia syndrome (Channelopathies)

a. Long QT syndrome (LQTS)

Rationale: Torsades de pointes is the most commonly found arrhythmia among patients with long QT syndrome (LQTS) and represents the main mechanism of sudden cardiac death. However, the risk of experiencing SCD is variable, depending on age, sex, and QTc interval duration, being estimated at 15%–70% in a lifetime (151). Identifying patients with a high risk of developing malignant ventricular arrhythmias should be a primary concern.

Evidence: The prevalence of LQTS has been estimated to be 1 in 2,000 live births (152). Currently, 10 types of LQTS have been described, and of them, LQT1, LQT2, and LQT3 account for the majority of cases with an estimated prevalence of 45%, 45%, and 7%, respectively.

The 12-lead ECG is a very useful risk stratification tool in these patients. The risk of SCD is related to the length of the QTc, with patients who have a QTc of >500 ms having a higher risk (153, 154). T wave alternans may be present in patients with LQTS and is a marker of electrical instability. Vijayakumar et al have proposed the use of noninvasive ECG imaging of cardiac electrophysiological substrate mapping as a potential useful tool in risk stratification of patients with LQTS (155).

The usefulness of EPS in risk stratification of patients with LQTS has thus far been disappointing. Bhandari et al conducted a study in 15 patients with LQTS together with prior syncope or aborted SCD (156). Programmed ventricular stimulation failed to induce sustained monomorphic VT in any of the patients. Rapid polymorphic VT was induced in 40% of the patients, with a protocol using up to three extrastimuli with and without isoprenaline administration. However, during a follow-up period of 28 ± 17 months, the presence of NSVT had no prognostic value in identifying high-risk patients for future SCD.

The 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death have established a class III, LOE C for the EPS in the evaluation of patients with LQTS (135).

Indications (135): none (class III, LOE C)

b. Short QT syndrome (SQTS)

Rationale: Short QT Syndrome (SQTS) is a rare cardiac channelopathy diagnosed in the presence of a QTc of ≤330 ms (157) that is associated with an increased risk of malignant ventricular arrhythmias. Risk stratification in this population of patients is still a matter of debate. As CA is often the first manifestation of the disease in this population of patients (158), early identification of high-risk individuals is of great interest.

Evidence: For secondary prevention of sudden cardiac death, ICD implantation is justified and indicated (135, 152), with no role for an EPS. For the primary prevention of SCD, the best diagnostic strategy for identifying patients with the highest risk of SCD has not been established, the main reason being the lack of clear independent risk markers. Syncope and a very short QTc interval do not optimally identify patients with the highest risk of SCD (152).

Giustetto et al (159) performed an EPS with programmed ventricular stimulation in 28 patients with SQTS. Eight patients (28.5%) had a history of CA. During programmed ventricular stimulation, ventricular fibrillation (VF) was induced in 16 patients (57%), of which seven patients (44%) had mechanically induced VF. Among these patients, three had an aborted SCD and five had syncope. Among the 12 patients in which VF was not induced, five had an aborted SCD and two had syncope. On the basis of these results, the EPS sensitivity for the induction of relevant ventricular arrhythmias was low (37%), whereas its negative predictive value was better but still modest (58%).

The 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death have established a class III, LOE C for EPS in the evaluation of patients with SQTS (135).

Indications: none (class III, LOE C) (135)

c. Brugada Syndrome

Brugada syndrome (BrS) is an inherited arrhythmogenic disease that presents with a characteristic ECG and a tendency to develop syncope or CA from VF (160). An ECG aspect of ST-segment elevation of ≥2 mm in the right precordial leads V1 and/or V2 positioned in the second, third, or fourth intercostal space, which occurs either spontaneously or after provocative drug test with intravenous administration of class I antiarrhythmic drugs (such as ajmaline, procainamide, flecainide, or pilsicainide) is considered as causative for the syndrome.

Rationale: In patients with BrS, the incidence of arrhythmic events defined as either sustained VT or VF or appropriate ICD therapy or sudden death syndrome is reported to range from 1% per year in asymptomatic patients to 3.2% per year in patients with syncope and is as high as 13.5% per year in patients with a history of sudden CA (161). Therefore, stratification of CV risk by identifying patients at a higher risk of SCD who are eligible for ICD implantation is of utmost importance.

Evidence: During EPS, programmed ventricular stimulation can induce VF in up to 39% of asymptomatic patients with BrS and in 68–83% of patients with BrS who experienced resuscitated sudden cardiac death or syncope (162), and this is the argument for which the EPS has been proposed to be used for identifying patients prone to develop future episodes of VF; thus, patients are considered as having a high arrhythmic risk. However, there is currently conflicting evidence regarding the usefulness of the EPS in risk stratification for patients with BrS. After an initial positive trend of clinical trials supporting the

usefulness of the EPS in risk stratification of patients with BrS (163–168), several studies have showed that the correlation between VF inducibility at programmed ventricular stimulation and the future occurrence of spontaneous episodes of VF may actually be rather poor (169, 170). This is the main reason why there is yet no consensus about the value of EPS in predicting the outcome of patients with BrS.

In 2003, Brugada et al reported that the inducibility of VF during EPS was an independent predictor for future arrhythmic events (166), and this conclusion also supported by other studies (163–165, 167, 168, 171, 172). Giustetto et al (163) conducted a study on 166 consecutive patients, mean age 45 ± 14 years, of which 135 underwent an EPS. The mean follow-up period was 30 ± 21 months. The authors found that induction of VF during EPS was predictive of future arrhythmic events ($p = 0.004$). They also found that the EPS has a good negative predictive value (none of the patients with a negative EPS result developed arrhythmic events vs. 15% of patients with a positive EPS result). EPS was concluded to be useful in assessing arrhythmic risk in BrS, especially in patients with syncope.

Fauchier et al [161] also found that programmed ventricular stimulation may be useful both in BrS patients with syncope and in asymptomatic patients.

Despite these positive findings supporting the role of EPS in risk assessment of patients with BrS, recent studies have shown different results. The FINGER (France, Italy, Netherlands, GERmany) registry (169) aimed to assess the prognosis and risk factors of SCD in BrS on the largest series of patients with BrS published thus far (1029 consecutive individuals, of which 745 were men, with a median age of 45 years). The mean follow-up period was 31.9 (14–54.4) months. The study found that inducibility of ventricular tachyarrhythmias during EPS was not predictive of future arrhythmic events.

The PRELUDE (Programmed Electrical stimuLation predictive valuE) study (170) was specifically designed to assess the predictive accuracy of sustained VT/VF inducibility during programmed electrical stimulation and to identify additional predictors of arrhythmic events in patients with BrS but without history of VT/VF. The registry included 308 consecutive patients, of which 247 were men, with a median age of 44 years. All patients underwent an EPS at enrolment and were followed up every 6 months. The mean follow-up duration was 34 months. Programmed electrical stimulation was performed according to a standardized protocol. Even though ventricular tachyarrhythmias were induced in 40% of patients, arrhythmia inducibility was not a predictor of events at follow-up because more than half of arrhythmic events (9 of 14 events) occurred in noninducible patients. The conclusion of this study was that VT/VF inducibility during an EPS is unable to identify high-risk patients, and hence, EPS has a poor negative predictive value for the identification of high-risk patients.

Given the conflicting evidence published thus far, the use of EPS for the evaluation of arrhythmic risk in patients with BrS remains debated. However, according to a study performed by Brugada et al published in 2003 (166), the 2015 ESC Guidelines for the management of patients with ventricular arrhythmias established a class IIb, LOE C for ICD implantation considered in patients with a diagnosis of BrS who developed VF during PVS with two or three extrastimuli at two sites, thus suggesting that the EPS may indeed play a role in risk stratification of patients with BrS. Patients with resuscitated sudden cardiac death, those with documented spontaneous VF or sustained VT, and those with a spontaneous type-1 Brugada ECG pattern together with syncope qualify for direct ICD implantation and do not require an EPS for risk stratification. In all the other cases, the indication for an ICD is less obvious and the role of an EPS remains currently less well defined.

6.1. Indications

6.1.1. Class I

None.

6.1.2. Class II

1. EPS has no role in risk stratification in patients with BrS and resuscitated sudden cardiac death, those with documented spontaneous VF or sustained VT, and those with a spontaneous type-1 Brugada ECG pattern together with syncope. In all other cases, the use of the EPS may be discussed on a case-by-case basis (class IIb indication) (152). Programmed ventricular stimulation protocols should avoid a third extrastimulus or stimulation from the right ventricular outflow tract (173).
2. In patients with BrS and inducible VF, as an alternative to ICD therapy, electrophysiology testing with a class 1A antiarrhythmic drug (mainly quinidine) may be considered for assessing treatment efficacy (174) (this practice is currently limited).
3. Assessment of sinus node function and conduction disorders, especially in elderly patients, as well as the induction of SVTs (172).

6.1.3. Class III

1. Routine use for risk stratification in asymptomatic type-2 patients with BrS.

d. **Catecholaminergic Polymorphic VT**

Rationale: CPVT is a rare genetic condition characterized by the presence of polymorphic or bidirectional VT during physical effort or stressful situations, in the absence of a structural heart disease or QT prolongation, which can cause syncope and sudden cardiac death. The diagnosis can sometimes be difficult, as the resting 12-lead ECG is normal in these patients. It is usually based on exercise stress test, Holter ECG monitoring, and ILRs, together with genetic testing (152). Identifying patients who are at high risk of SCD is important, as not all carriers of the mutant genes experience SCD in their lifetime. The presence of aborted SCD is associated with a higher risk of arrhythmic events. The presence of syncope is not an effective predictive marker (152).

Evidence: An EPS for the evaluation of inducible ventricular arrhythmias in patients with CPVT has rarely been performed. Anecdotal cases have been published describing the induction of malignant ventricular arrhythmias during programmed ventricular stimulation (175), but no large randomized controlled trials assessing the role of an EPS in risk stratification of patients with CPVT have been conducted thus far. According to the 2013 HRS/EHRA/APHRS Expert consensus on the diagnosis and management of patients with inherited ventricular arrhythmias, the EPS has no diagnostic or prognostic value in CPVT, as either polymorphic or bidirectional VT is usually not inducible during programmed ventricular stimulation (152, 176, 177). The 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death have established a class III indication for EPS in the evaluation of patients with CPVT (135).

Therefore, the EPS has currently no role in the evaluation of patients with CPVT.

However, an EPS may be considered when catheter ablation of the PVC initiating the ventricular arrhythmia is desired, but current experience is limited (178).

6.2. Indications

None class III C (135)

7. Role of electrophysiological study in patients with progressive cardiac conduction disease (PCCD)

Rationale: Progressive Cardiac Conduction Disease (PCCD) is characterized by the presence of progressive conduction abnormalities in young individuals, usually less than 50 years old, who have otherwise a structurally normal heart, in the absence of skeletal myopathies. The presence of a family history of PCCD strongly supports the diagnosis. The disease cause has recently been found to be genetic in origin, with most forms having an autosomal dominant form of inheritance. The most frequently mutant gene is SCN5A, which explains the sometimes common phenotype with BrS. The most common form is called "Lenègre–Lev disease."

As one of the clinical manifestations of the disease is syncope, there is a justification for considering an EPS in this population of patients.

Evidence: The usefulness of an EPS in patients with PCCD is identifying candidates suitable for PM implantation, given the progressive character of the disease, as patients with a third-degree AVB have a high incidence of sudden death.

Affected individuals can present a wide degree of conduction abnormalities from a mild first-degree AVB to a complete AVB.

In the advanced stages of the disease (second-degree type 1 with symptoms and second-degree type 2 AVB, high-degree AVB, and third-degree AVB), PM implantation is the treatment of choice and no EPS is necessary (152). In patients with permanent or transient third-degree AVB, syncope is associated with an increased incidence of sudden death, regardless of EPS results (179).

Patients with a bifascicular block in association with an infranodal first-degree AVB, who present a concomitant symptomatic, advanced AVB, have an increased incidence of sudden cardiac death, and PM implantation should be performed, with no prior EPS.

Patients with less severe conduction disorders (first-degree AVB) need close follow-up with clinical examination, 12-lead ECG, Holter ECG, and echocardiography, independent of the presence or absence of symptoms, because of the progressive character of the disease.

7.1. Indications

As in patients with acquired AVB (see section 2).

Exception: patients with bifascicular block ± first-degree infranodal AVB, who can undergo PM implantation without prior EPS (152).

8. Role of electrophysiological study in patients with early repolarization syndrome

Rationale: The early repolarization pattern in the infero-lateral leads is associated with idiopathic VF (180, 181).

Definition: Early repolarization pattern + symptoms (resuscitated VF +/- polymorphic VT)

Evidence: Recommendations on the usefulness of EPS in patients with early repolarization syndrome mainly come from the study of Mahida et al (182), who performed programmed ventricular stimulation on 81 patients (age 36 ± 13 years, 60 males) with early repolarization syndrome and aborted sudden death due to VF. VF was inducible in only 22% of patients. During follow-up for 7.0 ± 4.9 years, the recurrence rate of VF, which was 33%, was similar in patients with and without VF induction during EPS. This demonstrated the low accuracy of EPS in identifying patients with a higher risk of recurrence. On the basis of these results, until further evidence, the EPS is believed not to have a role in stratifying arrhythmic risk in patients with early repolarization syndrome.

8.1. Indications

EPS should not be performed in patients with early repolarization pattern and history of syncope in the absence of other indications (class III) (183).

9. Role of electrophysiological study in patients with inherited structural heart disease

a. **Hypertrophic cardiomyopathy (HCM)**

Rationale: Patients with hypertrophic cardiomyopathy (HCM) have a higher incidence of supraventricular and ventricular arrhythmias (184). Ventricular arrhythmias represent an important mechanism of SCD in this population (135). The presence of left ventricular hypertrophy represents a contraindication for some antiarrhythmic medications (such as class IA and IC), and this further limits the therapeutic options to be applied in these patients. Patients with sustained VT or VF require ICD implantation. For the other patients with HCM, identifying patients who are candidates for an ICD, PM, or catheter ablation procedure is desirable.

Evidence: Current guidelines do not support the routine use of EPS for risk stratification in patients with HCM, as the sensitivity of PVS for VT induction in this population of patients is low (135, 184, 185). Furthermore, the routine use of EPS in patients with HCM who experienced syncope or other symptoms suggestive of arrhythmia (palpitations) is not recommended. A significant proportion of syncope in obstructive HCM cases has a hemodynamical cause (186). EPS can be, however, considered in selected cases, if the clinical context is suggestive of an arrhythmia (184).

A recently published report challenged the current guidelines concerning the use of EPS in the risk assessment of patients with HCM. According to Gatzoulis et al (187), who performed programmed ventricular stimulation in 203 patients with HCM together with at least one noninvasive risk factor for SCD, the combination of VT inducibility during PVS and an ESC score of $\geq$6% or an AHA indication for ICD implantation provided a 100% sensitivity and a 100% negative predictive value for identifying patients with HCM and a high and low risk, respectively, for SCD and appropriate ICD therapy. EPS is indicated in patients with SVTs (AFl, AT, AV nodal re-entry tachycardia, and accessory pathway-mediated tachycardias) to establish the correct diagnosis and guide the catheter ablation procedure (188).

Invasive EPS may be considered in selected patients with documented, symptomatic, monomorphic, sustained (>30 s) VT candidates for ablation (189, 190).

In HCM and concomitant rhythm disorders, an EPS may also be performed in those cases in which noninvasive tests suggest the presence of sinoatrial disease or an AVB (10, 88).

9.1. Indications

9.1.1. Class I

(1) Invasive EPS is recommended in patients with documented persistent or recurrent SVT (AFl, AT, AV nodal re-entry tachycardia, accessory AV pathway-mediated tachycardias) and in patients with ventricular pre-excitation candidates for ablation (class I, LOE C) (10, 88, 184, 188)

9.1.2. Class II

(1) Invasive EPS may be considered in selected patients with documented, symptomatic, monomorphic, sustained (>30 s) VT candidates for ablation (class IIb, LOE C) (189, 190).

9.1.3. Class III

(1) Invasive EPS with programmed ventricular stimulation is not recommended for sudden cardiac death risk stratification (class III, LOE C) (184).

b. **Dilated cardiomyopathy (DCM)**

Rationale: Patients with DCM have an increased risk of SCD due to malignant ventricular arrhythmias. Holter ECG monitoring shows the presence of NSVT in up to >70% of patients with DCM (191). Sudden cardiac death is reported in approximately 30%–40% in this subgroup of patients (192). Current risk stratification strategies for identifying patients at high risk of SCD rely mainly on LVEF% measurement. However, on the one hand, this marker fails to identify all patients with DCM who experience SCD, and on the other hand, not all patients with a low LVEF% die suddenly. Therefore, better risk stratification markers are needed.

Evidence: EPS plays a role in patients with DCM from two viewpoints: risk stratification (for identifying patients with a high risk of SCD who may benefit from an ICD implantation) and establishing a diagnosis of a supraventricular or ventricular arrhythmia that is amenable for catheter ablation.

Data about risk stratification of patients with DCM using an EPS are scarce (135, 193). In patients with DCM in which noninvasive methods diagnose sustained monomorphic VT or VF, an ICD implantation is recommended, and an EPS is not necessary. In patients with DCM in which the clinical setting suggests the presence of a sustained ventricular arrhythmia but noninvasive tests have failed to establish the diagnosis, an EPS may be considered.

Gatzoulis et al (194) studied the role of PVS in the primary prevention of SCD in patients with DCM. Even though in their study on 158 patients with DCM PVS was not able to identify patients with a higher mortality risk (the overall mortality did not show significant difference between patients with inducible and noninducible VT/VF during the 46.9 months of mean follow-up), a positive PVS was the only independent prognostic factor for future ICD discharge.

The most common arrhythmias in patients with DCM are ventricular in origin: PVC, NSVT, and less frequently encountered sustained monomorphic VT and polymorphic VT. The most common supraventricular arrhythmias are AF/AFl and AT (184, 195).

9.2. Indications

9.2.1. Class I

None.

9.2.2. Class II

(1) Invasive EPS with PVS may be considered for risk stratification of SCD (class IIb, LOE B) (135).
(2) An EPS may also be considered in patients with DCM who have sustained monomorphic VT to guide the catheter ablation procedure (195, 196).

c. **Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)**

Rationale: Patients with ARVC have a high prevalence of ventricular arrhythmias and an increased risk of sudden cardiac death. Risk stratification in this population of patients is important, as ICD implantation is associated with a reduction in cardiac mortality. Identifying patients with a high risk of ventricular arrhythmias is therefore of great interest.

Evidence: Currently, an EPS is not part of the standard diagnostic workup of patients with ARVC. However, care should be taken in distinguishing several subgroups of patients with ARVC, as the management of these patients differs according to the presence or absence of symptoms (syncope and palpitations), the presence or absence of documented sustained ventricular arrhythmias, and the presence or absence of aborted sudden cardiac death.

Patients with ARVC, aborted sudden cardiac death, and hemodynamically poorly tolerated VT.

The EPS has no role in the management of patients with ARVC, as these patients have a class I indication for ICD implantation (135).

Patients with ARVC and hemodynamically stable documented monomorphic ventricular tachycardia.

Programmed ventricular stimulation has a high sensitivity for arrhythmia induction in patients with ARVC who have documented sustained monomorphic VT (135). However, its role in risk stratification of these patients is debated.

Saguner et al (197) conducted a study on 69 patients with ARVC, of which 44 (71%) had documented sustained monomorphic VT before EPS. During programmed ventricular stimulation, sustained monomorphic VT was induced in 34 patients (55%). VF was induced in 15 patients (24%), but its induction was considered as nonspecific. The Kaplan–Meier survival curve demonstrated an event-free survival benefit (defined as the occurrence of cardiac death, heart transplantation, sudden cardiac death, VF, and VT with hemodynamic compromise or syncope) for patients without inducible sustained monomorphic VT (logrank p [0.008]) with a cumulative survival free from an adverse outcome of 72% (95% confidence interval [CI] 56% to 92%) in the group without inducible SMVT compared to 26% (95% CI 14% to 50%) in the other group after 10 years. The inducibility of SMVT during the EPS (HR 2.99, 95% CI 1.23 to 7.27) was associated with an adverse outcome on univariate Cox regression analysis and on multivariate analysis (HR 2.52, 95% CI 1.03 to 6.16, $p < 0.043$). On the basis of these findings, they concluded that the induction of sustained monomorphic VT during the EPS might predict an adverse outcome in patients with ARVC. Bhonsale et al (198) also found that VT inducibility during EPS is an independent strong predictor of appropriate ICD therapy in patients with ARVC.

In their study of 34 patients with ARVC, Pezawas et al (199) reported the inducibility of sustained monomorphic VT in 19 patients out of 22 who had clinical sustained VT before EPS. The ventricular rates of inducted VTs were similar to those of the clinical VTs. They concluded that in patients with ARVD, the induced VT and follow-up VT correlate well, and therefore, an EPS-guided strategy does not provide relevant additional information.

Therefore, in patients with spontaneously induced VTs, the 2015 ESC Guidelines on the management of patients with VA established a class IIa indication for ICD implantation, thus implying that an EPS is futile in these patients, unless a catheter ablation procedure is considered. If such a procedure is desired, an electro-anatomical mapping system-guided procedure can be performed to demonstrate areas of diseased myocardium and subsequently perform RF ablation (200, 201).

In patients with ARVC and wide-complex QRS tachycardia with left BBB morphology of unknown significance (VT/SVT with aberrant conduction/pre-excitation), when the 12-lead ECG is not helpful in making the differential diagnosis, an EPS should be considered.

Patients with ARVC and symptoms suggestive of malignant ventricular arrhythmia (palpitations and syncope) and/or NSVT but without a history of sustained monomorphic VT.

The EPS should be considered in such patients on the basis of a careful history taking and other useful paraclinical examinations (such as the presence of NSVT at Holter ECG monitoring), as the induction of monomorphic VT during programmed ventricular stimulation should lead to an ICD implantation (135).

Asymptomatic patients with ARVC with no history of sustained monomorphic VT.

The routine use of EPS in asymptomatic patients with ARVC without a history of sustained monomorphic VT is not recommended because the predictive value of inducibility of VT for the occurrence of VT during follow-up has been unsatisfactory (positive predictive value: 49%, negative predictive value: 54%). In their prospective multicenter study, Corrado et al (201) showed that patients at a high risk of ventricular arrhythmias could be identified on the basis of clinical presentation, irrespective of the electrophysiological study results.

9.3. Indications

9.3.1. Class I

None.

9.3.2. Class II

Invasive EPS with PVS may be considered for stratification of SCD risk (class IIb, LOE C) (135)

d. **Left ventricular noncompaction (LVNC)**

Rationale: There is increasing evidence that patients with LV noncompaction (LVNC) have a higher incidence of arrhythmias than the general population. However, no specific electrocardiographic or echocardiographic finding is predictive of VT inducibility (202). There is currently no consensus on the management of arrhythmias in these patients, and large evidence-based studies are lacking.

Evidence: Few relevant studies have been conducted in patients with LVNC and even fewer addressing arrhythmic risk stratification using an EPS in these patients. Steffel et al (202) performed an EPS in 24 patients with LVNC and induced ventricular arrhythmias in nine patients: three patients had monomorphic VT, two patients had VF, and five patients had nonsustained polymorphic VT. Supraventricular arrhythmias were inducible in seven patients (29.1%). During a follow-up period of 61.4 ± 50 months, of the nine patients with inducible VT, only three patients had VT recurrence, whereas for the 12 patients with no-inducible VT during the EPS, no VT recurrence was noted after a follow-up period of 30 ± 19 months, thus suggesting a good negative predictive value but a modest positive predictive value.

In their study, Kobza et al (203) showed that ICD implantation may be appropriate in patients with LVNC, both for primary and for secondary prevention of SCD, but an EPS was not used to guide ICD implantation in these patients (ICD implantation was based on the presence of malignant ventricular arrhythmias and/or the presence of a severely reduced LVEF%). Out of 12 patients with LVNC, 42% presented with appropriate ICD interventions after a follow-up period of 36 months. SVTs were frequent and present in 66% of their patients.

On the basis of these limited data, the role of EPS in establishing arrhythmic risk in this population of patients is currently vaguely determined. Its routine use in patients with LVNC should be discouraged. It might be considered in selected high-risk patients, with a history suggestive of malignant ventricular arrhythmias.

Indications: none (specific)

e. **Muscular Dystrophies**

Rationale: Muscular dystrophies represent a group of genetic diseases characterized by muscular weakness and rhabdomyolysis from a young age. There are currently nine types of muscular dystrophies. The two most common forms are represented by the X-linked Duchenne (DMD) and Becker (BMD) muscular dystrophies, with DMD being about three times more frequent than BMD (204). An overlap between the two above-mentioned types of dystrophies exist, i.e., the “intermediate muscular dystrophy” (IMD), which includes patients who are more severe than most BMD but less severe than typical DMD.

Myotonic dystrophy is another type of muscular dystrophy that has an autosomal-dominant inheritance. It is of two types: type 1 (DM1) due to mutations in the DMPK gene and type 2 (DM2) due to mutations in the CNBP gene.

Patients with muscular dystrophies develop a type of cardiomyopathy characterized by myocardial fibrosis, diastolic dysfunction (205–207), systolic dysfunction, and conduction disorders (208–210). For BMD, the incidence of cardiomyopathy is approximately 25% by the age of 6 years and almost 60% at 10 years (211, 212). As the prevalence of conduction disorders is high in patients with muscular dystrophies, regular Holter ECG monitoring is recommended (208–210). The prevalence of sudden death in this population of patient is significant, being mostly due to a paroxysmal complete AVB and sometimes due to malignant ventricular arrhythmias (213, 214).

The role of EPS is to identify patients with conduction disorders who require PM implantation.

Evidence: In patients with myotonic dystrophy, ECG alone is insufficient in identifying patients with severe conduction disorders. Simeon et al (215) performed 12-lead ECGs followed by an EPS on 212 patients with type 1 myotonic dystrophy (mean age 41 ± 13 years, males 48.6%). They found a high prevalence of a prolonged HV interval at EPS, with 90 patients (42.5%) having an HV interval of >70 ms. Sixty-four patients with abnormal ECG (63.4%) had a prolonged HV interval, but 23% of patients with a normal resting ECG also had a prolonged HV interval. During follow-up, complete AVB occurred in 31 of 206 cases (15%), with a rate of 2.5% per year. Importantly, the risk of AVB occurrence was not significantly different between patients with abnormal ECG and prolonged HV interval compared to patients with normal ECG and a prolonged HV interval (HR = 0.98; 95% CI = [0.40–2.35]; p = 0.95), stressing out the limited value of the 12-lead ECG in correctly identifying those patients with severe infrahisian conduction disorders (HV interval > 70 ms). The occurrence of AVB was higher in the presence of prolonged HV interval, independent of the resting ECG (p = 0.003). In the same study, at multivariate analysis, the two factors related to AVB occurrence were syncope and an HV interval ≥70 ms, thus pointing out the positive role of the EPS in identifying those patients with conduction disorders who require PM implantation. The authors suggested that an EPS should be systematically performed in adults with type 1 myotonic dystrophy, regardless of the resting ECG aspect (normal/abnormal).

The observation that a prolonged HV interval is predictive of complete AVB occurrence during follow-up has been suggested by other authors. In their study conducted on 100 patients with myotonic dystrophy, Laurent et al (216) assessed whether the implantation of a prophylactic PM in those patients with HV interval of ≥70 ms lowered the risk of sudden death; the risk attributed mainly to complete AVB occurrence. Forty-six patients were considered at risk of sudden death according to the criteria of Groh et al. (217). During an average follow-up for 74 ± 39 months, of the 49 who had PM implantation, only one sudden death occurred, thus demonstrating the importance of PM implantation in this population of patients.

Wahbi et al. (218) performed a retrospective study on 914 patients with confirmed type 1 myotonic dystrophy. An EPS was performed in 341 patients (70.2%), followed by implantation of a PM in those patients with an HV interval of >70 ms. During a median follow-up period of 7.4 years, PM implantation reduced sudden death compared to patients followed by ECG assessment

only (HR = 0.47, 95% CI, 0.26–0.84; p = 0.01). Overall, patients with conduction disease had a poorer survival, irrespective of the result of EPS, compared with those without. These data provide evidence that EPS is a useful tool in the management of patients with myotonic dystrophy. However, even after adjustment for baseline characteristics, there was just borderline statistical significance for an increase in survival in patients who underwent PM implantation compared to those who underwent a noninvasive strategy; as a result, the 2013 ESC Guidelines on the management of patients with bradyarrhythmias concluded that the small improvement observed in the overall survival of patients implanted with a PM in the study of Wahbi et al does not allow to draw firm conclusions.

9.4. Indications

9.4.1. Class I

None.

9.4.2. Class II

(1) An EPS may be performed in adult patients with myotonic dystrophy, even in the absence of conduction disorders on the surface ECG to identify patients with an increased risk for AVB development (HV > 70 ms), who can benefit from PM implantation (215–218).

10. Role of electrophysiological study in patients with acquired structural heart disease

a. Ischemic heart disease

Rationale: Coronary artery disease is a major cause of sudden cardiac death, with VT and VF being the underlying mechanisms in an important percentage of patients (219, 220). However, not all patients with ischemic heart disease experience significant ventricular arrhythmias throughout their lifetime. Therefore, prediction of the patients who have an increased risk of life-threatening ventricular arrhythmias is important. The role of the EPS in patients with coronary artery disease is to 1) assess the inducibility of VT in high-risk patients for ventricular arrhythmia occurrence; 2) evaluate loss of consciousness in selected patients with ventricular arrhythmias suspected as a cause; 3) assess the risks of recurrent VT or SCD; 4) assess the indications for ICD therapy, and 5) guide catheter ablation in appropriately selected patients.

Evidence: Three distinct clinical situations exist:

1) Patients with stable coronary artery disease in the absence of myocardial infarction

These patients do not have a straightforward indication for an EPS, unless the clinical context suggests the presence of an arrhythmia or conduction disorder or another element that might justify the performance of an EPS.

2) Patients with an acute coronary syndrome, within the first 48 hours

These patients do not have an indication for an EPS, as arrhythmias occurring during the first 48 hours after MI are not necessarily correlated with future arrhythmic events, even though controversies on this topic still exist (221, 222). Correction of acute ischemia is of utmost importance.

3) Patients post myocardial infarction

Three different time periods must be considered: a) the early phase after MI (first 40 days), b) the subacute phase (40 days–6 months after the MI), and c) the remote phase (>6 months after the MI). Along with LVEF, the EPS has been the only method tested in a randomized clinical trial that resulted in a mortality reduction when used to guide ICD implantation in the early, subacute, and remote phases after MI.

a) Early phase:

The rational argument for performing an EPS early after MI for risk stratification comes from animal studies, which showed that an electrical substrate that can sustain re-entry ventricular arrhythmias is present as early as day 8 after MI (223).

However, data from clinical trials supporting the role of EPS in risk stratification early after MI are contradictory. DINAMIT (224), BEST-ICD (225), and IRIS trials (226) have failed to show an overall survival benefit in the group of patients with EPS-guided ICD implantation. Contrary to these findings, in a subgroup of patients from the MUSTT trial (134), there was an overall survival benefit with an EPS-based ICD implantation strategy. In the Weastmed EPS/ICD observational studies (225), performance of an EPS early after MI resulted in a 2 year arrhythmia recurrence of 22% in the positive EPS group vs. 4% in the negative EPS group. Two other studies showed that performance of an EPS early after MI (median of 9 days after the acute event) was able to correctly identify patients at high risk for future arrhythmic events who benefit from an early ICD implantation (227, 228).

Patients with inducible VT during the EPS had high rates of recurrent VTs, with a significant proportion occurring early post-MI. Such strategy of early post-MI EPS-guided ICD implantation resulted in a low overall mortality.

The same group of authors subsequently showed that patients with impaired LVEF (FE < 40%) and a negative EPS have a low arrhythmia or sudden death rate in the absence of an ICD, thus suggesting a potential role for EPS in selecting candidates for ICD implantation in the early phase post-MI (229).

In conclusion, data from a randomized ICD trial showed a nonsignificant survival benefit of an early EPS-guided strategy of ICD implantation (225). Data from observational ICD studies showed that a positive EPS is able to correctly predict arrhythmia occurrence (227, 228), and a negative EPS is able to correctly predict survival in the absence of an ICD implantation (228). On the basis of these data, the benefit of an EPS-guided ICD implantation strategy in the early phase after MI currently remains unproven (230–232).

Indication: There is currently no indication for an EPS performance in the early phase after MI (class III).

b) Subacute phase after MI (40 days–6 months)

Data supporting the use of an EPS-guided risk stratification strategy in these phases after MI are more congruent. Two large multicenter studies have demonstrated the utility of EPS in identifying patients at high risk of ventricular arrhythmia recurrence.

In the Alternans Before Cardioverter Defibrillator (ABCD) trial (233), in patients with MI and reduced LVEF% (≤40%), EPS had a positive and a negative predictive value of 11% and 95%, respectively, in predicting appropriate ICD discharge or sudden death at 1 year.

In the Cardiac Arrhythmias and Risk Stratification After Acute Myocardial Infarction (CARISMA) trial (234), induction of sustained monomorphic VT during the EPS correctly predicted the future occurrence of spontaneous VT/VF.

c) Remote phase after MI (>6 months)

Data from the utility of EPS in this phase after a MI come from both observational studies and randomized clinical studies (131, 233, 235–241), most notably MADIT (237), MADIT II (242), and MUSTT (131).

In the MADIT trial (237), selecting candidates for ICD implantation on the basis of the LVEF% and the results of the EPS resulted in an absolute mortality reduction of almost 23%.

In the MADIT II trial (242), patients with a prior MI and advanced left ventricular dysfunction (LVEF% < 30%) underwent ICD implantation without a prior EPS. This strategy resulted in a substantial decrease in the risk of mortality (HR = 0.69, 95% CI, 0.51 to 0.93; P = 0.016) compared to patients who received medical therapy alone.

The MUSTT trial (131) demonstrated that in patients with a prior MI, low LVEF% (<40%), and nonsustained VT, an EPS-guided strategy to select suitable candidates for ICD implantation was translated into a reduction in mortality of 31%. In this study, a combination of LVEF% and the results of the EPS resulted in a mortality reduction that was more important than the one observed in the MADIT II trial (more than fourfold of the 5.6% reduction), which used the LVEF% as the sole criteria for selecting patients for ICD implantation.

However, even if LVEF% and EPS are taken together, their positive and negative predictive values are far from perfect, and studies have shown that combining several variables such as functional class, history of heart failure, nonsustained VT not related to bypass surgery, age, left ventricular conduction abnormalities, enrolment as an inpatient, and AF with the LVEF and the result of the EPS represents a better strategy to refine candidates for ICD implantation than a reduced EF alone, which predicts a 2 year arrhythmic death risk of <5% (243).

In conclusion: Randomized ICD trials have demonstrated the role of EPS, especially in combination with a reduced LVEF% and other variables, in appropriately selecting candidates for ICD implantation, which translates into a survival benefit in clinical practice.

4. Patients postantiarrhythmic surgery

The 2015 ESC guidelines for the management of patients with ventricular arrhythmias (135) recommend surgical ablation guided by preoperative and intraoperative electrophysiological mapping in experienced centers for patients with VT refractory to antiarrhythmic drug therapy after failure of catheter ablation by experienced electrophysiologists (Class I indication, LOE B) (244–247).

Surgical ablation is also recommended at the time of cardiac surgery (coronary artery bypass or valve surgery) in patients with clinically documented VT or VF after failure of catheter ablation (Class IIb indication, LOE C) (248, 249).

After surgery, VT recurrence is reported to be 10–20%, occurring predominantly during the first 90 days after surgery (245).

The median time to the first ICD therapy from the time of left ventricular reconstruction was reported to be 43 days, and most first therapies (67%) occur within the first 63 days (247).

An EPS is therefore desirable in patients who underwent antiarrhythmic surgery to test for the inducibility of VT and select potential candidates for ICD implantation.

10.1. Indications

10.1.1. Class I

(1) EPS in patients with CAD is recommended for diagnostic evaluation of patients with remote MI with symptoms suggestive of ventricular tachyarrhythmias, including palpitations, presyncope, and syncope (135, 250).

10.1.2. Class II

(1) In patients with previous MI and BBB, EPS with programmed ventricular stimulation is particularly advisable (10).
(2) EPS with programmed ventricular stimulation should be considered in survivors of a MI with preserved LV function and otherwise unexplained syncope (135, 251) (class IIa, LOE C)
(3) In patients with a prior MI, LVEF <40%, and nonsustained VT, performance of an EPS with programmed ventricular stimulation is indicated for selecting suitable candidates for ICD implantation (134).
(4) In patients who underwent antiarrhythmic surgery, an EPS should be performed 2 weeks–6 months after the procedure to evaluate the result of surgery and select potential candidates for ICD implantation (135).

b. **Infiltrative Disease**

10.1.3. Amyloidosis

Rationale: Cardiac amyloidosis is sometimes complicated by conduction disorders. EPS can identify patients who require PM implantation.

Evidence: There are very limited data in literature about the usefulness of EPS in patients with amyloidosis. Several isolated case reports indicate the diagnostic role of EPS in characterizing conduction abnormalities in patients with amyloidosis and cardiac involvement (252–254). In the largest study published thus far, involving 25 patients with biopsy-proven AL amyloidosis and cardiac involvement, Reisinger et al (255) performed an invasive EPS with the goal of assessing the spectrum of electrophysiological abnormalities and their prognostic implications, especially in relation to sudden cardiac death. The main abnormality found was alteration of the infrahisian conduction, expressed by a prolongation of the HV interval, with a mean HV of 79 ± 18 ms (range 50–110 ms), with 23 patients (92%) having abnormal values. Twenty-three patients died during the follow-up period, with a median duration of survival of 3 months (range 0.5–50). By using multivariate analysis, a prolonged HV interval was found to be the only independent predictor of sudden death ($p < 0.05$), thus suggesting a possible role for EPS in the diagnosis management of patients with cardiac amyloidosis. Larger studies are needed to better understand the role of EPS in this population of patients.

EPS may identify patients who are at high risk of sudden death by identifying those patients with a prolonged HV interval (255). Until further evidence, the indication to perform an EPS depends on the severity of the conduction disorder and should follow current international recommendations (10).

Indications: none specific.

10.1.4. Sarcoidosis

Rationale: Cardiac sarcoidosis is complicated by conduction disorders and ventricular arrhythmias, which can clinically manifest as syncope or sudden cardiac death. The substrate of ventricular arrhythmias is usually represented by fibrosis of the right and

left ventricles, which favor the development of macro-re-entry circuits. EPS may help identify patients at risk for malignant ventricular arrhythmias. Several reports exist on catheter ablation being effective in the treatment of atrial and ventricular arrhythmias in patients with cardiac sarcoidosis. Ablation with or without antiarrhythmic drugs is presently a treatment option for VT in this high-risk population, even though recurrences are common.

Evidence: The 2017 ACC/AHA/HRS Guidelines for the Evaluation and Management of Patients With Syncope indicate a class IIa for EPS performance in patients with sarcoidosis and syncope, in whom an arrhythmic etiology is suspected (183). However, recent data show that EPS may also play a role in asymptomatic patients with cardiac sarcoidosis. On the basis of the premise that in patients with sarcoidosis cardiac involvement is often silent and may lead to sudden death, Mehta et al (256) performed programmed ventricular stimulation in 76 asymptomatic patients with biopsy-proven sarcoidosis who had evidence of cardiac sarcoidosis on positron emission tomography or cardiac MRI and induced VT in eight patients (11%). These patients subsequently received an ICD implantation. After a median follow-up of 5 years, six of the eight patients with inducible ventricular arrhythmias had recurrent VTs or died, versus 1 of 68 patients in the noninducible group, thus suggesting a good positive and negative predictive value of EPS in patients with cardiac sarcoidosis.

There are currently data in literature reporting on the success of the catheter ablation procedure in patients with sarcoidosis who develop atrial (257) or ventricular arrhythmias (258–268). An EPS always precedes a catheter ablation procedure, thus making it a useful diagnosis tool in patients in whom a catheter ablation procedure is desired. However, recurrences are common after RF catheter ablation in this patient population, with some requiring multiple ablation procedures, antiarrhythmic medication, and ICD implantation (256, 259, 263, 269).

10.2. Indication

10.2.1. Class I

None.

10.2.2. Class II

(1) EPS is reasonable in patients with cardiac sarcoidosis and syncope of suspected arrhythmic etiology (183, 256)
(2) EPS may be considered for the differential diagnosis of VT arising from the right ventricle in ARVC, benign RVOT tachycardia, or sarcoidosis (270).
(3) EPS may be considered preceding catheter ablation in patients with documented ventricular arrhythmias, in whom such a procedure has been chosen as a treatment strategy.

11. Role of EPS in patients with congenital heart disease

Rationale: Patients with CHD have a higher incidence of arrhythmias and conduction disorders than the general population. The spectrum of arrhythmias is wide, which ranges from isolated premature atrial or ventricular contraction, AF, AFl to sustained hemodynamically unstable VT and VF. Conduction disorders comprise SND, AV conduction disorders, and intra-atrial or intraventricular conduction disorders. Clinical manifestations vary from the absence of symptoms to palpitations, chest pain, dyspnea, presyncope, syncope, and sudden cardiac death. Sudden cardiac death is mainly due to malignant ventricular arrhythmias. Its annual incidence is reported to be 0.09% per year in the entire CHD population (271). CHD with the greatest known risk of late SCD are ToF, TGA, ccTGA, aortic stenosis (AS), and UVHs (272, 273). Identifying patients at risk for sudden cardiac death is of great interest, as ICD implantation is associated with a reduction in mortality in these patients (274, 275).

The role of the EPS in patients with CHD is 1) to diagnose and determine the nature of arrhythmia in patients with CHD and clinical suspicion of rhythm disorders (e.g., palpitations); 2) to evaluate the cause of unexplained syncope (arrhythmia, conduction disorder, and others); 3) to identify patients who are eligible for device implantation (PM and ICD); 4) before catheter ablation of supraventricular or ventricular arrhythmias; and 5) to establish prognosis.

Evidence:

Arrhythmias in patients with CHD

Risk estimates for supraventricular and ventricular arrhythmias as well as for various conduction disorders in heart defects (CHD) of simple, moderate, and severe complexity have been published elsewhere (275).

In what concerns the development of supraventricular arrhythmias, it is believed that about half of 20 year olds with CHD will develop an atrial tachyarrhythmia during their lifetime (276). The prevalence of ventricular arrhythmias is variable, depending on the type and severity of the CHD. They are infrequent in patients with Mustard, Senning, and Fontan surgery. Isolated PVCs are more frequent in valvular aortic stenosis, pulmonary stenosis, and ventricular septal defect. VTs occur with a reported incidence of 1–2% over 5 years for young adults with tetralogy of Fallot (275).

In patients with CHD, EPS may play a role in risk assessment of some types of CHD, such as in patients with tetralogy of Fallot. Khairy et al (277) reported in a study on 252 patients with repaired tetralogy of Fallot that inducible sustained monomorphic and polymorphic VT during programmed ventricular stimulation was an independent risk factor for the future development of clinical VT and sudden cardiac death. However, programmed ventricular stimulation is not recommended as a general risk assessment tool for all patients with tetralogy of Fallot, and the exact role of PVS for correctly identifying candidates for RF ablation and ICD implantation needs to be further elucidated (278). Programmed ventricular stimulation should be performed in patients with additional risk factors, such as left ventricular systolic or diastolic dysfunction, nonsustained VT, QRS duration of $\geq$180 ms, and extensive right ventricular scarring (277).

In other forms of CHD, such as transposition of the great arteries with intra-atrial baffles, EPS seems to offer little prognostic value (279).

Conduction disorders in patients with CHD

The most frequently encountered conduction disorders in CHD are SND, BBB, and nonspecific intraventricular conduction disorders. Different degrees of AVB may also be encountered.

CHD that is associated with conduction disorders more frequently includes atrial septal defect, AV septal defects, and Ebstein's anomaly but can be found in almost any CHD, depending on the severity of the condition and the surgical status (corrected/not corrected).

In patients with an atrial septal defect, SND was reported to develop in 36% of patients and complete AVB in 14% of patients. Development of late SND and complete AVB does not seem to be related to redo procedures (280).

In Ebstein's disease, RBBB and first-degree AVB are common findings. In the absence of ventricular pre-excitation (after catheter ablation of associated accessory pathways), RBBB is found in up to 94% of patients (281).

Indications for EPS for the assessment of conduction disorders in CHD follow the same recommendations as those for the general population (see sections 1, 2, and 3).

11.1. Indications

11.1.1. Class I

1. Electrophysiological testing is indicated in adults with unexplained syncope and "high-risk" CHD substrates associated with primary ventricular arrhythmias or poorly tolerated atrial tachyarrhythmias, such as tetralogy of Fallot, transposition of the great arteries with atrial switch surgery, or significant systemic or single ventricular dysfunction *(LOE C)* (80, 277, 282).
2. Patients with spontaneous sustained VT should undergo invasive EP evaluation if catheter ablation is contemplated (283).

11.1.2. Class IIa

1. Electrophysiological testing with programmed atrial and ventricular stimulation can be useful in adults with CHD and life-threatening arrhythmias or resuscitated sudden cardiac death when the proximate cause for the event is unknown or there is potential for therapeutic intervention at the time of the electrophysiological procedure *(LOE B)*. (272, 277, 279, 284, 285).
2. Programmed ventricular stimulation can be useful in risk stratifying adults with tetralogy of Fallot who have additional risk factors for sudden cardiac death, such as left ventricular systolic or diastolic dysfunction, nonsustained VT, QRS duration of $\geq$180 ms, and extensive right ventricular scarring *(LOE B)* (277, 282, 286–288).
3. Invasive EP evaluation is reasonable in patients with unexplained syncope and impaired ventricular function. In the absence of a defined and reversible cause, ICD implantation is reasonable (272).

11.1.3. Class IIb

1. Electrophysiological testing may be considered in adults with CHD and palpitations suggestive of sustained arrhythmia when the conventional diagnostic workup is unrevealing *(LOE C) (272).*
2. EP testing may be considered for patients with ventricular couplets or nonsustained VT to determine the risk of sustained VT (272).

11.1.4. Class III

1. Programmed ventricular stimulation is not indicated as a screening tool to routinely risk stratify patients with tetralogy of Fallot at large *(LOE B) (277, 278).*
2. Programmed ventricular stimulation does not appear to be of value for risk stratifying adults with transposition of the great arteries with prior atrial switch surgery, in the absence of symptoms *(LOE B)* (279)
3. Prophylactic antiarrhythmic therapy is not indicated for asymptomatic patients with isolated premature ventricular beats (272).

11.2. Recommendations for electrophysiological study prior to adult CHD surgery

11.2.1. Class IIa

A preoperative EPS can be useful in adults with CHD together with any of the following criteria to identify and map arrhythmia substrates that may be addressed surgically with ablation or incisional lesion sets:

1. History of unexplained syncope or sustained VT not attributed to correctable predisposing causes *(LOE B)* (277, 289–294).
2. Documented sustained SVT, excluding AF *(LOE C)* (289, 292, 295).
3. Ventricular pre-excitation (*LOE B/C*) (150, 296, 297).

11.2.2. Class IIb

A preoperative EPS may be considered in adults with CHD and any of the following criteria to identify and map arrhythmia substrates that can be addressed surgically with ablation or incisional lesion sets:

1. Nonsustained rapid atrial or ventricular tachyarrhythmias *(LOE C)* (292, 298).
2. Moderate or complex CHD known to be at high risk for atrial arrhythmia development but without documented sustained arrhythmia *(LOE C)* (299).
3. History of palpitations or symptoms thought to be related to arrhythmia *(LOE C)* (275).
4. AF in the setting of a triggering supraventricular arrhythmia *(LOE C)* (300).

11.2.3. Class III

1. A preoperative EPS is not indicated in adults with simple forms of CHD, no history of palpitations or arrhythmia symptoms, and no significant documented arrhythmia by noninvasive testing *(LOE C)* (275).
2. A preoperative EPS is not indicated in adults with CHD and permanent or persistent AF without evidence of a triggering supraventricular arrhythmia *(LOE C)* (275).

12. Role of electrophysiological study in patients with unexplained syncope

The utilization of the EPS in evaluating patients with syncope has lately been decreasing, especially because of the rapid development of long-term heart rhythm monitoring devices such as loop recorders, which have a higher capability of identifying the arrhythmic origin of syncope, and because of changes in recommendations of management of patients with syncope in the context of a low LVEF (301). These patients currently have an indication for an ICD implantation, regardless of the mechanism of syncope (135, 302). Registry data show that <2% of patients with unexplained syncope evaluated by cardiologists undergo EPS (303–308).

The diagnostic yield of the EPS for determining the cause of syncope varies greatly according to the pretest probability (309, 310) and to the EPS protocol used by the operator. In patients with established heart disease and a high pretest probability, the prevalence of a positive test is approximately 50% (311), whereas in patients without heart disease, it is only approximately 10%.

Rationale: To identify the cause of syncope in patients with 1) suspected intermittent bradycardia, 2) in patients with BBB, and 3) in patients with suspected tachycardia. The main mechanisms of syncope in these patients are conduction disorders and supraventricular and ventricular arrhythmias.

Evidence: The strongest evidence on the usefulness of the EPS in diagnosing the cause of syncope discussed in the present document relies on the 2009 ESC Guidelines on the management of patients with syncope (301) and on the 2017 ACC/AHA/HRS Guideline for the Evaluation and Management of Patients with Syncope (183). Both these documents cite the same studies (77, 311–317) performed on a number of 625 patients with syncope who underwent an EPS, which showed that positive results occur mainly in patients with structural heart disease (coronary artery disease, valvular disease, cardiomyopathy, and conduction disorders). Of the 406 patients with either established cardiac disease or an abnormal 12-lead ECG, 41% had a positive EPS (of them, 21% had VT and 34% had a bradycardia) (311); of the 219 patients without known cardiac disease, only 5% had a positive EPS (1% with VT and 10% with evidence of substrate for symptomatic bradycardia).

The sensitivity and specificity of the EPS to establish the diagnosis of SND and AV conduction disorder in patients with syncope are variable, depending on patients' characteristics and on the pretest probability of a bradycardia mechanism (16, 56, 318). Induction of VT at programmed ventricular stimulation carries a poor prognosis, while the lack of induction predicts a low risk of future VT occurrence (319).

The role of the EPS in patients with syncope due to suspected ventricular arrhythmias in the context of an acquired nonischemic heart disease remains less clearly defined (320–325) (193–198).

As a general rule, in patients with syncope, an EPS is recommended when bradyarrhythmias or tachyarrhythmias are suspected on the basis of the patient's clinical symptoms (e.g., palpitations) and results of noninvasive tests, especially in patients with structural heart disease (class IIa indication (183)). EPS is not recommended in patients with syncope and a normal ECG in the presence of a normal cardiac structure and function, unless an arrhythmic etiology is suspected (class III indication (183)).

12.1. Indications (326)

12.1.1. Class I

(1) In patients with ischemic heart disease, EPS is indicated when initial evaluation suggests an arrhythmic cause of syncope, unless there is already an established indication for ICD (LOE B).
(2) In patients with unexplained syncope and bifascicular block, EPS is highly sensitive in identifying patients with intermittent or impending high-degree AVB (10, 327)

12.1.2. Class IIa

None.

12.1.3. Class IIb

(1) In patients with syncope preceded by sudden and brief palpitations, EPS may be performed when other noninvasive tests have failed to make the diagnosis.
(2) In patients with BrS, ARVC, and HCM, an EPS may be performed in selected cases (LOE C).
(3) In patients with high-risk occupations, in whom every effort to exclude a cardiovascular cause of syncope is warranted, an EPS may be performed in selected cases (LOE C).

12.1.4. Class III

(1) EPS is not recommended in patients with normal ECG, no heart disease, and no palpitations (LOE B).

12.2. Diagnostic criteria (326)

1. EPS is diagnostic, and no additional tests are required, in the following cases:
   a. Sinus Bradycardia and prolonged CSNRT (>525 ms) (class I, LOE B).
   b. BBB and either a baseline HV interval $\geq$100 ms or second- or third-degree His-Purkinje block is demonstrated during incremental atrial pacing, or with pharmacological challenge (class I, LOE B).
   c. Induction of sustained monomorphic VT in patients with previous MI (class I, LOE B).
   d. Induction of rapid SVT, which reproduces hypotensive or spontaneous symptoms (class I, LOE B).
1. An HV interval between 70 and 100 ms should be considered diagnostic (class IIa, LOE B).
2. The induction of polymorphic VT or VF in patients with BrS, ARVC, and patients resuscitated from CA may be considered as diagnostic (class IIb, LOE B).
3. The induction of polymorphic VT or VF in patients with ischemic cardiomyopathy or DCM cannot be considered as a diagnostic finding.

13. Role of electrophysiological study in survivors of cardiac arrest

Rationale: Sudden cardiac death due to CA is sometimes the first manifestation of a cardiac disease. The four mechanisms underlying sudden CA are VF, VT, asystole, and pulseless electrical activity (former electromechanical dissociation). Resuscitated patients who have VF or VT as the underlying mechanism not related to a reversible acute cause may benefit from an ICD implantation. EPS with programmed ventricular stimulation plays a role mainly in identifying patients who suffered the CA due to VT. A transitory reversible cause (such as the first 48 hours of an acute myocardial ischemia episode; electrolyte disorders: hyper/hypokalemia, hyper/hypocalcemia, and hypomagnesemia; and endocrine diseases: thyrotoxicosis) should be excluded before the performance of an EPS.

Evidence: Sudden cardiac death usually occurs in patients with (overt or underdiagnosed) structural heart disease. The risk of recurrent CA remains high after an initial event. Several clinical studies performed in the 1980s have showed that, in the absence of antiarrhythmic drugs, ventricular arrhythmias (including nonsustained or sustained monomorphic VT, polymorphic VT and VF) can be induced in a high number of patients with resuscitated CA (between 58% and 81%) (219, 220, 328–331). Sustained monomorphic VT can be induced in up to 50% of these patients. Antiarrhythmic drugs often fail to prevent recurrent ventricular arrhythmia episodes in such patients and are not superior to placebo in reduction of overall mortality (332). Moreover, a strategy based on antiarrhythmic drug administration and testing of ventricular arrhythmia inducibility during an EPS is not useful in correctly identifying patients at high risk of future recurrences and such a strategy is considered as obsolete (see section 15).

Unlike antiarrhythmic drugs, ICD implantation decreases mortality in survivors of CA due to VFib/VT (333). Documenting a potentially lethal arrhythmia preceding the sudden CA episode justifies the implantation of an ICD in the secondary prevention of SCD (class I indication), after exclusion of an acute, reversible cause.

The performance of an EPS in such a case is futile, as its result does not alter patient management. However, even in the absence of documentation of a malignant ventricular arrhythmia shortly preceding the CA episode, if the clinical suspicion for such an entity is high, an ICD implantation should be performed (135, 334–336).

Contrary to this strategy, less robust evidence suggests that performance of an EPS may be routinely justified before ICD implantation (337). EPS provides a benefit in risk stratification for future tachyarrhythmic events and SCD and should particularly be considered in patients with LVEF ≥35% (338).

In survivors of CA with no apparent underlying structural heart disease (based on the 12-lead ECG, transthoracic echocardiography, and no evidence of coronary artery disease), the CASPER registry (339) data showed that a staged cascade screening strategy, which includes the performance of an EPS along with a 12-lead ECG, signal-averaged ECG, telemetry, cardiac MRI, provocative exercised-based or pharmacological tests (epinephrine infusion, procainamide), ventricular biopsy, and genetic testing, was associated with an increased diagnostic accuracy.

In conclusion, in survivors of CA, the currently generally accepted attitude is direct ICD implantation without prior performance of an EPS, with rare exceptions.

13.1. Indications

13.1.1. Class I

None.

13.1.2. Class II

(1) Patients surviving CA caused by bradyarrhythmia (35).
(2) Class IIb – survivors of CA with no apparent underlying structural heart disease after initial evaluation including a 12-lead ECG, echocardiography, signal-averaged ECG, cardiac MRI, provocative exercised-based or pharmacological tests (epinephrine infusion, procainamide), with or without ventricular biopsy with or without genetic testing (181).

13.1.3. Class III

(1) Patients surviving a CA during the acute phase (<48 h) of an MI (35).
(2) Patients with CA resulting from clearly definable specific causes such as reversible ischemia, severe valvular aortic stenosis, or noninvasively defined congenital or acquired LQTS (35).
(3) Patients with Early Repolarization Syndrome (see section 8).

14. Role of electrophysiological study in patients with undocumented palpitations

Rationale: The prevalence of paroxysmal SVT in the general population in the US is estimated to be 2.25/1,000 persons and the incidence 35/100,000 person-years (95% CI, 23 to 47/100,000) (83). In out-of-hospital settings, episodes of paroxysmal supraventricular and VTs frequently terminate before an ECG can be recorded and a diagnosis established. In between episodes of palpitations, the ECG is frequently nondiagnostic and 24 h Holter ECG monitoring has limited diagnostic value in patients with infrequent palpitations (81). External and internal loop recorders are progressively becoming increasingly useful in establishing a diagnosis in patients with undocumented palpitations (340) but do not always provide a positive diagnosis. In patients in whom history taking is evocative of a paroxysmal arrhythmia, EPS can reproduce the rhythm disturbance and establish a correct diagnosis. In the case of a positive EPS, it can most of the times be followed by catheter ablation and provide a long-term cure. However, the sensitivity of an EPS is highly dependent on the pretest probability of an arrhythmia diagnosis. History taking and the clinician's judgment are important tools in selecting suitable candidates for an EPS, as not all patients complaining of palpitations have a corresponding rhythm disorder (341, 342).

Evidence: Valles at el (342) assessed the diagnostic and the prognostic values of EPS in 172 patients with undocumented palpitations, of which 99% presented a sudden onset, 65% abrupt termination, and 56% had symptoms lasting for >5 minutes. EPS was positive in 86 patients (50%): 43 patients had AV nodal reentrant tachycardia, 9 patients had orthodromic reentrant tachycardia, and 34 patients had nonsustained AT/AF. Long-lasting episodes (>5 min), abrupt termination, and neck palpitations predicted positive EPS findings and were associated with reentrant SVT ($p < 0.001$).The initiation of AT/AF was associated with age > 50 years and structural heart disease ($p < 0.001$).

Tsiachris et al (343) showed on a population of 78 patients that the EPS has a reliable sensitivity in patients with undocumented palpitations suggestive of paroxysmal arrhythmias, with the EPS providing a diagnosis in 66.6%.

The sensitivity of EPS for the induction of tachycardias in the EP laboratory can be increased by using different types of pacing protocols and medication such as isoproterenol (344–348), atropine (349), and adrenaline (98, 350).

14.1. Indications (35)

14.1.1. Class I

(1) Patients with palpitations who have a pulse rate documented by medical personnel as inappropriately rapid and in whom ECG recordings fail to document the cause of the palpitations
(2) Patients with palpitations preceding a syncopal episode

14.1.2. Class II

(1) Patients with clinically significant palpitations, suspected to be of cardiac origin, in whom symptoms are sporadic and cannot be documented. Studies are performed to determine the mechanisms of arrhythmias, direct or provide therapy, or assess prognosis.

14.1.3. Class III

(1) Patients with palpitations documented to be due to extracardiac causes (e.g., hyperthyroidism)

15. Role of electrophysiological study in guiding drug therapy

Rationale: In the pre-ICD era, an approach toward ventricular arrhythmias consisting of antiarrhythmic drug administration followed by an invasive EPS to test for arrhythmia induction susceptibility was considered suitable for evaluating the efficacy of antiarrhythmic drugs. However, there is currently sufficient evidence to conclude that such a strategy is not capable of correctly identifying patients at risk of future arrhythmia recurrence nor it is associated with an improved survival of patients. Therefore, such practice has become obsolete.

Evidence: Initial experience with studies conducted in the 1970s and the 1980s was encouraging (219, 329, 331, 351–354), and tested antiarrhythmic drugs included procainamide, quinidine, lidocaine, diphenylhydantoin, disopyramide, and amiodarone. Suppression of inducible VT or VF was reported to vary between 26% and 80% in patients with resuscitated CA (355–359). In the 1990s, a strategy based on EPS was found to be better than the one based on Holter ECG monitoring in predicting antiarrhythmic drug efficacy for ventricular tachyarrhythmias (176.txt). However, these studies were limited owing to the small number of patients included, the reduced follow-up time, and the limited positive and negative predicted value of the EPS. It is currently known that recurrences are common in patients treated with antiarrhythmic drugs, even after a negative EPS (360). This can be explained by the limited efficacy of antiarrhythmic drugs, the progressive nature of the underlying disease (such as ischemic heart disease, arrhythmogenic right ventricular cardiomyopathy), and the unsatisfactory negative predictive value of the EPS.

In the SCD-HeFT study (361), amiodarone did not reduce overall mortality compared to placebo in patients with heart failure and an EF < 35% after a mean follow-up of 45 ± 5 months. In the MUSTT study (131), which tested the role of electrophysiologically guided antiarrhythmic drug treatment versus no therapy in patients who were at high risk of ischemic heart disease with reduced left ventricular function (LVEF ≤40%) and nonsustained VT, the subgroup analysis showed that the benefit of antiarrhythmic drug treatment was only due to ICD implantation. No difference was found between patients who had inducible arrhythmias treated exclusively with antiarrhythmic drugs and those who were randomized to no drug treatment.

Therefore, it is currently considered that the EPS has no role in guiding drug therapy. An exception may be in some patients with BrS and inducible VF, as an alternative to ICD therapy, where electrophysiology testing with a class 1A antiarrhythmic drug (mainly quinidine) may be considered for assessing treatment efficacy (174) (see section 6c).

15.1. Indications

15.1.1. Class I

None.

15.1.2. Class II

(1) In patients with BrS and inducible VF, as an alternative to ICD therapy, electrophysiology testing with a class 1A antiarrhythmic drug (mainly quinidine) may be considered for assessing treatment efficacy (174) (this practice is currently limited).

15.1.3. Class III

For all other purposes than the ones mentioned above.

16. Role of electrophysiological study in patients who are candidates for or who have cardiac implantable electronic devices

Rationale: The current main role of the EPS is to 1) identify patients who will benefit from catheter ablation of cardiac arrhythmias and 2) to identify patients who require the implantation of a cardiac electronic device (PM of defibrillator).

Evidence:

A. Patients who are candidates for cardiac implantable electronic devices (CIED)

These patients may present narrow QRS complex tachycardias, large QRS complex tachycardias, or conduction disorders (such as SND, AVB, or BBB). These patients may require either a PM or an ICD implantation. The indication for such a device may be straightforward, without the need of an EPS (such as in patients with NYHA class II, III, or ambulatory class IV heart failure and reduced LVEF < 35%, who have an indication for an ICD implantation in the primary prevention of sudden cardiac death (135)), or may require the performance of an EPS either for establishing a positive diagnosis (such as in patients with suspected paroxysmal bradycardia (10)), or for the differential diagnosis (such as in cases of wide QRS complex tachycardias). For the role of the EPS in patients requiring a PM implantation, please refer to section 1, section 2, section 3, section 7, section 9e, section 10b, and section 12. For the role of the EPS in patients requiring an ICD implantation, please refer to section 5, section 6, section 9, section 10, section 11, and section 13.

B. Patients who have cardiac implantable electronic devices

The three main types of cardiac implantable electronic devices (CIEDs) used currently in clinical practice are PMs, defibrillators, and loop-recorders. All these types of implantable devices have the capability of heart rhythm monitoring and arrhythmia/conduction disorders storage for further analysis. An EPS is therefore rarely needed to make a positive diagnosis in CIED carriers. However, in these patients, EPS may be indicated for the differential diagnosis of recorded tachycardias, in patients in whom radiofrequency catheter ablation in desired and deemed suitable. It is important to mention that most modern PMs and ICDs have the capability of performing programmed ventricular stimulation and in some cases, a standard multicatheter EPS may not be needed.

16.1. Indications

A. Patients who are candidates for cardiac implantable electronic devices (CIED)
   - For PM implantation, please refer to section 1, section 2, section 3, section 7, section 9e, section 10b, and section 12.
   - For ICD implantation, please refer to section 5, section 6, section 9, section 10, section 11, and section 13.

B. Patients who have Cardiac Implantable Electronic Devices
   - PM carriers:
     - Patients with documented supraventricular or ventricular arrhythmias in whom a catheter ablation procedure is contemplated.
     - Patients with documented tachycardia suspected to be of ventricular origin who might require device upgrading to an ICD.
   - ICD carriers:
     - Patients with documented supraventricular or ventricular arrhythmias in whom a catheter ablation procedure is contemplated.
   - Loop recorder carriers:
     - Patients with documented tachycardias to guide management: catheter ablation procedure or ICD device implantation.

17. Role of the electrophysiological study in patients who develop conduction disorders after transcatheter aortic valve replacement (TAVR)

Rationale: Conduction disorders are common after TAVR, with up to 20% of patients requiring PM implantation after the procedure (362), due to either complete AVB, high-degree AVB, newly developed BBB with an increased HV interval (>70 ms) at EPS, alternating BBB, or development of tachycardia–bradycardia syndrome. However, prospective follow-up data on this population of patient are scarce owing to the fact that TAVR is a relatively new technique and questions still remain regarding the proper selection of patients who require PM implantation (such as patients who develop isolated BBB or patients with permanent AF who develop bradycardia but not complete heart block after TAVR).

Evidence: Electrophysiological abnormalities, notably prolongation of the AH and HV intervals, are common in patients who undergo TAVR and can be demonstrated with the use of an EPS (363). Few data exist on the utility of the EPS in selecting patients who are eligible for PM implantation in patients post TAVR.

Kostopoulou et al. (364) performed a study on 45 patients undergoing TAVR with the CoreValve, using electrocardiographic monitoring and EPS. By using univariate analysis, they demonstrated that the baseline HV predicted a complete AVB and that an increased HV interval (>70 ms) predicted PM implantation.

Makki et al (365) performed a study on patients undergoing TAVR, of which 14% (n = 24) underwent PM implantation. The mean follow-up period was 22 months. Indications for PM implantation were third-degree AVB (CHB; 15/24, 63%), left BBB and abnormal EPS (7/24, 29%), alternating BBB (1/24, 4%), and tachycardia–bradycardia syndrome (1/24, 4%). PM dependency defined as underlying ventricular asystole, complete heart block, or >50% ventricular pacing occurred in 33% of patients during follow-up, seven of whom had resting CHB and one with CHB during EPS. This study questions the use of the EPS in accurately predicting the need for PM implantation.

Rivard et al (366) performed an EPS before and after TAVR in their group of 75 patients and found that a prolonged delta-HV interval of ≥13 ms was strongly associated with the development of complete AVB after TAVR. In patients with newly developed LBBB after TAVR, a post-procedural HV interval of ≥65 ms was also predictive of AVB development.

17.1. Indications (366)

17.1.1. Class I

None.

17.1.2. Class II

(1) Newly developed BBB (implantation of a permanent PM is indicated if HV interval ≥ 65 ms).
(2) The presence of BBB before TAVR (implantation of a permanent PM is indicated if the delta-HV interval pre- and post-TAVR is ≥ 13 ms).

17.1.3. Class III

(3) Patients who develop complete AVB post TAVR (permanent PM implantation is indicated).

Conflict of interest

None.

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None.

Appendix A. Supplementary data

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REVIEW

Intravascular pulmonary venous ultrasound imaging for catheter ablation of atrial fibrillation

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ABSTRACT

Introduction: Atrial fibrillation is the most common cardiac arrhythmia. The development of electroanatomical mapping is an increase demand for advanced intracardiac imaging techniques of the left atrium and pulmonary veins. IVUS can demonstrate quantitative changes like lumen and wall thickness as well as qualitative changes of the pulmonary wall. IVUS could also provide relevant real time imaging of the atrial and pulmonary venous wall during catheter ablation.

Areas covered: The Medline and Embase databases were searched for preclinical and clinical studies of IVUS in patients with ablation of atrial fibrillation or left atrial arrhythmias. This article reviews the 15 years of preclinical and clinical experience with IVUS evaluating the pulmonary veins.

Expert commentary: IVUS has proven to be a valuable imaging technique in the management of atrial fibrillation ablation. The understanding of the relation between morphological changes and functional results of catheter ablation, combined with the safety profile have made it appealing for interventionists.

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Catheter ablation; IVUS; pulmonary vein; left atrium; radiofrequency; intracardiac echocardiography

1. Introduction

The development of electroanatomical mapping for patients with complex arrhythmias is an increasing demand for advanced intracardiac imaging techniques. Pulmonary angiography, computed tomography (CT), magnetic resonance imaging (MRI), and transesophageal echocardiography are currently used to analyze the pulmonary veins (PVs) [1].

Fluoroscopy remains the cornerstone of imaging to guide electrophysiology interventions [2]. However, several limitations of fluoroscopy like radiation exposure of the doctor and patient, poor resolution for soft-tissue structures, and the use of iodinated agents for contrast imposed searching for new imaging techniques [3]. Imaging tools can be divided in noninvasive and invasive. Noninvasive tools include CT, MRI [4], and echocardiography. Invasive tools include transesophageal echocardiography, intracardiac echocardiography (ICE), intracardiac endoscopy, and electroanatomical mapping.

Intravascular ultrasonography (IVUS) can demonstrate quantitative changes like lumen and wall thickness as well as qualitative changes of the pulmonary vessel area or vessel wall [5]. The ablation techniques have increased the interest in pulmonary venous wall structure and venoatrial junction anatomy. This review will summarize IVUS for PV imaging during ablation of atrial fibrillation.

2. Characteristics of imaging system

Catheter-based ultrasound started to be used in animals as early as 1960 [6]. Intracardiac and intravascular echography is possible using a small ultrasound transducer mounted on the tip of a catheter that can be introduced inside the heart by percutaneous means: venous or arterial. It is over the last decade that important development of the ultrasound technique took place (Figure 1).

Frequency used with intravenous ultrasound determines the resolution of the image. Increased frequency gives better resolution between two separated points but with lesser penetration in depth. Available probes for IVUS have between 8 and 50 MHz frequencies [7].

For the evaluation of the coronary arteries, IVUS with high-frequency transducers (20–40 MHz) are used, providing high-resolution images of the epicardial arteries but with limited tissue penetration of few millimeters. On the other hand, intracardiac echography uses lower-frequency transducers of 5–10 MHz which are capable of good tissue penetration of up to 12 cm [8].

The system used for inferior vena cava filter placement has an 8-F, 8.3-MHz IVUS catheter inserted through the right femoral vein [9]. The system used for pulmonary artery assessment consists of 3.5-F, 30-MHz ultrasound catheters connected to an intravascular imaging console. The transducer rotates 1800 times per minute, and it provides 30 images per second. The axial and lateral resolutions are 0.1 and 0.3 mm [10]. With the older 6-F ultrasound catheters, proximal and larger vessels can be examined >4.0 mm. The new 3.5-F, 30-MHz IVUS catheters allow the assessment of subsegmental arteries with a small size diameter <3.0 mm.

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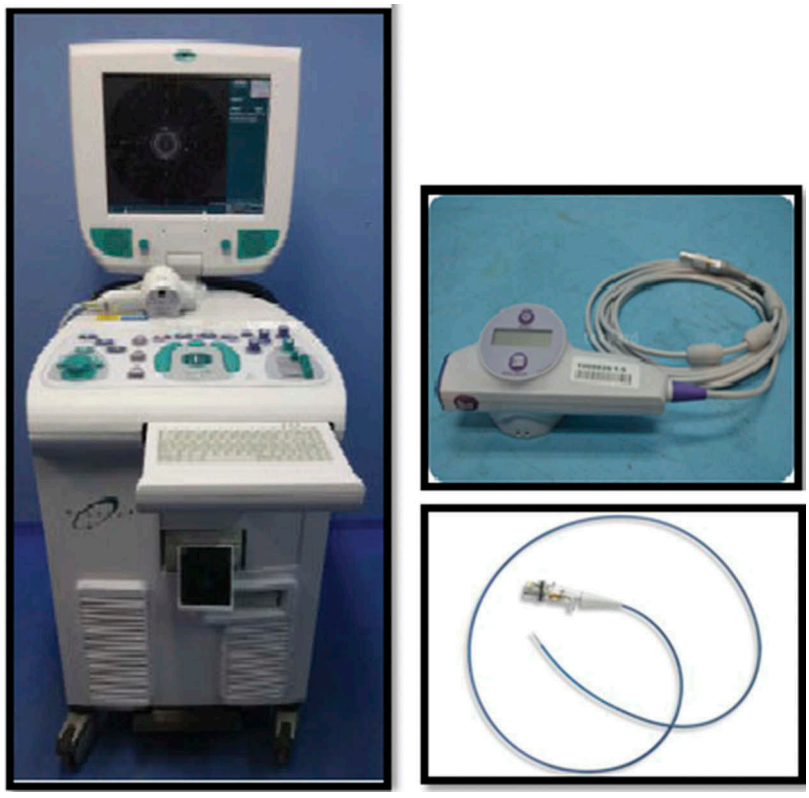

Figure 1. Imaging system for IVUS. The system provides a three-dimensional as well as a circumferential view for electrophysiological mapping.

There are two types of IVUS catheters: mechanical and electronic [11]. They both can produce 360 degree imaging of the vein. The image is perpendicular on the long axis of the catheter.

2.1. Mechanical IVUS

Mechanical IVUS has an ultrasound crystal which can be moved proximally and distally inside the vein but with lack of deflectability. The rotating element permits creation of a radial 360 degree image which is perpendicular to the axis of the catheter. It also provides a 4-cm-deep radial field of view with a single-plane tomographic in the horizontal plane imaging.

2.2. Electronic IVUS

Electronic IVUS consists of an array of up to 64 circular elements that produces a whole image from each element of the transducer. It also has Doppler capability like pulsed, continuous, color, and tissue Doppler. It permits a tissue penetration of 12 cm with scanning in the longitudinal plane with 90-degreee sector image and four-direction tip articulation for better deflectability [12].

3. Technique

For IVUS examination of the PVs, a 30 MHz catheter is mounted on a guidewire that is advanced using fluoroscopic guidance through the femoral vein inside the right atrium and then inside the left atrium and PVs using transseptal approach [13]. The IVUS probe is advanced at the distal part of the vein with automatic or manual pullback to identify sleeves of atrial tissue inside the PVs.

4. Histological characterization of the normal pulmonary venous wall

The wall of the PVs comprises three layers: endothelium – the inner layer, media, and adventitia on the outside of the vein. Myocardial sleeves can extend from the left atrium to the PVs and pass between the adventitia and media of the wall. The myocardial bundles are arranged in varying orientations [14,15,16].

5. Ultrasonic characterization of the normal pulmonary venous wall

IVUS can determine the exact lumen diameter of the vein. In the study of Cabrera et al., it ranged from 9 to 22 mm with a mean of 12.5 mm [17].

Experimental studies established the ability of IVUS to characterize the architecture of the arterial and venous wall [18–20]. At the level of venoatrial junction, IVUS images show a three-layered pattern with an inner echodense layer of thin appearance, an intermediate black payer, and an outer echodense layer (Figure 2). The black intermediate layer consisted of sleeves of atrial myocardium that extended over the venous media. Cabrera et al. [17] demonstrated the ability to describe the trilaminar architecture of the venous wall using a 30-MHz ultrasound catheter. The middle hypoechogenic layer

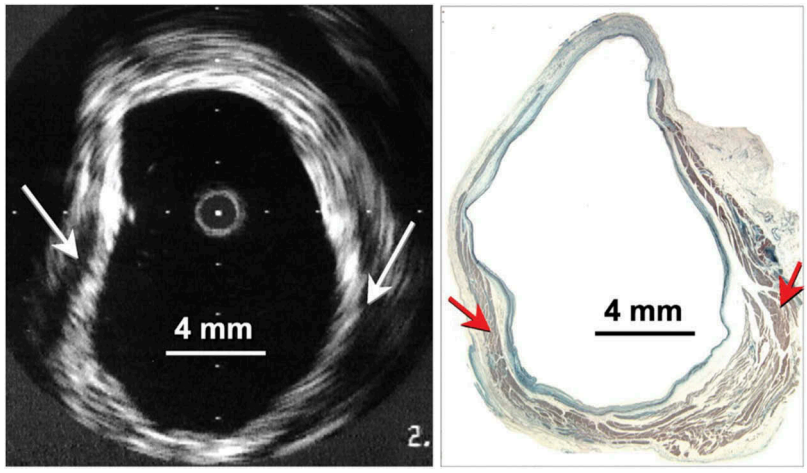

Figure 2. Echographic cross-section obtained *in vitro* from a right superior pulmonary vein of a specimen from a 70-year-old man (left) with corresponding histological section (right). The irregular middle layer in the histological section consists of a thick sleeve of atrial myocardium measuring 3 mm at the anteroinferior quadrant of this vein. The corresponding ultrasound image is a thick hypoechogenic stratum (arrows). In this case, the intermediate stratum is thicker than the inner and outer layers. This is the most prevalent cross-sectional ultrasonic pattern at the venoatrial junctions. Reproduced from Cabrera J. et al [17], with permission from, Wolters Kluwer Health, Inc. Copyright © 2002.

represents the sleeves of atrial myocardium inside the PVs. Thus, the echolucent layer is bordered by an inner and outer echodense layers in patients presenting myocardial sleeves. The hypoechogenic layer is thicker at the venoatrial junction and thinner toward the hilum of the lung. In some instance, the ultrasonic appearance of the venous wall is altered by fibrosis inside the myocardial sleeves with echoreflective lines crossing the hypoechogenic layer [21].

This layer was present in 30 of 32 veins (94%) in the study of Cabrera et al. [17]. The layer had its maximum thickness at the venoatrial junction 2.6 ± 0.8 mm and progressively decreased until it disappeared at 2 cm distance from venous orifice. More distally, IVUS of the PV showed absence of this intermediate layer. The medial diameter of the innermost layer ranged from 0.12 to 1.7 mm with a mean value of 1.4 ± 0.3 mm.

6. IVUS to guide ablation of atrial fibrillation

Endocardial anatomy cannot be assessed by fluoroscopy. Traditionally, fluoroscopy has guided catheter positioning, but left atrial tachycardia and flutter may necessitate good knowledge of left atrial anatomy [22]. This is especially true for the PVs, ostia, and bifurcations that are critical landmarks remaining invisible during fluoroscopy. Anatomic variations of the PVs can be assessed using low-frequency intracardiac echocardiography. Ultrasound also permits the visualization of the fossa ovalis and the interatrial septum for a transseptal puncture without complications [23].

IVUS identifies the arrhythmogenic substrate and guides ablation lesion creation. It can assess the electrode–tissue contact and stability during radiofrequency (RF) application and can be used for improved contact with the tissue and increased RF lesion at the target zone [24]. Using IVUS, changing in tissue characteristics can be assessed during ablation, and linear lesions without gaps can be created for a complete line inside the left atrium. Lesion creation can be confirmed by IVUS when tissue appearance changes after RF application [25].

Circumferential approach, as described by Pappone et al. [26], does not benefit from IVUS aimed to define the myocardial sleeves at the venoatrial junctions. Nevertheless, ablation approach to the ostial portion of the veins can benefit of IVUS using high-frequency probes. It may also serve as a guide to target the application of energy at the level of myocardial sleeves. Another benefit could be the selection of the optimal level of energy to be applied in different zones of the venoatrial junction as lesion size can be estimated during the procedure [27].

The use of IVUS during the ablation procedure can minimize the risk of *vein stenosis*. IVUS images can provide valuable information on the distal limits of the muscular sleeves and their thickness at the level of the PVs [28]. It helps accurate targeting during the ablation procedure. Cabrera et al. demonstrated that cross-sectional and longitudinal IVUS imaging using high-frequency 3.2-F, 30-MHz probes is able to describe the three-dimensional architecture of the pulmonary venous wall: the inner layer is echogenic and constituted of endothelium and connective tissue of the media, the middle layer is hypoechogenic and corresponds to the myocardial sleeves of the left atrium inside the PVs, and the outer layer given by the adventitia which is a fibro-fatty tissue. The myocardial sleeve is thicker at the level of venoatrial function, 2.7 ± 0.6 mm, and is decreased toward the hilum of the lung [29]. IVUS visualization guides ostial lesion formation, preventing intrapulmonary vein energy delivery and minimizing the risk of pulmonary stenosis or occlusion.

The system permits simultaneous visualization of the circular mapping catheter and the atrial muscular sleeves inside the PVs [30]. It allows placement of the mapping catheter directly on the wall areas with regional thickening demonstrated to be myocardial sleeves. At this level, electrograms show high-frequency potentials. On the other hand, wall areas without regional thickening show only far field potentials without any high-frequency potentials. Guerra et al. found 100% specificity for recordable PV potentials in zones with wall

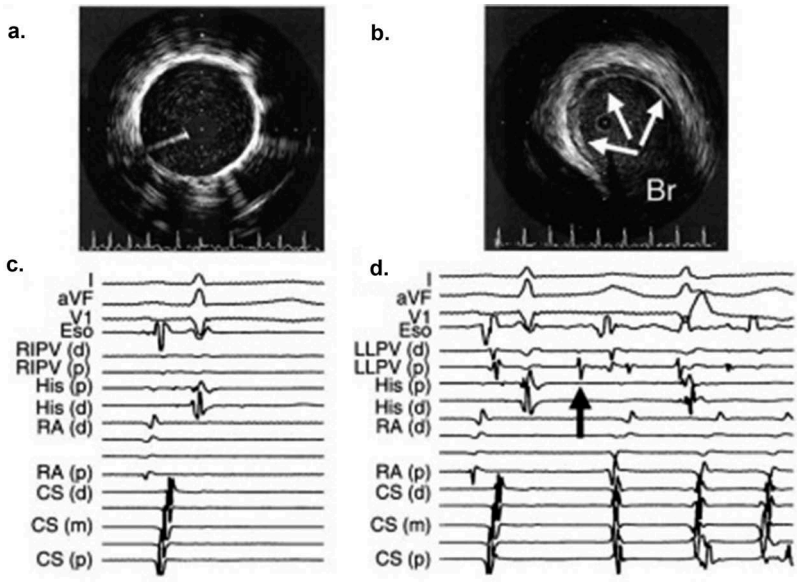

Figure 3. Intravascular ultrasound (IVUS) and intracardiac recordings from 2 pulmonary veins (PV). Smooth-contoured right inferior (RI) PV shows no evidence of thickening (a). Left lower (LL) PV has crescent-shaped area of thickening (arrow) (b). Intracardiac tracings taken while mapping catheter is in each of 2 veins: in RIPV, recordings from PV show only far field atrial signals (c); high-amplitude and high-frequency potentials recorded from LLPV, and initiation of atrial fibrillation from vein (arrow) (d). To better illustrate difference between veins with and without focal thickening, electrophysiology catheters were withdrawn before capturing images. Luminal artifact is from guidewire used with IVUS catheter. Br: Branch; CS: coronary sinus; (d): distal; eso: esophageal lead; LL: left lower; (m): mid; (p): proximal; RA: right atrium. Reproduced from Guerra PG. et al [31], with permission from, Elsevier Copyright © 2003.

thickening on IVUS. They showed how to differentiate between arrhythmogenic and nonarrhythmogenic PVs. Atrial tissue confers arrhythmogenicity and can be evaluated by IVUS [31]. This technique can guide the correct positioning of the ablation catheter on eccentric areas of thickening that are origins of atrial tachycardia, atrial fibrillation, or atrial premature depolarization (Figure 3).

6.1. Identification of PV ostium with intracardiac echocardiography

Intracardiac echocardiography which uses different parameters (5–10 MHz) compared to IVUS can identify the ostium of the PV, the relationship between the veins in case of common ostium of an upper and lower vein, and the ridge between left superior pulmonary vein and left atrial appendage [32]. The structures are important because radiofrequency ablation is delivered at this level in most of the procedures for complete isolation of the veins. The placement of the circular mapping catheter at the level of the ostium can be challenging with 5 mm shift inside the vein in the study of Marrouche et al. [33] when ICE is not available for correct localization of the ostium.

6.2. Identification of previous lesions using IVUS

IVUS probes can be used to guide ultrasound transducers (high-intensity focused ultrasound [HIFU]) by showing the anatomy of the veins and also detects past lesions by echographic characteristics. Wong et al. proposed a device that uses ultrasound imaging to locate PVs and heart walls and also create ablation lesions using HIFU. Created lesions have a diameter of 1–3 mm and a depth of 4 mm. Lesions are created at 44–55°C, and the presence of ultrasound array permits the creation of contiguous lesion patterns [34].

6.3. Identification of PV stenosis with IVUS

PV stenosis is one of the complications that can appear during RF ablation for atrial fibrillation. It is defined as a decrease in lumen size of more than 50%. The incidence varies from 0% to 38% [35]. Clinical manifestations of PV stenosis can be dyspnea, cough, hemoptysis, chest pain, recurrent lung infections, or pulmonary hypertension. The most precise methods for the diagnosis are CT or MRI with assessment of PVs before and after the ablation procedures [36]. Both ICE and IVUS can prevent RF delivery inside the PV. Reposition outside the vein and confirmation of contact with the ostium are indicated in case of power delivery inside the vein [37].

Angioplasty with stenting of the PVs is associated with good success [38]. The restenosis rate after a successful angioplasty varies from 14% to 57% [39]. Images obtained with IVUS before angioplasty of the vein provides useful information on the vessel size, length, and stent size that is needed to maintain the normal diameter of the vein. After the angioplasty, IVUS verifies the stent position, deployment, and length, and it can reduce the risk of restenosis [40].

7. Expert commentary and five-year view

Muscular architecture of the pulmonary venous wall cannot be assessed using ICE.

The unique advantage of IVUS over ICE is that IVUS provides accurate information on the presence or absence of muscular sleeves inside the PVs.

Veins with muscular sleeves should be ablated and veins without muscular sleeves should be spared.

An opportunity in the field is to couple IVUS systems with a catheter that also performs ablation. Such a catheter could allow real-time direct imaging of the muscular sleeve–electrode interface and lesion formation at the endocardial level without need for a separate catheter dedicated to IVUS. Surely the field of imaging will continue to evolve rapidly for the benefit of patients that need catheter ablation for atrial fibrillation.

Key issues

- The development of pulmonary vein isolation increases the demand for advanced intracardiac imaging techniques.
- Intracardiac ecography cannot provide information on the presence of muscular sleeves inside the pulmonary veins.
- IVUS serves as a guide to place radiofrequency application at the level of myocardial sleeves, that represent arrhythmogenic substrate for atrial fibrillation.

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Declaration of interest

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Cycle length characteristics differentiating non-sustained from self-terminating ventricular fibrillation in Brugada syndrome

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Aims Limited information is available on self-terminating (ST) ventricular fibrillation (VF). Understanding spontaneous fluctuations in VF cycle length (CL) is required to identify arrhythmia that will stop before shock. Using Brugada syndrome (BS) as a model, the purpose of the study was to compare ST-VF and VF terminated by electrical shock and to look for spontaneous fluctuations in ventricular CL.

Methods and results Occurrence of ST-VF and VF was studied in 53 patients with 46 VF episodes: (i) spontaneously, (ii) during defibrillation threshold testing, (iii) during programmed ventricular stimulation (PVS). Fifteen presented ST-VF (average duration 25 s): 11 during PVS, 1 during defibrillation threshold testing, and 3 spontaneously (at device interrogation). Self-terminating ventricular fibrillation was compared with 31 VFs terminated by electrical shock. Mean ventricular CL was longer (192.5 ± 22 vs. 149 ± 19 ms) ($P < 0.0001$) and CL became longer or did not change in ST-VF (187 ± 28 vs. 200 ± 25 ms) (first vs. last CL)(NS) in contrast with progressively shorter CL in electrical shock-terminated VF (177 ± 14.5 vs. 139 ± 12 ms) (first vs. last CL before electrical shock) ($P < 0.0001$). Ventricular fibrillation had more CL variability (average 16.4 ± 6.5 ms) for the first 50 beats than ST-VF (average 4.08 ± 2) ($P < 0.0001$). Cycle length range for the first 50 beats was 9.6 ± 1 ms for ST-VF and 44 ± 15 for VF ($P < 0.002$).

Conclusion Self-terminating ventricular fibrillation in BS was not rare (28%). Ventricular CL was longer and progressively increased or did not change in ST-VF compared with electrical shock-terminating VF. Cycle length variability and CL range could differentiate VF and ST-VF within the first 50 beats. These parameters should be considered in the algorithms for VF detection and termination.

Keywords Ventricular fibrillation • Ventricular programmed stimulation • Implantable cardioverter defibrillator • Brugada syndrome

The prognostic value of electrophysiological studies in Brugada syndrome (BS) remains controversial. Studies[1] in BS suggested that programmed ventricular stimulation (PVS) can predict events using the induction of ventricular fibrillation (VF),[2–6] the presence of ventricular effective refractory period <200 ms and QRS fragmentation[7] despite a moderate diagnosis value.[8] Outside this syndrome, it was exceptional to induce a VF in the absence of underlying heart disease.[9]

Implantable cardioverter defibrillator (ICD) is now frequently indicated. Some patients present ventricular tachycardia (VT) that stop spontaneously. Implantable cardioverter defibrillator therapies are usually set exclusively on a time-based criterion.

The purpose of the study was to compare non-sustained or self-terminating (ST) VF and VF terminated by electrical shock and to look for spontaneous fluctuations in ventricular cycle length (CL) that could predict the spontaneous arrest of arrhythmia before electrical shock delivery.

Population of study

This retrospective study included 53 patients, 50 males and 3 females aged from 21 to 74 years, mean age 45 ± 13, with type 1 Brugada pattern.

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What's New?

- Limited information is available on self-terminating (ST) ventricular fibrillation (VF). The purpose of the study was to compare ST-VF and VF terminated by electrical shock and to look for fluctuations in ventricular cycle length (CL) during both arrhythmias. Among 53 Brugada syndromes (BS), 15 presented ST-VF (28%) and 31 had VF. Cycle length was longer and became progressively longer or was unchanged in ST-VF compared with progressively shorter CL in VF. Ventricular fibrillation had more CL variability and longer CL range within first 50 beats than ST-VF ($P < 0.0001$, 0.002).
- Self-terminating VF was frequent in BS.
- Mean ventricular CL was longer and progressively increased or did not change in ST-VF compared with VF.
- Cycle length variability and CL range was higher in patients with ST-VF than in patients with VF, can differentiate VF and ST-VF within the first 50 beats.

The type 1 Brugada electrocardiogram (ECG) pattern was defined in the presence of coved ST elevation (>2 mm) in one or more leads from V1 to V3, either spontaneous or induced by class I anti-arrhythmic drug administration. Spontaneous type 1 pattern was defined when at least one ECG documented a type 1 pattern in the absence of anti-arrhythmic drugs. A type 1 ECG pattern recorded in II–III intercostals spaces was considered as a sign of diagnosis. Type II ECG pattern was defined in the presence of a >2 mm J point elevation and >1 mm saddleback-type ST elevation with positive T-wave. Type III pattern was defined as a <1 mm saddleback- or coved-type ST elevation. Sodium channel blocker used was ajmaline (1 mg/kg intravenous in 5 min). Testing was performed in subjects with type II or III patterns. The test was considered positive only if a coved-type 1 ECG pattern was documented. Individuals with type II or III patterns in whom anti-arrhythmic drugs did not reproduce a type 1 pattern were excluded from the study.

Patients were seen for various reasons: 14 asymptomatic patients had a family history of early sudden death before the age of 40 years in the absence of known heart disease; 14 patients were asymptomatic but they had a spontaneous type 1 pattern. Eighteen patients were studied for syncope; five patients were resuscitated from cardiac arrest and two had a monomorphic VT.

Methods

All patients underwent echocardiography, laboratory tests, and other examinations, in order to exclude the presence of an underlying structural heart disease. In all cases, electrophysiological study (EPS) was proposed but was not performed in four patients, three with resuscitated sudden death and one with spontaneous VT.

Electrophysiological study

Patients underwent investigations in the absence of anti-arrhythmic drugs after giving informed written consent. Complete EPS including the PVS was carried out, according to a previously reported protocol.[9] EPS included programmed atrial stimulation with one and two extrastimuli, PVS up to three extrastimuli in two sites of right ventricle at 2 CLs (600, 400 ms). The decrement was 10 ms from 350 ms until the ventricular effective refractory period or 200 ms. Short coupling intervals (<200 ms) were not used in our study.

Positive EPS was defined when a sustained ventricular arrhythmia (>30 s) or requiring shock was induced. For the purpose of this study, only the tachyarrhythmias with ventricular rate >275 bpm were included. Ventricular fibrillation was defined as a polymorphic VT leading to collapse and requiring shock. A defibrillation shock was given when the patient lost consciousness. Self-terminating VF was defined as a polymorphic VT, with ventricular rate >275 bpm lasting at least 15 s and stopping spontaneously before loss of consciousness. In these last patients no other arrhythmia was induced, despite a complete PVS. Monomorphic VT when the rate was <275 bpm was excluded.

The measurement of ventricular CL was made on the ventricular recording lead either during EPS or at ICD interrogation. We used calipers provided by the EP soft (Bard/Pruka/Marquette). We measured each RR interval on the surface ECG in order to correspond with the intracardiac electrogram from the RV catheter. The speed used was most of the time 50 mm/s, but we also used 100 mm/s. For every 10 beats we made the average. For every 10 cumulative beats we made the average 0–10 beats, then 0–20 beats, then 0–30 beats, and so on. We calculated the standard deviation for the first 10 beats, then for the first 20 beats, then for the first 30 beats, and so on up to 50 beats. We made the average for the standard deviation of the first 50 beats for the electrical-shock terminated VF group and the average for the standard deviation of the first 50 beats for the spontaneous terminated VF group.

Defibrillator sensing and discrimination algorithms were based on cumulative averages. This was why we used cumulative CL variability (that is 0–10, 0–20 beats, and so on). By the 50th beat the device should be able to conclude, if VF will stop spontaneously or will necessitate electrical shock.

Implantable cardiac defibrillator implantation

Patients were informed of their potential risk, which was based mainly on the history of resuscitated sudden death, VT, or the history of syncope in association with the presence of a spontaneous type 1 pattern. The decision to implant an ICD was taken after written informed consent had been provided.

All ICD implanted were capable of recording and storing ECG data at the time of episodes of shock. Ventricular back-up pacing was programmed at a rate of 40 bpm.

Implantable cardioverter defibrillator was implanted in 48 patients. Twenty-five patients were symptomatic (syncope 18, spontaneous VF 5, spontaneous VT 2) and 23 patients were asymptomatic; in these last patients the indications was the pattern of ECG and the induction of VF ($n = 10$), the pattern of ECG, the induction of VF and a history of familiilial sudden death ($n = 7$), and only the pattern of ECG and the history of familial sudden death ($n = 6$). Two asymptomatic patients without a history of familial history of sudden death, but with inducible VF were treated with hydroquinidine. Programmed ventricular stimulation became negative with the drug. Implantable loop recorder was used in three remaining patients without spontaneous arrhythmias and without inducible VF.

Follow-up

Follow-up examinations were performed every 6 months or in the event of symptoms. All patients were followed up for at least 1 year. Mean follow-up was 6 ± 4 years. In patients with ICD, analysis of arrhythmias and of appropriate and inappropriate shocks was also performed.

Table 1 Values of cycle lengths (CL)

	ST-VF	VF	
Number	15	31	
Mean CL (ms)	192.5 ± 22	149 ± 19	$P < 0.0001$
First CL (ms)	187 ± 28	177 ± 14.5	NS
Last CL (ms)	200 ± 25	139 ± 12	$P < 0.0001$

ST-VF, self-terminating ventricular fibrillation; VF, ventricular fibrillation requiring electrical shock to stop it.

Statistical analysis

Data are expressed as means ± standard deviation (SD). For categorical variables the χ^2 test was performed. The independent-sample *t*-test procedure was used for continuous variables. A *P* value <0.05 was considered statistically significant. All statistical analyses were performed by using the SPSS package for Windows (version 17. 0.1, SPSS Inc). The diagnosis value was defined according to classical data: the sensitivity of the test was the proportion of patients who had the sign who test positive for it. Specificity of the test was defined as the proportion of patients who did not have the sign who will test negative for it. The positive predictive value was the proportion of positive test results that were true positives. The negative predictive value was defined as the proportion of patients with a negative test result who were correctly diagnosed.

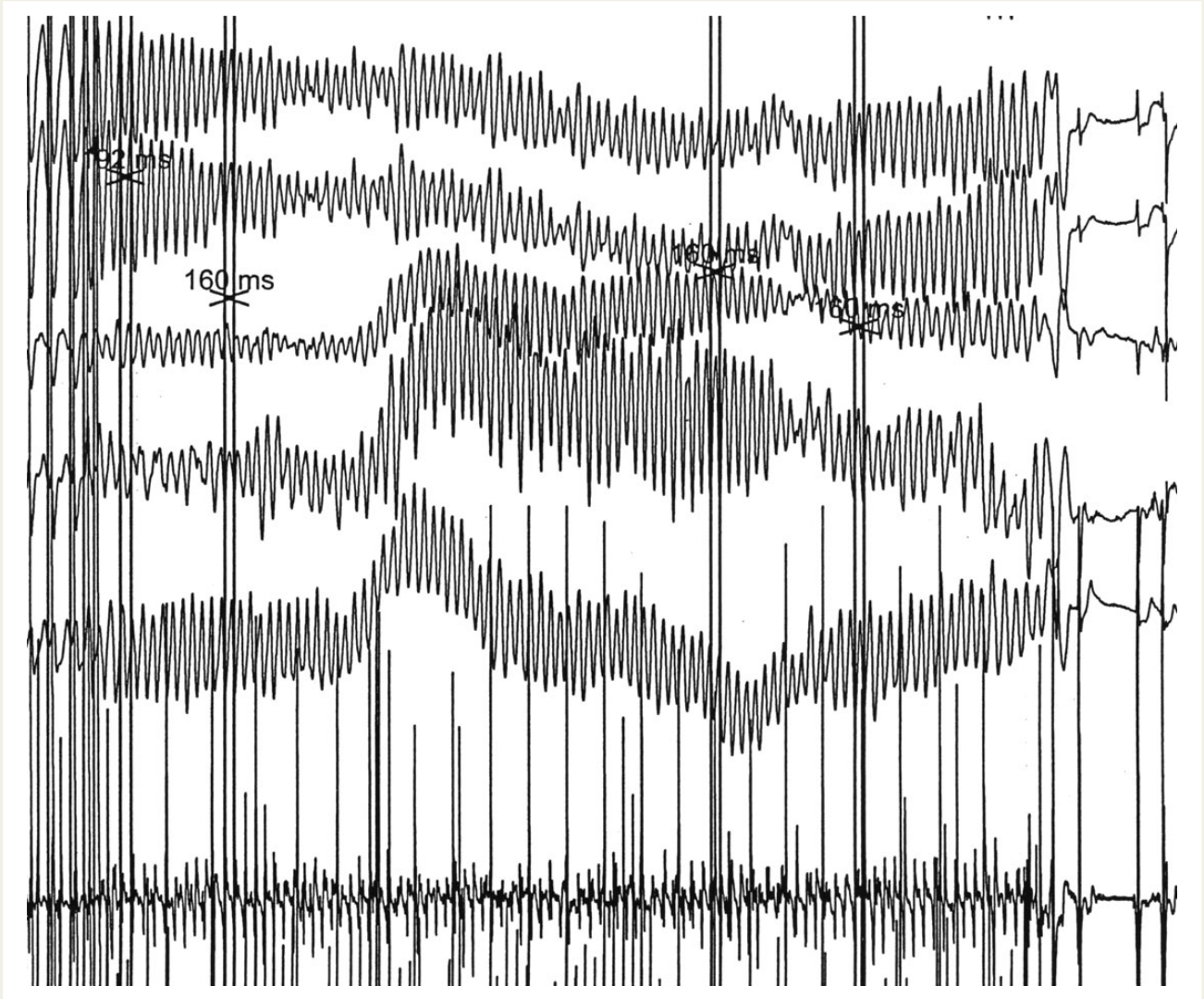

Figure 1 Self-terminating polymorphic VT; CLs increased. The total duration of VT was 17.5 s. The leads were DI, DII, AVF, V1, V6, His bundle electrogram. *A* and *B* reported the same ECG in 25 mm/s (beginning and then end).

Results

Number of VF and self-terminating VF

Fifty-three patients with 46 arrhythmia episodes were included. Of these 53 patients, 15 presented ST-VF (average duration 25 ± 14 s), 11 patients during PVS, 1 patient during defibrillation threshold testing, and 3 patients spontaneously (revealed at device interrogation). The duration varied from 15 to 47 s. Self-terminating VF (average duration 37 ± 11 s) was compared with 31 VF's terminated by electrical shock (internal or external). Ventricular fibrillation was induced by PVS in 29 patients and occurred only at device interrogation in 2 patients.

Characteristics of induced ventricular arrhythmia or ventricular arrhythmias recorded at ICD interrogation

Differences in ventricular CLs were noted and are reported in *Table 1*. Mean ventricular CL was longer (192.5 ± 22 vs. 149 ± 19 ms) ($P < 0.0001$) and the CL became progressively longer or did not change in ST-VF (187 ± 28 vs. 200 ± 25 ms) (NS) (*Figure 1*) in contrast with progressively shorter CL in electrical shock-terminated VF (177 ± 14.5 vs. 139 ± 12 ms) ($P < 0.0001$) (*Figure 2*). The length of the first ventricular beats tended to be longer in ST-VF than in VF, but the differences were not statistically significant.

Table 2 reported the changes of ventricular CL 10 beats per 10 beats. The average of standard deviation of the mean ventricular VF CLs in VF and then of ST-VF, for every group of 10 beats up to 50 beats indicated a higher value in VF than in ST-VF (16.4 ± 6.5 vs. 4.09 ± 2 ms) corresponding to more CL variability (*Figures 1 and 2*) ($P < 0.0001$). Cycle length range for the first 50 beats was 9.6 ± 1 ms for ST-VF and 44 ± 15 ms for VF ($P < 0.002$) (*Table 2*).

Table 3 reports the diagnosis value of mean ventricular CL and changes within first 50 beats to discriminate VF from ST-VF. The cut-off data of CL changes ≥20 ms seems to have the best diagnosis value to differentiate VF from ST-VF.

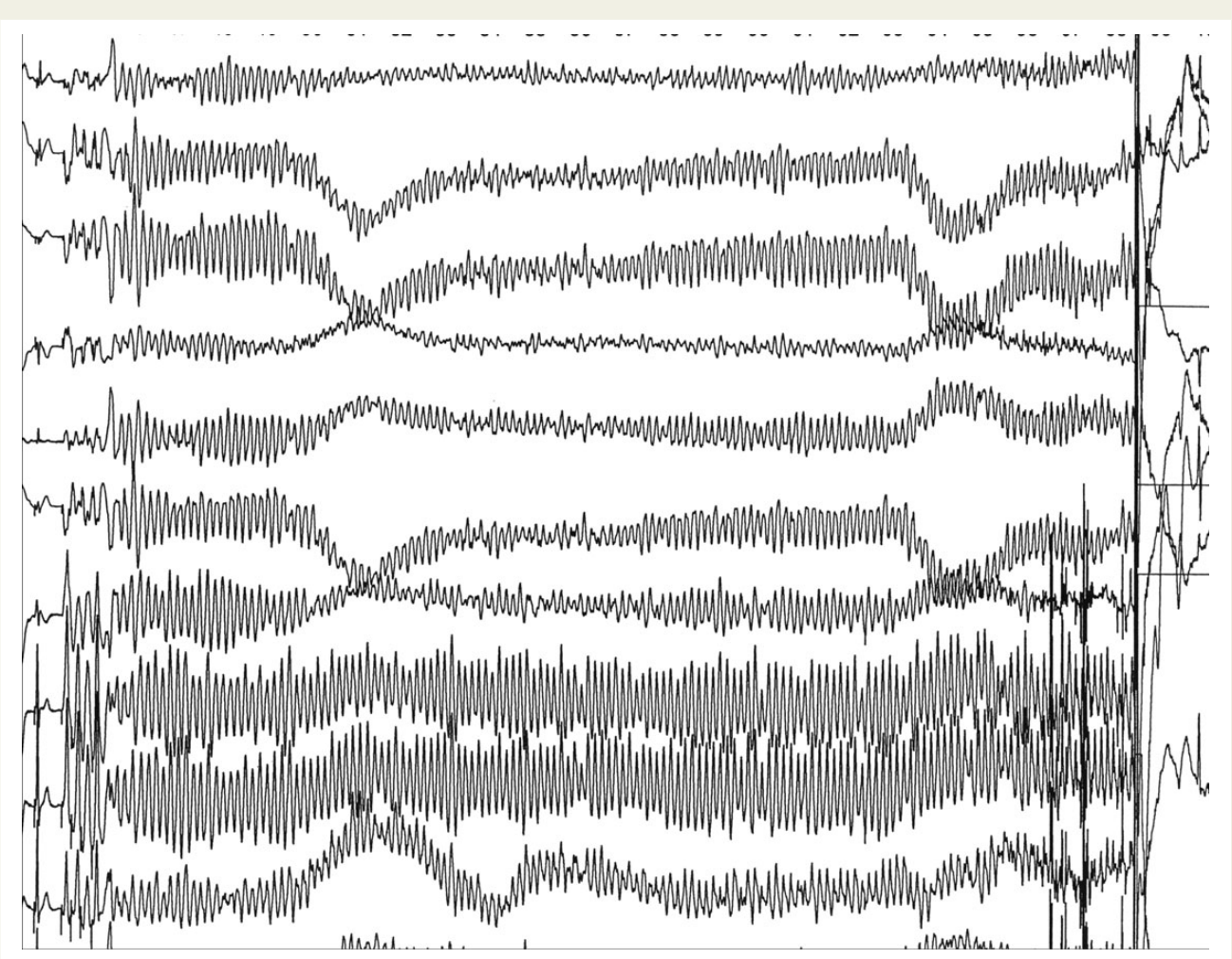

Figure 2 Ventricular fibrillation stopped by electrical shock. Ventricular CLs are short. The variability of CLs should be noted with a shortening of CL from the beginning to the end. *A* and *B* reported the same ECG in 25 mm/s (beginning and then end).

Table 2 Values of the mean ventricular VF cycle lengths (CL) (ms) in VF and then ST-VF, for every group of 10 beats, from the beginning of tachycardia up to 50 beats; the mean and standard deviation (SD) were calculated for 0–10 beats, then 0–20 beats, then 0–30 beats, and so on up to 50 beats. The second column reports VF cycle range between the minimal and maximal intervals for each group of 10 consecutive beats (ms): (max: maximal, min: minimal, ave = average)

	Max–min (ms)	CL (0–10)	SD (0–10)	CL (0–20)	SD (0–20)	CL (0–30)	SD (0–30)	CL (0–40)	SD (0–40)	CL (0–50)	SD (0–50)
1 VF	48	188	14.01	169	26.16	161	23.64	156	21.97	153	19.86
2 VF	53	192	17.12	180	16.26	171	20.07	163	22.21	159	22.14
3 VF	26	168	2.3	170	2.83	168	4.0	163	10.99	159	12.12
4 VF	58	168	4.1	156	16.26	151	14.57	141	23.84	140	20.73
5 VF	39	206	10.21	193	18.38	184	19.85	182	16.62	181	14.89
6 VF	27	157	8.15	158	2.12	154	7.93	150	10.68	146	11.9
7 VF	60	179	20.31	194	21.9	185	22.18	176	25.3	171	24.91
8 VF	60	173	21.14	161	16.97	158	12.8	156	11.7	147	21.64
9 VF	27	179	15.45	171	21.6	166	11.7	165	10.04	162	10.40
	Ave (all) 44 ± 15										
1 ST-VF	9	173	3.01	173	2.88	175	2.36	175	3.28	174	3.29
2 ST-VF	11	165	4.06	166	2.92	167	1.73	166	2.87	164	4.64
3 ST-VF	9	211	3.80	202	4.5	201	7.78	196	5.12	199	6.27
4 ST-VF	10	195	2.69	197	2.89	196	2.28	199	2.99	198	2.98
5 ST-VF	9	201	4.86	199	3.01	210	4.09	215	5.12	216	4.68
	Ave (all) 9.6 ± 1**										

**$P < 0.002$.

Table 3 Diagnosis value of mean ventricular cycle length (CL) (ms) and the changes (Ch) within first 50 beats (maximal–minimal CL) to discriminate VF from ST-VF (sensitivity, se; specificity, sp; positive predictive value, PPV; negative predictive value, NPV)

	CL < 150	CL < 160	CL < 170	CL < 180	Ch ≥ 10 ms	Ch ≥ 20 ms	Ch ≥ 30 ms
Se	33%	37%	78%	89%	100%	100%	67%
Sp	100%	100%	80%	80%	80%	100%	100%
PPV	100%	100%	87.5%	80%	90%	100%	100%
NPV	45%	62.5%	67%	75%	10%	100%	62.5%

Discussion

We reported differences in ventricular CLs for ST-VF and VF requiring electrical shock. Mean CL and last CL were longer in the first case than in the second. Moreover, the CL increased or remained unchanged in patients with ST VF, until its termination and the CL decreased in patients with VF before syncope and electrical shock. The cut-off data of CL changes ≤20 ms seem to have the best diagnosis value for the differentiation of a VF from a ST-VF.

Polymorphic VT is frequently induced in patients with underlying heart disease, but rarely in patients without heart disease. Several years ago several studies have attempted to recognize the characteristics of non-sustained polymorphic VT that could be associated with sustained VT or VF.[10–13] However, none of them reported similar data.

In patients with previously documented or probable sustained VT, it was shown that it was necessary to continue PVS irrespective to the rate and duration of the induced non-sustained VT.[10] The use of non-sustained polymorphic VT as an endpoint for stimulation was shown as improving the specificity of PVS but also as impairing the yield of monomorphic VT.[11] In young patients with normal heart, aggressive stimulation protocols appeared to be required for the induction of sustained VT and non-sustained polymorphic VT was reported as a response to aggressive PVS of uncertain significance.[12]

In the case of BS the diagnosis value of the induction of a sustained VF is debated, considered as a powerful predictor of arrhythmic events during follow-up for some authors,[1,3] or unable to identify high-risk patients for other authors.[2,5–6] Only sustained VF was considered as abnormal in these different studies. In the

present study ST-VF appeared as not rare. Some patients present this arrhythmia at ICD interrogation. The measurement of the ventricular CLs before electrical shock would be interesting to avoid the shock in a patient with ST-VF beside the number of ventricular premature beats. Our results might represent the possibility of discriminating sustained VF and non-sustained VF according to the CL in terms of device programming. The changes of the CL with a mean decrease of >20 ms could be a good predictor of VF.

Other authors heave studied the CLs of VF. However, main studies concern the differences between induced and spontaneous VF. Lever *et al.*[13] had studied the degree of organization of VF in terms of the regularity of the electrical activity within the ventricle. They reported that measurements showed a statistically greater degree of regularity for induced VF than in spontaneous episodes. Sánchez-Muñoz *et al.*[14] have compared the spectral characteristics of the electrical signal recorded by an ICD during induced and spontaneous VF and they have shown that clinical and induced VF episodes in humans have different spectral characteristics.

Limitations of the study

The clinical application to automatic measurement of ventricular CLs before electrical shock has not been still developed.

The main problem is the low number of studied patients. A prospective and multicentre study is required to evaluate the significance of this arrhythmia.

Another important data have not been studied. *Figures 1* and *2* indicate marked differences of QRS amplitude with lower amplitude of QRS complexes before spontaneous interruption or electrical shock in patients with VF than in patients with ST-VF. QRS amplitude was not studied in the present study and could be another important parameter that could help to discriminate VF and ST-VF.

At least, when a polymorphic VF is induced, we are awaiting the loss of consciousness to perform the electrical shock. Fifteen seconds as minimal duration of polymorphic VT is arbitrary. This was the minimal time noted in this group to have the loss of consciousness. These patients have no underlying myocardial heart disease and the tolerance is probably better than in patients with low left ventricular ejection fraction. We cannot know if the data would be still the same for patients with advanced heart disease.

At least, CL may be a better determinant of loss of consciousness than it is a determinant of ST-VF.

Conclusion

Self-terminating VF in BS was not rare and could occur during PVS, defibrillation threshold testing, or spontaneously. Ventricular fibrillation CL was longer and progressively increased or did not change in ST-VF compared with electrical shock-terminating VF. These two parameters could be used for ICD programming, but other parameters are probably required.

Conflict of interest: None declared.

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Intracardiac echocardiography for transseptal puncture. A guide for cardiac electrophysiologists

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Abstract

The key to a successful catheterization of the left heart chambers is the safe transseptal puncture. Intracardiac echocardiography (ICE) is an attractive tool used in cardiac catheterization and electrophysiology labs to provide detailed images that can facilitate transseptal puncture. ICE permits a direct visualization of the endocardium and precisely locates the needle and the sheath against the interatrial septum. Two different ICE catheters are available: a phased array and a mechanical transducer, both being currently used in clinical practice. This paper describes the technique used for guiding transseptal puncture with ICE. Due to its advantages, ICE has currently become an important tool used to maximize the safety of the transseptal puncture and increase efficacy of interventional cardiology procedures.

Keywords: transseptal puncture; intracardiac echocardiography; left atrium; interatrial septum; tenting

Introduction

In the catheterization laboratory transseptal puncture (fig 1) is mostly used for radiofrequency ablation of atrial fibrillation [1,2], left accessory pathway ablation [3], balloon mitral valvuloplasty [4], closure of the left atrial appendage [5], atrial septal defect and ventricular septal defect closure [6], patent foramen ovale (PFO) closure [7], aortic valvuloplasty or transaortic valve replacement (TAVR) [8] and pulmonary valvuloplasty [9]. The key to a successful catheterization of the left heart chambers is a safe transseptal puncture.

Intracardiac echocardiography (ICE), first described in 1981, is an attractive tool in cardiac catheterization

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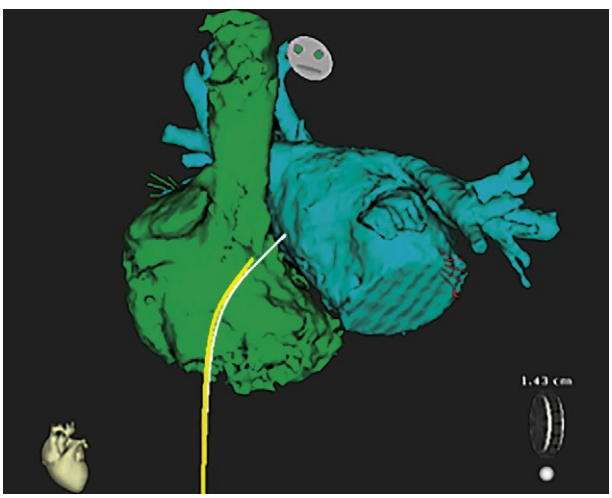

Fig 1. Computed tomography reconstruction of the left and right atrium. Fosa ovalis is the "real" interatrial septum between the right atrium and the left atrium (red circle). Around the fosa lies adipose tissue with small arterial branches, therefore the transseptal puncture should not be performed in the muscular part of the septum as it may complicate with pericardial effusion. The white arrow shows the direction of the catheter from the inferior vena cava towards the fosa ovalis during transseptal puncture.

and electrophysiology labs to provide detailed real-time near-field and far-field images that can facilitate transseptal puncture. Images can be stored using DICOM standards and used for continuing education and medical research [10].

ICE permits direct visualization of the endocardium and precisely locates the transseptal needle and the sheath in contact with the interatrial septum. ICE should be the preferred option for guiding a safe transseptal access in cases of a modified interatrial septum anatomy: thickened septum, floppy septum, interatrial septal aneurysm, lipomatous hypertrophy, previous suture of the septum after cardiac surgery, device closure of an atrial septal defect (ASD) [11]. The technique can be used also in cases with abnormal right atrial structures that interfere with the introduction of the needle, sheath and dilator into the right atrium, such as a prominent Eustachian ridge or a Chiari network [12-14]. Transesophageal echocardiography (TEE) is an alternative to ICE in these cases. Even though TEE can provide more views than ICE, ICE reduces the patient's discomfort, the probe being introduced through the femoral vein under local anaesthesia, thus avoiding general anaesthesia and its associated risk of aspiration pneumonia [15]. Other situations where ICE guidance is desirable are lead implantation in pregnant women, extraction of cardiac devices, pacemaker related endocarditis, retrograde double balloon valvuloplasty and endomyocardial biopsy [16].

In this paper we will review in a stepwise manner the technique used for ICE-guided transseptal puncture. This technique allows a safe crossing of the interatrial septum with minimal radiation exposure and without the need of general anaesthesia.

Currently available ICE systems

For visualization of the cardiac chambers, 2 different ICE catheters are available (fig 2). The first one is the phased-array ultrasound catheter, which consists of a 64-element transducer (ViewFlex from Saint Jude or AcuNav from Siemens-Biosense Webster) that uses multiple frequencies of 5-10 MHz, providing 90º sector images; it has modifiable depth control, allowing pulsed color and continuous Doppler imaging. The transducer is mounted on a 8 Fr four-way steerable catheter (see movie 1 on the journal site), introduced through the femoral vein inside the right atrium; it permits a penetration depth ranging from 2 mm to 12 cm. The second catheter (Ultra ICE from Boston Scientific) has a 9 MHz single element mechanical transducer that is mounted on an 8 Fr nonsteerable catheter, permitting 1800 rotations per minute. This transducer allows a 360º cross-sectional image in the radial plane [17].

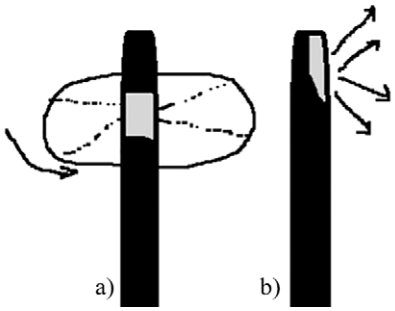

Fig 2. ICE probe. Schematic drawing of the 2 transducers types used for intracardiac echocardiography: rotational probe permits 180º image (a) and phased array probe permits a 90º sectorial image (b).

Utility of ICE to guide the transseptal puncture

In the center of the muscular interatrial septum lies a thin fibrous structure called the „fossa ovalis". This structure is derived from the septum primum and septum secundum and is the true septal wall between the left atrium and the right atrium [18]. Transseptal puncture should be performed at this level to avoid any pericardial effusion. Traditionally, the localization of fossa ovalis has been done by fluoroscopy. More recently, TEE and ICE have been used to guide the transseptal puncture.

Fluoroscopy provides limited anatomical information for the right and left anatomical structures. The fossa ovalis can be located fluoroscopically in the following way: the plane of the mitral valve and the left atrium can be identified by inserting an electrophysiology catheter inserted in the coronary sinus; the position of the aortic valve can be located by placing an electrophysiology catheter at the level of His bundle or, alternatively, by placing a coronary angiography catheter in the aortic bulb, close to the aortic valve. For safety reasons, the fluoroscopic method requires 2 catheters: one in the coronary sinus and one at the level of the His or inside the aorta; a long transseptal sheath, a dilator and a Brockenbrough transseptal needle are also needed. The transseptal sheath together with the dilator are inserted into the right femoral vein and then advanced on a supporting guidewire at the level of the superior vena cava (SVC). The guidewire is then removed and the transseptal needle is inserted inside the dilator. The ensemble is then carefully retracted from the SVC into the right atrium. When the transseptal sheath is sufficiently descended and it reaches the foramen ovale, a sudden discrete movement towards the left atrium can be observed. This „jump" is a sign that allows the operator to know that the sheath is at the level of the foramen ovale [11].

ICE imaging to guide to transseptal puncture

The standard approach uses a long transseptal sheath and a dilator that cover a Brockenbrough needle which are placed against the fosa ovalis. The system is introduced through the right or left femoral vein through an appropriate sized sheath (8 or 10 F) until it reaches the SVC [11]. The probe is advanced with a gentle anterior tip deflection to avoid entering venous branches on the way to the right atrium. By pulling back the probe from the SVC to the inferior vena cava (IVC), important structures of the right atrium can be identified: the orifice of the SVC, the right atrial appendage, the crista terminalis, the interatrial septum, the orifice of the coronary sinus, the tricuspid valve, the orifice of the IVC. Other structures, in close proximity to the right atrium can be visualized: the pulmonary artery, the ascending aorta with the aortic root, the right ventricle, the left ventricle and the cardiac valves. Another approach is to introduce the ICE catheter into the right atrium via the right subclavian or internal jugular vein (fig 3).

STEP 1: „Home view"

In this view the transducer is located in the mid-right atrium, aligned parallel with the SVC. The transducer is maintained in the neutral position in the same manner as outside the body, with the probe facing anteriorly. In this view the right atrium, right ventricle and tricuspid valve should be clearly seen (fig 4). A pericardial effusion should be excluded before any transseptal puncture.

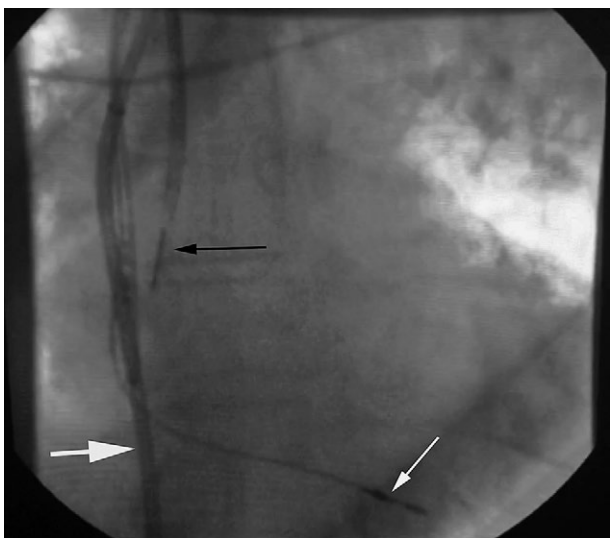

Fig 3. Superior approach. Radiological image with placement of the catheters during transseptal puncture using a superior approach. The ICE probe (black arrow) is inserted through the right subclavian vein in the middle of the right atrium. It is oriented towards the interatrial septum. The needle, dilator and sheath (large arrow) are introduced through the inferior vena cava. At the apex of the right ventricle an active fixation pacing lead can be observed (white arrow).

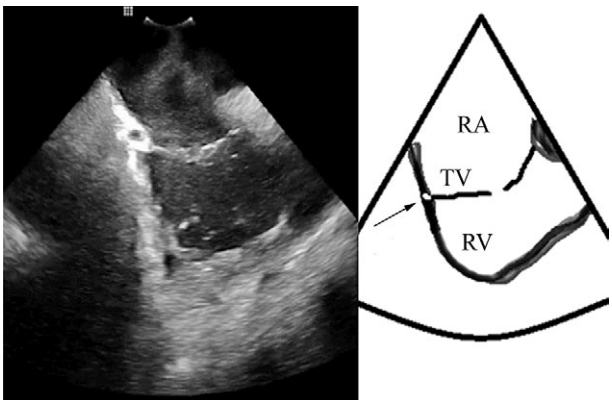

Fig 4. "Home view". Before any transseptal puncture the pericardium is verified for pericardial effusion. In the "home view" with the probe placed in the middle of the right atrium the following structures are visible: the right atrium (RA), ventricle (RV) and tricuspid valve (TV). At the level of the tricuspid valve the right coronary artery can be observed (arrow).

By rotating the catheter 30° clockwise, the aortic valve and the ascending aorta come into view, in close proximity to the right ventricular outflow tract (RVOT), the tricuspid valve and the pulmonary artery (fig 5, fig 6).

By performing a clockwise rotation of 60° from the „home view", the left ventricle, the mitral valve and the left atrium can be seen. In the anterior part of the left atrium, close to the mitral valve, the left atrial appendage (LAA) can be identified. If TEE was not performed previous to the transseptal puncture, ICE can be used to exclude the presence of a LAA thrombus by directly visualising the LAA and by measuring the velocity at 1 cm inside LAA (fig 7).

A counter clockwise rotation of 60° should bring back the „home view".

STEP 2: „Septal view"

From the „home view" the ICE probe is flexed posteriorly and rotated clockwise 90°, so the transducer faces the interatrial septum. This view is comparable with the bicaval view from TEE with superior/inferior orientation of the interatrial septum (fig 8, fig 9). On a chest X-ray, the position of the catheter will correspond to the lateral wall of the right atrium. The image obtained with this position shows the interatrial septum, the right and left atria, the coronary sinus and the pulmonary veins or the LAA, depending on the exact location of the transducer, facing posterior (for the pulmonary veins) or anterior (for the LAA).

From this view, by further clockwise rotation (180° from the „home view") the right pulmonary veins can be examined. A longitudinal view of the right pulmonary veins can be obtained by deflecting the ICE probe in a right to left plane.

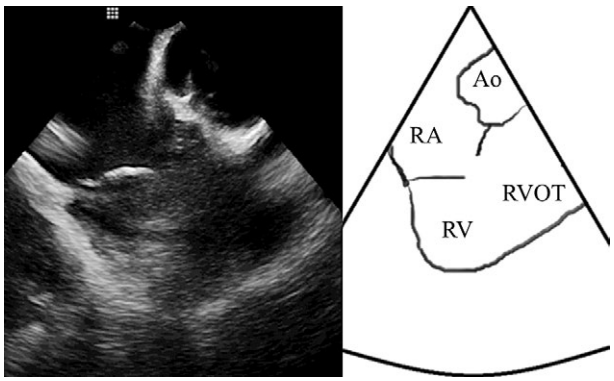

Fig 5. "Home view with aortic bulb". By making a slight 30° clockwise rotation from the "home view", the aortic bulb can be visualized close to the right cavities (RA – right atrium, RV – right ventricle). The aortic bulb (Ao) is an anterior structure that should be avoided during the transseptal puncture because of the bleeding risk. RVOT – right ventricular outflow tract

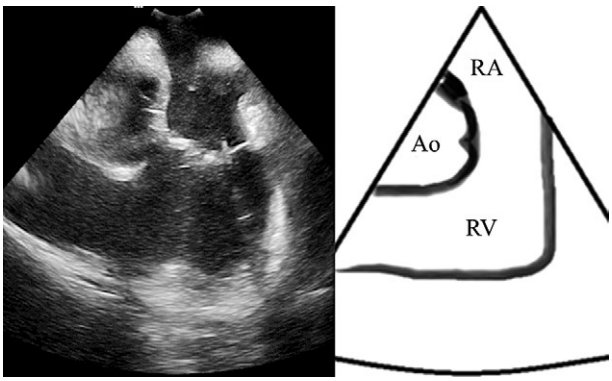

Fig 6. Superior approach to "Home view". The image shows the "home view" with the ICE probe inserted in the superior vena cava via a right subclavian vein. Compared to the same view obtained with the probe inserted from the inferior vena cava, the aorta is on the left side of the right ventricular outflow tract (RVOT). RA – right atrium, RV – right ventricle

By further applying a clockwise rotation, the transducer will move near the tricuspid valve annulus and inferior to the aortic valve, obtaining the „short axis view". In this view the aorta will be displayed together with the interatrial septum offering anterior/posterior orientation for the transseptal puncture. This view corresponds to the „short-axis view" in TEE but the near-field is represented by the right atrium and not the left atrium like in TEE.

STEP 3: Tenting of the fosa ovalis

When the sheath and the dilator are positioned in the middle of the fossa the „tenting effect" occurs, because of the fibroelastic consistence of the fosa ovalis. The presence of this sign allows a precise puncture of the septum outside the muscular part of it, which can lead to pericardial effusion (fig 10).

In order to avoid complications, the fossa ovalis should be accurately visualized. The septum should be crossed in the posterior part of the fossa to avoid puncture of the aortic root. A puncture that is made anteriorly directs the needle, sheath and the catheters towards the left atrial appendage risking perforation. Furthermore, an anterior puncture makes the manipulation of electrophysiology catheters difficult in the posterior part of the left atrium and pulmonary veins. In order to guide such a posterior puncture of the fosa ovalis, the ICE catheter is rotated clockwise, to visualize the left superior pulmonary vein (LSPV) and left inferior pulmonary vein (LIPV). The superior and inferior position of the transseptal needle against the septum can be assessed by slightly advancing the ICE probe along the septum. The anterior and posterior position of the needle against the septum can be assessed by performing a clockwise (posterior) and counter clockwise (anterior) rotation. For

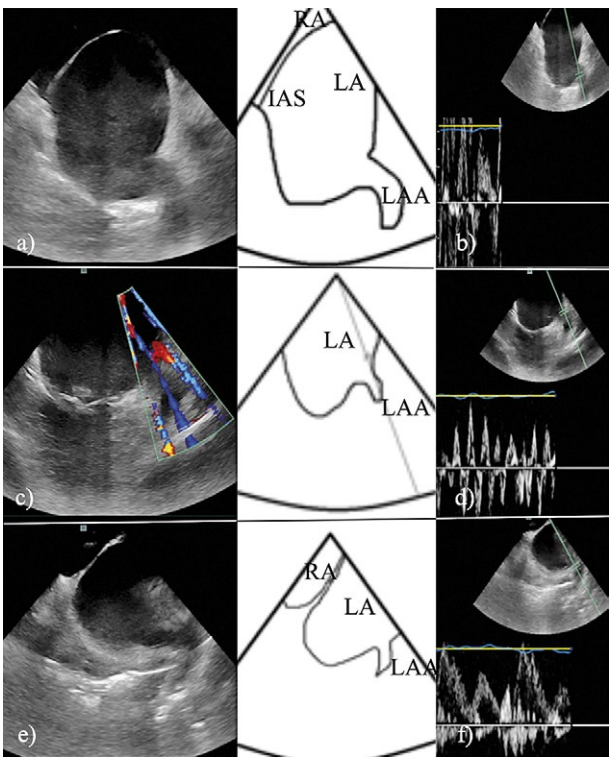

Fig 7. Left chambers. An anterior rotation from the "home view" brings the left atrial appendage (LAA) into image: a) The "septal view" shows the interatrial septum between the right atrium (RA) and left atrium (LA). The left appendage is also visible with no thrombus at this level; b) pulsed Doppler characterization of the left atrial appendage flow; c) color Doppler of the LAA; d) pulsed Doppler of the LAA shows emptying velocities of 25-30 cm/sec, the patient being in atrial fibrillation; e) interatrial septum between the right and left atria; f) pulsed Doppler of the LAA shows normal flow during sinus rhythm.

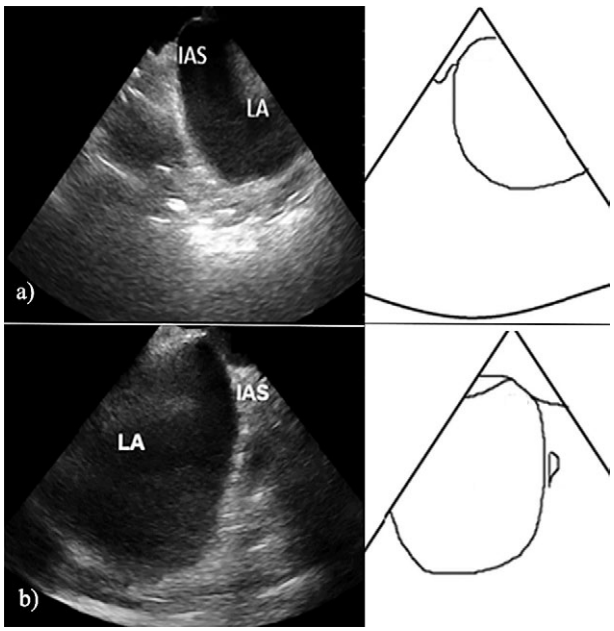

Fig 8. Septal view. Visualization of fosa ovalis from the inferior and superior approach: a) note that the septum between the right and left atrium is convex towards the right atrium, making it difficult to position the sheath and dilator on the fosa ovalis; b) interatrial septum seen from the superior vena cava in a right subclavian approach.

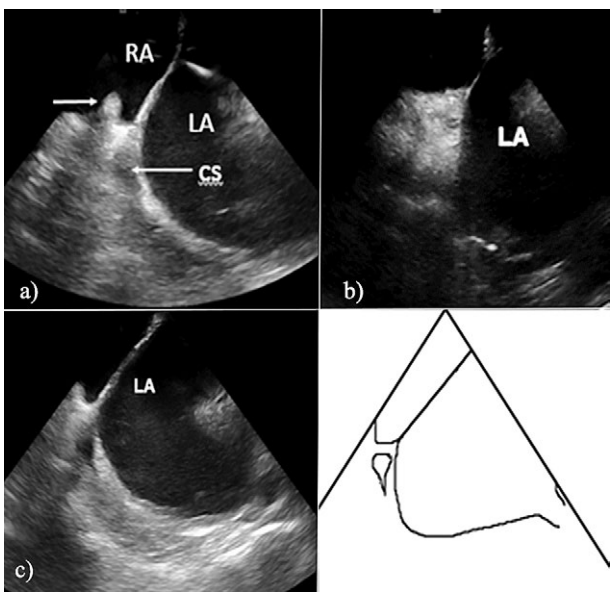

Fig 9. "Septal view". Visualization of fosa ovalis: a) Eustachian ridge (ER) and coronary sinus (CS) are also visible at the level of right atrium. Eustachian ridge is an atrial structure that separates the orifice of the inferior vena cava from the ostium of the coronary sinus and continues with the crista terminalis; b) small fosa ovalis in a patient with lipomatous septum; the puncture should be performed at the level of the fosa and not the hypertrofiated septum; c) in this patient the septum is long and thick. Coronary sinus is also visible (Cs)

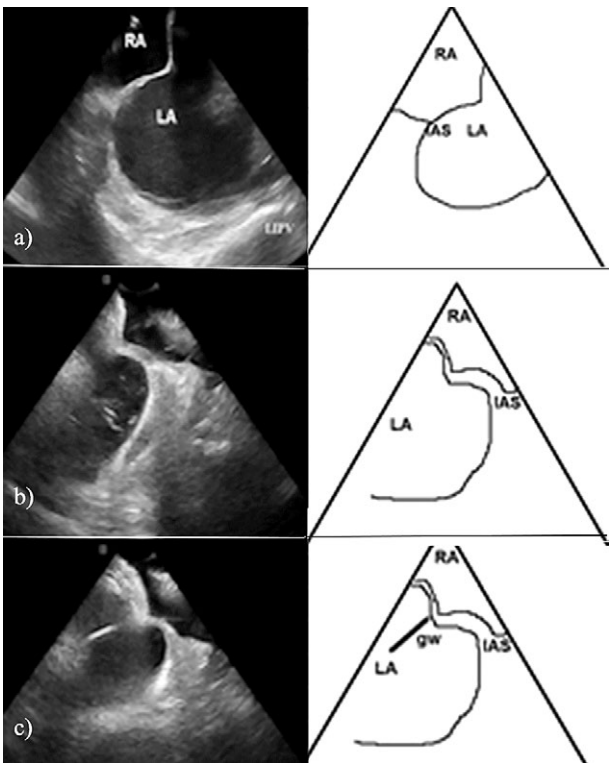

Fig 10. Brockenbrough needle against the fossa ovalis: a) typical "tenting" of the fossa ovalis, just before the puncture; the ICE probe was inserted through the inferior vena cava; b) tenting of the interatrial septum with the ICE probe inserted through the superior vena cava (please note the inverse image compared with a); c) passing of the interatrial septum with the guidewire

the aortic valve visualization an anterior alignment of the transseptal needle is required, while for the far-field pulmonary vein visualization a posterior alignment of the needle is needed.

STEP 4: Crossing the interatrial septum

After the optimal positioning of the dilator and sheath against the fossa ovalis with visualization of the tenting sign, the needle is advanced inside the left atrium. Injection of physiological serum or contrast dye inside the left atrium confirms successful puncture by the presence of microbubbles in the LA (fig 11). After a successful puncture, a guidewire is advanced into the LSPV or LIPV to stabilise the transseptal sheath and the dilator. The system is then advanced back and forth through the septum to dilate the puncture site. After the transseptal puncture is performed, anticoagulation with unfractionated heparin is carried out, in order to maintain an ACT (activated clotting time) of 2-3 times the normal value.

After the retraction of the Brockenbrough needle a second transseptal puncture is performed and the ablation catheter with the lasso catheter are advanced inside the left atrium and pulmonary veins.

STEP 5: Left atrium and pulmonary veins

Once the transseptal puncture is made, ICE can give important information on the number, position and size of the pulmonary veins, as well as the presence of a common trunk between the 2 left veins. The LAA can be assessed in terms of size, form, anterior position and spatial relationship with the pulmonary veins (fig 12). It will also offer real-time information on the precise location of the ablation catheter and lasso catheter inside the left atrium or pulmonary veins (fig 13-16). Contact with the antrum of the pulmonary veins can also be assessed, as well as the exact position of the lasso catheter inside the pulmonary vein.

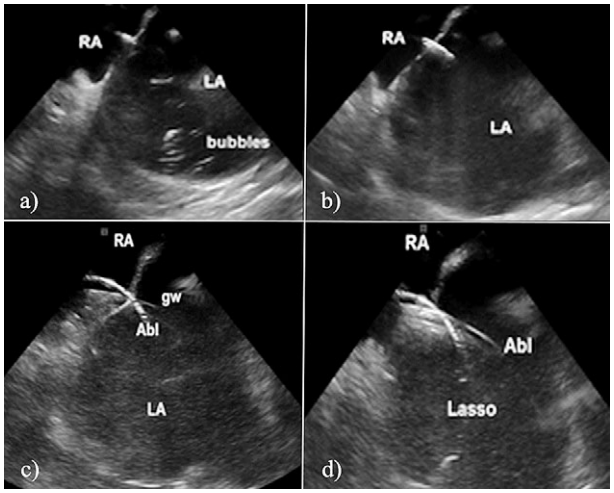

Fig 11. Successful transseptal puncture: a) bubbles in the left atrium confirm the successful transseptal puncture. Serum or contrast dye can be injected in the left atrium as they both show bubbles; b) transseptal sheath passes the septum and goes inside the left atrium; c) a second guidewire (gw) is inserted through the interatrial septum, beside the ablation catheter; d) using the second guidewire another transseptal sheath is introduced in the left atrium together with a Lasso catheter.

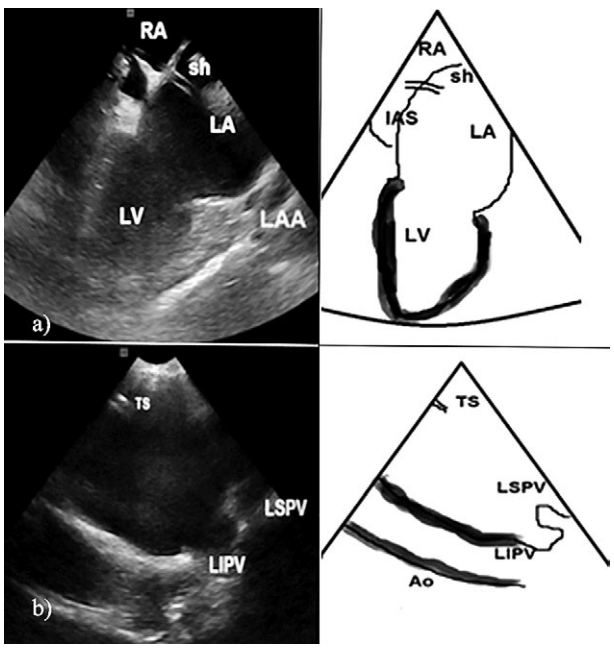

Fig 12. Anterior and posterior puncture of the fossa ovalis: a) transseptal puncture was performed in the anterior part of the fosa ovalis; therefore, the left ventricle and LAA are visible b) transseptal puncture was performed in the posterior part of the fosa ovalis; therefore, the left superior and inferior pulmonary veins are visible.

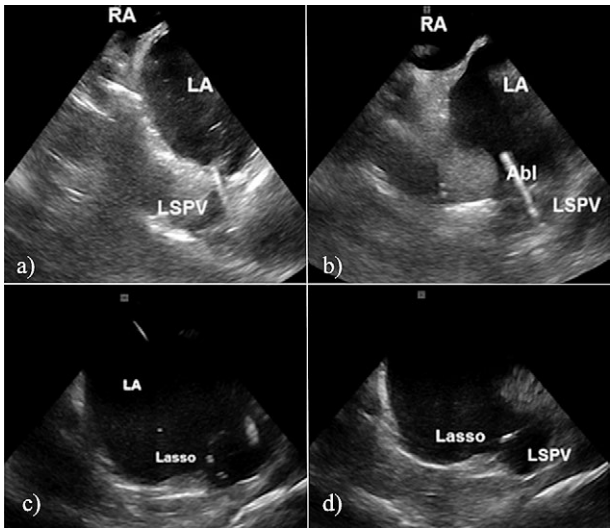

Fig 13. Ablation and Lasso catheter inside the left superior pulmonary vein: a) the ablation catheter is deep inside the LSPV towards the pleura of the left lung; b) the ablation catheter is retraced towards the ostium of the LSPV; c) lasso catheter inside the LSPV.

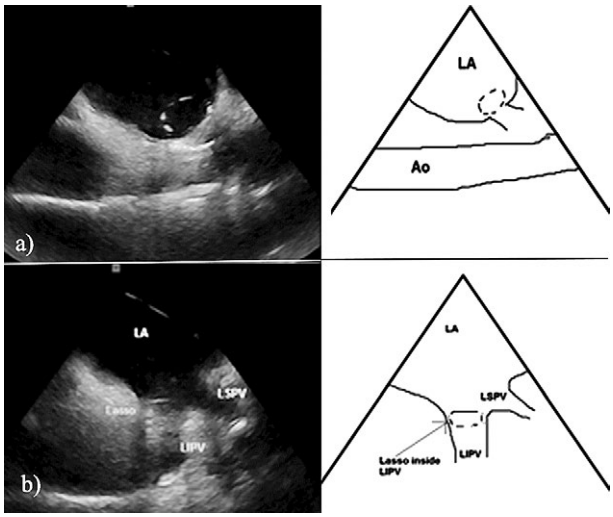

Fig 14. Lasso catheter inside the left inferior pulmonary vein: a) lasso catheter at the level of the left inferior pulmonary vein; b) both left superior and inferior pulmonary veins are visible; the Lasso catheter is inserted in the LIPV.

STEP 6: Left ventricular long-axis view

At the end of the procedure, the catheters and the sheaths are retracted inside the right atrium, leaving a small atrial septal defect. Because of the small size of the catheters, the residual defect is small and clinically insignificant. It usually closes completely within 3 months [19]. Before the ICE catheter is completely removed, it should be flexed anteriorly and rotated to pass from the right atrium through the tricuspid valve inside the right ventricle. From this position, the left ventricle can be visualized and a pericardial effusion can be excluded at the end of the ablation procedure (fig 17).

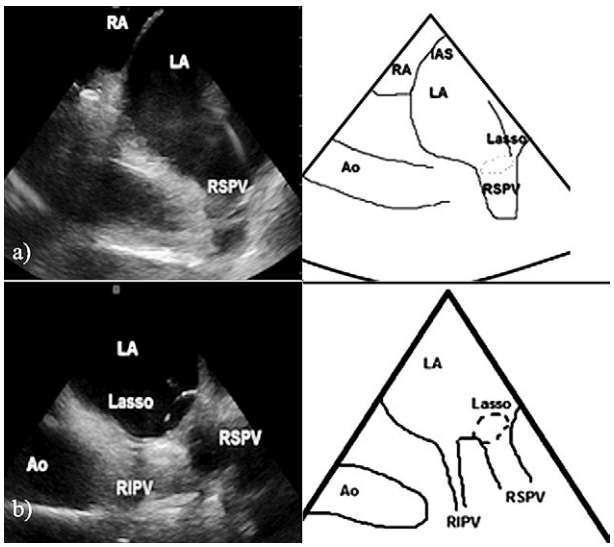

Fig 15. Lasso catheter at the level of the right superior pulmonary vein: a) from the "septal view", a clockwise rotation brings into image the right superior pulmonary vein (RSPV). The vein is distal to the ICE probe; therefore, it is situated in the bottom of the image, draining in the body of the right atrium; b) A further rotation of the probe will display superior and inferior right pulmonary veins. A Lasso catheter is inserted at the ostium of the RSPV.

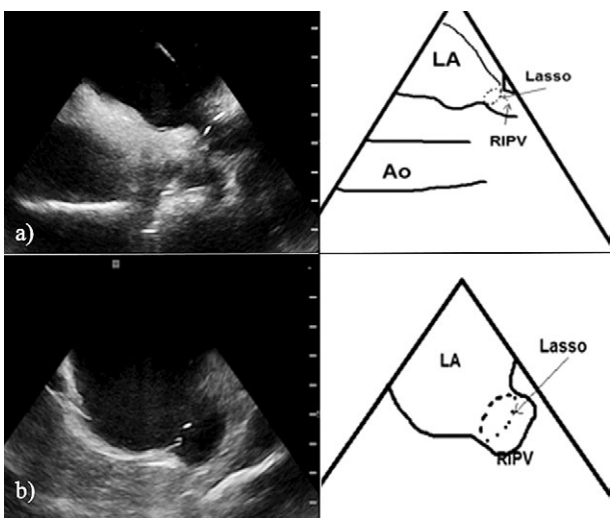

Fig 16. Lasso catheter at the level of the right inferior pulmonary vein: a) from the septal view a further clockwise rotation will bring the RIPV into image. RIPV is more posterior compared to RSPV which is an anterior vein. A Lasso catheter is inserted at the level of the RIPV ostium.

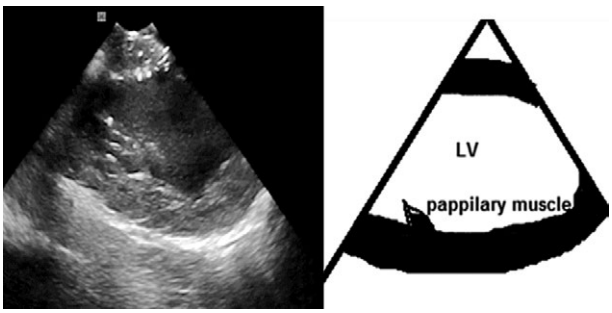

Fig 17. Left ventricular view. There is no pericardial effusion at the end of procedure.

Complications of transseptal puncture

In patients with abnormal anatomy the transseptal puncture is difficult because of the atypical position of the interatrial septum. Radiological guidance without ICE does not permit a good localization of the septum and complications can occur: pericardial tamponade, aortic root puncture, arterial embolism with atrial thrombus, perforation of pulmonary veins or of the inferior vena cava [20]. ICE-guided puncture was developed to avoid life threatening complications and to increase the success rate of an effective puncture in the case of an abnormal septum location.

Conclusion

ICE is used in the electrophysiology laboratory to increase the safety of the transseptal puncture and to guide the catheter ablation procedures. It allows for early detection of procedure-related complications such as pericardial effusion, aortic root puncture or catheter thrombosis. It can be used by the cardiac electrophysiologist without the presence of a dedicated sonographer in the EP room. Importantly, it significantly reduces contrast dye administration and X-ray radiation exposure and may avoid general anaesthesia. For all these reasons, ICE is a valuable tool that should be part of any modern electrophysiology laboratory or catheterization lab dedicated to structural heart disease interventions.

Conflict of interest: none

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Review

Anatomical-MRI Correlations in Adults and Children with Arrhythmogenic Right Ventricular Cardiomyopathy

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Abstract: Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a rare disease in which the right ventricular myocardium is replaced by islands of fibro-adipose tissue. Therefore, ventricular re-entry circuits can occur, predisposing the patient to ventricular tachyarrhythmias, as well as dilation of the right ventricle that eventually leads to heart failure. Although it is a rare disease with low prevalence in Europe and the United States, many patients are addressed disproportionately for cardiac magnetic resonance imaging (MRI). The most severe consequence of this condition is sudden cardiac death at a young age due to untreated cardiac arrhythmias. The purpose of this paper is to revise the magnetic resonance characteristics of ARVC, including the segmental contraction abnormalities, fatty tissue replacement, decrease of the ejection fraction, and the global RV dilation. Herein, we also present several recent improvements of the 2010 Task Force criteria that are not included within the ARVC diagnosis guidelines. In our opinion, these features will be considered in a future Task Force Consensus.

Keywords: arrhythmogenic right ventricular cardiomyopathy; fibro-fatty; myocyte; cardiac MRI

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1. Introduction

Arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVC) is a cardiomyopathy that generally affects the right ventricle and often has familial transmission. However, sporadic cases are described within the literature as well [1]. ARVC mostly affects young adults, with 80% of patients being under 40 years old. From a pathophysiological standpoint, the main ARVC anomaly is desmosome dysfunction. Desmosomes are membrane proteins with major roles in cell adhesion, signal transmission, and cell differentiation. Hence, desmosome dysfunction leads to cellular disorders in both muscles and the skin [2].

Cardiac magnetic resonance imaging (MRI, CMR) is a non-invasive technique that is able to acquire multiplanar images, with excellent contrast of soft tissues and without the use of ionizing radiation. Therefore, CMR is deemed to be the best imaging method for the characterization of the right ventricle and the muscle tissue changes within ARVC [3]. Even though the presence of a cardiac defibrillator has been considered a contraindication for older MRIs, current 1.5 Tesla MRIs allow image acquisition from these patients as well. Understandably, the image quality is poorer in the presence of metallic implantable devices [4]. There are several other imaging methods that have been used for RV assessment in ARVC, including cardiac ultrasound and RV angiography. With the exception of secondary RV aneurysm, echocardiography and RV angiography cannot provide information regarding the structure of the ventricular wall and the replacement of the myocardium with adipose or fibrous tissue, which is the hallmark of ARVC [5]. Due to the small number of ARVC cases in the general population, the experience of radiologists or cardiologists in the analysis of ARVC CMR images is limited. An accurate diagnosis requires experience and a large number of examined cases [6]. Hence, this review focuses on the implications of CMR in the identification and characterization of ARVC-related lesions.

2. Brief Pathology Considerations in ARVC

ARVC is a disease in which the muscle tissue of the right ventricle is replaced by adipose and fibrous tissue, leading to severe ventricular arrhythmias such as ventricular tachycardia (VT) or ventricular fibrillation (VF) [7]. In general terms, arrhythmic manifestations emerge in the second to fourth decades of life [8] and are represented by arrhythmias originating from within the right ventricle: from rather simple arrhythmias such as premature ventricle contractions (PVCs) to more complex ones such as VT or VF [9]. In the general population, 20% of deaths in young adults under 35 years may be attributable to ARVC [10,11].

In ARVC, three stages of evolution can be described using anatomical and histological data [12,13]. Understandably, these stages are correlated with clinical manifestations of the disease. In the first stage of minor histological changes [14,15], the alterations may be so discreet that they essentially cannot be visualized on ultrasound, angiography, MRI or endomyocardial biopsy. However, this stage is not considered harmless, as the minor lesions can activate re-entry circuits, generating dangerous ventricular arrhythmias. In the second "symptomatic" stage, there is marked infiltration of the myocardium with adipose and fibro-adipose tissue, which can lead to ventricular tachycardia, ventricular fibrillation, and sudden cardiac death. Furthermore, in the third stage, the "end-stage" of the disease, the RV damage is massive, and biventricular dilation occurs, with irreversible heart failure [2,10].

2.1. Right Ventricle Pathological Features in ARVC

ARVC can be characterized by the abnormal predominance of either adipose tissue or fibro-adipose tissue that replaces the normal RV myocardium. Regardless of the pathological form, this myocardium replacement can be associated with several other entities, such as RV dilation, RV or RV outflow tract (RVOT) aneurysm, concomitant impairment of the left ventricle, presence of inflammatory infiltrates in the ventricular myocardium, and even dilation of the right atrium [13–20]. Of note is the fact that lesions are initially limited at the subepicardial level and later progress towards the endocardium, with the impairment of the entire ventricular wall (Figure 1). This explains why incipient forms are described in patients without any symptoms but with alterations of the subepicardial ventricle [21].

In general terms, the replacement with adipose and fibro-adipose tissue occur in the "triangle of dysplasia", a specific area that is delineated by the anterior infundibulum, the apex of the right ventricle, and the inferior wall of the right ventricle [3,18–24]. However, dysplasia lesions can also occur in the posterior wall, interventricular septum, and right atrium [2,6,10,12,13]. The implication of the interventricular septum often leads to con-

duction abnormalities, such as right bundle branch block, atrio-ventricular conduction disorders, and even septal intramyocardic VT.

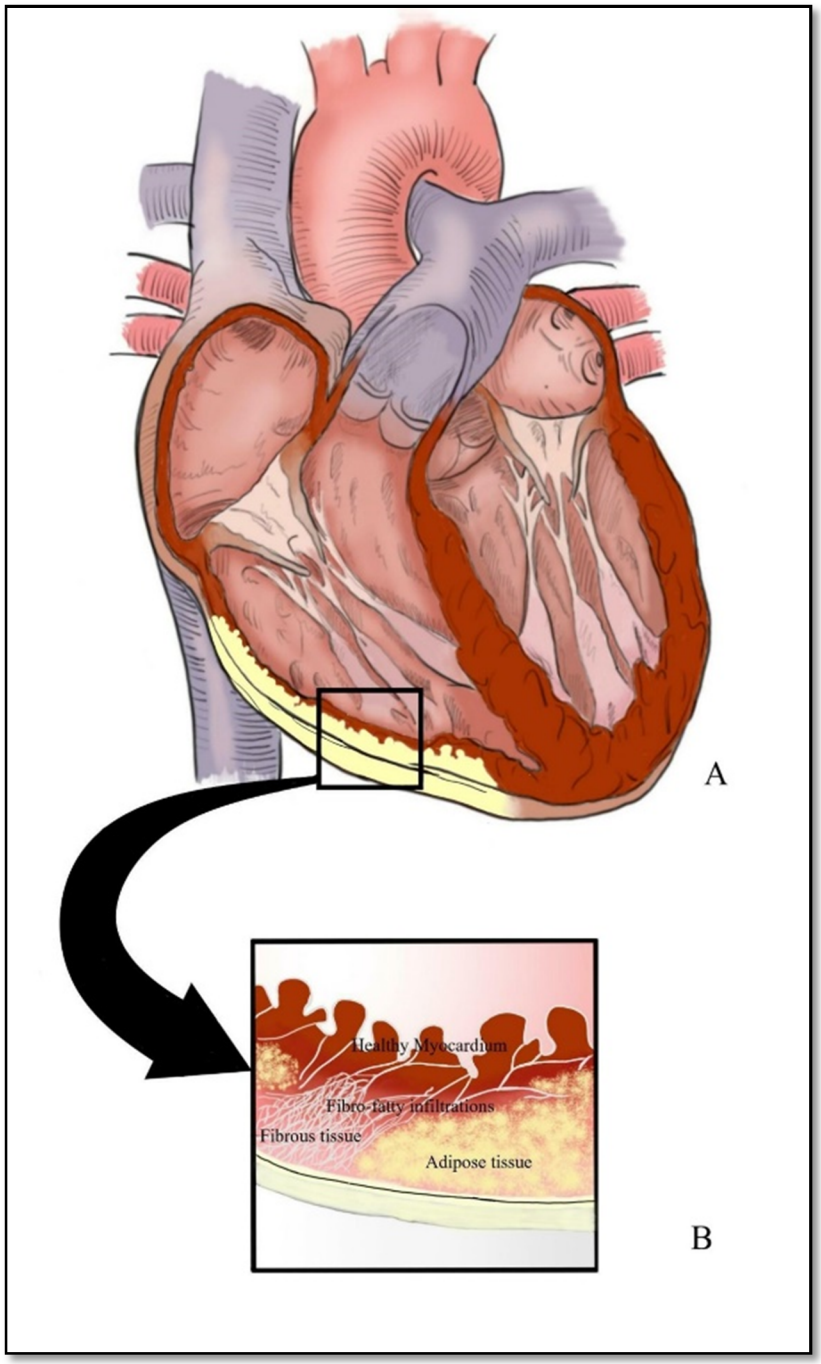

Figure 1. Representation of the white-yellow discoloration of the myocardium on macroscopic examination (**A**) and fibrous-adipose tissue deposition proceeding from the epicardial region towards the subendocardial portion of the myocardium (**B**).

The main histopathological alterations within the "triangle of dysplasia" are the decrease in number of myocardial fibers and the abundant invasion of subepicardial fat within the myocardium. The "triangle of dysplasia" term has been used since the 1980s when Marcus et al. described 22 ARVC cases [16] where the location of the adipose replacement of the myocardium was located at the level of the triangle. Furthermore, in 13 patients, an aneurysm was detected and had the same location—within the "triangle of dysplasia". When the lesion was examined microscopically, interstitial infiltration with

adipose tissue was observed within the triangle, with marked decrease of myocardial fibers and hypertrophy with dystrophic small nuclei in the remaining fibers. In addition, it should be mentioned that necrosis is an uncommon feature in patients with ARVC and was only found in 10.64% of patients in the Mu study [18], but contrarily in a higher percentage of 54.5% by Nava et al. [25].

With respect to the presence of inflammatory cells, differences between the adipose and fibro-adipose forms are described in the medical literature. Thus, in 17% of the patients with adipose form, fibro-inflammatory infiltrates are present compared to 100% in patients with fibro-adipose form. These inflammatory infiltrates may be accountable to some extent for the dilation of the right ventricle, in the sense that 67% of patients with fibro-adipose form had dilation of RV compared to 8% of those with fibrous form in the study performed by the Padua group [9]. Even if RV dilation is more important in the fibro-adipose group, the thickness of the opposite ventricular wall is higher in patients with adipose form due to the particular disposition of the epicardial and subepicardial adipose tissue [9].

As for the weight of hearts autopsied with ARVC, the differences between adipose and fibro-adipose form are not significant as they also depend on the age of autopsied patients. In the study of the Padua group, the heart weighted 432 g for fibro-adipose type ARVC and 481 g for adipose form. However, in the presence of right ventricular aneurysms, the total weight of the heart increases proportionally to the volume of the aneurysm.

2.2. Left Ventricle Pathological Features in ARVC

Animal studies have shown that 83% of cats with ARVC and 35% of dogs with ARVC had concomitant left ventricular damage. In humans, Nava et al. [19] described two cases of left ventricular involvement during 11 autopsies. One of the most important limits of this study is that the autopsies did not include the dissection of the left ventricle in 9 of 11 cases; therefore, the number of LV impairments could be higher. Furthermore, out of the 11 autopsies, 6 had fatty form ARVC and 5 had fibro-fatty form ARVC. Of the 11 autopsies, 8 hearts had dilation of the right ventricle and 3 had severely dilated RV. Rastegar et al. found concomitant left ventricle (LV) involvement in 55% of patients with abnormal CMR. Moreover, 9% had only isolated LV involvement, without impairment of the right ventricle [26].

2.3. The Pathology of Right Atrium Involvement in ARVC

Fox et al. examined the right atrium of 12 cats that died of ARVC, observing that 10 of them had concomitant left ventricular involvement, whilst 2 of them had biatrial impairment [27]. Basso et al. found that 48% of the 23 dogs autopsied for ARVC had concomitant LV involvement, and 35% of the autopsied dogs presented concomitant right or left atrium involvement [28].

To certify right atrium involvement in patients with ARVC, Li et al. compared histological changes of the RA from three patients with ARVC with three other patients with permanent atrial fibrillation [29]. In patients with ARVC, RA microscopy revealed a decrease in the number of cardiomyocytes and an abundant development of adipocytes, as well as interstitial fibrosis. However, in patients with permanent atrial fibrillation, microscopy revealed a decrease in the number of cardiomyocytes and an increase in adipocytes, fibrosis, and inflammation. The inflammatory cells involved were T lymphocytes and macrophages, mixed with necrotic cells.

2.4. Moderator Band: Pathological Features in ARVC

The moderator band is anatomically found within the "triangle of dysplasia". As such, if the myocardium within the dysplasia triangle is affected by ARVC, the pathophysiological changes will also reflect upon the moderator band. Furthermore, the fibro-fatty tissue can extend from the moderator band to the insertion place in the right ventricular wall, where aneurysms or bulging may occur. In addition, the fibro-fatty tissue that affects the moderator band may also involve the right branch of the conduction system con-

tained within the moderating band, resulting in a complete or "incomplete" right bundle branch block. On ultrasound examination, the moderator band will appear thickened and hyperlucent due to the structural changes [30,31].

In the Bauce study, of 120 individuals taken into consideration, 40 had ARVC, 40 were endurance athletes, and 40 were healthy individuals [32]. Compared to the control group, patients with ARVC showed moderate band hypertrophy as well as hyperechogenicity on cardiac ultrasound examination. However, the changes in the moderate band were similar when the group of athletes was compared to that of patients with ARVC and could not be considered as key element of distinction between the two categories of individuals. Yoerger et al. also compared the moderator band as visualized by echocardiography in a group of 29 patients with ARVC with a control group of 29 healthy individuals [33]. One-third (31%) of those with ARVC presented moderator band hyperechogenicity, which was a good criterion for discriminating between the two groups. D'Ascenzi et al. showed on a group of over 1000 Olympic athletes that the moderator band hyperechogenicity was present in five healthy individuals (0.5%), and that this cannot be a criterion that would be highly specific for ARVC [34]. Sometimes the deposition of adipose tissue inside the moderator band is well delimited, forming "pseudotumors" that are visible both during non-invasive examinations such as cardiac ultrasound or cardiac MRI, or during autopsy [35].

3. Cardiac MRI Features in Arrhythmogenic Right Ventricular Cardiomyopathy

Due to desmosome dysfunction, the RV muscle is replaced with fibrous or fatty tissue. This replacement leads to thinning of the right ventricular wall [36], dilation of the RV, and a consecutive increase in the size of the heart [13,15–18]. Furthermore, the pathological alterations in ARVC are not limited solely to the right ventricle but may also include the LV. The involvement can be regional or diffuse at the level of the interventricular septum or at the level of the LV free wall. Depending on the technique used to evaluate the right ventricle—autopsy, endomyocardial biopsy, cardiac ultrasound, or cardiac MRI—LV involvement in ARVC varies between 16% and 76% (Figure 2) [25,37].

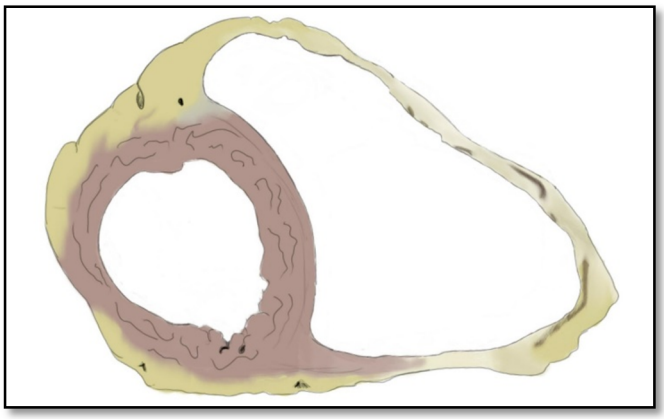

Figure 2. Representation of a cross-section of the heart with an enlarged right ventricle and fibro-fatty replacement of the ventricular wall; signs of left ventricular involvement are also present.

Several other studies showed concomitant involvement of the right atrium in some cases of ARVC [38–40]. Brembilla-Perrot et al. showed a higher susceptibility to atrial arrhythmias in patients with ARVC, which implies that the disease is not limited to RV but may also affect the RA [41]. The implication of the RA is of practical importance for a number of reasons. First and foremost, when detecting fibro-adipose replacement inside the right atrium in a patient with ARVC, one should consider an antiarrhythmic drug to prevent episodes of atrial arrhythmias. Secondly, in this category of patients, if an internal cardiac defibrillator is implanted for the prevention of sudden cardiac death, double chamber defibrillators are preferred in order to differentiate between ventricular

and supraventricular arrhythmias. In addition, atrial arrhythmias increase the risk of stroke and peripheral embolism, and therefore some patients with ARVC might benefit from long-term anticoagulation. Moderator band alterations have been described in ARVC in the past as well. As such, it is abundantly clear that the cardiac lesions in ARVC are not located only within the RV, but may alter other cardiac structures as well, prompting a thorough MRI evaluation of these entities.

3.1. Right Ventricle CMR Evaluation in ARVC

The Task Force Criteria for the diagnosis of ARVC include morphological and functional characteristics of the right ventricle demonstrated by cardiac MRI. It is often used as a first-line examination for supporting an ARVC diagnosis because it is able to objectively identify alterations in accordance with the Task Force Criteria. Moreover, some authors consider cardiac MRI as the gold standard in the diagnosis of ARVC as it provides information on right ventricular volumes, segmental contraction, and ejection fraction [42,43]. However, it must be noted that MRI alone does not provide sufficient major criteria for a definite diagnosis of ARVC as other Task Force Criteria are required. If the diagnosis is based only on cardiac MRI criteria, inaccuracies may occur, as adipose tissue may also be present inside the right ventricle in physiological conditions [44].

The first Task Force Criteria for the diagnosis of ARVC were proposed by McKenna et al. in 1994 [45]. In 2010, Marcus et al. [12] proposed new, revised criteria that increased the sensitivity and specificity of the ARVC diagnosis. These new criteria included information from cardiac MRI which are illustrated in Figures 3–6 below:

(a) **RV contraction disorders and functional abnormalities**
Unlike the initial diagnostic criteria, the 2010 Revised Task Force Criteria [12] are quantitative rather than qualitative. Three types of changes were included: (1) segmental RV contraction abnormalities, (2) dilation of the RV, and (3) reduction of the RV ejection fraction. It is notable that intramyocardial fat or delayed enhancement are not included in the criteria for differential diagnosis strictly because these changes can be found in healthy people or in other diseases affecting the right ventricle. The association between akinesia/dyskinesia or RV regional contraction asynchrony with RV volume dilation or RV ejection fraction <40% is considered a major criterion for the diagnosis. As mentioned beforehand, the Revised Criteria are quantitative. Therefore, RV dilation is defined as the ratio of RV volume/body surface area > 110 mL/sqm in men or >100 mL/sqm in women. The minor criterion is defined as the presence of akinesia/dyskinesia with decreased ejection fraction of 40 to 45%, contraction abnormalities, or increased RV volume between 100 and 110 mL/sqm in men or 90 and 100 mL/sqm in women. It is worth noting that microaneurysms as well as segmental RV dilatations were removed from the Diagnostic Criteria because they are rather subjective and challenging to evaluate.

(b) **Decrease of the RV ejection fraction (EF)** is a diagnostic key element and occurs when several areas of impaired contraction cumulate and impair the general contractility function or when the dilated right ventricle. Taking into consideration the degree of EF decrease <40% or between 41% and 45% is rather important, as this criterion, together with the contraction abnormalities, may represent either a minor or major diagnostic criterion for ARVC [12,45].

(c) **RV dilation** is also a key element for the diagnosis of ARVC. It can be segmental or global. Segmental expansion can affect only the RVOT or parts of the RV such as the basal free wall or the middle third of the free wall. It is a diagnostic criterion with high sensitivity and specificity for ARVC (Figure 3). Only the global dilation of RV is considered a diagnostic criterion for ARVC because segmental dilatation is rather difficult to interpret [12,45].

(d) **Intramyocardial adipose tissue disposition—"obsolete"**
Although intramyocardial fat has long been a diagnostic criterion for ARVC, it is no longer used because other pathological or physiological conditions can lead to

this appearance in cardiac MRI. In normal people, epicardial fat can penetrate to the myocardium and endocardium, with no clear demarcation between the epicardium and the myocardium, leading to misinterpreted images as ARVC. When intramyocardial fat is detected, it will be considered pathological only if it is associated with contraction abnormalities of the corresponding wall [12,45]. Fat in ARVC appears as hyperintense intramyocardial signal at T1 spin-echo. Adipose tissue infiltrates mainly the RVOT, the free wall of the right ventricle, the intracavitary trabeculae, the moderating band, and the right side of the interventricular septum (Figure 4). Tansey et al. showed on autopsies of individuals without known heart disease that 85% of them had myocardial infiltrates with adipose tissue [46]. Mainly, the RVOT, free wall of RV wall, apex, and RV antero-lateral wall are affected, but these intramyocardial deposits do not change the thickness of the ventricular wall or the regional contraction. If the deposits extend from the epicardium to the endocardium, crossing the myocardium, then the ventricular wall may increase in size as a normal feature of the adipose distribution. It seems that these fat deposits in healthy people increase with age and are more common in obese people without being pathological [47].

(e) **Thinning of the RV wall**
This is a component that was not included in the Task Force Criteria for the diagnosis of ARVC [12,45]. This is because the reports of different authors were not consistent with regards to the thinning or thickening of the ventricular wall. Therefore, thinning of the wall is considered pathological only when associated with contraction abnormalities at the same level [48] (Figure 6).

(f) **Hypertrabeculation** of intracavitary structures such as papillary muscles or moderator band occurs as a result of infiltration with adipose tissue. Although it can be present in up to 40% of patients with ARVC, it can also occur in various other diseases; therefore, it is not considered a Task Force Criterion for the diagnosis of ARVC.

(g) **Delayed enhancement**
The significance of delayed enhancement in cardiac MRI is fibrosis, edema, or inflammation [49]. It is not possible to clearly differentiate the exact cause of the increase in the extracellular volume. The abnormal tissue causes gadolinium retention while normal myocardial tissue does not. It is estimated that approximately 67% of patients with ARVC have delayed enhancement of the ventricular walls. In the study of Tandri et al. [49], 6 out of 10 patients with ARVC presented induced VT during electrophysiological study, and 4 did not have induced VT. It is relevant to mention that among patients with inducible VT, all six had delayed enhancement in cardiac MRI, and among those who were not inducible, only one had delayed enhancement in MRI.

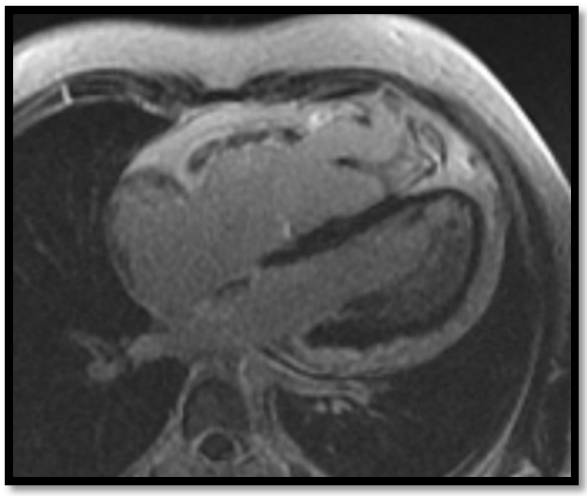

Figure 3. Cardiac MRI image of ARVC in a 35-year-old adult male with enlargement of the right ventricle [50] (Case courtesy of Dr Azza Elgendy, Radiopaedia.org, rID: 57972).

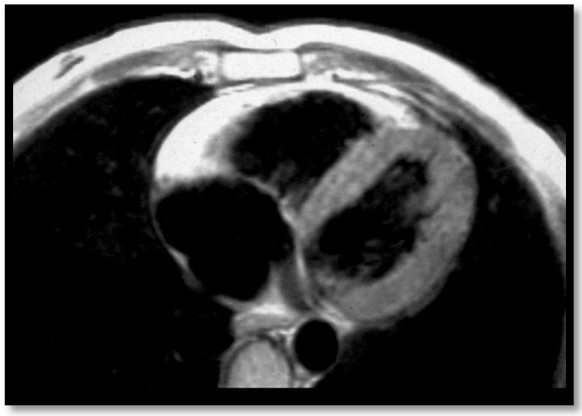

Figure 4. Cardiac MRI. Please note fatty replacement and myocardial atrophy of the RV free wall in a patient with ARVC. Adapted from Thiene, G. et al. (2007) [51] (under the Creative Commons Attribution 2.0 License).

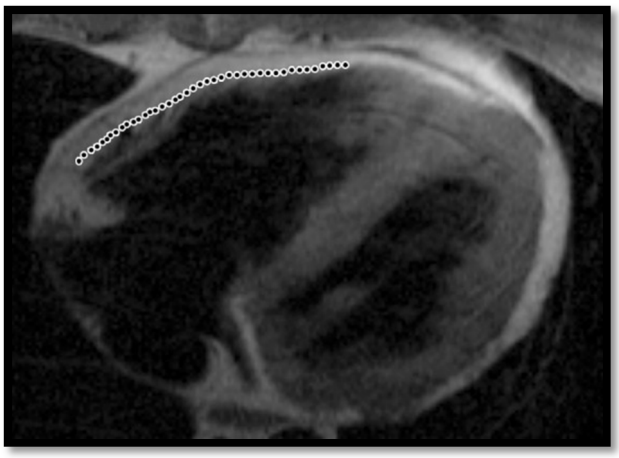

Figure 5. Cardiac MRI showing fatty infiltration of the RV free wall with preserved myocardial thickness. Reproduced from Rastegar, N. et al. (2014) [52] with permission from (Radiological Society of North America) (RSNA).

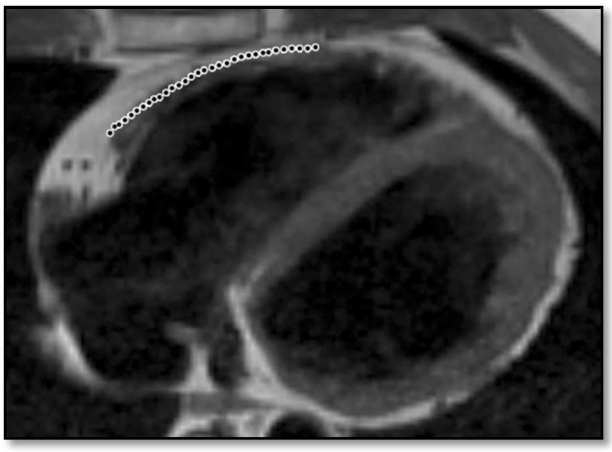

Figure 6. Cardiac MRI showing fatty infiltration of the RV free wall, resulting in thinning of the ventricular wall. Reproduced from Rastegar, N. et al. (2014) [52] with permission from RSNA (Radiological Society of North America).

3.2. Left Ventricle CMR Evaluation in ARVC

Although Marcus et al. proposed New Task Force Criteria for the diagnosis of ARVC in 2010 [12], neither right atrium nor left ventricular involvement were included as diagnostic elements. To verify the presence of left ventricular involvement, El Ghannudi et al. performed cardiac MRI in 21 patients with ARVC. A 1.5 Tesla Siemens MR system was used with Cine MR in axial sections to evaluate the left ventricle. The end-systolic and end-diastolic volumes of the LV, the ejection fraction, and the presence of late gadolinium enhancement after intravenous administration were assessed. The criteria used to quantify LV damage were LVEF < 55%, the presence of late gadolinium enhancement, LV dilation with an end-diastolic volume of >95 mL/sqm, or the presence of wall motion abnormalities. Of the 21 patients, 7 (33%) with ARVC had left ventricular dilation, 5 patients (24%) had a reduced LV ejection fraction <55%, and 4 patients (19%) had segmental contraction abnormalities of the left ventricle. At the same time, 3 out of 21 patients (14%) had late gadolinium enhancement, although they had no history of myocarditis or coronary heart disease. In conclusion, 52% of all patients had some form of LV impairment [53]. Figure 7 illustrates the left ventricular involvement in an ARVC patient.

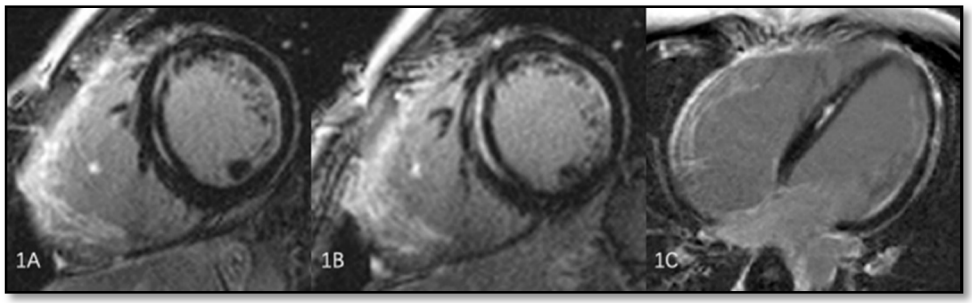

Figure 7. Left ventricular involvement in a patient with ARVC (1A → 1C). Please note delayed gadolinium enhancement in the septal wall of a patient with ARVC. Reproduced from Shen et al. (2019) [54] (under the Creative Commons Attribution 4.0 License).

In the study by Berte et al., left ventricular involvement was detected in 66% of the 32 patients with ARVC by using cardiac MRI and electroanatomic voltage mapping [55]. In 22 of them, cardiac MRI was performed using a 1.5 Tesla Siemens system, with cine MRI images. Evaluation of the left ventricle found 14 patients (64%) with late enhancement, 2 (9%) with contraction abnormalities, and 6 (27%) with decreased LV ejection fraction. However, no correlation was found between the presence of the PKP2 mutation and left ventricular involvement.

Furthermore, it was thought that LV involvement occurs at a later stage in the evolution of ARVC, but several cases were described in which LV involvement was more important than RV involvement or cases with isolated LV impairment [56]. As we are now 11 years away from the latest Task Force Diagnostic Criteria published in 2010, our opinion is that the time to include LV involvement in the diagnostic criteria of ARVC has come.

3.3. Right Atrium Involvement: CMR Evaluation of ARVC

In the Zghaib et al. [38] study on 66 patients with ARVC, the analysis of the right atrium was performed by cine-MRI with a 1.5 Tesla device. The volumes of the left atrium and the right atrium were measured, as well as atrial strain and strain rate using cine-MRI. The authors found higher atrial volumes in patients with ARVC (indexed LA volume of 42.6 mL compared to 31.4 mL in the control group and indexed RA volume of 43.5 mL compared to 29.5 mL in the control group, respectively), as well as lower contractile function and higher atrial stiffness. Furthermore, high atrial volumes and low contractile function were associated with more atrial arrhythmic events compared to the control group [39,40].

In order to prove RA involvement in ARVC, Bourfiss et al. examined 71 patients who met the 2010 Task Force Diagnostic Criteria for ARVC and compared them with 40 patients with idiopathic RVOT ventricular tachycardia [40]. In all of these patients, cardiac MRI was performed using a Philips 1.5 Tesla MRI scanner. The longitudinal and transversal diameters of the atria as well as the contractile function were evaluated for both groups. The 71 patients were also divided into three groups: 37 patients with PKP2 mutation, 14 patients with non-desmosome mutation, and 20 with no mutation. The authors showed that the volume of the RA and the LA were higher in patients who had no identified mutation and the atrial contractile function was lower in the same category of patients. In addition, it has been shown that RA volume was higher in ARVC patients compared to family members who have not been confirmed with ARVC. Atrial arrhythmias were present in 30% of those with PKP2 mutation, 14% of those with non-desmosome mutation, and 30% of those without identifiable mutation. Atrial arrhythmias are essential findings since ARVC patients are generally ICD carriers and might have inadequate defibrillator interventions (26% compared to 12% in the control group) and may develop heart failure (11% vs. 0% in the control group) or die during the follow-up period (11% vs. 2% in the control group) [40]. Figure 8 presents a schematic overview of the right atrial involvement in ARVC.

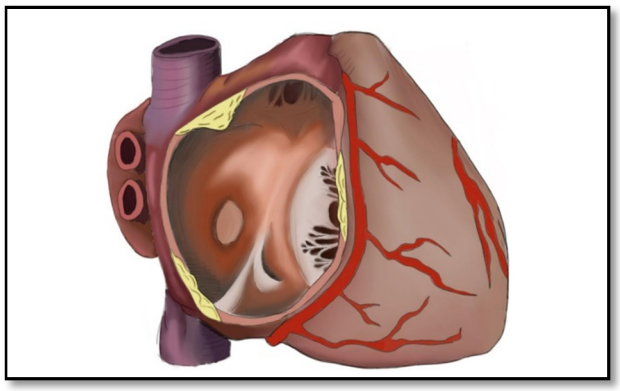

Figure 8. Right atrial involvement in ARVC. The atrial wall is replaced with yellow fibro-fatty tissue.

In the study of Brembilla-Perrot et al., a total of 47 individuals with ARVC confirmed by right ventricular angiography were compared to a control group that did not have ARVC. In 69% of patients with ARVC, supraventricular arrhythmias were induced during programmed atrial stimulation with up to three extra stimuli. The authors hypothesized that supraventricular arrhythmias could occur before ventricular tachycardias in ARVC [41].

Furthermore, Hadi et al. measured RA and LA diameter of 23 patients with ARVC and compared the obtained values with normal values [57]. A 1.5 Tesla Siemens MRI with electrocardiographic trigger was used. The authors showed that 18 (78.2%) patients with ARVC had increased RA diameter; however, LA diameter was normal in all 23 subjects [57].

3.4. Moderator Band Involvement in ARVC: CMR Features

Although changes of the moderator band are visible during autopsy and present on cardiac ultrasound, these examinations cannot differentiate between the pathological ARVC and the athlete's heart. In the Luijkx et al. study performed with an Achieva Philips MRI of 1.5 Tesla, there were no particular changes of the moderating band seen in CMR [58]. The study included 132 patients, 66 with ARVC, 33 healthy athletes, and 33 non-athlete individuals. Although 91% of patients with ARVC had contraction abnormalities of the right ventricular wall, none presented moderator band changes. However, bulging at the site of insertion of the moderator band inside the right ventricular wall was present in two athletes, but in none of the patients with ARVC.

In the Tavano et al. study, adipose tissue infiltrating the moderator band appeared as a hyper-intense intramyocardial spin-echo T1 signal that extended to the septum or free

right ventricular wall as well as to the intracavitary trabeculae [59]. Along with moderator band "hypertrophy", the authors also noted hypertrabeculations within the right ventricle.

Certainly, the thickening of the moderator band is a feature of ARVC, and it can detected with better performing MRI devices, but its diagnostic value remains limited given its presence in the athlete's heart; further studies will need to determine its value and specificity. Sievers et al. showed on 29 healthy individuals that segmental contraction abnormalities in the right ventricular wall may occur near the insertion of the moderator band [60]. Minor dyskinesia, hypokinesia, or wall bulges were present in 93% of cases, and these changes were located near the moderator band. Only seven individuals had contraction abnormalities not related to the moderator band. Nevertheless, these subtle possible changes underline the importance of the examiners experience in interpreting cardiac MRI images.

4. Review of Unique ARVC Characteristics in Children

The causative genes in ARVC encode proteins of mechanical cell junctions (plakoglobin, plakophilin, desmoglein, desmocollin, desmoplakin) and are the main cause for intercalated disk remodeling [61]. In general, there are no visible changes of the right ventricle at the birth of the child. Although symptoms have been reported during early childhood, the more severe manifestations of the disease occur in young adults [62,63].

ARVC generally affects patients of 20 to 40 years of age, but cases have also been reported in young children, schoolchildren, and adolescents. ARVC clinical manifestations may begin in adolescence due to the completion of intercalated disc development and/or the necessity of a certain level of exercise before ARVC manifests [63]. In 1994, Pawel et al. [64] described the youngest child who died of ARVC—a 7-year-old boy who was preparing for a fitness test at school and presented cardiorespiratory arrest that could not be resuscitated. An autopsy showed biventricular fibro-fatty infiltration of the walls. In the series of Marcus [65], Blomstrom-Lundqvist [66], and Nava [19] that included unselected patients with ARVC, 5% to 30% were children, and death was also reported in the childhood period. One of the deaths that occurred in the series published by Blomstrom-Lundqvist [66], which included 15 patients, was a child. Furthermore, in the series of Daliento et al. [67], which included 17 patients with a mean age of 14.9 years, two children were reported as deceased and two presented with ventricular fibrillation due to RV fibro-fatty replacement. More surprising is the fact that of the 60 patients <35 years of age autopsied in the series of Thiene et al., 50% were children, and sudden death was the first sign of the disease [68]. In twins, the disease can be present in both of them no matter if they are identical or non-identical twins. The disease may manifest similarly in both siblings, with ventricular fibrillation, or may manifest differently, depending on the degree of damage of the right ventricle [69].

Furthermore, Groeneweg et al. reported a large series of >1000 patients and family members with ARVC [70]. Only four of them were children <13 years of age. The authors described ECG changes and Holter ECG abnormalities long before CMR changes, a feature that is not common in adults. Furthermore, in children, right ventricular structural abnormalities were mild, with RV enlargement being rare and low ejection fraction even rarer. Small subtricuspid dyskinesia was described in pediatric ARVC, which is uncommon in adults. Additionally, the number of false-positive CMR cases is increased in children due to physiological or pathological conditions of adipose tissue distribution, mimicking ARVC.

Unlike adults, children have more subtle changes in RV segmental contraction, which may be absent on cardiac ultrasound but may be present on cardiac MRI examination. Furthermore, fibro-fatty infiltration is associated in a vast majority of cases with abnormal contraction of the ventricular wall (Figure 9). This would be an additional argument for using MRI in the diagnosis of ARVC in children. Pilichou et al. found that contrast-enhanced cardiac magnetic resonance may detect left dominant types of ARVC even before morpho-functional modifications occur [71]. Furthermore, the DeWitt et al. study analyzed the phenotypic manifestations of arrhythmogenic cardiomyopathy in children

and adolescents. The authors reported left dominant arrhythmogenic cardiomyopathy, or biventricular arrhythmogenic cardiomyopathy in 32 patients aged 15.1 ± 3.8 years. Moreover, the DeWitt study identified ARVC in 16 patients, left dominant arrhythmogenic cardiomyopathy in 7 patients, and biventricular in 9 patients. In five of the seven patients with left dominant arrhythmogenic cardiomyopathy, imaging features preceded ECG findings: MRI revealed mild LV dysfunction, epicardial late gadolinium enhancement, and wall motion abnormalities before repolarization abnormalities on the surface ECG [62].

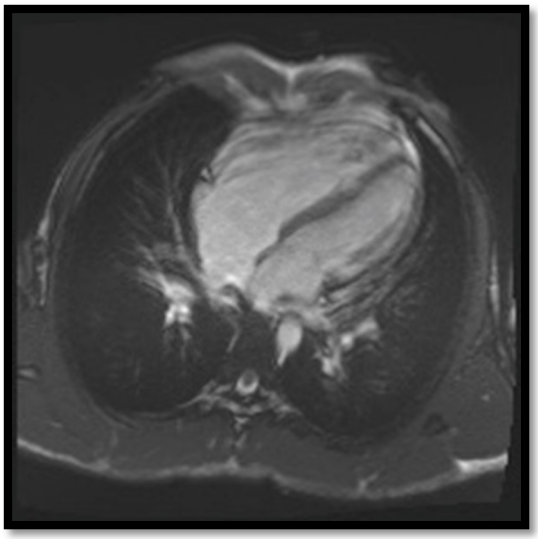

Figure 9. Pediatric ARVC in a 10-year-old male confirmed by Cardiac MRI. The right ventricle has a thin wall with fibro-fatty infiltration and development of an aneurysm; the RV volume is increased [72]. (Case courtesy of Dr Vlad Barskiy, Radiopaedia.org, rID: 69431).

In this regard, Marcus et al. [73], Scalco et al. [74], and Grosse-Wortmann et al. [75] showed different accuracy of the criteria used in the diagnosis of ARVC, depending on the age of the patient. In children, cardiac MRI had the highest precision for the diagnosis of ARVC compared to adults.

To demonstrate cardiac MRI's suitability as a single method in the diagnosis of ARVC, Staab et al. [76] evaluated 79 young people <18 years of age with suspected disease. A PKP2 or DSP gene mutation was identified in 12 of them. Of the 12, cardiac MRI examination identified 5 patients with major MRI criteria and 6 patients with minor MRI criteria. A total of 92% of these patients had MRI Task Force criteria for ARVC. In addition, Deshpande et al. [77] reported a series of 16 pediatric cases with ARVC. Three of these patients presented fibro-fatty replacement of the RV myocardium on endomyocardial biopsy. Magnetic resonance imaging was performed in four patients using 1.5 Tesla systems. From those, MRI was diagnostic in three patients, proving characteristic findings of RV regional wall motion abnormalities with systolic dysfunction and RV dilatation. All these patients also presented left ventricular dysfunction, with a mean ejection fraction of 36.66% [77].

The CMR cutoff values in the Task Force Criteria for ARVC were based on a comparison of adult ARVC probands and controls; thus, future research should also focus on pediatric patient validation and the establishment of pediatric ARVC diagnosis criteria.

Furthermore, it is worth noting that in children with ARVC, the differential diagnosis must always include acute myocarditis. Martins et al. [78] used CMR to show the presence of active myocardial inflammation in a case series of six children with a genetic diagnosis of ARVC who had myocarditis-like symptoms and no evidence of a viral etiology. Several theories have been proposed to explain this finding: the damaged myocardium is more vulnerable to viral infection, whilst in familial forms of ARVC, some viruses can trigger

the desmosome injury [79,80], and myocarditis-like episodes can represent active stages of ARVC [81–83].

5. Cardiac MRI Pitfalls in ARVC

Physiological conditions as well as right ventricular abnormalities can cause suspicion of ARVC on cardiac MRI [68,84–87]. Inaccurate MRI interpretation can have serious repercussions, including the need for an internal cardiac defibrillator, antiarrhythmic medication with sotalol and amiodarone, and the probability of a poor prognosis. As a result, radiologists and cardiologists should improve their skills in recognizing the disease and distinguishing it from other illnesses with comparable symptoms. The presence of fat on cardiac MRI is not diagnostic for ARVC; therefore, it was not even included in the Diagnostic Criteria [12,45]. When myocardial fat is physiologically present, it is better distributed at the level of RV than the LV. Since it is widely dispersed on the RVOT and free wall of the RV, there is an overlap with the disposition of the fat in the ARVC. However, it is noteworthy that when fat distribution is physiological, the RV does not dilate, and the RV ejection fraction does not drop. Table 1 presents a series of ARVC mimics that may hamper the identification of ARVC-related lesions on CMR.

Table 1. Differentials: ARVC mimics detected by cardiac MRI.

No.	Type	Limitations
1	Epicardial fat	Epicardial adipose tissue is distributed in the antero-apical region of the right ventricle in 15% of the general population; furthermore, in obese patients, the percentage can increase to 50% which should be differentiated from the adipose tissue of ARVC [88].
2	Moderator band	Contraction abnormalities observed near the insertion of the moderator band. Images can be misinterpreted as akinesia, dyskinesia, or hypokinesia of the ventricular wall. Sievers et al. showed in 29 healthy individuals that small contraction abnormalities occurred in 93% of the examined individuals near the moderator band [60].
3	Short-axis images	Another limitation of cardiac MRI comes from the scarce analysis of short-axis images. The incidences are used for the correct assessment of the right ventricular size. If short-axis images are not used, there is a 20% chance that the radiologist will incorrectly measure right ventricular size and inadvertently assuming RV dilation [86].
4	Adipose tissue	Adipose tissue infiltration of the right ventricular myocardium can be misinterpreted as arrhythmogenic dysplasia. False positive images of intramyocardic adipose tissue may be recorded by the radiologist. Furthermore, pericardial fat distributed on the surface of a thin myocardium may give a false image of adipose infiltration. The inter-individual reproducibility of adipose tissue images is poor, by virtue of (a) adipose tissue disposition at the epicardial and pericardial level in healthy individuals, and sometimes intramyocardial; (b) epicardial fat disposition at the level of the right atrioventricular groove—in cardiac MRI, this area is rather difficult to distinguish from the subtricuspid muscle zone, which might be affected by ARVC; (c) the right ventricular wall is thin, at 3–5 mm, and therefore the spatial resolution on cardiac MRI is poor, which can lead to diagnostic confusions [86,89,90].
5	Athlete's heart	Another possible source of error in athletic individuals is the enlargement of the right ventricle associated with intense and long duration physical activity. Large ventricular and RVOT diameters can be misinterpreted as ARVC, but the increase in the RA and RV size is symmetrical compared to the asymmetrical changes produced by ARVC [79,80,82,83].
6	Viral myocarditis	Viral myocarditis can affect the regional contraction of the right ventricle; the decrease in contractility can be misinterpreted as being related to ARVC [32,58,87].
7	Right ventricular myocardial infarction	In myocardial infarction, necrotic tissue is replaced by fibrous or adipose tissue (which is called "fibrous or adipose metaplasia"). Post-infarction lesions of the right ventricle resemble and should be differentiated from ARVC lesions, especially if infarction occurred > 6 months prior to cardiac MRI [91,92]

Table 1. *Cont.*

No.	Type	Limitations
8	Dilated cardiomyopathy (DCM)	In dilated cardiomyopathy, in addition to areas of fibrosis, lymphocyte infiltration, and myocyte degeneration, myocardial fibro-adipose infiltration may be present. These fatty infiltrates may be present in 18–24% of DCM cases [92,93].
9	Uhl's anomaly	Uhl's anomaly is a rare congenital disease without areas of fibro-fatty dysplasia. However, there is complete absence of the myocardium that causes the ventricular wall to be thin. Uhl's disease is extremely rare and generally the diagnosis is made post-mortem. Echocardiography shows a dilated right ventricle, with thin walls 1–2 mm at all levels. In cardiac MRI, the ventricular wall is extremely thin, the myocardium of the free wall is missing, and the trabeculations at the apical level are minimal. Although there is no fibro-fatty infiltration, the systolic function is impaired. The differentiation in cardiac MRI between the two diseases is critical because Uhl's disease progresses towards right heart failure, in contrast to ARVC, which leads to life-threatening ventricular arrhythmias. For Uhl's disease, no primary prevention is available, but for ARVC, there is a primary prevention of sudden cardiac death by implanting an internal cardiac defibrillator [94–97].
10	Rib cage abnormalities	Another possible source of error is the structural change of the rib cage. In pectus excavatum, the position of the heart within the thorax changes and the heart becomes compressed between the sternum and the vertebral column, giving a false image of dilated right ventricle. In addition, the mediastinum may be shifted to the left and may mimic right ventricular dyskinesia, which can be interpreted as ARVC.
11	Box-shaped RV	Physiological changes of the right ventricle may mimic ARVC. In case of a box-shaped right ventricle, the anterior wall has an irregular trajectory, with a slight protrusion of the middle portion of the anterior wall, which can be confused with a dyskinetic RV [98].
12	Sarcoidosis	Sarcoidosis is another source of confusion in that the areas affected by granulomas may be hypokinetic, become aneurysmal, or have delayed enhancement, thus mimicking ARVC [99].
13	Lipomatous hypertrophy of the interatrial septum	Lipomatous hypertrophy of the interatrial septum is characterized by accumulation of adipose tissue inside the interatrial septum; the transverse diameter of the septum increases over 2 cm. This change must be differentiated from ARVC with concomitant atrial impairment. Nonetheless, in lipomatous hypertrophy, the oval fossa is spared, and contrast enhancement is never present [100].
14	Hypertrophic cardiomyopathy	Hypertrophic cardiomyopathy. In this disease, 11% of patients may have deposits of adipose tissue inside the hypertrophied myocardium. However, the differentiation between the two diseases is straightforward because in ARVC, the myocardium is not thickened but is replaced with fat [100].
15	Cardiac lipomas	Cardiac lipomas are the second most common benign tumors of the heart, after myxomas. Unlike ARVC, lipomas may be located intramyocardially; however, cardiac lipomas are well defined and sometimes encapsulated [101].
16	Cardiac liposarcoma	Liposarcomas are a type of aggressive but very rare tumors that look inhomogeneous on cardiac MRI and generally affect the right chambers, starting with the right atrium and extending to the right ventricle. However, these tumors are destructive, affecting and destroying blood vessels and heart valves, a feature that helps in the differential with ARVC [102].
17	Radiological experience	The radiologist interpreting images of suspected ARVC should have sufficient experience, considering the fact that in early stages of the disease the differential diagnosis must be made with other diseases that have similar characteristics [84,103].

6. Concluding Remarks

Arrhythmogenic right ventricular cardiomyopathy is diagnosed using major and minor Task Force criteria, which include quantitative and qualitative cardiac MRI variables. CMR diagnostic criteria typically involve global dilatation of the right ventricle, as well as contraction abnormalities that result in reduced systolic function. Segmental dilation of

the RV or minor microaneurysms that do not alter the overall systolic function of the RV have been excluded from the Diagnostic Criteria because they are difficult to interpret and have lower sensitivity and specificity for the diagnosis of ARVC. CMR allows for three-dimensional imaging of the RV, has multi-planar capabilities, excellent spatio-temporal resolution, has the ability to assess the same patient across time, and is a non-invasive procedure. For all these reasons, CMR has become the primary imaging technique for identifying and assessing patients with ARVC. Nonetheless, there are many pitfalls and physiological or pathological situations that might resemble ARVC in cardiac MRI, which have to be distinguished from ARVC since the prognosis differs in each of these cases. The implantation of an internal cardiac defibrillator is a crucial choice in the care of patients with ARVC in order to prevent sudden cardiac death.

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Formula to estimate left atrial volume using antero-posterior diameter in patients with catheter ablation of atrial fibrillation

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Abstract

In patients undergoing atrial fibrillation (AF) ablation, an enlarged left atrium (LA) is a predictor of procedural failure as well as AF recurrence on long term. The most used method to assess LA size is echocardiography-measured diameter, but the most accurate remains computed tomography (CT).

The aim of our study was to determine whether there is an association between left atrial diameters measured in echocardiography and the left atrial volume determined by CT in patients who underwent AF ablation.

The study included 93 patients, of whom 60 (64.5%) were men and 64 (68.8%) had paroxysmal AF, who underwent AF catheter ablation between January 2018 and June 2019. Left atrial diameters in echocardiography were measured from the long axis parasternal view and the LA volume in CT was measured on reconstructed three-dimensional images.

The LA in echocardiography had an antero-posterior (AP) diameter of 45.0 ± 6 mm (median 45; Inter Quartile Range [IQR] 41–49, range 25–73 mm), longitudinal diameter of 67.5 ± 9.4 (median 66; IQR 56–88, range 52–100 mm), and transversal diameter of 42 ± 8.9 mm (IQR 30–59, range 23–64.5 mm). The volume in CT was 123 ± 29.4 mL (median 118; IQR 103–160; range 86–194 mL). We found a significant correlation ($r = 0.702$; $P < .05$) between the AP diameter and the LA volume. The formula according to which the AP diameter of the LA can predict the volume was: LA volume = AP diam^3 + 45 mL.

There is a clear association between the left atrial AP diameter measured on echocardiography and the volume measured on CT. The AP diameter might be sufficient to determine the increase in the volume of the atrium and predict cardiovascular outcomes.

Abbreviations: AF = atrial fibrillation, AP = antero-posterior, CMR = cardiac magnetic resonance, CT = computed tomography, DCM = dilated cardiomyopathy, diam = diameter, HCM = hypertrophic cardiomyopathy, LA = left atrium, LAA = left atrial appendage, LAVI = left atrial volume index, LSPV = left superior pulmonary vein, vol = volume.

Keywords: computed tomography, diameter, echocardiography, left atrium, volume

1. Introduction

The size of the left atrium (LA) is an independent predictor of cardiovascular events such as myocardial infarction, heart failure, atrial fibrillation, stroke, and cardiovascular mortality.[1,2] It has been also been shown to be predictive of the effectiveness of radiofrequency ablation in terms of acute success and long-term recurrences.[3,4]

For the evaluation of LA size the most used examination is echocardiography, and the most available parameter in registries and populational studies is the antero-posterior (AP) diameter.[5] Current guidelines recommend AP diameter for LA size assessment, but volume is a more objective measurement to evaluate LA dilatation. In addition to echocardiography, other imaging techniques can be used, the most accurate being

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The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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computed tomography (CT), an examination that is required for other purposes,[6] such as: calculation of the coronary calcium score or angio-tomography of the coronary arteries.[7]

There are different methods for estimating left atrial volume using one diameter of the LA: the prolate ellipsoid formula, the sphere formula, and the cube formula. The most accurate of these 3 in the study of Jiamsripong, was the cube formula.[8] Our study aimed to determine whether a simple measurement such as anteroposterior diameter on echocardiography can estimate the volume of the LA measured on CT, and find a simple formula that can approximate the LA volume.

2. Materials and method

2.1. Study population

We included 93 patients with atrial fibrillation who underwent catheter ablation between January 2018 and June 2019. The study was approved by the Ethics Committee of the Rehabilitation Clinical Hospital of Cluj-Napoca and all subjects signed informed consent.

Prior to the ablation procedure, a transesophageal echocardiography was performed to rule out a thrombus in the left atrium or LA appendage. A chest CT with contrast media was used to determine the atrial anatomy and the number of pulmonary veins.

2.2. Size measurements

AP, longitudinal, and transverse diameters were measured in bidimensional echocardiography from the parasternal long-axis and apical views as recommended by the American Society of Cardiology and European Association of Echocardiography.[9] AP measurement was performed at the level of the aortic sinuses at the end of ventricular systole, during its maximal dimension.[10] Longitudinal and transverse diameters were measured from the apical 4-chamber and 2-chamber views using the inner-to-inner edge method. Volume measurements were made after integrating CT images into the Carto Biosense Webster or NAVX Saint-Jude system, on the three-dimensional reconstructions of the LA and pulmonary veins. The atrial volume was measured outside the venous ostia, without including the pulmonary veins and left appendage,[11] in end-systole when the LA is at its maximum size. All echography and CT measurements were performed before the ablation procedure.

2.3. Statistical analysis

The distribution of continuous variables is presented as mean and standard deviation. Categorical variables are indicated in percentages. For the correlation between the diameters and the volume of the LA, the Spearman correlation was used. The relationship between LA diameter and volume was assessed using cubic regression and was plot against CT volume using Bland–Altman method. SPSS Statistics for Windows, Version 21.0. (Armonk, NY: IBM Corp.) was used for all the statistical analysis considering a significant value of P below .05.

3. Results

Of the 93 patients included in the study (mean age 53 ± 10.7 years, 35.5% women) 68.8% had paroxysmal atrial fibrillation and the rest had persistent atrial fibrillation.

The LA in echocardiography had an AP diameter of 45.0 ± 6 mm (median 45; Inter Quartile Range [IQR] 41–49, range 25–73 mm), longitudinal diameter of 67.5 ± 9.4 (median 66; IQR 56–88, range 52–100 mm), and transversal diameter of 42 ± 9 mm (IQR 30–59, range 23–64.5 mm) (Table 1). Most of the patients had an enlarged LA as they had atrial fibrillation and were addressed for catheter ablation. Only 21.5% (n = 20) of patients had a normal LA, all of them being with paroxysmal AF. The measured volume in CT was 123 ± 29.4 mL (median 118; IQR 103–160; range 86–194 mL). The distribution of both AP diameter and volume is shown in Fig. 1.

Using the Spearman analysis, there was no significant correlation between the longitudinal or transversal diameter and the LA volume but we observed a significant correlation (r = 0.702; $P < .05$) between the AP diameter and the LA volume. The correlation was stronger in women, in patients who had persistent atrial fibrillation and those without interatrial block on 12-lead ECG (Table 2).

The formula according to which the AP diameter of the LA can predict the volume was determined using cubic regression: LA volume = AP diam^3 + 45 mL (Fig. 2). Compared with our formula (vol = AP diam^3 + 45 mL), the cube formula (vol = diam^3) yielded

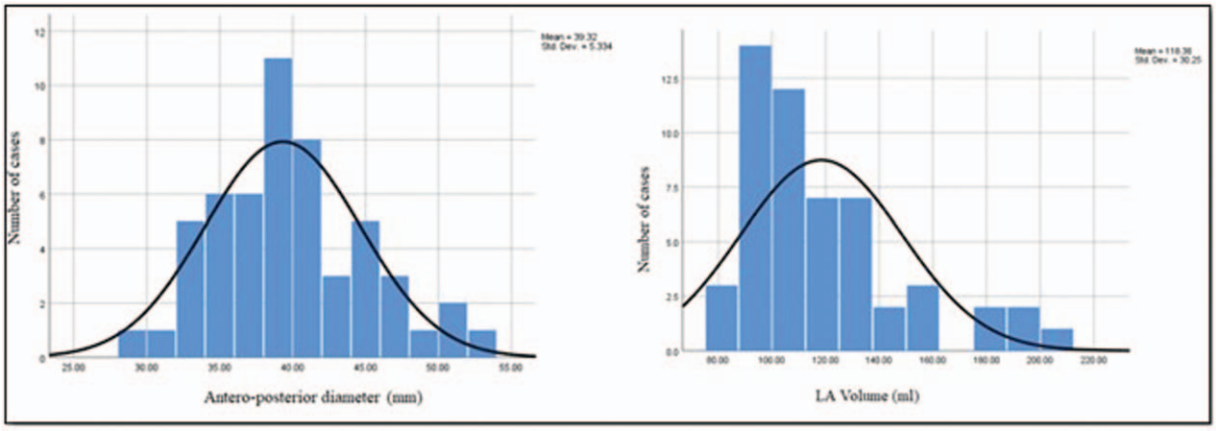

Figure 1. Distribution of left atrial diameter and volume in the population of 93 patients.

Table 1

Values for left atrial dimensions.

	AP diameter	Long diameter	Trans diameter	LA volume in cmc
Mean ± SD	45.0 ± 6	67.5 ± 9.4	42 ± 8.9 mm	123 ± 29.4
Range (min–max)	25–73	52–100	23–64.5	86–194

AP = antero-posterior, LA = left atrium.

smaller values ([106.2 ± 27.6 mL vs 63.4 ± 27.5 mL respectively], [$P < .001$]). Using Bland–Altman difference plot analysis of the agreement between 2 different formulas, we found that our formula was better than the old cube formula in estimating the measured volume of the LA.

The Bland–Altman graph[12] (Fig. 3) shows how the difference between our method and Cube method increases at smaller LA volumes. The difference between these 2 methods was constant across the entire range of LA volumes from 70 to 150 mL.

To determine which of the 2 formulas is more accurate in predicting left atrial volume, a simple linear regression was used between the measured volume determined by contrast-enhanced CT and the volume obtained with that specific formula. Thus, for the cube formula, high beta coefficients and a statistically significant $P < .05$ were obtained, demonstrating measurement bias between the cubic formula and the measured (Table 3). On the other hand, using our method, the beta coefficients were close to 0 and the P statistically insignificant $P > .05$, proving that there is no bias between our method and the measured volume (Table 4).

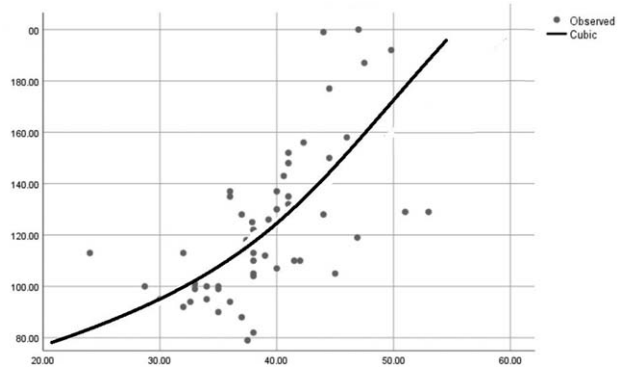

Figure 2. Cubic regression line estimates left atrial volume by the formula LAV = diam^3 + 45 mL.

4. Discussion

The exponential increase in the number of atrial fibrillation ablations in recent years, has stimulated the interest in the evaluation of left atrial volume,[13] because it is proved to be a crucial predictor of the short- and long-term results of ablation, as well as an indicator of structural remodeling.[14] Because the measurement of volume in CT imaging is time-consuming and labor-intensive, researchers explored simple methods to evaluate

Table 2

Pearson's correlation between AP diameter and LA volume in specific categories.

Category	R_1	P value
Male gender	0.574	.001
Female gender	0.768	<.001
Paroxysmal AF	0.540	<.01
Persistent AF	0.726	<.01
Interatrial block	0.61	<.0001
Without interatrial block	0.810	<.0001

AF = atrial fibrillation, AP = antero-posterior, LA = left atrium.

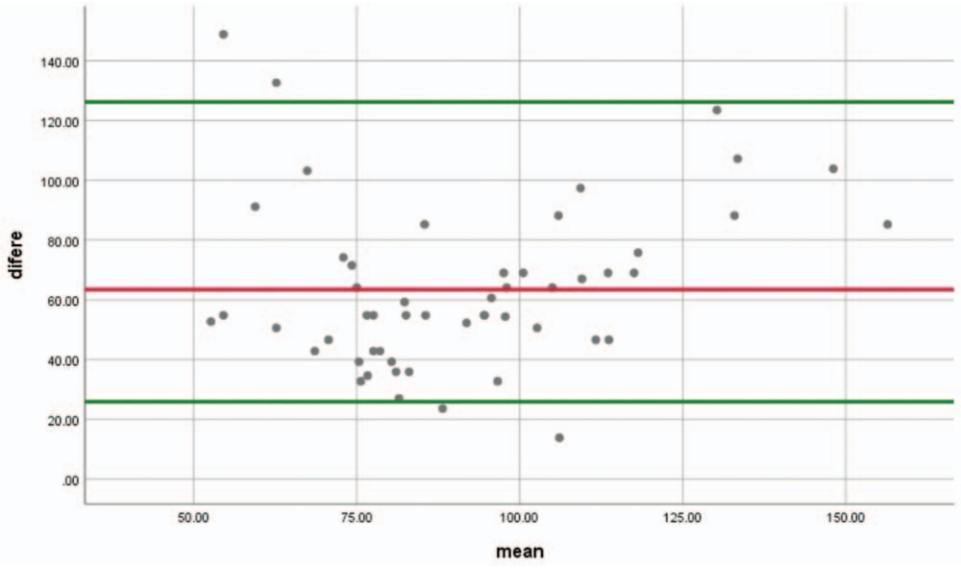

Figure 3. Bland–Altman plot of the difference between our formula and Cube formula versus the average of both formulas for left atrial volume estimation.

Table 3

Simple linear regression between: Cubic Formula and LA volume determined by computed tomography shows high unstandardized beta coefficient and significant *P* values < .05 demonstrating proportional bias between the methods.

Coefficients					
	Unstandardized coefficients		Standardized coefficients		
Model	*B*	Std. Error	Beta	*t*	Sig.
1 (Constant)	8.201	15.553		0.527	0.600
Mean	0.076	0.132	0.080	0.572	0.570

LA = left atrium.

Table 4

Simple linear regression between: our Formula and LA volume determined by computed tomography shows unstandardized beta coefficient close to 0 and non-significant *P* values > .05 demonstrating lack of proportional bias between the 2 methods.

Coefficients					
	Unstandardized coefficients		Standardized coefficients		
Model	*B*	Std. Error	Beta	*t*	Sig.
1 (Constant)	41.657	15.251		2.731	0.009
Mean	0.238	0.162	0.201	1.469	0.148

LA = left atrium.

LA volume using simple formulas, derived from simple measurements.

In this study we described our formula for estimating left atrial volume, based on AP diameter measured in echocardiography. Measurement of the AP LA diameter is simple and rapid and is part of the standard echocardiographic evaluation. It has been, for a long period of time, the only available method to determine LA size.[15] Although currently, recommendations strongly suggest use of LA volume as standard for LA size assessment, AP diameter is still used on a large scale for registries and cohorts such as the Framingham Heart Study.[16]

Our study demonstrates that LA volume can be predicted with good accuracy by using a simple measurement of the AP diameter. According to the American Society of Echocardiography, values <38 mm in women and <40 mm in men for AP diameter[17] are normal. In our study most of the patients (88.2%) had a dilated LA related to the fact that they were patients with paroxysmal or persistent atrial fibrillation.

LA volume is directly related to LA diameter, though it is biased to think that this relation between a linear and a three-dimensional measure would be linear. Furthermore, the estimations of the left atrial volume according to the cube method ($vol = diam^3$) or sphere method: ($vol = 4\pi/3 \times diam^3$) are insufficient, because LA is a non-cuboid, non-spherical cavity. However, the cubic method is a reasonable assumption, as evidenced by studies that have compared the CT LA volume with the volume estimated by cube formula ($vol = diam^3$).[18] In order to be more accurate, we used in our study non-linear cubic regression based on the measured values of LA volume in 93 patients undergoing catheter ablation of atrial fibrillation. Consequently, the formula that best estimates the left atrial volume is $vol = APdiam^3 + 45$ mL.

The difference between our Formula and the old cube formula is that 45 mL is added to the volume of the cube. This is because the LA does not have a perfectly cubic shape, and parts that are situated anterior, posterior, superior, and inferior to the cube (Fig. 4) have been approximated to 45 mL by non-linear cubic regression. Cubic regression, is similar to the linear regression currently used in statistics, except that the formula includes a polynomial equation in which the diameter is raised to power 3.

In clinical practice, it is often necessary to compare our method with a standard of measurement. We compared our formula using Bland–Altman plot of difference between estimated and observed volumes. A very good overlap was obtained between our formula and the volume measured by CT.

In contrast to our study, Havranek et al[19] demonstrated that the AP diameter does not estimate LA volume as measured by LA direct catheter mapping. It is important to mention that in the

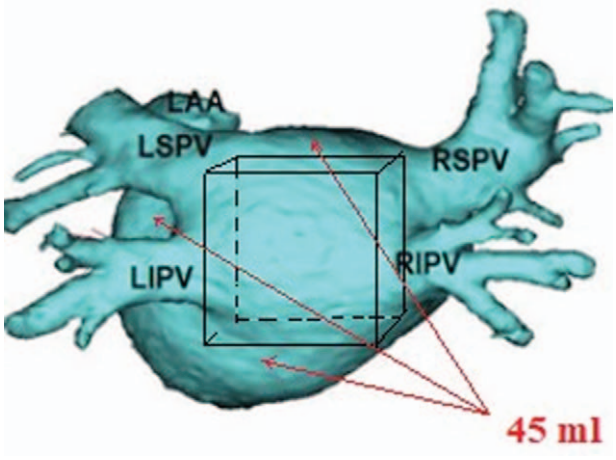

Figure 4. The cube formula is insufficient to approximate the volume of the left atrium because the left atrium does not have a cubic shape. If a cube is included inside the left atrium there are anterior, posterior, upper, and lower portions that are not taken into account as volume. Our Formula also includes these zones, approximating by regression the extra volume as counting 45 mL in addition to diameter raised to the 3rd power.

study of Havranek et al[19] the volume of the LA was based on mapping of the LA with the ablation catheter inserted inside the cavity, and "walking through" all areas of the atrium. However, in our study the volume of the LA was measured directly by CT, which we consider to be more accurate than the reconstruction of the LA with the catheter. For example, the junction between the LA and the pulmonary veins is difficult to determine and is based on the appearance of the intracardiac electrograms at the atrial and venous level as well as the measurement of local impedance, which can overestimate the atrial volume. In the study by Piorkovski et al who compared the CT image of the LA with the three-dimensional reconstruction performed with the catheter, the differences in size came from the fact that manipulation of the catheter through the transseptal puncture is difficult in the right upper and lower pulmonary veins. Therefore, the distance between right superior pulmonary vein and left superior pulmonary vein as well as between right superior pulmonary vein and the respective esophagus as well as the line around the ostium of the right veins, do not correspond to the real measurement made on the cardiac CT. The differences between the 2 techniques are 4 to 7 mm,[20] which can influence the total atrial volume.

In normal canine hearts, Fries et al[21] demonstrated that left ventricle, right ventricle, and right atrium volumes measured in cardiac magnetic resonance (CMR) correlated better with three-dimensional echocardiography than CT. However, LA volume in CMR best correlated with CT. It has also been shown that compared to two-dimensional, three-dimensional echocardiography correlates better with computer tomography in dogs. Furthermore, two-dimensional evaluation of the volume by the area-length method or by the bidimensional disc method overestimates the left atrial volume compared with CT.[22]

Studies that compared the left atrial volume measured by the 2 methods: echocardiography and CT imaging in humans, showed significant differences between them, always the volume from CT being the largest: Agner et al[23] compared LA volume measured by echocardiography with CT imaging. In echo, volume was assessed using modified Simpson method from apical fur and 2-chamber views and was underestimated compared with CT imaging (60 vs 80 mL/m$^{2;}$, $P < .001$). Also the study of Shin et al[24] showed the same results: echo based LA volume was underestimated compared with CT imaging (77.7 mL with area-length method vs 73.4 mL with Simpson method vs 126.8 mL with CT imaging; $P < .001$). Nedios et al[25] correlated different LA diameters from echocardiography and CT imaging with LA volume measured in CT imaging. He found better correlation for CT-imaging derived diameters:transverse diameter with LA volume $r = 0.69$; supero-inferior diameter with LA volume $-r =$ 0,58; AP with LA volume $r = 0.60$. Instead, the correlation with the AP diameter determined on echocardiography was moderate, but still significant $r = 0.43$; $P < .001$. The authors concluded that the best diameter for left atrial volume estimation is the transverse diameter. However, they had to perform CT imaging to obtain this measurement. The echocardiography measurement is much faster, and does not have the drawbacks of CT imaging. Christiaens study[26] also showed differences and underestimations of left atrial volume estimated on echocardiography compared with that measured on CT imaging: LA vol = 32 mL/m^2 with cubic formula, 46 mL/m^2 with ellipsoid formula, 48 mL/m^2 with Simpson formula, 52 mL/m^2 with diameter-length formula, 59 mL/m^2 with area-length formula and 74 mL/m^2 with CT imaging. We can easily observe from this study that the difference between the volume measured with CT imaging and the volume estimated by the cube formula using echocardiography is approximately 42 mL, a value close to that found in our study. Arsanjani et al[27] in a study of 64 patients also showed that the volume measured on CT imaging is higher than that measured on echocardiography using the biplane area-length method: 92 mL versus 68 mL, $P < .01$.

It is well known that atrial remodeling, especially in patients with atrial fibrillation and dilated LA occurs assimetrically, due to the limitations imposed by the sternum and the spine. Therefore the increase of the LA occurs less in the AP direction and more in the supero-inferior and medio-lateral direction.

The remodeling of the LA makes this structure impossible to fit in a sphere, cube, or an ellipsoid. Therefore, volume estimation formulas based on atrial diameter are insufficient. However, using a robust analysis such as cuboid regression, a formula can be developed to estimate the volume, taking into account the asymmetric atrial remodeling. This formula is: LA vol = diam^3 + 45.

As for different atrial remodeling due to different etiologies, we would like to mention that most of our patients had lone atrial fibrillation or related to hypertension, diabetes, or obesity. There was no patient with valvular etiology or dilated cardiomyopathy (DCM). Only one patient had hypertrophic cardiomyopathy (HCM), so it is impossible to perform a subgroup analysis. In the study of Sabatino et al[28] left atrial volume indexed to body surface area was 17 mL/m^2 in controls and 59 mL/m^2 in patients with restrictive cardiomyopathy. Left atrial volume index was higher compared with control in patients with DCM, restrictive and hypertrophic cardiomyopathy. Differences in left atrial volume index were not significant between DCM and HCM groups.

The size of the LA is an important marker in stratifying the cardiovascular risk.[29,30] Although the diameter is not the ideal measurement, it is the fastest, easiest, and most used measurement in large population studies and clinical registries. It is reasonable that left atrial volume is a better predictor of outcomes than AP diameter. This has been demonstrated in patients with electrical cardioversion.[31] Abecasis et al[32] showed that a LAV >145 mL was associated with significantly higher AF recurrence after AF ablation. Helms et al[33] found a 135 mL LAV cut-off for AF recurrences. Similar results have been reported by other studies in different patient cohorts. Therefore, any information on the relationship between AP diameter in echo and LA volume in CT, may be of practical value.

4.1. Limitations

This is a single-center study with the inherent limitations of the small number of patients.

We did not evaluate intra and inter-observer variability on different parameters, but this kind of work had already been performed by Ortiz De Murua et al,[34] Sievers et al,[35] and Nedios et al[25] showing a strong correlation between measurements.

Another limitation is that we did not compare LA volume measured in CT with the LA volume measured in Cardiac MRI, which the gold-standard for estimating LA dimensions.

We do not know if the formula applies to other categories than patients with dilated LA. We included selected patients with paroxysmal and persistent atrial fibrillation that underwent catheter ablation. For non-dilated LA, the formula for estimating the volume might be different.

CT imaging also has some drawbacks. First, there may be errors in the evaluation of the LA volume and second, a number of patients may have contraindications to this examination therefore another examination should be used. In terms of CT imaging measurement errors, the gold standard for measurements of chamber volumes[36] is considered CMR. CMR has been found reproducible[37] for measuring LA dimensions both in healthy and AF patients.[38] Agner et al[23] compared for the first time LA volume measured by CMR with volume measured by CT. They observed an overestimation of the left atrial volume measured by CT $80 \pm 16\,mL/m^2$ versus CMR 73 ± 16 $mL/m^2\,mL$, the *P* value being statistically significant (<.01). Difference between the 2 techniques come from the fact that CT uses a single heart beat to acquire the whole heart image whether CMR uses an average of 12 heart beats per slice. Furthermore, usage of different software packages for quantification produces differences in spatial and temporal resolution between CMR and CT.

There is another problem in assessing left atrial volume on CT imaging. Namely, the exclusion of the left appendage and pulmonary veins. The connection between the pulmonary veins and the LA is made at the level of the antrum, which is not always symmetrical, and when the veins are excluded, a smaller or larger part of the antrum is also excluded. This is similar to the exclusion of left atrial appendage, where the ostium is not perfectly round or oval, so that a small volume might be lost from measurements. However, Christiaens et al[39] estimate these losses to be <10 mL and would be similar to those obtained on 3D echocardiography when excluding left atrial appendage and pulmonary veins.

Volume measurement by CT imaging requires three-dimensional reconstruction, exclusion of anatomical structures, and selection of the chamber of interest which is labor-intensive, time-consuming process. Furthermore, CT imaging requires exposure to ionizing radiation and the use of contrast agents. In our hospital, if creatinine is >1.3 mg% the examination is declined by the radiologist. However, new diagnostic tools, like 3D echo and CMR are available for patients with known allergy to intravenous contrast media, renal impairment with low glomerular filtration rate, and hyperthyroidism, that can be aggravated by iodinated agents.

5. Conclusions

Left atrial AP diameter is a simple and quick ultrasound measurement that can predict LA volume in CT imaging. We propose a simple formula: $vol = AP\ diam^3 + 45\,mL$ to estimate LA volume using the diameter. This estimation might be convenient for a number of studies and registries in which determination of LA volume was not planned.

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Writing – review & editing: Gabriel Cismaru, Dana Pop, Dumitru Zdrenghea, Radu Rosu, Andrei Cismaru.

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Is Ablation of Atrial Flutter Always Safe?

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Background: *Radiofrequency ablation of typical atrial flutter is largely used and is considered as safe. The purpose of the study was to evaluate the prevalence and the causes of severe adverse event (AE) following atrial flutter ablation.*

Methods: *Ablation of typical flutter was performed by conventional method with an 8-mm-tip electrode catheter, a maximum power of 70 W, and a maximum target temperature of 70° for 60 seconds in 883 patients, (685 males and 198 females aged from 18 to 93 years [64 ± 11.5]; 664 had heart disease [HD]).*

Results: *AE occurred in 44 patients (5%). AE was life threatening in 14 patients: poorly tolerated bradycardia (transient complete atrioventricular block [AVB] or sinus bradycardia [SB] <40 beats per minute) associated with cardiac shock and acute renal failure in five patients, tamponade (n = 1), bleeding leading to death (n = 1), various AE-related deaths (n = 2), ventricular tachycardia-related death (n = 1), definitive complete AVB (n = 3), and right coronary artery occlusion-related complete AVB (n = 1). Less serious AE occurred in 30 patients: transitory major SB or second- or third-degree AVB (n = 23), bleeding (n = 4), transient ischemic attack (n = 1), and various AE (n = 2). Most of the bradycardia was related to β-blockers or other antiarrhythmic drugs used to slow atrial flutter. Factors of AE were female gender (36% vs 22%, P < 0.02) and the presence of ischemic (P < 0.03) or valvular HD (P < 0.01).*

Conclusions: *AE following atrial flutter ablation occurred in 5% of patients. Most of them are avoidable by control of anticoagulants and arrest of rate-control drugs used to slow the rate of atrial flutter. (PACE 2012; 00:1–6)*

atrial flutter, ablation, complication

Introduction

Typical atrial flutter is a common arrhythmia, representing about 10% of hospitalizations for supraventricular tachycardia in adults. The incidence in a Western population is 82 cases per 100,000 inhabitants.[1] The reentrant circuit through the isthmus cavotricuspid is located in the right atrium and the left atrium is then activated passively. Therefore, radiofrequency (RF) ablation of atrial flutter appears as a reasonable approach regarding feasibility, effectiveness, and is considered as a low procedural risk.[2–7] The success rate is approaching 95%. The RF energy is delivered on the isthmus away from atrioventricular (AV) node and His bundle and the risk of complications such as hematoma, AV block (AVB), and tamponade is considered as very low. However, the studies about possible complications remain rare.[8] Most of the studies on ablation-related complications concern all indications of ablation. But adverse events are not predictable and could develop during any invasive procedure.[9–12]

The purpose of the study was to assess the prevalence and the predictors of the occurrence of adverse events during RF ablation procedure of typical atrial flutter in a high number of patients from a single center.

Population

Eight hundred eighty-three patients, 685 males and 198 females aged from 18 to 93 years (mean 64 ± 11.5), were consecutively admitted for the RF ablation of typical atrial flutter between February 1995 and June 2011. Atrial flutter was chronic in 697 patients and paroxysmal in 187 patients.

Six hundred sixty-four patients had an underlying heart disease. The following heart diseases were ischemic heart disease in 150 patients (22%), valvular heart disease in 98 patients (15%), hypertensive heart disease in 172 patients (26%), dilated cardiomyopathy in 82 patients (12%), chronic lung disease in 78 patients (12%), congenital heart disease in 32 patients (5%), and various heart diseases in 52 patients (8%).

Methods

At the time of ablation, the full anticoagulation was not required during the first

No disclosure.

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years of inclusion in patients without heart disease and was systematic since 2000 in all patients. This anticoagulation was begun 3 weeks before ablation. Anticoagulation was maintained at least one month after ablation. Preprocedural international normalized ratio (INR) varied from 1.8 to 3. Heparin was used only in patient with low INR and CHADS2 score $\geq$2. Transesophageal echocardiogram was performed in most of these last patients. In patients with valvular prothesis, antivitamins K were generally stopped and replaced by heparin at curative dosages.

We generally recommended keeping antiarrhythmic drugs in patients with history of atrial fibrillation. β-blockers or other rate-control drugs were not stopped when the rate in flutter was still rapid.

Ablation of atrial flutter by RF was performed by the conventional method using a "HALO" catheter placed at the coronary sinus whose poles record the activity at the coronary sinus isthmus and lateral wall right of the right atrium. Energy was delivered by a RF catheter 8 mm to use a maximum power of 70 W and a maximum target temperature of 70°. Four senior operators associated or not with fellows performed most of the ablations.

Among patients with permanent atrial flutter, sinus rhythm was obtained by applying an RF current at the right isthmus followed by obtaining an isthmus block; only the latter objective was achieved for patients in sinus rhythm.

The validation of the ablation was retained after cessation of atrial flutter and obtaining a stable bidirectional isthmus block after ablation.

Adverse events were defined as major if they were life threatening and required admission in intensive care unit or as minor if they regressed without the need of monitoring in intensive care unit.

Statistical Analysis

The following criteria were analyzed: age, sex, history of heart disease (hypertensive, ischemic, valvular, congenital, dilated cardiomyopathy), and medical therapies used at the time of ablation.

Initially, we used χ^2 and analysis of variance method for measuring the degree of influence of explanatory variables. Continuous variables were compared with the *t*-test. A P-value <0.05 was considered statistically significant. All statistical analyses were performed by using the SPSS package for Windows (version 17. 0.1, IBM, Armonk, NY, USA).

Results

General Results

Adverse events occurred in 44 patients. The prevalence of adverse events was 5%. Major adverse events occurred in 14 patients and led to the death of four patients. Minor events occurred in 30 patients.

Mechanism and Causes of Adverse Events:

Major Events

Poorly tolerated bradycardia (either complete AVB or prolonged sinus bradycardia [SB] less than 40 beats per minute [bpm]) occurred in five patients who developed a cardiac shock (n = 4) despite temporary pacing or a cardiac arrest which was resuscitated. Immediately after the restoration of sinus rhythm, we attempted to stop atrial pacing several times to evaluate the evolution of spontaneous heart rate and to avoid a temporary pacing with its infectious risks. Finally, atrial pacing was continued, because heart rate remained too slow. Despite this, the patients developed acute renal failure and collapse. Atrial pacing should be continued for several days. Patients were treated in the medical intensive care unit. They received noradrenaline infusion. One woman aged 78 years developed atrial fibrillation with rapid AV conduction. The duration of shock varied from several hours to 3 days.

The five patients survived without sequelae. However, two of these patients required a pacemaker implantation for poorly tolerated SB. All bradycardias were related to the drugs used to slow the rate of atrial flutter as digoxin, β-blockers, or calcium inhibitors present at the time of ablation. These drugs did not really slow the rate of atrial flutter, but a major SB occurred when sinus rhythm was restored. The depressor effect of β-blockers and calcium inhibitors on myocardium could be also suspected. These five patients all had a heart disease, four patients had a moderate renal impairment of diabetic origin, and one patient had a systemic lupus erythematosus. The ablation of flutter was difficult in two patients, requiring more than 30 applications of RF energy on isthmus and a duration of more than 2 hours and 30 minutes.

One year later, the woman who developed permanent atrial fibrillation after noradrenaline infusion had another cardiac shock. The shock occurred just after His ablation indicated for still rapid atrial fibrillation.

Definitive complete AVB occurred in three other patients who required a pacemaker implantation: two patients developed complete AVB incidentally, following a displacement of the catheter on the His bundle, and another one developed permanent complete AVB after a septal

application of RF energy because ablation was unsuccessful at conventional sites of ablation. Complete AVB was permanent and not regressive.

Another patient aged 59 years with known coronary artery disease developed a complete AVB associated with acute coronary syndrome. He had a type II diabetes mellitus. We noted the occurrence of a complete AVB and a ST-segment elevation in inferior leads, although the patient was totally asymptomatic. The procedure was stopped. Coronary angiography was performed urgently. The patient remained in complete AVB. Less than half an hour after the acute event, the coronarography angiography revealed the acute occlusion of the segment 3 of the right coronary artery, just after the junction of middle/distal third of artery and before the bifurcation into left retroventricular artery and posterior interventricular artery. Initial balloon angioplasty of the right coronary artery and stent implantation were performed. A normal AV conduction was immediately restored. The case was previously reported.[13]

Another patient aged 78 years with advanced ischemic dilated cardiomyopathy and implantable cardiac defibrillator for a spontaneous ventricular tachycardia (VT) died of refractory VT the day following an apparently uncomplicated flutter ablation.

A woman aged 64 years presented tamponade several minutes after obtaining complete isthmus block. Surgical pericardial drainage was complicated by accidental ligation of the circumflex artery and a lateral infarction.

Indirect complications lead to the death of three patients. One 60-year-old woman with a valvular cardiac prothesis died of intracranial hemorrhage; oral anticoagulant had been replaced by heparine and the accident occurred when oral anticoagulant was reintroduced. One 60-year-old patient died of gastrointestinal hemorrhage and one 77-year-old patient with chronic lung disease developed acute respiratory failure and died several days later of fistulae between the esophagus and pleura. This last complication was probably without ablation relationship and could be a consequence of a prolonged intensive care unit stay.

Minor Complications Occurred in 30 Patients

Bradycardias were the most frequent complications and occurred in 24 patients. A major SB (less than 40 bpm) occurred after interruption of atrial flutter and progressively improved in nine patients. All patients were treated by a drug used to slow the rate of atrial flutter. Complete AVB or second-degree AVB occurred in 14 patients; one patient with known coronary artery disease developed a complete AVB associated with acute coronary syndrome. AVB regressed under trinitrine and antithrombotic therapy. Complete AVB was traumatic in two patients with left bundle branch block. Restoration of a normal AV conduction was spontaneous at the end of ablation. Five complete AVBs were transitory and related to the drugs taken by the patient. Six complete AVBs or second-degree AVBs were vagal-related and provoked by a chest pain at the time of RF energy application.

Embolic-related stroke occurred in one 44-year-old patient without apparent heart disease who presented initially with atrial flutter with 1/1 atrial conduction. Heparin was initiated and ablation was performed after 8 days of heparin therapy. The patient presented a cerebral embolic event several hours after atrial flutter ablation. The event was spontaneously regressive without important sequelae at day 2.

Acute coronary syndrome occurred after atrial flutter ablation in one 78-year-old patient several hours after ablation, but regressed after nitroglycerin.

One 66-year-old patient developed subdural hematoma, but symptoms and hematoma regressed spontaneously.

Vascular local complications at the puncture site occurred in three patients with valvular heart disease and required local surgical treatment.

A medium-sized pericardial effusion occurred in one 74-year-old patient but did not require drainage.

Factors Associated with Adverse Events

Table I reports the factors associated with the occurrence of adverse event.

This study did not demonstrate that age is a risk factor for a complication, despite a trend toward older ages observed in patients with adverse event than in other patients (66 ± 11 vs 64 ± 12 years; $P < 0.2$).

Female gender was a significant predictor of adverse event ($P < 0.02$).

The presence of heart disease was not significantly associated with a risk of adverse event. However, the risk depended on the nature of heart disease. Adverse events were significantly more frequent in patients with ischemic heart disease and valvular heart disease than in patients without heart disease ($P < 0.03$, $P < 0.01$). Surprisingly, hypertensive heart disease was less frequent in patients with adverse events than in those without complications.

Anticoagulation-related bleeding in patients with valvular heart disease was the cause of events in this population. Major events occurred in these patients when oral anticoagulants were replaced by heparin and when two or more drugs were used for anticoagulation. Patients

Table I.

Factors Associated with Adverse Avents (AE)

	AE+	AE−	P-value
Number	44	839	
Age (years) (M ± SD)	66 ± 11	64 ± 12	0.2
Female gender (N)	16 (36%)	182 (22%)	<0.02
No HD (N)	7 (16%)	214 (25.5%)	0.15
Ischemic HD (N)	12 (27%)	138 (16%)	0.06
Valvular HD (N)	9 (20%)	89 (10.6%)	<0.04
Hypertensive HD (N)	3 (7%)	169 (20%)	<0.02
Dilated cardiomyopathy (N)	4 (9%)	78 (9%)	NS
Congenital HD (N)	3 (7%)	29 (3%)	0.06
Various HD (N)	6 (13.6%)	46 (5%)	<0.02
Number of RF applications	15 ± 9	17 ± 11	0.18

AE+ = AE occurrence; AE− = absence of AE; HD = heart disease; M = mean; SD = standard deviation; N = number; NS = non-significant; SD = standard deviation.

Table II.

Percentage of Complications in the Two Periods of Admission

	1994–2002	2003–2011	
Number of ablations	236	647	
Total complications	10 (4%)	34 (5.5%)	NS
Major complication	1 (0.4%)	13 (2%)	0.09

NS = non-significant.

with valvular prothesis required a more important anticoagulation.

Surprisingly, we did not find any change in the percentage of complications over time in relation with the learning curve (Table II). The percentage of major events even tends to increase probably because of the care of patients with more multiple pathologies.

There was no correlation with the duration of the procedure and the number of RF energy applications.

Discussion

Outside the classical catheterism-related complications, we report specific complications related to the abrupt changes of heart rate when sinus rhythm is restored. They were frequently rate-control drugs related. The prevalence of atrial flutter ablation-related adverse events was similar to the prevalence of complications reported after diagnostic electrophysiological studies and RF catheter ablation in patients with tachyarrhythmias.[9–12] There were four indirect deaths. They were due mainly to anticoagulants-related complications in patients with associated advanced heart disease. Such condition was rarely encountered for the ablations of reentrant tachycardia or accessory pathways. The patients were younger and without associated multiple pathologies.

Some complications were not specific and were related to catheterization or ablation as tamponade, pericardial effusion, or local vascular events. However, some of these complications could be favored by the full anticoagulation required before permanent atrial flutter ablation.[14] When anticoagulation needed to be important as in valvular heart disease, the risk of hemorrhage should not be underestimated. Major events occurred in our patients when oral anticoagulants were replaced by heparin and when two or more drugs were used for anticoagulation. At the opposite, insufficient anticoagulation could be associated with a risk of embolic event.[14,15] The risk was very low in this study (0.1%) and the event concerned a patient with a score 0 of CHA2DS2–VASc.

Some other complications could be directly related to atrial flutter ablation. The most frequent complication was a bradycardia (3.7%), generally reversible but sometimes life threatening (1%). Pacemaker implantation was needed in 0.57% of our population.

Complete AVB occurring during ablation of atrial flutter was rare but was previously reported. This adverse event was principally reported after ablation of a slow pathway in patients with AV node reentrant tachycardia[16] or after ablation of anteroseptal accessory pathway.[9–11] In the case of atrial flutter ablation, Garcia-Cosio et al.[17] assessed this risk to 9.6% of which half were complete AVB and half sinus dysfunction in 1998 in a series of 62 patients, whereas Almendares et al.[18] evaluated the risk to 1.1% in 2005 in their study with a sample of almost the same size (86 patients). In 2002, Schmieder et al.[19] evaluated the risk of bradycardia to 0.82% in a larger sample size. Recently, Belhassen et al.[8] reported a risk of bradycardia of 0.6% among 913 patients. The occurrence rate of AVB related to the procedure and requiring pacemaker implantation was not negligible (0.12%).

Complete AVB occurring during ablation of atrial flutter could be induced by an inadvertent application of energy on the normal AV conduction system. For Belhassen et al.,[8] AVB mostly affected patients with a preexisting complete left bundle branch block.

It could be also explained as an ischemic complete AVB which developed after the thrombosis of coronary artery near the ablation site.[13,20–24] The stress provoked by the procedure and the pain caused by the application of RF energy were possible factors of thrombosis.[25] Another hypothesis was that the artery was under endocardial at this level and that the current application favored its thrombosis. Damage of the right coronary artery with intramural hemorrhage adjacent to the side of the lesion were reported.[24] Acute right coronary occlusion during ablation of atrial flutter was first reported by Ouali et al.[20] and then by different authors.[13,21–23] ST-segment elevation without other complication resolved with antithrombotic therapy or angioplasty.[13] The high-voltage output from the RF generator and the lack of sufficient cooling effect could be associated with aggravation of a coronary artery stenosis. Ventricular fibrillation or cardiac arrest in the periprocedural period could be the initial or only clinical manifestation. Septal or lateral RF delivery could increase the risk of coronary occlusion.[21]

Some authors[21] recommended the evaluation of the coronary status before ablation in patients with known coronary artery stenosis, but could be difficult to perform. The risk of systematic coronary angiography could be higher than the limitations of such a complication. Smaller tipped catheters, energy titration (to minimally effective dose), saline irrigation, or cryoablation could help avoid this serious complication.[21]

In this study, ischemic heart disease was more frequently associated with adverse events. However, the bradycardia associated with ablation and ischemic heart disease was more frequent because of the rate-control drugs used to treat ischemic heart disease and atrial flutter than to an acute coronary ischemia. We draw attention to the risk-taking β-blockers or other rate-control drugs. The effect is not the same on the AV node and sinus node. The patient could develop a significant SB at the interruption of atrial flutter during ablation, which could have significant clinical consequences mainly in patients with advanced heart disease. Heart rate suddenly went from one fast frequency to a very slow rhythm. This change was poorly tolerated hemodynamically. We recommend therefore the cessation of beta blockers or other rate-control drugs before the ablation procedure or at least a reduction of the dosage. SB was generally well-tolerated except in some patients either old or with advanced heart disease because they developed a low renal output with its consequences. The complication was not specific of atrial flutter ablation and could be observed after a cardioversion or His bundle ablation for rapid atrial fibrillation. Several causes could be suspected as the abrupt changes of heart rate, the role of drugs, presence of associated heart disease, and of a moderate renal impairment.

Another specific and exceptional complication related to atrial flutter ablation could be a risk of monomorphic VT.[26] The site of VT origin was the inferobasal right ventricle adjacent to the previous atrial isthmus ablation area. The most likely mechanism for the VT was scar-related reentry, the scar being the result of previous RF lesions in the atrial isthmus. This complication could be the cause of the death of one of our patients.

Bohnen at al.[27] reported that aside from ablation type, renal insufficiency was the only independent predictor of a major complication, whereas age, gender, body mass index, INR level, hypertension, coronary artery disease, diabetes, and prior cerebrovascular accident were not associated with increased risk.

Limits of the Study

This is a single center report.

Some of these complications are not specific as bradycardias noted after restoration of sinus rhythm when isthmus RF ablation was performed. They can be observed after restoration of sinus rhythm by another method as cardioversion. Therefore, the prevalence of complications could be overestimated.

In addition, larger periprocedural risk could be associated with the use of a 8-mm-tip catheter. A preset temperature of 55° and 25-W energy using 4-mm-tip catheter could be sufficient. However, the technique used for ablation could explain only a minority of complications.

Conclusion

In conclusion, atrial flutter ablation was generally safe but minor and major complications could occur more frequently in women, in patients with valvular and ischemic heart disease. Therefore, it is especially important to perform these procedures in a hospital with coronary angiography or cardiac surgery services available in case major adverse events occur. Other avoidable risks were the absence of interruption or decrease of dosage of rate-control drugs in patients with heart disease and presenting with flutter and fast AV conduction. The replacement of oral anticoagulants agents by heparine in patients with valvular heart disease could be discussed.

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Is isoproterenol really required during electrophysiological study in patients with Wolff-Parkinson-White syndrome?☆

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Abstract We have studied the results of electrophysiological study (EPS) in patients with Wolff-Parkinson-White syndrome (WPW) and spontaneous adverse clinical presentation and determined whether isoproterenol added incremental value.

Methods: EPS was performed in 63 patients with WPW and adverse clinical presentation at baseline. EPS was repeated after infusion of isoproterenol in 37 patients, including 25 without criteria for a malignant form at baseline.

Results: Atrioventricular orthodromic tachycardia was induced 44%, antidromic tachycardia in 11%, atrial fibrillation (AF) in 68% at baseline. At baseline EPS, criteria for a malignant form (AF induction and shortest CL <250 ms) were noted in 60%; tachycardia was not inducible in 16%. All the patients met the criteria for a malignant form after isoproterenol.

Conclusions: EPS at baseline missed 16% of patients at risk of life-threatening arrhythmias who had no inducible tachyarrhythmia and 40% without classical criteria for malignant form.

Keywords: Wolff-Parkinson-White syndrome; Electrophysiological study; Isoproterenol; Sudden death

Although most patients with pre-excitation will not have adverse clinical presentation, sudden cardiac death can occur and can be a presenting feature in some individuals.[1–3] It is very difficult to determine the exact risk, but estimates range between 0.02–0.1% per year.[1,4] Various risk markers have been identified over the years. These include male sex, multiple accessory pathways, refractory period less than 250 ms and shortest RR interval during atrial fibrillation of<250 ms.[5] The risk of sudden cardiac death is thought to be due to ventricular fibrillation, secondary to rapidly conducting atrial fibrillation (AF),[1,6] which is itself thought to arise secondary to an episode of supraventricular tachycardia in mostly young patients.[5]

Several non invasive tests are available, but they lack specificity.[7] Therefore, electrophysiological study remains a very powerful tool in investigations of asymptomatic patients with Wolff-Parkinson-White syndrome (WPW) type ECG when non-invasive tests are equivocal.[7] beta-Adrenergic stimulation that occurs during exercise activity or stress may result in shortening of the anterograde refractory period of the accessory pathway, leading to increased ventricular rates during AF. Isoproterenol infusion has been used by several groups[7–9] to reproduce the effects of beta-adrenergic stimulation and has been shown to shorten the refractory period of the accessory pathway. However, none of these studies have conclusively shown that data obtained after isoproterenol infusion are associated with a risk of death.

Therefore, the diagnostic value of isoproterenol in electrophysiological testing of patients with WPW is not well defined. Initial studies did not use isoproterenol and the follow-up did not indicate an adverse prognosis in studied patients.[7,8] Recent studies used isoproterenol but the data about the prognostic significance of the infusion are unknown.[9] Moreover, the adverse prognosis reported in some patients of the last study concerned patients with documented rapid AF at Holter monitoring.

In the past years, the treatment for pre-excitation syndrome has changed with the development of ablation techniques. The number of accessory pathway ablations has considerably increased. Therefore, the natural history of the pre-excitation syndrome became difficult to evaluate.

☆ Conflicts of Interest: None.

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The aim of this study was a confirmative study to determine whether testing with isoproterenol in addition to baseline testing added any incremental value in identifying electrophysiological malignant features in high risk patients. To do this, we looked at a group of patients with WPW who had already manifested a being high risk (having presented with adverse clinical features) who underwent electrophysiological study with a view to ablation.

Methods

Study population

The study population consisted of patients with spontaneous adverse presentation-related WPW referred to a single centre in 1990 and 2011.

Inclusion criteria were the patients with WPW who presented with a documented life-threatening hemodynamically not tolerated arrhythmia, with collapse or syncope and requiring emergency treatment (cardioversion or intravenous drug).

Patients with WPW who presented with hemodynamically well-tolerated arrhythmia or patients who presented with syncope without documented arrhythmia or asymptomatic patients with pre-excitation in whom rapid AF was induced were excluded from the study.

Patients were studied as part of standard of care. Written informed consent was obtained in all patients.

Electrophysiological study

Electrophysiological study (EPS) was carried out without sedation as previously described.[10] Briefly incremental atrial pacing was performed until the highest rate conducted 1/1 through the accessory pathway and/or the atrioventricular node. Programmed atrial stimulation at a basic cycle length of 600 and 400 ms with the introduction of one and two extrastimuli was performed. When a fast supraventricular tachycardia was induced, the protocol was generally stopped, except in patients studied several years earlier. In the absence of induction of a tachycardia conducted through the accessory pathway at a rate higher than 250 bpm, isoproterenol (0.02 to 1 $\mu g.min^{-1}$) was infused to increase the sinus rate to at least 130 bpm and the pacing protocol was repeated.[11,12] Arterial blood pressure was continuously monitored during the study by an external sphygmomanometer (Baxter HealthCare, Tokyo, Japan). Ablation was recommended for all patients presenting with malignant forms of WPW. The first ablations were performed in 1994 in our department. Catheter ablation of accessory pathway was proposed during the same time in patients with induced rapid supraventricular tachycardia and those with a spontaneous or detected malignant form.

Definitions

The location of the accessory pathway was determined with the 12-lead ECG recorded in maximal preexcitation. The diagnosis of multiple pathways was retained only if ECGs in maximal preexcitation were clearly different or if the sites of ablation were also clearly different. In the left free wall location, the ablation could require the application of radiofrequency energy apparently at two sites, but it could be the same large accessory pathway. Sustained AF or reciprocating tachycardia was defined as a tachycardia that lasted longer than 1 minute. Anterograde conduction was evaluated by the measurement of the shortest atrial cycle length at which there was 1 to 1 conduction over the accessory pathway and the shortest atrial tachycardia cycle length at which there was 1 to 1 conduction over the accessory pathway. Accessory pathway effective refractory period was determined at a cycle length of 600 ms and 400 ms in control state and only 400 ms after isoproterenol. WPW syndrome was considered as malignant and at risk of sudden death at electrophysiologic study when the following association was observed[5]: induced sustained AF or atrial tachycardia and the shortest RR interval between pre-excited beats was less than 250 ms in the control state or less than 220 ms after isoprotereol during atrial pacing. Orthodromic atrioventricular re-entrant tachycardia (AVRT) induction alone was not considered as a criterion for a high-risk form of preexcitation syndrome.

Statistical analysis

Data are expressed as means ± standard deviation (SD). All variables were tested for a Gaussian distribution by visual inspection of the histogram and Shapiro Wilk test. Non-normally distributed data are reported as median (interquartile range). For categorical variables, the chi-squared (χ^2) test was performed. The paired t-test procedure was used to analyse variables. A P value <0.05 was considered statistically significant. All statistical analyses were performed by using the SPSS package for Windows (version 17. 0.1, SPSS Inc., Chicago, IL, USA).

Results

Clinical characteristics

Sixty three patients (mean age 38 ± 18 years, 68% males) were included in the study. Age range varied from 11 to 74 years and 26 (41%) were more than 40 years of age at the time of presentation (Table 1). Fifty seven presented with syncope and documented arrhythmia and 6 other patients were resuscitated from a ventricular fibrillation (VF). Presenting arrhythmia was ventricular fibrillation in 6, AF in 46, antidromic tachycardia in 4, wide atrial tachycardia in 3 and other supraventricular tachycardia without clear mechanism in 4 patients. In the latter cases, ECG was recorded in one lead in emergency before cardioversion and was of poor quality. Cardioversion was required in 31 patients to stop the tachycardia.

Pathway location in all patients is shown in Table 1. Thirty nine were left-sided, 2 were right-sided and 22 were septal. One of the patients with septal accessory pathway had 2 accessory pathways, (postero-septal and antero-septal). The total number of patients with WPW referred to the centre within this time period was 782. Seven hundred nineteen patients were excluded because they were asymptomatic (n = 278) or they have presented a syncope without documented

Table 1
Clinical data of the study population.

Subjects	63
Age (years)	38±18
Sex (male)	43 (68%)
Clinical presentation	
Syncope	57 (90.5%)
Cardiac arrest	6 (9.5%)
Presenting arrhythmia (%)	
AF	46 (73%)
VF	6 (9.5%)
ADT	4 (6.3%)
WCT	3 (4.8%)
SVT	4 (6.3%)
Location of pathway	
Anteroseptal	4 (6.3%)
Posteroseptal	17 (27%)
Left lateral	39 (62%)
Right lateral	2 (3.2%)
2 APs	1 (1.6%)

AF: atrial fibrillation, VF: ventricular fibrillation, ADT: antidromic tachycardia, WCT: wide complex tachycardia, SVT: supraventricular tachycardia.

arrhythmia (n=94) or well-tolerated AF (n=24) or AVRT (n=323). Therefore, spontaneous adverse presentation represented 8% among unselected patients with WPW. The clinical data of this population were previously reported.[10]

Baseline results

Electrophysiological study was carried out in all patients.

General results (Table 2): The shortest atrial cycle length at which there was 1 to 1 conduction over the accessory pathway was 223±30 ms and ranged from 167 to 333 ms. AVRT was induced in 28 patients, antidromic tachycardia in 7 patients and AF in 43 patients. The mean accessory pathway refractory period was 225±28 ms and ranged from 170–310 ms. Eight patients had a refractory periods of more than 250 ms; 260 ms in 7 patients and 310 ms in a 57 year old who presented with fast AF conducted over the accessory pathway with a cycle length of 230 ms and requiring cardioversion.

- 1:1 pacing at baseline with a cycle length less than 250 ms was obtained in 49 patients (78%). The combination of 1:1 pacing at control state with a cycle length<250 ms and induction of AF in the control state was obtained in 38 patients (60%). Three of these patients had also inducible antidromic tachycardia. They had all the criteria of a malignant form with the shortest RR interval between pre-excited beats less than 250 ms during induced sustained AF. Four patients had no inducible tachycardia in control state and in 5 patients, only AVRT was induced. Antidromic tachycardia was induced in 2 patients.
- Fourteen patients had a 1 to 1 conduction over the accessory pathway≥250 ms at baseline. There were no inducible arrhythmias in 6 (9.5%) of these 14 patients at baseline. Arrhythmias were induced at baseline in 8 of these 14 patients, AVRT in 4 patients, AF in 2 patients and antidromic tachycardia in 2 patients. Three of the 4 patients with AVRT had also inducible AF. In the patients with induced AF, the shortest RR interval was≥250 ms (1 patient had an RR interval of 250 ms) and ranged from 250 to 341 ms.

Results with isoproterenol

The repetition of electrophysiological study was not performed in 25 patients who had major signs of malignancy in control state. The data of patients without signs of malignancy at baseline (n=25) are detailed on the Flow chart Fig. 1.

- General results (Table 2): Mean shortest atrial cycle length at which there was 1 to 1 conduction over the accessory pathway with isoproterenol was 194± 15 ms. AVRT was induced in 15 patients, AF in 25 patients and antidromic tachycardia in 7 of the patient population. Shortest atrial cycle length at which there was 1 to 1 conduction over the accessory pathway was less than 250 ms in all patients and less than 220 ms in 94.5% of the patients tested. Two patients with shortest atrial cycle length<250 ms at baseline had no important shortening after isoproterenol (231 vs 240 ms and 222 vs 240 ms).
- Among the patients with 1:1 conduction at baseline with a cycle length less than 250 ms and without induced AF at baseline (n=11), 4 had no inducible tachycardia at baseline and they had induced AF after isoproterenol (Fig. 2); 2 of them had also induced also antidromic tachycardia with a mean cycle length<200 ms. The 2 patients with only inducible antidromic tachycardia at baseline had inducible AF. Among the patients with 1:1 conduction at baseline with a cycle length<250 ms and only inducible AVRT (n=5), 5 had induced AF and one had also induced antidromic tachycardia with a mean cycle length<200 ms.
- Out of the 14 patients with shortest atrial cycle length at which there was 1 to 1 conduction over the AP≥250 ms at baseline (n=14), all patients had a shortest atrial cycle length at which there was 1 to 1

Table 2
Electrophysiological data of the study population (parameters with and without isoproterenol).

	Without isoproterenol	With isoproterenol	P value
Number of patients	63	37	
Shortest atrial CL with 1 to 1 conduction over AP (ms)	223±30 ms	194±15 ms	<0.001
Refractory period (ms)	225±28	191±18	<0.001
Induction of AVRT	28 (44%)	15 (41%)	NS
Induction of ADT	7 (11%)	7 (19%)	NS
Induction of AF	43 (68%)	26 (70%)	NS
high risk patients	38 (60%)	26 (70%)	

CL: cycle length; CS: control state; AVRT; atrioventricular re-entrant tachycardia, ADT: antidromic tachycardia, AF: atrial fibrillation; high risk patients: shortest RR interval between pre-excited beats<250 ms in CS, <220 ms after isoproterenol and AF at baseline and/or isoproterenol.

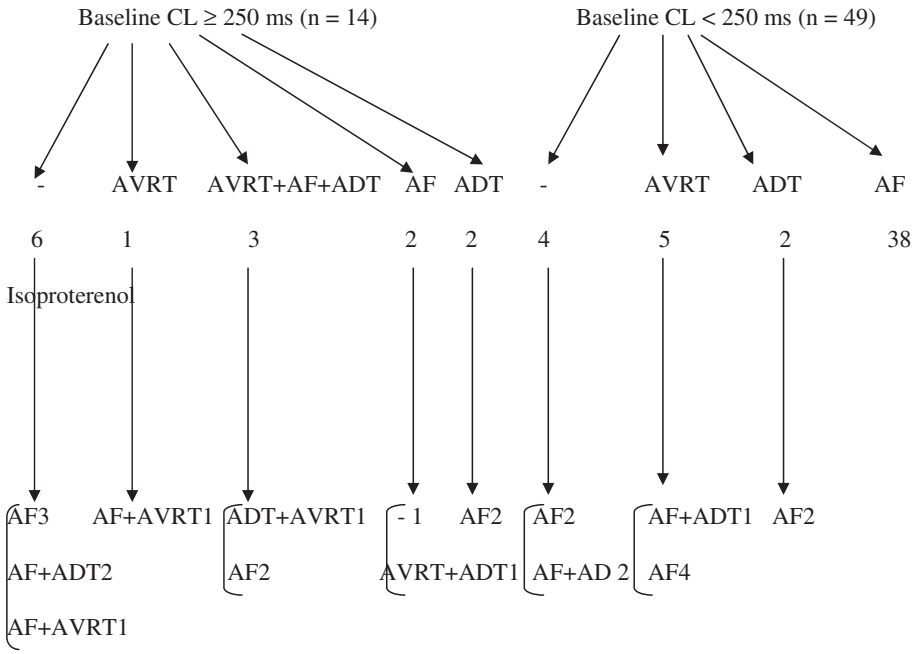

Fig. 1. Flow chart reporting the data of the 25 patients without signs of malignancy at baseline (Cl: cycle length, - absence of arrhythmia induction, AVRT: atrioventricular reentrant tachycardia, AF: atrial fibrillation, ADT: antidromic tachycardia).

conduction over the accessory pathway < 220 ms and 10 < 200 ms after isoproterenol. Mean values were 275 ± 24 ms in control state and 202 ± 8 ms after isoproterenol. In 7 patients, 6 with no inducible arrhythmias and 1 with AVRT in control state, 7 had induced AF and 2 had also induced antidromic tachycardia with a mean cycle length < 220 ms. The details of induced arrhythmias are reported in the Flow chart Fig. 1.

- In the total group of 25 patients shortest atrial cycle length at which there was 1 to 1 conduction over the accessory pathway was less than 220 ms in all patients and less than 200 ms in 10 patients (40%) of the patients tested. 1 to 1 conduction over the accessory

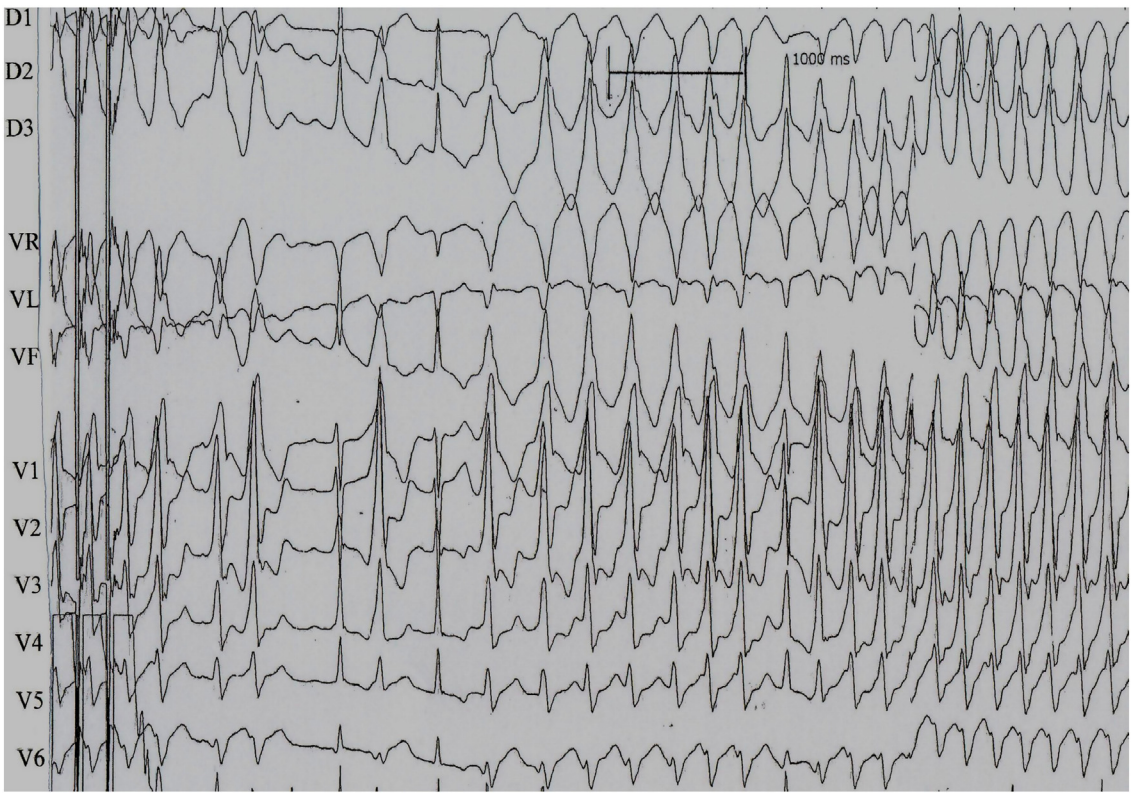

Fig. 2. Induction of AF conducted over accessory pathway at a rate of 290 bpm (cycle length 207 ms (cycle length 207 ms). 12 lead surface ECG.

Table 3
Data of patients without electrophysiological signs of malignancy at baseline before and after isoproterenol.

	Without isoproterenol Patients without signs of malignancy in CS	With isoproterenol Patients without signs of malignancy in CS	P value
Number of patients	25	25	
Shortest atrial CL with 1 to 1 conduction over AP (ms)	251±35 ms	194±13	<0.001
Refractory period (ms)	220 ±20	193±18	<0.05
Induction of AVRT	9 (36%)	6 (24%)	NS
Induction of ADT	5 (20%)	7 (28%)	NS
Induction of AF	5 (20%)	17 (68%)	<0.0006
High risk patients	0	100%	

CL: cycle length; CS: control state; AVRT; atrioventricular re-entrant tachycardia, ADT: antidromic tachycardia, AF: atrial fibrillation; high risk patients: (shortest RR interval between pre-excited beats<250 ms in CS, <220 ms after isoproterenol and AF at baseline and/or isoproterenol).

pathway was 200 ms in 11 patients (44%) between 207 and 214 ms in 4 patients (16%).

Table 3 summarized the data of patients without the criteria for an electrophysiological form of preexcitation (shortest RR interval between pre-excited beats less than 250 ms during induced sustained AF) before and after isoproterenol. After isoproterenol all patients had the electrophysiological criteria for a malignant form (Table 3).

Specific results among patients who presented a ventricular fibrillation

They were 6 patients, 5 males and one female, aged from 12 to 72 years (mean age 37±21). In one of them there were no criteria of malignancy in control state; no tachycardia was inducible and maximal rate conducted by accessory pathway was 240 bpm. After isoproterenol AF conducted with cycle length<200 ms was induced.

Discussion

This study is a retrospective analysis of patients with WPW-related adverse presentation, who presented with adverse cardiovascular symptoms. This study shows certain key findings. Firstly, WPW-related adverse presentation was common in patients over the age of 40 years and accounted for 26 patients (41%) of our population. Secondly, in patients who had already manifested as high risk, only 49 patients (78%) had antegrade 1:1 conduction over accessory pathway at less than 250 ms under baseline conditions, but all had 1:1 conduction below 220 ms with isoproterenol. When we consider only the induction of an arrhythmia, electrophysiological study performed only in control state missed at least 10 patients (16%) at risk of life-threatening arrhythmias who had no inducible supra-ventricular tachyarrhythmia in control state. When criteria of malignancy (shortest RR interval between pre-excited beats less than 250 ms during induced sustained AF) were considered only 38 patients (60%) were identified in control state. Baseline testing without isoproterenol would, therefore, not have identified about a third of these patients as being "high risk" based on traditional criteria.

Similar findings were reported 20 years ago by Sharma and all[8,13,14] in a small cohort of 9 survivors of sudden cardiac death; a short RR interval<250 ms was identified in 78% of patient population, but in all patients with isoproterenol.

The PACES/HRS Expert Consensus Statement on the Management of the Asymptomatic Young Patient with a Wolff-Parkinson-White Electrocardiographic Pattern,[15] reported recently that the prognostic value of the addition of isoproterenol for risk stratification has not been adequately studied in any group (adults and children).

Although most subjects will remain asymptomatic, there is a small but definite risk of sudden cardiac death. This is clearly regrettable as catheter ablation is now considered a safe and efficacious treatment of WPW,[16] providing high success rate and with minimal, but not zero complication rates. However, even in the asymptomatic patients, some had the accessory pathway in which antegrade refractory period was shorter than 250 msec. They may result in rapid ventricular conduction over the accessory pathway when AF develops.[17] For asymptomatic patients, risk stratification is therefore essential.[18–22] A variety of noninvasive testing has been used, but lacks specificity.

The risk of sudden cardiac death with WPW depends on the ability of the pathway to conduct rapidly in the antegrade direction. Several non-invasive tests are currently used and are the first line investigation of patients with WPW. They do however lack specificity[18] and therefore invasive electrophysiological study is sometimes used.[19–23] The study includes the measurement of the minimum cycle length allowing 1:1 conduction in the antegrade direction, shortest RR interval in AF and refractory period.[20–22] With testing in control state alone, some patients would be labelled not at "high risk" based on conventional factors. Conduction properties of accessory pathway's change with isoproterenol[11,12,14] and therefore it would seem logical to perform these tests under catecholamine exposure, as most of the malignant forms present under conditions of heightened adrenergic tone. At EPS, isoproterenol infusion and bicycle exercise test were shown to shorten accessory pathway compared to baseline testing.[23]

Most of the previous studies reported only the facilitation of tachycardia induction by isoproterenol. The problem, however, is that while isoproterenol testing increases the

sensitivity, it does so at the expense of the specificity of the test.[19,24]

This study has important implications in that age cannot be used as a cut-off for "safety" of a pathway.[24] Pathway characteristics change unpredictably with age with some having very little change.[18,19,21] First episode of AF might occur later in life.

We have also shown that testing with isoproterenol improves sensitivity. Isoproterenol, however, while increasing the sensitivity decreases the specificity.[11,12,14,24] Therefore, this would imply that more patients would end up needing ablation than would otherwise have to prevent sudden cardiac death. Three large registry data[26–28] are often quoted where the risk of death ranged from 0.007%- 0.2%, cerebrovascular accident from 0.2 to 0.5%. Even in symptomatic patients, where the risks of ablation are high e.g. septal pathways, testing with and without isoproterenol might provide a better risk assessment and therefore the patient can make an informed consent. However among the 60 patients who accepted the accessory pathway ablation, a reappearance of preexcitation was noted in 5 patients and in 5 other patients ablation failed. This relatively high incidence of failure was mainly noted before the years 2000. These patients who refused ablation or with a failure of ablation, were the really important patients to evaluate.

Limitations

The data was collected independently at the time of the procedure and therefore not liable to have been biased by the investigators. Finally, we do not have data on the symptoms of the patients prior to the episode. However, these patients had not seen a cardiologist with palpitations prior to these events.

We have not evaluated the specificity of the test because actually ablation of AP is proposed in patients with electrophysiological criteria of malignancy in control state or after isoproterenol.

The definition of high risk patients at EPS can be debated because there many other definitions retained in the literature. It was the definition that we have used in previous studies on the preexcitation syndrome.[10,11,19,25]

Conclusions

Electrophysiological study performed only in control state missed at least 40% of patients with a preexcitation syndrome and adverse presentation and without the classical criteria for a malignant form. Isoproterenol increased the sensitivity of electrophysiologic study to detect malignant form from 60 to 100%. Patients with life threatening features can present at any age and testing with isoproterenol should be routing in patients undergoing EPS for WPW.

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The value of adrenaline in the induction of supraventricular tachycardia in the electrophysiological laboratory

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Aims The most commonly used drug for the facilitation of supraventricular tachycardia (SVT) induction in the electrophysiological (EP) laboratory is isoprenaline. Despite isoprenaline's apparent indispensability, availability has been problematic in some European countries. Alternative sympatomimethic drugs such as adrenaline have therefore been tried. However, no studies have determined the sensitivity and specificity of adrenaline for the induction of SVT. The objective of this study was to determine the sensitivity and specificity of adrenaline for the induction of SVT.

Methods and results Between February 2010 and July 2013, 336 patients underwent an EP study for prior documented SVT. In 66 patients, adrenaline was infused because tachycardia was not induced under basal conditions. This group was compared with 30 control subjects with no history of SVT. Programmed atrial stimulation was carried out during baseline state and repeated after an infusion of adrenaline (dose ranging from 0.05 mcg/kgc to 0.3 mcg/kgc). The endpoint was the induction of SVT. Among 66 patients with a history of SVT but no induction under basal conditions, adrenaline facilitated induction in 54 patients (82%, $P < 0.001$). Among the 30 control subjects, SVT was not induced in any patient (0%) after infusion. Adrenaline was generally well tolerated, except for two patients (3.0%), where it had to be discontinued due to headache and high blood pressure or lumbar pain.

Conclusion Adrenaline infusion has a high sensitivity (82%) and specificity (100%) for the induction of SVT in patients with prior documented SVT. Therefore, it could serve as an acceptable alternative to isoprenaline, when the latter is not available.

Keywords Adrenaline • Isoprenaline • Supraventricular tachycardia • Electrophysiological study

Introduction

Isoprenaline, a beta-adrenergic drug, commonly used in clinical practice for its properties of increasing heart rate can induce supraventricular tachycardia (SVT) in the electrophysiology (EP) laboratory.[1,2] Despite its apparent indispensability, availability has been problematic in Eastern Europe. Alternative sympatomimethic drugs like adrenaline have therefore been tried.

The sensitivity and specificity of isoprenaline for the induction of paroxysmal atrial fibrillation have already been reported.[3] Although adrenaline is known to facilitate the induction of SVT, its sensitivity and specificity in the EP laboratory have not previously been evaluated.

The purpose of this study was to determine the sensitivity and specificity of adrenaline for the induction of SVT during the electrophysiological (EP) study.

Methods

Study subjects

From February 2010 to July 2013, a total of 336 patients with clinically documented paroxysmal SVT (PSVT) were referred to our department

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What's new?

- Adrenaline can be used for the induction of SVT in patients with paroxysmal documented SVT.
- It may also be considered in patients who undergo an electrophysiological study to determine the mechanism of their palpitations and/or syncope, if no documentation of arrhythmia exists (12-lead electrocardiogram), after having undergone a complete negative set of noninvasive tests.
- Because adrenaline cannot always facilitate the induction of SVT in patients with a history of paroxysmal SVT even at infusion rates of 0.3 μg/kg/min, it is important to be aware of the fact that the addition of other drugs such as atropine or isoprenaline might be necessary to induce and assess the mechanism of SVT before catheter ablation.

for an EP study ± radiofrequency catheter ablation procedure. Sixty-six patients necessitated adrenaline infusion because under basal conditions no PSVT was induced. Twenty-four patients were men (36.4%) and 42 women, with a mean age of 49.2 years. Patients with known coronary artery disease, hypertrophic obstructive cardiomyopathy, severe aortic or mitral valve stenosis were excluded from the study. All patients had recurrent episodes of PSVT documented by 12-lead electrocardiogram (ECG).

A group of 30 subjects with no history of tachycardia constituted the control group. The EP study was performed in these patients for the following reasons: to assess the sinus node function and atrioventricular (AV) conduction in 10 patients, to investigate the cause of syncope in 8 patients, to determine the refractory period of an accessory pathway in 7 patients and prior to ventricular extrasystole ablation in 6 patients. Adrenaline was infused in all and a complete EP study was conducted.

Electrophysiological study

The EP study was performed in non-sedated patients in the post-absorptive state after an informed consent was obtained. All patients were in sinus rhythm at the beginning of the study.

Heart catheterization was performed through the right femoral vein with four multielectrode catheters. Electrograms were recorded from the high right atrium, the bundle of His, coronary sinus, and the right ventricle.

Atrial and ventricular programmed stimulation as well as overdrive pacing was conducted, to determine the conduction properties and refractoriness of the AV node, to exclude the presence of an accessory pathway, to induce and to stop SVTs, and to perform the differential diagnosis of PSVT.

Our atrial programmed stimulation protocol employed delivery of up to three atrial extrastimuli at two atrial sites and at two atrial drive pacing lengths (600 and 400 ms).

If no arrhythmia was induced at the basal state, adrenaline was consecutively administered. Infusion was started at 0.05 μg/kg/min and up-titrated until an increase in the basal heart rate by at least 50% was noticed, to at least 100 beats/min (maximum 150 beats/min or 400 ms of cycle). The amount of adrenaline required to induce the desired changes in heart rate ranged from 0.1 to 0.3 μg/kg/min. Attempts to induce SVT by atrial and ventricular programmed stimulation and overdrive pacing were repeated during adrenaline infusion. For patients in which adrenaline infusion was not sufficient for SVT induction, atropine 1 to 2 mg iv was administrated.

Statistical analysis

Statistical analysis was performed using the SPSS Statistics version 21.0 (SPSS, Inc.). Descriptive statistics were used to summarize patient characteristics. Means and standard deviations were used for normally distributed continuous variables as well as counts and proportions for categorical variables. The McNemar test for related samples was performed to compare in a pairwise fashion the fraction of patients with inducible PSVT before and after adrenaline infusion.

Results

In 115 out of 336 patients (34.2%), there was no need for drug provocation: 50 patients (44%) with AV node re-entry tachycardia (AVNRT), 44 patients (38%) with AV re-entry tachycardia (AVRT) conducted retrogradely through an accessory pathway, and 21 (18%) with atrial tachycardia (AT).

In 221 out of 336 patients (65.8%) without induction in the basal state, we used medication for SVT induction. For patients included in our study from February 2010 to July 2012, we used atropine and isoprenaline (isoprenaline was available in our EP laboratory during this period of time). For patients included in our study from July 2012 to July 2013, we used atropine and adrenaline (because isoprenaline was not available in our EP laboratory during this period of time).

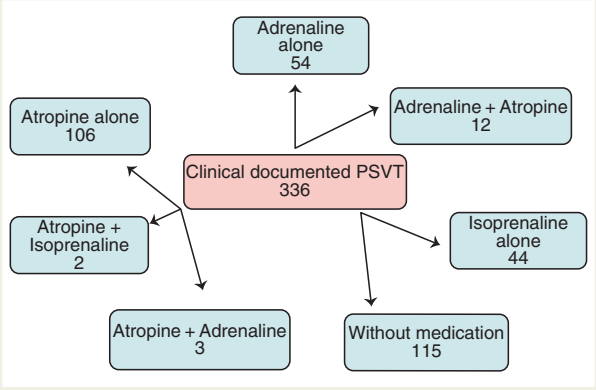

Figure 1 The population included in the study and the distribution of drugs used for SVT induction. PSVT, paroxysmal supraventricular tachycardia. Adrenaline + atropine indicates that tachycardia was not induced after the administration of adrenaline alone, so atropine was administered on top to facilitate the induction of SVT. Atropine + adrenaline indicates that tachycardia was not induced after the administration of atropine alone, so adrenaline was administered on top to facilitate the induction of SVT. Overall, three patients necessitated adrenaline infusion for SVT induction after the administration of atropine: one patient had dual-AV nodal physiology but no tachycardia was induced after atropine alone was administrated; AVNRT was induced after subsequent adrenaline infusion and slow pathway ablation was successfully performed; for the second patient, no SVT was induced after adrenaline infusion, but he also had dual-AV nodal physiology, thus slow pathway ablation was performed; the third patient had no SVT induction after adrenaline infusion, no evidence of dual-AV nodal physiology and the procedure was terminated.

Concerning the use of adrenaline or atropine, the choice of one drug or the other as the initial medication for facilitating the induction of SVT was left to the physician's free will. Consequently, one doctor used adrenaline first for SVT induction and another doctor used atropine first for SVT induction. If no SVT was induced after the administration of the first drug, then the other drug was added (*Figure 1*).

Effects of adrenaline in patients with supraventricular tachycardia

Sixty-six patients (19.6%) received adrenaline for SVT induction. Among the 66 patients with prior documented PSVT, using the above-mentioned stimulation protocols, no SVT was induced under basal conditions (prior to adrenaline administration).

After the infusion of adrenaline, sustained SVT was induced in 54 patients. Of these 54 patients, 40 had AVNRT, 11 patients had orthodromic AVRT using a concealed accessory pathway, and 3 patients had focal ATs arising from the right atrium. The sensitivity of the adrenaline test defined as the percentage of inducible sustained SVT was 82%.

We had no patient with a concealed accessory pathway and concomitant AVNRT induction.

For the 12 patients in whom tachycardia could not be induced after adrenaline infusion, atropine was added. Paroxysmal supraventricular tachycardia was subsequently induced after the administration of atropine in 11. Among them, eight patients had AVNRT, three patients had AVRT, and one patient had AT. In one patient no arrhythmia was induced but slow pathway ablation was performed because documented ECG during tachycardia was suggestive of AVNRT, and the EP study revealed the presence of dual-AV nodal morphology (*Figure 2*).

A related-samples McNemar change test used for nominal data showed significant difference between SVT induction before and after the administration of adrenaline, $P < 0.0001$.

Effects of adrenaline in control subjects

Among the 30 control subjects, SVT was not induced during the EP study, neither before nor after infusion of adrenaline. The specificity, defined as the percentage of negative test in the control group, was 100%.

Diagnostic accuracy

The sensitivity and specificity of adrenaline for the induction of PSVT were 82 and 100%, respectively. The positive and negative predictive values were 100 and 71%. The overall diagnostic accuracy was 88% (*Table 1*).

Adverse effects

Adrenaline was generally well tolerated. Side effects were tremor (for which the infusion was not discontinued because it was considered tolerable by the patient), headache, and lumbar pain. The adrenaline infusion was discontinued prematurely in 2 of 96 patients (2.1%). In the first patient, headache was attributed to high systolic blood pressure >180/110 mmHg, which appeared during infusion of adrenaline at rates of 0.2 μg/kg/min. The symptoms resolved after discontinuation of adrenaline. The other patient presented lumbar pain that disappeared after the discontinuation of infusion.

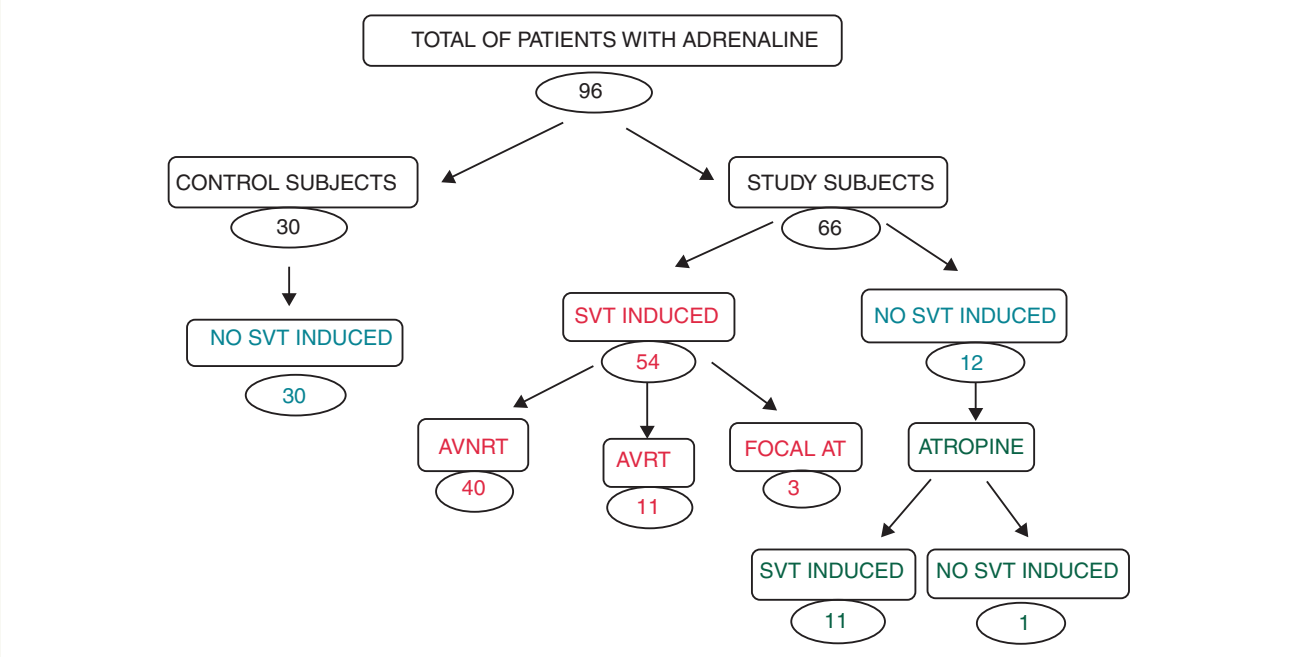

Figure 2 Effects of adrenaline in control subjects and in patients with documented SVT. SVT, supraventricular tachycardia; AVNRT, atrioventricular node reentrant tachycardia; AVRT=atrioventricular reentrant tachycardia using an accessory pathway as the retrograde limb; AT, atrial tachycardia.

Table 1 Diagnostic accuracy of adrenaline for the induction of SVT

Sensitivity	Specificity	PPV	NPV
82%	100%	100%	71%

Data shown in percentages are positive predictive value (PPV) and negative predictive value (NPV).

Induction of non-specific arrhythmias occurred in the form of runs of premature atrial contractions (four patients = 4.2%), non-sustained AT (one patient = 1.0%), ventricular premature beats (three patients = 3.1%), but none of these influenced the overall result of the EP study.

There were no ECG changes suggestive of ischaemia in any of the patients.

Discussion

Main findings

This study demonstrates that adrenaline has a high sensitivity and specificity for the induction of SVT in patients with paroxysmal documented SVT.

In a prior study, Brembilla-Perrot *et al.*[1] reported a sensitivity of 90% and a specificity of 100% for isoprenaline in the diagnosis of SVT.

Huycke *et al.*[2] found a sensitivity of 67% and a specificity of 100% for isoprenaline-facilitated induction of AVNRT. However, the number of patients was lesser (20 patients) than in the study of Brembilla-Perrot (67 patients).

Stellbrink *et al.*[4] randomized 80 patients to receive either atropine or isoproterenol before AVNRT ablation. The inducibility in the isoproterenol group increased from 58% in the baseline state to 93% after isoproterenol infusion ($P < 0.001$).

Pauriah *et al.* studied 63 patients with Wolff Parkinson White syndrome and spontaneous adverse clinical presentation (syncope or resuscitated ventricular fibrillation, VFib). At baseline orthodromic tachycardia was induced in 44% and antidromic tachycardia in 11%. After isoproterenol infusion, inducibility increased to 68.2% for orthodromic tachycardia and 22.2% for antidromic tachycardia.[5]

In the absence of isoprenaline, it appears that adrenaline might be an acceptable alternative, due to its high sensibility and specificity, of 82 and 100%, respectively. In our study, adrenaline was generally well tolerated with minimal side effects and with a low percentage of premature discontinuation of 2.1%.

Electrophysiological effects of adrenaline and dosage

An alternative approach to the adrenergic initiation of tachycardias facilitated by isoprenaline could be the use of adrenaline or noradrenaline. Furthermore, the use of a vagolytic agent such as atropine could facilitate the induction of tachycardias by leaving the action of natural catecholamines unopposed by the parasympathetic system and thus induce tachycardia.[6]

Adrenaline is a nonselective agonist of alpha- and beta-adrenergic receptors, and thus its activity, side effects, and efficacy differ from isoprenaline. The overall EP effects of adrenaline result from stimulation of the beta-adrenergic receptors. Stimulation of the alpha-adrenergic receptors by adrenaline has no effect on the AV node, but prolongs the effective refractory period of the atrium and the ventricle, partially offsetting the shortening of refractory periods mediated by beta-receptor stimulation.[6,7]

The mechanism by which adrenaline induces sustained SVT may be multifactorial. In physiological doses, adrenaline shortens the effective refractory period of the atrium, AV node, and ventricle and improves AV node conduction. Episodes of tachycardias induced by adrenaline are attributed to the acceleration of the sinus rate, which might sufficiently shorten the retrograde refractory periods of additional pathways (accessory pathway, slow nodal pathway) to permit retrograde conduction up the additional pathway to the atrium, thus causing an echo beat and initiate tachycardia.[6,7]

Because adrenaline can reproduce stress hypokalaemia, another mechanism by which adrenaline might have facilitated the induction of SVT would be a reduction in intracellular potassium.[8]

Probably the best way to estimate adrenergic activity after intravenous infusion is the measurement of plasma concentration of adrenaline.[9] Although plasma adrenaline concentrations were not measured in our study, prior studies have determined the plasma adrenaline concentrations corresponding to the infused doses. Accordingly, an adrenaline infusion of 0.001–0.313 μg/kg/min would correspond to a plasma concentration of 0.005–3 μg/L.[10–16] In our study, the doses of adrenaline required to induce the desired change in heart rate ranged from 0.1 to 0.3 μg/kg/min.

Previous studies have demonstrated that constant rate infusions are characterized by the attainment of a steady state in plasma concentrations within 5–10 min. Furthermore, steady-state concentrations are directly proportional to the rate of infusion[14] In our study, adrenaline infusion was started at a dose of 0.05 μg/kg/min rate and increased every 5 min to obtain the desired increase in the heart rate, or up to a dose of 0.3 μg/kg/min. This was effective in increasing the heart rate and subsequently inducing SVT by programmed atrial stimulation.

Safety of adrenaline in patients with concealed accessory pathways

By giving adrenaline there is a theoretical risk of unmasking antegrade conduction and inducing VFib in patients who have a concealed accessory pathway. There are data in the literature indicating that isoprenaline can facilitate the unmasking of antegrade conduction of the accessory pathway.[17] In the case of atrial fibrillation initiation, the pathway can conduct rapidly to the ventricles and induce VFib. However, the risk is relatively small. Our EP laboratory is properly equipped to handle such cases (defibrillator, intubation, mechanical ventilation, etc.).

Limitations

One limitation of this study is that the effects of adrenaline were assessed in conscious sedated or non-sedated patients. It is not clear whether adrenaline would have similar properties if administrated to patients under general anaesthesia.

The induction of ATs is not necessarily clinical tachycardia. In this case, the patients were always asked for their symptoms. If they were asymptomatic or their symptoms did not suggest it to be clinical tachycardia, AT was considered non-specific. The induced and clinical tachycardia may be different but may look the same on the surface ECG. However, the *P* wave during AT and the presence of non-sustained or sustained arrhythmia should make the difference between non-specific and specific ATs.

Finally, because the effects of adrenaline may be time-dependent, it is possible that SVT may have been induced at lower doses if more time was allowed before the increase of the infusion rate.

Conflict of interest: none declared.

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