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Efficacy and safety of cryoablation of para-Hisian and mid-septal accessory pathways using a specific protocol: single-center experience in consecutive patients

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Abstract

Purpose Radiofrequency (RF) catheter ablation of para-Hisian (P-H) and mid-septal (M-S) accessory pathways (APs) is a potentially harmful procedure due to their close location to the A-V node. Conversely, cryoablation (CA) appears safer in this setting. The aim of this study was to assess the efficacy and safety of CA of these APs using a specific protocol.

Methods Fifty-three patients undergoing CA for P-H (45) or M-S (8) APs were included. CA was performed with a 4-mm catheter at − 75 °C for 480 s in the site where conduction block over the AP was obtained by a specific cryomapping protocol. Optimal catheter-tissue contact was achieved by inferior or superior vena cava approach. In case of failure, a 6-mm catheter and/or trans-septal catheterization (TSC) were considered. Normal AV conduction was monitored throughout CA, which was interrupted in case of its inadvertent modifications.

Results In 46 patients (87%), CA was successful. Reasons for failure were as follows: lack of AP interruption (3 patients), intraprocedure AP conduction resumption (3), or transient A-H interval prolongation (1). Failure was associated with more aggressive approach including multiple procedures, greater use of 6-mm catheters, TSC, and longer CA applications. No major complications were observed. Three out of 46 patients (6.5%) experienced relapse of AP conduction during follow-up and were successfully re-treated by CA.

Conclusions CA of P-H and M-S APs is highly safe and effective and a specific protocol for cryomapping and CA could lead to a low recurrence rate at follow-up.

Keywords Wolff-Parkinson-White syndrome · Catheter ablation · Accessory pathways · Cryomapping · Cryoablation

Abbreviations

AP	Accessory pathways
A-V	Atrio-ventricular
AVRT	Atrio-ventricular re-entrant tachycardia
AVB	Atrio-ventricular block
CA	Cryoablation
DAP	Dose area product
EP	Electrophysiological study
IVC	Inferior vena cava
M-S	Mid-septal
P-H	Para-Hisian
RF	Radiofrequency
SD	Standard deviation
SVC	Superior vena cava
TSP	Trans-septal
VPE	Ventricular pre-excitation

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1 Introduction

Radiofrequency energy (RF) catheter ablation of para-Hisian (P-H) and mid-septal (M-S) accessory pathways (APs) is associated with an increased risk of potential complications due to their anatomical close relationship with the normal atrio-ventricular (A-V) conduction system [1]. Cryoablation (CA) has been regarded as a safer alternative thanks to two specific cryothermal energy properties: cryomapping, which creates initially reversible lesions through a progressive tissue freezing, and cryoadhesion, which lets a firm catheter-tissue contact during cryomapping and ablation. Despite the high safety profile of CA, the long-term efficacy is still lower than RF ablation [1]. The aim of the present study was to assess the efficacy and safety of CA of P-H and M-S APs in a cohort of consecutive patients using a specific protocol for cryomapping and CA.

2 Methods

2.1 Patient population

A cohort of 53 consecutive patients undergoing electrophysiologic study (EP) and catheter ablation of P-H or M-S APs from 2003 to 2017 was retrospectively considered. Table 1 reports the clinical features of this population. Most patients had a younger age, the majority (77%) had manifest ventricular pre-excitation (VPE), no signs of structural heart disease, and had undergone a previous EP procedure in another center. In the last subgroup of 33 patients, 14 (42%) had received an unsuccessful RF ablation. Asymptomatic patients qualified for ablation only if sustained atrio-ventricular re-entrant tachycardia (AVRT) was reproducibly induced and/or the AP was capable of extremely fast conduction [2]. In Table 2, the clinical characteristics are subdivided according to the AP location. No statistically significant difference was found between the two groups, except for a greater number of patients referred from other centers (84 vs. 38%; $p = 0.01$) and of those who had previously undergone an EP procedure (69 vs. 24%; $p = 0.04$) in the P-H group. This study conforms to the Declaration of Helsinki on human research and was approved by the Ethical Committee at our institution. Patients or their legal guardian signed informed consent.

Table 1 Clinical characteristics of the considered population

	n. (%)
Patients	53
Male gender	32 (60)
Age (mean value ± SD)	26 ± 14 (range 12–61) years
Manifest VPE	41 (77)
Asymptomatic patients	11 (21)
Structural heart disease	4 (8)
Prior use of AADs	18 (34)
Patients referred from other centers	41 (77)
Patients with previous EP procedures	33 (62)
Para-Hisian AP	45 (85)
Mid-Septal AP	8 (15)

AADs, anti-arrhythmic drugs; *AP*, accessory pathway; *EP*, electrophysiologic study; *SD*, standard deviation; *VPE*, ventricular pre-excitation

Table 2 Clinical features according to the AP location

	P-H (%)	M-S (%)	*p* value
Patients	45 (85)	8 (15)	0.0001
Male gender	28 (62)	4 (50)	0.70
Age (mean value ± SD)	26 ± 14	24 ± 15	0.25
Manifest VPE	35 (78)	6 (75)	1.00
Asymptomatic patients	7 (16)	4 (50)	0.05
Structural heart disease	3 (7)	1 (13)	0.49
Prior use of AADs	14 (31)	4 (50)	0.42
Referred from other centers	38 (84)	3 (38)	0.01
Previous EP procedure	31 (69)	2 (25)	0.04

AADs, anti-arrhythmic drugs; *EP*, electrophysiologic study; *SD*, standard deviation; *VPE*, ventricular pre-excitation

2.2 Electrophysiologic study

The procedure was performed by two experienced operators in the fasting non-sedated state after withdrawal of any anti-arrhythmic drug for at least five half-lives. Multipolar catheters were introduced by the right femoral vein and the left or right antecubital vein and advanced to the high right atrium, coronary sinus, His bundle area, and right ventricular apex. Antegrade and retrograde conduction properties of the AP were assessed and induction of AVRT was tested at baseline and during continuous isoproterenol up to 4 mcg/min, if required. Burst pacing with progressive shortening of the pacing cycle length until the lack of atrial capture was used to induce atrial fibrillation and test the shortest pre-excited R-R interval.

Location of the AP was defined by using both bipolar and unipolar recordings during sinus rhythm and/or AVRT. Only in case of P-H location, if the positioning and stability of the CA catheter were unsatisfactory using the inferior vena cava (IVC) approach, then a superior vena cava (SVC) approach was used by advancing the catheter through an antecubital vein (Fig. 1a–d). An AP had a P-H location if a distinct His-bundle potential was recorded during sinus rhythm in the site where the earliest ventricular bipolar electrogram preceding the delta-wave and coincident with a fast and negative intrinsicoid ventricular deflection in the unipolar recording was observed. If VPE hampered His-bundle recording or the AP had concealed conduction, then its location relative to the His-bundle was defined during orthodromic AVRT based on the earliest retrograde atrial activation in bipolar recordings and negative atrial intrinsicoid deflection in the unipolar recording (Fig. 2a). An AP had a M-S location if, based on the above electrophysiologic criteria, it was localized in an area bounded superiorly by the proximal His-bundle potential and inferiorly by the roof of the coronary sinus as assessed by the 30° left anterior oblique fluoroscopic projection view. During the EP procedure, catheters were manipulated carefully to

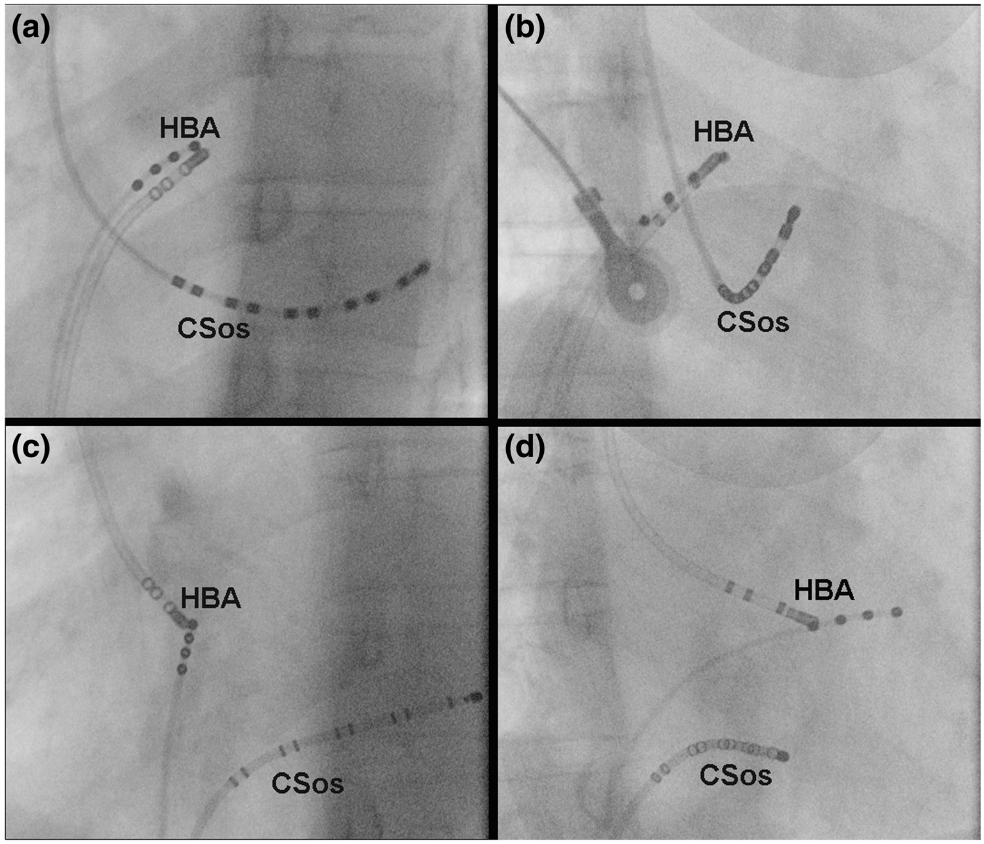

Fig. 1 **a**–**d** Fluoroscopic image in 30° left (**a**, **c**) and right (**b**, **d**) anterior oblique view of the cryoablation catheter positioned via inferior (**a**, **b**) and superior (**c**, **d**) vena cava access. Abbreviations: CSos, coronary sinus os; HBA, His-bundle area

avoid traumatic lesions and consequent conduction modification of the A-V node, right bundle branch, and AP.

2.3 Cryoablation protocol

CA was performed in the same procedure with a dedicated console (Cryoconsole, Medtronic CryoCath, Kirkland Quebec, Canada) and a 7F 4-mm-tip catheter (Freezor, Medtronic CryoCath, Kirkland Quebec, Canada) was initially used; in case of failure, a 7F 6-mm-tip catheter was used (Freezor Xtra, Medtronic CryoCath, Kirkland Quebec, Canada). Whenever a left component of the AP was suspected, trans-septal (TSP) catheterization was performed and the left antero-septal region beneath the aortic valve mapped. In the most suitable area, the ablation catheter was positioned so that the A/V ratio in the distal electrode pair was > 1 to prevent permanent lesion to the right bundle branch. In this site, cryomapping was applied using a specific protocol (Fig. 3), already described elsewhere [3]. Briefly, an application of 30 s at − 30 °C was delivered in the most suitable site. If it interrupted conduction over the AP with no modification of normal conduction, then direct transition to CA at − 75 °C up to 480 s was performed. If cryomapping was unsuccessful, after defrost, further 30-s applications were tested step-by-step, decreasing for each test the temperature by 10 °C to a minimum of − 70 °C. If cryomapping was ineffective at − 70°, then a 6-mm-tip catheter was used. Throughout the cryomapping protocol steps, the cryocatheter was firmly kept in the most suitable position, assessed by stability of bipolar recordings (Fig. 2a). Electroanatomic mapping system (EAM) compatible with the cryocatheter was not used to assess catheter stability throughout the procedure because of the significant catheter deformation visualized by the system that based on previous experience was due to the abrupt impedance change during ice formation at the catheter tip. Figures 2b and 4a show interruption of AP conduction during cryomapping. Throughout CA, normal A-V conduction and suppression of arrhythmia inducibility were tested using programmed electrical stimulation, while the catheter/tissue contact was maintained by cryoadherence (Figs. 4b and 5a–b). If during CA, prolongation of the A-H interval or appearance of right bundle branch block was observed, cryoenergy delivery was promptly interrupted and resumption of the baseline conduction properties was assessed. Similarly, if any increase of the degree of the VPE during sinus rhythm or if interruption of the AVRT over the antegrade re-entry limb was observed, cryomapping or CA was immediately stopped to avoid inadvertent damage to the normal A-V conduction system. After successful ablation, the absence of conduction resumption over the AP was assessed for 60 min. If AP conduction resumed, then further CA was performed.

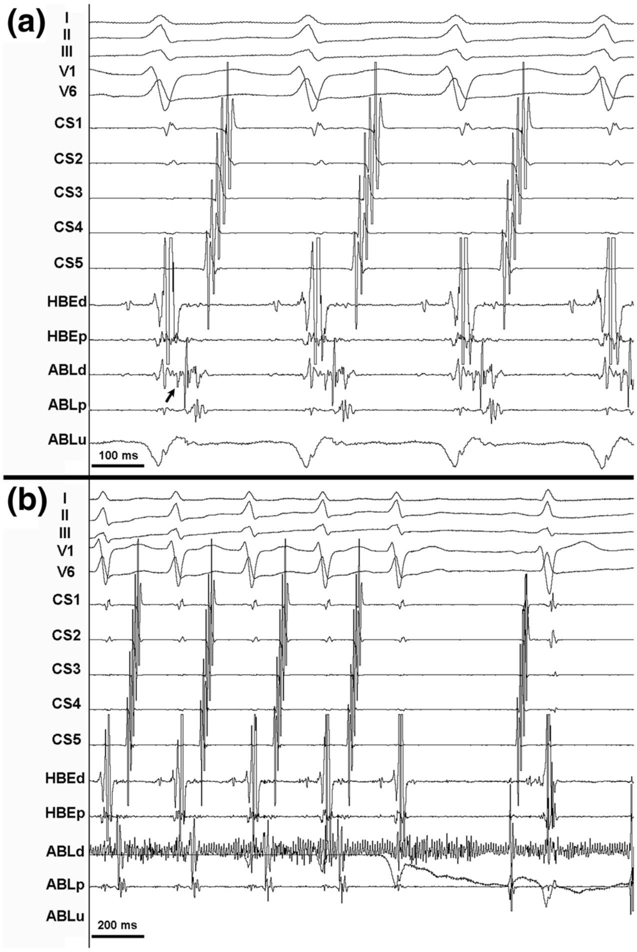

Fig. 2 **a**–**b** Mapping and cryoablation during orthodromic atrioventricular re-entry tachycardia in a case of para-Hisian accessory pathway. In this and in the following figures, tracings are as follows from top to bottom: surface ECG, coronary sinus from distal (CS1) to proximal (CS5), distal (HBEd), and proximal (HBEp) His-bundle electrograms, distal (ABLd) and proximal (ABLp) bipolar recordings form the cryoablation catheter and unipolar (ABLu) recording from the distal electrode of the same catheter. In **a**, the earliest retrograde atrial activation is observed in ABLd, where the shortest V-A interval with a putative Kent bundle potential is observed between the ventricular and atrial deflection (arrow); in ABLd, a far-field His-bundle potential is also observed. Of note, bipolar signals at the target site are stable over time, indicating good catheter/tissue contact. In **b**, during test application at − 40 °C, conduction interruption over the accessory pathway is obtained with tachycardia interruption

2.4 Follow-up

Patients were discharged after 24 h from the procedure with no antiarrhythmic drugs. For patients with previous manifest VPE, a weekly 12-lead ECG was recorded for 5 weeks and a visit was planned at 2 months. For patients with concealed AP, Holter monitoring and a visit were scheduled at 6 months. Thereafter, all patients were invited to refer to our center or to the referring cardiologist in case of any symptom possibly of cardiovascular origin.

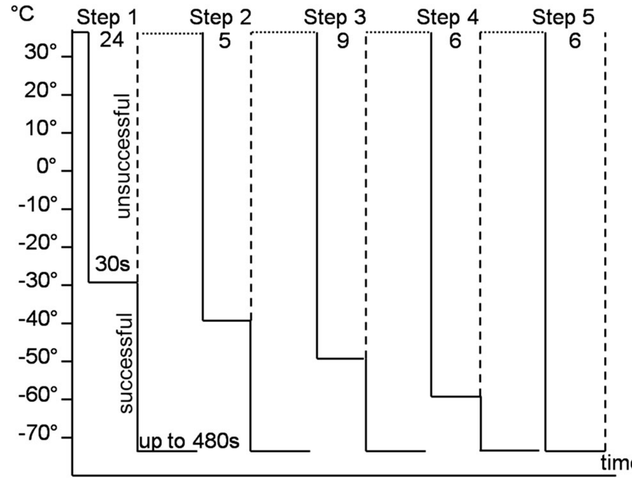

Fig. 3 Schematic representation of the step-by-step protocol for cryomapping. Numbers below the step indicate the number of patients with conduction interruption over the accessory pathway in each step

2.5 Statistics

Continuous variables are expressed as mean ± standard deviation (SD), if normally distributed according to D'Agostino–Pearson test for normality. Student's *t* test for independent samples with a confidence interval of 95% was used for metric variables; otherwise, either logarithmic transformation of variables or nonparametric tests (Mann–Whitney) were used. A chi-squared test was performed to examine whether there was an association between categorical variables; when the sample size was too small for the chi-squared test to be valid, a Fisher exact test was used. All data were analyzed using MedCalc version 12.5.0 (MedCalc Software). P values < 0.05 were considered significant.

3 Results

3.1 Localization of the APs and procedural data

Fifty-three patients underwent 57 procedures. In two cases (4%), multiple APs were observed: a P-H AP was associated with a posterior-septal one in a patient and a M-S AP was associated with a posterior-septal in the other. The SVC approach was used in 29/45 patients (64%) with a P-H location of the AP. The mean procedural and CA times were 181 ± 42 min and 556 ± 298 s, respectively. The mean fluoroscopy time was 17 ± 12 min with a corresponding dose area product of 51 ± 44 Gy·cm^2.

3.2 Acute success and reasons for acute failure

As shown in Table 3, in 87% of the patients, the procedure was acutely successful. Noteworthy, the 14 patients referred to our center after unsuccessful RF ablation, CA was successful

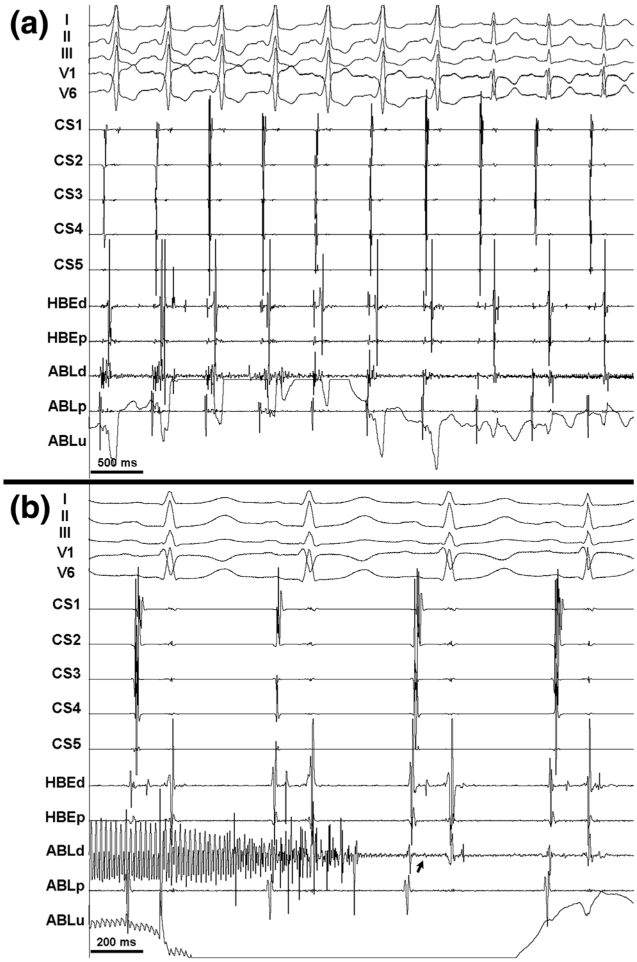

Fig. 4 **a**–**b** Cryomapping at − 30 °C and ablation during sinus rhythm in a patient with a manifest para-Hisian accessory pathway. In **a**, early after application initiation, pre-excitation disappears on surface ECG in the third last beat with no modification of the A-H and H-V interval in HBEd. In **b**, during defrost, after cryoablation at − 75 °C for 480 s, the artifact due to ice formation disappears in ABLd and a His-bundle potential is seen in the same electrogram (arrow). Notably, A-H and H-V intervals in HBEd are normal

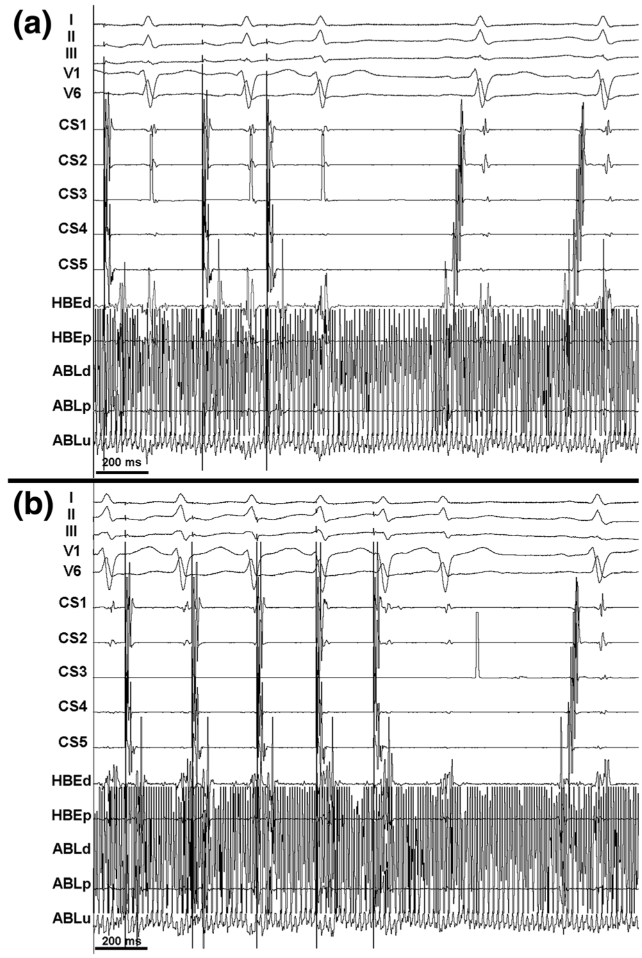

Fig. 5 **a**–**b** Same patient as in Fig. 2. In **a**, after tachycardia interruption during cryomapping programmed atrial stimulation from coronary sinus (p = 400, 220 ms) fails to induce re-entry during cryoablation at − 75°C, responsible for massive artifact on the ablation catheter recordings. In **b**, incremental atrial pacing up to 200 ms shows preserved conduction over the normal AV conduction pathway during a 480-s cryoablation

in most cases (11/14; 79%). During step-by-step cryomapping, conduction block over the AP was reached at a mean temperature of − 41 ± 16 °C (range from − 20 to − 70 °C). The number of patients with a successful cryomapping at each step is reported in Fig. 3. In 7 patients (13%), 6 with P-H and 1 with M-S location of the AP, the procedure was unsuccessful despite multiple CA procedures. The causes for failure were different: in 3 cases, block of AP conduction was never observed even at the maximum lower temperature using a 6-mm-tip catheter, in 1 patient with P-H AP, the procedure was aborted for transient A-H interval prolongation during CA, and in another 3 APs, the conduction persisted at the end of the procedure after transient successful CA and despite further CA applications; in this latter group, 1 case with M-S AP experienced transient prolongation of the A-H interval.

No complication was observed during the procedure. In the two cases with transient A-H interval prolongation, the A-V node conduction properties returned to baseline soon after defrosting. In one case, in whom TSP catheterization was performed, acute pericarditis associated with minimal pericardial effusion requiring no intervention was observed after 2 days. In none of the unsuccessfully treated cases, switch to RF ablation was considered safe.

3.3 Comparison between successful and unsuccessful cases

Table 3 compares different clinical and procedural parameters in successfully vs. unsuccessfully treated cases. No statistically significant difference was found between the two groups, except for a longer cryoablation time, more frequent use of the 6-mm-tip catheter, and the TSP catheterization in the group of

Table 3 Comparison between patients with and without procedural success

	Acute success	Acute failure	*p* value
Patients	46 (87)	7 (13)	
Procedures per patient, *n*	1	1.6 ± 0.8	
Age, years (mean ± SD)	26.5 ± 14.3	21.4 ± 7.4	0.55
Male gender, *n* (%)	27 (59)	5 (71)	0.69
Manifest VPE, *n* (%)	35 (76)	6 (86)	1.0
Structural heart disease, *n* (%)	4 (9)	0 (0)	1.0
6-mm-tip catheter, *n* (%)	8 (17)	5 (71)	0.0069
P-H AP, *n* (%)	39 (85)	6 (86)	1.0
M-S AP, *n* (%)	7 (15)	1 (14)	1.0
Cryoablation time, s (mean ± SD)	523 ± 281	930 ± 247	0.01
Patients with previous EP procedure, *n* (%)	28 (61)	5 (71)	0.70
Patients with previous RF ablation, *n* (%)	11 (24)	3 (43)	0.36
TSP approach, *n* (%)	2 (4)	4 (57)	0.0004
SVC approach in P-H APs, *n* (%)	23/39 (59)	6/6 (100)	0.11

AP, accessory pathway; *EP*, electrophysiologic study; *M-S*, mid-septal; *P-H*, para-Hisian; *RF*, radiofrequency; *SD*, standard deviation; *SVC*, superior vena cava; *TSP*, trans-septal approach; *VPE*, ventricular pre-excitation

patients with acute failure, associated with a greater number of procedures per patient.

3.4 Follow-up

During follow-up, three patients with P-H AP (6.5%) had resumption of AP conduction. The temperature at which AP conduction was interrupted was not predictive of recurrence, since in these three patients, the values were − 30, − 40, and − 70 °C, respectively. A re-do procedure using the same methodology was successful.

4 Discussion

4.1 Main findings

CA of P-H and M-S APs with a specific protocol used in this study achieves very good results in term of acute success and safety. This has to be considered especially in the light that the patients in our series were consecutive but represented a selected group of cases referred from other centers after an invasive EP procedure. In fact, in 3/7 patients who received an unsuccessful CA, a previous RF ablation had been unsuccessful as well. Although a temperature lower than 30 °C was reached during cryomapping and prolonged cryothermal energy applications were delivered according to this protocol, no major complications were recorded, underpinning a great safety profile of the used protocol. During follow-up, the recurrence rate was acceptable and observed only in P-H APs.

4.2 Ablation of P-H APs

Since its introduction in the 1980s, RF ablation of APs is regarded as a highly safe and effective procedure in both adults and children [4]. Nonetheless, a lower efficacy and safety profile is reported for RF ablation of septally located APs, in particular P-H APs, in which the risk of A-V block could be as high as 12.9% [1]. In this particular setting, which includes young healthy individuals and possibly athletes, this risk is unacceptable, although many of these patients may have a class I indication for ablation. The peculiar biophysics properties of cryothermal energy, which include slow lesion formation and cryoadherence effect [5], well explain the far higher safety profile of CA compared to RF ablation, quantified in 0% vs. 5.4%, respectively, of persistent A-V block in a recently published meta-analysis [1]. However, in this study [1], the advantage of CA is counterbalanced by a definitely higher recurrence rate compared to RF ablation (21.1% vs. 7.1%, respectively). Table 4 shows data of CA of P-H and M-S APs in previously published papers [6–20], each including more than 10 APs. These data confirm a good acute success with only minor complications of CA with, however, a non-negligible rate of recurrences. Different technical variables, such as a longer time to effect during cryomapping [14, 21] or a longer time to success [12], avoidance of bonus application [16, 21], and the size of freezing electrode [15, 16, 19, 22], may play a role in higher recurrence rate in patients treated with CA. However, none of these variables have shown an overwhelming importance in determining recurrences, with the only potential exception of an abrupt vs. a gradual disappearance of conduction over the AP during

Table 4 Overview of the previously published papers with cryoablation

First author	*n*. APs (P-H/M-S)	Cryomapping Min T (°C) and time (s)	CA time (s)	Acute success rate	Persistent complications	Follow-up recurrences	Success after recurrence retreatment
Gaita [6]	20 (11/9)	− 30 (60)	240	20/20 (100%)	0	4/20 (20%)	20/20 (100%)
Atienza [7]	22 (10/12)	− 30 (45)	240	20/22 (91%)	2 RBBB	3/20 (15%)	19/20 (95%)
Kirsh [8]	16 (11/5)	− 30 (60)	240	12/16 (75%)	0	0/12 (0%)	12/12 (100%)
Drago [9]	11 (7/4)	− 30 (60)	240–480	9/11 (82%)	0	3/9 (33%)	6/9 (67%)
Bar-Cohen [10]	12 (0/12)	− 30 (10–20)	240 + 240	9/12 (75%)	1 RBBB	7/9 (77%)	2/9 (22%)
Gaita [11]	39 (24/15)	− 30 (NA)	240	37/39 (95%)	0	8/37 (20%)	37/37 (100%)
Kaltmann [12]	14 (9/4)	− 80 (25)[a]	240	13/14 (93%)	0	1/13 (8%)	13/13 (100%)
Bastani [13]	27 (27/0)	− 30 (20)	240	26/27 (96%)	0	7/26 (27%)	24/26 (92%)
Drago [14]	52 (35/17)	≤ − 30 (60)[b]	240–480	50/52 (96%)	0	12/50 (24%)	NA
Ergul [15]	24 (24/0)	− 30 (30–45)	NA	23/24 (96%)	0	2/23 (9%)	23/23 (100%)
Yildirim [16]	25 (25/0)	− 30 (60)	240–300	23/25 (92%)	2 RBBB	1/23 (4%)	22/23 (96%)
Insulander [17]	100 (NA)	− 30 (20)	240	81/100 (81%)	0	11/81 (14%)	70/81 (86%)
Karadeniz [18]	28 (20/8)	− 30 (45)	240–360	28/28 (100%)	0	2/28 (7%)	26/28 (93%)
Swissa [19]	50 (50/0)	− 30 (30)	240	47/50 (94%)	0	7/47 (15%)	47/47 (100%)
Jang [20]	26 (16/10)	− 40 (10)	240	23/26 (88%)	1 I° AVB; 2 RBBB	3/23 (13%)	20/23 (87%)
Total	466	− 30 to − 80 (10–60)	240–480	421/466 (90%)	8 (1.8%)	71/421 (17%)	341/371 (92%)
Present study	53	− 41 ± 16 (up to 30 s)	556 ± 298	46/53 (87%)	0	3/46 (6.5%)	46/46 (100%)

APs, accessory pathways; *AVB*, atrio-ventricular block; *CA*, cryoablation; *Min T*, minimum temperature reached; *M-S*, mid-septal; *P-H*, para-Hisian; *RBBB*, right bundle branch block. *NA*, not available

[a] Initially tested during cryoablation

[b] Two different protocols used: (1) − 30° for 60 s (2) from − 30 to − 70 with a 10° decremental step each 10 s

cryothermal energy delivery [15]. These studies generally report a less aggressive cryomapping and CA protocol, compared to the one used in the present study, which leads to fewer recurrences during follow-up, preserving the high safety profile. On the other hand, different more aggressive cryomapping and CA protocols could be taken into account, with the aim to get a prompt interruption of conduction over the AP and to avoid tissue edema related to repetitive applications, which may prevent success. However, our protocol could be better compared to other possibly more aggressive strategies. In fact, an initial more aggressive application may produce inadvertent modification of normal A-V conduction forcing early interruption of the application and potentially leading to unsuccessful ablation.

4.3 Analysis of unsuccessful cases

Interestingly, in our patient series, acute failure was associated with longer cryoablation times, more frequent use of the 6-mm-tip catheter, and TSP approach. This shows that in these cases, the AP was resistant to a more aggressive approach, suggesting a more complex or deeper anatomical substrate not suitable for CA. Whether RF energy ablation would have been successful in some of these cases is unknown. However, the clinical conditions of these patients did not justify a more aggressive approach at risk of major complication. Even more interesting, A-H interval prolongation was observed in 1 out of 8 patients with M-S APs and in only 1 out of 45 patients with P-H APs. This is in line with a previous report [1], which shows that mid-septally located APs, being in close proximity to the compact A-V node, are more frequently associated with damage to A-V node conduction induced by RF ablation.

4.4 Limitations

The major limitation of this single-center study is its retrospective nature with data collection over more than 10 years in a relatively small cohort of patients. Moreover, the potential usefulness of larger (> 6 mm) electrodes and lower CA temperatures was not investigated. However, since the considered population mainly involved younger and healthy patients, we considered safety a priority and, therefore, only 4-mm or 6-mm-tip catheters were used. Finally, follow-up visits were planned in the first months after ablation and, after this period, further contacts were left to the discretion of the patients or referring physician and therefore, late recurrences cannot be excluded. Nevertheless, it has been reported that the vast majority of the recurrences occur in the first months after CA [14].

5 Conclusions

A specific protocol for cryomapping and CA for P-H and M-S APs is associated with a lower recurrence rate, and a high safety profile. Successful CA can be obtained at first procedure even in patient with unsuccessful prior RF ablation. Failure is possibly related to anatomic features of the AP, which is resistant to an even more aggressive CA approach in repeated procedures.

Compliance with ethical standards

This study conforms to the Declaration of Helsinki on human research and was approved by the Ethical Committee at our institution.

Conflict of interest Dr. De Ponti has received educational grants from Medtronic; none for the other authors.

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