

Right ventricular rapid pacing in catheter ablation of atrial fibrillation: a novel application for cryoballoon pulmonary vein isolation

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Abstract

Background Cryoballoon ablation (Arctic Front, CryocathTM) represents a novel technology for pulmonary vein isolation (PVI). The initial phase of a freeze is crucial for cryolesion formation which is determined by local temperature depending on blood flow. We investigated the impact of right ventricular rapid pacing (RVRP) on temperature kinetics in patients (pts) with paroxysmal atrial fibrillation (PAF).

Methods and results Right ventricular rapid pacing was performed from the RV apex. Absolute minimal temperature (MT, °C), temperature slopes [time (s) to 80% MT; dT/dt], area under the curve (AUC) and arterial blood pressure (ABP, mmHg) were compared (group I: with RVRP vs. group II: without RVRP). RVRP (mean duration 55 ± 7 s) was performed in 11 consecutive PAF pts (41 PVs, age 58 ± 9 years, LA size 44 ± 6 mm, normal ejection fraction). Only freezes with identical balloon positions were analyzed (11/41 PVs). RVRP (cycle length 333 ± 3 ms) induced a significant drop in ABP (group I: 45 ± 3 mmHg vs. group II: 100 ± 18 mmHg, $p < 0.001$). MT was not different between group I and group II (-45.0 ± 4.4 vs. $-44.3 \pm 3.4^\circ\text{C}$, $p = 0.46$), whereas slope (38.0 ± 4.6 s vs. 51.6 ± 14.4 s, $p = 0.0034$) and AUC (1090 ± 4.6 vs. 1181 ± 111.2 , $p = 0.02$) was significantly

changed. In one pt, a ventricular tachycardia was induced. PVI was achieved in 41/41 PVs.

Conclusion Right ventricular rapid pacing significantly accelerates cryoballoon cooling during the initial phase of a freeze possibly suggesting improved cryolesions.

Keywords Right ventricular rapid pacing · Atrial fibrillation · Pulmonary vein isolation

Introduction

Catheter ablation using radiofrequency current (RFC) for pulmonary vein isolation (PVI) has been established in the treatment of paroxysmal atrial fibrillation (PAF) [1]. Inducing contiguous left atrial (LA) linear lesions using “RFC point-by-point” burning is technically complex and requires a three-dimensional (3D) reconstruction system [2, 3]. In addition, RFC energy-related complications such as PV stenosis, stroke, atrio-esophageal fistula and “man-made” atrial tachyarrhythmias (ATa) have further limited this ablation approach [4–7]. In contrast, the novel cryoballoon system (CryocathTM, Montreal Canada) allows straightforward acute PVI solely based on fluoroscopy [8, 9]. However, cryothermal energy (CTE) lesion formation is determined by stable local cryoballoon/tissue contact, local PV tissue temperature and rapid tissue cooling [10]. Effective long-term CTE ablation may be compromised by incomplete cryoballoon adhesion to the PV due to antero-grade PV flow which pushes the balloon back to the LA and “ice-ball” formation acting as an isolator preventing lesion growth to deeper layers [10, 11]. Therefore, the initial phase of a cryoballoon freeze is crucial. Further on, warming convective blood flow has shown to decrease CTE lesion sizes [12]. Right ventricular rapid pacing

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(RVRP) has been used to facilitate percutaneous aortic valve implantation [13]. RVRP reduces cardiac output, stroke volume, cardiac motion and PV flow which should result in (1) improved local PV/balloon contact due to minimized anterograde PV flow pushing the balloon back to the LA and (2) reduced convective cryoballoon warming by both PV and LA blood flow.

We tested the hypothesis whether RVRP (1) affects cryoballoon temperature and (2) can be safely performed in patients with PAF.

Methods

Inclusion and exclusion criteria

Between December 2007 and March 2008, a total of 11 patients with PAF were included in this study and provided written informed consent. The study subjects met the following inclusion criteria: a history of highly symptomatic PAF (≥ 1 episode/week) despite treatment with ≥ 1 antiarrhythmic drug (AAD). Exclusion criteria were defined as a LA diameter ≥ 55 mm, severe left ventricular hypertrophy (LV wall thickness ≥ 15 mm), known presence of coronary artery disease, reduced left ventricular ejection fraction (EF $< 55\%$), LA thrombus, prior stroke or heart failure.

Cryoballoon catheter

The principle of the “single big cryoballoon” technique for PVI (Arctic Front, CryocathTM, 28 mm diameter, 10.5F shaft) has been previously described in detail [9]. In brief, the refrigerant N₂O is delivered into the inner balloon where it undergoes a liquid to gas phase change resulting in an inner balloon cooling temperature of approximately -80°C . The catheter is equipped with central lumina which are used for (1) the insertion of the guide wire (Amplatz stiff wire) and (2) injection of contrast medium (diluted 1:1 ratio with 0.9% saline) for PV angiograms. Using the “over-the-wire” technique in conjunction with the steerable sheath (12F, FlexCath[®], CryocathTM), the balloon can be navigated to each PV ostium.

Ablation procedure

Vital parameters such as arterial blood pressure (ABP) and oxygen saturation were continuously monitored throughout the entire procedure. All procedures were performed under deep sedation using boli of midazolam and fentanyl as well as a continuous infusion of propofol (1%). After placing 6F decapolar catheters into the coronary sinus and to the His bundle region, two transseptal punctures were performed

using a modified Brockenbrough technique to introduce two 8F sheaths (SL1; St. Jude Medical) into the LA. One puncture site in the fossa ovalis was rather posterior, the other more anterior. Thereafter, heparin boli were repeatedly administered to maintain the activated clotting time between 250 and 300 s. Selective PV angiographies were performed to identify the PV anatomy in standard angulations (RAO 30°, LAO 40°). A Lasso catheter (Biosense Webster) was placed at the PV ostium via the posterior sheath to record PV potentials (sinus rhythm and coronary sinus pacing) using a conventional computerized EP system (AXIOM Sensis, Siemens). The more anterior SL1 sheath was exchanged for the 12F transseptal sheath (FlexCath[®]) in order to introduce the cryoballoon (28 mm) catheter into the LA. Both transseptal sheaths were constantly flushed with heparinized saline (500 IE/50 ml, 8F: 10 ml/h, 12F: 20 ml/h). The 28 mm balloon was maneuvered to all PV ostia. To assess the exact position of the inflated balloon in relation to the PV–LA region, contrast medium (Imeron[®]) diluted with saline 0.9% (1:1 ratio) was injected from the distal lumen of the cryoballoon catheter. After each freeze, PV conduction was reevaluated by positioning the Lasso catheter at the same location within the PV as before the CTE application. Ablation endpoint was PV entrance and exit block confirmed by the Lasso catheter. The phrenic nerve (PN) was constantly paced (10 V, 2.9 ms) from the superior caval vein when freezing at the right PVs. The position of the cryoballoon during each freeze was documented by cine for all applications. No intraprocedural imaging except for fluoroscopy was used.

Right ventricular rapid pacing

A 6F non-steerable catheter (Medtronic, Torqur) was inserted in the right ventricular apex (RVA) via the left femoral vein. Systemic ABP was monitored from the left femoral artery. An external biphasic defibrillator (Lifepak, Medtronic) was always on standby. The RVA pacing threshold was determined and the stimulation output was doubled assuring reliable ventricular capture (Biotronik UHS 20 stimulator). The cryoballoon was navigated to the target position at the PV ostium, which was documented using fluoroscopy before each freeze. One freeze (300 s) was performed with RVRP (group I) at a cycle length of 330–335 ms for 45–60 s (Fig. 1). The other freeze (300 s) was performed without RVRP (group II) with the cryoballoon in the identical position to allow for an intra-individual PV comparison. To exclude the impact of different cryoballoon positions on balloon temperature, only freezes with identical balloon positions in standard RAO 30° and LAO 40° position were subsequently included in the analysis (Fig. 2). Local temperature was continuously

Fig. 1 Right ventricular rapid pacing (CL 330 ms) induced reproducible significant drop of blood pressure. Surface ECG leads I, II. CS coronary sinus, RVA right ventricular apex

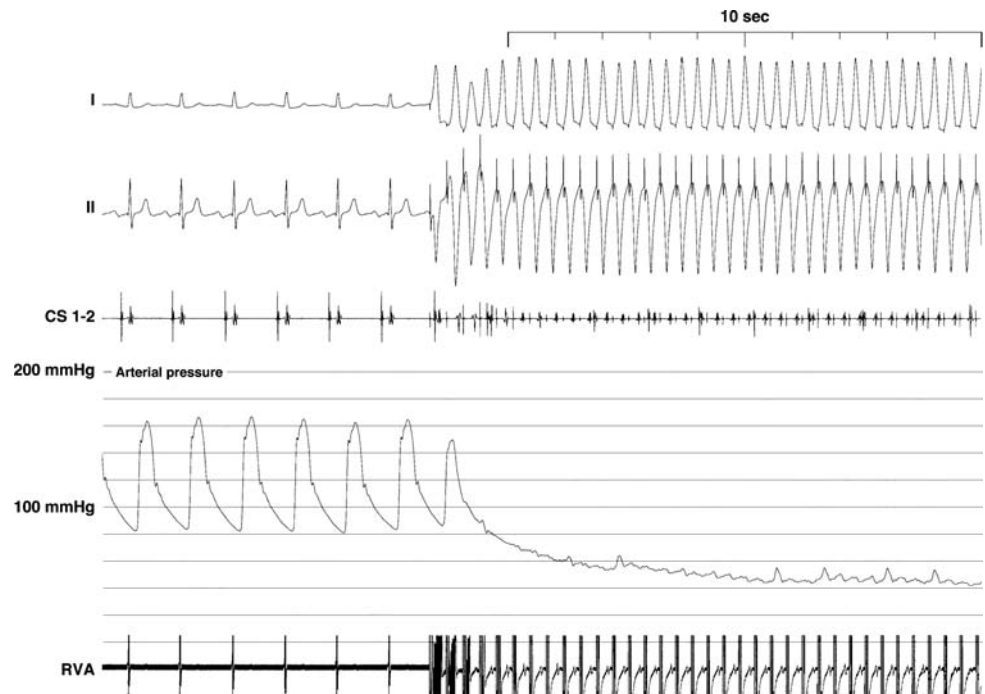
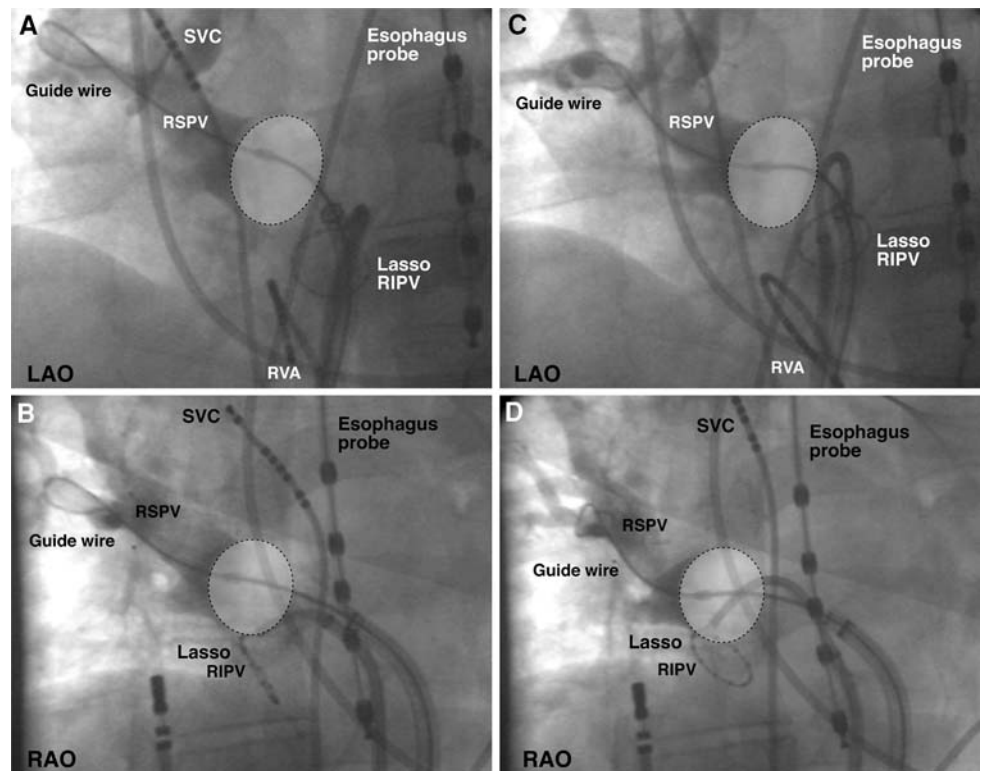


Fig. 2 Identical cryoballoon positions with (group I) and without RVRP (group II) which allow intra-individual PV temperature comparisons. Cryoballoon position with occlusion of a RSPV depicted in RAO and LAO angulations (a, b) using RVRP (group I). Similar cryoballoon position and occlusion of the RSPV in RAO and LAO angulations (c, d) in the same patient without RVRP (group II). RVRP right ventricular rapid pacing, RSPV right superior pulmonary vein, RIPV right inferior pulmonary vein, SVC superior vena cava, RVA right ventricular apex



monitored from the thermocouple integrated in the proximal part of the cryoballoon for all freezes and subsequently analyzed with special emphasis on (1) minimal temperature, (2) temperature slopes, defined as the time in seconds to reach 80% of the minimal temperature and (3) the area

under the temperature curve (AUC) during the RVRP maneuver. The initial freezing phase was characterized by a two-step temperature fall with a rapid, linear phase followed by a more gradual temperature drop, separated by a biphasic “notch” representing the gradual opening of the

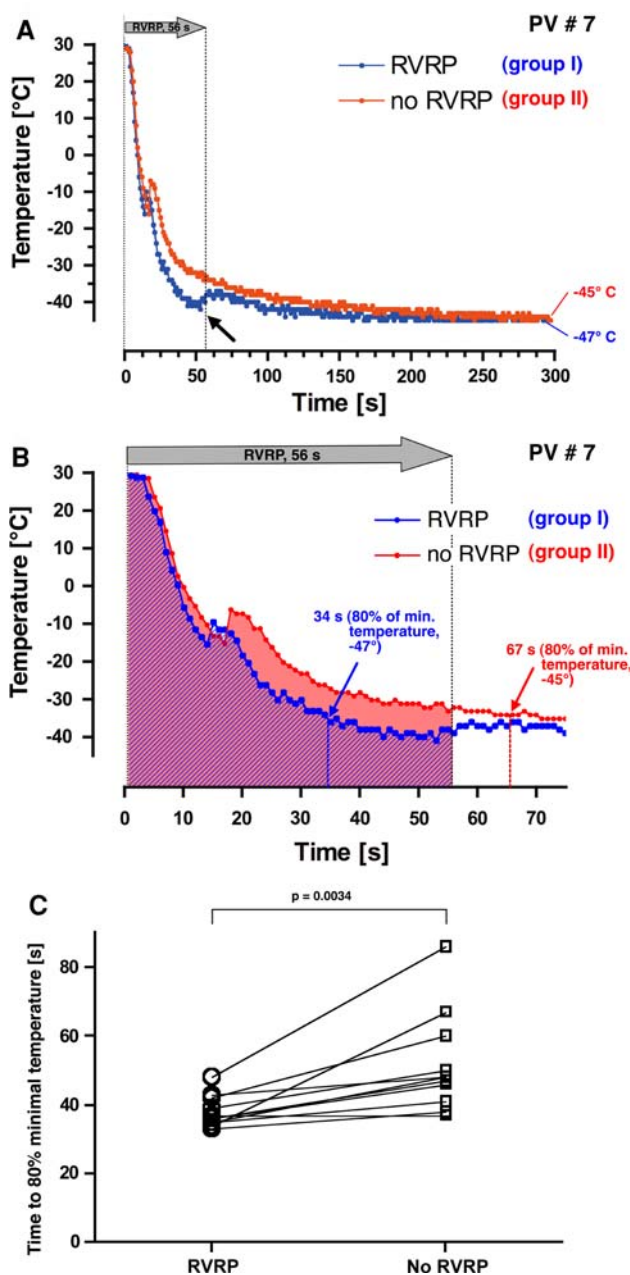


Fig. 3 a Typical temperature curves plotted for group I and group II (PV #7). Note the faster drop of temperature in group I and the arrow pointing to the “re-warming” in group I indicating increased LA/PV flow after cessation of RVRP (56 s). Minimal balloon temperature is indicated for each group (300 s). **b** Magnification of the initial 75 s indicating the area under the curve (AUC) during RVRP (56 s, PV #7) for both groups (group I: scaffold area, group II: red area). Arrows mark the different temperature slopes (time to reach 80% of the total minimal temperature) (group I: 34 s, group II: 67 s). AUC area under the curve, LA left atrium, RVRP right ventricular rapid pacing, PV pulmonary vein. **c** Temperature slopes (time to reach 80% of minimal temperature, s) for all analyzed PVs are significantly different: RVRP (group I) vs. no RVRP (group II), p value = 0.0034

mechanic valves which control the liquid N₂O flow from the console into the balloon. Thereafter, a plateau is reached where the internal balloon temperature slowly and linearly decreases to the minimal temperature at the end of ablation (Fig. 3a).

RVRP to facilitate PVI

In one right inferior PV (RIPV) in which the PV ostium could not be directly occluded by the cryoballoon, RVRP was attempted to reduce anterograde PV flow and therefore improve direct cryoballoon occlusion.

Post ablation treatment

In all patients, pericardial effusion and pneumothorax were ruled out (transthoracic echocardiogram, chest X-ray) after the procedure. After ablation, patients were treated with intravenous heparin (target PTT 50–70 s). Oral anticoagulation was started the next day. All patients received phenprocoumon targeting an INR value of 2.0–3.0 for at least 3 months.

Endpoints

The primary endpoints were defined as RVRP-induced changes of minimal temperature, temperature slope and area under the curve. The secondary endpoint was defined as procedure-related complications.

Statistical analysis

Data of mean \pm standard deviation (SD) were used to describe continuous variables with normal distribution. The Student's t test was performed to calculate differences between both groups. A p value < 0.05 was considered statistically significant.

Results

Patients

Eleven patients (10 males, mean age 58 ± 9 years) were enrolled in the study (Table 1). All patients had a history of PAF with a mean duration of 7 ± 4 years and were refractory to AAD treatment ($n = 2 \pm 1$). In 6/11 patients, arterial hypertension was present, no structural heart disease was known (Table 1).

Table 1 Patients' demographics

Patient	Gender	Age (years)	Concomitant heart disease	Hypertension	LV EF	LA size (mm)	Duration of PAF (years)	Number (<i>n</i>) of failed AAD
1	Male	59	None	No	Normal	41	8	2
2	Male	44	None	No	Normal	42	5	2
3	Male	47	None	Yes	Normal	38	2	3
4	Male	52	None	Yes	Normal	40	3	2
5	Male	62	None	Yes	Normal	44	5	1
6	Male	71	None	Yes	Normal	43	2	2
7	Male	64	None	Yes	Normal	53	10	2
8	Female	66	None	Yes	Normal	51	15	2
9	Male	56	None	No	Normal	38	10	3
10	Male	67	None	No	Normal	54	0.5	2
11	Male	52	None	No	Normal	42	5	3
Mean		58	na	na	na	44	7	2
STD		9	na	na	na	6	4	1
Total (<i>n</i>)		na	0	6	na	na	na	na

Table 2 PV diameter defined by PV angiography

	Patients (<i>n</i> = 11)				
	RSPV	RIPV	LSPV	LIPV	LCPV
Number of PVs (<i>n</i> = 41)	11	11	8	8	3
Diameter (mm)	19 ± 2.9	17 ± 3.6	19 ± 2.1	18 ± 1.8	29 ± 5.3

Pulmonary vein angiographies

In 11 patients, a total of 41 PVs were identified. Mean PV diameters as calculated from baseline PV angiographies are summarized in Table 2.

Procedural data

The mean procedure and fluoroscopy times including PN pace mapping were 180 ± 33 and 30 ± 11 min, respectively. The total balloon time (defined as time of cryoballoon inside the LA) was 99 ± 31 min. A mean of 171 ± 33 ml contrast medium was required for PV angiographies. Successful acute PVI was achieved in all patients (41/41 PVs, 100%).

RVRP and balloon temperature

Right ventricular rapid pacing was performed in all patients (*n* = 11, 41 PVs). In 11/41 PVs, identical cryoballoon positions with (group I) and without (group II) RVRP were obtained allowing comparative temperature analysis. RVRP was performed with a mean cycle

length of 333 ± 3 ms for 55 ± 7 s. RVRP significantly reduced mean systemic blood pressure (group I: 45 ± 3 mmHg vs. group II: 100 ± 18 mmHg, *p* value < 0.001) (Table 3). Typical temperature curves with RVRP (group I) and without RVRP (group II) from PV #7 (RSPV) are shown in Fig. 3a, b. RVRP mediated a significantly faster drop of balloon temperature (group I: 38 ± 4.6 s vs. group II: 52 ± 14.4 s, *p* = 0.0034) resulting in a reduced AUC (group I: 1090 ± 98.6 vs. group II: 1181 ± 111.2, *p* = 0.02) (Table 3). Intriguingly, in group I, cessation of RVRP was immediately followed by balloon re-warming of 4.3 ± 1.2°C in three PVs (Fig. 3a), which was never observed in group II. There was no difference in minimal temperature at the end of ablation (group I: -45 ± 4.4°C vs. group II: -44 ± 3.4°C, *p* = 0.46) (Table 3).

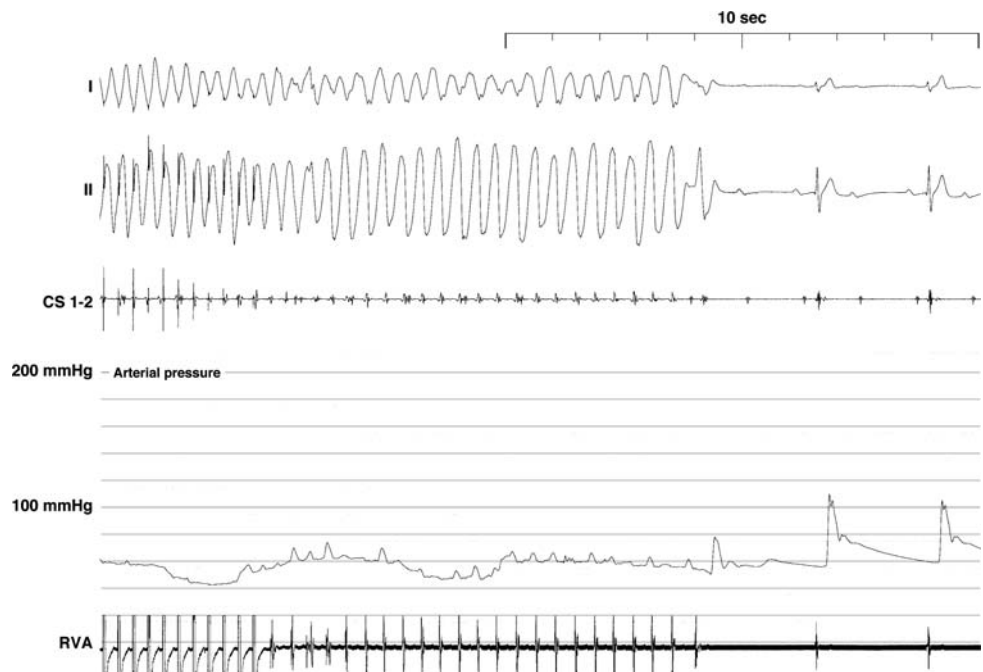
RVRP to facilitate PVI

The RVRP maneuver enabled direct cryoballoon occlusion of one RIPV ostium resulting in electrical PVI which could not be obtained without rapid pacing. Using the RVRP technique, the anterograde PV flow-mediated cryoballoon

Table 3 RVRP results

PV (#)	PV location	RVRP CL (ms)	RVRP duration (s)	Mean arterial pressure (mmHg)			Minimal temperature (C°)		Slope: time to 80% minimal temperature (s)		AUC (55 s)	
				Group I RVRP	Group II no RVRP	Δ (%)	Group I RVRP	Group II no RVRP	Group I RVRP	Group II no RVRP	Group I RVRP	Group II no RVRP
1	LSPV	335	42	43	85	49	-50	-49	33	38	1,312	1,177
2	LIPV	330	53	44	85	48	-44	-47	37	37	973	978
3	RSPV	330	47	50	100	50	-52	-49	36	46	1,148	1,426
4	RIPV	330	61	45	94	52	-39	-39	48	86	1,098	1,198
5	LSPV	335	49	47	109	57	-48	-47	35	48	1,075	1,287
6	LIPV	335	60	44	107	59	-39	-42	43	48	964	1,150
7	RSPV	335	56	47	116	59	-47	-45	34	67	1,014	1,116
8	RIPV	335	63	46	136	66	-43	-44	42	60	1,054	1,177
9	LIPV	335	57	39	71	45	-45	-43	35	41	1,072	1,135
10	RSPV	330	58	45	105	57	-48	-40	36	47	1,103	1,133
11	RIPV	330	59	40	95	58	-40	-42	39	50	1,175	1,216
Mean		333	55	45	100	55	-45	-44	38	52	1,090	1,181
STD		3	7	3	18	6	4.4	3.4	4.6	14.4	98.6	111.2
<i>p</i> value < 0.05				<i>p</i> < 0.001*			<i>p</i> = 0.46		<i>p</i> = 0.0034*		<i>p</i> = 0.02*	

Fig. 4 Induction of a non-sustained polymorphic VT (CL 415 ms) with RVRP. RVRP right ventricular rapid pacing. CL cycle length, RVA right ventricular apex, CS coronary sinus



push into the LA was diminished leading to improved balloon positioning and RIPV occlusion.

Procedural complications

The secondary endpoint of a complication was achieved in one patient (pt #1). A polymorphic VT (cycle length 415 ms) was twice induced during RVRP. The first VT was non-sustained and terminated spontaneously (Fig. 4). The second

VT required DC shock (360 J). No further complications and in particular no PN lesions were observed. PN pacing itself was not affected by the use of RVRP.

Discussion

Pulmonary vein isolation has become the cornerstone for catheter ablation of AF. CTE ablation via a balloon

catheter represents a novel technology with the potential to achieve acute PVI with a single application [8, 14]. However, preliminary data indicate that CTE ablation failures are associated with recovered PV conduction [15]. Thus, techniques with the potential not only to facilitate acute PVI but to also improve long-term PVI rates are clearly warranted. Stable cryoballoon contact and low temperatures within the PV ostium tissue are mandatory for successful CTE lesion growth. However, antegrade PV flow pushes the balloon back into the LA hampering stable balloon positioning at the PV ostium. Despite of nearly complete cryoballoon PV occlusion, convective balloon warming by (1) local PV flow and (2) general LA flow may contribute to decreased CTE lesion extension.

Acute RVRP hemodynamic effects

We demonstrated a significant RVRP-induced drop of systemic ABP. Precisely timed reduction of cardiac output by RVRP has been previously used to facilitate stable balloon positioning for valvuloplasty [16] or for percutaneous aortic valve implantation [13]. Tachycardia has been linked to reduced LA/PV blood flow [17]. Using our setting, the timing of RVRP could be simply and precisely adapted to the needs of the intervention and was limited to the crucial initial phase of the cryoballoon freeze.

Implications of RVRP for cryoballoon ablation

Cryoballoon ablation represents a novel straightforward technology for PVI. In contrast to the highly focussed ultrasound (HIFU) balloon ablation system, cryoballoon lesions require perfect local balloon/tissue contact. If the cryoballoon was perfectly placed occluding the PV ostium, the balloon would then “freeze and stick” at the PV ostium during the initial temperature fall. However, incomplete cryoballoon PV occlusion with contrast leakage indicating high convective heat transfer would result in incomplete PV isolation. This is particularly true for inferior PVs which are not in direct alignment with the balloon/sheath system after transseptal puncture in which perfect balloon positioning can be challenging, time consuming and even futile [8]. In our series, complete direct balloon occlusion of one RIPV ostium was only achieved with the help of the RVRP maneuver. This observation may be explained by the reduced antegrade PV flow during RVRP although more data are certainly required.

Moreover, the initial phase of a freeze is crucial for CTE lesion formation. Different cooling rates lead to various types of injury to the cardiac tissue. In order to irreversibly damage cardiac cells, a fast cooling rate has been shown to be very important [10, 18]. When a cryocatheter is used at its coldest temperature attainable, cells near the location of

the cryoapplication are subject to a fast cooling rate. This generates intracellular ice crystals, ultimately damaging cell organelles and membranes permanently. This injury mechanism has been shown to be the most effective. As the cryoapplication continues, the forming ice-ball acts as an insulator between the cells surrounding the ice formation and the cryocatheter. The cells in the vicinity of the ice-ball are still being affected by the cold but the cooling rate in this specific area has considerably slowed. At these slower cooling rates, the injury mechanism is instead caused by solution effects which stem from the formation of extracellular ice crystals. Cells continue to be damaged but this injury mechanism is not as effective as intracellular ice formation [18].

Our principle idea is based on taking advantage of a reduced PV/LA flow by the RVRP maneuver and thereby faster cryoballoon cooling which is supported by the observation of significantly steeper temperature curves and smaller AUCs in group I (RVRP). These findings may indicate improved local balloon/tissue contact and perhaps enhanced CTE lesion growth. Interestingly, the immediate balloon re-warming phenomenon after cessation of RVRP was exclusively observed in group I (Fig. 3a) and may indicate the resumption of PV/LA blood flow. An inverse relation between convective flow and CTE lesion size in myocardium has been recently demonstrated in an *in vitro* model [12]. Notably, the absolute minimal balloon temperature did not differ between both groups which could be explained by the fact that RVRP was solely performed during the initial phase of the freeze and the lowest temperature was achieved at the end of the freeze.

Safety

A concern with RVRP is the potential for provoking ventricular tachyarrhythmia. Rapid pacing induced ventricular tachyarrhythmia (VT) in the setting of percutaneous aortic valve implantation for severe aortic stenosis has been reported to be a very rare finding [13]. In contrast, most patients scheduled for AF ablation are lacking a significant structural heart disease. RVRP induced VT should be a rare finding in this patient population. Nevertheless, in one of our patients RVRP induced polymorphic VTs. Obviously, immediate access to defibrillation is mandatory when performing RVRP which is a standard setting in an electrophysiologic laboratory.

Limitations

In this study, only a small number of patients and PVs have been analyzed. Temperature measurements could not be directly measured in LA/PV tissue but were derived from

the proximal cryoballoon. To test the principle idea of RVRP effects on temperature, we did allow only intra-individual PV comparisons requiring an identical balloon position which was obtained in 11/41 PVs. Due to the study design, we cannot rule out altered conditions for the second freeze. We did not visualize PV blood flow by the use of online TEE measurements (Doppler flow). Our findings of significantly altered temperature curves may suggest improved CTE lesions but we do not know to what degree RVRP increases lesion size and whether this technique is associated with improved clinical outcome. This needs to be tested in a prospective randomized study.

Conclusion

Right ventricular rapid pacing significantly accelerates cryoballoon cooling during the initial phase of a freeze suggesting improved cryothermal lesion formation. The impact of RVRP on lesion size and clinical outcome needs to be determined.

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