

Typical atrial flutter can effectively be treated using single one-minute cryoapplications: Results from a repeat electrophysiological study

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Abstract

Purpose Catheter-based cryoablation (cryo) has proven to be as effective as radiofrequency energy (RF) ablation for the treatment of arrhythmias. Nevertheless, the duration of cryoapplications has been reported as being significantly longer than RF applications.

Methods Thirty-seven consecutive patients (28 men; mean age 59 ± 14 years) with typical atrial flutter (AFL) underwent cryo of the cavotricuspid isthmus (CTI). Applications of 1 min were delivered with a 10-French, 10-mm tipped catheter (CryoCor™). If bidirectional CTI block was not obtained after 12 1-min applications, applications of 3 min were selectively delivered to areas of conduction breakthrough. The endpoint of the procedure was creation of bidirectional CTI block and non-inducibility of AFL.

Results A median of 7 (range 3 to 12) 1-min applications were given along the CTI with a mean temperature of $-88.6 \pm 2.3^\circ\text{C}$. Mean fluoroscopy and procedure time were 27 ± 14 min and 110 ± 28 min respectively. Five patients required additional 3-min applications; in one patient an overextended ablation catheter prevented the completion of the index-procedure. The acute success rate of the index-procedure was 97%. In 12/24 patients, two with AFL recurrence, resumption of CTI conduction was found 4 months post-ablation. In all patients bidirectional CTI block was re-obtained after a median of one 1-min

application. No additional AFL recurrences occurred, after a mean follow-up of 37 ± 3 (range 30 to 44) months.

Conclusions Cryo of AFL can successfully be performed using the same application duration as used for RF ablation. Both acute and long-term results are comparable to RF ablation. AFL recurrences occurred in only a minority of patients with resumption of CTI conduction.

Keywords Arrhythmia · Ablation · Catheter ablation · Atrial flutter

1 Introduction

Catheter-based cryoablation (cryo) has proven to be an effective, safe and versatile tool for arrhythmia treatment. Despite several advantages, it still requires relatively long procedure times compared to radiofrequency energy (RF) catheter ablation. Historically, lesion formation during cryo is subject to several factors including cooling temperature [1], application duration, repetition of an application [2] and convective heating [3, 4], the combination of which can considerably prolong procedure time. We have shown that a high efficacy can be maintained when single instead of repeated freeze thaw cycles are used, which results in a significant reduction of the procedure time [5]. Other studies have shown that typical atrial flutter (AFL) can be effectively treated when the duration of a cryoapplication is reduced from 5 to 2 min [6–9]. However, it is unknown if procedural and long-term efficacy remain unaffected if short cryoapplication times (similar to RF) are used. Biomedical engineering has enabled deeper cooling temperatures and catheter refinements that allow for a reduction of the application duration. Other factors like contact pressure,

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catheter-tip orientation and tip-size also play an important role in cryo [10, 11]. These developments in cryotechnology may have rendered short application times effective. The purpose of the current study was to prospectively evaluate the acute and long-term efficacy of cryo for AFL using single 1-min applications.

2 Patients and methods

2.1 Patients

Thirty-seven consecutive patients (28 men; mean age of 59 ± 14 , range 18 years to 78 years) were included. In 23 patients the AFL burden could be assessed. This burden of clinical AFL was documented for a median of 8 months, ranging from 1 month to 105 months. Ten patients required two or more cardioversions at the emergency department. In the remaining 14 patients total AFL burden could not be determined.

The study was approved by the hospital ethics committee and informed consent was obtained from all patients for both the index-procedure and a repeat electrophysiological study scheduled 4 months after the index-procedure. The demographic characteristics of the patients are shown in Table 1. Twenty-four patients (65%) also had a history of atrial fibrillation. In four of these patients (17%) atrial fibrillation organised into AFL during treatment with class IC anti-arrhythmic drugs (AAD).

Table 1 Demographics

Patients	37
Age, years	59 ± 14
Sex, M/F	28/9
Structural heart disease, n	24
Hypertensive	10
Ischemic	4
Dilated	3
Valvular	1
Hypertensive/ischemic	3
Hypertensive/Dilated	2
Hypertensive/Valvular	1
Mean left ventricular ejection fraction, %	54 ± 15
Mean left atrial size, mm	45 ± 7
Concomitant atrial fibrillation, n	24
Pacemaker/ICD, n	4/2
IC AFL, n	4
Class III AAD (amiodaron/sotalol/both), n	6/10/1
Other AAD, n	16

n number of patients; *AAD* anti-arrhythmic drugs; *IC AFL* organisation of atrial fibrillation to atrial flutter during; treatment with IC anti-arrhythmic drugs; *ICD* intracardiac defibrillator

2.2 Ablation procedure

The ablation procedure was performed according to a technique previously defined [7]. AAD were not discontinued before the procedure. All patients were studied in the fasting state under local anaesthesia. Intravenous heparin was given as a 100 IU/kg bolus dose directly after insertion of the venous sheaths, and the activated clotting time was kept at 300–350 sec by additional heparin bolus throughout the remainder of the procedure.

Three multipolar catheters were advanced in the right atrium through insertion of a femoral vein. One 20-pole electrode catheter (2-mm interelectrode spacing, Halo catheter, Biosense Webster, Diamond Bar, CA, USA) was positioned around the tricuspid annulus for sequential activation mapping. A quadripolar catheter and a decapolar catheter were placed at the His-bundle and in the coronary sinus respectively. Cryo was performed using the Cryo-Cor™ Cardiac Cryoablation System [7]. A steerable 10-French bipolar catheter with a 10-mm tip was used in combination with a long venous sheath (St Jude Medical, SL2; 12F; Daig Co, Minnetonka, MN, USA) for mapping and ablation of the cavotricuspid isthmus (CTI). After initial fluoroscopic positioning of the ablation catheter at the CTI, all subsequent repositioning was done with the aid of anatomic (fluoroscopic) and electrophysiological guidance. The 12-lead ECG and intracardiac electrograms were recorded and stored by the BARD LabSystem Pro. Electrograms were analyzed at a gain setting of 0.1 to 0.2 mV/cm and at a sweep speed of 100–200 mm/s. Entrainment to confirm isthmus dependency of the AFL circuit was performed in patients with only AFL and in patients with AFL and a few episodes of atrial fibrillation. In patients with AFL and frequent atrial fibrillation episodes, entrainment was not performed to avoid induction of atrial fibrillation. If atrial fibrillation was present an attempt was made to regain sinus rhythm by means of flecainide infusion and/or internal or external cardioversion. Both catheter-tip temperature and system pressure were monitored throughout the procedure to ensure consistent catheter-tip energy delivery. Linear lesions were created at a target temperature of -90 °C, using single 1-min cryoapplications in a ventriculo-atrial fashion, starting at the tricuspid annulus edge. If a complete line of block was not achieved within 12 1-min applications, additional 3-min applications were used. This cut-off value was used based on our previous experience with an 8-mm tipped RF catheter where a mean of 12 applications were necessary to obtain CTI block [12]. After documentation of bidirectional isthmus conduction block, incremental atrial pacing from the proximal coronary sinus was performed without and with isoproterenol infusion ($1-3$ µg/min) to induce AFL. Thirty minutes were taken to monitor CTI reconnection after CTI block was obtained. On the resumption of CTI

conduction, further cryoapplications were delivered until complete block was obtained again, whereafter another 30-min observation was used to confirm CTI block. As stated above, a maximum of 12 1-min applications (including all applications prior to isoproterenol infusion) were allowed to meet procedural endpoints. Thereafter, 3-min applications were used.

Procedural endpoints were the assessment of bidirectional CTI block and non-inducibility of AFL. Procedure time was defined as the time interval between the first femoral vein puncture for catheter insertion and the last cryoapplication.

2.3 Post-ablation management

A 24-h Holter monitor was given immediately after the procedure until hospital discharge and thereafter, if symptoms suggested an arrhythmia recurrence. Only in patients with pre-existing atrial fibrillation, AAD were continued after the ablation procedure. Oral anticoagulation was started the day of the ablation. After 3 months the necessity for long-term anticoagulation was reassessed by the number of AFL/atrial fibrillation recurrences and the presence of risk factors for thromboembolic complications. Patients living in the region of Maastricht were followed-up at our outpatient clinic at 1- and, thereafter, every 3 months. For patients, from outside this region, follow-up was obtained by the referring Cardiologist. In case of documentation of AFL, the patient was again referred to our hospital for further evaluation and re-ablation. All patients were instructed to contact our center or the nearest hospital if they had any symptoms (e.g. palpitations, chest discomfort) which could indicate a recurrence. Electrophysiological re-evaluation was performed either after 4 months and/or if there was a recurrence of AFL. In case of resumption of isthmus conduction a second ablation was performed using 1-min applications at areas of conduction breakthrough in an attempt to regain complete bidirectional CTI block. The electrograms were observed from the ablation catheter-tip just before the delivery of energy. The amplitude of the atrial and ventricular component was used for gap localisation along the CTI (ventricle, atrioventricular groove, atrium and atrium-inferior vena cava transition). Conduction times measured during the electrophysiological re-evaluation were not compared directly to those obtained during the index-procedure, since identical electrode positions could not be guaranteed.

2.4 Statistical analysis

All data are expressed in mean \pm SD or median and range. To compare baseline characteristics between patients with persistent CTI block and those with CTI reconnection an

unpaired *t*-test was used for continuous variables and the chi-square (or Fisher's exact) test for categorical variables. When normality and equal variance analyses failed, a Mann-Whitney rank sum test was used instead of an unpaired *t*-test. For differences between patients with persistent CTI block, CTI reconnection and undetermined CTI conduction (no repeat electrophysiological study) a Kruskal-Wallis test was used for continuous variables and the chi-square test for categorical variables. The significance level was set at $p < 0.05$.

3 Results

Details of the electrophysiological study and cryo procedure are summarized in Table 2. All patients had a documented typical AFL. In one patient an overextended cryoablation catheter necessitated the use of RF ablation to complete the procedure. This patient was excluded from further analysis. In another patient an abnormal atrial anatomy prevented adequate cannulation of the coronary sinus prolonging fluoroscopy time. In this patient 11 1-min applications were delivered to observe isthmus conduction delay before the procedure was prematurely terminated. This patient did not show any AFL recurrence during 40 months of follow-up.

The median number of 1-min freezes needed to obtain the procedural endpoints was 7 (range 3–12). Five patients (14%) required additional 3-min applications (median 2, range 2–5). The average temperature during 1-min cryodelivery was -88.6 ± 2.3 (range -83 to -93) °C and the mean nadir temperature was -89.0 ± 2.3 (range -85 to -93) °C. Isoproterenol infusion was used in all but three patients, in whom repeated bouts of atrial fibrillation already occurred during atrial pacing. Nine patients (25%) showed recovery

Table 2 Electrophysiological characteristics of the index-procedure

AFL, CCW/CW	34/3
Cycle length, ms	252 \pm 44
Patients requiring cardioversion,	8
Chemical, and	3
Electrical	8
Successful 1-min-application, n	31/36 (86%)
Number of 1-min-applications	7 \pm 2
Temperature, °C	-88 ± 2
Fluoroscopy time, min	27 \pm 14
Procedure time, min	110 \pm 28
Acute success, n	35/36 (97%)
Recurrence AFL, n	2/36 (6%)

AFL atrial flutter; CCW counterclockwise; CW clockwise; n number of patients

of isthmus conduction during isoproterenol infusion. In all patients bidirectional CTI block could be re-established after a median of two 1-min applications (range 1–3; eight patients), and two 3-min applications. No additional applications were required during a second observation period.

Cardioversion of atrial fibrillation was performed in eight patients. Sinus rhythm was obtained by internal cardioversion ($n=2$), external cardioversion ($n=3$), or intravenous administration of flecainide followed by external cardioversion ($n=3$). Mean fluoroscopy and procedure time were 27 ± 14 (range 8 to 58) and 110 ± 28 (range 61 to 180) minutes respectively.

3.1 Follow-up

After a mean follow-up of 37 ± 3 (range 30 to 44) months, a recurrence of AFL was registered in only two patients (6%), 2 months and 3 months after the index-procedure respectively. Eleven patients declined a repeated electrophysiological study, despite previous informed consent and one patient died of a non-cardiac cause 2 months after the index-procedure. A total of 24 patients underwent a repeated electrophysiological study including both patients with AFL recurrence. In these two patients, the arrhythmia terminated after one and two 1-min cryoapplications at the atrioventricular groove. Complete bidirectional CTI block was seen in 12 patients (50%) even though significant fewer cryoapplications were used at the index-procedure compared to those patients that showed resumption of CTI conduction ($P=0.004$; Table 3). Furthermore, no 3-min applications were

required during the index-procedure for those patients who underwent a repeat electrophysiological study.

In the majority of patients in whom isthmus reconnection was observed, gaps were found at the atrioventricular groove (58%). Details concerning their second ablation procedure are depicted in Table 4. AFL occurred in four patients: in two patients AFL recurred (as mentioned above) and in the other two patients AFL was induced with incremental atrial pacing. Procedural endpoints were met in all patients after a median of one 1-min application (range 1–3) without the need of additional applications after isoproterenol infusion. The patients did not report any discomfort during cryodelivery [13]. No complications were seen, including groin hematomas or pseudo-aneurism formation despite the large diameter of the sheath used.

Of the 24 patients with atrial fibrillation prior to the procedure, six patients (25 %) underwent additional pulmonary vein isolation during follow-up because of recurrent symptomatic episodes.

4 Discussion

4.1 Major findings

The present study demonstrates that a reduction in application duration as low as 1 min is feasible during cryo of AFL, resulting in shorter procedure times compared to previous cryoablation protocols [5–8], while maintaining similar clinical efficacy. Although a substantial number of

Table 3 Baseline characteristics of CTI conduction properties

	Repeat EPS		No Repeat EPS
	CTI block	CTI conduction	Undetermined
Patients	12	12	12
Age, years	56 ± 18 (18–78)	63 ± 10 (51–77)	57 ± 12 (25–71)
Concomitant AF, n	7	10	7
LA size, mm	45 ± 10 (29–63)	43 ± 3 (38–47)	46 ± 9 (30–58)
AFL, CCW/CW	10/2	12/0	11/1
AFL cycle length, ms	261 ± 54 (190–328)	251 ± 59 (180–360)	245 ± 30 (200–300)
Total number of successful 1-min cryoapplications	6 ± 2 (3–8)***	8 ± 2 (5–12)	8 ± 4 (4–12)
Additional 3-min applications, n	0**	0	5
Reconnection during isoproterenol, n	6**	2	1
Temperature, °C	-86 ± 2 (–81–90)	-87 ± 3 (–83–94)	-87 ± 1 (–85–88)
Fluoroscopy time, min	21 ± 12 (8–54)***	26 ± 6 (16–43)	39 ± 20 (11–78)
Procedure time, min	99 ± 22 (67–134)	110 ± 24 (73–145)	119 ± 42 (61–180)
Acute success, n (%)	12 (100)	12 (100)	11 (92)
Recurrence AFL, n (%)	0**	2 (17)	0
Follow-up, months	38 ± 4 (30–41)	38 ± 5 (31–47)	36 ± 4 (30–41)

EPS electrophysiological study; AF atrial fibrillation; n number of patients; LA left atrium; AFL atrial flutter; CCW counter-clockwise; CW clockwise

* $P<0.05$ compared to patients with CTI conduction, ** $P<0.05$ compared to patients with or undetermined CTI conduction

Table 4 Electrophysiological and ablation characteristics of patients with CTI conduction recovery

	1	2	3	4	5	6	7	8	9	10	11	12
Index procedure												
Pre-ablation AAD	amio	flec	amio	BB	flec	dys	sot	amio	sot	flec	sot	sot
LA size, mm	43	42	41	46	38	41	45	43	42	47	41	42
Concomitant arrhythmias	AT	AF	AF/VT	AF	AF	AF	AF	AF	AF	CMT/AT	AF	AF
AFL, CCW/CW	CCW	CCW	CCW	CCW	CCW	CCW	CCW	CCW	CCW	CCW	CCW	CCW
Cycle length, ms	266	240	320	220	300	240	220	220	200	360	220	180
Conduction recovery during isoprenaline	no	yes	– ^a	yes	no	no	no	no	no	no	no	no
Successful 1-min-applications	9	6	12	4	8	7	11	5	9	7	9	8
Additional applications 1-min/3-min	–	2/0	–	3/0	–	–	–	–	–	–	–	–
Repeat procedure												
Recurrence AFL	yes	no	no	no	yes	no	no	no	no	no	no	no
Pre-ablation AAD	sot	flec	amio	BB	flec	dys	sot	none	sot	flec	sot	sot
AFL induction	no	no	yes	no	no	no	no	no	no	no	yes	no
Location terminal applications/gaps	AV	VC	AV	AV	VC	AV	VC	VC	AV	AV	A	AV
Conduction recovery during isoprenaline	no	no	– ^a	no	no	no	no	no	no	no	no	no
Successful 1-min-applications	3	2	1	2	1	1	1	1	1	1	2	2

See text for more details

^a no isoprenaline infusion, because of repeated bouts of atrial fibrillation during atrial pacing

AAD anti-arrhythmic drugs; amio amiodarone; flec flecainide; BB beta-blocker; dys dysopyramide; sot sotalol; LA left atrium; AFL atrial flutter; CMT circus movement tachycardia; AT atrial tachycardia; CCW counter-clock wise; CW clockwise; AV atrioventricular groove; A atrial tissue between the atrioventricular groove and inferior caval vein, VC atrium-inferior caval vein transition

patients revealed resumption of CTI conduction 4 months after cryo, AFL recurred in only two patients (6%).

4.2 Refinements in cryothermia: Cryo vs. cryo

As opposed to early catheter development using smaller catheter-tips and higher nadir temperatures [6, 8, 9, 14], current equipment presented herein enables large lesion formation reflected by stable CTI conduction block at the minimum duration of cryodelivery. Applications were delivered using a 10-F, 10-mm catheter-tip at a mean temperature of –88.6°C the combination of which allowed a decrease in the duration of cryodelivery as low as 1 min per application per site. Lesion formation during cryothermia is a complex process involving the synergetic effects of the initiated expanding cold front during freezing and its anticipated thawing. As a result shifts in membrane permeability and osmotic state inflict irreversible cell damage by massive intracellular swelling ultimately leading to membrane disruption and loss of cell integrity. Ablation temperatures beyond –50°C are known to cause irreversible

tissue damage [15] and may enhance passive conduction to deeper myocardial layers. Deep cooling temperatures may also delay total thaw duration augmenting the deleterious effects of affected frozen cells. In addition, contraction of surrounding (micro) vessels as tissue temperature decreases may further add to cell decay [15]. Cryo at mean tip-temperatures of –88.6°C obtained in our study have not been previously reported and may have an advantage regarding the abovementioned cumulative effects.

The repetition of a cryoapplication supported by evidence from cryosurgery [2, 16] has long been advocated for percutaneous applications, since it is known to enhance tissue injury. This may be because previously damaged cell structures act as a syncytium to facilitate thermal conductivity of the following cold front thereby allowing deep penetration and subsequently more tissue loss [2]. In conjunction with recent reports [6, 8, 14], our study supports the reduction in number of applications per site during transvenous cryodelivery either being the result of site specific cryoredundancy or differences in biophysics compared to its extra-luminal counterpart.

Contrary to 1 min of single cryodelivery used in this study, ablation protocols from previous studies used at least 2 min per application and allowed an increase in application time up to 5 min to obtain acute and long-lasting success [6, 8, 9, 14]. Furthermore, the number of applications necessary to maintain CTI block used in these studies was similar compared to our study indicating equal lesion formation. Counterintuitively, in our study patients with stable CTI block required significant fewer applications compared to patients that showed conduction recovery, suggesting that other factors like CTI anatomy (eg. pouch-like configuration) [17] and catheter-tip orientation may also be important. In an experimental model, Tse et al [18] favoured the use of long application times, repetition of applications and horizontal positioning of the catheter-tip in order to gain maximal tissue injury. Even at maximum target temperatures of approximately -78°C obtained by single 2.5-min applications in combination with a 6.5-mm catheter-tip, lesion geometry could be sufficient to override CTI dimensions [19] thus prohibiting excess cryodelivery and its attendant delay in procedure time.

4.3 CTI conduction recovery

In the current study, a large proportion of patients showed isthmus reconnection, without a recurrence of AFL. Resumption of CTI conduction is not infrequently seen, but only a few studies systematically re-evaluated CTI conduction. While complete CTI block is associated with a high long-term success, most studies have focussed on AFL recurrences, withholding possible conduction recovery incapable of AFL re-initiation. Anselme et al [20] reported conduction recovery in up to 45% of patients (18/40) treated with RF 1 month after the index-procedure. The recurrence of AFL was low, though might have been obscured at early re-evaluation where wound healing may still be in progress. Schumacher et al [21] performed a repeat electrophysiological study in 38/41 patients one year after RF ablation. The authors used non-inducibility of AFL regardless of CTI block as the primary endpoint. Only 2/22 patients experienced AFL recurrence after previous confirmation of bidirectional CTI block, contrary to the 7/13 and 6/6 patients with either unidirectional block or only ≥ 10 ms CTI delay respectively. This high incidence of AFL recurrence may be due to differences in primary endpoints and the lack of isoproterenol infusion [22] during the observation period, which proved effective in 25% of our patients. Montenero et al [14] reported a CTI recovery rate of 31%, 3 months after treatment with cryo. While the authors considered this as a possible reservoir for AFL re-initiation, no AFL recurrence was reported during 9 months of follow-up. These data confirm that CTI conduction recovery does not necessarily imply AFL recurrence and

that CTI block after 3 months likely precludes future recovery. In our study population, two patients without recurrent AFL were susceptible to AFL induction, suggesting a higher recurrence rate than we described. One cannot exclude the possibility that the high CTI reconnection rate was due to the short cryoapplication time. Moreover, early re-ablation could in part have prevented future AFL from re-occurring, thereby masquerading a higher AFL recurrence rate. On the other hand, no resumption of AFL was found during substantial long-term follow-up even though 30% of patients declined re-evaluation. This may indicate either stable CTI block or sufficient CTI delay to prevent maintenance of a reentry circuit in the right atrium. Deprived blood supply and differences in cell-to-cell (mal) orientation [23] may have altered conduction properties of the remaining viable cells and subsequently their critical coupling necessary for the development of AFL. The abovementioned effects may have also increased the action potential duration of embedded viable cells thereby influencing their susceptibility and dose-response to AAD [24, 25]. In addition, one may hypothesize that some patients with sufficient CTI delay may have had at least in part AF secondary to degeneration of AFL, thereby decreasing the amount of reinitiated AFL [26].

Gaps were mainly found at the level of the tricuspid valve ridge emphasizing the need for adequate catheter alignment to the underlying tissue to obtain maximum lesion size. Although cryoadherence facilitates catheter stability during freezing initial positioning prior to delivery remains vital. The pouch-like configuration of the isthmus may hamper an optimal tip-tissue interface necessary to obtain sufficient injury of deeper myocardial layers. Possibly longer applications or repeated ones are required in this region to prevent future recurrences.

4.4 Cryoablation vs. RF ablation

By lowering single freeze duration in conjunction with a 10-mm catheter-tip, the procedure time was comparable to the procedure time obtained by conventional RF ablation using 4-mm or 8-mm catheter-tips [12, 13, 27]. Shorter RF ablation times have been reported when using a maximal voltage-guided approach. One has to consider that procedure time is not always adequately defined and a 30-min waiting period is not uniformly included.

In addition, the mean number of applications necessary to obtain bidirectional CTI block was not different from that required during conventional RF delivery [21]. Fluoroscopy time was also comparable to RF, suggesting a similar time span for catheter handling [27]. More importantly, these parameters could be adjusted to RF standards without compromising acute (97%) and long-term (94%) efficacy.

4.5 Study limitations

The current study was conducted in a small group of patients. Only two-thirds of the study population agreed to undergo re-evaluation, which may have biased the observed CTI conduction recovery and its relation to AFL recurrences. As in most studies reporting on long-term efficacy of AFL, follow-up was mainly based on symptoms. Therefore, we cannot exclude a higher recurrence rate due to asymptomatic episodes of AFL.

5 Conclusions

Cryo of AFL can successfully be performed with 1-min applications, using a 10-mm catheter-tip, resulting in short procedure times. Both acute and long-term results are comparable to RF ablation. A high CTI reconduction rate was observed at follow-up but was not associated with a similar degree of AFL recurrences. The clinical relevance of this finding could not be answered by this study.

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