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Acute success and short-term follow-up of catheter ablation of isthmus-dependent atrial flutter; a comparison of 8 mm tip radiofrequency and cryothermy catheters

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Abstract

Objectives To compare the acute success and short-term follow-up of ablation of atrial flutter using 8 mm tip radiofrequency (RF) and cryocatheters.

Methods Sixty-two patients with atrial flutter were randomized to RF or cryocatheter (cryo) ablation. Right atrial angiography was performed to assess the isthmus. End point was bidirectional isthmus block on multiple criteria. A pain score was used and the analgesics were recorded. Patients were followed for at least 3 months.

Results The acute success rate for RF was 83% vs 69% for cryo (NS). Procedure times were similar (mean 144 ± 48 min for RF, vs 158 ± 49 min for cryo). More applications were given with RF than with cryo (26 ± 17 vs. 18 ± 10, $p<0.05$). Fluoroscopy time was longer with RF (29 ± 15 vs. 19 ± 12 min, $p<0.02$). Peak CK, CK-MB and CK-MB mass were higher, also after 24 h in the cryo group. Troponin T did not differ. Repeated transient block during application (usually with cryoablation) seemed to predict failure. Cryothermy required significantly less analgesia ($p<0.01$), and no use of long sheaths ($p<0.005$).

The isthmus tended to be longer in the failed procedures ($p=0.117$). This was similar for both groups, as was the distribution of anatomic variations. Recurrences and complaints in the successful patients were similar for both groups, with a very low recurrence of atrial flutter after initial success.

Conclusions In this randomized study there was no statistical difference but a trend to less favorable outcome with 8 mm tip cryocatheters compared to RF catheters for atrial flutter ablation. Cryoablation was associated with less discomfort, fewer applications, shorter fluoroscopy times and similar procedure times. The recurrence rate was very low. Cryotherapy can be considered for atrial flutter ablation under certain circumstances especially when it has been used previously in the same patient, such as in an AF ablation.

Keywords Arrhythmia · Catheter ablation · Atrial flutter · Atrial fibrillation · Radiofrequency · Cryothermy

1 Introduction

Atrial flutter is a common arrhythmia [1], difficult to suppress with medication [2], and is associated with significant symptoms. Since it was first proposed [3–5], ablation for atrial flutter has increasingly been used for its therapy, especially since induction of bidirectional cavo-tricuspid isthmus block was shown to be associated with better immediate outcomes and lower recurrence rates [6–11]. Failure to successfully ablate atrial flutter in the long-term may be due to particular anatomic problems [12–14], poor catheter stability in this region, and incorrect interpretation of isthmus block. Important developments in the field of atrial flutter ablation have been a better understanding of the anatomy of the isthmus, refinements of the definition of bidirectional isthmus block, and the arrival of new catheter technology.

Numerous studies have compared different energy types, different catheter tip sizes and different energy settings [15–19], as well as the use of advanced cardiac mapping

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systems [20]. The preferred tools now are 8 mm, or irrigated tip catheters [21]. From a recent meta-analysis it would appear that these two technologies are equally effective with acute success quoted at 84% and 85% for the primary catheter chosen before changeover, whereafter final success rates of up to 99% can be achieved [22]. Not all studies have this high success rate and the preponderance of studies on ablation of atrial flutter suggest that these high success rates are not repeated in all centers [23]. Also of importance is a clinical recurrence rate, in the face of acute success, of at least 5 to 12% when using radiofrequency [19, 24, 25]. Disadvantages of radiofrequency (RF) energy include pain, overheating with "popping", char formation and risk to coronary arteries.

Cryoablation is a relatively recent addition to the transvenous ablation armamentarium and has been shown to be comparable to RF for some arrhythmias. It may have some advantages over RF, especially as regards discomfort during ablations [17, 26]. The development of 6 and 8 mm tip cryocatheters has increased the interest in this technology for atrial flutter ablation. As far as we are aware there have been no randomized comparative studies published comparing 8 mm tip cryocatheters with 8 mm tip RF catheters.

2 Methods

2.1 Patient population

Consecutive patients with ongoing symptoms and documented atrial flutter with or without fibrillation were included. At least one recent episode of atrial flutter (within the last 6 months) was documented on a 12 lead ECG and was suggestive for isthmus dependency. Patients with drug-induced flutter (and prior AF) could be included, and had their drug therapy continued after ablation. Patients were excluded if they had undergone a previous flutter ablation, if thrombus was present in the atria, or after previous cardiac surgery for valvular or congenital heart disease. Baseline investigations included a standard echocardiogram, a simple questionnaire asking about clinical well-being and a subjective assessment of the arrhythmia burden both in terms of duration and frequency. The study was approved by the ethics committee of our institution. All patients signed written informed consent.

2.2 Assessment before ablation

Antiarrhythmic drugs, except for AV nodal slowing agents, and amiodarone, were discontinued at least five half-lives prior to ablation. Patients were studied in the fasting, post-absorptive state. A coronary sinus (CS) catheter was inserted through the left subclavian vein, and a multipolar circular right atrial catheter with alternating 2–10–2 mm interelectrode distance was positioned from the right groin, with the tip positioned immediately lateral to the planned position of the isthmus line and anterior to the crista terminalis. Heparin 100 U/kg was given and a further 5 U/kg given if the procedure lasted longer than 180 min.

If the patient was in sinus rhythm, isthmus conduction was confirmed by pacing. If flutter was present, entrainment was performed to confirm isthmus dependence, and the patient left in flutter. If AF was present, the patient was cardioverted after a transoesophageal echocardiogram, and then isthmus conduction confirmed. Absence of isthmus conduction or non-isthmus dependence was not seen in the selected patients. No induction of arrhythmia was attempted if patients had sinus rhythm.

Radiological assessment of the right atrial isthmus was made in a right anterior oblique (RAO) 30°, and a left anterior oblique (LAO) 45° view (each with 40 cc at 18 cc/s). Angiograms were acquired digitally to allow for post-hoc analysis. The treating physician was able to view the angiographic findings to optimize the planned ablation line. The isthmus length was assessed from the inferior hinge point of the tricuspid valve to the IVC at the end of atrial diastole (the frame before opening of the tricuspid valve) [14]. Morphology was assessed visually as to the presence of a Eustachian valve or a recess, as well as to the general shape i.e. flat or concave.

2.3 Ablation procedure

The catheters were a 9Fr 8 mm tip catheter (FreezorMax, Cryocath Technologies Inc, Kirkland, Canada) with a cryoconsole for the cryoablation group, and a 7Fr 8 mm tip single sensor catheter (EPT Blazer II, Boston Scientific, Natick, MA, USA) with an EPT-1000XP generator for the radiofrequency group. A large curve was initially selected in both groups, with change out of catheter curve during the study only as necessary. Applications of −75°, for 4 min were given with cryothermy, and applications of 60 Watt, for 60 s, targeted at 60°C for RF. Lines were made with discrete applications between the tricuspid valve and the inferior vena cava at an approximately 6 o'clock position in LAO 45°, unless otherwise dictated. If termination of atrial flutter occurred, or if the patient was in sinus rhythm, continuous pacing from the proximal coronary sinus was employed to continually assess isthmus conduction. After the first line, a new assessment of conduction was performed. If conduction over the isthmus remained present, gaps were sought. If there was still isthmus conduction, a slightly more medial or lateral line was made. In no patient was an attempt made to perform a septal ablation line. Final assessment of acute block was confirmed after 30 min waiting.

The end point for successful ablation was induction of complete bidirectional isthmus block, defined as the presence of reversal of activation on the lateral and septal wall when pacing the CS os and low lateral RA, the presence of widely split potentials along the isthmus line, by activation mapping across the isthmus, and by differential pacing. All 4 were required before calling the ablation successful. In the case where bidirectional block was not achieved, ablation was stopped when no large, sharp signals could be identified over a broad area of the isthmus.

As pain perception was assessed, sedation was standardized. Before venous puncture 5 mg of diazepam was given intravenously, and repeated at the patient's request. Fentanyl 50 μg intravenously was given when the patient requested pain control and the physician considered this necessary. This was repeated as needed. Dosages of both diazepam and fentanyl were recorded.

In the initial 40 patients creatine kinase (CK) and CK-MB were taken before the procedure, 2 and 24 h after the start of the procedure. For the final 22 patients the laboratory had changed the measurement to CK mass. We then modified the protocol to measure CK-MB mass, Troponin T, and Myoglobin at 4 and 24 h after the start of the procedure.

No crossover, other than in catheter curve, was allowed in an attempt to remove any possible bias. Change over to an irrigated tip ablation catheter was also not allowed. In patients in whom no block could be induced, a repeat procedure was scheduled not earlier than 6 weeks after the initial ablation, at the physicians' discretion. The choice of energy source at that time was at the physicians' discretion.

Patients were all questioned with regard to pain perception using a visual analogue score, where patients are shown a line from 0 to 10, where 0 is no pain, and 10 is the highest pain level imaginable, and were asked to point to the position on the line where their pain level during ablation was.

2.4 Follow-up

All patients received an event-recorder for the first 6 weeks after the procedure and were requested to send at least daily strips as well as strips made during symptoms. Patients visited the outpatient clinic 6 weeks after the procedure. After this period all patients were asked to report symptoms and if these were present were given a further event monitor until documentation of symptoms was obtained. If at all possible a 12 lead ECG was also obtained. A second assessment with a questionnaire was performed after 3 months, again asking a question about general clinical well being and also symptom burden in regard to duration and frequency. Clinical files were followed up after 9 months.

2.5 Statistical analysis

For patients in whom another ablation was performed (AVNRT in two, and pulmonary vein ablation in six others) procedure and fluoroscopy times were limited to the flutter approach, which was done first, including 30 min waiting time. Biomarker assessment was not done in these patients. Continuous variables are expressed as mean ± standard deviation, with medians as necessary. Parametric and non-parametric tests were used where appropriate. A p-value of <0.05 was considered significant.

3 Results

3.1 Patient data

62 patients were included as planned, with clinical characteristics as outlined in Table 1. There were no significant differences in any of the parameters between the group assigned to radiofrequency (RF group) versus that assigned to cryotherapy (cryo group). The large number of patients with prior AF is due to the fact that we had initially taken a decision to perform isthmus ablation first in all patients with AF who had shown typical atrial flutter on any 12-lead ECG, prior to performing a left atrial procedure, initially in a separate procedure and only later in the same session.

3.2 Angiographic data

Right atrial angiography was not performed in 4 patients because of mild renal dysfunction or allergy to contrast material. The angiogram was of insufficient quality in eight others.

The mean isthmus length was 35.2±14.6 mm and its topography was assessed as being flat or only mildly concave in 28, markedly concave in 19 and showed a pit or aneurysm in 10. A clear Eustachian valve was seen on six angiograms.

Table 1 Demographics

	All	Cryo	RF	p value
Number	62	32	30	
Age (years±SD)	56±10	55±11	56±9	NS
Male/female	27/5	27/5	28/2	NS
Atrial fibrillation history	47 (76%)	25 (78%)	22 (73%)	NS

Cryo Cryoablation; *NS* not significant; *RF* radiofrequency; *SD* standard deviation

3.3 Ablation data

Assessment of acute results showed bidirectional isthmus block, using the criteria mentioned, in 47 of 62 patients (76%). This was in 25 of 30 patients (83%) of the RF group and in 22 of 32 (69%) of the cryo group (NS). In 1 patient in the RF group the procedure was terminated because of recurrent AF with early recurrence and inability to assess isthmus block. This patient was taken as a failure which was confirmed at the time of a subsequent AF ablation. Procedural data for all patients are given in Table 2.

In the successful patients the number of applications to ensure block in the whole group was 17 ± 11. It was 23 ± 13 in the RF group and 12 ± 6 in the cryo group ($p<0.005$). Total ablation time was $1,283\pm777$ s and $2,905\pm1,245$ s ($p=0.0001$). In those in whom bidirectional block could not be achieved, the total number of applications was 33 ± 14. For RF and cryo the values were 39 ± 21 applications with a total time of $2,724\pm1,102$ s vs 29 ± 8 applications with a time of $5,873\pm1,337$ s ($p<0.03$ and <0.0011, respectively).

In 22 of 30 in the RF group and 25 of 32 in the cryo group, a single line at approximately 6 o'clock was drawn. In the RF group two lines were drawn in seven, and three in one. In the cryo group two lines were made in four, and three lines in three. The need to draw more than one line was associated with failure of the procedure in four of eight in the RF group and five of seven in the cryo group (NS).

Short lived block, either recurring during the application or immediately thereafter, occurred in one patient in the RF group and in six in the cryo group, with a trend to statistical significance ($p=0.091$), with it being a predictor of failure if it occurred more than three times. In five patients in the RF group and one patient in the cryo group, conduction recurred later during a waiting period (with a median of 15 min) requiring further applications (NS). In only one patient in the RF group was late recurrence associated with failure to induce bidirectional block. In no patient in whom bidirectional block was present at the end of the 30 min waiting period did isoprenaline change this. The average power applied in the RF group was 52 ± 6 W.

In the RF group the signal was significantly diminished at the end of each application whether isthmus block was present or not, while there tended to be preservation of signals on the cryoablation catheter after ablation across the isthmus until block occurred. Only then were low voltage signals seen.

Failures were not significantly associated with length of the isthmus (39.2 ± 23.5 vs 34 ± 9.0 mm in success, although there was a trend to this ($p=0.12$) There was no significant difference in anatomy between the two groups.

3.4 Procedure data and complications

The overall procedure time was 160 ± 49 min, with no difference between 170 ± 48 min in the RF group and 151 ± 49 min in the cryo group. Overall fluoroscopy times were 28 ± 14 min, with a difference between 33 ± 15 min in the RF group and 23 ± 11 min in the cryo group ($p<0.02$).

Change of catheter curve occurred in one patient in the RF group from large to standard curve. An SL1 sheath

Table 2 Procedure data and recurrent arrhythmias

	All	Cryo	RF	p value
Number	62	32	30	
Application number	22 ± 13	18 ± 10	25 ± 16	0.05
Ablation time (s)	$2,742\pm1,930$	$3,792\pm1,900$	$1,459\pm950$	<0.001
Acute success	47 (76%)	22 (69%)	25 (83%)	NS
Single line	47 (76%)	25 (78%)	22 (73%)	NS
2 lines	9 (15%)	2 (6%)	7 (24%)	0.073
3 lines	4 (6%)	3 (9%)	1 (3%)	NS
Reversal of block during application	7 (11%)	6 (19%)	1 (3%)	0,091
Reversal of block during 30 min	6 (10%)	1 (3%)	5 (7%)	NS
Isthmus length (mm)	35 ± 15	35 ± 17	36 ± 11	NS
Sheath usage	7 (11%)	0 (0%)	7 (23%)	<0.005
Recurrent arrhythmias				
Flutter (typical)				
After success	1 (2%)	0 (0%)	1 (4%)	NS
After failure	11 (73%)	7 (70%)	4 (50%)	NS
Flutter (atypical)	1 (2%)	0 (0%)	1(3%)	NS
Atrial tachycardia	5 (8%)	2 (6%)	3 (10%)	NS
Atrial fibrillation	28 (45%)	13 (41%)	15 (50%)	NS

The numbers are given with the standard deviation.

Cryo Cryoablation; *NS* not significant; *RF* radiofrequency

(Daig, Minnetonka, MN, USA) was used in seven patients in the RF group for stability, while no sheath usage occurred in the cryo group ($p=0.005$). During the procedure, six patients required cardioversion for induced AF, four in the RF group and two in the cryo group (NS). There were two small pericardial effusions seen on echocardiography without further significance (one in each group).

For the initial 40 patients there was a significantly higher peak CK and CK-MB after cryo (Table 3). This remained so after 24 h. For the last 22 patients we observed the same for CK-MB mass, but not for Troponin T (Table 3).

In assessing the level of comfort during the procedure and the pain experienced by patients, similar numbers from both groups assessed sedation as adequate (67% for RF and 63% for cryo). The pain scores given at the end of the procedure were not significantly different (42.9 ± 24.0 for RF and 43.7 ± 15.8 for cryo). Diazepam was given as standard at the beginning of the procedure and as necessary thereafter for discomfort related to having to lie still for protracted periods. The usage of diazepam was statistically similar in both groups (7.4 ± 3.4 mg in the RF group and 8.0 ± 3.1 mg in the cryo group). However, a significantly higher usage of fentanyl in the RF group was observed (70.0 ± 44.9 μg vs 10.0 ± 22.1 μg; $p<0.01$).

3.5 Follow-up results

Patients were followed up for between 90 and 411 days (138 ± 81 days, median 90 days), which was similar in both groups ($p=$ns).

A total of 6 patients were taking no antiarrhythmic medication prior to ablation and this increased to 13 post isthmus ablation.

Table 3 Biomarkers after catheter ablation

	All	Cryo	RF	p value
Procedure values				
CK (U/l)	141±96	184±102	96±60	0.02
CK-MB (U/l)	27±16	36±17	18±8	0.011
CK-MB mass (μg/l)	18±21	33±24	4.4±1.2	0.004
Troponin T (μg/l)	0.49± 0.32	0.54± 0.38	0.39± 0.27	NS
Values after 24 hrs				
CK (U/l)	264±245	289±173	136±74	0.022
CK-MB (U/l)	37±28	51±30	18±6	0.011
CK-MB mass (μg/l)	8.4±7.3	12±10	5.16±3.3	0.07
Troponin T (μg/l)	0.44± 0.30	0.54± 0.36	0.38± 0.29	NS

The numbers are given with the standard deviation.
CK Creatine kinase; *Cryo* cryoablation; *NS* not significant; *RF* radiofrequency

Recurrent arrhythmias were frequent in both groups of patients. ECG documented recurrent flutter occurred only in one patient from the RF group. A further procedure confirmed recovery of isthmus conduction. This recurrence was seen at 14 months post ablation, whereas he had previously had monthly episodes of flutter. One other patient had symptoms with an apparently non-isthmus dependent flutter documented on ECG on day 1 post ablation and not since, and elected not to have a further procedure. We cannot exclude asymptomatic arrhythmias but at least during the first 6 weeks, patients sent in daily event monitor transmissions, which one would hope would have captured at least some asymptomatic recurrences, particularly of atrial flutter.

In 11 of 15 patients in whom the initial procedure failed, a redo procedure was performed after the elected period of 6 weeks because of documented recurrent flutter. The redo procedure required a small number of point touch ups in five patients (three in the RF group and two in the cryo group), while more extensive diffuse isthmus applications were required in six (one in the RF group and five in the cryo group). In those undergoing repeat ablation, success was achieved in all and during follow up no recurrent atrial flutter was noted.

Previously undocumented atrial tachycardias were also seen in both groups (three in the RF group, and two in the cryo group). ECG documented AF recurrence occurred in 28 patients, at a similar rate in both groups (15 in the RF group and 13 in the cryo group). The likelihood of asymptomatic recurrences is probably higher for atrial fibrillation but was not the primary focus of this study.

4 Discussion

4.1 Acute success

This study showed an acute success rate of 83% for an 8 mm tip RF catheter vs. 69% for an 8 mm tip cryocatheter. This non significant difference is clearly concerning. However, the cryoablation group required significantly less applications to achieve success, with a similar procedural duration, significantly lower fluoroscopy time, and with a much lower requirement for analgesia with fentanyl. Arrhythmia recurrences in the initially successful patients were similar with a very low flutter recurrence rate.

The acute success rate with 8 mm tip RF compares favorably with that found in the meta-analysis of Da Costa et al. [22]. However, the acute results for cryotherapy are lower than in previously published studies. The shorter fluoroscopy time using cryotherapy is related to cryoadherence during applications [26]. With the catheter firmly attached, no fluoroscopy to check position is required. This

is also reflected in the fact that no long sheaths were necessary. A lower requirement for analgesia has previously been described and this study confirms this finding [17, 26].

4.2 Difficulties during ablation

Recurrence during or shortly after ablation occurring more commonly in the cryo group probably relates to a reversible cooling effect at the periphery of the ice ball which recovers during or shortly after termination of ablation, while the central lesion acutely formed is more permanent. The more common recurrence during the waiting period after RF ablation probably relates to a longer reversal time of the acute RF effects (either edema or temperature effect).

4.3 Cryoablation for flutter

Cryoablation may have some advantages over RF in addition to those mentioned above such as less thrombogenicity [27], and maintenance of tissue architecture with homogenous well delineated lesions [28]. A 10Fr, 6.5 mm tip catheter showed acute success of 94–100% and 6 month recurrence rates of 0–25% [17, 29, 30]. A system with 7Fr, 6 mm tip catheters showed success in 87% to 88% using a septal line, without symptomatic recurrences, but with resumption of isthmus conduction at repeat study at 6 months in 30–35% [31, 32]. Using a 9Fr, 8 mm tip increased success rates to 100% with symptomatic recurrence of 0% to 10% and recurrent conduction at 1 to 3 months in 19% to 32% [32–34]. There is some discussion as to whether 3, 4 or 8 min of ablation are needed for adequate lesion formation [33, 35].

Higher peak CK levels, confirmed by the high CK-mass in the last patients, suggest that the damage caused by cryotherapy may be more extensive despite the lower number of applications. Several explanations are possible. The first is that the CK levels may be underestimated after RF, which denatures proteins in another way than cryotherapy. Troponin T levels are more accurate in estimation of myocardial damage, but they also tended to be higher, be it not significantly. This may suggest that lesions are equal with both approaches.

4.4 Future developments

Newer data suggest that ablation per point guided by the maximal voltage may be a useful technique, but this has not been confirmed for cryotherapy [36].

4.5 Study limitations

This study was a single centre, largely single operator study involving a relatively limited number of patients with a high population of AF patients, making follow-up rather complicated. In present practice and later in this series, patients with the combination are often treated in one session, which still leaves physicians the choice whether cryo should be used for flutter, following its use for the pulmonary veins [37]. We only studied the acute and short-term success, while flutter recurrence may happen at more than 4 months of follow-up. While we attempted to exclude asymptomatic recurrences especially in the first 6 weeks, we cannot exclude the possibility of these, especially of AF and also late after the ablation. Isthmus conduction recovery is also possible in asymptomatic cases. In the RF group we limited the power to 60 W to ensure safety and this may be too conservative. Further, in our practice routine use of long sheaths was discouraged. At the time of this study use of an 8 mm tip with RF was considered as effective as irrigated tip ablation, so we elected to use this approach for the RF group. More recent studies have shown higher success rates than we obtained and have also suggested alternatives in the approach. These include the use of irrigated tip catheters and long sheaths as well as other technical issues and newer techniques such as maximal voltage guided ablation. A higher success rate for RF would clearly have been even more prejudicial to cryotherapy in this study. We were also extremely critical in our assessment of isthmus conduction, using multiple criteria. Angiograms were also performed in fixed views and not based on other catheter positions as has been suggested by others [14].

5 Conclusion

Acute success with cryotherapy for atrial flutter ablation, while non-statistically less effective in this study, requires fewer applications and is associated with a significantly lower requirement for pain relief. While our acute results for both cryotherapy and RF may not be as high as those in some comparable studies the recurrence rate was only 2.5% in the RF group, with no clinical recurrence in the cryo group. While cryotherapy cannot perhaps be advocated as first line therapy, it may be useful in certain circumstances. Certainly, if cryoablation is performed for AF, and if the isthmus needs to be ablated, cryotherapy might be used as well [37].

References

1. Granada, J., Uribe, W., Chyou, P. H., Maassen, K., Vierkant, R., Smith, P. N., Hayes, J., Eaker, E., & Vidaillet, H. (2000). Incidence and predictors of atrial flutter in the general population. *Journal of the American College of Cardiology, 6*, 2242–2246.
2. Natale, A., Newby, K. H., Pisano, E., Leonelli, F., Fanelli, R., Potenza, D., Beheiry, S., & Tomassoni, G. (2000). Prospective randomized comparison of antiarrhythmic therapy versus first-line radiofrequency ablation in patients with atrial flutter. *Journal of the American College of Cardiology, 35*, 1898–1904.
3. Rosenblueth, A., & Garcia Ramos, J. (1947). Estudios sobre el flutter y la fibrilacion. II. La influencia de los obstaculos artificiales en el flutter auricular experimental. *Archivos del Instituto Cardiología de México, 17*, 1–19.
4. Feld, G. K., Fleck, R. P., Chen, P. S., Boyce, K., Bahnson, T. D., Stein, J. B., Calisi, C. M., & Ibarra, M. (1992). Radiofrequency catheter ablation for the treatment of human type 1 atrial flutter. Identification of a critical zone in the reentrant circuit by endocardial mapping techniques. *Circulation, 86*, 1233–1240.
5. Cosio, F. G., Lopez Gil, M., Arribas, F., & Goicolea, A. (1993). Radiofrequency catheter ablation for the treatment of human type 1 atrial flutter. *Circulation, 88*, 804–805.
6. Poty, H., Saoudi, N., Abdel Aziz, A., Nair, M., & Letac, B. (1995). Radiofrequency catheter ablation of type 1 atrial flutter. Prediction of late success by electrophysiological criteria. *Circulation, 92*, 1389–1392.
7. Poty, H., Saoudi, N., Nair, M., Anselme, F., & Letac, B. (1996). Radiofrequency catheter ablation of atrial flutter. Further insights into the various types of isthmus block: application to ablation during sinus rhythm. *Circulation, 94*, 3204–3213.
8. Da Costa, A., Romeyer-Bouchard, C., Zarqane-Sliman, N., Messier, M., Samuel, B., Kihel, A., Faure, E., & Isaaz, K. (2005). Impact of first line radiofrequency ablation in patients with lone atrial flutter on the long term risk of subsequent atrial fibrillation. *Heart, 91*, 97–98.
9. Bertaglia, E., Zoppo, F., Bonso, A., Proclemer, A., Verlato, R., Coro, L., Mantovan, R., D'Este, D., Zerbo, F., & Pascotto, P. (2004). Long term follow up of radiofrequency catheter ablation of atrial flutter: clinical course and predictors of atrial fibrillation occurrence. *Heart, 90*, 59–63.
10. O'Callaghan, P. A., Meara, M., Kongsgaard, E., Poloniecki, J., Luddington, L., Foran, J., Camm, A. J., Rowland, E., & Ward, D. E. (2001). Symptomatic improvement after radiofrequency catheter ablation for typical atrial flutter. *Heart, 86*, 167–171.
11. Anné, W., Willems, R., Van der Merwe, N., Van de Werf, F., Ector, H., & Heidbuchel, H. (2004). Atrial fibrillation after radiofrequency ablation of atrial flutter: preventive effect of angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, and diuretics. *Heart, 90*, 1025–1030.
12. Cabrera, J. A., Sanchez-Quintana, D., Ho, S. Y., Medina, A., & Anderson, R. H. (1998). The architecture of the atrial musculature between the orifice of the inferior caval vein and the tricuspid valve: the anatomy of the isthmus. *Journal of Cardiovascular Electrophysiology, 9*, 1186–1195.
13. Cabrera, J. A., Sanchez-Quintana, D., Ho, S. Y., Medina, A., Wanguemert, F., Gross, E., Grillo, J., Hernandez, E., & Anderson, R. H. (1999). Angiographic anatomy of the inferior right atrial isthmus in patients with and without history of common atrial flutter. *Circulation, 99*, 3017–3023.
14. Heidbuchel, H., Willems, R., van Rensburg, H., Adams, J., Ector, H., & Van de Werf, F. (2000). Right atrial angiographic evaluation of the posterior isthmus: relevance for ablation of typical atrial flutter. *Circulation, 101*, 2178–2184.
15. Rodriguez, L. M., Nabar, A., Timmermans, C., & Wellens, H. J. (2000). Comparison of results of an 8-mm split-tip versus a 4-mm tip ablation catheter to perform radiofrequency ablation of type I atrial flutter. *American Journal of Cardiology, 85*, 109–112 A9.
16. Schreieck, J., Zrenner, B., Kumpmann, J., Ndrepepa, G., Schneider, M. A., Deisenhofer, I., & Schmitt, C. (2002). Prospective randomized comparison of closed cooled-tip versus 8-mm-tip catheters for radiofrequency ablation of typical atrial flutter. *Journal of Cardiovascular Electrophysiology, 13*, 980–985.
17. Timmermans, C., Ayers, G. M., Crijns, H. J., & Rodriguez, L. M. (2003). Randomized study comparing radiofrequency ablation with cryoablation for the treatment of atrial flutter with emphasis on pain perception. *Circulation, 107*, 1250–1252.
18. Feld, G., Wharton, M., Plumb, V., Daoud, E., Friehling, T., & Epstein, L. (2004). Radiofrequency catheter ablation of type 1 atrial flutter using large-tip 8- or 10-mm electrode catheters and a high-output radiofrequency energy generator: results of a multi-center safety and efficacy study. *Journal of the American College of Cardiology, 43*, 1466–1472.
19. Calkins, H., Canby, R., Weiss, R., Taylor, G., Wells, P., Chinitz, L., Milstein, S., Compton, S., Oleson, K., Sherfesee, L., & Onufer, J. (2004). Results of catheter ablation of typical atrial flutter. *American Journal of Cardiology, 94*, 437–442.
20. Nakagawa, H., & Jackman, W. M. (1998). Use of a three-dimensional, nonfluoroscopic mapping system for catheter ablation of typical atrial flutter. *Pacing and Clinical Electrophysiology, 21*, 1279–1286.
21. Scavee, C., Jais, P., Hsu, L. F., Sanders, P., Hocini, M., Weerasooriya, R., Macle, L., Raybaud, F., Clementy, J., & Haissaguerre, M. (2004). Prospective randomised comparison of irrigated-tip and large-tip catheter ablation of cavotricuspid isthmus-dependent atrial flutter. *European Heart Journal, 25*, 963–969.
22. Da Costa, A., Cucherat, M., Pichon, N., Messier, M., Laporte, S., Romeyer-Bouchard, C., Mismetti, P., Lopez, M., & Isaaz, K. (2005). Comparison of the efficacy of cooled-tip and 8-mm-tip catheters for radiofrequency catheter ablation of the cavotricuspid isthmus: a meta-analysis. *Pacing and Clinical Electrophysiology, 28*, 1081–1087.
23. Thornton, A. S., & Jordaens, L. J. (2005). Atrial flutter: Watch and control? *Europace, 7*, 413–414.
24. Hsieh, M. H., Tai, C. T., Chiang, C. E., Tsai, C. F., Yu, W. C., Chen, Y. J., Ding, Y. A., & Chen, S. A. (2002). Recurrent atrial flutter and atrial fibrillation after catheter ablation of the cavotricuspid isthmus: A very long-term follow-up of 333 patients. *Journal of Interventional Cardiac Electrophysiology, 7*, 225–231.
25. Tai, C. T., Chen, S. A., Chiang, C. E., Lee, S. H., Wen, Z. C., Huang, J. L., Chen, Y. J., Yu, W. C., Feng, A. N., Lin, Y. J., Ding, Y. A., & Chang, M. S. (1998). Long-term outcome of radio-frequency catheter ablation for typical atrial flutter: risk prediction of recurrent arrhythmias. *Journal of Cardiovascular Electrophysiology, 9*, 115–121.
26. Kimman, G. P., Theuns, D. A., Szili-Torok, T., Scholten, M. F., Res, J. C., & Jordaens, L. J. (2004). CRAVT: A prospective, randomized study comparing transvenous cryothermal and radiofrequency ablation in atrioventricular nodal re-entrant tachycardia. *European Heart Journal, 25*, 2232–2237.
27. Khairy, P., Chauvet, P., Lehmann, J., Lambert, J., Macle, L., Tanguay, J. F., Sirois, M. G., Santoianni, D., & Dubuc, M. (2003). Lower incidence of thrombus formation with cryoenergy versus radiofrequency catheter ablation. *Circulation, 107*, 2045–2050.
28. Rodriguez, L. M., Leunissen, J., Hoekstra, A., Korteling, B. J., Smeets, J. L., Timmermans, C., Vos, M., Daemen, M., & Wellens, H. J. (1998). Transvenous cold mapping and cryoablation of the AV node in dogs: Observations of chronic lesions and comparison to those obtained using radiofrequency ablation. *Journal of Cardiovascular Electrophysiology, 9*, 1055–1061.
29. Manusama, R., Timmermans, C., Limon, F., Philippens, S., Crijns, H. J., & Rodriguez, L. M. (2004). Catheter-based cryoablation

permanently cures patients with common atrial flutter. *Circulation*, *109*, 1636–1639.

30. Daubert, J. P., Hoyt, R. H., John, R., Chinitz, L., Martin, D. T., Fellows, C., Feld, G., Pelkey, W., & Sehra, R. (2005). Performance of a new cardiac cryoablation system in the treatment of cavotricuspid valve isthmus-dependent atrial flutter. *Pacing and Clinical Electrophysiology*, *28*(Suppl 1), S142–S145.

31. Montenero, A. S., Bruno, N., Antonelli, A., Mangiameli, D., Barbieri, L., Andrew, P., Murphy, O., O'Connor, S., & Zumbo, F. (2005). Long-term efficacy of cryo catheter ablation for the treatment of atrial flutter: results from a repeat electrophysiologic study. *Journal of the American College of Cardiology*, *45*, 573–580.

32. Montenero, A. S., Bruno, N., Antonelli, A., Mangiameli, D., Barbieri, L., Andrew, P., & Zumbo, F. (2005). Comparison between a 7 French 6 mm tip cryothermal catheter and a 9 French 8 mm tip cryothermal catheter for cryoablation treatment of common atrial flutter. *Journal of Interventional Cardiac Electrophysiology*, *13*, 59–69.

33. Montenero, A. S., Bruno, N., Zumbo, F., Antonelli, A., Fiocca, L., Barbieri, L., De Bernardi, F., Andrew, P., & Affinito, V. (2005). Cryothermal ablation treatment of atrial flutter-experience with a new 9 French 8 mm tip catheter. *Journal of Interventional Cardiac Electrophysiology*, *12*, 45–54.

34. Kuniss, M., Kurzidim, K., Greiss, H., Berkowitsch, A., Sperzel, J., Hamm, C., & Pitschner, H. F. (2006). Acute success and persistence of bidirectional conduction block in the cavotricuspid isthmus one month post cryocatheter ablation of common atrial flutter. *Pacing and Clinical Electrophysiology*, *29*, 146–152.

35. Manusama, R., Timmermans, C., Philippens, S., Crijns, H. J., Ayers, G. M., & Rodriguez, L. M. (2004). Single cryothermia applications of less than five minutes produce permanent cavotricuspid isthmus block in humans. *Heart Rhythm*, *1*, 594–599.

36. Posan, E., Redfearn, D. P., Gula, L. J., Krahn, A. D., Yee, R., Klein, G. J., & Skanes, A. C. (2007). Elimination of cavotricuspid isthmus conduction by a single ablation lesion: observations from an maximum voltage-guided ablation technique. *Europace*, *9*, 208–211.

37. Van Belle, Y., Janse, P., Rivero-Ayerza, M. J., Thornton, A. S., Jessurun, E. R., Theuns, D., & Jordaens, L. (2007). Pulmonary vein isolation using an occluding cryoballoon for circumferential ablation: feasibility, complications, and short-term outcome. *European Heart Journal*, *28*, 2231–2237.