Transvenous Cryothermal Catheter Ablation of Re-Entry Circuit Located Near the Atrioventricular Junction in Pediatric Patients

Efficacy, Safety, and Midterm Follow-Up

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<table>
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<tr>
<th>OBJECTIVES</th>
<th>We investigated the safety and efficacy of cryoablation in the treatment of pediatric patients with accessory pathways (APs) located near the atrioventricular junction and with atrioventricular nodal re-entrant tachycardia (AVNRT).</th>
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<tr>
<td>BACKGROUND</td>
<td>Few studies concern cryoablation in a significant number of pediatric patients involving treatment for supraventricular tachycardias (SVTs) with the reentry circuit located near the atrioventricular junction.</td>
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<td>METHODS</td>
<td>Twenty-six pediatric patients (age range: 5 to 20 years) were treated; 14 had AVNRT, 10 had Wolff-Parkinson-White syndrome, and 2 had re-entrant SVT due to a concealed AP. Electrophysiologic study was performed with diagnostic catheters, and cryoablations were performed with a 7-F 4-mm-tip catheter (Freezor, CryoCath Technologies Inc., Kirkland, Canada). Cryomapping, used to identify the tissue site for safe arrhythmia ablation, was performed at −30°C for a maximum of 60 s. Cryoablations were from 4 to 8 min long at −75°C. Acute end points were noninducibility of AVNRT by programmed atrial stimulation at baseline or during isoproterenol performed 30 min after procedure, as well as noninducibility and conduction block over the AP. The chronic end point was arrhythmia recurrence after intervention.</td>
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<td>RESULTS</td>
<td>No permanent cryo-related complications or adverse outcomes were reported. Twenty-four (92%) patients were acutely successful. During follow-up (range: 1 to 22 months), seven (29%) patients experienced arrhythmia recurrence.</td>
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| CONCLUSIONS| Acute results demonstrate cryoablation of SVTs with the reentry circuit located near the atrioventricular junction to be safe and efficacious in pediatric patients. However, the etiology of recurrences reported after intervention need further investigation. (J Am Coll Cardiol 2005;45:1096–103) © 2005 by the American College of Cardiology Foundation

Radiofrequency (RF) ablation for treatment of supraventricular tachycardias (SVTs) in pediatric patients was introduced into clinical practice in the late 1980s (1). Since then, RF ablation has evolved into the treatment of choice for many different tachyarrhythmias in young patients (1–8). However, despite the success of RF ablation, there are reported safety and efficacy concerns that have been raised. Most notably, RF ablation treatment for patients with atrioventricular nodal re-entrant tachycardia (AVNRT), Wolff-Parkinson-White (WPW) syndrome, and other SVTs carries a definite risk for atrioventricular (AV) block because lesion creation within the region of the septum is close to the AV node or His bundle (6,9,10). Also, RF catheter ablation of septal accessory pathways (APs) has been identified as technically challenging in children due to the setting of small cardiac dimensions (3). Acute success rates for RF ablation of various SVTs in pediatric patients have been reported to be between 82% and 100% (4,11–14), and recurrence rates are between 0% and 14% (3,4,11). The risk rate of AV block in RF ablation of APs close to the AV junction or AVNRT in pediatric patients has been reported to be between 1.6% and 3% (3,9). Hence, there is a drive to investigate alternative types of ablation energies that are equally or more efficacious than RF, but safer (15). This is especially so in pediatric patients undergoing ablation treatment given the medical and quality-of-life consequences of permanent AV block. The first report of transvenous cryoablation was in the early 90s (16), and it was not soon after such preclinical studies that trials involving humans were conducted.

Preclinical and clinical studies have suggested that cryo energy has potential advantages over RF energy for catheter ablation (10,17–20). Some of the identified benefits of cryo include reversibility of conduction block, catheter stability, and less procedural discomfort for the patient (20). The reversibility of conduction block in particular, via a technique known as cryomapping, is an especially useful safety benefit of cryo in clinical practice. Cryomapping allows for the evaluation of the acute effects of cryo on the structures to be ablated before creating a permanent lesion (21,22). This is probably the principal reason why no incidence of permanent AV block has yet been reported among the many cryo catheter ablation procedures that have been performed in the adult population (10,20,22–25).

Despite the weight of evidence from adult patients, the safety and efficacy of cryo catheter ablation for treatment of
specific arrhythmias has only been investigated in a handful of pediatric patients (26). To our knowledge, there are few studies that have investigated cryo catheter ablation treatment of SVTs in a significant number of pediatric patients over a reasonably long follow-up period (e.g., six-month follow-up and beyond). This study sought to investigate the safety and efficacy of percutaneous cryothermal ablation in the treatment of pediatric patients with AVNRT and APs located near the AV junction.

METHODS

Patients. The study population consisted of 26 consecutive patients who were selected for cryoablation treatment in our institution in the period between August 2002 and April 2004. The selected patients either had AVNRT or an AP located near the AV junction. The local ethics committee approved the protocol, and informed consent was obtained from all patients or their parents before the procedure. There were 14 patients with AVNRT, 10 patients with WPW syndrome, and 2 patients with a re-entrant SVT due to a concealed AP. Previous RF ablation was apparent in one patient with AVNRT and three patients with WPW syndrome. The one patient with AVNRT had unsuccessful RF ablation three years before their cryoablation procedure, and after the failed RF ablation had received flecainide and propranolol. The three patients with WPW had unsuccessful RF ablation about one year before their cryoablation procedure. Specifically, the RF ablation procedures in two of these three WPW patients, one an right anteroseptal AP patient and the other a mid-septal AP patient, were interrupted because of the risk of AV block due to the fact that the RF ablation catheter was too close to the bundle of His, after the occurrence of a fast junctional rhythm during RF energy delivery. Antiarrhythmic drugs were stopped five half-lives before the cryoablation procedure.

Cryoablation system. The cryoablation system consists of a central console (Cryo Console, CryoCath Technologies Inc., Kirkland, Canada) and a steerable 7-F catheter (Freezor, CryoCath Technologies Inc., Kirkland, Canada) with a 4-mm-tip electrode using N2O as refrigerant fluid. The cryoablation system has been previously described elsewhere (22).

Cryomapping. Cryomapping (also referred to as ice mapping) was performed by progressive reduction in the tip temperature to −30°C for a maximum time of 60 s. This caused transient and reversible loss of electrical function at the target site and enabled the acute effects of cryo at a site to be analyzed before the creation of a permanent lesion. When cryomapping was positive (e.g., disappearance or modification of conduction was demonstrated through the slow pathway with no re-induction of tachyarrhythmia and disappearance of ventricular pre-excitation) (Fig. 1), then the tip temperature was decreased further to create a permanent lesion. When cryomapping produced unwanted effects (e.g., transient AV block or lengthening of the PR interval by >50%), cryoapplication was stopped to allow tissue rewarming and reversibility of the loss in electrical function. Subsequently, the cryo catheter was repositioned to a new target site, and cryomapping was repeated.

Cryoablation. Ablation was performed by cooling the tissue temperature to −75°C. Freezing was maintained at the lowest attainable temperature for a minimum of 4 min to a maximum of 8 min to create a permanent lesion. There was one patient who had cryo energy delivery for only 2 min; the rationale for this deviation from the minimum requirement is explained in the Results section. During cryoablation, surface electrocardiogram (ECG) and endocavitary signals were continuously monitored. If conduction recurrence or arrhythmia induction were apparent, the catheter was repositioned at an adjacent site, and cryomapping was repeated.

Ablation procedure for AVNRT. The procedure was performed under general anesthesia induced with sevoflurane and propofol and maintained with sevoflurane or isoflurane. A thermal mattress was used to maintain normal body temperature. A standard electrophysiologic study (EPS) was conducted before the procedure to confirm the arrhythmia diagnosis and after the procedure to test the inducibility of the SVT. Quadrupolar catheters were positioned in the His bundle region and in the right atrium via the right femoral vein, and a multipolar catheter was positioned in the coronary sinus via the left subclavian vein. Surface ECG leads and endocardial potentials were recorded and stored on a multichannel recorder (Bard System, Billerica, Massachusetts). Cryoablation was performed in patients with both: 1) an A-H jump clearly diagnostic of dual AV nodal physiology (defined as a sudden prolongation of the A-H interval by 50 ms or greater when shortening the cycle length of atrial pacing or the coupling interval of the atrial extrastimulus by 10 ms); and 2) inducible AVNRT (isoproterenol infusion [0.01 to 0.04 μg/kg/min with incremental steps]). If the A-H jump alone was apparent in a patient, then the ablation was not performed. After confirmation of the diagnosis and following the determination of a reproducible protocol for AVNRT induction, the cryo catheter was inserted through the right femoral vein and directed toward the myocardium. A slow pathway ablation was performed using either an electrogram-guided approach, with mapping of the slow potential or the sharp
Figure 1. (A) Cryomapping electrogram of a patient with an anterior septal accessory pathway. (B) Postcryoablation electrogram of a patient with an anterior septal accessory pathway. RAO = right anterior oblique.
patients had a physical exam and ECG before discharge.

Postablation assessment. The relationship between duration of exposure to cryo energy and lesion size. In the present study, there were cases where the duration of exposure to cryo was beyond 4 min; this was due to the investigator opting to use a longer cryo application time given results from earlier cases that suggested possible recurrence after procedure. The ablation procedure was considered successful if AVNRT was noninducible by the programmed atrial stimulation protocol after ablation, either before or during isoproterenol infusion performed 30 min later.

Ablation procedure of APs. Two patient groups were considered—those with manifest ventricular preexcitation and those with concealed APs. In patients with manifest ventricular preexcitation, the site of earliest ventricular activation was identified during sinus rhythm. It was characterized by a short local AV interval, with local activation preceding the onset of the delta wave on the surface ECG. After identification of the possible ablation site, cryomapping was performed, and, if there was a sudden loss of ventricular preexcitation, it was followed by creation of a permanent lesion (Fig. 1). In patients with concealed APs, the parahisian area was carefully mapped during AV re-entrant tachycardia, and the site of earliest retrograde atrial activation was localized. Cryomapping was performed at this site and, if successful, as indicated by interruption of tachycardia in the retrograde limb with no modification of AV conduction parameters, was followed by permanent lesion formation. A postablation EPS was performed immediately in all cases, and then repeated 30 min later to demonstrate normal AV node conduction as well as confirm complete and persistent interruption of the conduction over the AP and noninducibility of the arrhythmia.

Postablation assessment. An echocardiography was performed 24 h after procedure on all patients. In addition, patients had a physical exam and ECG before discharge.

RESULTS

Demographics, patient diagnoses, and EP study characteristics. The mean ± SD age of patients was 13.2 ± 3.6 years. The distribution of males to females involved in this study was 14 to 12.

Of the 26 patients, 14 (54%) had AVNRT, 10 (38%) had WPW syndrome, and 2 (8%) had a concealed AP. All 14 patients with AVNRT had dual AV nodal physiology and a reproducible inducible AVNRT. Inducibility was demonstrated in 2 (14%) of 14 patients with AVNRT at baseline, and in 12 (86%) of 14 patients during isoproterenol infusion alone. One (4%) patient had previous ductus arteriosus, two (8%) had a patent foramen ovale, and four (15%) had previous RF ablation.

In all cases, cryomapping was performed during fixed overdrive pacing or atrial extrastimulus testing with a coupling interval critical for AVNRT induction and/or slow pathway conduction. In the other patients, the EPS revealed the presence of a concealed AP in the right anteroseptal region in two patients, as well as a right manifest AP in the anteroseptal region in five patients, in the midseptal region in four patients, and in the posterior region in one patient. In those patients with a concealed AP, an SVT was induced in one case at baseline and in the other during isoproterenol infusion.

Acute success—safety and efficacy. There was only one patient with AVNRT who had transient first-degree AV block. This event occurred during the cryomapping step of the procedure. This transient conduction disturbance disappeared immediately during defrost, and there were no further conduction disturbances noted. During the actual cryoablation step of the procedure, a single cryoapplication was delivered, very close to the site where the transient complication with cryomapping had occurred, to create a permanent cryolesion. Although acute success was achieved in this patient, follow-up assessment indicated recurrence of AVNRT eight months after the procedure. No other complications were reported in any patient. Specifically, no pericardial effusion or thrombotic formation was observed with echocardiography performed 24 h after procedure.

Cryoablation was successfully performed at intervention in 24 (92%) of 26 patients. A total of 13 (93%) of 14 patients with AVNRT, 10 (100%) of 10 patients with WPW syndrome, and 1 (50%) of 2 patients with a concealed AP experienced acute success with cryo. In one patient who underwent a successful ablation of a right midseptal manifest AP, two other SVTs, due to different concealed APs in the anteroseptal and anterior region, remained inducible; successful ablation of these two APs was achieved. There were no echoes or slow pathway conduction after ablation; any AVNRT or single echo was eliminated during the procedure.

There were no patients who crossed over from cryoablation to RF ablation. The one AVNRT patient who expe-
rienced acute failure with cryo went on to receive oral therapy with flecainide (5 mg/kg) and was successful on this medication; this patient had previously failed on this anti-arrhythmic medication before ablation. The patient with a concealed AP who experienced acute failure recently underwent a second cryoablation that was an acute success. Unlike the point of entry used in this cohort of 26 patients, for the second cryoablation, the catheter was introduced into the subclavian vein (reportedly giving more catheter stability), and the duration of cryoapplication for permanent cryolesion formation was only 2 min. This less than standard cryoapplication duration was utilized because the target site yielded an excellent His bundle electrogram that was clearly visible after the SVT interruption.

**Procedural characteristics.** A single cryoapplication was delivered in 10 patients (4 with AVNRT, 5 with WPW syndrome, and 1 with a concealed AP); 2 cryoapplications were delivered in 6 patients; 3 or more cryoapplications were delivered in 10 patients. Cryoapplications were delivered with a mean temperature of $-74 \pm 1.8^\circ C$ for a mean duration of $5.7 \pm 1.5$ min. The mean number of cryoapplications and fluoroscopy time was $3 \pm 2$ and $38.7 \pm 21.4$ min, respectively. The mean fluoroscopy times for patients with AVNRT, WPW syndrome, and concealed APs were $33.8 \pm 13.1$ min, $38.8 \pm 24.8$ min, and $61.3 \pm 29.9$ min, respectively.

A couple of notable observations were made during our experience with cryoablation in these 26 pediatric patients. A junctional rhythm did not develop in any treated patient. However, in one patient with AVNRT, a transient lengthening of AV conduction was observed during a second cryoablation in the midseptal area; it occurred 120 s after a temperature of $-75^\circ C$ was reached. Consequently, cryoablation was stopped, and a complete recovery of the AV interval subsequently ensued after tissue re-warming. Moreover, the SVT was no longer inducible in this patient. No other patients experienced significant modification of the A-H interval while in sinus rhythm, either at baseline or during isoproterenol infusion at the end of the procedure. In other cases (one patient with a right midseptal WPW and one patient with AVNRT) only a maximum temperature of $-70^\circ C$ was reached; this phenomenon was probably due to an excessive blood re-warming effect. Although both these patients were acute successes with only one and two cryoapplications delivered to each, respectively, both patients experienced arrhythmia recurrence during the follow-up period.

The electrophysiological and ablation characteristics associated with patients who were acute successes or failures with cryo at intervention are shown in **Table 1**.

**Long-term success—follow-up outcomes.** No patients were lost to follow-up. During follow-up (range: 1 to 22 months), 7 (29%) of 24 patients who were acutely successful had arrhythmia recurrence. A Kaplan-Meier curve (Fig. 2) shows the cumulative proportion of the 24 acutely successful patients who were without arrhythmia recurrence up to 12 months’ follow-up. There were five patients who had ECG-documented arrhythmia recurrence, whereas two patients had recurrence documented in patient diary records.

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**Table 1.** Electrophysiological and Ablation Characteristics Associated With Those Patients Who Were Acute Successes or Failures With Cryo at Intervention

<table>
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<tr>
<th>Parameters</th>
<th>Acute Success (n = 24)</th>
<th>Acute Failure (n = 2)</th>
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<tr>
<td>Type of arrhythmia, n</td>
<td>13 AVNRT; 1 concealed AP; 10 WPW syndrome</td>
<td>1 AVNRT; 1 concealed AP</td>
</tr>
<tr>
<td>Previous RF ablation, n (%)</td>
<td>4 (17%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Cryomapping temperature (°C), mean ± SD; range</td>
<td>$-30 \pm 2$; $-27$ to $-40$</td>
<td>$-30 \pm 0$</td>
</tr>
<tr>
<td>Cryoapplications, mean ± SD; range</td>
<td>$2 \pm 2$; 1 to 9</td>
<td>$5 \pm 2$; 3 to 6</td>
</tr>
<tr>
<td>Cryoablation temp (°C), mean ± SD; range</td>
<td>$-74 \pm 2$; $-70$ to $-76$</td>
<td>$-75 \pm 0$</td>
</tr>
<tr>
<td>Duration of cryoablation temp (min), mean ± SD; range</td>
<td>$6 \pm 2$; 2 to 8</td>
<td>$5 \pm 1$; 4 to 5</td>
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<tr>
<td>Procedure time (min), mean ± SD</td>
<td>$243 \pm 71$; 115 to 460</td>
<td>$342 \pm 88$; 280 to 405</td>
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<tr>
<td>Fluoroscopy time (min), mean ± SD</td>
<td>$36 \pm 18$; 15 to 100</td>
<td>$77 \pm 25$; 59 to 95</td>
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AP = accessory pathway; AVNRT = atrioventricular nodal re-entrant tachycardia; RF = radiofrequency; WPW = Wolff-Parkinson-White.

**Figure 2.** Kaplan-Meier curve showing the cumulative proportion of acutely successful patients without arrhythmia recurrence reported up to a fixed time point of 12 months follow-up.
Among those patients with AVNRT, one patient experienced recurrence at two months after intervention while another patient was recurrent at eight months after procedure. All recurrent patients with WPW syndrome experienced recurrence within one month of intervention. Neither of the two patients with concealed APs, one of whom was an acute failure with cryo but received a second successful ablation, experienced arrhythmia recurrence during the follow-up period.

A combination of warmer than average temperatures and lower than average number of cryoaapplication deliveries to the target site may have played a role in the arrhythmia not being permanently eradicated in recurrent patients. The average age of recurrent and recurrence-free patients was 12.7 ± 4.3 years and 13.7 ± 3.5 years, respectively. Hence, differences in sensitivity to cryotherapy of younger myocardial cells were an unlikely factor determining recurrence in this group of patients.

The electrophysiologic and ablation characteristics associated with those acutely successful patients who either did or did not experience arrhythmia recurrence during follow-up are shown in Table 2.

**DISCUSSION**

This study documents the use of a 7-F 4-mm-tip cryoablation catheter for treatment of pediatric patients with SVTs due to AVNRT and manifest or concealed APs located near the AV junction. There were no permanent cryo-related complications or adverse outcomes reported at intervention or during follow-up. There was no incidence of permanent AV block. Twenty-four (92%) patients were acutely successful. During follow-up (range: 1 to 22 months), seven (29%) acutely successful pediatric patients experienced arrhythmia recurrence. Arrhythmia recurrence was identified in three patients within 24 h of the procedure, in one patient within the first month of follow-up, in one patient within the sixth months of follow-up, and two patients within the first year of follow-up. The outcome for these seven patients who had arrhythmia recurrence is that one patient with AVNRT was subsequently ablated with RF; one patient with a posterior septal AP was subsequently ablated with RF; one patient with AVNRT is presently on drug therapy due to frequent recurrences being experienced; three patients (two with anteroseptal AP and one with midseptal AP) are off drug therapy because they have not experienced recurrences despite the occurrence of ventricular preexcitation; one patient with AVNRT is off drug therapy because only brief, sporadic, and non-documented palpitations are experienced.

Although the results of the present study demonstrate an excellent safety and acute success profile for cryoablation in the treatment of SVTs in which the reentry circuit is located near the AV junction in a pediatric population, the number of arrhythmia recurrences during the long follow-up period requires explanation. An attempt at addressing this issue has been made by assessing the electrophysiological and ablation characteristics associated with patients who were acute failures as well as those acutely successful patients who later experienced arrhythmia recurrence (Tables 1 and 2). Although difficulties were anticipated due to scar tissue caused by previous RF ablation around the target site, results show that previous RF ablation does not appear to have a negative impact on the acute success of cryo.

Results do show that patients who showed acute failure with cryo had over double the number of ablations (5 vs. 2) and over twice the fluoroscopy time (77 min vs. 36 min) than those who experienced acute success with cryo. These increases may point toward acute failure cases being particularly difficult arrhythmias to localize and then penetrate with deep and wide permanent lesions. Apart from the difference in ablation temperatures, there appears to be no specific electrophysiological or ablation characteristics that explain the arrhythmia recurrences (Table 2). Certain patients who had arrhythmia recurrence may not have been exposed to cryoaablation temperatures for the minimum time period required. The time range of exposure to cryoaablation temperatures among the seven patients who had arrhythmia recurrence was 2 to 8 min, as opposed to the required 4 to 6 minutes.
The 18 patients who experienced long-term success with cryo had a time range of exposure to cryoablation temperatures of 4 to 8 min. Again, results also showed that whether patients underwent previous RF ablation did not have a negative impact on long-term success.

Elimination of all jumps, echoes, and evidence of slow pathway conduction may not decrease the recurrence rate. The issue may well be not what must be eliminated to prevent recurrence but rather how much time must be taken after an acutely successful cryoablation to be sure that a chronically successful cryoablation was performed. The recurrences arising during long-term follow-up in acutely successful patients may well be due to the targeted tissue housing cells that remain in a “hibernated state” after ablation, and with these cells being viable they have the capacity to resume their arrhythmic activity after ablation. Moreover, the capacity of these hibernating cells to rejuvinate after ablation may be greater in pediatric patients than adult patients. This may explain the higher recurrence rate reported in this present study versus similar studies in which adult patients have been treated with cryo.

**Study limitations.** This study has limitations. First, this study was not controlled. It was a single arm study with no randomized comparison to either RF catheter ablation or other treatment strategies. Nonetheless, this study ultimately sought to document our experience with a 7-F, 4-mm cryo catheter for treatment of SVTs in which the reentry circuit is located near the AV junction in a pediatric population. Second, this study involved only 26 patients. Despite this, the study population did have a follow-up period of up to 22 months with a low drop-out rate. Third, arrhythmia recurrence was reported by a combination of patient diary records as well as ECG-documented recurrences, the former of which could be more subject to misinterpretation and/or reporting errors. Finally, discomfort with cryo could not be evaluated in this pediatric population as all patients were under general anesthesia during the procedure. Nonetheless, studies in both adult and pediatric patients have reported an absence of discomfort with cryo energy delivery (20,26).

**Conclusions.** Safety and efficacy of cryoablation treatment for 26 pediatric patients (age range: 5 to 20 years) with SVTs in which the reentry circuit is located near the AV junction in the pediatric population was investigated over a follow-up period of almost two years. There were no cryo-related complications or adverse outcomes reported at intervention or during follow-up. Twenty-four (92%) patients were acutely successful with cryo. During follow-up, seven (29%) acutely successful pediatric patients experienced arrhythmia recurrence. Preliminary investigation of electrophysiological and ablation characteristics did not clearly identify possible predictors of long-term success or reasons why certain patients experienced arrhythmia recurrence over the lengthy follow-up period. Further investigation of this issue is required.

**Acknowledgments**

All intervention and follow-up data were analyzed by an independent organization (Atlas Medical Science Writers Inc., Montreal, Canada). For disclosure purposes, this organization has previously analyzed data as well as compiled biomedical and regulatory documentation for CryoCath Technologies and other medical device, pharmaceutical, and biotech companies, as well as university groups involved in arrhythmia research. The authors particularly wish to thank Dr. Peter Andrew.

**References**