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CRYOABLATION OF CARDIAC ARRHYTHMIAS

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CONTENT

ABSTRACT

This thesis evaluates the safety and efficacy of cryoablation in supraventricular tachyarrhythmias.

In **Study I,** the acute and long-term outcome of cryoablation therapy of typical atrioventricular nodal reentrant tachycardia (AVNRT) was studied in a large series of patients (n=312). Acute procedural success in AVNRT with cryoablation was achieved in 99% of patients with a recurrence rate of 5.8% during a mean follow-up period of 22 months, which is similar to the expected outcome after radiofrequency ablation (RF). There were no long-term complications related to the use of cryoablation. Additionally, it was shown that further reduction of the recurrence rate may be achieved by using the endpoint of complete slow pathway elimination compared with residual slow pathway conduction.

In **Study II** the clinical usefulness of cryoenergy for the ablation of perinodal atrioventricular reentrant tachycardia (AVRT) was investigated. Cryomapping of substrates adjacent to the AV-node may improve safety of the procedure. Acute procedural success with cryoablation in superoparaseptal and septal accessory pathways was achieved in 96% of the patients with a recurrence rate of 27% during a median follow-up of 33 months. The total success rate was 89% after a second cryoablation. Thus, acute and long-term results were similar to those reported for RF but without any complications related to the conducting system.

In **Study III** the safety and efficacy of cryoablation of atrial tachycardia (AT) with high risk of ablation-related injuries was evaluated. AT foci originated from the para-hisian area, the vicinity of the sinus node, and the crista terminalis adjacent to the phrenic nerve were studied. Acute procedural success was achieved in 96% of patients with a recurrence rate of 12% during a mean follow-up period of 16 months. The total success rate after a second cryoablation was 92%, which is similar to that reported for RF ablation but without any permanent complications.

In **Study IV** cryoablation was compared to RF ablation for the treatment of cavotricuspid isthmus-dependent atrial flutter with emphasis on clinical success, safety, and procedure-related pain. The acute ablation success was 95% in the RF group and 92% in the cryoablation group (NS). The long-term success after six-month of follow-up was 92% for RF and 86% for cryoablation (NS). RF ablation caused significantly more pain compared to cryoablation both in terms of average and peak pain perception.

In **conclusion,** cryoablation of AVNRT, of high risk AVRT, and of AT are safe and effective alternatives to RF ablation without causing any permanent complication related to the conducting system and the phrenic nerve. Moreover, cryoablation of isthmus-dependent atrial flutter is not inferior to RF but with less procedure-related pain.

LIST OF ORIGINAL PAPERS

This doctoral thesis is based on the following papers, which will be referred to in the text by their Roman numerals. The papers are appended at the end of the thesis.

I

Hamid Bastani, Jonas Schwieler, Per Insulander, Fariborz Tabrizi, Frieder Braunschweig, Göran Kennebäck, Nikola Drca, Bita Sadigh and Mats Jensen-Urstad. Acute and long-term outcome of cryoablation therapy of typical atrioventricular nodal reentrant tachycardia. Europace (2009) 11, 1077-1082

II

Hamid Bastani, Per Insulander, Jonas Schwieler, Fariborz Tabrizi, Frieder Braunschweig, Göran Kennebäck, Nikola Drca, and Mats Jensen-Urstad. Cryoablation of superoparaseptal and septal accessory pathways: a single center experience. Europace (2010) 12, 972-977

III

Hamid Bastani, Per Insulander, Jonas Schwieler, Fariborz Tabrizi, Frieder Braunschweig, Göran Kennebäck, Nikola Drca, Bita Sadigh and Mats Jensen-Urstad. Safety and efficacy of cryoablation of atrial tachycardia with high risk of ablation-related injuries. Europace (2009) 11, 625-629

IV

Hamid Bastani, Nikola Drca, Per Insulander, Jonas Schwieler, Frieder Braunschweig, Göran Kennebäck, Jari Tapanainen and Mats Jensen-Urstad. Cryothermal versus Radiofrequency Ablation as Atrial Flutter Therapy: a Randomized Comparison.
In manuscript.

LIST OF ABBREVIATIONS

AF	Atrial fibrillation
AFL	Atrial flutter
AP	Accessory pathway
AH	Atrial-to-His
AT	Atrial tachycardia
AV	Atrioventricular
AVNRT	Atrioventricular nodal reentrant tachycardia
AVRT	Atrioventricular reentrant tachycardia
BCB	Bidirectional conduction block
CI	Confidence Interval
CS	Coronary sinus
DAVN	Dual AV nodal
CTI	Cavo-tricuspid isthmus
ECG	Electrocardiogram
EP	Electrophysiological
ER	Event recorder
ES	Extra stimulus
IVC	Inferior vena cava
LAO	Left anterior oblique
LVEF	Left ventricular ejection fraction
RA	Right atrium
RAO	Right anterior oblique
RF	Radiofrequency
SD	Standard deviation
SN	Sinus node
SVC	Superior vena cava
TA	Tricuspid annulus
TV	Tricuspid valve
VAS	Visual analogue scale
WPW	Wolf Parkinson White

INTRODUCTION

Radiofrequency (RF) ablation has become a standard form of therapy for most cases of supraventricular tachycardias [1-4], atrial flutter [5-6], atrial fibrillation [7-8], and ventricular tachycardia (VT) [9-10]. Although RF ablation has been proven to be highly effective, RF has several limitations as an energy source. For example, because the tissue destruction caused by RF energy is permanent, all clinical effects created by RF are essentially irreversible [11]. This translates into the inability with RF ablation to test the clinical effect of a lesion, which has important implications for ablation in close proximity to critical structures such as the atrioventricular (AV) node. RF energy is also associated with an increased risk of tissue charring and thrombus formation with potential for systemic embolization [12-14] in particular in association with ablation of large surface areas in patients with atrial fibrillation (AF) or left ventricular tachycardia [12,14]. Additionally, the ability to create effective lesions with RF energy requires adequate catheter tissue contact as well as catheter stability. Furthermore, the use of RF energy within or around vascular structures may lead to complications such as coronary sinus injury or spasm [15], coronary sinus thrombus and adherence of RF catheter to the coronary sinus wall [16-17], coronary artery stenosis and thrombosis [16-17], and pulmonary vein stenosis [18-19].

As a result of these limitations, the use of cryothermal energy has recently gained increasing attention as an alternative energy source for the ablation of cardiac arrhythmias. In fact, cryothermal energy offers several potential advantages over RF energy including improved catheter stability during lesion formation [20-21], potential for assessment of lesion effect before delivery of irreversible lesions, also known as cryomapping [22-23], decreased thrombogenecity [20, 24-25], safety within or near vascular structures [26-27] and significantly decreased levels of perceived pain by patients [68]. Despite this, systematic research into the clinical application of cryoablation has been scarce. Therefore, the present thesis was designed to assess the safety and efficacy of cryoablation in the treatment of selected supraventricular tachycardias.

History of cryothermal energy

Cold has been used clinically for thousands of years for its anesthetic and anti-inflammatory effects. The earliest known mention of cold as remedy comes from Imhotep during the third Egyptian dynasty around 2600 BC. Imhotep is considered by many to have been the first published physician and perhaps the only physician to achieve official status as a god. Writings attributed to Imhotep were discovered on papyrus that was purchased in Luxor by Egyptologist Edwin Smith in 1862 (Figure 1).

The papyrus contains the description of 48 battlefield injuries and mentions the concept of cold compresses. The beneficial effects of cold in these cases reflect its utility as an anesthetic and anti-inflammatory agent.

The earliest descriptions in modern time of the use of cryothermal energy, in which carbon dioxide was used for the creation of transmural cardiac lesions, were provided by Hass and Taylor in 1948 [28]. They demonstrated the ability of hypothermia to produce a homogeneous, sharply demarcated lesion. Of particular interest was the resumption of normal function by epicardial vessels within minutes after removal of the freezing instrument from the epicardium. They also noted the ability to produce transmural lesions in any cardiac chamber, without danger of rupture, aneurysmal dilation or intracardiac thrombosis [28-29] (Table 1).

Figure 1. *Part of the Edwin Smith papyrus.*

In 1964, Lister and Hoffman described reversible conduction block in the AV node after rewarming of a cryothermal energy lesion, which is currently referred to as cryomapping [30]. Since then, numerous groups of investigators have developed cryothermal technology, from an experimental energy source for the creation of intracardiac lesions in animals to a modern alternative energy source in humans [20, 24, 31-32].

Cryosurgery has been an integral part of the surgical management of cardiac arrhythmias since the late 1970s [33]. Before cryothermal systems were available, surgical ablation consisted primarily of surgical resection [34]. Some of the early reports of modern cryothermal mapping were provided by the cardiac surgical experience with cryothermal energy [35]. Intraoperative cryoablation has been shown to be safe and effective and has been successfully used in humans to map or ablate the AV node [31], accessory pathways [36], AV nodal re-entrant tachycardia (AVNRT) [37], atrial flutter [38], and VT (in combination with subendocardial resection) [39-41].

In 1980, Camm et al. described the ability to create reversible partial and complete conduction block in the AV node by placing a cryothermal energy probe in the His bundle position and cooling the tissue to between 0°C and -10° C [35]. They were able to demonstrate AH prolongation followed by complete dissociation, which completely resolved on rewarming. In 1998 Dubuc and co-workers demonstrated the feasibility of creating reversible cryothermal energy lesions by a transvenous steerable electrode catheter in dogs [20]. In 1999, Khairy et al. published early clinical experiences of percutaneuos transvenous catheter cryoablation in humans [32]. Recently, further technical advancement of transvenous cryoblation has made it possible for invasive cardiac electrophysiologists to treat a broad range of cardiac arrhythmias [23, 32, 42].

***Table 1**. Historical landmarks in transvenous cardiac cryoablation*

Year	Authors	Contribution
1948	Hass &Taylor	Used cryothermal energy for the creation of transmural cardiac lesions
1963	Cooper	Developed first cryosurgical apparatus
1964	Lister & Hoffman	Described reversible conduction block by cryothermal energy
1977	Harrison et al	Performed cardiac cryosurgery with a hand-held probe
1991	Gillette et al	Conducted an animal study with a transvenous cryocatheter
1998	Dubuc et al	Used of steerable cryocatheter system with pacing and recording electrodes
1999	Khairy et al	Used percutanous transvenous cryocatheter ablation in humans

Biophysics of cryothermal energy

The application of cryothermal energy to cardiac tissue results in the formation of a well-demarcated hemispherical block of frozen tissue, an ice ball [33]. The tissue goes through a series of stages before forming into a stable lesion. The main stages in the creation of a cryothermal energy lesion include the following: (1) freeze/thaw phase, (2) hemorrhage and inflammatory phase, and (3) replacement fibrosis phase [33,43-45]. Therefore, the lesions created by cryothermal energy sources are morphologically different in the acute and chronic phases.

Freeze/thaw phase

This phase results in the initial changes associated with direct cryothermal lesion application that occurs within the first hours after delivery. In this stage, freezing results in the formation of intracellular and extracellular ice crystals. The ice crystals do not penetrate cellular membranes; rather they cause compression and distortion of intracellular organelles. More importantly, extracellular ice crystal formation removes extracellular free water and causes intracellular desiccation. Furthermore, because of the withdrawal of water caused by freezing, the remaining water becomes hyperosmotic, and concentrations of electrolytes become elevated intracellularly, contributing to cell death. Once thawing begins, first in the extracellular matrix, the hypotonic fluid moves back into the cells, causing the cells to swell and cell membranes to rupture. The thawing of ice crystals also results in increased membrane permeability in mitochondria and disruption of intracellular transport mechanisms. Once these changes occur, irreversible cell death takes place.

Hemorrhage and inflammatory phase

The second stage of myocardial damage consequent to cryotherapy is characterized by the development of hemorrhage, edema and inflammation (coagulation necrosis), which are evident within 48 hours after thaw. By one week after the thaw, the now inflammatory lesions have become sharply demarcated by macrophages, lymphocytes, and fibroblasts and collagen stranding has begun.

Replacement fibrosis phase

The third and final phase in the evolution of a cryothermal energy lesion is the replacement fibrosis phase. A number of weeks after ablation, the myocardial tissue within the lesion are become replaced by dense collagen and fat. A short while afterwards, the lesion is densely fibrotic, and up to three months later it has decreased to its final size.

Differences between Cryo and RF

The characteristics of lesions created by cryothermal energy differ from those created by RF energy and have been well described by a number of investigators [20-21, 46]. Unlike heat that destroys cells by coagulation and tissue necrosis with potential for thrombus formation and aneurysmal dilation, cryothermal energy involves a distinct pathophysiologic process. Lesions created by a 4-minute cryoablation application at temperatures lower than –50º C are grossly hemispherical in shape with a sharply defined interface with normal myocardium and well-preserved architecture (Figure 2). Because they are not associated with any significant endothelial damage, they are also typically free of surface thrombosis [25].

These findings are in contrast to lesions created by RF, which are less sharply demarcated and have an architecture that is not as well-preserved. In addition, these lesions may be associated with surface endothelial disruption and therefore are more likely to be associated with surface thrombosis [47-48]. Khairy et al. demonstrated that RF ablation resulted in lesions of greater area (RF in median 42.0 mm^2 vs. Cryo 20 mm^2; P=0.002) and nearly significantly larger volume (RF in median 94.6 mm^3 vs Cryo 43.2 mm^3; P=0.06) but not depth compared with cryolesions (RF mean 6 mm vs Cryo 4.9 mm; P= NS) [25]. Colder temperatures, however, were though associated with deeper lesions. For example, achieving a peak temperature 10°C colder resulted in an average lesion 0.38 mm deeper (P=0.0001) [25].

Since a RF lesion is created with the beating heart moving in contact with the catheter, the lesion is delivered over an area slightly larger than the catheter tip as the result of a "brushing" effect. As the cryoablation catheter is frozen to the tissue during cryoablation, this allows the delivery of a focused lesion without a similar "brushing" effect [20-21], and without the possibility to adjust or move the catheter during lesion formation. Thus, cryoadhesion provides stable contact, eliminates cathter movement during ablation and results in stable delivery of cooling into the target area, potentially limiting the risk of collateral damage. In addition, this feature permits programmed stimulation during an application and no further fluoroscopy is needed when cryoadhesion occurs.

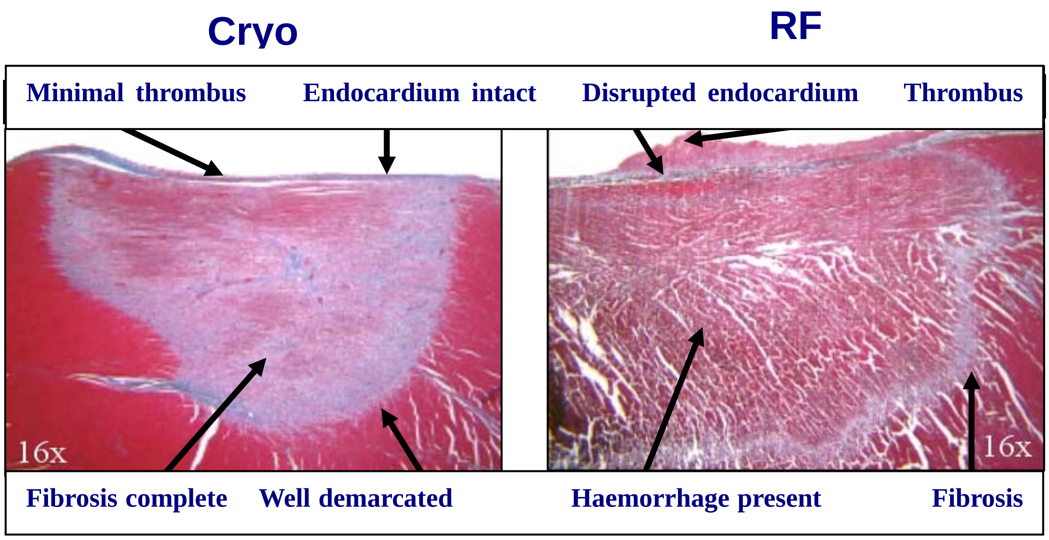

***Figure 2**. Schematic diagram comparing lesion architecture between a cryoablation lesion (right) and a RF lesion (left); reproduced with permission from reference 25.*

Cryomapping (ice-mapping) and cryoablation

Once the ablation target is identified, the operator can choose between two modes of operation. Typically, a cryomapping application is performed first and is used to assess the electrophysiological effect of the application. This allows the operator to cool the target tissue to approximately -30° C. Should the operator note an undesired effect of the cryomapping lesion such as prolongation of the AH interval or complete AV block, the cryomapping can be terminated, with complete recovery of conduction within seconds after rewarming and without any risk for permanent damage. Hence, the cryomapping procedure can be repeated as many times as the operator chooses until a favourable position is reached and the cryoablation mode is started. During cryoablation mode, the temperature is further decreased to below - 75° C for up to four minutes, resulting in a permanent lesion. Should the operator note an undesirable electrophysiologic effect during cryoablation, the cryoapplication can be terminated. If it is terminated immediately upon the appearance of the unwanted effect conduction typically returns to normal on rewarming with no residual conduction abnormality.

Components of a cryoablation system

The cryoablation system consists of a steerable catheter controlled by a microprocessor-based electromechanical refrigeration console. Catheters and console are used together to deliver fluid refrigerant from a storage tank inside the console to the catheter tip and, in accordance with the principles of heat extraction, remove vaporized refrigerant by evacuation through a scavenging hose. These devices all rely on the Joule-Thomson effect, whereby a refrigerant at high pressure, for example, liquid N_2O, flows down the central lumen of an injection tube and then evaporates at the tip of the catheter into the outer shaft at lower pressure, causing cooling of the catheter tip.

Catheters

Cryoablation catheters achieve tissue freezing by delivery of a refrigerant (typically N_2O) through an infusion channel to an evaporation chamber in a thermally-conductive tip electrode resulting in marked heat removal from the catheter tip and contiguous tissue. Another channel is under vacuum for evacuation of the expanded nitrogen gas (Figure 3). By removing heat from tissue, cryothermal systems achieve the cooling and freezing of the tissue to affect cellular function and activity.

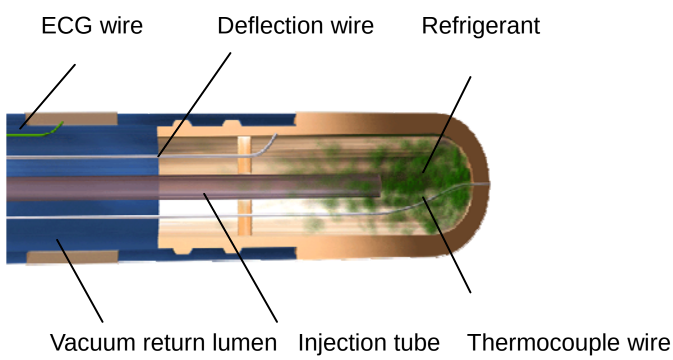

Figure 3. *Schematic figure demonstrating the CryoCath Freezor cryocatheter internal design. The cryocatheter is a lumen catheter containing passageways for the delivery of liquid refrigerant and removal of refrigerant in vapor form. A thermocouple, for temperature sensing, is embedded in the tip of the catheter and ECG wire for ECG signal. Reproduced with permission of Medtronic, Inc.*

Cryo console

The console allows the operator two modes of operation. The first is Cryomapping mode, in which the tip is cooled to a temperature of - 30º C for up to 60 seconds. Cryomapping allows the delivery of an application with reversible effect. The second mode is the Cryoablation mode, which cools the electrode tip to -75º C for usually four minutes, resulting to permanent lesion. Cryoablation may be initiated at any time during a cryomapping application or without any prior cryomapping. The cryoablation system is depicted in Figure 4.

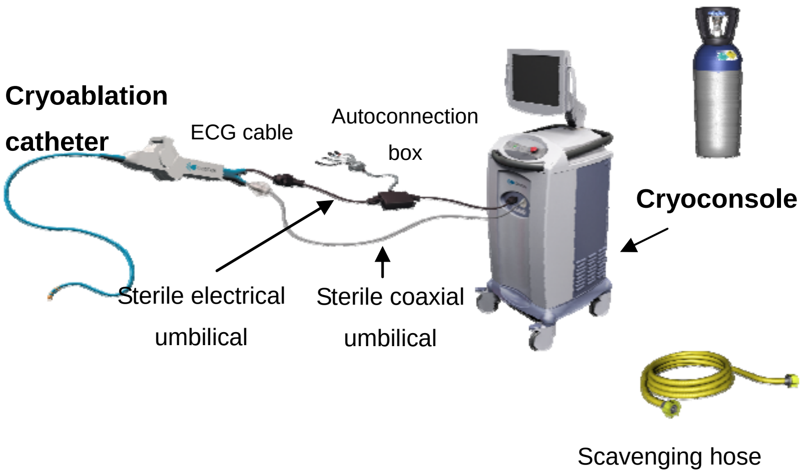

Figure 4. *Cryoablation system consisting of a steerable catheter, console and connectors. The cryocatheter and console are connected by a coaxial tube that delivers fluid nitrous oxide (N2O) to the catheter and removes refrigerant vapor from the catheter. The coaxial tube also shields the liquid refrigerant from the warming effects of ambient air in the electrophysiology (EP) laboratory. The gas removed from the catheter to the console is evacuated through a scavenging hose into the scavenging line of the EP laboratory. Reproduced with permission of Medtronic, Inc.*

Technical aspects

The efficacy of a cryoablation system depends on two important phenomena: heat pump capacity and heat transfer efficiency. The heat pump capacity is related to the amount of heat the refrigeration system can remove, and how much of that heat comes from the ablation site is correlated to the heat transfer efficiency.

Heat pump capacity

Temperature control and refrigerant-flow control are important parameters to determine the efficacy of cryoablation systems [133]. During a cryoablation procedure, pressurized refrigerant is delivered to the catheter tip to achieve and sustain a predefined ablation temperature or flow. This continuous temperature/flow control compensates for heat-load changes due to blood circulation during a cardiac cycle or adjustments in tip-tissue interface. The cryoablation console includes algorithms that control refrigerant delivery to maintain a preset temperature value (mode) or flow value (mode). In temperature mode, the catheter-tip temperature largely depends on tip orientation in relation to the tissue (Figure 5). If the catheter tip is held parallel to the tissue, the temperature sensor will be positioned in the bloodstream. As a result, the sensor will read a warm temperature, prompting the system to deliver more refrigerant to the tip to achieve the predefined temperature value. If the catheter tip is held perpendicular to the tissue, the temperature sensor will be positioned at the tip-tissue interface. A relatively small amount of refrigerant at the catheter tip will provide a cold-temperature reading because the tip temperature is not influenced by blood flow.

The perpendicular position will generate a colder temperature than the parallel position, but cooling performance in the parallel position is much greater than in the perpendicular position, even if the temperature reading indicates the opposite. The advantage of temperature mode is that it remains sensitive to the heat-load environment [133]. In flow mode, the catheter tip is flooded with a predefined volume of refrigerant, providing consistent cooling power independently of tip temperature or position. In flow mode, the system does not recognize the difference between high or low heat loads; instead, it provides a constant flow of refrigerant and is normally limited by flow capacity in the catheter.

Heat transfer efficiency

The nature and extent of the contact between the cooled catheter tip and the tissue are as important to the efficacy of cryoablation as the cooling capacity of the system. The catheter tip must be designed for high thermal conductivity and biocompatibility for use in the bloodstream [133].

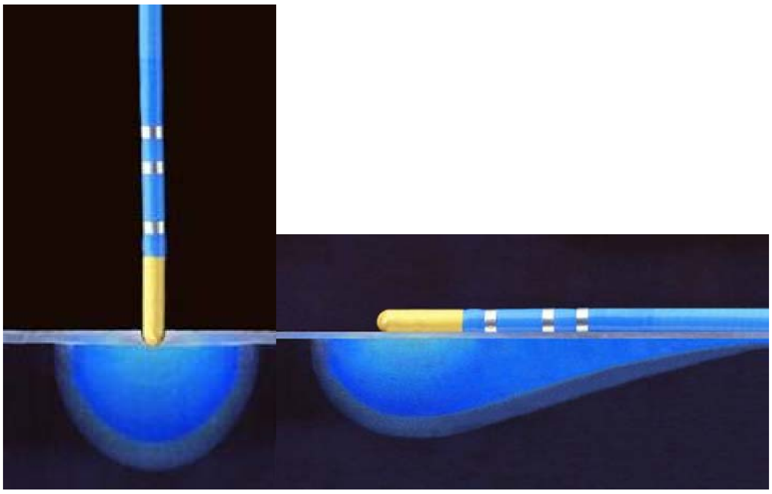

Figure 5. *The catheter tip parallel to the tissue produces a larger lesion compared to perpendicular position. Reproduced with permission of Medtronic, Inc.*

Important Factors for cryoablation efficacy

Cryoablation efficacy is defined as the tissue temperature and lesion size that must be achieved to stop an arrhythmia from recurring. Several parameters have been shown to be important for cryolesion formation and morphologic characteristics of cryolesions.

Effects of Blood Flow

While the endocardial applications require high cooling power (high refrigerant flow) to offset the heat load of flowing blood, epicardial applications require less cooling power due to the absence of blood flow at the tip of the catheter. Low-flow areas result in larger and deeper cryolesion formation [74]. Therefore, cryoablation has an advantage in trabeculated areas, also ablating inside of the low-flow “pouch” during typical isthmus ablation.

Freezing Duration

Cryo application time is clinically an extremely important issue. A duration of four minutes typically is required, because lesion size continues to expand during the cryoablation application, up to a duration of two to three minutes (Figure 6). Therefore, applications shorter than four minutes may not result in complete lesion delivery.

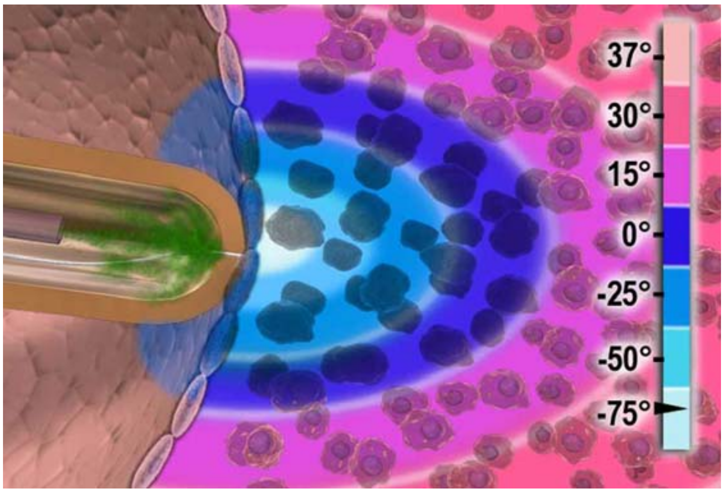

Figure 6: *Schematic diagram shows that as the catheter tip is cooled, the adjacent cardiac tissue is also cooled. The longer the catheter is cooled, the larger the ice ball formation and the larger the lesion created, with an upper limit of approximately two to three minutes of application when cooling to –75 ºC. The lowest temperature and fastest freezing rate are generated at the point of contact (distal catheter tip). Slower cooling rates are obtained for tissue peripheral to the contact point. Reproduced with permission of Medtronic, Inc.*

Double Freezing (freeze/thaw/freeze)

Double freezing results in a deeper and larger lesion because of repeated freeze/thaw effects on cell membranes [75].

Contact Pressure

Increased pressure results in faster freezing, because of compression of the tissue and decreased warming effects of intra-myocardial flow [76].

Catheter Size

Larger catheter size results in larger lesions since the catheter tip in contact with myocardium is “protecting” that area from direct blood flow washout effects and additionally larger catheter size can incorporate larger diameter channels, supplying more refrigerant and, therefore, increasing freezing power [77]. A relatively large catheter tip at -50ºC can produce a larger lesion than a relatively small catheter tip at -75 ºC. There is a direct correlation between tip size and the volume of refrigerant that is delivered to the target site (Figure 7).

Refrigerant

Another important factor is the quality of refrigerant, which clearly affects heat transfer in cryoablation procedures. Refrigerant that is delivered to the cooling chamber in a liquid state exchanges more heat than refrigerant in a gaseous state. Only nitrous oxide-based cryocatheters (-80°C) are available for transvenous catheter ablation. Other coolants are available in surgical probes with much lower boiling temperatures and are more effective. The most widely used coolant in surgical settings is liquid nitrogen (N2), which boils at (-196°C). Argon gas-based (boiling point at = -160°C) cryosurgical devices are also available.

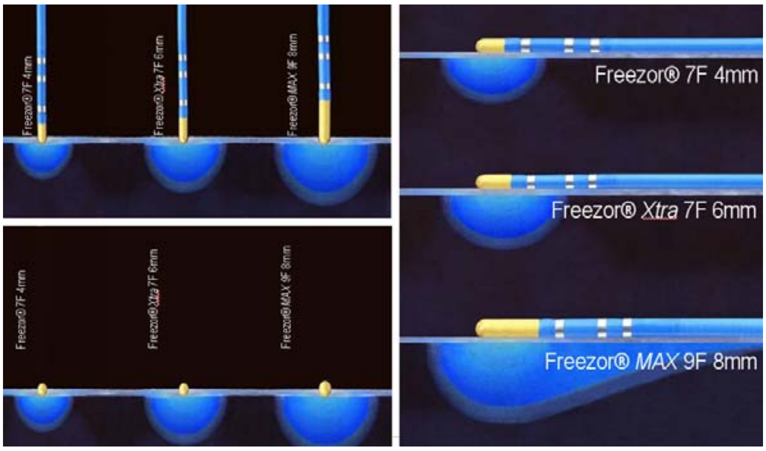

Figure 7. *Larger tip sizes produce greater lesions because more refrigerant is delivered to the tissue. Reproduced with permission of Medtronic, Inc.*

AIMS OF THE THESIS

The overall objective of this research work has been to study the safety and efficacy of cryoablation in supraventricular tachyarrhythmias. Specific aims are outlined below.

Study I.

To study the acute and long-term outcome of cryoablation therapy of typical atrioventricular nodal reentrant tachycardia (AVNRT) in a large series of patients.

Study II.

To investigate the clinical usefulness of cryomapping for ablation of perinodal accessory pathways and to evaluate the acute and long-term results of transvenous cryoablation of septal and superoparaseptal accessory pathways.

Study III.

To study the safety and efficacy of cryoablation of atrial tachycardia with high risk of ablation related injuries.

Study IV.

To compare cryoablation and radiofrequency ablation in the treatment of CTI-dependent atrial flutter with emphasis on clinical success, safety and procedure-related pain.

MATERIAL AND METHODS

Patients

Study I

Between January 2003 and May 2007, all consecutive patients undergoing ablation of typical (slow–fast) AVNRT using cryothermal energy were included. During this period, 312 patients with typical AVNRT underwent cryoablation.

Study II

The study population consisted of all patients undergoing a first transvenous catheter ablation procedure of a superoparaseptal or septal AP using cryothermal energy between January 2004 and December 2008. During this five-year period, 464 patients underwent transvenous catheter ablation of AP at our institution. Twenty-seven (5.8%) of these patients had an AP located either in the superoparaseptal (n=18) or in the septal (n=9) region.

Study III

The study population consisted of all patients undergoing a first transvenous catheter ablation procedure for high-risk-located AT using cryothermal energy between May 2004 and July 2007. During this period, 164 patients underwent transvenous catheter ablation of AT at our institution. Twenty-six of these patients were considered to have high-risk-located AT and constituted the study population. The AT foci distribution was as follows: close to the AV node (n=14); in the vicinity of the sinus node (n=7); and at the crista terminalis adjacent to the phrenic nerve (n=5).

Data Collection (*Studies I- III)*

Crucial demographic, clinical, and EP information was collected prospectively by the treating electrophysiologist at the time of the EP study and stored in an electronic database containing all consecutive EP studies at the Karolinska University Hospital (FileMaker Inc., Santa Clara, CA, USA).

Study IV

Between January 2007 and May 2010, all consecutive patients referred to our institution for ablation therapy of ECG-documented typical CTI-dependent AFL were considered for inclusion. Patients above the age of 18 were included if they had symptomatic CTI-dependent AFL documented on a 12-lead ECG with typical ECG appearance of negative saw tooth waves in the inferior limb leads and positive deflections in V1 or positive saw tooth waves in the inferior limb leads and negative deflections in V1. Patients with a history of atrial fibrillation were only included if they had predominant atrial flutter under chronic treatment with class I or III antiarrhythmic agents. Patients were excluded if they had prior ablation for AFL, atrial flutter related to recently undergone surgery, hyperthyroidism or other severe disease, an inability to adhere with the study protocol, predominant atrial fibrillation, and contraindication to warfarin.

Data Collection and pre-ablation assessment (*Study IV)*

Patients were assessed by medical history, physical examination and a standard transthoracic echocardiography. Routine laboratory tests were obtained within 72 hours before the procedure. In all patients with persistent AFL warfarin was continued before ablation with a target INR between 2-3. Antiarrhythmic drugs were continued before and during the ablation. All data were collected, using standardized case report forms (CRF). In the electrophysiology laboratory, the operator opened a sealed, opaque envelope containing the randomization assignment.

Data Collection and post-ablation follow-up (*Study IV)*

An ECG was taken within six hours after the procedure. Upon discharge, all patients were instructed to contact the study coordinators in case of any symptoms suggestive of arrhythmia recurrence. In this case, rhythm was assessed using a 12-lead ECG, Holter–monitoring or Event Recording (ER), depending on the symptoms. Patients also received a diary to note any symptoms of arrhythmia following the ablation. Relapse was defined as ECG documented CTI-dependent AFL. All patients were routinely seen after six months in the outpatient clinic. At this follow-up visit, a physical examination, an ECG recording, and a review of the patient diary were performed, and all patients were also intensively questioned about arrhythmia or other cardiac-related symptoms. A second ablation procedure, predetermined with RF energy, was scheduled for patients with a relapse of symptomatic and documented common AFL.

Definitions (*Studies II-III)*

Superoparaseptal AP

Pathways were classified as superoparaseptal if an AP activation potential as well as a His bundle potential were simultaneously recorded from a mapping catheter placed at the His bundle region. At fluoroscopy, the tip of the mapping catheter was near the His-catheter in different radiological views.

Septal AP

Pathways were classified as right septal if either the earliest anterograde ventricular activation or an AP potential was recorded from a catheter located in an area bounded superiorly by the tip electrode of the His bundle catheter and inferiorly by the CS ostium, excluding AVNRT and septal or parahissian ectopic atrial tachycardias.

Atrial tachycardia near the atrioventricular node

Atrial tachycardia originating near the AV node or the His bundle is characterized by the presence of His-bundle potential in the local electrogram or by fluoroscopic proximity of the ablation site to the His-bundle, excluding AVNRT and AVRT.

Atrial tachycardia near the sinus node

Atrial tachycardia originating from the SN complex is located at the superior aspect of the crista terminalis with identical or almost identical P wave and intracardiac activation sequence during tachycardia and sinus rhythm.

Atrial tachycardia near the phrenic nerve

Atrial tachycardia originating along the lateral right atrium and with high output (10 mA) pacing resulted in phrenic nerve stimulation.

Ablation procedure *(Studies I-III)*

Antiarrhythmic drug medication was discontinued five half-lives before the study. All procedures were performed under light sedation, under local anesthesia, and in the fasting state. Heparin was given routinely. A conventional EP study was performed with diagnostic catheters positioned in the right ventricle apex, in the coronary sinus, and in the His position.

AVNRT (Study I)

The diagnosis of typical AVNRT was confirmed. After standard EP assessment, an 8 F 6-mm cryocatheter Freezor Extra (Medtronic Cryo-Cath, Minneapolis, MN USA) was positioned fluoroscopically across the tricuspid annulus starting just anterior and slightly inferior to the coronary sinus ostium. A local atrial electrogram with a terminal fractionated component and an A/V ratio of 1:3 or 1:4 was sought. A combination of electrogram analysis looking for slow pathway potentials and anatomical approach were used to identify appropriate target sites for ablation. Fluoroscopy with RAO 30º and LAO 60° projections was used. In case of inadequate catheter stability, a long sheath (SR0, St. Jude Medical, Sylmar, CA, USA) was used. In patients who had dual AV nodal physiology with a clear jump (more than 50 ms), echo beats, complete circles, or reproducibly inducible AVNRT at baseline, cryomapping was performed during atrial extrastimulus testing with a coupling interval critical for slow pathway conduction and/or AVNRT induction. If there was no clear jump and/or AVNRT was difficult to induce at baseline, the prolongation of the antegrade AV refractory period during atrial extrastimulus testing was used to identify the potential ablation sites.

At the location of interest, cryomapping at -30°C for a maximum of 20 s was performed. If there was a clear effect on the arrhythmia substrate such as non-inducibility, loss of slow pathway conduction, or prolongation of refractory period within this time, cryoablation with a goal temperature of - 80°C for 240 s was applied. In case of no effect within 20 s or AV prolongation, cryomapping was stopped and then repeated at a new target site. Programmed stimulation was performed to test the effectiveness of the therapy during cryoablation. If AVNRT was still inducible or if AV prolongation or AV block occurred, cryoablation was terminated and cryomapping at new sites was done.

Both cryomapping and cryoablation were initiated during sinus rhythm. Following successful cryoablation, arrhythmia induction was attempted for 30 minutes to confirm the effectiveness of the slow pathway ablation using non-inducibility as endpoint. Jumps with or without single nodal echoes were accepted, but not complete circles (two or more nodal echo beats) after 30 minutes. Isoproterenol infusion was used during arrhythmia induction both before and after cryoablation when deemed appropriate.

AP (Study II)

A 12-lead surface ECG during pre-excitation was obtained and analyzed. The delta-wave morphology was used to predict the site of origin. Both AV conduction and refractoriness in the anterograde and retrograde direction were evaluated by incremental atrial and ventricular pacing as well as by extrastimulus (ES) technique. Atrial single and double premature ES and incremental pacing were used to induce tachycardia. In addition, isoproterenol infusion was used when the tachycardia was not inducible at baseline.

After the standard electrophysiologic assessment, an 8 F 6-mm cryocatheter Freezor Extra was advanced to the area of interest. Subsequently, the arrhythmia substrate was mapped by combining electrogram analysis and anatomical location with fluoroscopy. Biplane fluoroscopy (RAO 30° and LAO 60º) was used. In case of inadequate catheter stability, a long sheath (SR0, St. Jude Medical) was used.

In patients with pre-excitation, the localization of the AP was identified by careful mapping of the atrial and ventricular activation pattern using distal unipolar and bipolar electrograms, specifically the shortest AV interval, the earliest anterograde ventricular activation to surface delta wave during sinus rhythm, and “QS” morphology on unipolar leads.

In those with concealed AP, the earliest atrial activation during orthodromic tachycardia and/or sinus rhythm with intermittent ventricular pacing was used. At the location of interest, cryomapping at -30º for a maximum of 20 s was attempted followed by re-evaluation of the arrhythmic substrate or inducibility. If the patient had pre-excitation, cryomapping was done either during sinus rhythm or tachycardia, monitoring for a loss of delta wave or termination of the orthodromic tachycardia, respectively. In the case of concealed AP, cryomapping was done either during orthodromic tachycardia or intermittent ventricular pacing to terminate the tachycardia or to create retrograde block in the AP, respectively.

The cryoenergy was discontinued if no effect was achieved within the first 20 seconds of cryomapping. If there was a clear effect on the arrhythmia substrate, such as loss of delta wave, non-inducibility, or retrograde block of conduction through the AP, cryoablation with a goal temperature of -80ºC for 240 s was done. Programmed stimulation was performed to test the effectiveness of the therapy during cryoablation. AV conduction was closely monitored during cryomapping as well as during cryoablation. The ablation was immediately stopped if any sign of impairment of AV conduction or ineffective result was found. Following successful cryoablation, arrhythmia induction was attempted for 30 minutes to confirm the effectiveness of the ablation using non-inducibility and conduction block in the anterograde and retrograde direction in AP as endpoints.

AT (Study III)

A 12-lead surface ECG during AT was obtained and analyzed. The P-wave morphology was assessed to predict the site of tachycardia origin. After a conventional diagnostic EP study, the diagnosis of AT was confirmed. Isoproteronol infusion was used when the tachycardia was not inducible at baseline. An 8 F 6-mm cryocatheter Freezor Extra was advanced to the area of interest. The arrhythmia substrate was mapped by combining electrogram analysis and anatomical location.

A non-contact mapping system (Ensite, St Jude Medical) was used for mapping and ablation of AT near the SN (Figure 8). In cases with AT foci along the lateral right atrium, fluoroscopy was performed every 10 to15 s during cryoablation to observe the respiratory motion of the right hemidiaphragm and the ablation was stopped if an impairment was seen. At potential target sites, cryomapping at -30°C for a maximum of 20 s was performed. If AT became non-inducible or tachycardia terminated, cryoablation with a goal temperature of -80°C for four min was performed. The AV-nodal conduction and sinus cycle length were continuously monitored during cryomapping and cryoablation. Procedural success was defined as non-inducibility 30 minutes after the last cryoapplications.

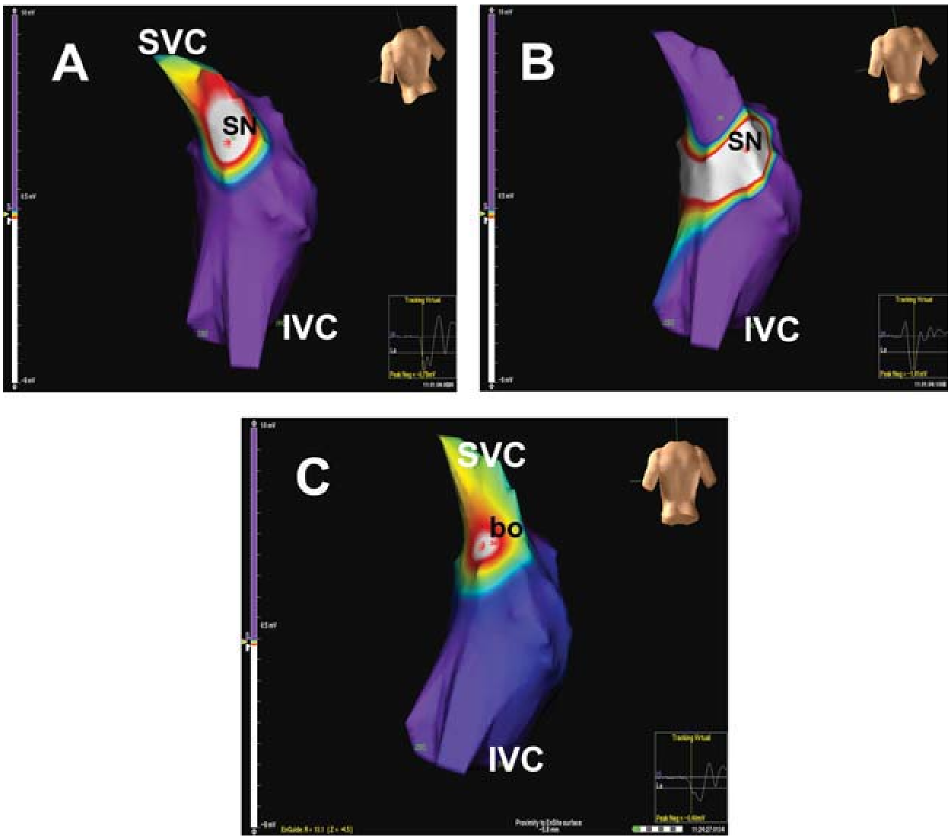

Figure 8. *Non-contact mapping in atrial tachycardia (AT) near the sinus node. (A) and (B) Sequence of early endocardial breakthrough during sinus rhythm at baseline, in an isopotential map. (C) An early breakout during AT, in a newly created isopotential map indicating the origin of the AT in the vicinity of the sinus node. SVC, superior vena cava; IVC, inferior vena cava; SN, sinus node; bo, breakout.*

Ablation procedure (*Study IV*)

Patients underwent EP-study in the fasting state with a light sedation under local anesthesia. The standard fluoroscopy or a 3D non-fluoroscopic mapping system (Ensite NavX) was used. In the presence of atrial flutter a CTI-dependent re-entrant loop was verified by demonstration of concealed entrainment from the CTI and an activation pattern around the tricuspid annulus (TA) consistent with CTI-dependent AFL either using the ablation catheter or by a 7 F duodecapolar Halo catheter (Daig, St. Jude Medical, USA) positioned around the TA. In patients in sinus rhythm, stimulation at the CS-ostium and the infero-lateral part of the right atrium was performed to demonstrate conduction through the CTI before ablation.

In patients randomized to the RF group, the procedure was performed using a 7 F 3.5-mm tip open-irrigated catheter (Biosense-Webster, Inc. USA) to create an ablation line between the tricuspid valve and the inferior vena cava (IVC). Continuous RF energy was delivered with preset parameters of 30 to 40 Watts with a goal temperature of 40-42ºC and a cut-off limit of 48 ºC.

In the Cryo group, cryoablation was performed using a sequential application technique point-by-point from the TV annulus to the IVC. A steerable 9 F, 8-mm-tip cryocatheter Freezor Max (Medtronic Cryo-Cath) was used. Ablation was performed at a target temperature of –80 ºC. Each application lasted for 240 s. Acute ablation success was defined as complete bidirectional conduction block (BCB) in the CTI persistent 30 minutes after final energy delivery.

Pain was evaluated using a Visual Analogue Scale (VAS) ranging from 0 (“no pain at all) to 10 (“the worst possible pain”). The VAS score was determined before starting the application, during the application, and at the end of each application.

Follow-up (*Studies I-III*)

Clinical follow-up was based on outpatient visits, medical records, and telephone contacts. A 12-lead surface ECG was obtained in all patients at the long-term follow-up. Holter monitoring or an EP study was done depending on the presented symptoms. In addition, a symptom questionnaire was sent to all patients. Patients were asked whether they were totally free from arrhythmia symptoms, significantly better, somewhat improved, or if the symptoms were unchanged or had deteriorated. They were also asked about the frequency of symptoms: daily, several times per week, once per week, or less. Furthermore, if they had experienced a recurrence of arrhythmia symptoms, they were asked to describe these symptoms. Finally, the patients were asked about current anti-arrhythmic drug therapy. If recurrence was suspected, the patient was subjected to further investigation. Recurrence was defined as ECG-documented tachycardia, relapse of pre-excitation (delta-wave), or return of clinical symptoms identical to those before cryoablation.

Follow-up (*Study IV*)

An ECG was taken within six hours after the procedure. Upon discharge all patients were instructed to contact the study coordinators if any symptoms suggestive of arrhythmia recurred. In this case, rhythm was assessed using a 12 lead ECG, Holter–monitoring, or Event Recording (ER), depending on the symptoms. Patients also received a diary to record any symptoms of arrhythmia following the ablation. Relapse was defined as ECG documented CTI-dependent AFL. All patients were routinely seen after six months in the outpatient clinic. At this visit a physical examination, an ECG recording and, a review of the patient diary were performed. In addition, all patients were also intensively questioned about arrhythmia or other cardiac-related symptoms.

Statistical analysis *(Study I-III)*

Data are presented as median and range or mean±SD as appropriate. Continuous data were compared using Mann–Whitney U test or Student´s t-test. For categorical data, proportions were analyzed using the chi-square test. $P<0.05$ was considered significant. Statistical analyses were performed using commercially available software (Statistica, version 8.0, StatSoft Scandinavia AB).

Statistical Analysis *(Study IV)*

The primary analysis was designed to test the hypothesis that cryoablation was non-inferior to RF with regard to success rate at the six-month follow-up with an upper margin of 10% difference between the groups. Power calculation was based on a predicted 95% success rate using RF ablation. Thus, 75 patients were required in each group to demonstrate non-inferiority of cryo with a statistical power of 80% ($\alpha = 0.05$ and $\beta = 0.2$). The calculation is based on the following formula: $N= [2\pi (1- \pi) / \delta^2] \times 7.9$ or $N=[2x0.95x0.05/0.01] \times 7.9 = 75.05$, where $\pi = 0.95$ (success rate for the standard method) and δ (pre-defined non-inferiority margin) = 0.1.

Normally distributed data were expressed as mean ± SD, and non-normally distributed data are given as median and range. Continuous data were compared using Mann-Whitney U test or Student´s *t*-test. For categorical data, proportions were analyzed using a chi-square test. Statistical analyses were performed using commercially available software. Event free survival rates were estimated with the Kaplan-Meier method.

For analysis of the learning curve for the participating electrophysiologists, a bootstrap regression was performed with 3000 replications, with replacement, drawn from the original sample. This was due to non-normal distributed procedure time. Each sample was set to have the same number of subjects drawn regarding each half of the learning time. The results from this analysis are presented as mean procedure time with 95% bias corrected accelerated (BCa) confidence intervals. The Intercooled Stata 11.0 statistical software (Stata Corp LP, College Station, TX, USA) was used for the bootstrap regression analysis.

RESULTS

Study I

Acute and long-term outcome of cryoablation therapy of typical atrioventricular nodal reentrant tachycardia

Aim

To study the acute and long-term outcome of cryoablation therapy of typical atrioventricular nodal reentrant tachycardia in a large series of patients.

Results

Efficacy

Acute success was achieved in 309 of 312 patients (99%). Total procedure time was 128±52 min (median 120 min) and fluoroscopy time was 18±14 min (median 20 min). During a mean follow-up of 673±381 (median: 588 days), the overall recurrence rate was 18 of 309 (5.8%), giving a total success rate of 94.2% after a primary successful cryoablation. Of these 18 patients, 16(89%) were successfully re-ablated. Thus, the total success rate after a second cryoablation session was 98%.

Safety

A total of 20 procedure-related episodes of transient second- or third-degree AV block occurred in 16 patients (5%) either during cryomapping (n=7) or during cryoablation (n =13). The AV conduction was restored within seconds after thawing. No permanent AV block was reported during the follow-up period of 672±380 (median: 588 days).

Two procedure-related complications occurred. One patient developed a small pneumothorax after catheterization of the subclavian vein and the other a pseudoaneurysm in the groin. Both patients were treated conservatively and recovered completely.

Predictors of recurrence

Recurrence was more likely in patients with transient procedure-related AV block (4/18, 22%) compared with those without transient AV block (12/294, 4%; $P < 0.001$). The recurrence rate in patients with residual dual AV nodal pathway post-ablation was 9% (11/123) compared with 4% (7/189) in those with complete block of slow pathway conduction ($P = 0.05$). Furthermore, AVNRT recurrence was associated with a trend towards a longer procedure time ($P = 0.058$).

Conclusion

Cryoablation of AVNRT can be performed with a high acute success rate and a reasonable recurrence rate at long-term follow-up. Additionally, further reduction of the recurrence rate may be achieved with complete elimination of slow pathway as endpoint compared with residual slow pathway conduction.

Study II

Cryoablation of superoparaseptal and septal accessory pathways: a single center experience

Aim

To investigate the clinical usefulness of cryomapping for ablation of perinodal accessory pathways and evaluate the acute and long-term results of transvenous cryoablation of septal and superoparaseptal accessory pathways.

Results

Efficacy

Acute procedural success was achieved in 26 out of 27 patients (96%). After a mean follow-up of 956±511 days, seven patients (27%) had recurrences. Of these seven, 5 (71%) underwent a second successful cryoablation. No further recurrences were seen during 786 ± 484 days in the five patients with a redo procedure. The final success rate was 89% (24 out of 27) (Figure 9).

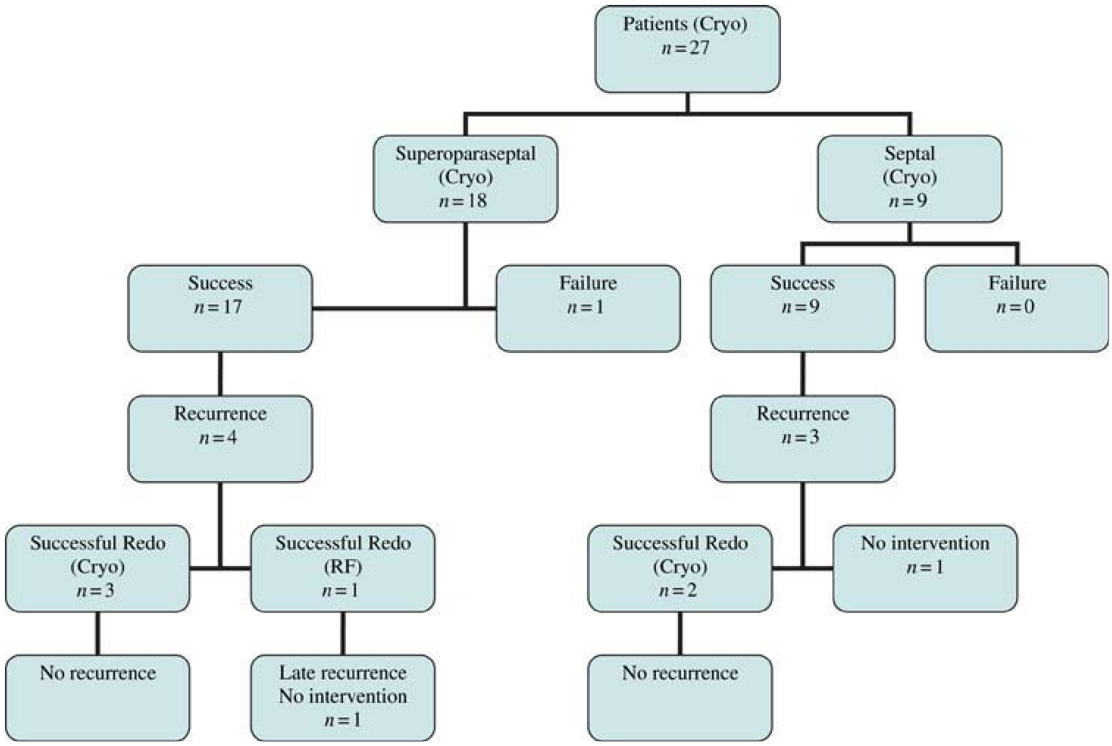

Figure 9. *Flow chart of success and recurrence rates of all ablated patients.*

Total procedure and fluoroscopy time was 163±61 and 30±22 minutes, respectively. The procedural characteristics are summarized in Table 2.

Table 2 *Procedural characteristics*

Substrate	N.	Cryo success	Procedural time (min) Median (range)	Fluoroscopy time (min) Median (range)	Cryo-duration (sec) Median (range)	Recurrence rate (%)
All AP	**27**	**26 (96%)**	**150(70-330)**	**21 (6-81)**	**450 (240-2464)**	**7/26=27%**
Superoparaseptal	18	17	150(80-330)	20(6-80)	401 (240-2464)	4/17(23%)
Septal	9	9	165(70-220)	30 (7-81)	480 (240-1031)	3/9 (33%)

Safety

No patient showed prolongation of the AH interval during cryomapping. However, despite negative cryomapping, two patients, one with a superoparaseptal and the other with a septal located AP, developed transient 2^{nd} degree AV block during cryoablation that lasted 10 and 25 seconds, respectively. No permanent PR interval prolongation was observed at long-term follow-up.

Predictors of recurrence

Compared to those without mechanical block (5/20, 25%; p = 0.006), recurrence was more likely in patients with catheter-induced transient AP block (6/7, 86%) due to catheter manipulation. Furthermore, recurrence rate was higher in those who had a previous RF ablation attempt (p=0.03).

Conclusion

Cryoablation is a safe and effective alternative therapy for superoparaseptal and septal APs. Procedure-related mechanical AP block predicts a higher recurrence rate.

Study III

Safety and efficacy of cryoablation of atrial tachycardia with high risk of ablation-related injuries

Aim

To study the safety and efficacy of cryoablation of atrial tachycardia with high risk of ablation-related injuries. The atrial tachycardia foci originated from the para-hisian area, the vicinity of the sinus node, and the crista terminalis adjacent to the phrenic nerve.

Results

Efficacy

Acute procedural success was achieved in 25 of 26 patients (96%). Patients were followed up for a mean of 493±258 days. Three patients (12%) had late recurrences. Two of these underwent a second successful cryoablation. No further recurrences were seen during 383±53 days in the two patients who had a redo procedure, giving a total success rate of 92%.

Total procedure and fluoroscopy time were 197±47 and 26±18 min, respectively.

Safety

No patient showed prolongation of the AH interval during cryomapping. One patient had transient AH prolongation during cryoablation. No impairment of SN function was observed.

In a total of 28 procedures, two patients developed phrenic nerve palsy during cryoablation of ATs along the lateral right atrium. In one case, the palsy completely recovered within one day, and in the one case it fully recovered after five months.

Conclusion

Cryoablation of high-risk-located AT foci is a safe and effective alternative to RF therapy.

Study IV

Cryothermal versus Radiofrequency Ablation as Atrial Flutter Therapy: A Randomized Comparison

Aim

To compare cryoablation and radiofrequency ablation in the treatment of CTI-depenent atrial flutter with emphasis on clinical success, safety and procedure-related pain.

Results

Screening

A total of 565 patients with a diagnosis of AFL were screened for the study. Of these patients, 153 met all inclusion criteria and were enrolled and assigned to RF (n=75) or Cryo (n=78). A great majority of excluded patients (n=315) did not meet the inclusion criteria: No ECG documentation of AFL (n= 49), procedure in general anesthesia (n= 7); re-do-procedure (n= 60); unable to follow up due to referrals from other counties (n= 51); AFL ablation in association with AT, WPW syndrome, AVNRT and His ablation (n= 37); predominant atrial fibrillation (n= 98); refused or inability to consent (n= 13); and others (n= 97).

Two patients in the RF group were excluded from the analysis due to demonstration of atrial tachycardia during the index procedure. No patient was lost during follow-up. The clinical characteristics are given in Table 3.

Table 3 *Baseline patient characteristics*

	RF	Cryo	*P-value*
Patients (n.)	75	78	
Gender, male	59 (79%)	71 (91%)	*0.54*
Age (y)	65(34/82)	65(36/82)	*0.94*
History of atrial fibrillation	35 (47%)	43 (55%)	*0.44*
Cardiovascular disease	37 (49%)	49 (63%)	*0.12*
Arterial hypertension	19 (25%)	31 (39%)	*0.08*
CAD*	5 (7%)	12 (15%)	*0.46*
Congestive Heart failure	9 (12%)	8 (10%)	*0.82*
Diabetes mellitus	6 (8%)	4 (5%)	*0.75*
Echo			
LVEF†	55 (25-55)	55 (15-55)	*0.47*
LVEF $\leq$ 40%	6 (8%)	9 (11%)	*0.72*
LA-dimension short axis (mm)	40(27-62)	41(30-56)	*0.27*

Values are given as number, percentage or median (range)
*CAD, Coronary Artery Disease
†LVEF, Left Ventricular Ejection Fraction

Efficacy (primary endpoint)

Acute ablation success was achieved in 71 of 75 patients (95%) in the RF group and in 72 of 78 patients (92%) in the Cryo group (p=0.58). The success rate after the six-month follow-up was 92% (69/75) for RF and 86% (67/78) for Cryo; p=0.28, (Figure 10).

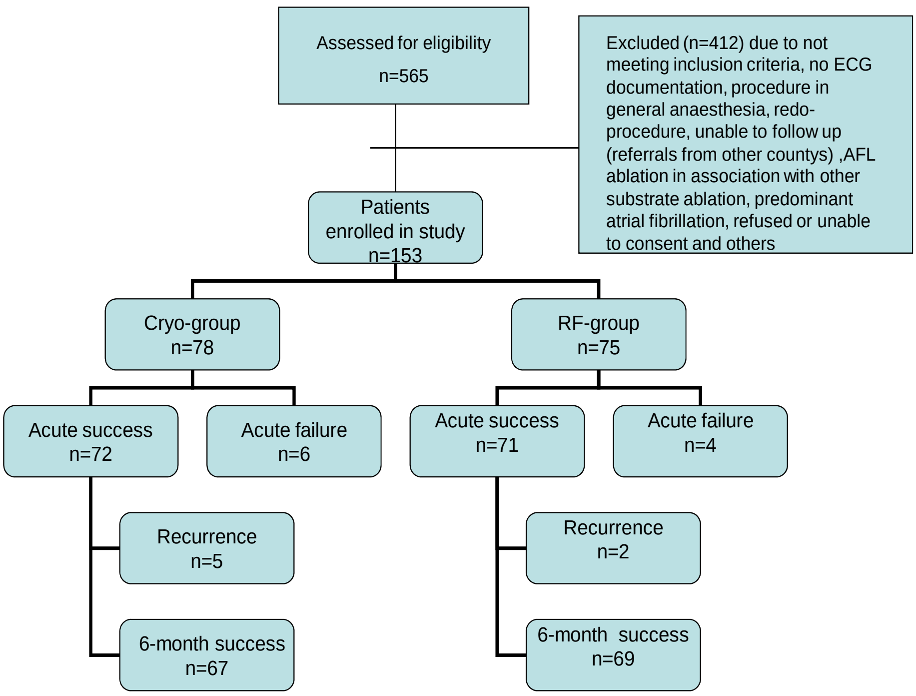

Figure 10. *Flowchart of acute procedural and six-months follow-up results.*

Safety (secondary endpoint)
Pain Perception

The pain perception was markedly higher for RF than Cryo both regarding the mean and peak pain during ablation. Furthermore, there was a significant difference in need of intravenous analgesic and sedative medication with lower doses required for Cryo (Table 4).

Procedural characteristics

Procedural time was on average 36 minutes longer in the Cryo group; $p < 0.001$. The median conduction time delay during pacing from proximal CS to the low lateral right atrium measured 30 minutes after successful ablation was 140 ms (92-230 ms) in the RF group and 141 ms (90-212 ms) in the Cryo group. The corresponding intervals for pacing from the low lateral right atrium was 146 ms (100-232 ms) for RF and 144 ms (105-200 ms) for Cryo (Table 4).

Table 4 *Procedural characteristics*

	RF	Cryo	*P-value*
Patients (*n*.)	75	78	
Fluroscopy time	22±15	18±12	*0.06*
Procedural time	116±41	152±54	*< 0.001*
Cumulative energy (sec)	72495	214617	*< 0.001*
Pain perception (VAS*peak*)	6.8±2.4	1.8±2.2	*< 0.001*
Pain perception (VAS*average*)	4.6±2.0	0.7±1.2	*< 0.001*
Morphine dose (mg)	11.6±6.0	5.4±3.0	*< 0.001*
Diazepam dose (mg)	8.7±5.4	6.9±3.8	*0.01*
AA*cs* pace	143±29	145±25	*0.87*
AA*lat* pace	145±27	146±21	*0.79*

Values are given as number (percentage) or as mean±SD. VAS = visual analog scale 0-10; SR = sinus rhythm; AFL = atrial flutter; AF = atrial fibrillation.
AA*cs* pace = Conduction time delay during pacing from proximal coronary sinus to the low lateral right atrium. AA*lat* pace = Conduction time delay during pacing from the low lateral right atrium to the proximal coronary sinus

Complications

The only observed clinical complication was a groin hematoma in one patient in the RF group. No late complications were observed in any group.

Conclusions

In this large prospective, randomized, single center study, we show that cryoablation of isthmus-dependent atrial flutter is not inferior to RF but with significantly less procedure-related pain.

GENERAL DISCUSSION

In this thesis, we investigated the safety and efficacy of cryoablation in different supraventricular tachyarrhythmias, in order to better understand the capabilities and limitations of this novel technology in clinical practice.

RF-ablation of most arrhythmic substrates has been shown to be a safe and an effective treatment; however, RF energy is associated with several disadvantages, such as the operator`s difficulty in predicting the result of the lesion before producing permanent damage to the tissue because the electrophysiologic effect appears as the lesion is forming. This is particularly important when ablation is performed in the vicinity of the AV node, His bundle, coronary arteries, the phrenic nerves, or the sinus node, where a significant risk for damage to these structures has been reported. RF ablation is also associated with significant pain perception during lesion delivery in ablation of CTI- dependent atrial flutter.

Cryoenergy has been widely used in the past for open heart surgery ablation of arrhythmogenic substrates [31, 36-37, 40]. Recently, this technique has been adapted to transvenous catheter ablation. Cryoenergy enables prediction of the effectiveness and safety of the lesion. First, a transient and reversible loss of function can be created (cryomapping) before additional deep cooling creates an irreversible lesion (cryoablation); and second, the catheter tip adheres to the endocardial tissue and therefore the risk of dislodgment during the procedure is avoided [23, 33]. Based on these considerations, use of cryoenergy should be particularly advantageous when ablation is performed in proximity to critical structures.

Clinical Advantages of Cryothermal Energy

The unique biophysical properties of cryothermal energy have a number of advantages, that can overcome the important limitations of RF energy. The results presented in this thesis show that cryoablation is an effective and safe therapy for several types of cardiac arrhythmias such as AVNRT, high risk located AT, perinodal AVRT, and atrial flutter.

Efficacy

Cryoablation in AVNRT

In Study I, it is shown that acute procedural success in AVNRT with cryoablation was achieved in 99% of patients with a recurrence rate of 5.8% during a mean follow-up period of 22 months and without any ablation-related long-term complications. Since the early 1990s, multiple studies have shown that the efficacy of RF ablation is extremely high in the treatment of AVNRT with primary success rates ranging from 96 to 100% and with late recurrence rates from 1 to 6.9% [1, 78–80]. Since in most series the reported results were not based on intention-to-treat analysis, the true procedural efficacy of RF-ablation may be slightly lower. Although cryoablation of AVNRT has been suggested as a safer alternative to RF energy, there is a large variation in the published success rates concerning cryoablation for AVNRT [9, 23, 50, 81-84]. A possible explanation for the inferior effectiveness in earlier studies is the use of a 4-mm tip cryoablation catheter, whereas we exclusively used a 6-mm tip in our study [96]. In addition, the high success rate in our report may be related to the approach with systematic cryomapping and ablating only at positions with prompt effect on the arrhythmia substrate.

Cryo vs. RF

In contrast to RF ablation, no junctional rhythm is observed during cryoablation of the slow pathway, but the method offers several other parameters to predict the potential effectiveness of the ablation site, such as disappearance of dual AV-node physiology and non-inducibility of the AVNRT during cryomapping. Sinus rhythm usually persists throughout cryoablation of the slow pathway which allows constant monitoring of the AV conduction as well as assessment of the presence or absence of slow pathway function by programmed stimulation during cryoablation [85].

Because the acute and long-term success rate of RF-ablation in treatment of AVNRT is extremely high, it is difficult to conceive an alternative ablation method that is significantly more effective. The main reason to consider cryoablation is to improve the safety profile without sacrificing the effectiveness. Three randomized prospective trials have addressed the question of whether cryoablation of AVNRT is equivalent to RF-ablation. In one of these trials [50], no significant difference was found in acute or long-term efficacy between cryo- and RF-ablation. However, the two other studies [49, 84] suggested superior long-term efficacy of RF-ablation compared to cryoablation. Still, as one can see in table 5, the effectiveness of both technologies is extremely high both regarding acute and long-term success. The combined results of all studies in Table 5 show a recurrence rate of 7.8% with cryo and 3.4% with RF.

Table 5. *Comparison of acute success and recurrence rate in published studies using Cryoablation versus RF in AVNRT*

	Patients(n)		**Acute Success (%)**		**Recurrences (%)**		**Persistent AV Block (n)**	
Study	**CRYO**	**RF**	**CRYO**	**RF**	**CRYO**	**RF**	**CRYO**	**RF**
Kimman et al. (2004) 50	30	33	93	91	10	9	0	0
Zrenner et al. (2004) 49	100	100	97	98	8	1	0	1
Gupta et al. (2006) 86	71	71	85	97	19.8	5.6	0	1
Collins et al. (2006) 87	57	60	95	100	8	2	0	0
Avari et al. (2008) 88	38	42	97	95	2	2	0	2
Chan et al. (2009) 89	80	80	97.5	95	9	1.3	0	2
Schwagten et al.(2010) 90	144	130	97	95	7.5	6.5	0	2
Opet et al. (2010) 83	123	149	93	95	10	3	0	1
Deisenhofer et al. (2010) 84	251	258	96.8	98.4	9.4	4.4	0	3
Total	**894**	**923**	**94**	**96**	**7.8**	**3.4**	**0**	**12**

Residual dual AV nodal pathway

The significance of residual dual AV-nodal pathway in predicting late recurrence of AVNRT is still inconclusive. Gupta et al. [86] showed a significant higher recurrence rate following successful cryotherapy, if an echo beat was still inducible after ablation compared with complete slow pathway block, whereas Khairy et al. [91] did not find that a residual dual pathway conduction is a predictor for higher recurrence rate. In our study that included a large patient population, complete abolishment of the slow pathway was not intentional, but we found a borderline significant relationship between recurrence rate and the residual slow pathway conduction. This may suggest that the ideal endpoint of cryotherapy in slow–fast AVNRT should be defined as complete abolishment of the slow pathway conduction if the circumstances are suitable for repeated energy delivery.

Cryoablation in high risk located AVRT

In study II, acute procedural success with cryoablation in superoparaseptal and septal accessory pathways was achieved in 96% (26/27) of patients with a recurrence rate of 27% (7/26) during a median follow-up period of 33 months and without any ablation related long-term complications. Importantly, 71% (5/7) of patients underwent a new successful cryoablation, giving a total success rate of 89% after a second cryoablation procedure. Thus, acute and long-term results were similar to those described for RF but without any complications.

The superoparaseptal and septal APs account for only a minority of all APs and comprised only 6% of all APs ablated during the study period (five years) in our center. This may explain the fact that published data regarding the usefulness of cryoablation for the treatment of perinodal APs is still limited [42,92].

Previous reports of RF-ablation of superoparaseptal and septal APs have shown primary success rates ranging from 71 to 100%, with recurrence rates of 15 to 25% and the risk for AV block varying between 0 and 36% [54-55, 93-95]. RF-ablation of perinodal APs has an increased risk of inadvertent damage of the normal conduction system. This knowledge may influence both the patient's willingness to undergo an ablation procedure and the electrophysiologist's decision to complete the procedure when the risk for complication is perceived high. The use of low-energy RF has been recommended to reduce the risk for AV block [56,95], but this technique is associated with a higher incidence of recurrences [56, 97-98].

Accelerated junctional rhythm during RF energy delivery has been reported in up to 5% of patients undergoing ablation of septal or superoparaseptal APs [100]. Cryomapping/ablation does not result in an accelerated junctional rhythm. Importantly, the absence of this rhythm during cryothermal therapy does not mean that the risk for damage to the AV node or His bundle is absent. Our data in study II, demonstrate that AV block may develop during cryoablation despite negative cryomapping. Therefore, our results underline the importance of close monitoring of AV conduction during the entire cryoablation procedure.

Catheter-induced AP block

In study II, catheter-induced trauma resulted in transient mechanical AP block in 11 out of 27 (41%) patients. The high incidence of catheter-induced trauma caused by the cryocatheter in this study is comparable with previous studies, that used different RF catheters [98,100]. Belhassen et al. reported as much as 38% block of AP conduction in one or both directions due to catheter manipulation in right superoparaseptal (anteroseptal) APs [100]. Haissaguerre and co-workers reported transient mechanical block in right superoparaseptal (anteroseptal) APs in 42% [98]. The superficial subendocardial location of perinodal APs, particularly the right superoparaseptal APs, makes these pathways susceptible to mechanical trauma [98,100]. Our experience shows a less favorable late outcome with significantly higher recurrence in patients with catheter-induced AP block compared to those without block. This is consistent with previous observations, suggesting that cryothermal energy was actually delivered at a location different than where the mechanical block was encountered [92]. In contrast to the RF catheter, the tip of the cryoablation catheter adheres to the endocardium during energy delivery and does not move, whereas the tip of an RF ablation catheter moves across the endocardial surface with each heartbeat, increasing the affected surface area. Generally, accessory pathways are very small discrete structures. RF-ablation of such structures may be possible even when the catheter tip is not precisely on the target. As the cryolesions are more focused due to cryoadherence, it is important that the cryo-catheter tip is located exactly on the target to achieve success [23].

Cryoablation in high risk located AT

Acute procedural success was achieved in 96% (25/26) of patients in study III, using cryoablation in AT foci originating from the vicinity of the AV node, the sinus node, and the phrenic nerve. The recurrence rate was 12% (3/25) during a mean follow up period of 16 months. No further recurrences were seen in 67% (2/3) of patients who had a redo-procedure, giving a total success rate of 92%, which is similar to that of RF-ablation but without any permanent complications.

RF-ablation as a treatment of AT has a primary success rates ranging from 80 to 100%, with late recurrence rates up to 20% and complication rates up to 12% [55, 101-106]. Although cryothermal therapy has emerged as an alternative to RF-ablation in the treatment of AVNRT [23, 27] and perinodal accessory pathways [42, 92], very few data have been published regarding the use of cryoablation for the treatment of AT. Data are limited to a small number of patients or case reports [107-108]. The effectiveness profile in study III supports the conclusion that cryoablation enables effective treatment in high-risk-located AT that otherwise might remain untreated.

Cryoablation in atrial flutter

In study IV, we conducted the Cryothermal versus Radiofrequency Ablation as Atrial Flutter Therapy (CRAFT), which was a non-inferiority and an appropriately powered randomized, controlled study to compare systematically cryo with RF for treatment of CTI-dependent AFL with emphasis on clinical success, safety, and procedure-related pain. The results presented in this study show an acute ablation success of 95% in the RF group and of 92% in the cryo group (NS), with achievement of BCB as the predefined ablation endpoint. In our study the long-term success after the six-month follow-up was 92% for RF and 86% for cryo (NS), results that are consistent with recently published studies [66, 68-69, 110-112]. Previous studies of cryoablation in atrial flutter have shown acute success rates between 56 and 100% and recurrence rates from 0 to 20% (Table 6).

Table 6. Comparison of acute success and recurrence rate in published studies using cryoablation with 8-mm catheter tip in atrial flutter

Study	Patients (n)	Acute Success (%)	Mean Follow-up (months)	Symptom Recurrences (%)
Montenero et al. (2005) [110]	77	96	6	0
Collins et al. (2006) [69]	14	93	15	14
Kuniss et al. (2006) [113]	50	100	1	10
Wang et al. (2007) [114]	9	100	22	0
Thornton et al. (2008) [115]	32	69	4	0
Malmborg et al. (2009) [116]	20	56	15	20
Kuniss et al. (2009) [117]	90	89	3	11

Kuniss et al. [117] recently found that persistence of BCB in patients treated with cryoablation reinvestigated by a new electrophysiological study after three months was inferior to that of patients treated with RF. Despite this discrepancy, the acute and long-term clinical success in that study was comparable with our results.

Safety

Reversible effects of cryoablation

The principle drawback to RF-ablation in AVNRT and, perinodal AVRT/AT is the risk of irreversible AV block during the procedure, requiring implantation of a permanent pacemaker [49,54-55,85,87,89-91,93-95]. This complication is particularly devastating in young individuals who may be faced with many decades of pacemaker follow-up, generator changes, and potential lead complications.

One of the most important characteristics of cryothermal energy is the ability to create reversible electrophysiologic effects (cryomapping).

Dubuc and co-workers showed first in dogs, that complete AV nodal conduction block could be created by cooling tissue down to between -20ºC and -30ºC and then completely recovered after re-warming. Gross and microscopic examinations could not identify any evidence of important tissue injury in the AV junction region. These authors further determined that a temperature of approximately -30°C is required to interrupt the tissue electrophysiologic properties, that it takes approximately 10 to 20 seconds of cooling to achieve this temperature, and that re-warming with restoration of AV conduction takes up to 20 seconds [20]. The feasibility of cryomapping in humans was also later demonstrated by Dubuc and co-workers [22]. They were able to demonstrate that reversible AV block could be induced by cooling the tissue of the AV node to -30ºC, and that further cooling at the site of successful AV block to -60ºC would result in permanent AV node ablation. Finally, several clinical studies have validated the concept of cryomapping on larger clinical scale [23, 49-50].

The broad temperature window between reversible electrophysiologic effects and irreversible tissue damage, seen with cryothermal energy, is in strong contrast to RF-related hyperthermal injury [11]. During RF energy delivery, hyperthermal tissue injury leading to reversible loss of excitability occurs at a median tissue temperature of 48ºC (range 42.7ºC to 51.3ºC), whereas irreversible tissue destruction and irreversible loss of excitability typically occurs at tissue temperatures greater than 50ºC [11, 52]. The "window of temperature" for RF is, in fact, so narrow that it is meaningless to attempt creating reversible lesions.

The irreversibility of RF lesions becomes a concern when ablations are performed in close proximity to structures critical for normal conduction, e.g., superoparaseptal, septal AP, or the slow pathway region of the AV node. This fact results in a small but clinically important risk of permanent AV nodal conduction block in conjunction with perinodal ablation. Cryothermal energy in these cases allows the operator to "test" the electrophysiologic effects of a lesion before it is made permanent and to abort ablation at a site with potentially harmful effects (Figure 11).

In Studies I-III, we found that cryomapping was an extremely useful tool as far as perinodal substrates were targeted for ablation. No patient developed permanent AV block. These results are in line with other studies of cryothermal ablation [49-50, 84-85, 87-91] and are in contrast to RF studies reporting AV block in over 1% for fast pathway ablation (5,3%) or slow pathway ablation (1-2%) of AVNRT in highly experienced centers [1, 12].

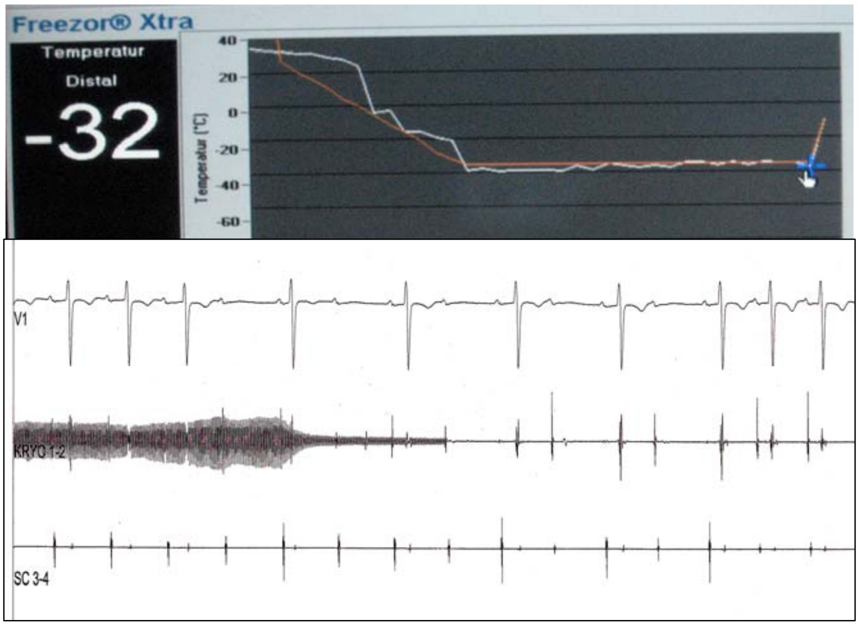

Figure 11. *The reversible effect of cryomapping on the compact AV node. After onset of cryomapping at a temperature of -30ºC for 36 seconds, 2:1 AV block occurred. On rewarming, the normal AV conduction was immediately resumed.*

The risk of creating permanent AV-block has also been described for ablation of atrial tachycardias in the triangle of Koch (12,5%) [53] and for AP ablation in the perinodal regions (range 0 to 36%) [54-55, 57, 93-95].

Transient AV block

In study I, 5% of the patients developed transient second- or third-degree AV block either during cryomapping or during cryoablation. A majority of these patients were followed long term by ECG Holter monitoring without any indication of delayed AV block development and no permanent AV conduction disturbances were seen. Therefore, it seems that transient AV block during cryomapping or cryoablation is a benign phenomenon with no risk for long-term complications. This is in contrast to RF, where even very short RF applications may be sufficient to create immediate or late AV block [12, 84]. Of note, studies I-III included several patients in particular young ones, who had previously been subjected to an attempt for RF ablation that was aborted due to concern of a potential risk for AV block. However, these patients subsequently underwent successful cryoablation without any complications. In published reports of RF ablation of perinodal substrates, success rates are calculated only for those individuals who actually underwent an ablation. These reports do not specify how many patients with AVNRT who had undergone an EP study but in whom ablation was never attempted due to an estimated high risk of AV block [1,119-120]. It is Thus likely that a certain number of patients will never be referred for curative treatment of their arrhythmia due to the perceived risk of AV-node injury if RF ablation is the only treatment option.

As a consequence, these “safety-features" of cryoablation make it possible for less experienced electrophysiologists to perform AVNRT ablation earlier in their training and for low-volume EP laboratories to keep complication rates low.

In a recent large series of more than 1300 cryoablation procedures in our center, we did not experience any single case of acute permanent AV block and no late AV block in the patients with transient AV block after long-term follow-up [121]. Although this study had no control arm with RF-ablation, assuming a low complication rate of AV block of 1% during RF procedures, we might have avoided a considerable number of pacemaker implants in a relatively young population with a median age of 51 years [121].

Cryoablation of substrates near the phrenic nerve

RF ablation of arrhythmia substrates originating in the vicinity of the phrenic nerve carries an increased risk of irreversible phrenic nerve palsy [53,106]. Cryoablation is well suited for ablation in the region close to the phrenic nerve.

Study III shows high long-term success rate of cryoablation in atrial tachycardia originating in the proximity of the phrenic nerve; along the lateral right atrium without any sign of persistent phrenic nerve palsy.

The premise for cryoablation procedures to avoid phrenic nerve injury involves continuous pacing of the phrenic nerve with high output (10mA), from the ablation catheter proximal to ablation site. Capture of the right hemidiaphragm should be monitored, e.g., by fluoroscopy. At the location of interest, cryomapping at - 30°C is perfomed for 30-40 seconds. If this does not lead to cessation of diaphragmatic stimulation, cryoablation with a goal temperature of -80ºC for 240 s is applied. However, despite negative cryomapping two patients in study III developed phrenic nerve palsy during cryoablation of ATs along the lateral right atrium. In one case, the palsy completely recovered within one day, and in a seconds case it fully recovered after five months. It is, therefore important to maintain careful monitoring for phrenic nerve function during the entire ablation application. In contrast to RF, phrenic nerve palsy caused by cryoablation seems to recover more quickly and completely than the palsy caused by RF-therapy [122-123].

Cryoablation of substrate near the sinus node

In humans, the sinus node is a spindle-shaped structure, 10- to 20-mm long and 2-to 3-mm wide and thick. It lies less than 1 mm from the epicardial surface and laterally in the RA sulcus terminalis at the junction of the SVC and right atrium. This anatomical location may to some extent explain why RF-ablation in this region carries an increased risk of complications such as sinus node dysfunction and phrenic nerve palsy [106].

In addition, RF-ablation may cause narrowing of the SVC-RA junction [124], which may lead to acute or late superior vena cava (SVC) syndrome with irreversible SVC stenosis [106, 125-126].

Our results show that cryoablation can be performed with a high long-term success rate and a low complication risk in patients with AT in the vicinity of the sinus node due to the cryomapping technique as well as cryoadhesion with excellent catheter stability.

Improved catheter stability with cryoablation

Cryoadhesion is an advantageous characteristic of cryothermal therapy which gives an increased catheter stability during lesion creation as the heat-extraction process binds the catheter tip firmly to the targeted tissue. Clinically, fast temperature decline during cooling reflects good contact with the endocardium, whereas inability to quickly achieve maximal negative temperatures at the catheter tip indicates poor contact. With RF energy delivery, the catheter must be held in place by the operator to ensure adequate delivery of power and subsequent tissue heating to the region to obtain the desired electrophysiologic effect. Additionally, cardiac motion during RF ablation creates a brushing effect of the catheter on the cardiac tissue, that may make the lesion less precise and may increase the risk of undesired damage to adjacent structures, particularly near critical conduction tissue.

Cryothermal energy is associated with ice ball formation at the tip of the catheter and adherence of the catheter to the endocardial surface [20-21]. This effectively eliminates the possibility of catheter dislodgement from the desired location once ice ball formation has occurred. The increased stability of the cryocatheter may also explain the more focal nature of cryothermal energy lesion, which has been investigated in Studies I-III. No further fluoroscopy is needed after cryoadhesion occurs. In study IV, we found a trend toward shorter fluoroscopy time associated with cryoablation in AFL compared to RF, which may be related to the feature of cryoadherence during applications as earlier discussed [50]. However, in the same study the procedure time was longer for the cryo group as the cryo energy requires longer time for lesion formation point by point [46, 127].

Furthermore, the increased catheter stability after ice-ball formation allows programmed stimulation to be used during the ablation procedure, to confirm the clinical effect of the lesion, without any concern for catheter dislodgement (study I-IV).

Decreased thrombogenicity with cryoablation

Another characteristic of cryothermal energy is the decreased thrombogenicity compared with RF [25, 45]. Whereas hyperthermic energy results in coagulation and tissue necrosis, [11, 57] cryothermal energy preserves tissue architecture with minimal thrombus formation [24-25]. The overall risk of thromboembolic complications related to RF therapy ranges from 0.6% to 0.8% [12-14, 58]. However, this risk increases from 1.8% to 2.0% when RF is performed in systemic cardiac chambers and can reach as high as 2.8% when it is performed for left ventricular VT [12, 14].

Although some investigators have suggested that the thromboembolic risk is related to the presence of intracardiac catheters rather than delivery of RF energy, there is evidence to the contrary. Manolis et al. showed that D-dimer levels increased two-fold after a diagnostic electrophysiologic study (EP study) compared to baseline, but after ablation with RF energy D-dimer increased six-fold [70]. Although this study was underpowered to demonstrate a difference in clinical events, there is clearly a thrombogenic effect associated with the delivery of RF energy.

Epstein and colleagues [13] reported an increased thrombous risk associated with prolonged RF duration, further supporting the association of RF energy with increased thrombogenicity. The use of intravenous heparin protocols and post procedure antithrombotic treatment as well as temperature feedback to control RF current delivery and monitoring for impedance rise have not been shown to successfully eliminate thromboembolic risk [13-14, 59-61].

Cryothermal energy lesions cause tissue destruction in an entirely different manner and have biophysical properties that make these lesions significantly less thrombogenic, or even clinically non-thrombogenic [20, 24-25]. In our studies (I-IV) with more than 440 cryoprocedures, we did not find any clinical event related to increased thrombogenicity.

Minimal risk to vascular structures in cryoablation

Delivery of RF lesions within venous structures such as the coronary sinus or pulmonary vein (PV) is associated with a risk of endoluminal thrombosis, venous stenosis, perforation possibly leading to tamponade, or damage to adjacent arterial structures [15, 18-19, 58]. Ablation of septal AVRT and typical or atypical AVNRTs occasionally require ablation within venous structures, such as the coronary sinus. RF ablation of CTI-dependent AFL may injure the right coronary artery. Furthermore, PV ablation in AF require the delivery of ablation lesion at the ostia or adjacent to the PVs. Delivery of RF lesions is associated with a known risk of PV stenosis [18-19]. Cryothermal energy ablation has proved to be less harmful to vascular structures. Cryoablation effects on the arteries depend on the extent and depth of cryolesion into arterial walls. In cases where conventional transvenous cryocatheters (-80ºC) are placed adjacent to the artery, usually no major damage or occlusion of the artery could be found. However, coronary spasm has been reported clinically with ablation of CTI dependent AFL [129]. No thrombosis of the arteries has been demonstrated, when -80º C freezing with conventional size catheters is applied next to the artery. Intimal hyperplasia is a primary and non-specific vessel response to the injury and is frequently observed after cryo injury to coronary arteries [130-132].

There are no systematic experimental studies with regard to freezing effects on SVC, but, at least clinically, no cases of superior vena cava thrombosis or stenosis have been reported with cryo. Because vein stenosis after cryoapplication has not been reported in smaller diameter veins, such as pulmonary veins, it is highly unlikely that cryoablation can cause superior vena caval stenosis [64-65].

Catheter ablation within the coronary sinus using cryothermal energy has been investigated in animals by Skanes et al. and Yagi et al. [62-63]. Both groups were unable to demonstrate thrombus formation or damage to the coronary sinus and concluded that this technique is safe and feasible. Bredikis and co-workers used cryoablation to ablate posteroseptal and left paraseptal accessory pathways through the coronary sinus, and no acute thrombosis was observed in humans [132]. In studies I-IV, no damage to coronary vessels was seen.

Less pain perception with cryoablation

RF-therapy is associated with significant perception of pain during lesion delivery, compared with similar ablations using cryothermal energy [68]. Afferent pain fibers in the myocardium are frozen, instead of being thermally stimulated. Collins and co-workers showed improved pain score in patients undergoing cryoablation for atrial flutter compared with RF ablation [69]. In study IV RF ablation caused significantly more pain compared to cryoablation both in terms of average and peak pain perception as estimated by the VAS scale. In fact, cryoablation was perceived as nearly pain free by the patients.

Use of analgesic and sedative medication was compared in this randomized study, with significant lower dosages of these medications for cryo. A lower requirement for analgesia and less discomfort in patients undergoing cryoablation have previously been described and our results reinforce these findings [68, 115]. To reduce patient discomfort, some centers offer general anesthesia during RF-ablation of AFL, which obviously can be obviated by the use of cryotherapy. Cryoablation may also be useful for patients who do not tolerate conscious sedation well. It can be speculated that pain-related deep breathing or body movement may increase the risk for complications using RF ablation. However, in this study, no complication occurred in any treatment groups.

Disadvantages of cryoablation

Although there are several advantages to using cryoablation in selected cardiac arrhythmias, there are also disadvantages. The currently available cryoablation catheters are stiffer than the comparable RF catheters. For this reason, there is a greater risk of mechanical injury to the arrhythmia substrates using cryoablation. This may contribute to the slightly lower success rate using cryoablation. Because the cryo-catheter is also less flexible than RF catheters, it is more difficult to make more advanced maneuvers such as loops. In addition, the current catheters are unidirectional, which may require the use of preformed sheaths to aid catheter placement. With cryoablation, there may only be a transient effect if the ablation target in a zone of cells is only temporarily affected by cooling. This may result in the need for a longer waiting period after an ablation. Lastly, the cryoablation catheters are more expensive as they are more complicated and must be built by hand.

Summary

Cryothermal energy is a useful, painless and preferable tool in certain clinical scenarios. These may include cases in which the risk of AV block is high (superoparaseptal and septal APs, or parahisian AT) or moderate (AVNRT or posteroseptal APs) during RF ablation. They may also include cases in which there is a need to ablate in close proximity to phrenic nerve, sinus node, venous structures, coronary artery, or CTI. There are also clinical scenarios in which RF is the energy source of choice, such as left lateral AP. Therefore, cryothermal energy should not be considered as a technology to replace RF, but rather as a complementary tool to RF that can treat a broad spectrum of clinical arrhythmias with a high level of efficacy and few complications.

CONCLUSIONS

- Cryoablation of AVNRT can be performed with a high acute success rate and a reasonably low recurrence rate at long-term follow-up without any risk for permanent AV block.
- Transient AV block during cryoablation of AVNRT is most likely a benign phenomenon.
- Further reduction of the recurrence rate may be achieved with complete elimination of slow pathway as endpoint in cryoablation of AVNRT.
- Cryoablation is a safe and effective therapy for superoparaseptal and septal APs.
- Procedure-related mechanical AP block of superoparaseptal and septal APs predicts a higher recurrence rate.
- Cryoablation of atrial tachycardia originating from the vicinity of the AV node, sinus node, and phrenic nerves is a safe and effective alternative to RF therapy.
- Cryoablation of isthmus-dependent atrial flutter is as effective as RF but with less procedure-related pain.

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