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Kryoballon-Ablation von Vorhofflimmern: Klinische Effektivität und Entwicklung von Sicherheitsstrategien zur Vermeidung von Komplikationen

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Inhaltsverzeichnis

1. Einleitung

1.1. Epidemiologie und Pathophysiologie von Vorhofflimmern

Vorhofflimmern (VHF) ist die häufigste anhaltende Rhythmusstörung beim Erwachsenen mit weltweit steigender Prävalenz (1). Schätzungen zufolge werden bis 2060 annähernd 18 Millionen Patienten in Europa betroffen sein (2). Vorhofflimmern ist mit einer erhöhten Mortalität, sowie einer erhöhten Rate von Schlaganfällen, Herzinsuffizienz und anderen kardiovaskulären Erkrankungen assoziiert (3). Symptome und Komplikationen der Rhythmusstörung führen zu einer messbaren Reduktion der Lebensqualität und interventionelle Maßnahmen zur Rhythmuskontrolle verbessern die Lebensqualität im Langzeitverlauf (4). Die Zahl der VHF-assoziierten Hospitalisationen nimmt zu mit entsprechend steigenden Behandlungskosten (Zunahme um 24% im Zeitraum 2001-2010 in den USA) (5).

In der Pathophysiologie von VHF wirken multiple Faktoren zusammen, mit unterschiedlicher Gewichtung beim einzelnen Patienten. Die Hauptrisikofaktoren für das Auftreten dieser Rhythmusstörung sind Diabetes, Herzinsuffizienz, Übergewicht, koronare Herzerkrankung, Hypertonie, zunehmendes Alter und genetische Prädisposition (6). Diese ätiologischen Faktoren führen zu strukturellen Veränderungen der Vorhöfe, welche das Auftreten von VHF begünstigen. Andererseits führt die Rhythmusstörung selbst zu elektrophysiologischen und strukturellen Vorhofveränderungen, was langfristig zu einer Chronifizierung der Erkrankung führt. Im natürlichen Verlauf schreitet die Rhythmusstörung entsprechend typischerweise über ein Stadium selbstlimitierter Episoden (paroxysmales VHF) zu einem kontinuierlichem Stadium fort (persistierendes VHF).

Elektrophysiologisch ist VHF durch hochfrequente, ungeordnete (fibrillatorische) elektrische Aktivität der Vorhöfe gekennzeichnet, wodurch die mechanische Vorhoffunktion zum Erliegen kommt. Die Aufrechterhaltung der fibrillatorischen Aktivität kann einerseits durch multiple, ohne räumliche Ordnung auftretende und sich selbst erhaltende Depolarisationswellen erklärt werden („multiple wavelet“ Hypothese) (7), andererseits

wurden lokalisierte, hochfrequente Entladungen nachgewiesen, welche in entfernteren Myokardarealen zu fibrillatorischer Aktivität führen (8).

Klinisch führt die hochfrequente elektrische Vorhofaktivität in der Regel zur schnellen, unregelmäßigen Kammerüberleitung mit Palpitationen und variabel ausgeprägten Symptomen einer Herzinsuffizienz. Da die strukturellen Veränderungen der Vorhöfe die Sinusknoten-Region mit einschließen können, kann es nach spontaner Terminierung von VHF zu symptomatischen Pausen bis zum Einsetzen der Sinusknoten-Funktion kommen (Brady-Tachy-Syndrom). Die hochfrequente Vorhofaktivität kann darüber hinaus zur Verzögerung der AV-nodalen Überleitung mit resultierender Bradykardie führen. Werden die Vorhofdepolarisationen normofrequent auf die Kammern übergeleitet, kann die Rhythmusstörung asymptomatisch verlaufen, sofern keine Komplikationen eintreten. Ein pathophysiologischer Faktor in der Assoziation von VHF und embolischen Schlaganfällen bzw. systemischen Thromb-Embolien ist die fehlende atriale Kontraktion mit verminderter Blutflussgeschwindigkeit insbesondere im linken Vorhofohr.

1.2. Therapie von Vorhofflimmern

Die Therapie von VHF umfasst folgende Domänen: 1. die Behandlung akut limitierender Symptome bzw. hämodynamischer Instabilität, 2. die Behandlung prädisponierender Risikofaktoren, 3. die Vermeidung thromb-embolischer Komplikationen durch Risiko-adaptierte orale Antikoagulation, und 4. die langfristige Behandlung von Symptomen durch Erhaltung des Sinus Rhythmus (Rhythmuskontrolle) oder medikamentöse Kontrolle der Kammerfrequenz. Maßgeblich für die grundsätzliche Entscheidung zur Rhythmus- oder Frequenzkontrolle sind individuelle Symptomatik, Begleiterkrankungen, Wirkung und Verträglichkeit von rhythmus- oder frequenzkontrollierenden Medikamenten, sowie das Stadium der Erkrankung. Mit fortlaufender kontinuierlicher Dauer der Rhythmusstörung (ein Jahr und länger) sinkt jedoch die Erfolgsrate therapeutischer Maßnahmen zum Erhalt des Sinus Rhythmus.

Zur Rhythmuskontrolle liegen zwei Therapiemodalitäten vor, die medikamentöse antiarrhythmische Therapie sowie, seit Beginn der 2000er Jahre, die Katheterablation. In mehreren randomisierten Studien konnte hierbei eine Überlegenheit der Katheterablation hinsichtlich erfolgreicher Rhythmuskontrolle nachgewiesen werden (9). Auf Basis dieser Studienergebnisse besteht für die Katheterablation gemäß der aktuellen europäischen Leitlinien eine Klasse I Indikation bei symptomatischem paroxysmalen VHF, eine Klasse IIa Indikation bei symptomatischem persistierenden VHF bei Therapieversagen einer antiarrhythmischen Medikation (10).

1.3 Katheterablation von Vorhofflimmern

Die Grundlage für die interventionelle Behandlung von VHF mittels Katheterablation geht auf Haissaguerre und Mitarbeiter mit der Beobachtung zurück, dass hochfrequente Entladungen aus den atrialen Muskellaschen der proximalen Pulmonalvenen VHF-Episoden auslösen können (8). Solche ektopen Foci konnten durch Radiofrequenzstrom (RFS)-Ablation in den Pulmonalvenen eliminiert werden, was bei einem Teil der Patienten zum Ausbleiben weiterer VHF-Episoden während der Nachbeobachtungszeit führte (8). Bei der RFS-Ablation wird ein Elektrodenkatheter in Kontakt mit dem zu behandelnden Myokardareal gebracht, und anschließend hochfrequenter Wechselstrom angelegt, wobei die im Gewebe entstehende Widerstandswärme zur Hitzekoagulation im Bereich der Katheterspitze führt. Die Anwendung dieses Verfahrens, welches für den endokardialen Einsatz entwickelt wurde, innerhalb dünnwandiger Körpervenen birgt das Risiko klinisch bedeutsamer Pulmonalvenen-Stenosen, sodass die Elimination der Foci zugunsten einer Isolation der gesamten Pulmonalvene verlassen wurde (Pulmonalvenen-Isolation, PVI). Diese wurde zunächst durch selektive Ablation der Muskellaschen am venösen Ostium durchgeführt (segmentale PVI). Die Entwicklung 3-dimensionaler Mappingsysteme und aktiver Kühlung der Katheterspitze ermöglicht heute die Ablation kontinuierlicher zirkumferentieller Läsionen, in der Regel um beide ipsilateralen Pulmonalvenen-Ostien (zirkumferentielle PVI), wofür eine höhere Erfolgsrate hinsichtlich der Erhaltung des Sinus Rhythmus gezeigt wurde (11).

Voraussetzungen für eine dauerhafte PVI ist einerseits eine transmurale Nekrose aller Gewebsschichten in die Tiefe, andererseits eine ununterbrochene Kontinuität der einzelnen Läsionen entlang der zirkulären Ablationslinie. Dies erfordert eine stabile Katheterführung, was aufgrund der großen anatomischen Variabilität der PV-Ostien ein hohes Maß an technischer Fertigkeit verlangt und mit entsprechend langer Lernkurve verbunden ist. Eine besondere Schwierigkeit stellt hierbei eine schmale Muskelleiste dar, welche die linksseitigen PV antero-lateral gegen den Eingang des linken Vorhofohres abschließt. Über weitere trans-septale Zugangänge können ein oder zwei zirkuläre Elektrodenkatheter in das linke Atrium eingebracht werden, um die Spannungssignale von einer oder beiden ipsilateralen Pulmonalvene(n) während der Ablation abzuleiten (einfache oder doppelte „Lasso“ –Technik) (12). Zur Visualisierung der Katheter werden neben der Röntgen- Durchleuchtung Mappingsysteme eingesetzt, welche eine dreidimensionale Rekonstruktion des linken Atriums, sowie eine kontinuierliche, nicht auf Röntgenstrahlung basierende Ortung des Ablationskatheters ermöglichen.

1.4 Kryoballon-Ablation

Um die Durchführung einer PVI gegenüber der Standard-RFS-Ablation in technischer Hinsicht zu vereinfachen, wurde ein Ballon-gestütztes Verfahren nach dem Prinzip der Kryoablation entwickelt (13). Im Gegensatz zur sequentiellen, fokalen RFS-Ablation zielt die Kryoballon-Ablation auf eine simultane Läsionsentwicklung um einzelne PV-Ostien ab und ermöglicht so im Idealfall die Isolation von Pulmonalvenen durch eine einzige Energieabgabe. Hierzu wird ein Ballonkatheter über einen trans-septalen Zugang in das linke Atrium eingebracht. Das Manipulieren des Katheters erfolgt unter Röntgendurchleuchtung über einen Führungsdraht, mit welchem die jeweilige Zielvene sondiert wird. Nach Inflation wird der Ballon an das Gefäßostium gepresst, sodass der Blutfluss in der behandelten Pulmonalvene temporär zum erliegen kommt. Der Ballon hat hierbei idealerweise zirkumferentiellen Kontakt mit der veno-atrialen Übergangsregion. Dies wird durch Angiographie über die Ballonkatheter-Spitze verifiziert. Daraufhin wird Kühlmittel (N_2O) unter

Druck in den Ballon gepumpt, wo es expandiert und die Ballonoberfläche abkühlt (Joule-Thomson Effekt). An der Gewebekontaktfläche entstehen hierbei Temperaturen im Bereich von -30 bis -60 ºC. Durch Eisbildung kommt es zu einem festen Anhaften des Ballons am Gewebe (Kryoadhesion). Am Ende der Kryoablation wird durch Unterbrechen des Kühlmittelflusses der Ballonkatheter passiv wiedererwärmt und bei einer Temperatur von +20 ºC deflatiert. Das Ziel ist eine ringförmige Kälteläsion, welche die Pulmonalvene elektrisch isoliert. Über einen weiteren trans-septalen Zugang wird ein zirkulärer Elektrodenkatheter in das linke Atrium eingebracht, um die elektrische Isolation der Pulmonalvene zu verifizieren. Im Laufe der Entwicklung des Systems wurde der Führungsdraht durch einen zirkulären Elektrodenkatheter ersetzt, der sowohl zur mechanischen Führung des Ballonkatheters, als auch zur Registrierung von Pulmonalvenen-Signalen dient. Im Falle einer fortgesetzten Leitung der Pulmonalvene muss die Ablation mit unterschiedlicher Ballon-Positionierung wiederholt werden. Daten aus der Tumor-Kryochirurgie legen zudem nahe, dass eine Wiederholung von Gefrierzyklen zu einer tieferen Gewebspenetration der Nekrosezone führt, was möglicherweise einen positiven Effekt auf die Ausbildung einer dauerhaften, transmuralen Läsion hat.

2. Der Habilitation zugrundeliegende Originalarbeiten

Folgende ausgewählte 12 Arbeiten liegen der Habilitationsschrift zugrunde:

1. **Fürnkranz A**, Julian JK, Schmidt B, Wohlmuth P, Tilz R, Kuck KH, Ouyang F. Ipsilateral pulmonary vein isolation performed by a single continuous circular lesion: role of pulmonary vein mapping during ablation.
   Europace. 2011 Jul;13(7):935-41

2. **Fürnkranz A**, Köster I, Chun KR, Metzner A, Mathew S, Konstantinidou M, Ouyang F, Kuck KH. Cryoballoon temperature predicts acute pulmonary vein isolation.
   Heart Rhythm. 2011 Jun;8(6):821-5

3. Chun KR*, **Fürnkranz A***, Köster I, Metzner A, Tönnis T, Wohlmuth P, Wissner E, Schmidt B, Ouyang F, Kuck KH. Two versus one repeat freeze-thaw cycle(s) after cryoballoon pulmonary vein isolation: the alster extra pilot study.
   J Cardiovasc Electrophysiol. 2012 Aug;23(8):814-9
   * both authors contributed equally to this manuscript

4. **Fürnkranz A**, Chun KR, Nuyens D, Metzner A, Köster I, Schmidt B, Ouyang F, Kuck KH. Characterization of conduction recovery after pulmonary vein isolation using the "single big cryoballoon" technique.
   Heart Rhythm. 2010;7(2):184-90

5. **Fürnkranz A**, Bordignon S, Schmidt B, Gunawardene M, Schulte-Hahn B, Urban V, Bode F, Nowak B, Chun JK. Improved procedural efficacy of pulmonary vein isolation using the novel second-generation cryoballoon.
   J Cardiovasc Electrophysiol. 2013 May;24(5):492-7

6. **Fürnkranz A**, Bordignon S, Dugo D, Perrotta L, Gunawardene M, Schulte-Hahn B, Nowak B, Schmidt B, Chun KR. Improved one-year clinical success rate of pulmonary vein isolation with the second-generation cryoballoon in patients with paroxysmal atrial fibrillation.
J Cardiovasc Electrophysiol. 2014 Aug;25(8):840-4

7. **Fürnkranz A**, Brugada J, Albenque J, Tondo C, Bestehorn K, Wegscheider K, Ouyang F, Kuck KH. Rationale and Design of FIRE AND ICE: A Multicenter Randomized Trial Comparing Efficacy and Safety of Pulmonary Vein Isolation using a Cryoballoon Versus Radiofrequency Ablation with 3D-reconstruction.
J Cardiovasc Electrophysiol. 2014 Dec;25(12):1314-20

8. Kuck KH, Brugada J, **Fürnkranz A**, Metzner A, Ouyang F, Chun KR, Elvan A, Arentz T, Bestehorn K, Pocock SJ, Albenque JP, Tondo C; FIRE AND ICE Investigators. Cryoballoon or Radiofrequency Ablation for Paroxysmal Atrial Fibrillation.
N Engl J Med. 2016 Jun 9;374(23):2235-45

9. **Fürnkranz A***, Chun KR*, Metzner A, Nuyens D, Schmidt B, Burchard A, Tilz R, Ouyang F, Kuck KH. Esophageal endoscopy results after pulmonary vein isolation using the single big cryoballoon technique.
J Cardiovasc Electrophysiol. 2010 Aug 1;21(8):869-74
* both authors contributed equally to this manuscript

10. **Fürnkranz A**, Bordignon S, Schmidt B, Böhmig M, Böhmer MC, Bode F, Schulte-Hahn B, Nowak B, Dignaß AU, Chun JK. Luminal esophageal temperature predicts esophageal lesions after second-generation cryoballoon pulmonary vein isolation.
Heart Rhythm. 2013 Jun;10(6):789-93

11. **Fürnkranz A**, Bordignon S, Böhmig M, Konstantinou A, Dugo D, Perrotta L, Klopffleisch T, Nowak B, Dignaß AU, Schmidt B, Chun JK. Reduced incidence of esophageal lesions by luminal esophageal temperature-guided second-generation cryoballoon ablation.
Heart Rhythm. 2015 Feb;12(2):268-74

12. **Fürnkranz A**, Bordignon S, Schmidt B, Perrotta L, Dugo D, De Lazzari M, Schulte-Hahn B, Nowak B, Chun JK. Incidence and characteristics of phrenic nerve palsy following pulmonary vein isolation with the second-generation as compared with the first-generation cryoballoon in 360 consecutive patients.
Europace. 2015 Apr;17(4):574-8

3. Dargestellte Arbeiten

Ziel der dargestellten Arbeiten war es, eine neue Technologie der Vorhofflimmer-Ablation hinsichtlich Effektivität und Sicherheit zu untersuchen. Mit dem Einfließen dieser Ergebnisse in den technischen Entwicklungsprozess des Verfahrens sollte weiterhin der klinische Effektivitäts-Zuwachs der 2. Generation des Ballon-Katheters abgebildet bzw. mit dem Standard-Verfahren verglichen werden. Parallel dazu wurden Sicherheitsstrategien entwickelt, um Komplikationen an kollateralen Organen zu vermeiden.

3.1. Ablation von Vorhofflimmern mit unterschiedlichen Energieformen

Arbeit Nr. 1

Ipsilateral pulmonary vein isolation performed by a single continuous circular lesion: role of pulmonary vein mapping during ablation

Fürnkranz A, Julian JK, Schmidt B, Wohlmuth P, Tilz R, Kuck KH, Ouyang F.

Europace. 2011 Jul;13(7):935-41

Die Pulmonalvenen-Isolation (PVI) mit Hilfe von Radiofrequenzstrom-Ablation ist ein Standardverfahren bei der Behandlung von Vorhofflimmern. Die Notwendigkeit eines zirkulären Mapping-Katheters in der Zielvene während Ablation wird unterschiedlich beurteilt. Die vorliegende Arbeit ging der Fragestellung nach, ob eine lediglich anatomisch orientierte zirkumferentielle PVI mit einem dreidimensionalen Mappingsystem ohne simultane Ableitung der ipsilateralen PV-Signale durchgeführt werden kann. Hierzu wurden 50 Patienten mit Vorhofflimmern untersucht, bei welchen eine PVI mit Radiofrequenzstrom-Ablation unter Zuhilfenahme eines 3-dimensionalen Mappingsystems durchgeführt wurde. Ein oder zwei zirkuläre Mapping-Katheter wurden während Ablation in den behandelten PV platziert. Die abgeleiteten PV-Signale wurden digital gespeichert, jedoch während der Ablation für den Untersucher ausgeblendet. Nach Fertigstellung der zirkulären Ablationslinie wurden die Signale des/der zirkulären Elektrodenkatheter analysiert. Im Falle weiterhin nachweisbarer

elektrischer Leitung in die ipsilateralen PV wurde die zirkumferentielle Ablationslinie auf Leitungslücken untersucht und vollständig abladiert. Bei 42% der Patienten konnte eine vollständige PVI nach Ablation jeweils einer septalen und lateralen zirkumferentiellen Ablationslinie alleine auf Basis der anatomischen Rekonstruktion erzielt werden. Bei den übrigen Patienten konnten 8 Leitungslücken in 7 Patienten an den septalen PV, sowie 40 Leitungslücken in 29 Patienten an den lateralen PV nachgewiesen werden. Die dominierende Lokalisation von Leitungslücken an den lateralen PV war die antero-laterale Muskelleiste (ALM) zwischen PV und linkem Vorhofohr (27 von 40 Leitungslücken, 68%). Bezogen auf die lateralen PV im Sinus Rhythmus war das Zeitintervall zwischen Beginn der P-Welle im EKG und dem frühesten PV-Signal signifikant kürzer im Falle einer Leitungslücke am Vorhofdach im Vergleich zu anderen Lokalisationen. Umgekehrt führte ein Leitungsblock am Vorhofdach zu einer verzögerten Leitung in die lateralen PV mit Separation des atrialen Fernfeldpotentials vom PV-Potential. Zusammenfassend konnte gezeigt werden, (1) dass die zirkumferentielle PVI allein basierend auf einem 3-dimensionalen Mappingsystem ohne simultane Ableitung von PV-Signalen in der Mehrzahl der Fälle den prozeduralen Endpunkt der kompletten PVI verfehlt; (2) dass die ALM rein anatomisch unzureichend identifizierbar ist; und (3) dass ein initialer Leitungsblock am Vorhofdach die zusätzliche Elektrogram-basierte Identifikation der ALM aufgrund der hier abzuleitenden Doppelpotentiale erleichtert.

Arbeit Nr. 2

Cryoballoon temperature predicts acute pulmonary vein isolation

Fürnkranz A, Köster I, Chun KR, Metzner A, Mathew S, Konstantinidou M, Ouyang F, Kuck KH.

Heart Rhythm. 2011 Jun;8(6):821-5.

Die Pulmonalvenen-Isolation (PVI) mit dem Kryoballon stellt eine technisch gegenüber dem Standardverfahren der fokalen Radiofrequenzstromablation vereinfachte Methode zur Behandlung von Vorhofflimmern dar. Bei Verwendung der 1. Ballon-Generation wird

typischerweise eine lange Einzelapplikationszeit von 300 Sekunden pro Vene durchgeführt. Im Falle wiederholter ineffektiver Applikationen wird so die Prozedurzeit deutlich verlängert. Das Kryoballon-System registriert die Ballon-Temperatur während der Ablation mittels eines Sensors am proximalen Pol. Bei Verschlussposition des Ballons an der Pulmonalvene werden tiefe Ballon-Temperaturen (T_B) erreicht, da hierbei der Blutfluss um den Ballon minimiert wird. Ein vollumfänglicher Gewebekontakt des Ballons führt zur optimalen Entwicklung einer Kälteläsion mit elektrischer PVI. Ziel der vorliegenden Studie war es, die Ballon-Temperatur als frühen Prädiktor für eine erfolgreiche Ballon-Applikation zu evaluieren. Die Studienpopulation bestand aus 66 konsekutiven Patienten, bei welchen aufgrund von Vorhofflimmern eine Kryoballon-PVI mit vollständiger Erfassung der Ballon-Temperatur über die Applikationszeit durchgeführt wurde. Nach jeder Ballon-Ablation wurde die Zielvene mit einem zirkulären Mapping-Katheter hinsichtlich elektrischer Isolation untersucht. Allgemein wurden für die oberen PV tiefere T_B Werte als für die unteren PV erreicht. Gruppiert man individuelle Ablationen nach erfolgreicher/nicht-erfolgreicher PVI, konnten im Temperatur-Verlauf zu jedem Analysezeitpunkt im Mittel tiefere T_B Werte für die Gruppe der erfolgreichen Ablationen nachgewiesen werden. Um den Vorhersagewert von T_B hinsichtlich einer ineffektiven Ablation zu untersuchen, wurden Receiver Operating Characteristic (ROC) Kurven zu verschiedenen Ablationszeitpunkten erstellt. Nach 120 Sekunden konnte eine $T_B \geq -36°$ (obere PV) bzw. -33° (untere PV) eine ineffektive Ablation mit einem positiven Vorhersagewert von 82% bzw. 80% voraussagen. Eine minimale $T_B < -51°$ war invariabel mit erfolgreicher PVI assoziiert. Zusammenfassend wurde die T_B Analyse für die frühe Identifikation nicht erfolgreicher Ballon-Ablationen etabliert, wodurch ineffektive Energieabgaben mit Verlängerung der Prozedurdauer vermieden werden können.

Arbeit Nr. 3

Two versus one repeat freeze-thaw cycle(s) after cryoballoon pulmonary vein isolation

Chun KR*, **Fürnkranz A***, Köster I, Metzner A, Tönnis T, Wohlmuth P, Wissner E, Schmidt B, Ouyang F, Kuck KH; * both authors contributed equally to this manuscript

J Cardiovasc Electrophysiol. 2012 Aug;23(8):814-9

Bei der Kryoablation kardialer Gewebe wird basierend auf Daten aus der kryochirurgischen Tumorbehandlung eine Wiederholung von Gefrierzyklen (Bonus-Applikation) zur optimalen chronischen Ausbildung der Kälteläsion empfohlen. Ziel der vorliegenden Arbeit war es, zwei Strategien der Kryoballon-Ablation von Vorhofflimmern hinsichtlich ihres klinischen Langzeit-Erfolges zu untersuchen. Es wurden 51 konsekutive Patienten, bei welchen aufgrund von paroxysmalem Vorhofflimmern eine Kryoballon-Pulmonalvenen-Isolation durchgeführt wurde, untersucht. Bei 27 Patienten wurde nach erfolgreicher Isolation eine Bonus-Applikation an jeder Pulmonalvene durchgeführt (Grupp 1). Bei 24 Patienten wurden 2 Bonus-Applikationen durchgeführt (Gruppe 2). Die klinische Nachsorge und Erfolgskontrolle erfolgte mittels serieller 7-Tage Holter-EKG Untersuchungen bzw. implantierbarem Ereignisrekorder. Der primäre Endpunkt der Studie war die Dokumentation einer atrialen Tachyarrhythmie (Vorhofflimmern oder atriale Tachykardie) über ≥ 2 Minuten nach der Index-Prozedur. Eine komplette Pulmonalvenen-Isolation gelang bei 98% aller Patienten. Nach einer medianen Nachbeobachtungszeit von 384 Tagen wurde der primäre Endpunkt bei 48% der Patienten aus Gruppe 1, sowie bei 46% der Gruppe 2 beobachtet. Diese Differenz war statistisch nicht signifikant. Bezüglich der Eingriffs- und Durchleuchtungszeiten wurden keine signifikanten Unterschiede zwischen den Gruppen gefunden. Eine über den Zeitpunkt der Entlassung persistierende Parese des rechten N. phrenicus trat bei 2 Patienten der Gruppe 2 auf, wobei die Paresen jeweils nach der 2. Bonus Applikation an den septalen Pulmonalvenen beobachtet wurden. Bei diesen Patienten wurde die vollständige Erholung der N. Phrenicus-Funktion nach 172 bzw. 212 Tagen nachgewiesen. Zusammenfassend erbrachte die

Durchführung von 2 Bonus-Applikationen keinen klinischen Vorteil gegenüber einer Bonus Applikation. Die kumulative Energieabgabe kann zur Läsion kollateraler Gewebe führen.

3.2. Entwicklung der Kryoballon-Technologie

Arbeit Nr. 4

Characterization of conduction recovery after pulmonary vein isolation using the "single big cryoballoon" technique

Fürnkranz A, Chun KR, Nuyens D, Metzner A, Köster I, Schmidt B, Ouyang F, Kuck KH. Heart Rhythm. 2010;7(2):184-90

Eine wesentliche Ursache für rezidivierendes Vorhofflimmern nach Pulmonalvenen-Isolation ist die elektrische Leitungserholung einer oder mehrerer Pulmonalvenen. Ziel der vorgelegten Arbeit war es, Charakteristika der Leitungserholung nach initialer Pulmonalvenen-Isolation mit dem 28 mm Kryoballon zu untersuchen. Hierzu wurden 26 Patienten untersucht, bei welchen aufgrund von rezidivierenden atrialen Tachyarrhythmien eine 2. Katheterablation durchgeführt wurde. Die Zweitprozedur erfolgte mittels 3-dimensionalem Mappingsystem und fokalem Radiofrequenzstrom-Katheter. Alle Pulmonalvenen wurden mit Hilfe eines zirkulären Mapping-Katheters auf Isolation geprüft. Zur Identifikation diskreter Leitungslücken in den Kryo-Läsionen wurde die ipsilaterale veno-atriale Übergangsregion in 6 Ringsegmente aufgeteilt. Die erste Ablation erfolgte in jenem Segment mit dem frühesten Pulmonalvenen-Signal im Sinus Rhythmus. Die Lokalisation der Leitungslücken wurde durch Re-Isolation oder durch abrupte Änderung der Signalsequenz im zirkulären Mapping Katheter – als Hinweis auf zusätzliche Leitungslücken – bestätigt und 3-dimensional registriert. Die Analyse ergab ein spezifisches anatomisches Muster für das Auftreten von Leitungslücken mit Prädilektion für die unteren Segmente (85% der Patienten lateral; 77% septal) im Vergleich zu oberen Segmenten (42% lateral; 31% septal). Zudem wurde die Muskelleiste zwischen linkem Vorhofohr und lateralen Pulmonalvenen als

Prädilektionsstelle für Leitungslücken identifiziert (81% der Patienten). Die retrospektive Analyse der Kathetergeometrie der initialen Ballon-Prozedur zeigte einen signifikant höheren Deflektionsgrad des Schleuse/Ballon-Systems bei Ablation an den unteren im Vergleich zu den oberen Pulmonalvenen, was zu einem Verlust der zentralen Ausrichtung des Ballons entlang der Gefäßachse führte. Dies hatte zur Folge, dass die unteren Segmente bei Ablation typischerweise mit der nicht optimal gekühlten Polarregion des Ballons Kontakt hatten. Zusammenfassend konnte erstmals ein systematisches Muster für die Ausbildung von Leitungslücken nach Pulmonalvenen-Isolation mit der 1. Generation des Kryoballons nachgewiesen werden, als dessen Ursache die dezentrale Ballonposition in Zusammenhang mit einem frontalen Temperaturgradienten des Ballons angenommen werden kann.

Arbeit Nr. 5

Improved procedural efficacy of pulmonary vein isolation using the novel second-generation cryoballoon

Fürnkranz A, Bordignon S, Schmidt B, Gunawardene M, Schulte-Hahn B, Urban V, Bode F, Nowak B, Chun JK.

J Cardiovasc Electrophysiol. 2013 May;24(5):492-7

Das Kryoballon-System ermöglicht prinzipiell die elektrische Isolation einer Pulmonalvene mit einer singulären Energieapplikation. Die 1. Generation des Kryoballons ist jedoch durch eine inhomogene Temperaturverteilung an der Ballon-Oberfläche gekennzeichnet und wiederholte Energieabgaben sind häufig notwendig, um eine Pulmonalvenen-Isolation zu erzielen. Mit der 2. Generation des Ballons wurde das Kühlmittel-Injektionssystem überarbeitet mit dem Resultat einer homogenen Temperaturzone im Bereich der frontalen Ballon-Hemisphäre. Ziel der vorgelegten Arbeit war es, den Einfluss dieser technischen Modifikation auf die Prozedureffizienz zu untersuchen. Die Studienpopulation umfasste 60 konsekutive Patienten mit paroxysmalem oder persistierendem (< 6 Monate) Vorhofflimmern. Die ersten 30 Patienten wurden mit der 1. Generation des Kryoballons (CB1, 28 mm)

behandelt. Mit Verfügbarkeit der 2. Generation (CB2, 28 mm) wurde ab Patient 31 mit dem CB2 behandelt. Alle Operateure verfügten über eine langjährige Erfahrung in der Kryoablation von Vorhofflimmern. Ein in das Ballonsystem integrierter zirkulärer Elektrodenkatheter diente zur Registrierung von Pulmonalvenen-Signalen und als mechanische Führung. Die Applikationszeit betrug 300 (CB1), bzw. 240 (CB2) Sekunden. Die Isolationsrate mit einer Energieapplikation konnte unter der Verwendung des CB2 von 51% (CB1) auf 84% gesteigert werden. Prozedur- und Durchleuchtungszeit konnten im Vergleich zum CB1 signifikant gesenkt werden. Die Registrierung des Zeitpunktes der Isolation erfolgte signifikant häufiger mit dem CB2 (76%) im Vergleich zum CB1 (49%) aufgrund der Möglichkeit, den zirkulären Katheter proximal in der Pulmonalvene zu platzieren. Die mittlere Isolationszeit wurde von 79 (CB1) auf 52 (CB2) Sekunden gesenkt. Zusammengefasst konnte erstmals für das überarbeitete Kühlsystem des CB2 eine signifikante Steigerung der Effektivität an einer Reihe prozeduraler Parameter nachgewiesen werden.

Arbeit Nr. 6

Improved one-year clinical success rate of pulmonary vein isolation with the second-generation cryoballoon in patients with paroxysmal atrial fibrillation

Fürnkranz A, Bordignon S, Dugo D, Perrotta L, Gunawardene M, Schulte-Hahn B, Nowak B, Schmidt B, Chun KR.

J Cardiovasc Electrophysiol. 2014 Aug;25(8):840-4

Basierend auf dem Nachweis einer erhöhten prozeduralen Effektivität hatte die vorliegende Arbeit zum Ziel, die klinische Effektivität des Kryoballon-Systems der 2. Generation (CB2) hinsichtlich der Rhythmuskontrolle bei Patienten mit paroxysmalem Vorhofflimmern zu untersuchen. Es wurden 105 konsekutive Patienten mit paroxysmalem Vorhofflimmern untersucht. Die ersten 50 Patienten wurden mit der 1. Ballon-Generation (CB1), die übrigen 55 Patienten mit dem CB2 behandelt. Die klinische Nachbeobachtung erfolgte durch 3-Tage

Langzeit-EKG Untersuchungen nach 3, 6 und 12 Monaten, und anschließend halbjährig. Zusätzlich erfolgten Symptom-ausgelöste Langzeit-EKG Untersuchungen. Der Studienendpunkt war definiert als Dokumentation von Vorhofflimmern oder einer atrialen Tachykardie von > 30 Sekunden Dauer nach einer „Blanking"-Periode von 90 Tagen nach der Index-Prozedur. Membran-aktive Antiarrhythmika wurden innerhalb der „Blanking"-Periode abgesetzt. Die Nachbeobachtunsperiode betrug im Mittel 419 (CB1) und 414 (CB2) Tage. Der Endpunkt wurde bei 21 Patienten der CB1 Gruppe und bei 10 Patienten der CB2 Gruppe beobachtet. Die Kaplan-Meier-Schätzungen für Arrhythmie-freies Überleben nach einem Jahr betrugen 63,9% in der CB1 Gruppe und 83,6% in der CB2 Gruppe (P= 0,008; Log-Rank Test). Die multivariate Cox-Regressions-Analyse ergab als einzigen signifikanten Prädiktor für erfolgreiche Rhythmuskontrolle die Verwendung des CB2. Die Rate an peri-prozeduralen Komplikationen unterschied sich nicht signifikant zwischen den Gruppen. In Zusammenschau konnte für die 2. im Vergleich zur 1. Kryoballon-Generation eine signifikant höhere klinische Erfolgsrate hinsichtlich der Rhythmuskontrolle bei Patienten mit paroxysmalem Vorhofflimmern nachgewiesen werden.

Arbeit Nr. 7

Rationale and Design of FIRE AND ICE: A Multicenter Randomized Trial Comparing Efficacy and Safety of Pulmonary Vein Isolation using a Cryoballoon Versus Radiofrequency Ablation with 3D-reconstruction

Fürnkranz A, Brugada J, Albenque J, Tondo C, Bestehorn K, Wegscheider K, Ouyang F, Kuck KH.

J Cardiovasc Electrophysiol. 2014 Dec;25(12):1314-20

Die weltweit am häufigsten angewandten Techniken der Vorhofflimmerablation sind die Standard-Radiofrequenzstrom (RFS)-Ablation sowie die in ihrer Bedeutung zunehmende Kryoballon-Ablation. Direkte Vergleichsstudien zwischen den beiden Technologien waren bislang auf wenige, nicht-randomisierte Studien mit kleinen Patientenzahlen beschränkt. Die

vorliegende Arbeit hatte zum Ziel, das Protokoll einer prospektiven, randomisierten Studie zu entwickeln, um die wichtigsten Ablationstechnologien hinsichtlich Effektivität und Sicherheit zu vergleichen. Die primäre Studienhypothese ist die Nicht-Unterlegenheit der Kryoballon-Ablation gegenüber der RFS-Ablation mit Hilfe eines 3-dimensionalen Mappingsystems. Der primäre kombinierte Effektivitäts-Endpunkt umfasst: (1) dokumentierte Episoden (> 30 Sekunden) von Vorhofflimmern, Vorhofflattern oder einer atrialen Tachykardie; (2) Einnahme eines Membran-aktiven Antiarrhythmikums; und (3) Re-Ablation, jeweils nach einer „Blanking“ Periode von 90 Tagen. Das klinische Nachbeobachtungsprogramm ist auf intensives Monitoring asymptomatischer Rezidive atrialer Tachyarrhythmien ausgelegt und inkludiert wöchentliche telemetrische Rhythmusanalysen. Der Studienhypothese wurden auf Basis der Patientenselektion, der Ablations-Technik, sowie der klinischen Nachbeobachtungsmodalitäten die Resultate der jeweils gegen medikamentöse Therapie randomisierten STOP AF und THERMOCOOL AF Studie zugrunde gelegt. Demzufolge wurden Ereignis-freie Überlebensraten von 70% nach einem Jahr für beide Technologien angenommen und eine Nicht-Unterlegenheitsspanne von 10% definiert, welche unter Berücksichtigung des Behandlungseffekts der aktiven Kontrolle (RFS-Ablation) gegenüber medikamentöser Therapie als konservativ gelten kann. Unter Annahme von 2 Interimsanalysen, einer möglichen 5% „Drop-out“ Rate und einer 1:1 Randomisierung wurde eine Fallzahl von mindestens 572 Patienten berechnet. Vor Beendigung der Studie kann diese Fallzahl basierend auf einer verblindeten Stichprobengrößen-Analyse erweitert werden. Als primärer Sicherheitsendpunkt wurde eine Kombination aus Tod, cerebrovaskulärem Ereignis und eingriffsbedingten schwerwiegenden unerwünschten Ereignissen definiert. Zusammengefasst wurde das Protokoll einer multizentrisch ausgelegten Vergleichsstudie von Kathetertechnologien in der Vorhofflimmer-Ablation entwickelt und vorgelegt.

Arbeit Nr. 8

Cryoballoon or Radiofrequency Ablation for Paroxysmal Atrial Fibrillation

Kuck KH, Brugada J, **Fürnkranz A**, Metzner A, Ouyang F, Chun KR, Elvan A, Arentz T, Bestehorn K, Pocock SJ, Albenque JP, Tondo C; FIRE AND ICE Investigators.

N Engl J Med. 2016 Jun 9;374(23):2235-45

In der vorliegenden Arbeit werden die primären Effektivitäts- und Sicherheitsendpunkte der FIRE AND ICE Studie berichtet. Die Studienpopulation umfasste Patienten mit paroxysmalem Vorhofflimmern nach ineffektiver Therapie mit einem Klasse I, II oder III Antiarrhythmikum. Es wurden insgesamt 762 Patienten randomisiert, wovon 378 Patienten einer Kryoballon-Ablation, 384 Patienten einer Radiofrequenzstrom (RFS)-Ablation zugewiesen wurden. In der Kryoballon-Gruppe wurden 24% der Patienten mit der 1. Ballon-Generation behandelt. Die mittlere Nachbeobachtungszeit betrug 1,5 Jahre. Der primäre Effektivitäts-Endpunkt wurde bei 138 Patienten in der Kryoballon-Gruppe, und bei 143 Patienten in der RFS-Gruppe erreicht. Die entsprechenden Kaplan-Meier-Schätzungen über Ereignisraten nach einem Jahr betrugen 34,6% und 35,9% ($P < 0,001$ für Nicht-Unterlegenheit). Die mittlere Eingriffs- und linksatriale Instrumentierungszeit konnte in der Kryoballon-Gruppe signifikant gegenüber der RFS-Gruppe gesenkt werden. Die mittlere Durchleuchtungszeit war kürzer in der RFS-Gruppe. Bezüglich des primären Sicherheitsendpunktes wurde kein Unterschied zwischen den Gruppen gefunden. Die häufigsten (nicht-Arrhythmie-bezogenen) Komplikationen waren Leistenkomplikationen in der RFS-Gruppe (4,3%), sowie rechts-seitige Nervus phrenicus-Paresen in der Kryoballon-Gruppe (2,7%). Hiervon waren 80% der Fälle innerhalb von 3 Monaten vollständig reversibel. Zusammengefasst konnte gezeigt werden, dass die Kryoballon-Ablation bei verkürzter Eingriffsdauer bezüglich klinischer Erfolgsrate und Sicherheit dem Standardverfahren äquivalent war. Diese Ergebnisse wurden in der Empfehlung für die Kathetertechnik bei der Behandlung von paroxysmalem Vorhofflimmern in die aktuellen europäischen Leitlinien aufgenommen.

3.3. Entwicklung von Sicherheitsstrategien

Arbeit Nr. 9

Esophageal endoscopy results after pulmonary vein isolation using the single big cryoballoon technique

Fürnkranz A*, Chun KR*, Metzner A, Nuyens D, Schmidt B, Burchard A, Tilz R, Ouyang F, Kuck KH. * both authors contributed equally to this manuscript

J Cardiovasc Electrophysiol. 2010 Aug 1;21(8):869-74.

Atrio-ösophageale Fisteln sind eine seltene, aber lebensbedrohliche Komplikation nach Pulmonalvenen-Isolation. Endoskopische Untersuchungen konnten in manchen Fällen thermische Ösophagus-Ulzerationen nach Pulmonalvenen-Isolation mit variablen Größen eines Kryoballons nachweisen. Die vorliegende Studie zielt darauf ab 1. Temperaturänderungen im Ösophagus, und 2. die Inzidenz thermischer Schäden der Ösophagusschleimhaut im Zusammenhang mit einer Kryoballon Pulmonalvenen-Isolation unter alleiniger Verwendung des größeren 28-mm Ballons zu untersuchen. Die Rationale einer „Single Big Cryoballoon“ Strategie ist die überwiegend atriale Ballonposition und die Maximierung des Abstandes zu kollateralen Geweben. Die Studienpopulation umfasste 38 konsekutive Patienten mit Vorhofflimmern, bei welchen eine Kryoballon-Pulmonalvenen-Isolation (1. Generation) durchgeführt wurde. Die luminale Ösophagustemperatur (LET) wurde kontinuierlich mit einer Sonde gemessen, welche über 3 Temperatur-Sensoren verfügt. Die Distanz zwischen Sonde und Kryoballon wurde fluoroskopisch in 2 Ebenen bestimmt. Bei allen Patienten wurde 1-3 Tage nach der Prozedur eine Ösophagus-Endoskopie durchgeführt. Die durchschnittliche minimale LET war signifikant tiefer während Ablation der unteren Pulmonalvenen. Die tiefste gemessene LET (-6°C) wurde während Ablation an der linken unteren Pulmonalvene gemessen. Der maximale longitudinale Temperaturgradient betrug 26°C/cm, was die Bedeutung von Multisensorsonden bei der Bestimmung der tiefsten LET unterstreicht. Absenkungen der LET auf < 10°C traten nur bei

einer Distanz von < 15 mm vom Ballon-Zentrum in beiden Projektionsebenen auf. Endoskopisch wurden bei keinem Patienten Ösophagus-Schleimhautveränderungen nachgewiesen. Zusammengefasst wurden bei Verwendung der 1. Generation des 28-mm Kryoballons die Temperaturverteilung zwischen Ballon und Ösophagus-Lumen charakterisiert und trotz kurzzeitig tiefer LET keine Schleimhautschäden nachgewiesen.

Arbeit Nr. 10

Luminal esophageal temperature predicts esophageal lesions after second-generation cryoballoon pulmonary vein isolation

Fürnkranz A, Bordignon S, Schmidt B, Böhmig M, Böhmer MC, Bode F, Schulte-Hahn B, Nowak B, Dignaß AU, Chun JK.

Heart Rhythm. 2013 Jun;10(6):789-93

Die 2. Generation des Kryoballons weist eine effektivere Kühlung der Ballon-Oberfläche und einen erhöhten Kühlmittelfluss im Vergleich zur 1. Generation auf. Dies erhöht die klinische Effektivität, kann potentiell aber zu vermehrter Schädigung angrenzender nicht-kardialer Gewebe führen. Ziel der vorliegenden Arbeit war es, die Inzidenz von Ösophagus-schleimhaut-Schäden nach Pulmonalvenen-Isolation mit dem 28-mm Kryoballon der 2. Generation zu untersuchen. Die Studienpopulation umfasste 32 konsekutive Patienten mit Vorhofflimmern. Die luminale Ösophagustemperatur (LET) wurde während Ablation kontinuierlich über 3 Sensoren gemessen. Das Protokoll sah eine Ablationszeit von 2x240 Sekunden pro Pulmonalvene mit Unterbrechung der Kryoablation bei LET < 5° C vor. Bei allen Patienten wurde innerhalb von 3 Tagen nach der Prozedur eine Gastro-Ösophagoskopie durchgeführt. Bei 6/32 (19%) Patienten wurden flache Schleimhautulcera in retrokardialer Lokalisation gefunden. Die tiefste gemessene LET war signifikant unterschiedlich bei Patienten mit (0,3°C) und ohne Ösophagusläsion (22,3°C). Um den Vorhersagewert der minimalen LET (mLET) in Bezug auf Ösophagusläsionen zu bestimmen, wurde eine Receiver-Operator Characteristic Kurven-Analyse durchgeführt. Eine mLET ≤ 12

°C war mit einer Sensitivität von 100% und einer Spezifität von 92% prädiktiv für Läsionen. Eine Kontroll-Gastro-Ösophagoskopie nach durchschnittlich 16 Tagen zeigte eine komplette Abheilung bei allen Patienten mit Läsionen unter Protonenpumpen-Inhibitor-Therapie. Zusammenfassend konnte gezeigt werden, dass nach Pulmonalvenen-Isolation mit der 2. Kryoballon-Generation Ösophagusläsionen bei 19% der Patienten auftreten und dass eine mLET ≤ 12 °C einen hohen Vorhersagewert für die Entwicklung solcher Läsionen darstellt. Dies ermöglicht ein LET-gesteuertes Ablationsprotokoll zur Vermeidung einer Ösophagus-Schädigung.

Arbeit Nr. 11

Reduced incidence of esophageal lesions by luminal esophageal temperature-guided second-generation cryoballoon ablation

Fürnkranz A, Bordignon S, Böhmig M, Konstantinou A, Dugo D, Perrotta L, Klopffleisch T, Nowak B, Dignaß AU, Schmidt B, Chun JK.

Heart Rhythm. 2015 Feb;12(2):268-74

Nachdem die mLET als prädiktiver Parameter für Ösophagus-Läsionen nach Kryoballon-Pulmonalvenen-Isolation (KB-PVI) etabliert wurde, sollte in der vorliegenden Arbeit untersucht werden, ob ein LET-gesteuertes Ablationsprotokoll die Rate solcher Läsionen vermindert. Hierzu wurden 94 konsekutive Patienten nach KB-PVI untersucht. Das Ablationsprotokoll sah eine Unterbrechung der Kryoablation bei einer LET < 12°C (28 Patienten) bzw. < 15°C (66 Patienten) vor und entsprach in allen anderen Aspekten dem Standardprotokoll (s. Arbeit 10). Die Rationale für ein Anheben des LET-Schwellenwertes auf 15°C ergab sich durch die Beobachtung einer geringfügigen weiteren Absenkung der LET nach Unterbrechung der Ablation. Bei allen Patienten wurde innerhalb von 3 Tagen eine Gastro-Ösophagoskopie durchgeführt. Gegenüber dem Standardprotokoll wurde die Rate an thermischen Ösophagus-Läsionen durch eine LET-gesteuerte KB-PVI signifikant gesenkt (18,8 vs 3.2%). Die niedrigste Rate wurde bei einem LET-Grenzwert von 15°C beobachtet

(1,5%). Bei Patienten mit Läsionen wurde die Abheilung durch Kontroll-Endoskopie nach 1 Woche sichergestellt. Trotz vorzeitiger Unterbrechung der Kryoablation bei 27% der Patienten wurde das Prozedurziel der kompletten PVI bei allen Patienten erreicht. Nach einer mittleren Nachbeobachtungszeit von 268 Tagen unter Berücksichtigung einer „Blanking“ Periode von 90 Tagen nach Prozedur blieben 87% der Patienten frei von rezidivierenden atrialen Tachyarrhythmien. Zusammengefasst konnte gezeigt werden, dass ein LET-gesteuertes Protokoll das Auftreten von thermischen Ösophagus-Läsionen nach KB-PVI signifikant senkt ohne auf die akute oder chronische Erfolgsrate Einfluss zu nehmen.

Arbeit Nr. 12

Incidence and characteristics of phrenic nerve palsy following pulmonary vein isolation with the second-generation as compared with the first-generation cryoballoon in 360 consecutive patients

Fürnkranz A, Bordignon S, Schmidt B, Perrotta L, Dugo D, De Lazzari M, Schulte-Hahn B, Nowak B, Chun JK.

Europace. 2015 Apr;17(4):574-8

Die Schädigung des rechten Nervus phrenicus ist eine der häufigsten Komplikationen Ballon-basierter Ablationsverfahren von Vorhofflimmern. Dies ist auf den anatomischen Verlauf des Nervus phrenicus zwischen Vena cava superior und den rechten Pulmonalvenen (PV) zurückzuführen. Die Weiterentwicklung des Kryoballons zur 2. Geräte-Generation führte zu einer Effektivitäts-Steigerung, durch Zunahme des gekühlten Gewebevolumens kann es aber potentiell zu vermehrtem Auftreten kollateraler Gewebsschädigung kommen. Ziel der vorliegenden Arbeit war es, Inzidenz und Verlauf von Phrenicusparesen in Zusammenhang mit der Kryoballon-Ablation unter Verwendung der 1. und 2. Geräte-Generation retrospektiv zu untersuchen. Die Studienpopulation umfasste 360 konsekutive Patienten bei denen eine Kryoballon-Pulmonalvenen-Isolation durchgeführt wurde. Die 1. Ballon-Generation kam bei 106 Patienten (KB1-Gruppe), die 2. Generation bei 254 Patienten zum Einsatz (KB2-

Gruppe). Während Ablation der septalen PV wurde der rechte N. phrenicus kontinuierlich über einen Katheter in der Vena cava superior stimuliert (12 V / 2,9 ms Impuls, Intervall 1 sek.). Die Zwerchfellkontraktion wurde manuell überwacht. Bei Einschränkung der Zwerchfellmotilität wurde die Ablation unterbrochen, wobei das System den Ballon nach einer Auftwärmphase bei einer Temperatur von +20°C automatisch deflatiert. Eine Technik der aktiven Deflation zum Zeitpunkt der Unterbrechung des Kühlmittelflusses ohne vorherige Aufwärmphase kam ab Patient 178 in der KB2-Gruppe zum Einsatz. Eine über den Zeitpunkt der Entlassung hinaus persistierende Phrenicusparese trat bei 1,9% (KB1-Gruppe) und 2,8% (KB2-Gruppe) der Patienten auf (p = 0,6). Unterschiede zwischen den Gruppen wurden hinsichtlich der bis zum Auftreten kumulativen Ablationszyklen, der Zielvene, sowie der Abheilungsdauer gefunden. Phrenikusparesen durch Ablation an der rechten unteren PV wurden lediglich in der KB2-Gruppe beobachtet. In der KB2-Gruppe traten Phrenicusparesen nach weniger Ablationszyklen (1,1 vs. 3,5) auf, die Abheilungsdauer war verlängert (im Mittel 259 vs. 29 Tage). Mit zunehmender Fallzahl wurde ein Trend zu einer abnehmenden Inzidenz von Phrenicusparesen in der KB2-Gruppe gefunden: 4,8% in der untersten Quartile vs. 0% in der obersten Quartile (p = 0,08). Zusammenfassend konnte gezeigt werden, dass es unter Verwendung der 2. Ballon-Generation zu einer ausgeprägteren Schädigung des N. phrenicus kommen kann. Technische Anpassungen wie die aktive Deflation sowie ein intensives Monitoring während Ablation an der rechten unteren PV sind aussichtsreiche Maßnahmen zur Senkung des Risikos.

4. Zusammenfassung und Schlussfolgerung

Die Katheterablation ist ein wesentlicher Therapiebaustein in der Behandlung von Vorhofflimmern und stellt bei Versagen der medikamentösen Therapie die einzige Option zur Rhythmuskontrolle dar. Die höchste klinische Effektivität ist bei früher Intervention im Krankheitsverlauf nachgewiesen. Der hohen Inzidenz der Erkrankung steht eine hohe klinische Nachfrage dieser Therapieform mit stetig steigenden Interventionszahlen gegenüber. Dies stellt die klinische Technologie vor die Aufgabe, Methoden zu entwickeln, die auf die speziellen Anforderungen dieses Eingriffs optimiert, verhältnismäßig einfach erlernbar sind und einen hohen Grad an Sicherheit gewährleisten. In dieser Hinsicht stellt die Kryoballon-Technologie eine Weiterentwicklung gegenüber der Standard-Radiofrequenzstrom-Ablation dar, indem der komplexe Ablauf einer Pulmonalvenen-Isolation auf wenige Arbeitsschritte reduziert wird.

Die Ausbildung kryothermaler Läsionen wird über Anzahl und Dauer der Therapiezyklen bestimmt, wobei die Einzelapplikation mit 4-5 Minuten relativ lange erfolgt, was durch eine großflächige simultane Läsionsentwicklung ausgeglichen wird. Ineffektive Applikationen verlängern jedoch einerseits die Eingriffszeit und erhöhen andererseits das Komplikationsrisiko durch unerwünschte Wirkungen auf kollaterale Gewebe. Die Ergebnisse der Arbeiten im ersten Abschnitt tragen zu einem effektiveren Ablationsprotokoll bei, indem einerseits erfolglose Applikationen verkürzt werden, andererseits die Effektivität eines systematischen 2-Zyklen-Protokolls gegenüber eines 3-Zyklen-Protokolls gezeigt wurde.

Eine wesentliche Ursache für Rezidive von Vorhofflimmern nach Pulmonalvenen-Isolation ist die elektrische Rekonnektion durch spätere Ausbildung von Leitungslücken an inkompletten Ablationsstellen (14). Die 1. Generation des Kryoballons verfügt über ein Kühlmittel-Injektionssystem, welches die tiefsten Temperaturen ungefähr entlang eines äquatorialen Bandes erzeugt. Eine Analyse der Leitungslücken bei Patienten mit Vorhofflimmer-Rezidiv nach Ablation mit der 1. Produktgeneration zeigte ein systematisches Lokalisationsmuster, welches durch die relativ ineffektive Kühlung im Polbereich des Ballons erklärbar ist. Eine Überarbeitung des Injektionssystems realisierte bei der 2.

Produktgeneration eine homogene Kühlung der frontalen Ballonhemisphäre. Die Arbeiten im zweiten Abschnitt konnten zeigen, dass diese technische Modifikation einerseits zu einer signifikanten Effektivitätssteigerung während der Prozedur, andererseits zu einer Steigerung der klinischen Erfolgsrate in der Langzeitbeobachtung führt. Die Kryoballon-Technologie stellt damit ein System zur Verfügung, mit dem die Pulmonalvenen-Isolation in den meisten Fällen mit einer singulären Therapieabgabe erfolgt. Vergleichsstudien mit dem Standard-Radiofrequenzstrom-Verfahren waren zu diesem Zeitpunkt auf kleine, nicht-randomisierte Studien beschränkt bzw. wurden überwiegend unter Verwendung der 1. Ballon-Generation durchgeführt. Es bestand daher eine Evidenzlücke hinsichtlich repräsentativer, multizentrischer Vergleichsdaten dieser Technologien am aktuellen Entwicklungsstand. Die FIRE AND ICE Studie widmete sich dieser Fragestellung und konnte zeigen, dass bei signifikant verkürzter Eingriffszeit durch die Kryoablation ein gegenüber dem Standardverfahren äquivalentes klinisches Langzeitergebnis zu erzielen ist. Hierbei ist anzumerken, dass die Studie in 16 europäischen, auch bezüglich der Standard-Ablation hocherfahrenen Zentren durchgeführt wurde. Zieht man die relativ kurze Lernkurve des Kryoballon-Verfahrens in Betracht (15), so setzt diese Technologie nach adäquater Ausbildung auch Zentren bzw. Untersucher in den Stand, die Pulmonalvenen-Isolation auf hohem Qualitätsstandard durchzuführen, deren jährliche Untersuchungszahlen unterhalb jener von internationalen Referenzzentren liegen. Hierauf deutet auch eine Analyse des französischen FRENCH AF Ablations-Registers hin (16). Hinsichtlich der Eingriffssicherheit zeigte FIRE AND ICE für beide Technologien gleichermaßen ein niedriges peri-prozedurales Risiko, wobei sich jeweils Technologie-spezifische Komplikationsprofile abzeichneten.

Eine seltene aber lebensbedrohliche Komplikation nach Pulmonalvenen-Isolation ist die Ausbildung einer atrio-ösophagealen Fistel. Dies ist aufgrund der anatomischen Nähe des Ösophagus zur linksatrialen Hinterwand bzw. den Pulmonalvenen möglich. Der exakte pathophysiologische Verlauf ist nicht geklärt, da aber in manchen Fällen auch ösophago-perikardiale Fisteln nach Pulmonalvenen-Isolation beobachtet werden, liegt eine primäre Schädigung des Ösophagus nahe, mit möglicher Progression durch einen gastro-

ösophagealen Reflux (17). Eine Sicherheitsstrategie zur Reduktion der Schädigung herznaher Gewebe bei der Kryoballon-Ablation ist die alleinige Verwendung des größeren 28-mm Ballons. Hierbei sinkt das Risiko der Ablation innerhalb der Pulmonalvene, was den Abstand zu kollateralen Strukturen vergrößert und eine exzessive Ballon-Abkühlung durch den atrialen Blutstrom verhindert. Endoskopische Untersuchungen nach Kryoablation mit beiden (23/28-mm) Ballon-Größen konnten Ösophagus-Schleimhautläsionen nachweisen (18). Im Gegensatz dazu konnte hier gezeigt werden, dass bei alleiniger Verwendung des 28-mm-Ballons der 1. Generation solche Läsionen nicht zu beobachten sind. Die Einführung der 2. Ballon-Generation mit homogen nach frontal gerichtetem Temperaturprofil und höherem Kühlmittel-Fluss brachte die Notwendigkeit mit sich, Ösophagus-Läsionen auch bei Restriktion auf die 28-mm Größe neu zu untersuchen. Die Arbeiten im 3. Abschnitt zeigten einerseits, dass es nach Ablation mit dem 28-mm Ballon der 2. Generation zu ösophagealen Ulcera kommen kann, andererseits dass die Läsionsbildung in enger Assoziation mit der minimalen luminal gemessenen Temperatur (mLET) erfolgt. Dies zeigte zum einen den Nutzen einer Ösophagus-Temperatursonde, und ermöglichte zum anderen die Definition eines mLET-Grenzwertes, der bei der Kryoballon-Ablation nicht unterschritten werden sollte. Für die systematische Anwendung dieses mLET-gesteuerten Ablationsprotokolls konnte anschließend eine signifikante Reduktion der Rate an Ösophagus-Ulcera gezeigt werden.

Eine Schädigung des rechts-seitigen Nervus phrenicus wird häufiger nach Kryoballon-Ablation als nach Radiofrequenzstrom-Ablation beobachtet (19). Gemäß dem o.g. Entwicklungsprinzips der Kryoballon-Technologie war es möglich, dass die 2. Ballon-Generation zu einer erhöhten Inzidenz von Phrenicus-Paresen führt. Die retrospektive Analyse einer großen Patientenserie ergab hier keinen Unterschied in der Inzidenz, jedoch im Muster der assoziierten Zielvenen und der Abheilungsdauer. Mit zunehmender Erfahrung in der Verwendung der 2. Ballon-Generation und technischer Adaption (20) zeichnete sich ein progressiver Rückgang dieser Komplikation ab.

Zusammengefasst konnte die Kryoballon-Ablation als vereinfachtes Verfahren zur Durchführung der Pulmonalvenen-Isolation bei Patienten mit Vorhofflimmern in progressiven

Entwicklungsstufen etabliert werden. Die Äquivalenz der klinischen Langzeit-Effektivität gegenüber dem bisherigen Standard-Verfahren konnte in einer europäischen multizentrischen Studie gezeigt werden. Ein Beitrag zur Sicherheit des Verfahrens hinsichtlich ösophagealer Komplikationen wurde durch Entwicklung eines Temperatur-gesteuerten Ablationsprotokolls erbracht.

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Ipsilateral pulmonary vein isolation performed by a single continuous circular lesion: role of pulmonary vein mapping during ablation

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Aims Complete pulmonary vein isolation (CPVI) can be achieved by continuous circular lesions (CCL) around the ipsilateral pulmonary veins (PVs) guided by a 3D-mapping system. We investigated whether CPVI can be achieved with a single CCL around the isplilateral PVs without recording PV activity during ablation.

Methods and results Fifty patients with atrial fibrillation underwent ablation of CCLs around ipsilateral PVs guided by 3D mapping. One or two Lasso catheters were placed within the PVs. Lasso tracings were hidden to physicians during ablation. After completion of CCLs, Lasso tracings were evaluated. If PV activation was present, conduction gaps (CGs) were identified and ablated with guidance by the local electrogram and the Lasso catheter(s). In 21 patients (42%), CPVI was achieved after ablation of a single CCL around ipsilateral PVs. Pulmonary vein isolation was achieved in 43 patients (86%) in the right-sided PVs and in 21 patients (42%) in the left-sided PVs. In the remaining patients, there were eight CGs in right-sided CCLs and 40 CGs in left-sided CCLs. Conduction gaps along the left CCLs were found at the ridge between the PV ostia and the left atrial appendage in 27 out of 40 CGs (68%). Mean time from the P-wave onset to the earliest PV potential was 112 $\pm$ 35 ms in the presence of a CG at the roof, and 166 $\pm$ 59 ms in patients with CGs at other locations in left-sided CCLs ($P < 0.05$).

Conclusion Complete pulmonary vein isolation is difficult to achieve with a single CCL around ipsilateral PVs without continuous recording of PV activation during ablation.

Keywords Arrhythmia • Atrial fibrillation • Ablation • Mapping • Pulmonary vein

Introduction

Pulmonary vein isolation (PVI) has become the cornerstone in catheter ablation of paroxysmal and short-term persistent atrial fibrillation (AF).[1–3] It can be performed either with small circular lesions around each single pulmonary vein (PV) guided by a Lasso catheter within the PV[1] or with large continuous circular lesions (CCLs) around the ipsilateral PVs guided by a 3D-mapping system and the Lasso technique.[3,4] A recent trial has demonstrated that complete PVI with large CCLs leads to better outcome when compared with PVI with small circular lesions in patients with paroxysmal and persistent AF.[5]

Circumferential PVI is usually performed with one sheath for the ablation catheter and one (sometimes two) additional sheath(s) for the circumferential mapping catheter(s),[2,3,5] providing real-time information of left atrial to PV conduction during ablation. The use of multiple sheaths in the left atrium (LA) can make catheter manipulation difficult and increases procedural costs. In the present study, we prospectively investigated whether complete PVI can be achieved by a single CCL around ipsilateral PVs without guidance by a Lasso catheter within the PV.

Methods

Patient characteristics

This prospective study included 50 consecutive symptomatic patients (32 males; 58 $\pm$ 10 years; range 32–78 years) with paroxysmal AF in 43 and with persistent AF in 7 patients (persistent AF duration 5 $\pm$

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Table 1 Baseline patient characteristics ($n = 50$)

Age (year)	58 ± 10
Male (*n*)	32 (64%)
Paroxysmal AF (*n*)	43 (86%)
Persistent AF (*n*)	7 (14%)
Hypertension (*n*)	25 (50%)
CAD (*n*)	4 (8%)
Failed antiarrhythmics (*n*)	3 ± 1
AF duration (year)	7 ± 6
LA diameter (mm)	43 ± 5

4 months, *Table 1*). All patients had been ineffectively treated with a mean of 3 ± 1 antiarrhythmic drugs (AAD), including amiodarone in 21 patients (42%). Common-type atrial flutter had been previously documented in two patients. Primary hypertension had been documented in 25 patients (50%). None of these patients had previously undergone PVI. In seven patients structural heart disease was documented: coronary artery disease in four, moderate aortic valve stenosis in one, and rheumatic mitral stenosis with percutaneous mitral balloon valvuloplasty in two patients. The mean LA diameter was 43 ± 5 mm. Transoesophageal echocardiography was performed to rule out LA thrombi in all patients. Anticoagulation treatment with phenprocoumon was stopped on admission and replaced by intravenous heparin to maintain partial thromboblastin time at 2–3 times higher than the control value in all patients.

Electrophysiological study

All patients provided written, informed consent. The ablation procedure was performed by a single, well-experienced operator. Patients were kept on previous AAD and sedation was performed by continuous infusion of propofol. One multipolar 6-F catheters was positioned in the coronary sinus via the left subclavian vein. Placement of two (5 patients) or three (45 patients) 8-F non-steerable sheaths (SL1, St Jude Medical Inc., MN, USA) in the LA using a modified Brockenbrough technique has been described previously.[3] After transseptal catheterization, intravenous heparin was administered to maintain an activated clotting time of 250–300 s. The activated clotting time was monitored every 30 min and heparin dosage was adjusted accordingly. Additionally, continuous infusions of heparinized saline were connected to the transseptal sheaths (flow rate of 10 mL/h) to avoid potential thrombus formation or air embolism.

Three-dimensional electroanatomical mapping and irrigated radiofrequency ablation

The method of 3D electroanatomical mapping in the LA has been described previously.[3] Mapping was performed with a 3.5 mm tip catheter (ThermoCool Navi-Star, Biosense–Webster Inc., CA, USA) during sinus rhythm (SR) or AF. After reconstruction of the LA, each PV ostium identified by selective venography was tagged on the electroanatomical map. One or two decapolar Lasso catheters (Biosense–Webster Inc.) were placed within the PVs to record the PV potentials before ablation. Irrigated radiofrequency (RF) energy was delivered as previously described using a target temperature of 43°C, a maximum power of 30 W, and an infusion rate of 17 mL/min at the posterior and roof aspects of both CCLs.[3] Radiofrequency energy with a maximum power of 40 W and a flow rate of 25 mL/min was delivered to the anterior and inferior aspects of both CCLs. Continuous circular lesions were performed in the posterior wall ≈1 cm and in the anterior wall ≈5 mm from the angiographically defined PV ostia. Radiofrequency ablation was initially performed to create the right-sided CCls, and subsequently the left-sided CCLs.

During ablation, the Lasso recordings were hidden from all screens, but continuously stored in the background for later reviewing. Furthermore, the mapping catheter was strictly placed on the CCLs not to allow the investigator to check for ongoing PV conduction. After completion of the right- or left-sided single CCLs the investigators were unblinded to the Lasso tracings to evaluate whether there was ongoing PV conduction. In the latter case, location and number of conduction gaps (CGs) were identified by a sequence change or disappearance of PV activation during additional RF delivery at the CCL guided by the Lasso signals. The location of CGs was arbitrarily defined as roof, antero-superior, antero-inferior, inferior, postero-inferior or postero-superior. The procedural endpoint was defined as absence or dissociation of all PV potentials documented by the Lasso catheter(s) at least 30 min after PV isolation during SR.

Post-ablation care

Intravenous heparin was administered to all patients for 3 days after the procedure, followed by phenprocoumon for a minimum of 6 months. All patients were kept on the previously ineffective AAD for at least 3 months after the ablation whereupon AAD treatment was discontinued if no recurrent atrial tachyarrhythmia occurred. One day after the procedure, a surface echocardiogram (ECG), a transthoracic echocardiography, and a 24 h Holter ECG recording were performed. Holter ECG recordings were repeated at 1, 3, 6, and 12 months after the procedure.

Statistical analysis

Continuous variables were summarized as mean ± standard deviation, or median and lower and upper quartile where appropriate, and analysed using Student's *t*-test or Wilcoxon–Mann–Whitney test, respectively. Categorical variables were summarized as frequencies or proportions and analysed using cross tables, χ^2, and Fisher's exact test. A logistic regression model including left atrial diameter, duration of AF, age and presence of hypertension, or coronary artery disease was used to analyse the influence on residual LA–PV conduction after purely anatomically based circumferential ablation. Backward-, forward-, and stepwise selection procedures were applied to detect influential variables. The significance level of the score χ^2 for entering an effect into the model and of the Wald χ^2 for an effect to stay in the model was set to 10%. A P value of <0.05 was considered statistically significant.

Results

In 50 patients a total number of 194 PVs were identified including a left common PV in six patients. In 21 out of the 50 patients (42%), complete PVI was achieved after completion of single right- and left-sided CCLs (*Figure 1A*). In the remaining 29 patients (58%), additional RF delivery to the previous CCLs guided by the local electrogram and the Lasso catheter(s) was necessary to achieve complete PVI. The RF application times were 22 ± 4 min for the right-sided PVs and 24 ± 6 min for the left-sided PVs. The procedure time was 120 ± 39 min with a fluoroscopy time of 12 ± 6 min. No complications occurred during the procedure.

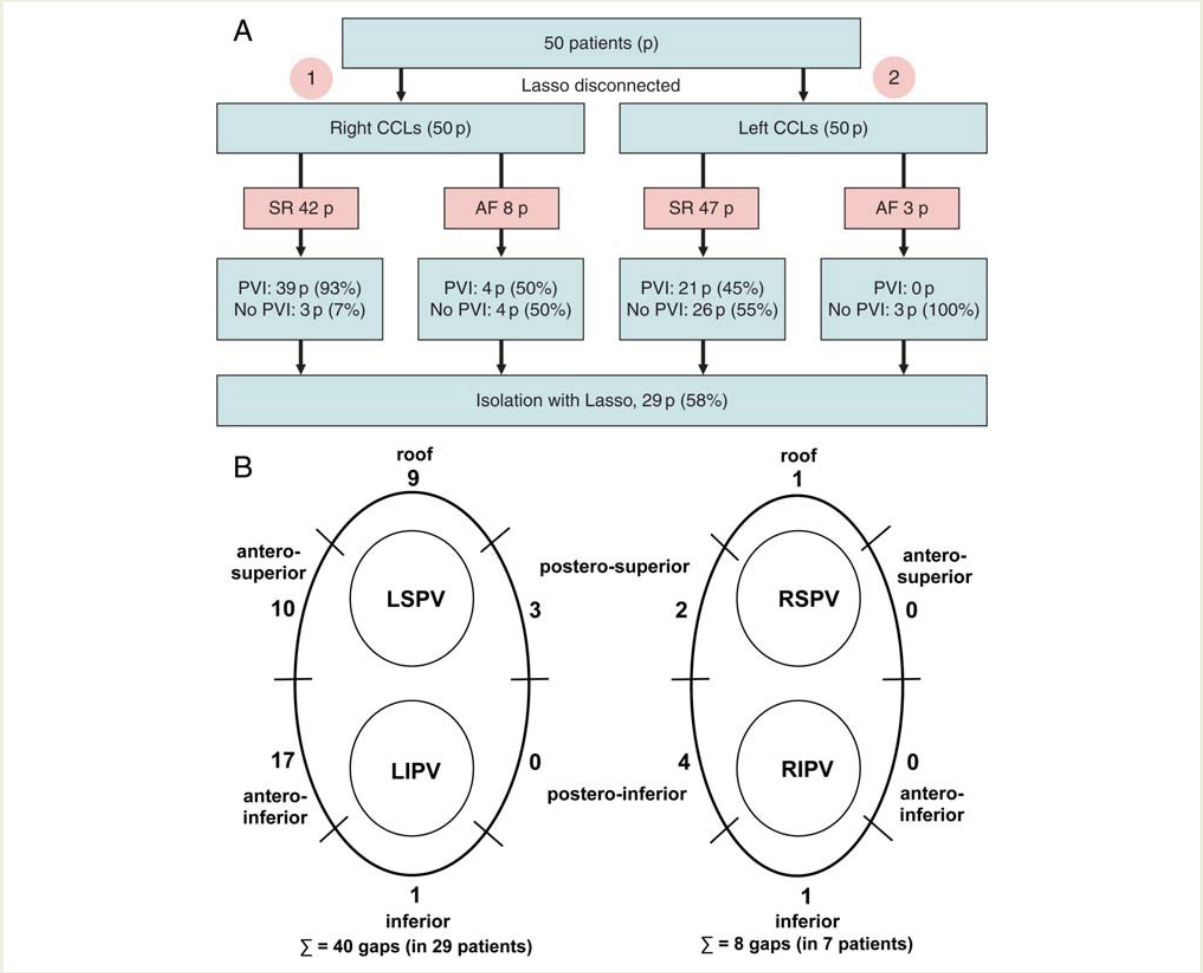

Figure 1 (*A*) Study outline. (*B*) Location of conduction gaps after anatomical completion of circular linear lesions. The scheme represents lateral and septal pulmonary vein ostia in postero-anterior view. One or two additional irrigated radiofrequency current applications abolished all conduction gaps. CCL, continuous circular lesion; SR, sinus rhythm; AF, atrial fibrillation; PVI, pulmonary vein isolation; LSPV, left superior pulmonary vein; LIPV, left inferior pulmonary vein; RSPV, right superior pulmonary vein; RIPV, right inferior pulmonary vein.

Complete isolation of right-sided pulmonary veins

Irrigated RF delivery on the right-sided CCLs was performed during SR in 42 patients and during AF in 8 patients. After completion of a single right-sided CCL in the patients with SR, PVI was achieved in 39 out of 42 patients (93%), whereas PV conduction remained in 3 patients. Mapping and ablation on the previous CCLs demonstrated a single CG in two patients, and two CGs in one patient. Location of the CGs was at the inferior, postero-inferior, and the postero-superior and postero-inferior segments of the previous CCLs, respectively (*Figure 1B*). In the eight patients with ablation during AF, PVI was demonstrated in four patients (50%) after completion of a single right-sided CCL. In the remaining four patients a single CG was demonstrated. Location of the CGs was at the postero-inferior segment in two patients, and at the superior and postero-superior segment in the remaining two patients (*Figure 1B*). One or two additional irrigated RF applications abolished all CGs. Conversion to stable SR occurred in two out of eight patients in AF during ablation of right-sided CCLs.

In summary, PVI of right-sided PVs was achieved in 43 patients (86%) by a single CCL without guidance by a Lasso catheter (*Figure 1A*).

Complete isolation of left-sided pulmonary veins

Electrical cardioversion was performed in three patients prior to left-sided PVI. Thus, irrigated RF delivery on the left-sided CCLs was performed during SR in 47 patients and during AF in 3 patients. After ablation of a single CCL around the left-sided PVs, PV isolation was achieved in 21 out of 47 patients with ablation during SR (45%). Pulmonary vein conduction remained in 26 out of 47 patients (55%) with ablation during SR and in all 3 patients with ablation during AF

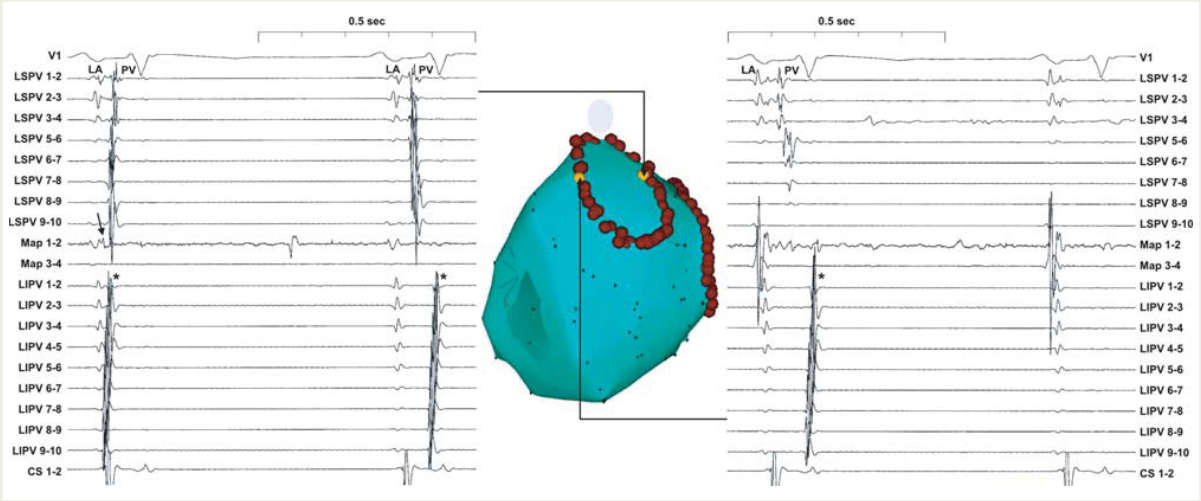

Figure 2 Mapping and ablation of two remaining conduction gaps after anatomical completion of left-sided continuous circular lesion. An anatomical 3-D electroanatomical-map in left lateral view is shown. Tracings are surface echocardiogram lead V1; Lasso recordings from left superior pulmonary vein; recordings from mapping catheter, Lasso recordings from the left inferior pulmonary vein, and recording from the coronary sinus catheter. Yellow point tags in the 3-D electroanatomical-map correspond to loci of pulmonary vein activation sequence change or pulmonary vein isolation during ablation (brown point tags) as indicated by arrows. Left panel: elimination of a postero-superior conduction gap is indicated by a sudden activation sequence change in the Lasso recordings during ablation. Arrow indicates far-field potential from left atrium; asterisk indicates pulmonary vein potential. Right panel: subsequent mapping and ablation in the same patient reveals a second antero-superior conduction gap with simultaneous isolation of lateral pulmonary veins demonstrated by elimination of the pulmonary vein potential in the Lasso recordings.

(*Figure 1A*). Mapping and ablation on the previous CCLs demonstrated a single CG in 20 patients, 2 gaps in 7 patients, and 3 gaps in 2 patients (*Figures 2* and *3*). Location of the gaps in the previous left-sided CCLs is shown in *Figure 1B*. Conversion to stable SR occurred in two out of three patients in AF during ablation of left-sided CCLs. One patient underwent electrical cardioversion after complete isolation of right- and left-sided CCLs.

During SR, the mean delay of PV activation (measured from the onset of the P-wave to the earliest PV potential recorded by the Lasso catheter) after completion of the left-sided CCLs was 149 $\pm$ 58 ms. In case of a CG at the roof, this delay was significantly shorter (112 $\pm$ 35 ms) when compared with the remaining patients with ongoing PV conduction (166 $\pm$ 59 ms; $P = 0.024$; *Figure 3B*). One or two additional irrigated RF applications abolished all CGs.

After electrical isolation of all PVs, spontaneous or catheter-induced activity within the isolated PVs dissociated from atrial activity occurred in 48 patients (96%) in right-sided PVs, and in 49 patients (98%) in left-sided PVs. In two patients in whom common-type atrial flutter in addition to paroxysmal AF had been previously documented, ablation along the cavotricuspid isthmus with conduction block was also performed.

Predictors of efficacy of purely anatomically based pulmonary vein isolation

A logistic regression model was used to analyse the influence of atrial diameter, duration of AF, age and presence of hypertension, or coronary artery disease on residual LA–PV conduction after purely anatomically based circumferential ablation. The right-sided and left-sided PVs were analysed separately.

Using this model, no association between the covariables and residual PV conduction after anatomically based CCL ablation was found for the right- or left-sided PVs (*Table 2*).

Follow-up

During the follow-up period of 10 $\pm$ 3 months, 37 out of 50 patients (74%) were in SR without antiarrhythmig drugs. Left atrial macro-reentrant tachycardia occurred in 4 out of 13 patients with recurrent atrial tachyarrhythmia; two patients presented with LA–PV-reentry tachycardia utilizing two CGs in the previous left-sided CCL, and two patients presented with perimitral flutter. Left atrial macroreentrant tachycardia was successfully terminated in all patients during the second procedure by PV-reisolation in two patients, or ablation with conduction block along the left atrial isthmus between the previous left-sided CCL and the mitral annulus in two patients, respectively. Of the remaining nine patients with recurrent AF, a second procedure revealed re-conduction into $\geq$1 PV in eight patients, which was successfully eliminated.

Discussion

The current study describes (i) the feasibility of achieving complete PVI by ablation of a single CCL around ipsilateral PVs when performed by a single well-experienced operator, (ii) the location of

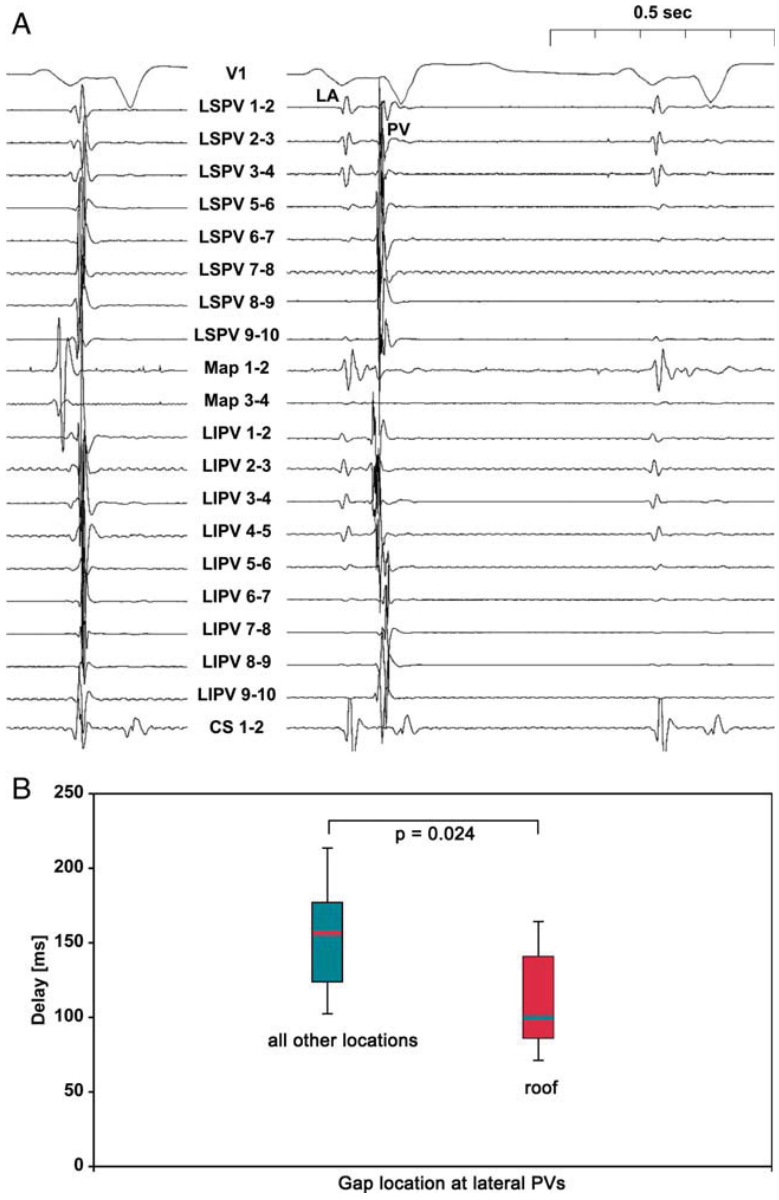

Figure 3 (*A*) Intracardiac recordings in a patient exhibiting residual dominant conduction at the left atrial roof after anatomical completion of left-sided continuous circular lesions. Tracings are surface echocardiogram lead V1; Lasso recordings from left superior pulmonary vein; recordings from the mapping catheter, Lasso recordings from the left inferior pulmonary vein, and recording from the coronary sinus catheter. Left panel: Lasso recordings from lateral pulmonary veins demonstrate lack of separation of left atrial far-field and pulmonary vein potential in sinus rhythm, indicating superior residual conduction in left-sided continuous circular lesion. Right panel: after mapping and ablation of a conduction gap at the left atrial roof, the delay of pulmonary vein activation with sequence change in the Lasso recordings demonstrates the presence of a second gap. Pulmonary vein activation now is delayed with respect to atrial far-field potential (left atrium) and P-wave onset. A single radiofrequency current application antero-inferior led to pulmonary vein isolation indicated by elimination of the pulmonary vein (PV) potential. (*B*) Delay of pulmonary vein potential in sinus rhythm (P-wave onset to earliest pulmonary vein potential in Lasso recordings) discriminates between conduction gaps at the left atrial roof vs. other locations in left-sided continuous circular lesions.

residual LA–PV conduction after ablation of single CCLs, and (iii) the impact of ongoing AF on acute success of anatomically guided PVI.

The importance of complete LA–PV disconnection as the electrophysiological endpoint of PVI to treat paroxysmal and persistent AF has been documented.[2] Complete PVI can be demonstrated by

Table 2 Impact of patient characteristics on efficacy of purely anatomically based complete pulmonary vein isolation

PVI achieved	Left-sided PVs			Right-sided PVs		
	Yes	No	*P* value	Yes	No	*P* value
LA (mm)	43 (41;48)	42 (40;43)	0.16	42 (38;46)	41 (40;48)	0.82
AF duration (year)	5 (4;8)	5 (3;8)	0.62	5 (3;8)	8 (4;15)	0.33
Age (year)	59 ± 11	58 ± 10	0.77	58 ± 10	63 ± 10	0.22
Hypertension	43%	55%	0.39	49%	57%	1.0
CAD	5%	10%	0.63	7%	14%	0.46

PVI, pulmonary vein isolation; LA, left atrial diameter; AF, atrial fibrillation; CAD, coronary artery disease.

the use of two simultaneous Lasso catheters placed in the ipsilateral PVs during ablation of CCLs.[2–4] However, using the 2-Lasso technique simultaneous isolation of ipsilateral PVs has been demonstrated in the majority of right- and left-sided PVs,[3] providing support for a single Lasso approach in routine clinical practice. However, the latter approach still requires double transseptal puncture, which may impact on procedural safety and result in difficult manipulation of two sheaths in the LA. Thus, we aimed to investigate whether a well-experienced operator would be able to achieve the endpoint of complete PVI by only anatomically based ablation of a single CCL around the ipsilateral PVs, thereby requiring only a single transseptal access.

In this study, we demonstrate ongoing PV conduction after completion of single CCLs guided by electroanatomical mapping in 58% (29 out of 50) of patients. Of these 29 patients, all exhibited residual conduction into the left-sided PVs, while 7 patients also showed residual conduction into the right-sided PVs (*Figure 1*). These data demonstrate that ablation of single CCLs using electroanatomical mapping fails to achieve the endpoint of complete PVI in a significant proportion of patients mainly due to residual conduction into the left-sided PVs. However, mapping with the ablation catheter inside the PV after anatomically based circumferential ablation can be used to identify and eliminate remaining CGs.[6–8]

The anatomy of left-sided PVs constitutes a challenge to antral CCL ablation mostly due to the muscular ridge between the PVs and the left atrial appendage that is a narrow (<5 mm) structure in the majority of patients, containing thick myocardium especially in its superior part.[9,10] Accordingly, the majority of CGs (27 out of 40, 68%) after completion of single left-sided CCLs was located at the anterior ridge (*Figure 1B*). The second most common site for residual conduction into the left-sided PVs was the LA roof (9 out of 40, 23%). This reflects the fact that, using a fixed-curved sheath, achieving good contact at this structure with the ablation catheter may be challenging, possibly impacting on lesion quality with fixed power settings. After completion of a single right-sided CCL, residual conduction was mostly present at the posterior wall (six out of eight, 75%; *Figure 1B*).

In the small subset of patients ablated during AF, 50% (four out of eight) of right-sided CCLs as well as 100% of left-sided CCLs (three out of three) failed to achieve PVI after completion of single CCLs. This may indicate that achieving continuous ablation lines is more difficult in the presence of AF because changes in local signals upon RF delivery indicative of lesion formation are easier to judge in SR. Moreover, catheter positioning at the anterior ridge at left-sided PVs is greatly facilitated by local potentials in SR.

Starting ablation of left-sided CCLs at the LA roof in SR usually results in different degrees of delay of PV activation due to conduction block into the left PVs via the fast conducting Bachmann's bundle. This facilitates catheter positioning during further ablation near the PV ostium by clear separation of atrial and PV signals. Conversely, ongoing PV conduction via a gap at the roof should result in short or no delay of PV with respect to atrial activation. Indeed, we found that in the presence of a CG at the LA roof in left-sided CCLs, there was no or minimal delay of PV activation (*Figure 3B*). This finding may facilitate mapping of CGs in the previous left-sided CCLs.

In a previous study, Tamborero *et al.*[6] randomly assigned patients to circumferential PVI with or without the use of a circular mapping catheter. In the single-catheter group PVI was assessed by mapping several sites within the surrounded region with the distal dipole of the ablation catheter. The study endpoint (freedom from arrhythmia recurrence after a blanking period of 3 months) occurred in 64.4% of patients in whom the circular mapping catheter had been used, as opposed to 42.5% in the single-catheter group. This may implicate a lower rate of chronic (or even acute) PVI without the use of a circular mapping catheter.

Limitations

This study has several limitations. (i) Lasso catheter(s) were not removed during ablation of CCLs, but Lasso tracings were hidden from all screens during ablation. Thus, in contrast to a true single-catheter procedure, Lasso catheter(s) still could have served as fluoroscopic markers of PV ostia. However, after identification of PV ostia, catheter navigation was mainly based on the electroanatomical mapping system. (ii) This study sought to investigate whether the endpoint of complete PVI can be achieved after ablation of single CCLs around ipsilateral PVs by a single well-experienced operator. No attempt was made to evaluate or abolish residual LA–PV conduction without the use of a spiral catheter inside the PV.[6–8] (iii) A non-steerable sheath was used in conjunction with the mapping catheter. The use of a steerable sheath possibly impacts on contact force and thus may have resulted in different isolation rates.[11] (iv) Our protocol used fixed energy settings for RF ablation at the anterior/superior or

posterior/inferior LA–PV junction. Further investigation is needed whether LA–PV conduction can be totally abolished with higher energy delivery. Finally, this study was a non-randomized, single-group feasibility study, thus, differences in clinical outcome or procedural parameters when, or when not, using a circular mapping catheter could not be evaluated.

Conclusion

Complete PV isolation by ablation of single CCLs around ipsilateral PVs is difficult to achieve without a continuous recording of PV activation, especially during AF. The majority of CGs in single CCLs are left sided and located at the lateral ridge between the left-sided PVs and the left atrial appendage. Furthermore, lack of delayed conduction into lateral PVs during SR indicates a CG at the roof in majority of the patients.

Conflict of interest: none declared.

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Cryoballoon temperature predicts acute pulmonary vein isolation

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BACKGROUND Cryoballoon pulmonary vein isolation (PVI) currently requires a long cryoballoon application (CBA) time of 240 to 300 seconds, thus repeated ineffective CBA prolongs procedure duration. We hypothesized that cryoballoon temperature (CBT) may be used to discriminate between effective and ineffective CBA during freezing.

OBJECTIVE This study sought to evaluate CBT as a predictor of CBA efficiency.

METHODS Sixty-six patients with atrial fibrillation underwent PVI using the single big (28 mm) cryoballoon technique. CBT was continuously recorded. After each CBA (300 seconds), a Lasso catheter (Biosense Webster, Inc., Diamond Bar, California) was placed into the target pulmonary vein (PV) to determine whether electrical PV disconnection was present. Only the first CBA at each PV was analyzed to avoid cumulative effects.

RESULTS The CBT was lower during CBA at superior compared with inferior PVs. When individual CBAs were grouped according to successful/failed PVI, CBT was lower for those CBAs that resulted in successful PVI at all time points analyzed. To test the performance of CBT to predict failed CBA, receiver-operator curves were constructed. A minimal CBT of $\geq -42°C/-39°C$ (superior/inferior PVs) predicted failed PVI with 73%/92% specificity (area under the curve 0.82/0.81); positive predictive value (PPV) 74%/74%. A minimal CBT of $< -51°C$ was invariably associated with PVI. After 120 seconds of freezing, a CBT of $\geq -36°C/-33°C$ (superior/inferior PVs) predicted failed PVI with 97%/95% specificity (area under the curve 0.82/0.76); PPV 82%/80%.

CONCLUSION Balloon temperature predicts successful target PVI during cryoablation and may serve in the early identification of noneffective balloon applications.

KEYWORDS: Arrhythmia; Atrial fibrillation; Balloon; Catheter ablation; Cryothermal

ABBREVIATIONS **AF** = atrial fibrillation; **CBA** = cryoballoon application; **CBT** = cryoballoon temperature; **LA** = left atrium; **NPV** = negative predictive value; **PNP** = phrenic nerve palsy; **PPV** = positive predictive value; **PV** = pulmonary vein; **PVI** = pulmonary vein isolation; **ROC** = receiver-operator curve

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Introduction

Cryoballoon technology is increasingly used to perform pulmonary vein isolation (PVI) in patients with atrial fibrillation (AF).[1-4] The device is designed to create circumferential lesions around the target PV, ideally with a single cryoballoon application (CBA). However, cryoablation vitally depends on balloon-tissue contact or pulmonary vein (PV) occlusion, because residual blood flow interferes with lesion formation. In addition, complete PV occlusion reduces surrounding blood flow, resulting in lower cryoballoon temperatures.[5] Failure to achieve complete balloon-tissue contact results in ineffective CBA. Because CBA is performed for 4 to 5 minutes, repeated ineffective CBA prolongs procedure duration. Different techniques to evaluate PV occlusion have been proposed, some of which require additional diagnostic tools such as intracardiac ultrasound.[5-8] The simplest and most widely used technique is angiography via the balloon tip.[1-4] Angiography, however, cannot be used to evaluate contact during freezing, and it has been shown that balloon dislocation may occur after initiation of CBA.[5]

Cryoballoon temperature (CBT) is measured continuously during CBA by a thermocouple in the proximal inner balloon (Figure 1). We hypothesized that CBT, a readily available parameter during cryoballoon PVI, may be used to discriminate between effective and ineffective CBA during freezing.

Methods

Patients

Between April 2006 and March 2010, a total of 134 patients underwent cryoballoon PVI using the single big cryoballoon technique.[1] In 66 of these patients, complete recordings of CBT over time during each CBA was available. These patients constitute the study population. Baseline clinical characteristics are shown in Table 1.

Cryoballoon ablation

The concept of the single big cryoballoon technique for PVI (Arctic Front, 28-mm diameter, Medtronic CryoCath LP, Pointe-Claire, Quebec, Canada) has been described in detail previously.[1] In brief, after double transseptal puncture, selective PV angiography was performed to identify the PV ostia in 2 projections (right anterior oblique 30°, left anterior oblique 40°). Baseline potentials

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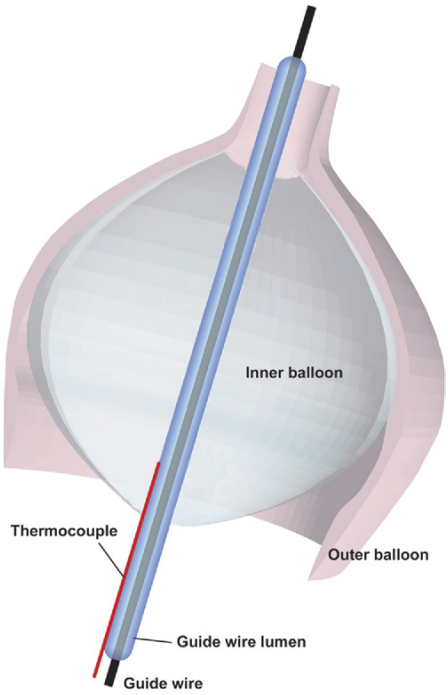

Figure 1 Cryoballoon device assembly. The thermocouple is located in the proximal inner balloon.

of all PVs were recorded with a Lasso catheter (Biosense Webster, Inc., Diamond Bar, California). The 28-mm balloon was maneuvered to all PV ostia by use of a steerable 12-Fr sheath (FlexCath, Medtronic CryoCath LP) and a guidewire (Amplatz Stiff Wire, Cook Inc., Bloomington, Indiana) inserted through the lumen of the balloon catheter. To asses the exact position of the inflated balloon in relation to the left atrial (LA)-PV junction, contrast medium was injected from the distal lumen of the cryoballoon catheter. CBA was performed for a target time of 300 seconds. The right phrenic nerve was constantly paced from the superior caval vein during freezing at the septal PVs. After each freeze, PV conduction was reevaluated by the Lasso catheter. If the PV was not isolated, the cryoballoon was repositioned and balloon to LA-PV contact was reevaluated by angiography before the next freeze. To increase long-term lesion durability,[9] one bonus application was delivered to each target PV after isolation had been achieved (51 patients). In 15 patients, 2 bonus lesions were applied

Table 1 Baseline patient characteristics (n = 66)

Age (yrs)	57 ± 11
Male (n)	52 (79%)
Paroxysmal AF	61 (92%)
Persistent AF	5 (8%)
Failed antiarrhythmic agents (n)	1.7 ± 1.0
AF duration (yrs)	6 ± 5
LA diameter (mm)	42 ± 5
Hypertension (n)	28 (42%)
Diabetes (n)	1 (1.5%)
Coronary artery disease (n)	4 (6%)

AF = atrial fibrillation; LA = left atrium.

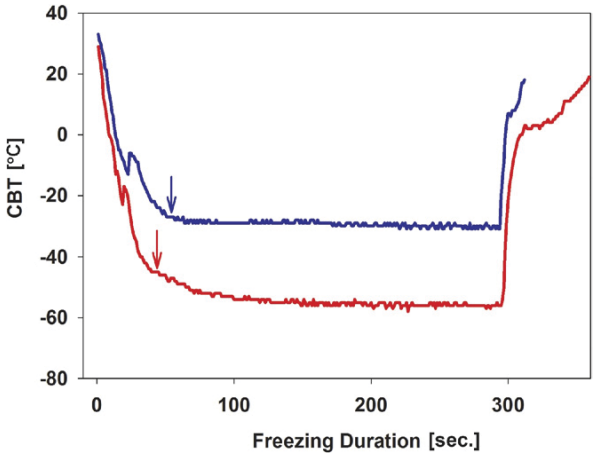

Figure 2 Typical cryoballoon temperature-time curve. Representative time course of cryoballoon temperature (CBT) during freezing at the left superior pulmonary vein (PV) with successful PV isolation (red) or remaining PV conduction (blue) after cryoballoon application. Arrows indicate start of temperature plateau phase (P-point).

due to enrollment in a prospective study that will be reported separately.[10] Thirty minutes after isolation of the last PV, remapping of all PVs was performed with the Lasso catheter to confirm PV disconnection. The ablation end point was the loss of all PV potentials at the end of the procedure.

Temperature curve analysis

Cryoballoon temperature-time curves during each freeze were acquired by the CryoConsole software (Medtronic CryoCath LP). CBT was measured by a thermocouple in the proximal inner balloon (Figure 1). To avoid the confounding effect of repeated CBA, only the initial freeze at each PV was analyzed. The transitional time point between the rapid and slow cooling phase (P-point) (Figure 2) was defined as the earliest time point at which temperature change was ≤0.1°C/sec averaged over a 10-second period. If a pull-down maneuver[1] was used to isolate the right inferior PV, P-point analysis was performed after completion of the pull down.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation. The Student *t* test was used to compare CBT according to PV location (paired), or PV conduction status after ablation (unpaired). The chi-square test was used to compare the proportion of superior and inferior PVs with isolation after the first CBA. Receiver-operator characteristic (ROC) curves were constructed to evaluate the performance of CBT as a predictor of ineffective CBA. The positive state was defined as ongoing LA-PV conduction after completion of the CBA. A value of $P < .05$ was considered statistically significant.

Results

Cryoballoon ablation

PV anatomy consisted of 4 individual PVs in 60 patients. In the remaining 6 patients, a left common PV was found (Table 2). In 5 of these patients with a short common trunk, superior and

Table 2 Procedural parameters of cryoballoon ablation

Vein	Diameter [mm]	Number of applications
LSPV	19 ± 3	2.5 ± 0.8
LIPV	17 ± 2	2.8 ± 1.4
LCPV	28 ± 4	4.2 ± 1.0
RSPV	18 ± 3	2.7 ± 1.2
RIPV	18 ± 3	3.0 ± 1.1
Procedure duration, min	190 ± 43	
Fluoroscopy time, min	32 ± 13	

LCPV = left common pulmonary vein; LSPV = left superior pulmonary vein; LIPV = left inferior pulmonary vein; RSPV = right superior pulmonary vein; RIPV = right inferior pulmonary vein.

inferior branches were isolated individually and included in the temperature analysis as left superior PV and left inferior PV, respectively. In 1 patient, the left common PV was isolated by sequentially performing CBA at the superior and inferior circumference and omitted from temperature analysis. Of a total of 263 individually targeted PVs, 159 (60%) were isolated by the first CBA. The proportion of PVs with isolation after the first CBA was not statistically different when comparing superior PVs to inferior PVs (64% versus 57%, respectively, $P = .26$). The average number of CBA per vein, including bonus CBA, is shown in Table 2. PV reconduction after initial PVI and bonus lesion application occurred in 3 of a total of 263 PVs (1.1%) after the waiting period. Of these 3 reconnected PVs, 1 PV had been isolated with the first balloon application, and the remaining 2 PVs had required >1 balloon application to achieve initial isolation. The proportion of PVs with isolation after the first balloon application exhibiting procedural reconnection was 1 of 159 (0.6%). All PVs were successfully reisolated with 1 to 3 additional CBAs. The end point of complete PVI was achieved in all patients. Procedure duration and fluoroscopy time were 190 ± 43 minutes and 32 ± 13 minutes, respectively. Procedure-related complications occurred in 4 patients. In 2 patients, right-sided phrenic nerve palsy (PNP) was present at the end of the procedure due to CBA at septal PVs (right superior PV and right inferior PV, respectively). In 1 of these patients, PNP resolved within 7 months. In the other patient, PNP continues to be present after 10 months. In 2 patients, transient symptoms of delayed gastric emptying were present after the procedure that resolved within 1 week, as described previously.[11]

Balloon temperature characteristics

Cryoballoon temperature-over-time curves generally showed a biphasic pattern with a rapid initial cooling phase, followed by a plateau phase with slowly decreasing temperature (Figure 2). The beginning of the plateau phase (i.e., the P-point) occurred at 48 ± 6 seconds (right superior PV), 54 ± 13 seconds (right inferior PV), 48 ± 9 seconds (left superior PV), and 46 ± 6 seconds (left inferior PV). CBT after increasing freezing duration at the 4 anatomical PVs is shown in Table 3. At each time point analyzed (P-point, 90, 120, and 300 seconds), CBT was lower during CBA at superior when compared with inferior PVs for both septal and lateral PVs (Table 3). Therefore, further temperature analysis was performed separately for superior and inferior PVs.

Performance of CBT to predict ineffective cryoablation

When individual CBA were grouped according to successful/failed PVI, CBT was lower for those CBAs that resulted in successful PVI at all time points analyzed (Table 4, Figure 3). To test the performance of CBT to discriminate between effective and failed CBA, ROC curves were constructed from CBT measurements at different time points during freezing (P-point, 90, 120, and 300 seconds). The results of the ROC statistics are shown in Table 5. Predictive performance increased with freezing duration with areas under the ROC curve between 0.71 and 0.82 (Table 5, Figure 3).

Proposed CBT cutoff indicating ineffective cryoablation

For minimal CBT at the end of freezing, the following cutoff values based on highest sensitivity and specificity were found: A CBT of ≥ −42°C at superior PVs predicted ongoing LA-PV conduction with 76% sensitivity and 73% specificity (positive predictive value [PPV]: 74%, negative predictive value [NPV]: 76%). A CBT of ≥ −39°C at inferior PVs predicted ongoing LA-PV conduction with 53% sensitivity and 92% specificity (PPV: 74%, NPV: 76%). On the other hand, a minimal CBT of < −51°C predicted PVI with 100% specificity for both superior and inferior PVs, i.e., all PVs were isolated at CBT below −51°C (Figure 3).

To guide the operator in the decision of whether or not to stop a presumably ineffective CBA early, a temperature limit needs to predict failed PVI with high specificity. For superior PVs, a CBT of ≥ −36°C at 120 seconds predicted ineffective CBA with 97% specificity (PPV 82%). For inferior PVs, a CBT of ≥ −33 °C at 120 seconds predicted ineffective CBA with 95% specificity (PPV 80%) (Figure 3).

Discussion

The main findings of this study are as follows. (1) Cryoballoon temperature may be used to discriminate between successful and failed CBA at various time points during freezing. (2) A high CBT predicted a failed freeze with high specificity. (3) Very low CBT was invariably associated with successful PVI.

Although the ideal freezing duration of a CBA remains to be determined, cryoballoon ablation is generally performed for 4 to 5 minutes.[1-4,9] During this period, the operator is usually blinded to ablation efficiency. Although a thin circular mapping catheter inserted through the central canal of the cryob-

Table 3 Cryoballoon temperature [°C] at different time points during freezing

PV	P-point	90 sec	120 sec	300 sec
RSPV	−37 ± 6*	−42 ± 7*	−44 ± 7*	−48 ± 7*
RIPV	−33 ± 5	−37 ± 6	−39 ± 6	−42 ± 7
LSPV	−38 ± 7†	−42 ± 7†	−44 ± 7†	−48 ± 7†
LIPV	−34 ± 5	−39 ± 6	−40 ± 6	−44 ± 7

Abbreviations as in Table 2.
*$P < .001$ vs. RIPV.
†$P < .01$ vs. LIPV (paired Student t test).

Table 4 Cryoballoon temperature [°C] according to acute ablation success

	P-point		90 sec		120 sec		300 sec	
PVI	Yes	No	Yes	No	Yes	No	Yes	No
Superior PVs	−40 ± 6	−33 ± 5*	−45 ± 7	−38 ± 5*	−47 ± 6	−39 ± 5*	−51 ± 6	−42 ± 6*
Inferior PVs	−35 ± 5	−31 ± 4*	−40 ± 6	−35 ± 5	−41 ± 5	−36 ± 5*	−46 ± 6	−39 ± 5*

PV = pulmonary vein; PVI = pulmonary vein isolation.
*$P < .01$ vs. yes (unpaired Student t test).

alloon may be used to monitor LA-PV conduction during freezing, the only available catheter at this time lacks the mechanical stability needed to achieve occlusive positions, especially at inferior PVs.[12] Thus, inefficient CBAs prolong procedure duration, leading to overtreatment.

Cryoballoon temperature is automatically monitored during freezing. It is affected by balloon occlusion of the treated PV because remaining PV blood flow has a rewarming effect on the cryoballoon, as demonstrated by additional temperature decrease after performance of the pull-down maneuver to close a remaining inferior leak.[1,9,13] Thus, CBT provides information about balloon-tissue contact that may explain the association of low CBT with cryoballoon ablation efficiency. The lower CBT at superior when compared with inferior PVs may result from higher contact forces due to better alignment of the sheath/balloon system to superior PVs[14] or regional hemodynamic differences such as the left atrial roof partially protecting the balloon from atrial blood flow.

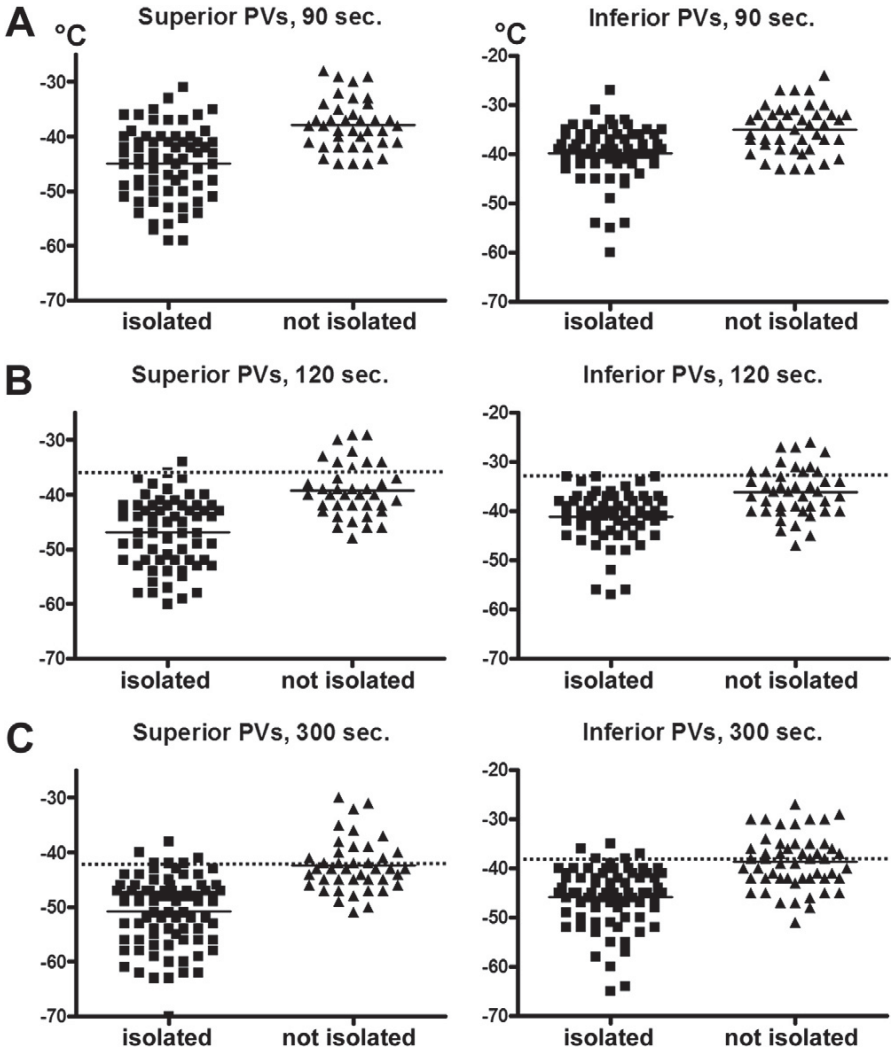

Figure 3 Cryoballoon temperature (CBT) according to acute ablation success. CBT at 90 **(A)**, 120 **(B)**, and 300 **(C)** seconds of freezing are shown for superior and inferior pulmonary veins (PV). CBT has been grouped according to successful PV isolation (isolated) or remaining PV conduction (not isolated) after cryoballoon application. Solid bars indicate group mean. Dotted lines indicate CBT cutoff differentiating successful/failed PV isolation (see text).

Table 5 Performance of cryoballoon temperature at indicated time points to predict failed pulmonary vein isolation

	Superior PVs				Inferior PVs			
CBT at	P-point	90 sec	120 sec	300 sec	P-point	90 sec	120 sec	300 sec
AUC	0.81	0.80	0.82	0.82	0.71	0.74	0.76	0.81
95% CI	0.72–0.89	0.71–0.88	0.75–0.90	0.75–0.90	0.60–0.81	0.64–0.84	0.67–0.86	0.73–0.88
P value	<.001	<.001	<.001	<0.001	<.001	<.001	<.001	<.001

AUC = area under the curve; CBT = cryoballoon temperature; CI = confidence interval.

Although there is overlap of CBT when comparing groups of successful and ineffective CBA (Figure 3), high and low temperature ranges may be defined that allow prediction of PV conduction status after CBA with high specificity. In this study, a minimal CBT ≥ -39°C/ -42°C (inferior/superior PVs) was highly indicative of a failed CBA. On the other hand, a CBT of < -51°C was invariably associated with PVI. In the setting of cryoballoon ablation performed by a single transseptal puncture,[5,7,8,15] these temperature values may guide the operator through the procedure until removal of the balloon catheter and conformation of ablation success by electrical mapping of the PVs is performed.

When comparing CBTs of efficient and failed ablations, a temperature difference was already apparent at the beginning of the plateau phase (Table 4) and temperature distributions continued to separate to provide for clinically useful cutoff values after 120 seconds (Figure 3). This provides an opportunity to interrupt inefficient freezing to shorten procedure duration and avoid overtreatment. In case of a CBT ≥ -33°C/ -36 °C (inferior/superior PVs) after 120 seconds of freezing duration, stopping of the CBA and balloon repositioning should be considered.

Study limitations

This study has limitations as follows. (1) We used a single big (28 mm) cryoballoon strategy. Because temperature characteristics may vary with balloon size, our analysis only applies to the 28-mm balloon. (2) CBT is measured during freezing, and inherently may not be used to evaluate balloon-tissue contact before ablation. However, it is a simple parameter provided by the cryoballoon system to estimate ablation efficiency during freezing. (3) CBT is measured by a thermocouple in the proximal inner balloon (Figure 1), not necessarily representing temperatures at the balloon-tissue interface. In addition to balloon occlusion of the target PV, other factors such as balloon position relative to the level of the PV ostium or atrial hemodynamics may influence the measurement. (4) Due to our protocol of systematic bonus lesion application to enhance long-term durability of the cryolesion,[9] this study does not provide data on procedural PV reconduction rate after the waiting time following a single cryoballoon application. However, in a previous study in 27 patients, no procedural reconduction was observed after the waiting time (>30 minutes) without the use of bonus lesion applications.[1] Furthermore, the procedural PV reconduction rate was reported to be low (2.8%) when extending the waiting time to 1 hour.[16] The association of CBT with long-term PVI remains to be determined.

Conclusion

CBT, a simple parameter provided by the cryoballoon system, may be used to discriminate between successful and failed PVI at various time points during freezing. Cutoff temperatures were defined that predicted failed ablation during freezing with high specificity. CBT may be used to guide cryoablation and avoid prolonged inefficient freezing.

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Two Versus One Repeat Freeze–Thaw Cycle(s) After Cryoballoon Pulmonary Vein Isolation: The ALSTER EXTRA Pilot Study

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Two versus One Repeat Freeze–Thaw Cycle(s). ***Background:*** **Repeated freezing (bonus applications) during cryoballoon pulmonary vein isolation (PVI) has been suggested to improve lesion durability. However, the long-term clinical effects of repeated freezing have not been investigated.**

Methods and Results: **A total of 51 patients (pts) with paroxysmal atrial fibrillation (AF) underwent PVI using the single big (28 mm) cryoballoon technique. One (27 pts, group I) or 2 bonus applications (24 pts, group II) were performed at all PVs subsequent to PVI. Clinical follow-up consisted of continuous rhythm monitoring by an implantable cardiac monitor (ICM, 24 pts) and serial 7-day Holter-ECG recording (7DH, 27 pts). The primary endpoint was defined as recurrent AF or atrial tachycardia.**

Acute PVI of all PVs was obtained in 50/51 pts (98%). The median (Q1;Q3) follow-up duration in this study was 384 (213;638) days. The primary endpoint occurred in 48% (group I, 15 pts ICM, 12 pts 7DH) and 46% (group II, 9 pts ICM, 15 pts 7DH), P = 0.84. Procedure- and fluoroscopy-time for group I versus group II was 193 ± 56 minutes versus 207 ± 27 and 33 ± 13 minutes versus 34 ± 11 minutes, respectively. Right phrenic nerve palsy (PNP) occurred in 3 pts (all group II, time to resolution: 128 ± 112 days). In 2 of these pts, PNP occurred during the second bonus application.

Conclusion: **Application of 2 when compared to 1 freeze–thaw cycle(s) following cryoballoon PVI did not result in improved clinical success but was associated with a higher complication rate.** *(J Cardiovasc Electrophysiol, Vol. 23, pp. 814-819, August 2012)*

atrial fibrillation, catheter ablation, cryoballoon, phrenic nerve paralysis, pulmonary vein isolation

Introduction

Catheter ablation using radiofrequency current (RFC) for pulmonary vein isolation (PVI) is a well-established therapy option for the treatment of drug resistant paroxysmal atrial fibrillation (PAF).[1,2] Applying contiguous left atrial (LA) linear lesions using RFC point-by-point ablation is technically complex and typically requires a 3-dimensional reconstruction system.[1] In contrast, the cryoballoon system represents an anatomically based ablation device that allows for simplified PVI with a favorable safety profile.[3-10] Creating permanent transmural lesions without increasing the risk for collateral damage remains the ultimate goal of PVI because AF recurrence is associated with recovered PV conduction independent of the utilized energy source and PV reisolation results in increased clinical success rates.[11,12]

Cryoballoon ablation is generally performed continuously for 240–360 seconds at each target PV.[3-9] It has been shown in experimental studies that repetition of the freeze–thaw cycle extends the necrotic effect to the peripheral areas of tissue freezing, resulting in enhanced lesion depth.[13] A high rate of PV isolation 10 ± 2 weeks after cryoballoon ablation was achieved with 2 repeat freeze–thaw cycles following acute PVI (bonus applications).[6] The ideal number of bonus applications, however, remains to be determined. Therefore, we investigated the clinical outcome following cryoballoon PVI with 2 different strategies: 1 compared to 2 bonus applications at each target PV.

Methods

Patients and Study Design

Previous data about the impact of bonus cryoballoon lesion applications on chronic clinical success were not available to support a hypothesis. Thus, we conducted a pilot study including 51 patients with PAF. We previously published our initial experience with the cryoballoon system reporting on our first 27 patients.[7] The following consecutive patients meeting entry criteria represent the cohort of this study. Patients were prospectively assigned to 2 groups: in group I 1 bonus application per vein was performed after isolation of the target PV had been achieved, and in group II

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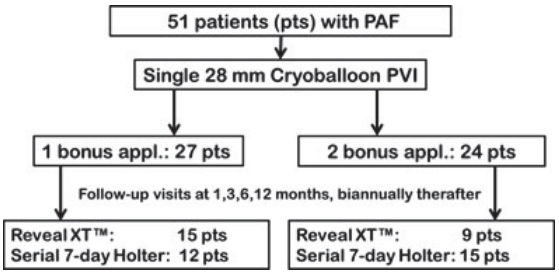

Figure 1. *Study outline.*

2 bonus applications were performed (Fig. 1). Patients with a history of highly symptomatic PAF ($\geq$ 1 episode/week) despite treatment with $\geq$ 1 antiarrhythmic drug were eligible for the study. Exclusion criteria were defined as a left atrial (LA) diameter $\geq$ 55 mm, severe left ventricular hypertrophy (LV wall thickness $\geq$ 15 mm), LA thrombus, prior stroke or acute heart failure. No preprocedural imaging (magnetic resonance or computed tomography) for patient selection was performed as previously described.[7]

Cryoballoon Ablation

Vital parameters such as arterial blood pressure and oxygen saturation were continuously monitored throughout the procedure. All procedures were performed under conscious sedation using boluses of midazolam, fentanyl, and a continuous infusion of propofol. The concept of the single big cryoballoon technique for PVI (Arctic Front, 28 mm diameter, Medtronic CryoCath LP, Pointe-Claire, Quebec, Canada) has been described in detail elsewhere.[7] In brief, following double-transseptal puncture, two 8F sheaths (SL1; St. Jude Medical, Inc., St. Paul, MN, USA) were positioned within the LA. Thereafter, heparin was repeatedly administered as a bolus to maintain an activated clotting time of 250–300 seconds. Selective PV angiography was performed to identify the PV anatomy using standard projections (RAO 30°, LAO 40°). A Lasso catheter (Biosense Webster, Inc., Diamond Bar, CA, USA) was placed along the PV ostium to record baseline PV potentials (sinus rhythm and coronary sinus pacing) using a conventional computerized EP system. The anterior sheath was exchanged for a 12F transseptal sheath (FlexCath, Medtronic CryoCath LP) over which the cryoballoon catheter was introduced into the LA. Both transseptal sheaths were continuously flushed with heparinized saline (10 IE/mL, 8F: 10 mL/h, 12F: 20 mL/h). To assess the exact position of the inflated balloon in relation to the PV ostium, contrast medium was injected from the distal lumen of the cryoballoon catheter. The cryoballoon was positioned in order to achieve a maximum of PV occlusion. A pull-down maneuver was used in the case of residual contrast medium run-off along the inferior balloon circumference.[7] Each cryoablation was performed for a target time of 300 seconds. The right phrenic nerve (PN) was constantly paced from the superior caval vein during freezing at the septal PVs. In the case of cessation or weakening of right hemidiaphragm contractions, freezing was immediately stopped. After each freeze, PV conduction was reevaluated by the Lasso catheter. If the PV was not isolated, the cryoballoon was repositioned and balloon to LA-PV contact reevaluated by angiography before the next freeze. If the PV was isolated, 1 or 2 bonus applications in occlusive balloon position were performed according to group assignment. If isolation required a pull-down maneuver, the same maneuver was performed for bonus applications. Ablation endpoint was the absence or dissociation of all PV potentials as confirmed by the Lasso catheter after a waiting period of 30 minutes.

Postablation Care and Follow-Up

All patients underwent a chest X-ray and transthoracic echocardiography to rule out pneumothorax or pericardial effusion after the procedure. Low molecular weight heparin was started 6 hours after the procedure and continued until an INR $\geq$ 2 was achieved. Phenprocoumon was started the following day. Patients were kept on a previous AAD treatment (19 patients in group I, 18 patients in group II), which was discontinued 3 months after the procedure if no recurrent atrial tachyarrhythmia occurred. In the case of recurrent atrial tachyarrhythmia, AAD treatment was continued/reinitiated and a redo procedure was performed if symptoms persisted.

Follow-up visits were scheduled at 1, 3, 6, and 12 months, and every 6 months thereafter. In the first 24 patients (15 patients in group I and 9 patients in group II) an insertable cardiac monitor (ICM; Reveal XT, Medtronic, Inc., Minneapolis, MN, USA) was subcutaneously implanted at a median (Q1;Q3) of 1 (1;2) day after the PVI procedure. Device characteristics and implantation procedure have been described previously.[14] In brief, the ICM is equipped with an automated AF/AT detection algorithm based on R–R interval variability during each 2-minute analysis period.

Sensitivity and specificity of automated AF/AT detection when compared to manually annotated continuous 46-hour Holter recordings have been reported as 96% and 85%, respectively.[14] In addition, ECG storage for automatically (up to 27 minutes) or patient activated (up to 22.5 minutes) events was interrogated during each follow-up visit to manually confirm AF/AT detection. In the remaining 27 patients (12 patients in group I and 15 patients in group II), 7-day Holter ECG recordings were performed at the time of the follow-up visits. Recordings were analyzed on a beat-to-beat basis by a cardiologist blinded to the patient's group assignment. The primary endpoint was defined as recurrent atrial tachyarrhythmia (AF or AT) lasting $\geq$ 2 minutes as documented by the ICM or 7-day Holter ECG. Secondary endpoints were procedure duration, fluoroscopy time, and complications.

Statistical Analysis

Continuous data were summarized by mean $\pm$ standard deviation or median and upper and lower quartile, where appropriate, and analyzed using Student's *t*-test or Mann–Whitney *U* test, respectively. Categorical data were summarized by frequencies and proportions, and analyzed using the chi-square and Fisher's exact test. Event-free rates from AF/AT were calculated by the Kaplan–Meier analysis and compared by the Wilcoxon test. A 2-sided P-value <0.05 was considered statistically significant.

Results

Patients

Clinical characteristics of the study patients are shown in table 1. At the time of the index procedure the mean age and left atrial diameter were 61 $\pm$ 11 and 60 $\pm$ 8 years, and 42 $\pm$ 7 and 44 $\pm$ 6 mm for group I and II, respectively. There was a tendency of a shorter PAF history in group I (5 $\pm$ 4 years)

TABLE 1
Patient Clinical Characteristics

	Group I (n = 27)	Group II (n = 24)	P Value
Age (years)	61 ± 11	60 ± 8	n.s.
Male (n)	22 (82%)	17 (71%)	n.s.
LA (mm)	42 ± 7	44 ± 6	n.s.
AF duration (years)	5 ± 4	7 ± 5	0.05
Failed AAD (n)	2 (1;2)	2 (1;3)	n.s.
CAD (n)	5 (19%)	2 (8%)	n.s.
Hypertension (n)	14 (52%)	15 (63%)	n.s.

LA = left atrium; AF = atrial fibrillation; AAD = antiarrhythmic drug; CAD = coronary artery disease.

TABLE 2
Procedural Characteristics

	Group I (n = 27)	Group II (n = 24)	P Value
RSPV Appl.	1.6 ± 1.4	1.3 ± 0.6	n.s.
RIPV Appl.	2.0 ± 1.7	1.6 ± 1.1	n.s.
LSPV Appl.	1.4 ± 0.7	1.3 ± 0.6	n.s.
LIPV Appl.	1.6 ± 1.2	1.7 ± 1.7	n.s.
Fluororoscopy duration (minutes)	33 ± 13	34 ± 11	n.s.
Procedure time (minutes)	193 ± 56	207 ± 27	n.s.

PV = pulmonary vein; RSPV = right superior PV; RIPV = right inferior PV; LSPV = left superior PV; LIPV = left inferior PV; LCPV = left common PV; Appl. = balloon applications excluding bonus application(s).

when compared to group II (7 ± 5 years, P = 0.05). Fourteen patients in group I and 15 patients in group II had a history of hypertension. Coronary artery disease was present in 5 patients of group I and 2 patients of group II.

Cryoballoon Ablation

In 51 patients, a total number of 196 PVs were identified, including a left common PV (LCPV) with early branching in 8 patients (6 in group I; 2 in group II). Superior and inferior branches of an LCPV were treated as individual PVs. Procedural parameters of the study patients are summarized in Table 2. The average number of balloon applications necessary to achieve complete PVI in a patient (excluding bonus applications) was 6.6 in group I and 5.9 in group II. The procedural endpoint of complete isolation of all PVs was achieved in 50 out of 51 patients (98%). In one patient of group II the right inferior PV (RIPV) could not be isolated. This patient remained free from recurrent AF/AT during follow-up. The procedure duration (groin puncture to sheath removal) was 193 ± 56 (group I) and 207 ± 27 (group II) minutes, fluoroscopy time was 33 ± 13 and 34 ± 11 minutes, respectively.

Procedure-related complications occurred in 4 patients (all from group II). One patient developed a femoral pseudoaneurysm that was treated by local thrombin injection. In 3 patients right phrenic nerve palsy (PNP) was present at the end of the procedure. In 2 of these patients PNP occurred during the second bonus application at the right superior PV (RSPV, 20 and 17 mm diameter). Repeat chest fluoroscopy demonstrated complete resolution of PNP by day 172 and 212, respectively. In one patient, PNP occurred during the first balloon application at a large RSPV (25 mm diameter). In this patient, no bonus application was performed at the RSPV. Repeat chest fluoroscopy demonstrated complete resolution of PNP at the following day.

Follow-Up

The median (Q1;Q3) follow-up duration in this study was 384 (213;638) days. During follow-up, the endpoint of recurrent AF/AT occurred in 13 of 27 patients (48%) in group I, and in 11 of 24 patients (46%) in group II. Kaplan–Meyer estimates of AF/AT-free survival after the index procedure are shown in Figure 2. There was no statistical difference between the groups with respect to the primary endpoint (P = 0.84). Out of 14 (group I) and 13 (group II) patients with stable SR, 3 (21%) and 2 (15%) patients refused to stop AAD therapy until the end of follow-up, respectively (P = n.s.). Irrespective of group assignment, recurrent AF/AT was detected in a higher proportion in those patients who received an ICM (63%) when compared with patients who received serial 72-hour Holter ECG recordings (33%, P = 0.04). During follow-up, one patient suffered from cerebellar hemorrhage associated with phenprocoumon overdosing 1 month following the procedure. This patient recovered with minimal neurological deficit.

Out of 24 patients with recurrent AF/AT, 5 patients had well-controlled symptoms on AAD therapy. A second procedure was performed in 9 patients in group I, and 10 patients in group II. All patients exhibited reconduction in ≥ 1 PV. The average number of PVs exhibiting reconduction in a patient was 2.8 ± 1.2 in group I and 2.4 ± 1.0 in group 2 (P = n.s.). PV reisolation was performed by RFC ablation using electroanatomical mapping.[12] Atrial tachycardia was present in 1 patient at the time of the 2nd procedure. Activation- and entrainment-mapping demonstrated perimitral flutter, which was terminated by ablation of the mitral isthmus with demonstration of conduction block.

In 5 patients, a 3rd procedure was performed (2 patients in group I, 3 patients in group II) due to recurrent AF (2 patients) or AT (3 patients). In 1 patient with recurrent paroxysmal AF, a conduction gap at the RIPV was found and PV reisolation was performed. One patient had progressed to persistent AF. In this patient, total PV isolation was demonstrated and ablation of complex fractionated atrial electrograms (CFAE) in the left atrium was performed, which resulted in conversion of AF to perimitral flutter, which was terminated by ablation of the mitral isthmus with demonstration of conduction block. Of the 3 patients with recurrent AT, 2 patients demonstrated total PV isolation and perimitral flutter, which was terminated as described above. One patient demonstrated a PV tachycardia from the RSPV that terminated upon reisolation of the vein. All other PVs were found to be isolated in this patient.

In one patient of group II, fourth and fifth procedures were performed due to recurrent AT. In the fourth procedure, a tachycardia from the superior caval vein (SVC) was demonstrated and terminated by isolation of the SVC. In the fifth procedure, a focal atrial tachycardia from the left posterior wall was demonstrated and successfully ablated, which led to stable SR in the patient.

Discussion

The main findings of the study are as follows: (i) performance of 2 repeat freeze–thaw cycles following cryoballoon

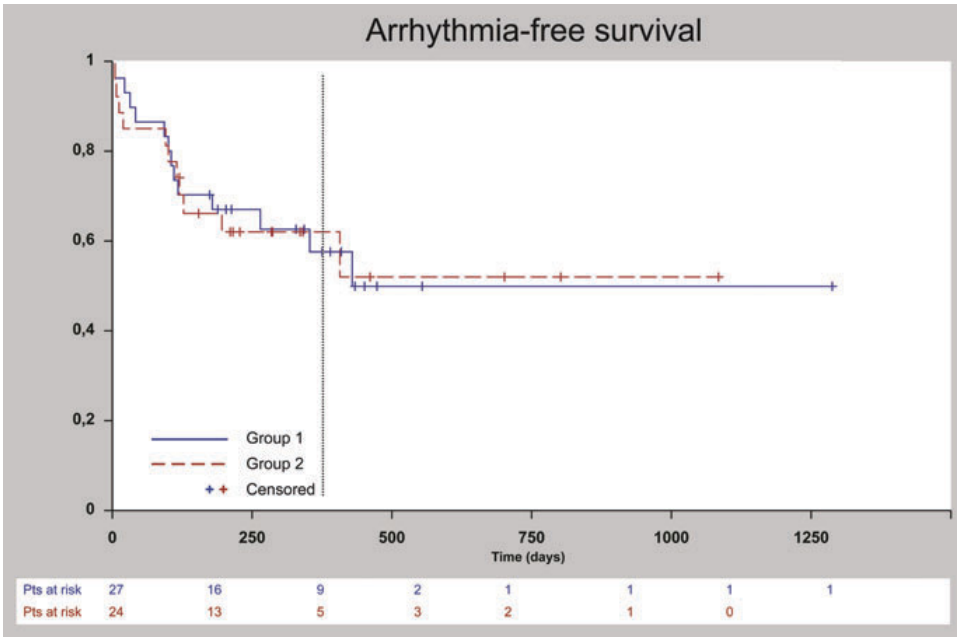

Figure 2. *Kaplan–Meier estimates of arrhythmia-free survival according to group assignment. Dotted line represents median follow-up duration (384 days). Arrhythmia-free survival was not different between the groups (*$P = 0.84$*, Wilcoxon test).*

PV isolation did not result in improved freedom from recurrent AF/AT when compared to a single repeat freeze–thaw cycle; and (ii) right phrenic nerve palsy, the main complication associated with cryoballoon PVI,[15] may occur as a result of a second bonus application, possibly due to extension of injury to the periphery of the cooled tissue volume.[13]

Earlier Studies

Ahmed *et al.*[16] investigated cryoballoon lesion durability in patients that underwent cryoballoon PVI employing a strategy of 2 bonus applications. A high rate of chronic PV isolation (88%) was demonstrated at invasive remapping 8–12 weeks following the index procedure. Whether a single bonus application is equally effective has not been investigated.

A number of studies reported on clinical success rates of cryoballoon PVI employing a strategy of 2 balloon applications per vein before determining PV conduction status (via a single transseptal puncture).[5,8,17,18] However, since such a protocol does not provide information about whether the initial freeze was effective, these studies are not representative of a systematic single bonus lesion strategy. To the best of our knowledge, a clinical comparison between the strategies of 1 versus 2 bonus lesion applications following cryoballoon PVI has not yet been performed.

Clinical Efficacy

In this study, there was no statistical difference in clinical efficacy of cryoballoon PVI performed with one (52%) when compared to 2 (54%) bonus applications. The time course of recurrent events was similar with respect to both strategies (Fig. 2). Since recurrent AF is strongly associated with PV reconduction following PVI in patients with PAF,[11,12] this may indicate similar durability of cryoballoon-induced lesions over time in both groups. Reported 1-year freedom from recurrent AF without a blanking period following cryoballoon PVI ranges from 48.9% to 64.3%.[15,19,20] Our reported rates of 52% (group I) and 54% (group II) fall within this range. However, the intense follow-up aimed at detection of asymptomatic AF episodes in the current study precludes direct comparison to previous reports. Whether a single bonus lesion improves clinical success when compared to no bonus lesion remains to be determined. To the best of our knowledge this question has only been addressed to date by an anecdotal report of 7 patients undergoing cryoballoon PVI without bonus lesion application followed by a prespecified second procedure regardless of symptoms.[16] The investigators found a very low rate of chronic PV isolation (14%), although this observation was limited by the fact that the series had been performed in the early experience of the authors with the cryoballoon.

When combining data from both treatment groups, recurrent AF/AT was detected in 63% in those patients that were followed with continuous automated AF detection by ICM, compared to 33% in patients that were followed with serial 7-day Holter ECG recordings. This observation is in line with previous studies comparing the sensitivity of intermittent with continuous rhythm monitoring for the detection of atrial tachyarrhythmia.[21,22] Ziegler *et al.* found a sensitivity and negative predictive value of 49% and 27%, respectively, for the detection of AT/AF episodes by annual 7-day Holter ECG recording when compared with continuous rhythm monitoring by an implanted pacemaker.[22] Although repeat Holter ECG recording improves detection sensitivity,[23] the higher incidence of recurrent AT/AF in patients that received an ICM may reflect a higher detection rate by continuous rhythm monitoring.

Procedural Parameters and Complications

Despite additional balloon applications in group II, differences between procedure duration and fluoroscopy exposure time between the groups were small (Table 2). This implicates a longer overall time spent to achieve occlusive balloon positions in group I, possibly due to anatomical differences. The average number of balloon applications necessary to achieve complete PVI was slightly higher in group I (6.6) when compared to group II (5.9). Whether such differences impacted on clinical outcome remains speculative.

Phrenic nerve palsy is the most common complication of cryoballoon PVI and has been linked to distal energy application relative to the PV ostium and thus PV to balloon size.[7,15] Out of 3 cases of PNP due to cryoballoon treatment of the RSPV in this study, 2 cases occurred during the second bonus application. Of note, the ratio of PV to balloon size in these patients (0.71 and 0.61) was smaller than in the patient with transient PNP after the first application (0.89). The latter ratio approximated a previously defined critical value of 0.93 to indicate PNP risk using the single big cryoballoon technique.[7] The occurrence of PNP during the second bonus cryoablation at relatively small PVs may reflect extension of tissue injury to collateral structures by repeated freeze–thaw cycles. Refreezing of previously frozen tissue has been found to be associated with faster and more extensive tissue cooling.[13] Accordingly, repeated freezing leads to larger frozen tissue volumes when compared to single freezing.[24] This has important safety implications. First, if PN function is unimpaired during one or even 2 occlusive cryoballoon applications, the operator may not feel save during additional cryoballoon treatment at this vein. Secondly, concerning the risk/benefit ratio of the procedure our data favor a single bonus application strategy.

Limitations

The limitations of our work are as follows: (1) since no previous data on the clinical impact of the number of bonus lesion applications during cryoballoon PVI were available, our aim was to conduct a pilot study with intense follow-up eventually to inform a randomized, sufficiently powered trial. The lack of any signal of a clinical benefit by performance of 2 when compared to 1 bonus lesion(s) in the pilot study puts such a large trial into question. However, we may not exclude small differences between the strategies on the basis of this study. (2) This study did not include routine invasive remapping of the PVs regardless of chronic clinical success; thus, minor differences in chronic PV isolation rates between the 2 strategies may not be excluded. However, in 19 patients undergoing a second ablation procedure (group I: 9; group II: 10 patients), there was no difference in chronic PV isolation rates between the treatment groups after the index procedure. (3) During the follow-up period continuous rhythm monitoring using an ICM was performed in 15 of 27 patients (56%) in group I and 9 of 24 patients (38%) in group II. This difference may have influenced AF/AT detection rates during follow-up. (4) Since the ECG storage capacity of the ICM is limited, manual confirmation of automated AF/AT detection could not be performed for all detected episodes, possibly leading to overestimation of the incidence of recurrent AF/AT.

Conclusion

Application of 2 freeze–thaw cycles when compared to 1 freeze–thaw cycle following cryoballoon PVI did not result in improved clinical success but was associated with a higher complication rate.

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Characterization of conduction recovery after pulmonary vein isolation using the "single big cryoballoon" technique

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BACKGROUND Pulmonary vein isolation using the cryoballoon technique (CB-PVI) has evolved into a simple and safe alternative for point-by-point radiofrequency ablation. Systematic analysis of conduction recovery occurring after CB-PVI and causing recurrent atrial fibrillation has not yet been performed.

OBJECTIVE The purpose of this study was to analyze conduction recovery after PVI using the single big (28-mm) cryoballoon technique.

METHODS Twenty-six patients with recurrent atrial tachyarrhythmia after previous CB-PVI underwent repeat ablation. Pulmonary vein (PV) reisolation was performed by antral irrigated radiofrequency ablation using electroanatomic mapping. For analysis of the location of conduction gaps, the ipsilateral LA–PV junction was divided into six equally distributed segments.

RESULTS PV reconduction frequently occurred into multiple (>2) PVs (54% patients). Conduction gaps could be abolished by single point ablation in 63% (lateral) and 41% (septal) of patients or by incomplete circular lesions in the remaining patients. A significantly higher number of patients exhibited conduction recovery at inferior segments (85% lateral, 77% septal) compared with superior segments (42% lateral, 31% septal). Furthermore, the ridge between PV ostia and left atrial appendage (LAA) was highly associated with reconduction into lateral PVs (81% of patients). Retrospective analysis of the initial CB-PVI-procedure revealed lower freezing temperatures at superior than inferior PVs as well as sharp catheter angulations with loss of central cryoballoon alignment to reach inferior PVs.

CONCLUSION Conduction recovery after CB-PVI occurs at a high incidence at inferior sites around ipsilateral PV ostia and the LAA–PV ridge. Modifications of the technique to ensure optimal balloon–tissue contact at predilection sites may improve long-term success rates.

KEYWORDS Arrhythmia; Atrial fibrillation; Balloon; Catheter ablation; Cryothermal energy

ABBREVIATIONS **AF** = atrial fibrillation; **CB** = cryoballoon; **LA** = left atrium; **LAA** = left atrial appendage; **LAT** = left atrial tachycardia; **LCPV** = left common pulmonary vein; **LIPV** = left inferior pulmonary vein; **LSPV** = left superior pulmonary vein; **PAF** = paroxysmal atrial fibrillation; **PV** = pulmonary vein; **PVI** = pulmonary vein isolation; **RFC** = radiofrequency current; **RIPV** = right inferior pulmonary vein; **RSPV** = right superior pulmonary vein

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Introduction

Complete pulmonary vein isolation (PVI) from the left atrium (LA) has become the cornerstone of ablative therapy in patients with paroxysmal atrial fibrillation (PAF).[1] Cryoballoon (CB) ablation is an emerging technology with the potential to simplify this complex procedure and lacks some of the potential serious complications associated with radiofrequency current (RFC) PVI, such as pulmonary vein (PV) stenosis.[2–5] We recently showed that CB-PVI can be performed successfully with exclusive use of a 28-mm balloon.[2] However, as with conventional PVI using RFC,[6] PV reconduction may lead to recurrent atrial fibrillation (AF) after CB-PVI.[7] Long-term outcome data of this relatively new technique are lacking.

In contrast to sequential point-by-point ablation by an RFC catheter, the cryoballoon technique consists of simultaneous energy deployment at the LA–PV junction; thus, PVI often can be achieved by a single cryothermal energy application.[2] Although this concept is technically attractive, it also implies that energy deployment cannot be varied along the resulting cryolesion. Such energy variation would be desirable at regions of enhanced muscular thickness, such as the ridge between the lateral PVs and the left atrial appendage (LAA). Moreover, cryoballoon ablation requires continuous tissue contact because convective heating by intervening blood flow or insulating ice formation interferes with tissue freezing.[8]

We hypothesized that areas of reconduction after CB-PVI are not randomly distributed around the PV ostia but are preferentially located at sites prone to poor balloon–

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tissue contact and/or with enhanced muscular thickness. Knowledge of such areas may be the basis for improved cryoballoon technique and long-term success. The aim of this study was to investigate conduction recovery after CB-PVI using the "single big (28-mm) cryoballoon" technique.

Methods

Patients

Between April 2006 and November 2008, 71 patients underwent CB-PVI for highly symptomatic PAF using the single big (28-mm) cryoballoon technique.[2] One bonus cryoballoon application per vein was performed after PVI had been achieved. All patients continued taking the previously ineffective antiarrhythmic drugs, which were discontinued after 1 month if no recurrent AF or left atrial tachycardia (LAT) occurred after the initial ablation procedure.

Thirty-five patients had either recurrent PAF (32 patients [45%]) or LAT (3 patients [4%]) after the initial procedure during a median (Q1;Q3) follow-up of 189 days (68;298) without a blanking period. The first episode of recurrent PAF/LAT occurred 21 days (8;88) after the CB-PVI procedure. Nine patients who had short episodes of AF that were well controlled with antiarrhythmic drugs refused a second procedure.

A repeat procedure was performed in 26 patients with symptomatic recurrent PAF (23 patients) or LAT (3 patients) after a median (Q1;Q3) of 144 (57;217) days following initial CB-PVI. These patients constitute the basis of the current study. The right inferior pulmonary vein (RIPV) could not be isolated at the CB-PVI procedure in 2 of these patients. Patient characteristics are listed in Table 1, and procedural parameters of initial CB-PVI are listed in Table 2.

Mapping and catheter ablation

The reablation procedure was performed with patients under sedation with continuous propofol infusion.[6] Two 8Fr SL1-sheaths (St Jude Medical, St. Paul, MN, USA) were advanced to the LA via a modified Brockenbrough technique. Intravenous heparin was administered to maintain an activated clotting time of 250 to 300 seconds. One or two decapolar Lasso catheters (Biosense Webster, Diamond Bar, CA, USA) were placed within the left-sided or right-sided ipsilateral PVs to confirm recovery of PV conduction. Three-dimensional electroanatomic mapping (CARTO XP, Biosense Webster) of the LA and selective PV angiograms were performed to identify all PV ostia. If discrete PV potentials were recorded in both of the ipsilateral PVs or branches of a common PV, one Lasso catheter was placed in the PV or branch with the earliest PV potential during ablation. Ablation (ThermoCool Navi-Star, Biosense Webster) was started at the antral level of the LA–PV junction at the site of the earliest PV potential. Irrigated RFC energy was delivered with a target temperature of 43°C, maximal power limit of 30 W (posterior LA) or 40 W (anterior LA), and infusion rate of 17 mL/min.

Table 1 Baseline characteristics of the study patients (n = 26)

Age (years)	59 ± 10
Male (n)	16 (62%)
Paroxysmal atrial fibrillation	26 (100%)
Hypertension (n)	14 (54%)
No. of failed antiarrhythmic drugs (n)	2 ± 1
Duration of atrial fibrillation (years)	8 ± 6
Left atrial diameter (mm)	43 ± 6

Table 2 Procedural parameters of initial cryoballoon pulmonary vein isolation

Vein	Diameter (mm)	No. of applications
Left superior pulmonary vein	20 ± 3	2.8 ± 0.9
Left inferior pulmonary vein	19 ± 3	3.2 ± 1.4
Left common pulmonary vein	30 ± 4	5.1 ± 3.6
Right superior pulmonary vein	19 ± 3	2.4 ± 0.8
Right inferior pulmonary vein	18 ± 3	4.1 ± 2.1
Procedural time (min)	219 ± 47	
Fluoroscopy time (min)	46 ± 20	

For analysis of the location of conduction gaps, the ipsilateral LA–PV junction was divided into six equally distributed segments (superior, anterosuperior, anteroinferior, inferior, posteroinferior, posterosuperior; Figure 2). The response to ablation at the initial segment was classified as PV reisolation (pattern 1), PV activation sequence change as recorded by the Lasso catheter (pattern 2), or no change (pattern 3). In case of PV reisolation, the ablation region was tagged on the electroanatomic map and the respective segment defined to contain a conduction gap. In case of PV activation sequence change, the respective segment was defined to contain a conduction gap, and ongoing PV conduction was attributed to an additional gap, which was ablated in a similar fashion (Figure 1A). If ablation at the initial segment did not affect PV conduction, ablation was continued in a circular fashion around the ipsilateral PV ostia guided by the earliest PV potential. An effort was made to achieve reisolation with the shortest antral ablation line (Figure 1B). Any of six antral segments around the ipsilateral PVs was defined as contributing to reconduction if PV reisolation necessitated ablation at the respective segment (Figure 2).

The procedural end-point was defined as (1) the absence of PV potentials documented with the Lasso catheter within all PVs at least 30 minutes after isolation and (2) no inducible atrial tachycardia after ablation in patients who presented with atrial tachycardia after initial CB-PVI.

Postablation care and follow-up after redo procedure

In all patients, pericardial effusion and pneumothorax were ruled out (transthoracic echocardiogram, chest X-ray film) after the procedure. After ablation, patients were treated

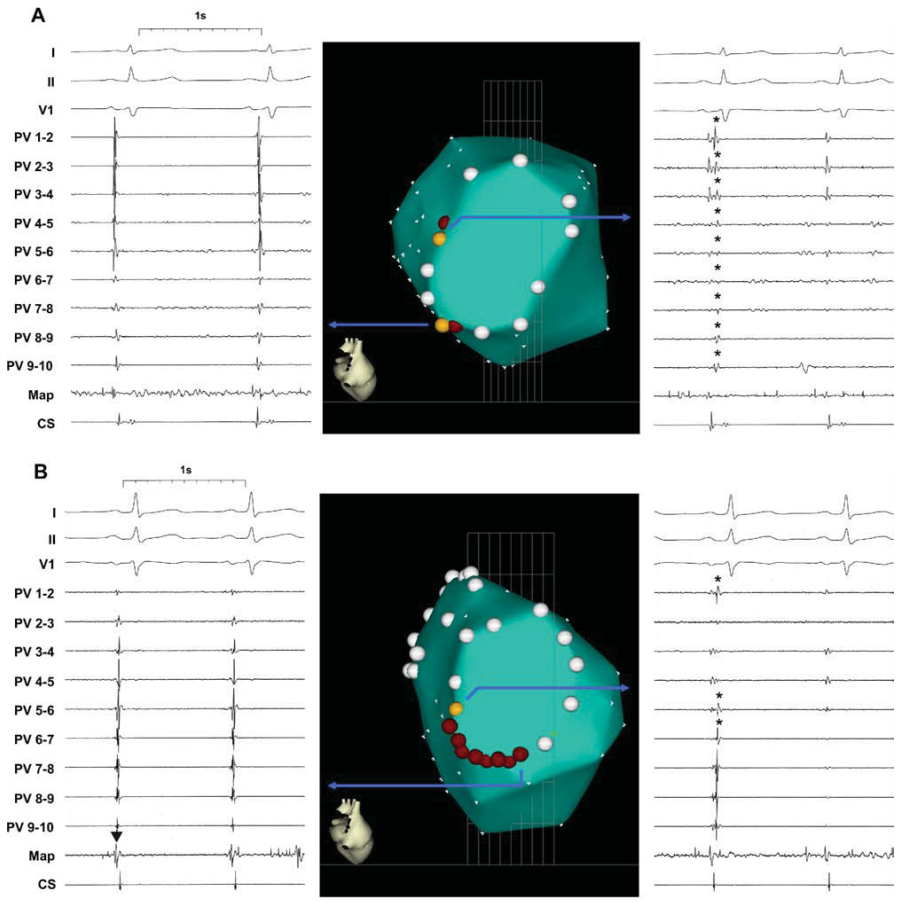

Figure 1 Reisolation of the septal pulmonary veins (PVs) in patients no. 2 and 16. Anatomic CARTO maps in the right lateral view and recordings from surface ECG leads I, II, and V_1, Lasso recordings from the right inferior pulmonary vein (PV1-2 to PV9-10), and recordings from distal mapping (Map) and coronary sinus (CS) catheters are shown. *Yellow point tags* in the CARTO maps correspond to loci of PV activation sequence change or PV isolation during ablation *(brown point tags)* as indicated by *arrows.* **A:** Sudden activation sequence change in the PV potentials recorded by Lasso catheter **(left)** indicates block of an inferior gap. Subsequent mapping and ablation revealed a second posteroinferior gap with reisolation of the right inferior PV **(right)** during ablation, as indicated by elimination of the PV potential *(asterisk).* **B:** Reisolation of the right inferior PV by linear ablation at the inferior antral segment. At the start of ablation **(left),** early PV activation is recorded by the mapping catheter *(arrowhead).* Reisolation occurred posteriorly **(right)** without prior activation sequence change, as indicated by elimination of the PV potential *(asterisk).*

with intravenous heparin (target partial thromboplastin time 50–70 seconds). Phenprocoumon was started the next day, targeting an international normalized ratio of 2.0–3.0 for at least 3 months. Previous antiarrhythmic therapy was continued for 1 month and then discontinued if patients were free of AF/LAT relapse. Surface ECG and 24-hour Holter ECG recording were performed 1 day after the procedure and repeated after 1, 3, 6, and 12 months or upon symptoms suggestive of recurrent AF/LAT. Recording was performed by the referring physician or in the ablation center. The clinical end-point was defined as the first documented AF/LAT episode ≥30 seconds in duration.

Temperature monitoring at initial CB-PVI

Cryoballoon temperature–time curves during each freeze were acquired using CryoConsole software (CryoCath Technologies, Montreal, Quebec, Canada). The temperature sensor is located in the back of the balloon and thus provides a rough estimate of tissue temperature near the balloon. The minimal temperature for a PV was defined as the lowest balloon temperature achieved during any freeze at that vein. Data from the superior and inferior branches of a left common pulmonary vein (LCPV) were included in the left superior pulmonary vein (LSPV) or left inferior pulmonary vein (LIPV) group, respectively, if the branches were isolated separately (5/7 LCPVs).

Analysis of balloon catheter positions at initial CB-PVI

To overcome the force exerted by PV blood flow, the balloon catheter must be pushed onto the PV ostium in order to achieve or maintain tissue contact. This is easiest to accomplish if the sheath, balloon, and guidewire are in direct alignment because the sheath and balloon catheter can be used in concert to create a strong pushing force (Figure 3A). To

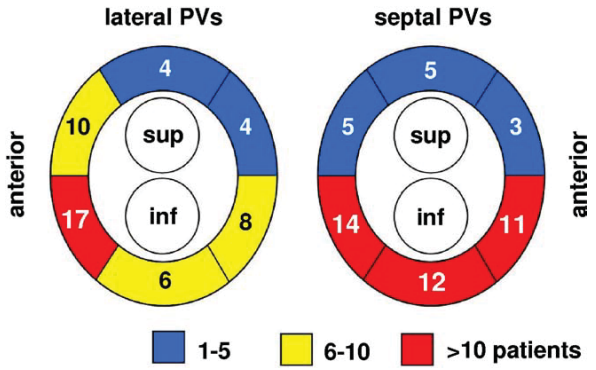

Figure 2 Location of pulmonary vein (PV) reconduction after cryoballoon PV isolation. Lateral and septal PV ostia are shown in the posteroanterior view. Any of six antral segments around the ipsilateral PVs was defined as contributing to reconduction if PV reisolation necessitated ablation at the respective segment. *Numbers* represent number of patients. Significantly more patients exhibited reconduction at inferior than at superior segments for both lateral and septal PVs. In addition, the left atrial appendage–PV ridge was a frequent site of reconduction at lateral PVs.

quantify the degree of deflection of the sheath/balloon system at individual PVs during initial CB-PVI, the angle between the catheter tip bearing the balloon and the proximal transseptal sheath (angle of alignment) was retrospectively analyzed from angiograms recorded before freezing (Figure 3) in the right anterior oblique 30° view for septal PVs or in the left anterior oblique 40° view for lateral PVs (or superior and inferior branches of an LCPV).

Statistical analysis

Data are given as mean ± SD or median and 25th and 75th percentiles (Q1;Q3) where appropriate. The Friedman test and exact method was used to compare predefined segments of septal or lateral PV ostia with respect to reconduction. Continuous variables were evaluated using the Student's t-test. $P < .05$ was considered significant.

Results

Of the 26 study patients, 18 were in sinus rhythm, 3 were in AF, 3 presented with LAT, and 2 presented with common-type atrial flutter at the time of the second procedure. The 2 patients who presented with atrial flutter also exhibited documented episodes of AF. In the patients with AF or atrial flutter, sinus rhythm was restored by external cardioversion or cavotricuspid isthmus ablation at the beginning of the procedure, respectively. In the 3 patients with LAT, mapping and ablation of LATs were performed prior to PV reisolation.

Among the 3 patients with LAT, three-dimensional and entrainment mapping demonstrated an LA macroreentrant tachycardia around the mitral annulus in 2. RFC energy (6.3 ± 0.6 applications) was delivered between the left-sided PVs and the mitral annulus, with termination of the tachycardia and bidirectional block of the mitral isthmus. In 1 patient, three-dimensional mapping demonstrated a focal atrial tachycardia originating from the posteroinferior LA 15 mm distant to the LIPV ostium. A single RFC application terminated the tachycardia and resulted in noninducibility.

Recovered PV conduction during sinus rhythm

In the 26 patients, a total of 97 PVs were identified, with an LCPV in 7 patients. LA–PV conduction was demonstrated in 67 PVs. In most patients, multiple PVs exhibited reconduction: 4 PVs in 5 (19%) patients, 3 PVs in 9 (35%), 2 PVs in 8 (31%), and a single PV in 4 (15%). With regard to individual PVs, recovered PV conduction was present in 19 (79%) of 24 RIPVs (excluding 2 patients in whom the RIPV could not be isolated at initial CB-PVI), 15 (79%) of 19 LIPVs, 12 (63%) of 19 LSPVs, 12 (46%) of 26 right superior pulmonary veins (RSPVs), and 7 (100%) of 7 LCPVs.

At septal PVs, the response to a single ablation at the initial segment was pattern 1 (isolation) in 4 patients and pattern 2 (sequence change and additional gap) in 5 patients.

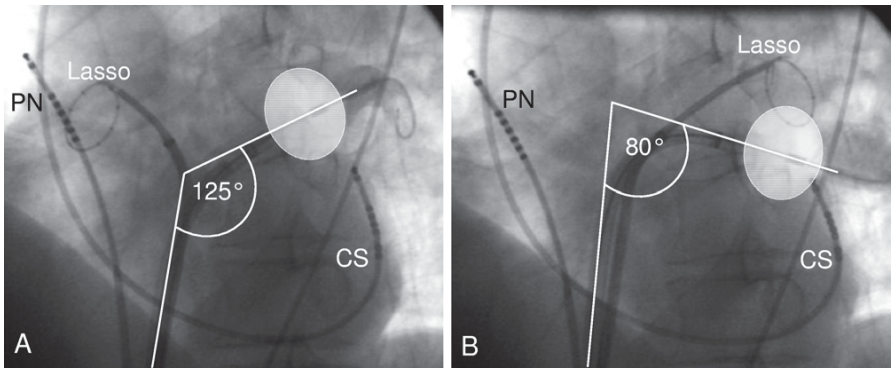

Figure 3 Analysis of catheter position at cryoballoon pulmonary vein (PV) isolation. Radiographs in the left anterior oblique 40° projection are shown. Contrast medium had been injected via the balloon tip to ensure occlusive position at the PV ostium. **A:** Balloon catheter at the left superior PV shortly before freezing. The angle between the shaft of the transseptal sheath and the balloon center is 125°. The Lasso catheter is in the right superior PV. **B:** Balloon catheter at the left inferior PV before freezing. The angle between the transseptal sheath and balloon is 80°. The Lasso catheter is in the left superior PV. CS = coronary sinus catheter; PN = diagnostic catheter placed at phrenic nerve capture site in superior caval vein.

In the latter patients, a single RFC application abolished the remaining gap (Figure 1A). Thirteen patients exhibited pattern 3 (no change), and short antral linear ablation involving more than one segment was needed in order to achieve reisolation (Figure 1B). In the remaining 4 patients, both septal PVs were isolated. Average RFC lesion length was 25 ± 24 mm.

At lateral PVs, pattern 1 was observed in 12 patients and pattern 2 in 3 patients, with one (2 patients) or two (1 patient) additional gaps abolished by a single RFC application. Nine patients exhibited pattern 3. In the remaining 2 patients, both lateral PVs were isolated. Average RFC lesion length was 20 ± 26 mm.

Total procedural time and radiation time were 150 ± 53 minutes and 18 ± 9 minutes, respectively. No procedure-related complications occurred.

Location of PV reconduction

In septal PVs, reisolation was most often achieved by antral ablation at inferior locations (Figure 2), involving inferior and anteroinferior segments in 12 (46%) and 11 (42%) of 26 patients, respectively, and posteroinferior segments in 14 (54%) of 26 patients. In contrast, ablation was performed at superior and posterosuperior segments in 5 (19%) of 26 patients and at anterosuperior segments in 3 (12%) of 26 patients ($P = .001$ for comparison between all segments).

In lateral PVs, the anterior aspect of the LA–PV junction ("ridge") most often contributed to PV reconduction, necessitating ablation of anteroinferior segments in 17 (65%) of 26 patients and anterosuperior segments in 10 (38%) of 26 patients. Posteroinferior segments were ablated in 8 (31%) of 26 patients, inferior segments in 6 (23%) of 26 patients, and superior and posterosuperior segments in 4 (15%) of 26 patients ($P = .002$ for comparison between all segments).

In summary, ablation at any inferior segment was performed in 77% (septal) and 85% (lateral) of patients, as opposed to superior segments in 31% (septal) and 42% (lateral) of patients.

Temperature monitoring at initial CB-PVI

Retrospective analysis of minimal balloon temperatures achieved during initial CB-PVI revealed significantly lower temperatures at superior PVs (or superior branch of an LCPV) compared with inferior PVs (or inferior branch of an LCPV) for both septal (–50°C ± 7°C vs –40°C ± 6°C; $P < .001$) and lateral (–49°C ± 7°C vs –43°C ± 4°C; $P = .004$) PVs. When separating PVs into those with and those without isolation at the reablation procedure, minimal temperatures during initial CB-PVI were as follows: LSPV: –50.4°C ± 2.9°C (isolated) versus –48.6°C ± 8.6°C (not isolated, $P =$ NS); LIPV: –47.0°C ± 3.5°C versus –42.1 ± 3.5 ($P =$ NS); RSPV: –51.9°C ± 6.4°C versus –46.3°C ± 5.8°C ($P = .038$); and RIPV: –39.6°C ± 4.2°C versus –40.7°C ± 6.4°C ($P =$ NS). The mean number of cryothermal energy applications at initial CB-PVI according to these groups were as follows: LSPV: 2.7 ± 0.8 (isolated) versus 3.0 ± 1.0 (not isolated, $P =$ NS); LIPV: 3,3 ± 1,5 versus 3,1 ± 1,5 ($P =$ NS); RSPV: 2.5 ± 0.6 versus 2.3 ± 1.1 ($P =$ NS); and RIPV: 3.6 ± 1.3 vs. 4.2 ± 2.3 ($P =$ NS).

Analysis of catheter positions at initial CB-PVI

Retrospective analysis of the angle of alignment representing the degree of deflection of the sheath/balloon system at individual PVs during initial CB-PVI was performed. For inferior PVs this angle was significantly smaller, that is, the degree of deflection was higher compared to that of superior PVs (RIPV: 85° ±18° and RSPV: 121° ±23°, $P < .001$; LIPV: 94° ± 20° and LSPV: 129° ± 28°, $P < .001$), resulting in loss of central balloon alignment (Figure 3).

Follow-up

During a median (Q1;Q3) follow-up of 98 days (39;283) without a blanking period, 18 (69%) of 26 patients remained free of recurrent AF or LAT. Four patients had improved symptoms that were well controlled with antiarrhythmic drugs.

Four patients underwent further ablation due to ongoing episodes of AF: One patient exhibited total PV isolation at the time of the second redo procedure, and a non-PV trigger was identified in the superior caval vein and subsequently isolated. In the remaining 3 patients, AF recurrence was again associated with PV reconnection (intervals between first and second redo: 296, 538, and 283 days). In 2 patients, conduction gaps identified at the second redo procedure were unrelated to those found at the first redo procedure and were located at the anterior ridge at lateral PVs. In the third patient, the second redo procedure was performed at another center (reisolation of RIPV and LSPV), and no information regarding the location of PV conduction gaps was retrievable.

Discussion

The main findings of this study were as follows. (1) In patients with PAF, the dominant recurrent atrial tachyarrhythmia after CB-PVI was AF. The incidence of LAT following CB-PVI was low. (2) Recurrent AF after CB-PVI was associated with LA–PV reconnection. Conduction gaps after CB-PVI using the single big cryoballoon technique occurred at a high incidence at the inferior LA–PV junction and the anterior ridge between PVs and LAA. (3) These conduction gaps could be eliminated by RFC ablation using electroanatomic mapping, with low procedural and radiation times.

Recurrent atrial tachyarrhythmia after CB-PVI

The majority of patients in this study presented with PAF as the recurrent arrhythmia. LAT was observed in only 3 patients after initial CB-PVI (4% of total CB-PVI cohort). In these patients, perimitral flutter was found in 2 and a non-PV focal tachycardia in 1. Thus, PV tachycardia was not observed following CB-PVI, whereas PV tachycardia was a common finding in patients with recurrent atrial tachyarrhythmia after PVI using RFC-induced circular linear lesions.[9] The underlying cause of this difference is not

known. Histologic study has shown that cryolesions are well circumscribed with sharp borders, whereas RFC lesions are less clearly demarcated from normal myocardium.[10] This may constitute a difference with respect to creation of a reentrant substrate.[6]

Predilection sites for LA–PV reconduction

The inferior segments of the LA–PV junction were most often affected by reconduction (Figure 2). For septal PVs, this resulted in reconduction of 79% of inferior PVs compared with 46% of superior PVs. For lateral PVs, the inferior ridge between LAA and PV ostia (anteroinferior segment) was the most common site for PV reconduction, followed by the superior ridge (anterosuperior segment). This may be due to enhanced muscle thickness at this structure. The frequent involvement of the superior ridge may have contributed to the relatively high rate of reconduction (63%) into the LSPV. Moreover, a venous "cross-talk" phenomenon is often observed during CB-PVI at lateral PVs, whereby isolation of ipsilateral PVs occurs simultaneously during freezing at the LIPV when initial freezing at the LSPV failed to achieve PVI due to residual conduction between the veins.[2]

A high incidence of inferior conduction gaps may result from a number of causes. When freezing is performed at inferior PVs, central alignment of the cryoballoon at the PV ostium often is not possible because the sheath/balloon system must be deflected in order to reach the target structure. This results in a smaller angle of alignment during CB-PVI of inferior compared to superior PVs (Figure 3). Consequently, at superior PVs, both sheath and balloon can be used to create a strong push onto the PV ostium to overcome PV blood flow, whereas at inferior PVs only the balloon catheter can be pushed through the deflected sheath, likely impacting on contact force. This may lead to incomplete balloon–tissue contact around inferior PVs. In support of this hypothesis is the observation that more balloon applications were needed to achieve isolation of inferior than superior PVs (Table 2).[2] Residual blood flow has been demonstrated to occur during the course of a cryoballoon application, even when the balloon occluded the PV ostium at the initiation of freezing.[11] It can be assumed that cryolesions created with poor tissue–balloon contact may acutely lead to PV isolation while being prone to later conduction recovery.

Another possible impact of the lack of central alignment of the cryoballoon on lesion quality is a temperature gradient from equator to distal pole of the balloon, with deepest temperatures just in front of the equator caused by injection of the refrigerant to this area. This could preferentially affect inferior sites around ipsilateral PV ostia, because at typical balloon positions for inferior PVs (small angle of alignment) this region is adjacent to the cryoballoon pole (Figure 3B).

The chronic course of cryoballoon-induced lesions is not well known. This study cohort included 2 patients who exhibited consecutive unrelated conduction gaps at the second and third ablation procedures. This finding implies that areas of reconduction had been formed after 46 and 149 days (interval between CB-PVI and first redo), respectively, demonstrating that conduction recovery may occur late in the course of a cryolesion.

Implications for the cryoballoon technique

The study data favor improved techniques to ensure good lesion quality at inferior sites around ipsilateral PVs as well as at the LAA-PV ridge. This can be achieved by repeated freezing with optimal balloon contact to these segments after successful PVI.

In light of the high incidence of inferior conduction recovery, a safety application at inferior PVs with central alignment and perfect contact to the inferior PV circumference should be considered, regardless of possible remaining leakage at the superior PV circumference. This may be of special importance when a "pull-down" maneuver was initially used to isolate an inferior PV, where freezing was started at the superior PV circumference, followed by pulling down the attached balloon to close an inferior gap.[2] During this maneuver, ice formation before pulling down may impact on lesion quality at the inferior PV circumference. Whether such modifications will lead to improved long-term success requires further investigation.

In principle, the cryoballoon technique could be used to close conduction gaps at redo procedures after initial CB-PVI.[4,7] However, the high incidence of multiple reconducting PVs with frequent involvement of the technically more demanding inferior PVs would result in long procedural and, more importantly, radiation times. Moreover, the predilection sites for conduction gaps would also apply for the second procedure. This may explain our observation of a higher success rate after the second procedure compared to reports of repeat CB-PVI.[7] On the other hand, use of conventional RFC energy in conjunction with electroanatomic mapping results in PV reisolation with low radiation exposure. Of note, the procedure times reported for this study include 3 cases of mapping and ablating atrial tachycardia before PV reisolation.

Relation of initial CB-PVI parameters to reconduction

The minimal temperature measured inside the balloon was shown to be a determinant of chronic PV isolation after CB-PVI in an experimental study.[8] Lower freezing temperatures have been associated with deeper cryolesions.[10] Retrospective analysis of minimal balloon temperatures at initial CB-PVI in our study patients revealed lower temperatures for superior than inferior PVs. This could result from poor balloon–tissue contact at inferior PVs or from local hemodynamic differences, such as covering of the balloon by the LA roof. Moreover, for all but the RIPV, minimal temperatures achieved at CB-PVI were lower at those veins where PV isolation was found at the redo procedure than at reconducting veins. However, this difference reached statistical significance only for RSPVs. This may be due to (1) a low

number of patients (e.g., data from RIPV with ongoing isolation represent only 5 cases); (2) a high incidence of "crossover" isolation of lateral PVs,[2] indicating considerable overlap of cryoballoon-induced lesions; or (3) the position of the temperature probe in the back of the balloon, which provides only a rough estimate of tissue temperatures. Thus, the intriguing possibility that modifications of the current technique to achieve lower balloon temperatures will improve long-term success deserves further investigation.

A higher number of cryothermal energy applications at individual PVs was not associated with ongoing PV isolation in this study. Rather, repeat applications necessary to achieve PVI may indicate difficulties in accessing a PV with the cryoballoon, possibly impacting on lesion quality. Whether more than one "bonus" application enhances durability of CB-PVI requires additional study.

Study limitations

This study has several limitations. Our findings were obtained with the cryoballoon technique using only the 28-mm balloon.[2] Different cryoballoon techniques may exhibit varying predilection sites for conduction recovery. Apart from angiography, no additional visualization of balloon–tissue contact, such as transesophageal ultrasound, was used. Furthermore, no attempt was made to map in detail the level of the previous cryolesions.[12] This may account for the need for more extensive antral ablation to achieve PV reisolation in many patients in this study. Finally, the study data suggest that use of RFC ablation in conjunction with electroanatomic mapping after initial CB-PVI is associated with a high success rate compared to reports of repeat CB-PVI.[7] However, a randomized study would be necessary to clarify this issue.

Conclusion

Conduction recovery after cryoballoon PVI using the single big (28-mm) balloon technique occurs at a high incidence at inferior locations around ipsilateral PV ostia and at the ridge between the lateral PVs and the LAA. Modifications of the cryoballoon technique to ensure optimal wall contact at predilection sites for reconduction and achieve lower balloon temperatures may improve long-term success rates.

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Improved Procedural Efficacy of Pulmonary Vein Isolation Using the Novel Second-Generation Cryoballoon

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Efficacy of the Novel Cryoballoon. ***Introduction:*** **The cryoballoon technology has the potential to isolate a pulmonary vein (PV) with a single energy application. However, using the first-generation cryoballoon (CB-1G) repeated freezing or additional focal ablation is often necessary. The novel second-generation cryoballoon (CB-2G) features a widened zone of optimal cooling comprising the whole frontal hemisphere. The aim of this study was to investigate the impact of the novel design on procedural efficacy of cryoballoon PV isolation (CB-PVI).**

Methods and Results: **Single transseptal CB-PVI using an endoluminal spiral mapping catheter was performed in 60 consecutive patients (CB-1G, 28 mm, 300 seconds application time: 30 patients; CB-2G, 28 mm, 240 seconds application time: 30 patients). When compared to the CB-1G, using the CB-2G increased single-shot PVI rate from 51% to 84% ($P < 0.001$) and decreased procedure duration (128 ± 27 vs 98 ± 30 minutes; $P < 0.001$), and fluoroscopy exposure time (19.5 ± 7.4 vs 13.4 ± 5.3 min; $P = 0.001$). Effective CB-2G PVI could be performed with increased real-time PVI visualization rate (49% vs 76%; $P < 0.001$). Time to PVI (T_{PVI}) was shorter in the CB-2G group (79 ± 60 vs. 52 ± 36 seconds; $P = 0.049$). Procedure-related complications occurred in 2 patients in the CB-1G group and 1 patient in the CB-2G group.**

Conclusions: **The CB-2G significantly improved procedural efficacy compared to the CB-1G and provided reliable T_{PVI} measurement. T_{PVI} may be used to adjust application time and number individually in future studies. Final conclusions regarding the safety profile of the CB-2G requires additional research.**
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atrial fibrillation, catheter ablation, cryoballoon, pulmonary vein isolation

Introduction

Cryoballoon pulmonary vein isolation (PVI) is increasingly used for the treatment of paroxysmal and short-lasting persistent atrial fibrillation (AF) because of the relative technical simplicity and steeper learning curve when compared to standard radiofrequency current ablation (RFA).[1-3] With this approach, a ring-shaped cryothermal lesion around a pulmonary vein may be created by a single ablation step, realizing single-shot PVI. The first-generation cryoballoon (CB-1G, Arctic Front™, Medtronic, Inc., Minneapolis, MN, USA) has become available in Europe in 2006 and was approved by the FDA in 2011. When freezing is initiated, the refrigerant (N_2O) is sprayed via 4 injection ports to a region just distal of the equator,[4] cooling the balloon surface with a temperature gradient with relatively higher temperatures at the distal pole (nose; Fig. 1). Inherently, efficient continuous lesions are created if the balloon is centered in the PV antrum. In contrast, eccentric balloon positions may lead to incomplete lesion formation of tissue contacting the nose,[5] resulting in specific patterns of PV reconduction sites.[5,6] Thus, a redesign of the cryoballoon has been suggested.[7] Furthermore, circumferential PV occlusion is pivotal, because PV-to-left-atrial blood flow continues during freezing at regions of poor balloon-tissue contact, antagonizing cryolesion formation.[8] Obtaining occlusive balloon positions requires considerable contact force and stable guidance over a wire or an endoluminal spiral catheter (eSC). Theoretically attractive by providing real-time PV potential (PVP) recording during freezing, the eSC must be positioned distal to the PV muscular sleeves to provide stability in approximately 50% of the veins using the first-generation cryoballoon.[9]

The second-generation cryoballoon (CB-2G, Arctic Front Advance™, Medtronic, Inc.) received a redesigned injection system distributing refrigerant homogenously to the frontal balloon surface, notably the distal pole (Fig. 1). In this study, we investigated the impact of the novel design on procedural efficacy of cryoballoon PVI.

Methods

Patients

A total of 60 consecutive patients with paroxysmal or short-lasting persistent AF resistant to at least one antiarrhythmic drug have been included in this study. Exclusion

Drs. Furnkranz, Schmidt, and Chun received honoraria payment for Medtronic educational lectures. Other authors: No disclosures.

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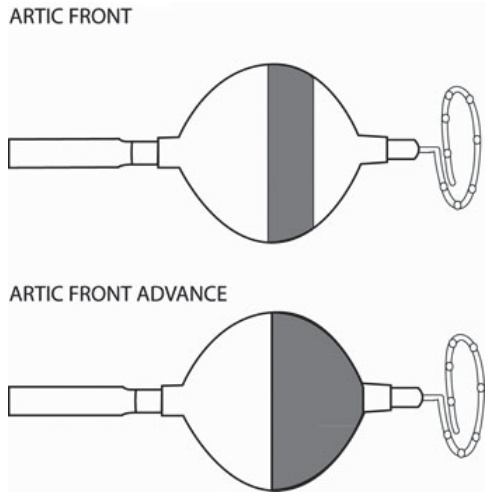

Figure 1. *Scheme showing the optimal cooling zone of the cryoballoon/mapping catheter system. Upper panel shows the first-generation cryoballoon (Arctic Front). The shaded area represents the zone of optimal cooling forming an equatorial band. The lower panel shows the second-generation cryoballoon (Arctic Front Advance). The zone of optimal cooling comprises the whole frontal hemisphere of the balloon.*

TABLE 1
Patient Baseline Characteristics

	Group 1 (CB-1G) N = 30	Group 2 (CB-2G) N = 30	P Value
Male (%)	73	50	n.s.
Age (years)	62 ± 12	67 ± 11	n.s.
Paroxysmal AF (%)	80	77	n.s.
Persistent AF (%)	20	23	n.s.
AF history (years)	3.4 ± 2.8	4.6 ± 5.0	n.s.
LA size (mm)	40 ± 4	40 ± 5	n.s.
LVEF (%)	62 ± 4	63 ± 6	n.s.
Comorbidities			
Hypertension (%)	63	80	n.s.
Diabetes (%)	13	17	n.s.
Stroke/TIA (%)	0	3	n.s.
Heart failure (%)	3	7	n.s.
CAD (%)	7	27	0,04

CB-1G = first-generation cryoballoon; CB-2G = second-generation cryoballoon; n.s. = nonsignificant; AF = atrial fibrillation; LA = left atrium; LVEF = left ventricular ejection fraction; TIA = transient ischemic attack; CAD = coronary artery disease.

criteria were continuous AF for > 6 months, a left atrium (LA) size > 55 mm and intracardiac thrombi. The first 30 patients received treatment with the 28 mm CB-1G. Upon availability of the CB-2G, patients received treatment with the 28 mm CB-2G, starting with patient 31. Baseline clinical characteristics of the study cohort are shown in Table 1. Phenprocoumon was stopped 1 day before the procedure, dabigatran or rivaroxaban was stopped 2 days before the procedure. Patients underwent transesophageal echocardiography to rule out left atrial thrombi immediately before the procedure. No further imaging was performed before PVI.

Cryoballoon Ablation

All procedures were performed under conscious sedation using boluses of midazolam, fentanyl and a continuous infusion of propofol. According to our initial strategy[2] we employed a single-device approach using exclusively the 28 mm balloon. In a subset of patients in the CB-2G group (N = 18), a temperature probe with 3 thermocouples separated by 10 mm (SensiTherm, St. Jude Medical, Inc., St. Paul, MN, USA) was inserted into the esophagus transorally under fluoroscopic guidance. For each cryoballoon application, minimal luminal esophageal temperature (LET) was recorded. LET measurement was observational only and not used to interrupt cryoenergy application. The principles of single transseptal 28 mm cryoballoon PVI have been described previously.[10] In brief, the cryoballoon was inserted into the LA guided by an eSC (Achieve^{TM}, 15 or 20 mm, Medtronic, Inc.). We aimed for an inferior puncture site in the fossa ovalis. To assess the exact position of the inflated balloon in relation to the PV ostium contrast medium was injected from the distal lumen of the cryoballoon catheter. The eSC was positioned as proximal as possible to provide PVP recording. A distal eSC position was required in case of: (1) occlusive or near-occlusive balloon position was not obtainable with a proximal eSC position, or (2) failure to isolate with the initial balloon application with a proximal eSC position. Fluoroscopic eSC position during successful balloon application was quantified by measuring the shortest distance between the proximal electrode of the eSC and the balloon surface (right-sided PVs and left superior PV: RAO 30°, left inferior PV: LAO 40°; Fig. 2). According to our standard protocol, target application time was 300 seconds in the CB-1G group.[2,5] Application time was restricted to 240 seconds in the CB-2G group by recommendation of the manufacturer. Cross-talk isolation of the LSPV was defined by freezing at LIPV position to ablate a remaining inferior conduction gap after an initial direct freeze at the LSPV.[2] A pull-down maneuver was defined by accepting an inferior leak of contrast medium throughout the first minute of freezing followed by pulling down sheath and balloon to achieve circumferential occlusion.[2] Time to sustained PVI (T_{PVI}) was defined as the time from freezing initiation to the last recorded PVP. Time to nonsustained PVI was defined as the time from freezing initiation to the last recorded PVP before temporary abolishment of the PVP during freezing with resumption of PV conduction during the procedure. Only the initial freeze at each PV was analyzed. If PVP visualisation during freezing was not possible because of a distal position of the eSC, PV mapping with the eSC positioned just distal to the angiographically identified ostium was performed after the freeze. Following successful PVI, one bonus application was performed for each PV.[11] The right phrenic nerve (PN) was constantly paced from the superior caval vein during freezing at the septal PVs. In case of cessation or weakening of right hemidiaphragm contractions, freezing was immediately stopped. Ablation endpoint was absence or dissociation of all PVP as confirmed by the eSC after a waiting period of 30 minutes.

Postprocedural Care

All patients underwent transthoracic echocardiography to rule out pericardial effusion after the procedure. Low-molecular-weight heparin (LMWH) was administered

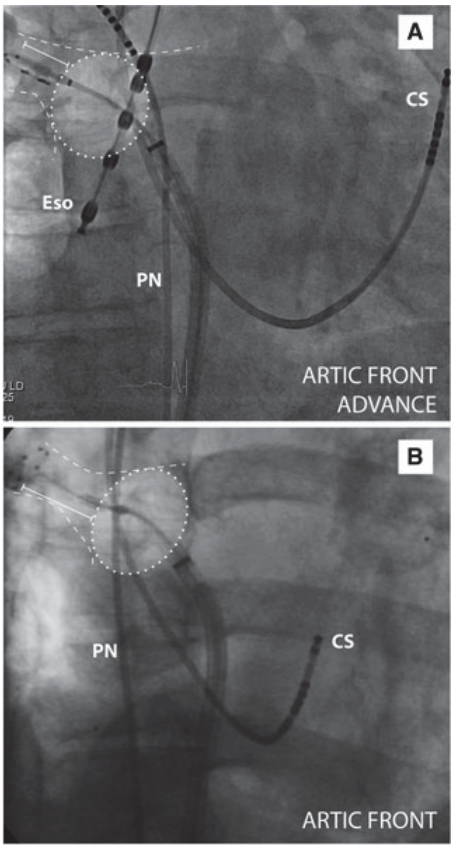

Figure 2. *Representative cryoballoon and Achieve catheter positions during freezing at the right superior pulmonary vein. Panel A: second-generation cryoballoon (Arctic Front Advance) during freezing at the right superior pulmonary vein (RAO 30°). Effective freezing was possible with a proximal mapping catheter position allowing for recording of pulmonary vein potentials during freezing. The measurement bar represents fluoroscopic distance from balloon surface to the most proximal electrode of the mapping catheter (11 mm). Panel B: first-generation cryoballoon (Arctic Front) during freezing at the right superior pulmonary vein (RAO 30°). Effective freezing necessitated a distal position of the mapping catheter to enhance mechanical stability of the balloon catheter. Pulmonary vein potentials could not be recorded from this position. Fluoroscopic distance from balloon surface to the most proximal electrode of the mapping catheter was 17 mm. CS = coronary sinus catheter; PN = catheter at phrenic nerve capture site in the superior caval vein; Eso = esophageal temperature probe.*

6 hours after ablation. Phenprocoumon (with overlapping LMWH until a therapeutic INR was achieved), or dabigatran or rivaroxaban was restarted on the following day according to the previous regimen and prescribed for at least 2 months. A proton pump inhibitor was administered for 2 weeks starting on the day of the procedure. In a subset of patients of the CB-2G group (11/30, 37%) magnetic resonance angiography of the PVs (Magneton Sonata, 1.5 Tesla, Siemens, Germany) was performed after the procedure to screen for asymptomatic PV stenosis. ECG-triggered flash-3D-angiography was performed using multiplanar reconstruction. Clinical follow-up including Holter ECG monitoring for at least 24 hours was performed 1 and 3 months after the procedure or upon symptoms. A history was taken focusing on symptoms suggesting arrhythmia recurrence or possible procedure-related complications (e.g., dyspnea, hemoptysis, or dysphagia). Atrial tachyarrhythmia recurrence was defined as documented AF, atrial flutter, or atrial tachycardia lasting > 30 seconds.

TABLE 2
Procedural Parameters

	CB-1G	CB-2G	P Value
Balloon applications per vein (excluding bonus)	1.8 ± 1.2	1,3 ± 0,8	<0.001
Distance to achieve proximal electrode (mm)	18 ± 8	12 ± 5	<0.001
T_{PVI} (seconds)	79 ± 60	52 ± 36	0.049
Procedure duration (minutes)	128 ± 27	98 ± 30	<0.001
Fluoroscopy exposure (minutes)	19.5 ± 7.4	13,4 ± 5,3	0.001
Contrast medium (mL)	134 ± 33	120 ± 34	n.s.

CB-1G = first-generation cryoballoon; CB-2G = second-generation cryoballoon; T_{PVI} = time from start of freezing to pulmonary vein isolation; n.s. = nonsignificant.

TABLE 3
Frequency of Single-Shot PVI and Real-Time PVI Visualization

	Single- Shot PVI			Real-Time PVI Visualization		
	CB-1G	CB-2G	P	CB-1G	CB-2G	P
LSPV	60%	77%	n.s.	57%	81%	0.054
LIPV	60%	100%	<0.001	57%	81%	0.054
LCPV	–	75%	–	–	25%	–
RSPV	37%	80%	0.001	53%	90%	0.002
RIPV	47%	80%	0.007	30%	60%	0,02
Overall	51%	84%	<0.001	49%	76%	<0.001

PVI = pulmonary vein isolation; PV = pulmonary vein; LS = left superior; LI = left inferior; LC = left common; RS = right superior; RI = right inferior; CB-1G = first-generation cryoballoon; CB-2G = second-generation cryoballoon; n.s. = nonsignificant.

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation and analyzed with Student's *t* test. Nominal variables were expressed as frequencies and proportions and analyzed with the chi-square test. A value of $P < 0.05$ was considered statistically significant.

Results

Cryoballoon Ablation

1G-Cryoballoon ablation

In 30 patients, a total of 117 PVs including 3 left common PVs (LCPV) with a short common trunk were identified. Superior and inferior branches of LCPVs were treated and reported as LSPV and LIPV, respectively. Procedural data are summarized in Tables 2–4. Complete PVI was achieved in all patients. The overall number of applications performed to achieve PVI (excluding the bonus application) was 1.8 ± 1.2. Single-shot PVI could be performed in 51% of PVs. Cross-talk isolation of the LSPV was performed in 27% of LSPVs. A pull-down maneuver at the RIPV was performed in 83% of patients. Visualization of PVP during freezing was possible

TABLE 4
Minimum Balloon and Esophageal Temperatures

	Min. Balloon-Temperature (°C)			Min. LET (°C)
	CB-1G	CB-2G	P	CB-2G
LSPV	−52 ± 5	−52 ± 6	n.s.	27 ± 9 (range 9–35)
LIPV	−48 ± 6	−48 ± 6	n.s.	30 ± 6 (range 17–35)
LCPV	–	−58 ± 3	–	20 ± 16 (range 2–34)
RSPV	−52 ± 6	−54 ± 7	n.s.	32 ± 3 (range 24–35)
RIPV	−44 ± 5	−50 ± 5	<0,001	26 ± 10 (range 4–35)
Overall	−49 ± 6	−52 ± 6	0,005	29 ± 8 (range 2–35)

PV = pulmonary vein; LS = left superior; LI = left inferior; LC = left common; RS = right superior; RI = right inferior; CB-1G = first-generation cryoballoon; CB-2G = second-generation cryoballoon; LET = luminal esophageal temperature; n.s. = nonsignificant.

in 49% of PVs, with a mean T_{PVI} of 79 ± 60 (range 17–245) seconds. In 19% of PVs nonsustained isolation was observed. Time to nonsustained isolation was 120±75 (range 29–289) seconds. Balloon temperatures at the time of nonsustained or sustained isolation were not statistically different: −36 ± 5 versus −40 ± 7 °C, P = 0.13, respectively. In the remaining PVs, the eSC had to be positioned too distal to record a PVP during freezing (Fig. 2). Average fluoroscopic distance from balloon surface to the proximal eSC electrode during successful freezing was 18 ± 8 mm (Fig. 2). Minimum balloon temperatures are shown in Table 4. Overall procedure duration (skin puncture to sheath removal) and fluoroscopy exposure duration was 128 ± 27 and 19.5 ± 7.4 minutes, respectively.

2G-cryoballoon ablation

In 30 patients, a total of 116 PVs including 4 LCPVs were identified. In all patients with a LCPV, the latter was treated as a single PV. The overall number of applications performed to achieve PVI was 1.3 ± 0.8. (P < 0.001 vs CB-1G; Table 2). Complete PVI was achieved in all patients. Single-shot PVI could be performed in 84% of PVs (P < 0.001 vs CB-1G; Table 3). Cross-talk isolation of the LSPV was performed in 8% of LSPVs (P = 0.064 vs CB-1G). A pull-down maneuver during freezing at the RIPV was performed in 57% of patients (P = 0.024 vs CB-1G). The proportion of balloon applications with real-time visualization of PVP increased to 76% in the CB-2G group (P < 0.001 vs CB-1G; Table 3). PVP visualization rates according to anatomical PV are shown in Table 3. Average distance from balloon surface to the proximal eSC electrode during successful freezing was 12 ± 5 mm (P < 0.001 vs CB-1G). Mean T_{PVI} was 52 ± 36 (range 10–178) seconds (P = 0.049 vs CB-1G; Table 2). Nonsustained isolation was observed in 1/116 (1%) of PVs (P < 0.001 vs CB-1G). Time to nonsustained PVI was 178 seconds. Overall, minimum balloon temperatures were lower in the CB-2G group (Table 4). Minimum LET values are shown in Table 4. Procedure and fluoroscopy exposure duration were 98 ± 30 (P < 0.001 vs CB-1G) and 13.4 ± 5.3 (P = 0.001 vs CB-1G) minutes, respectively. A unique phenomenon only observed in the CB-2G group was intravenous ice formation opacified by contrast medium stable throughout the thawing phase and persisting approximately 10 seconds until after balloon deflation (Fig. 3).[12] Stable ice caps could be observed in 9 patients. In another 3 patients in the CB-2G group, cryoadhesion of the eSC was present after balloon deflation, indicative of nonopacified ice formation within the PV.

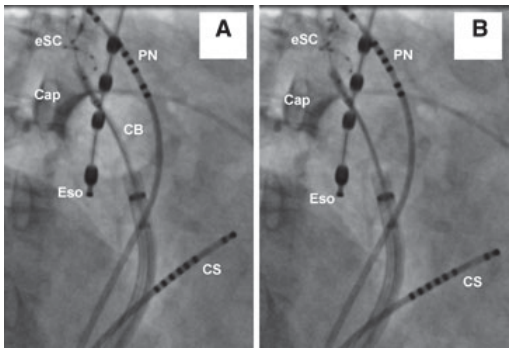

Figure 3. *Visible ice cap formation on second-generation cryoballoon stable until after deflation of the balloon. Panel A: fluoroscopic image (RAO 30°) of the cryoballoon (CB) during freezing at the right-superior pulmonary vein with ice cap (Cap) formation visible by frozen contrast medium. Panel B shows the situation immediately after thawing and deflation of the balloon, which automatically occurs when balloon temperature reaches +20 °C. The ice cap was still visible (Cap) for another 10 seconds. CS = coronary sinus catheter; Eso = esophageal temperature probe; PN = catheter at phrenic nerve capture site in the superior caval vein; eSC = endoluminal spiral catheter.*

Complications

Procedure-related complications occurred in 2 patients in the CB-1G group and 1 patient in the CB-2G group. In the CB-1G group right-sided PN palsy persistent after the procedure occurred in one patient. Repeat chest fluoroscopy at 3 months revealed complete recovery of phrenic-nerve function. In addition, femoral pseudoaneurysm occurred in one patient and was treated conservatively by local compression. In the CB-2G group one case of left-sided PN palsy occurred one day after the procedure. This patient had a left subclavian access for placement of the coronary sinus catheter and a hematoma at the puncture site was noted on day 1. Chest X-ray revealed doming of the left hemidiaphragm without pneumo- or hemothorax. Reexamination of procedural fluoroscopy recordings confirmed normal bilateral PN function throughout the procedure, excluding a direct ablation effect. Thoracic MRT revealed a small hematoma in the subclavian region. This patient felt mild exertional dyspnea, which persisted during follow-up (day 47). None of the remaining patients reported dyspnea or other symptoms suggestive of PV stenosis during follow-up. PV magnetic resonance angiography performed 18 ± 7 (range 6–28) days after the procedure in 11/30 patients of the CB-2G group showed no evidence of asymptomatic PV stenosis. One patient from the CB-2G group suffered a myocardial infarction (day 30) complicated by rupture of the left ventricular free wall and pericardial tamponade. He died after admission in a different hospital. This patient had a history of coronary artery disease with coronary artery bypass grafting performed 10 years earlier. A postmortem examination showed acute myocardial necrosis of the left ventricular free wall and septum with myocardial rupture and pericardial tamponade, which was concluded to be the cause of death.

Short-Term Follow-Up

Within the first 3 months after ablation, 11 patients (37%) of the CB-1G group and 4 patients of the CB-2G group (13%; P = 0.037) demonstrated early tachyarrhythmia recurrence. Ten (33%) patients in the CB-1G group and 6 patients (20%) in the CB-2G group were on antiarrhythmic drug (AAD) therapy throughout follow-up. Atrial tachycardia occurred in 1 and 3 patients in the CB1-G and CB-2G group, respectively. Early reintervention was performed in 2 patients. In 1 patient of the CB-1G group typical atrial flutter as well as AF was documented and ablation of the cavotricuspid isthmus was performed. Remapping of the PVs revealed electrical reconnection of all PVs and reisolation was performed using 3D-mapping and RFA. Another patient of the CB-2G group presented with incessant atrial tachycardia despite amiodarone therapy. A PV tachycardia originating from the RSPV was identified and successfully ablated by reisolation of the RSPV using RFA. All other PVs were found to be isolated in this patient. The remaining patients with recurrent tachyarrhythmia were treated by AAD and, if necessary, cardioversion.

Discussion

The main findings of this study are as follows. (1) Using the CB-2G improved the efficacy of cryoballoon ablation impacting on several procedural parameters. Notably, the frequency of single-shot isolation significantly increased to 84% when compared to the CB-1G. This resulted in shortened procedure duration and fluoroscopy exposure time. (2) PV mapping during cryoablation was possible in the majority of PVs (76%) in the CB-2G group. This further enhanced the workflow of the procedure and allowed efficient measurement of T_{PVI}. A long T_{PVI} has been shown to correlate with incomplete lesion formation leading to PV reconnection.[13] Notably, T_{PVI} was significantly shorter in the CB-2G group.

A distinguishing feature of the cryoballoon is simultaneous lesion formation in the area of balloon-tissue contact, providing the possibility of single-shot PVI.[2] However, for this concept to fully work homogenous cooling of the balloon surface is required. This was not realized with the first-generation device exhibiting a zone of optimal cooling around the equator of the balloon[14] (Fig. 1). As a consequence, eccentric balloon positions may result in inhomogenous lesion formation. Thus, repeated freezing with varying balloon positions using different catheter techniques[2] or focal touch-up lesions are frequently necessary to obtain isolation.[3,15] Furthermore, analysis of the local re-conduction pattern at repeat ablation following cryoballoon PVI also suggested decreased chronic efficacy by this mechanism.[5] The second-generation device is characterized by a novel refrigerant injection system, extending the zone of optimal cooling to the distal pole around the nose of the balloon (Fig. 1). This was achieved by repositioning the injection coil 4,5 mm toward the nose and increasing the number of injection ports to 8, resulting in increased refrigerant flow when compared to the 28 mm CB-1G. Although the procedural endpoint of complete PVI was achieved in all patients in both treatment groups, use of the second-generation cryoballoon reduced radiation exposure time by 31% and total procedure time by 23%. The improved efficacy of the CB-2G found in this study may be explained by an increased area of balloon-tissue contact with optimal cooling. Furthermore, improved cooling of the nose may give rise to more extensive ice formation within the PV as demonstrated by the stable ice cap phenomenon (Fig. 3).[12] We hypothesize that intra-PV ice formation reduces PV blood flow during freezing, allowing for efficient cryolesion formation even in the absence of complete circumferential balloon contact and alleviating the need to push the balloon strongly onto the PV ostium. Accordingly, the eSC could be positioned relatively proximal in the CB-2G group, resulting in a significantly higher rate of PVP visualization during freezing (76%). Furthermore, catheter maneuvers such as crosstalk isolation and the pull down maneuver[2] were less often required in the CB-2G group. Effective measurement of T_{PVI} may provide the basis to further streamline the workflow of cryoballoon PVI. T_{PVI} has been found to reflect lesion quality in previous studies of cryoballoon PVI, with longer T_{PVI} predicting intraprocedural PV reconduction.[13] Intraprocedural PV reconduction rate and T_{PVI} were significantly lower in the CB-2G group. We suggest that T_{PVI} may guide application duration or the number of freeze-thaw cycles in future studies.

The frequency of periprocedural complications was comparable in both groups. The most frequently reported complication of cryoballoon PVI is right-sided PN palsy[16] because of the anatomical association of the septal PVs (especially the RSPV) to the right PN.[17] In this study, intraprocedural right PN palsy occurred in 1 patient in the CB-1G group. In another patient in the CB-2G group, left PN palsy was observed 1 day following the procedure with intact diaphragm contraction during ablation. To the best of our knowledge, left PN palsy associated with cryoballoon PVI has previously been described in 1 patient[18] and occurred during ablation, as consistently described for right PN palsy.[2,3] In our study, left PN palsy occurred after the procedure and was associated with hematoma formation following left subclavian venous access. Several cases of PN palsy following subclavian vein puncture have previously been described,[19,20] however, we cannot completely exclude a delayed effect from ablation.

We and others previously investigated LET changes during PVI using the CB-1G.[21,22] Although not directly compared in this study, minimal LET during ablation in the CB-2G group was in the range of previously published results. Symptoms suggestive of esophageal lesion formation did not occur in any of the study patients; however, to define a possible impact of the cryoballoon redesign on esophageal lesion formation, additional studies with systematic postprocedural esophagoscopy are necessary.

Limitations

This study constitutes a nonrandomized analysis of consecutive patients, including our initial patients treated with the novel CB-2G device. However, all operators were well trained in CB ablation and beyond the learning curve, minimizing time-dependent confounders. (2) Group size was small. However, a number of efficacy parameters differed significantly between the groups. Notwithstanding, conclusions about rare complications such as atrioesophageal fistula cannot be drawn from this data. (3) LET measurement was not performed in the CB-1G group. However, several prior studies reported on LET during CB-1G ablation.[21-23] (4) The aim of this study was to compare procedural efficacy of the CB-2G when compared to the CB-1G. Because of the novelty

of the CB-2G, only short-term clinical follow-up data could be provided at the time of publication of this manuscript. Notably, early tachyarrhythmia (< 3 months) recurrence following cryoballoon PVI may occur without later recurrence.[2]

Conclusion

The CB-2G significantly improved the efficacy of PVI with high rates of single-shot isolation when compared to the CB-1G. This resulted in shortened procedure duration and fluoroscopy exposure time. PV mapping during cryoablation was possible in the majority of PVs using the CB-2G. Reliable measurement of time to isolation during cryoballoon PVI may provide the opportunity to adjust application time and number individually in future studies. Final conclusions regarding the safety profile of the CB-2G requires additional research in a larger group of patients.

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Improved 1-Year Clinical Success Rate of Pulmonary Vein Isolation with the Second-Generation Cryoballoon in Patients with Paroxysmal Atrial Fibrillation

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Improved Efficacy of Second-Generation Cryoballoon. ***Background:*** **The second-generation cryoballoon (CB2) has recently been introduced featuring improved surface cooling. Increased procedural efficacy of pulmonary vein isolation (PVI) when compared to the first-generation balloon (CB1) has been reported. The aim of the study was to investigate the clinical outcome of cryoballoon PVI after 1 year using the CB2 as compared to the CB1.**

Methods and Results: **A total of 105 consecutive patients with paroxysmal atrial fibrillation (AF) were studied. Cryoballoon PVI (28 mm) was performed in 50 patients using the CB1, and in 55 patients using the CB2. Patients were scheduled for 72-hour Holter ECG recording at 3, 6, 9, and 12 months and every 6 months thereafter. The study endpoint was defined as recurrent AF or atrial tachycardia >30 seconds documented after a blanking period of 90 days after the procedure. Complete PVI was achieved in 49/50 (98%) and 55/55 (100%) patients in the CB1 and CB2 group, respectively. After a mean follow-up of 416 ± 75 days, 21 (CB1 group) and 10 (CB2 group) patients reached the study endpoint. Kaplan–Meier estimates of arrhythmia-free survival after a single procedure without AAD therapy after 1 year were 63.9% versus 83.6% (P = 0.008) in the CB1 and CB2 group, respectively. Persistent phrenic nerve palsy with delayed healing occurred in 2 (CB1 group) and 3 (CB2 group) patients.**

Conclusion: **Clinical outcome of PVI using the CB2 was significantly improved when compared to the CB1.** *(J Cardiovasc Electrophysiol, Vol. 25, pp. 840-844, August 2014)*

atrial fibrillation, catheter ablation, cryoballoon, phrenic nerve palsy, pulmonary vein isolation

Introduction

The cryoballoon (CB) technology offers the possibility of pulmonary vein isolation (PVI) with a single energy application. It is thus increasingly used to perform PVI in patients with atrial fibrillation (AF) as alternative to point-by-point radiofrequency (RF) current ablation.[1-6] The initial first-generation CB (CB1) was characterized by inhomogeneous surface cooling resulting in a systematic pattern of PV reconduction demonstrated in patients with recurrent AF.[7] Recently, the second-generation CB (CB2) was introduced featuring homogenous cooling of the entire frontal surface with increased refrigerant flow of the larger 28 mm balloon. Improved procedural efficacy with high rates of single-application PVI have been demonstrated using the CB2.[8] In this study, we investigated 1-year clinical efficacy rates after CB-PVI with the CB2 as compared to the CB1 in patients with paroxysmal AF (PAF).

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Methods

Patients

We prospectively studied 105 consecutive patients undergoing CB-PVI for symptomatic PAF. Patients with persistent AF or a left atrial diameter ≥55 mm were excluded. The first 50 patients received treatment with the CB1. Upon availability of the CB2, patients received treatment with the CB2, starting with patient 51.

Cryoballoon Ablation

We previously described in detail our technique of CB-PVI.[8,9] All procedures were performed by operators well-experienced in CB ablation. In brief, an octapolar diagnostic catheter was placed in the coronary sinus via the femoral or left subclavian approach. After single transseptal puncture, the 28 mm CB (Arctic Front or Arctic Front Advance, Medtronic, Inc., Minneapolis, MN, USA) was introduced into the left atrium via a 12F steerable sheath (FlexCath, Medtronic). PV mapping was performed before, during, and after freezing with an endoluminal spiral mapping catheter (eSC, Achieve, Medtronic). To assess the exact position of the inflated balloon in relation to the PV, ostium contrast medium was injected from the distal lumen of the CB catheter with the aim of complete PV occlusion before freezing. Target application time was 300 seconds using CB1, and 240 seconds using CB2. Following successful PVI, 1 bonus application was performed at each PV. Only the 28 mm CB was used; touch-up lesions with a focal catheter were

not performed. The right phrenic nerve (PN) was paced from the superior caval vein during freezing at the septal PVs. In case of cessation or weakening of right hemidiaphragm contractions, freezing was immediately stopped. Luminal esophageal temperature (LET) was measured in a subset of patients in the CB2 group (n = 36). The procedural endpoint was absence or dissociation of all pulmonary vein potentials as confirmed by the eSC after a waiting period of 30 minutes.

Postprocedural Care and Follow-Up

All patients underwent transthoracic echocardiography to rule out pericardial effusion after the procedure. Low-molecular-weight heparin (LMWH) was administered 6 hours after ablation. Phenprocoumon (with overlapping LMWH until a therapeutic INR was achieved), or dabigatran or rivaroxaban was restarted on the following day according to the previous regimen and prescribed for a minimum of 2 months. Thereafter, oral anticoagulation was prescribed according to current ESC guidelines.[10] A proton pump inhibitor was administered for 2 weeks starting on the day of the procedure. Patients were scheduled for outpatient clinic visits at 3, 6, 9, and 12 months and every 6 months thereafter at which time 72-hour Holter ECG recording was performed. In the case of symptoms suggestive of atrial tachyarrhythmia recurrence, additional visits and Holter ECG recordings were performed. A previously ineffective therapy with membrane-active antiarrhythmic drugs (AAD) was stopped within the first 3 months if patients were in stable sinus rhythm. The study endpoint was defined as recurrent AF or atrial tachycardia (AT) lasting >30 seconds documented after a blanking period of 90 days after the procedure.

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation and analyzed with the Student's *t*-test (2-sided). Nominal variables were expressed as frequencies and proportions and analyzed with the chi-square or Fisher's exact test (2-sided). To estimate arrhythmia-free survival, Kaplan–Meier curves were constructed. Survival data were compared with the log-rank test. To adjust the primary endpoint to baseline characteristics, a Cox regression analysis was performed. The prespecified covariates were balloon type, age, sex, time since PAF diagnosis, LA size, ejection fraction, presence of hypertension, diabetes, prior stroke/transitory ischemic attack, heart failure NYHA ≥ 2, and coronary artery disease. Hazard ratios and 95% confidence intervals (CI) were calculated. A value of $P < 0.05$ was considered statistically significant.

Results

Patients

The clinical baseline characteristics of the study patients are shown in Table 1. The groups were balanced with respect to age, sex, time since PAF diagnosis, and comorbidities.

Cryoballoon Ablation

Procedural data of CB-PVI in both groups are summarized in Table 2. A left common trunk treated as a single PV was found in 3 and 6 patients in the CB1 and CB2 group, respectively. An additional right middle PV was found in 1 patient in the CB2 group. Complete PVI was achieved in the CB1 group in 49/50 (98%) patients. In 1 patient, the right inferior PV (RIPV) could not be isolated despite 5 CB applications. In the CB2 group, complete PVI was achieved in all patients. Procedure duration (skin puncture to sheath removal), fluoroscopy exposure time, and number of balloon applications per patient were significantly lower in the CB2 group (Table 2). Isolation occurred in 89% of PVs during the first balloon application in the CB2 group as compared to 53% in the CB1 group ($P < 0.001$). Early interruption of freezing was performed at 4 PVs in 4 patients in the CB1 group due to weakening/loss of right hemidiaphragm contraction. In the CB2 group, early interruption of freezing was performed at 7 PVs in 7 patients. The reasons were weakening/loss of right hemidiaphragm contraction (5 patients) and excessive esophageal cooling (LET 0 °C and 5 °C in 2 patients, respectively). In all instances of early freezing interruption, PVI had already occurred and no additional freeze was delivered to the culprit PV.

TABLE 1
Patient Baseline Characteristics

	Group 1 (CB1) n = 50	Group 2 (CB2) n = 55	P Value
Male (%)	66	53	0.17
Age (years)	63 ± 10	62 ± 14	0.74
AF history (years)	4.2 ± 4.4	4.4 ± 4.7	0.89
LA size (mm)	39 ± 4	40 ± 4	0.58
LVEF (%)	62 ± 4	64 ± 5	0.09
Hypertension (%)	62	76	0.11
Diabetes (%)	12	15	0.7
Stroke/TIA (%)	2	6	0.62
Heart failure NYHA ≥2 (%)	10	4	0.25
CAD (%)	6	18	0.06
Amiodarone (%)	6	11	0.49
Flecanide/Propafenone (%)	30	16	0.1
Sotalol (%)	2	2	1
Dronedarone (%)	14	4	0.08

CAD = coronary artery disease; CB1 = first-generation cryoballoon; CB2 = second-generation cryoballoon; LA = left atrium; LVEF = left ventricular ejection fraction; TIA = transient ischemic attack.

TABLE 2
Procedural Data

	Group 1 (CB1) n = 50	Group 2 (CB2) n = 55	P Value
Complete PVI (%)	98	100	0.48
Duration (min)	137 ± 33	94 ± 24	< 0.001
Fluoro exposure (min)	21.5 ± 9.5	12.9 ± 4.5	< 0.001
Balloon applications/patient	10.4 ± 2.0	8.3 ± 1.3	< 0.001
Isolation with the first application (% PVs)	53	89	< 0.001

CB1 = first-generation cryoballoon; CB2 = second-generation cryoballoon; PVI = pulmonary vein isolation; PVs = pulmonary veins.

Complications

In the CB1 group, persistent phrenic nerve palsy (PNP) present at the time of discharge occurred in 2 patients (4%) despite early freezing interruption. In 2 additional patients, transient PNP with recovery of diaphragm motion following immediate freezing interruption was observed. PNP was exclusively observed at the right superior PV (RSPV) in the

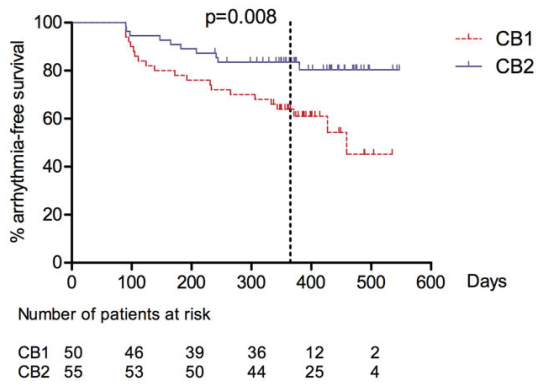

Figure 1. *Kaplan–Meier estimates of arrhythmia-free survival after pulmonary vein isolation using the first-generation (CB1) or second-generation (CB2) cryoballoon. Dotted line indicates 365 days. For a high quality, full color version of this figure, please see Journal of CardiovascularElectrophysiology's website: www.wileyonlinelibrary.com/journal/jce*

CB1 group. Access site complications occurred in 2 patients (4%), 1 femoral pseudoaneurysm (treated by local compression) and 1 subcutaneous hematoma at the left subclavian vein puncture site. Both patients recovered completely.

In the CB2 group, persistent PNP occurred in 3 patients (5.4%). In 2 of these patients, PNP occurred during freezing at the RIPV. In 1 patient, delayed left-sided PNP was detected at routine chest X-ray 1 day postprocedure with unimpaired intraprocedural diaphragm movement. In 4 additional patients (7.2%), transient PNP occurred during freezing at the RSPV (2 patients) or the RIPV (2 patients). Following immediate cessation of the freeze, diaphragm movement recurred to normal in all 4 patients. There was no statistically significant difference in the rate of transient and/or persistent PNP between the groups. Access site complications in the CB2 group occurred in 2 patients (3.6%), 1 AV fistula (spontaneous occlusion demonstrated during follow-up), and 1 left-sided hemothorax following left subclavian vein access (treated by percutaneous drainage). Both patients recovered completely.

Follow-Up

The follow-up period was 419 ± 79 days in the CB1 group and 414 ± 72 days in the CB2 group (P = n.s.). In addition to serial Holter ECG recordings, 6 patients in the CB2 group received a transtelephonic monitor transmitting weekly rhythm strips. The study endpoint occurred in 21 patients in the CB1 group and in 10 patients in the CB2 group. Kaplan–Meier estimates of arrhythmia-free survival are shown in Figure 1. Recurrent AF/AT occurred in a significantly larger proportion of patients in the CB2 group (P = 0.008; log-rank test). Kaplan–Meier estimates of freedom from AF/AT off AAD after 365 days were 63.9% of patients in the CB1 group and 83.6% of patients in the CB2 group.

In multivariate Cox regression analysis, the only significant predictor of AF-/AT-free survival was the use of the CB2 (HR 0.38; 95% CI 0.17–0.93; P = 0.032). Early recurrence of AF documented upon symptom-triggered visits within the blanking period occurred in 13 (26%) and 7 patients (12.7%, P = 0.08), of whom 7 and 4 also exhibited recurrent AF after blanking in the CB1 and CB2 group, respectively. Early recurrent AF was treated by AAD therapy for up to 3 months after the procedure.

In the CB1 group, recurrent AF/AT was managed with repeat catheter ablation using RF energy in 14 patients after 241 ± 139 days. Reconduction of ≥1 PV was observed in every patient and PV reisolation was performed. The mean number of reconnected PVs was 2.9 ± 1.1. Ablation of the cavotricuspid isthmus in addition to PV reisolation was performed in 4 patients who exhibited typical right atrial flutter in addition to recurrent AF. AT occurred in 1 patient. Mapping revealed perimitral flutter, which was terminated by ablation of an anterior line. In 7 patients, AF symptoms were well controlled with rate control (3 patients) or class I AAD therapy (4 patients) and repeat catheter ablation was not performed.

In the CB2 group, recurrent AF/AT was managed with repeat catheter ablation in 6 patients after 201 ± 62 days. Reconduction of ≥1 PV was observed in 4 patients and PV reisolation was performed using RF energy or the CB2 (1 patient). In the 6 patients undergoing a redo procedure, the mean number of reconnected PVs was 0.8 ± 0.8 (P = 0.001 vs. CB1 group). AT occurred in 2 patients, in whom all PVs were found to be isolated. In 1 patient, perimitral flutter was diagnosed and terminated to sinus rhythm by ablation of an anterior line. In the other patient, the clinical tachycardia was identified as perimitral flutter and changed to a different tachycardia during ablation of an anterior line with subsequent identification of a focal tachycardia from the left atrial posterior wall, which was terminated to sinus rhythm by focal ablation. In 4 patients, AF symptoms were well controlled with rate control (2 patients) or class I AAD therapy (2 patients) and repeat catheter ablation was not performed.

Repeat chest fluoroscopy in patients with PNP demonstrated recovery of PN function after 21 and 36 days in the 2 patients in the CB1 group, and after 170, 251, and 483 (left PN) days in the 3 patients in the CB2 group. No complications after discharge during follow-up did occur.

Discussion

The main results of the study are: (1) the single-procedure clinical success rate of CB2-PVI off AAD after 1 year was 83.6% and (2) this constituted a significant improvement when compared to the CB1 (63.9%, P = 0.008).

In the North American Arctic Front STOP AF Pivotal Trial, in which the CB1 was utilized, the success rate after a 90-day blanking period in the CB arm was reported as 69.9%, including 8% of patients on AAD therapy.[11] Acknowledging differences in the ablation protocol (repeated cryoablation during the blanking period in STOP AF), our findings in the CB1 group correspond to these results. A technical limitation of the CB1 was a temperature gradient from the equator to the distal pole of the balloon with less effective cooling around the balloon nose. This area is typically in contact with the lower circumference of the inferior PVs where conduction gaps were preferentially found during repeat procedures.[7,12] In the CB2, this limitation has been overcome by repositioning and doubling the number of injection ports, resulting in uniform cooling of the frontal balloon hemisphere.[8] In addition, refrigerant flow has been increased in the larger 28 mm CB2 variety. Together, these modifications have been shown to improve procedural and early clinical efficacy during short-term follow-up.[8,13] This study extends these preliminary observations, demonstrating

a significantly higher clinical success rate of CB2-PVI after 12 months.

With increased efficacy due to enhanced surface cooling, the CB2 may also be associated with a higher risk of collateral tissue damage.[1,14] The most common complication of CB-PVI is PNP. In a previous study, Casado-Arroyo *et al*. reported persistent PNP in 3/41 (7.3%) patients treated with the CB2.[15] In a cohort of 115 patients treated with the CB2, Metzner *et al*. reported a persistent PNP rate of 3.5%.[16] In STOP AF utilizing the CB1, persistent PNP occurred in 1.8% of all CB-treated patients (n = 228).[11] In this study, we did not find a statistically significant difference in the rate of transient or persistent PNP between the 2 balloons; however, this may be a result of relatively low patient numbers. Further studies in larger patient cohorts are needed to better define the risk of this complication associated with the CB2. Of note, we controlled diaphragm contraction by palpation. Measuring diaphragmatic electromyograms may provide a more sensitive method to rapidly detect PN injury while still reversible.[17,18]

In this early patient cohort treated with the CB2, systematic LET measurement with a predefined LET cut-off was not performed. We recently reported a high predictive performance of LET measurement with respect to esophageal ulcerations detected in postprocedural esophagoscopy.[19] Thus, our current strategy is to perform LET measurement routinely. Prospective evaluation of LET-guided CB-PVI is currently under investigation in our laboratory.

In the 3 patients with perimitral flutter diagnosed during repeat catheter ablation using 3D-mapping, scarring of the left atrial anterior wall with fractionated potentials was detected. The mitral isthmus between the anterior ridge of the lateral PVs and the mitral annulus showed normal potentials in all 3 patients. We do not assume that the anterior scar in those patients was caused by the CB; however, since we did not map the left atrium before PVI, a definite conclusion cannot be made. Further research including voltage mapping before and after CB-PVI is needed to clarify the pathogenesis of left atrial macroreentrant tachycardia after CB-PVI.

We aimed for at least 2 freeze–thaw cycles (bonus freeze) at all PVs. This concept has been applied by many operators using the CB1.[2,20-22] It is currently not known whether such a strategy impacts on clinical success when compared to a single freeze using the CB2. A dose titration algorithm with repeated freezing only in case of prolonged time from freezing initiation to PVI may be equally effective. This hypothesis is currently being tested in the ongoing ICE trial (DRKS-ID: DRKS00004937). The high single-shot isolation rate of the CB2 with simultaneous circumferential lesion formation may theoretically result in increased lesion durability by minimizing intermittent edema formation when compared to point-by-point ablation. The ongoing FIRE AND ICE trial (ClinicalTrials.gov Identifier NCT01490814) randomizing patients with PAF to PVI using RF versus CB ablation, including the CB2, will help to clarify this issue.

Limitations

This study was not randomized. We can therefore not exclude the influence of unmeasured confounders. However, all procedures were performed by experienced operators beyond the learning curve, minimizing a training effect. The decision for a sequential design was influenced by ethical considerations given the increased procedural and short-term clinical efficacy of the CB2.[8,13] The sample size was relatively small. Despite demonstrating a significant difference in clinical efficacy, the study was not powered to detect smaller differences in complication rates.

Conclusion

Clinical outcome of PVI using the CB2 was significantly improved when compared to the CB1. After 1 year, 83.6% (CB2) versus 63.9% (CB1) of patients were free of recurrent AF/AT without AAD therapy.

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Rationale and Design of FIRE AND ICE: A Multicenter Randomized Trial Comparing Efficacy and Safety of Pulmonary Vein Isolation Using a Cryoballoon versus Radiofrequency Ablation with 3D-Reconstruction

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Rationale and Design of Fire and Ice. ***Background:*** **Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia imposing substantial morbidity and mortality. Catheter-based pulmonary vein isolation (PVI) using radiofrequency current (RFC) has become a standard treatment for drug-resistant and symptomatic paroxysmal AF (PAF). In recent years, the cryoballoon-based technique is increasingly used as a promising alternative with a short learning curve.**

Methods: **The FIRE AND ICE trial is a prospective, randomized, controlled, open, blinded outcome assessment, noninferiority trial comparing cryoballoon-, and RFC-based PVI. Patients with drug-resistant PAF will be randomized in a 1:1 matrix in multiple European centers. The primary hypothesis is that cryoballoon ablation is not inferior to RFC ablation using 3-dimensional mapping with respect to clinical efficacy. The primary endpoint is defined as the time to first documented clinical failure, including: (1) recurrence of AF; (2) atrial flutter or atrial tachycardia; (3) prescription of class I or III antiarrhythmic drugs; or (4) re-ablation, whichever comes first, following a blanking period of 3 months after the index ablation procedure. The primary safety endpoint is a composite of death, stroke/transient ischemic attack, cardiac arrhythmias (apart from AF recurrence) causally related to the therapeutic intervention, and procedure-related serious adverse events.**

Conclusion: **The FIRE AND ICE trial compares 2 different technologies to perform catheter ablation of PAF with respect to efficacy and safety. It aims at providing objective data to guide selection and usage of ablation catheters in the treatment of AF.** *(J Cardiovasc Electrophysiol, Vol. 25, pp. 1314-1320, December 2014)*

atrial fibrillation, catheter ablation, cryoballoon, electrophysiology, radiofrequency ablation

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia imposing substantial morbidity and mortality. The prevalence of AF in the US population is estimated to be between 2.0 and 2.5 million, which is projected to increase 2.5-fold by the year 2050.[1] AF is associated with heart failure, thromboembolic events, and increased mortality.[1] In addition, AF frequently causes symptoms such as palpitations, dizziness, and exercise intolerance. As a result, the arrhythmia is responsible for approximately 365,000 hospital admissions in the US yearly.[2] Symptoms and associated morbidities lead to impairment of quality of life (QoL), and interventions to control AF have been shown to improve QoL during long-term follow-up care.[3]

Catheter ablation of AF has been demonstrated to be superior in the control of AF when compared to pharmacological intervention in a number of randomized clinical studies.[4,5] A central principle of this therapy is the electrical isolation of arrhythmogenic triggers in the muscular sleeves of pulmonary veins (PV).[6] As a result, catheter-based pulmonary vein isolation (PVI) has become a standard treatment for drug-resistant and symptomatic paroxysmal AF (PAF).[7,8]

The most widely used and established technique involves encircling of the pulmonary veins with a set of radiofrequency current (RFC)–induced lesions guided by a 3D-mapping system.[7] However, the technical complexity of this procedure involving a long learning curve restricts this therapy to a small number of patients in relatively few specialized centers. In an effort to simplify PVI, allowing a broader

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TABLE 1
Procedure-Related Adverse Events

Atrio-esophageal fistula
Cardiac tamponade
Percutaneous drainage
Requiring surgery
Stroke Transient ischemic attack
Pulmonary vein stenosis requiring intervention
Hemothorax
Pneumothorax
Sepsis/Endocarditis
Mitral valve injury
Retroperitoneal hematoma
Phrenic nerve palsy, persistent after procedure
Deep vein thrombosis
Aspiration with pneumonia
Femoral pseudoaneurysm or arterio-venous fistula
Conservatively treated
Requiring surgery
Hemoptysis

number of patients access to this therapy, the cryoballoon technology has been developed.[9] With this approach, a circular cryothermal lesion around a PV can be created by a single ablation step. Initial studies demonstrated promising results for both a short learning curve[10] as well as better AF control when compared with drug therapy. In the North American STOP-AF trial,[11] absence of AF was achieved in 69.9% of patients following cryoballoon ablation as compared to 7.3% of patients receiving antiarrhythmic drug (AAD) therapy after 1 year. However, prospective data comparing clinical efficacy and safety of this technique with conventional RFC-based ablation are limited to view small-scale studies.[12,13]

Methods

Primary Endpoint and Hypothesis

The primary hypothesis of the FIRE AND ICE study is that cryoballoon ablation is not inferior to RFC ablation using 3D mapping with respect to clinical efficacy (prespecified noninferiority margin is a hazard ratio of 1.43, corresponding to an absolute difference of 10% if the clinical efficacy of RFC is 70%). In case of noninferiority, a superiority analysis will be performed. The primary endpoint is defined as the time to first documented clinical failure, including: (1) recurrence of AF (>30 seconds); (2) atrial flutter (AFL) or atrial tachycardia (AT); (3) prescription of class I or III AAD; or (4) re-ablation, whichever comes first, following a blanking period of 3 months after the index ablation procedure. The blanking period is to allow for complete healing of ablation lesions.[7]

Secondary Endpoints

Key secondary endpoints of the study will assess patient care parameters, including: (1) total procedural duration; (2) total time of fluoroscopy; (3) time to recurrent AF, first symptomatic AF, or cardiovascular hospitalization; (4) number of cardiovascular hospitalization(s); and (5) QoL changes at 12 months compared with baseline.

Safety Analysis

The primary safety endpoint parameter is a composite of death, stroke/transient ischemic attack (TIA), cardiac arrhythmias (apart from AF recurrence) causally related to the therapeutic intervention, and procedure-related serious adverse events (SAE). A list of possible procedure-related adverse events based on previous clinical experience[14-17] and the definition of SAE is shown in Tables 1 and 2, respectively. Secondary safety outcome parameters are SAE of all types (and of each type separately) and the components of the composite primary safety outcome parameter. The parameters will be analyzed and compared per random group.

Study Design

The FIRE AND ICE trial is a prospective, randomized, controlled, open, noninferiority trial comparing cryoballoon- and RFC-based PVI. At multiple European centers, patients will be randomized in a 1:1 matrix (Fig. 1). Randomization will be stratified by age (≤65 years), providing balanced treatment assignment in both age cohorts (≤65 vs. >65 years). A randomization list will be created with blocking by investigational site. All trial investigators will have completed at least 50 procedures in at least 1 of the 2 study techniques to be able to participate in this trial. Each participating center will provide investigator(s) trained in both techniques. A minimum of 10 patients is requested per study site for purposes of pooled-data analyses. The study protocol has been approved by the ethical review committees at each site.

Participants

The study population will consist of patients with symptomatic PAF resistant to medical therapy, including class I or III AADs or a beta blocker, which is in accord with current European and US guidelines for the management of AF.[8,18] Inclusion and key exclusion criteria are summarized in

TABLE 2
Definition of a Serious Adverse Event

A serious adverse event (SAE) is an adverse event that
(a) Led to death
(b) Led to serious deterioration in the health of the patient, that either resulted in
1) A life-threatening illness or injury, or
2) A permanent impairment of a body structure or a body function, or
3) In-patient or prolonged hospitalization (>2 nights), or
4) Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function
c) Led to fetal distress, fetal death, or a congenital abnormality or birth defect

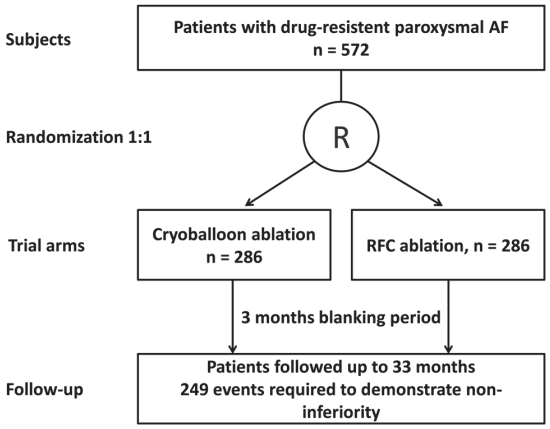

Figure 1. *FIRE AND ICE study design. AF = atrial fibrillation; RFC = radiofrequency current.*

Tables 3 and 4, respectively. A full list of exclusion criteria is provided in the online supplement. A signed, ethics committee/institutional review board approved informed consent form (written in accordance with country-specific applicable data privacy acts, the Declaration of Helsinki, and the applicable laws for research using medical devices) will be obtained from every patient prior to any trial-related procedure.

Interventions

After venous access, single or double transseptal puncture is performed. Selective PV angiography is performed to identify the PV anatomy including the ostial diameter. PV electrograms at baseline are recorded from all PVs by use of a circular mapping catheter to be compared to analogous recordings after ablation. With both techniques, PVI only will be performed as the gold standard. Additional left atrial linear or complex fractionated atrial electrogram (CFAE) ablation, or adenosine testing will not be performed. Concomitant ablation of previously documented CTI-dependent flutter may be performed at the index procedure using RFC regardless of the randomization group. The procedural endpoint is defined as absence or dissociation of all PV potentials as confirmed by the circular mapping catheter after a waiting period of 30 minutes after the last ablation. The procedural endpoint will be assessed by an independent ECG core lab on the basis of pre- and postablation electrograms as well as fluoroscopic documentation of the circular mapping catheter position during recording.

Cryoballoon ablation

The cryoballoon catheter is introduced into the left atrium (LA) via a guide wire or an integrated circular mapping catheter (Achieve, Medtronic CryoCath LP, Pointe-Claire, Quebec, Canada). Two different sizes of the cryoballoon (Arctic Front, Medtronic) are available, 28 and 23 mm diameter. Future developments of this product line (e.g., Arctic Front Advance) are allowed provided the operator has performed at least 10 additional procedures with the updated device. In general, cryoablation of the PV ostia using the 28 mm balloon will be attempted. If the diameter of the vein is $\leq$ 20 mm, a 23 mm cryoballoon may be used as first choice. Contrast medium is injected from the distal lumen of the catheter to assess the exact position of the inflated balloon in relation to the PV ostium. The cryoballoon is then positioned in order to achieve a maximum of PV occlusion as indicated by the lack of contrast medium run-off.[9] Each cryoablation is performed for a target time of 300 seconds (240 seconds with the Arctic Front Advance balloon). The right phrenic nerve (PN) is continuously stimulated from the superior caval vein during freezing at the right-sided PVs. In case of cessation or weakening of right hemidiaphragm contractions, freezing is immediately stopped and no further cryoballoon ablation will be performed at the respective PV. After freezing, PV conduction is re-evaluated by a circular mapping catheter. Alternatively, PV mapping is performed during freezing using an endoluminal spiral mapping catheter.[19] If the PV is not isolated, the cryoballoon is repositioned and balloon to LA-PV contact re-evaluated by angiography before the next freeze. If isolation of a PV cannot be achieved after a maximum of 5 freezes, no further cryoballoon applications are

TABLE 3

Inclusion Criteria

Symptomatic paroxysmal atrial fibrillation with at least 1 episode documented ($\geq$30 seconds)
Documented treatment failure of at least 1 anti-arrhythmic drug (Class I or III, or a β-blocker)
Age 18-75 years
Patient is mentally and linguistically able to understand the aim of the trial and to show sufficient compliance in following the trial protocol
Patient is able to verbally acknowledge and understand the associated risks, benefits, and treatment alternatives to therapeutic options of this trial

TABLE 4

Key Exclusion Criteria

Any previous left atrial ablation or surgery
Any cardiac surgery or percutaneous coronary intervention within 3 months prior to enrollment
Stroke or transient ischemic attack within 6 months prior to enrollment
Myocardial infarction within 3 months prior to enrollment
Ejection fraction $<$ 35%
Anteroposterior left atrial diameter $>$ 55 mm by transthoracic or transesophageal echocardiography
Right-sided pulmonary vein diameter $>$ 26 mm
Implanted prosthetic valve

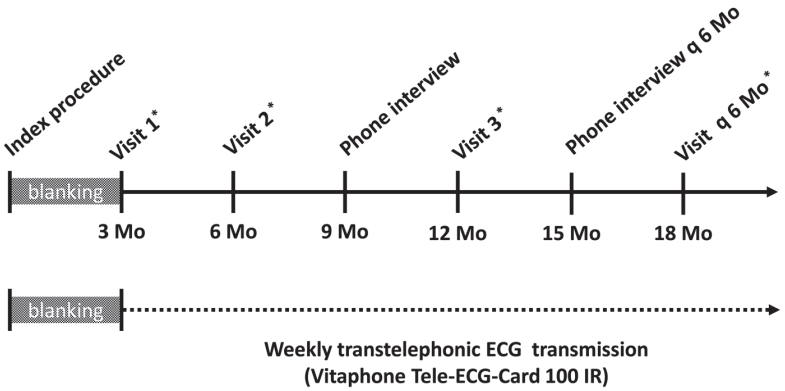

Figure 2. *Follow-up schema. *Physical examination, medical history, quality of life evaluation (SF-6D, EQ-5D).*

to be applied at this vein. In this case, ongoing LA-to-PV conduction will be accepted. Adjunctive linear ablation using a focal cryocatheter will not be performed. If the PV is isolated, 1 additional application is recommended at each PV.[20]

Radiofrequency current ablation

Three-dimensional computerized reconstruction of the LA is performed by use of the CARTO (Biosense Webster, Inc., Diamond Bar, CA, USA) mapping system. Thereafter, PV isolation is performed by a 3.5 mm open-irrigated tip RFC catheter (Thermocool Navi-Star, Biosense Webster, Inc.). Future developments of this product line (e.g., Thermocool Navi-Star SF, Thermocool SmartTouch) are allowed provided the operator has performed at least 10 additional procedures with the updated device. A circumferential lesion set around right-sided and left-sided PVs will be deployed.[21] Power settings will be according to the center's standard of care but not exceed 40 Watts at the anterior and inferior aspects, or 30 Watts at the posterior and superior aspect of the LA. The ablation time at each lesion site should be ≥30 seconds.[22] General guidelines for monitoring of RFC lesion formation (such as unipolar electrogram amplitude reduction or impedance drop) have been proposed by Wittkampf and Nakagawa.[22]

Follow-Up

Personal study visits are scheduled in the following intervals after the index procedure: 3, 6, and 12 months, and biannually thereafter. A telephone interview is scheduled at 9 months and biannually thereafter (Fig. 2). Patients are provided with an event recorder and will transmit a transtelephonic ECG recording once a week regardless of symptoms during the entire study period. In addition, patients are instructed to transmit ECG recordings upon symptoms. Office visits include medical history, physical examination, and a 12-lead ECG. QoL will be assessed by EQ-5D and SF-6D questionnaires at baseline and biannually thereafter. A blanking period of 3 months following the index procedure is defined. During the blanking period, early recurrent atrial tachyarrhythmia (ERAT; including AF, AT, or AFL) will be reported but excluded from the primary analysis and may be managed by AADs (excluding amiodarone), cardioversion, or re-ablation with the technique and ablation protocol according to group assignment. When deciding about early re-intervention, the time-dependent risk of late recurrence associated with ERAT in the blanking period should be considered.[23] After the blanking period, AADs have to be stopped.

Statistical Considerations, Sample Size, and Power Determination

In the STOP-AF trial, 1-year freedom from AF after cryoballoon PVI following a blanking period of 90 days off AAD was reported in 69.9% of patients.[11] The prospective, randomized THERMOCOOL AF trial most adequately informs the expected treatment effect of RFC ablation in FIRE AND ICE in terms of patient selection, ablation technique, and follow-up.[5] In THERMOCOOL AF, the 1-year rates of freedom from AF after 90 days of blanking were 66% as compared to 16% in the AAD group. Based on these data, event-free 1-year survival rates of 70% in both groups are assumed. The analysis will be performed using the noninferiority log-rank test[24] with a noninferiority margin for the hazard ratio of 1.43, corresponding to a 10% absolute difference from 70%. A noninferiority margin of 10% preserves > 50% of the lower bound of the 95% confidence interval of the treatment effect of the active control (RFC ablation) versus AAD as described above.[25] Based on a group sequential design with 2 interim analyses for early stopping, 249 events are required to demonstrate noninferiority with a power of 80%. The interim analyses will occur after 125, 187, and 249 documented first primary endpoints have been observed in the per-protocol population and adjudicated by the Endpoint Review Committee (ERC). The primary endpoint is met if the 1-sided nominal P-value is less than 0.0021 at the first interim analysis, 0.0097 at the second interim analysis, or 0.0215 at the final analysis for both the per-protocol and intention-to-treat populations. If events occur at the assumed rates and patients are enrolled at a uniform rate over 18 months, then enrollment of 544 subjects is expected to result in 249 events within 12 months after the last enrollment if patients remain under observation and at risk through the end of trial. To cope with a potential loss-to-follow-up rate of 5%, a minimum of 572 patients will be enrolled in the trial and randomized 1:1 to the 2 trial arms. Withdrawn patients will not be replaced. Before end of recruitment, the sample size may be adapted in a blinded manner. One-sided noninferiority and superiority tests will be performed at a level of

TABLE 5
Study Organization

Principal Investigator	**Prof. Dr. Karl-Heinz Kuck, Hamburg, Germany**
Co-chairman	Prof. Dr. Josep Brugada, Barcelona, Spain
Steering Committee	Dr. Jean-Paul Albenque, Toulouse, France
	Prof. Dr. Josep Brugada, Barcelona, Spain
	Prof. Dr. Karl-Heinz Kuck, Hamburg, Germany
	Prof. Dr. Claudio Tondo, Milan, Italy
	Non-voting members
	Dr. Alexander Fürnkranz, Frankfurt, Germany, Scientific Study Coordinator
	PD Dr. med. Kurt Bestehorn, IKKF GmbH, Munich, Germany
	Dr. Ralf Meyer, Medtronic International Trading Sárl, Tolochenaz, Switzerland
Endpoint Review Committee	Dr. Malte Kuniss, Bad Nauheim, Germany
	Prof. Dr. Thorsten Lewalter, Munich, Germany
	Prof. Dr. Lars Lickfett, Mönchengladbach, Germany
Data Safety Monitoring Board	Dr. Riccardo Cappato, Milan, Italy
	Prof. Dr. Hein J.J. Wellens, Maastricht, Netherlands
	Dr. David Wyn Davies, London, UK
	Prof. Jan G.P. Tijssen, Amsterdam, The Netherlands
ECG Core Laboratory	Prof. Dr. Ellen Hoffmann, Munich, Germany
Clinical Research Organization	Genae Associates NV, Antwerp, Belgium
Sponsor	Medtronic International Trading Sàrl, Tolochenaz, Switzerland
Funding provided by	Medtronic International Trading Sàrl and Medtronic, Inc.
ClinicalTrials.gov Identifier	NCT01490814

2.5%. Since the 2 procedures are closed, a 2.5% family-wise 1-sided error rate, corresponding to a 5% 2-sided rate, is preserved.

Study Organization and Status

FIRE AND ICE is a trial organized by Genae Associates NV, Antwerp, Belgium, and sponsored by Medtronic International Trading Sàrl, Tolochenaz, Switzerland. Study organization is detailed in Table 5. The Steering Committee (SC) represents the trial leadership. Its members are responsible for the scientific and clinical aspects of the trial execution and for the reviewing of recommendations by the Data Safety Monitoring Board (DSMB). The SC is responsible for reporting the trial results. An independent ERC blinded to group assignment adjudicates all outcome events. The DSMB regularly monitors the recruitment and conduct of the trial, data quality, and timeliness, the distribution of therapies within the trial groups, serious adverse events, and further adverse events selected to their discretion during the course of the trial. An independent ECG core laboratory reviews all intracardiac recordings documenting the procedural endpoint. FIRE AND ICE has started enrollment in January 2012. Completion of the study is expected end of 2015.

Discussion

The FIRE AND ICE trial compares 2 different technologies to perform catheter ablation of PAF. Both techniques are in routine clinical use worldwide, yet large-scale prospective randomized trial data comparing efficacy and safety of the procedures are lacking. In light of the rapidly expanding field of catheter ablation of AF with an exponential rise of ablations performed worldwide each year, FIRE AND ICE will fill this important research gap. While RFC ablation is the technique most widely adopted by clinical electrophysiologists, cryoballoon ablation is a rapidly growing field being available in Europe since 2006 and recently approved for use in the US.

There are fundamental differences in the 2 technologies both in energy form and delivery. RFC-induced tissue lesions are created by sequentially moving a pointed tip catheter along the desired ablation line, thereby heating the underlying tissue.[21] The catheter is freely movable during ablation and considerable operator expertise is needed in order to stabilize the catheter at the target tissue in the beating heart and during respiratory movements. Continuous lesion creation is imperative for a durable electrical barrier. In contrast, cryoballoon-induced lesions are created by positioning a balloon at the PV orifice with—ideally—circumferential tissue contact. During ablation the balloon adheres to the tissue, and a ring-shaped lesion is simultaneously created by freezing.[9] Operators may acquire this technique with a short learning curve.[10]

However, despite this immediate technical advantage, little is known about the chronic course of a cryoballoon-induced relative to an RFC-induced lesion. This is a main factor determining clinical success because previous studies have shown that recurrent LA-to-PV re-conduction is pivotal in arrhythmia recurrence after catheter ablation of PAF.[26,27] Furthermore, it remains to be shown that possible safety advantages of cryothermal lesions such as low thrombogenicity demonstrated in preclinical trials[28] translate into the clinical arena when compared to extensively investigated RFC ablation.[14] These questions are addressed by the FIRE AND ICE trial.

Conclusion

The FIRE AND ICE trial compares 2 different technologies to perform catheter ablation of PAF with respect to efficacy and safety—the cryoballoon versus RFC-ablation using a 3D-mapping system. By providing objective comparative data it aims at guiding clinicians during their selection and usage of ablation catheters in the treatment of AF.

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Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's website:

Online supplement

ORIGINAL ARTICLE

Cryoballoon or Radiofrequency Ablation for Paroxysmal Atrial Fibrillation

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ABSTRACT

BACKGROUND

Current guidelines recommend pulmonary-vein isolation by means of catheter ablation as treatment for drug-refractory paroxysmal atrial fibrillation. Radiofrequency ablation is the most common method, and cryoballoon ablation is the second most frequently used technology.

METHODS

We conducted a multicenter, randomized trial to determine whether cryoballoon ablation was noninferior to radiofrequency ablation in symptomatic patients with drug-refractory paroxysmal atrial fibrillation. The primary efficacy end point in a time-to-event analysis was the first documented clinical failure (recurrence of atrial fibrillation, occurrence of atrial flutter or atrial tachycardia, use of antiarrhythmic drugs, or repeat ablation) following a 90-day period after the index ablation. The noninferiority margin was prespecified as a hazard ratio of 1.43. The primary safety end point was a composite of death, cerebrovascular events, or serious treatment-related adverse events.

RESULTS

A total of 762 patients underwent randomization (378 assigned to cryoballoon ablation and 384 assigned to radiofrequency ablation). The mean duration of follow-up was 1.5 years. The primary efficacy end point occurred in 138 patients in the cryoballoon group and in 143 in the radiofrequency group (1-year Kaplan–Meier event rate estimates, 34.6% and 35.9%, respectively; hazard ratio, 0.96; 95% confidence interval [CI], 0.76 to 1.22; P<0.001 for noninferiority). The primary safety end point occurred in 40 patients in the cryoballoon group and in 51 patients in the radiofrequency group (1-year Kaplan–Meier event rate estimates, 10.2% and 12.8%, respectively; hazard ratio, 0.78; 95% CI, 0.52 to 1.18; P=0.24).

CONCLUSIONS

In this randomized trial, cryoballoon ablation was noninferior to radiofrequency ablation with respect to efficacy for the treatment of patients with drug-refractory paroxysmal atrial fibrillation, and there was no significant difference between the two methods with regard to overall safety. (Funded by Medtronic; FIRE AND ICE ClinicalTrials.gov number, NCT01490814.)

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According to a 2012 expert consensus statement, catheter ablation of drug-refractory paroxysmal atrial fibrillation is a class I level A indication,[1] and pulmonary-vein isolation is the standard approach.[1-3] The two most frequently used ablation technologies for pulmonary-vein isolation differ in the energy source and mode of application. The most common method is the use of radiofrequency current applied in a point-by-point mode, which leads to cellular necrosis by tissue heating; the other method is the use of cryogenic energy applied with a balloon in a single-step mode, which leads to necrosis by freezing (Fig. 1). Radiofrequency ablation for atrial fibrillation requires only limited use of fluoroscopy, because catheter guidance is achieved with the use of an electroanatomical mapping system,[1,4] but the approach demands extensive training.[1] The complexity of radiofrequency ablation technology has restricted ablation therapy for atrial fibrillation to a few specialized centers and has limited the availability of ablation therapy. Cryoablation for atrial fibrillation requires more extensive fluoroscopic guidance to position the balloon catheter at the pulmonary veins. The cryoballoon was developed to create a circular lesion around each pulmonary vein in a relatively simple manner.

A Quick Take is available at NEJM.org

Some small studies have compared the two types of ablation catheters.[5-10] The current study was designed to compare the performance of the rather complex yet well-established approach of radiofrequency ablation with that of the apparently simpler approach of cryoballoon ablation in a larger population of patients with paroxysmal atrial fibrillation.

Methods

Trial Design

The FIRE AND ICE trial was a multicenter, randomized, noninferiority, parallel-group, open-label trial, with blinded end-point assessment, in which cryoballoon ablation was compared with radiofrequency ablation. The trial was investigator-initiated; the steering committee was responsible for design, execution, and conduct of the study (see the Supplementary Appendix, available with the full text of this article at NEJM.org). Local ethics review committees at each center approved the study. A data and safety monitoring board reviewed interim results and monitored the safety of the patients. An end-point review committee, the members of which were unaware of the treatment-group assignments, adjudicated primary safety and efficacy events. All members of the steering committee approved the statistical analyses and interpretation of the data. The decision to publish the results and decisions regarding the contents of the manuscript were made by the steering committee. The authors attest to the accuracy of the data and of all analyses and to the fidelity of this report to the trial protocol, which is available at NEJM.org.

The trial was funded by Medtronic, with trial oversight by FGK Representative Service as legal sponsor. A contract research organization (the Institute for Clinical Cardiovascular Research, Munich, Germany) collected, monitored, maintained, and analyzed the data. During the trial, the contract research organization became insolvent. Legal sponsorship and trial oversight was transferred to Medtronic for completion of the trial, and a second contract research organization (Genae, Antwerp, Belgium) was hired. Data transfer between the two contract research organizations occurred without the sponsor handling the data, and blinding with regard to the treatment-group assignments was preserved.

Study Participants

Sixteen centers in eight countries participated in the trial (see the Supplementary Appendix for the list of investigators). Patients with symptomatic paroxysmal atrial fibrillation that was refractory to class I or class III antiarrhythmic drugs or beta blockers were enrolled. Patient eligibility was determined according to the inclusion and exclusion criteria listed in Tables S1 and S2 in the Supplementary Appendix.[4] All participants gave written informed consent. After enrollment, patients were randomly assigned, in a 1:1 ratio, to undergo ablation with pulmonary-vein isolation attempted with the use of a cryoballoon (cryoballoon group) or by means of radiofrequency current (radiofrequency group). Randomization was stratified according to center and age (≤65 vs. >65 years).

Interventions

The ablation methods are described in the Supplementary Appendix. In brief, in the cryoballoon group, operators attempted pulmonary-vein isolation by placing the device (with fluoro-

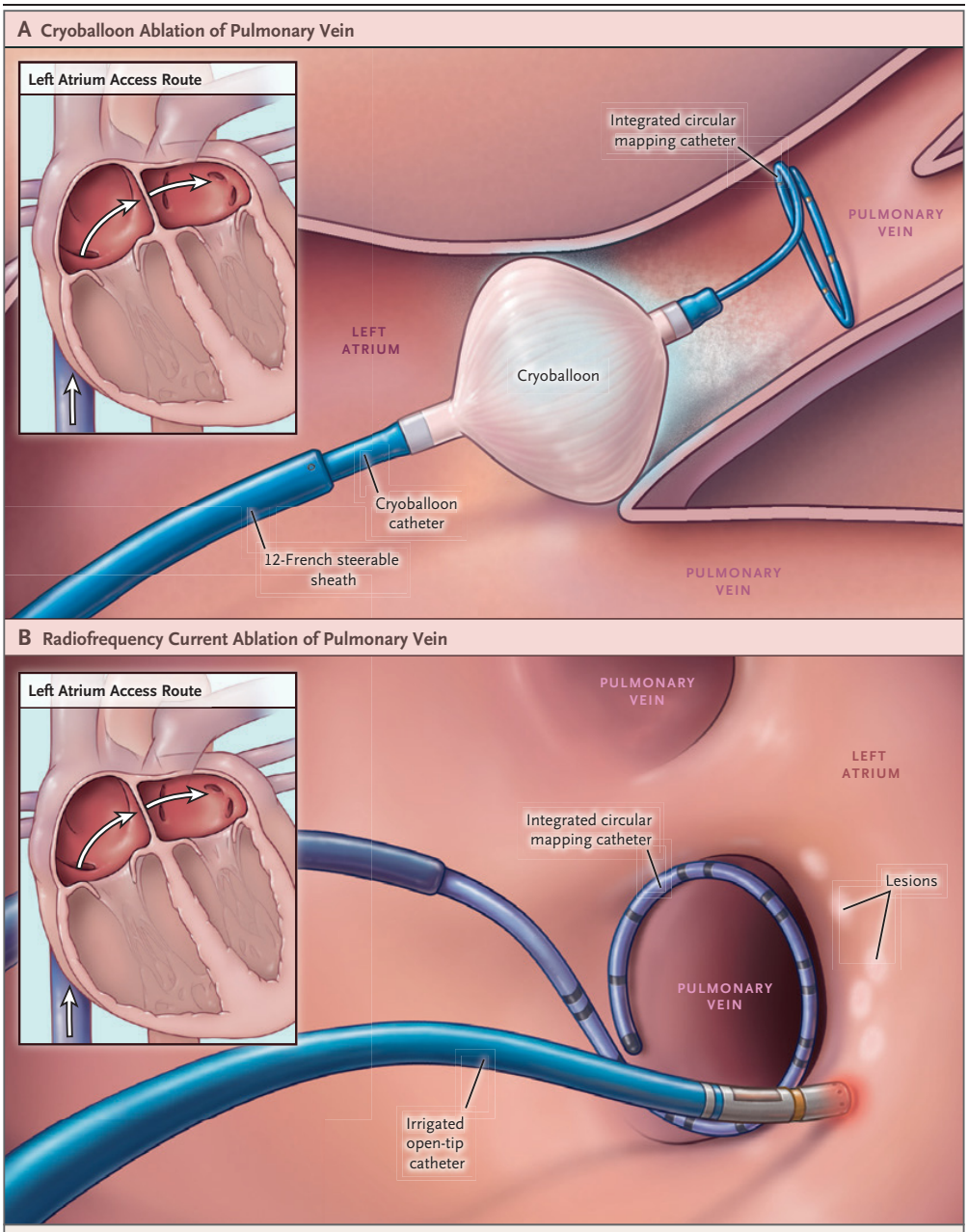

Figure 1. Catheter Ablation Methods.

Panel A shows the cryoballoon system, a single-step approach in which a balloon delivers subzero temperatures to the pulmonary-vein antra. Panel B shows the radiofrequency catheter ablation system, which uses heat-energy transfer to tissue and delivers a series of point-by-point connected lesions with assistance from a three-dimensional navigational system.

scopic guidance) at each pulmonary-vein antrum, advancing it toward the pulmonary vein to achieve occlusion, and then cooling the tissue by filling the balloon with a liquid refrigerant. In the radiofrequency group, operators attempted pulmonary-vein isolation by creating a contiguous circular lesion around each pulmonary-vein antrum with point-by-point applications of radiofrequency energy, using electroanatomical navigation (Fig. 1).

STUDY FOLLOW-UP

After the index ablation procedure, in-office visits were scheduled at 3, 6, and 12 months and every 6 months thereafter (Fig. S1 in the Supplementary Appendix). At each visit, a medical history was obtained, a physical examination was performed, and a 12-lead electrocardiogram (ECG) and a 24-hour Holter monitor recording were obtained. A review of arrhythmia symptoms was conducted by telephone interview at 9 months and every 6 months thereafter. Patients were asked to provide a weekly transtelephonic ECG recording during the study and to transmit ECGs whenever symptoms of arrhythmia were felt. All follow-up assessments were performed by study personnel who were unaware of the treatment assignments.

END POINTS

The primary hypothesis was that catheter ablation with the use of the cryoballoon would be noninferior to radiofrequency ablation with respect to a prespecified efficacy criterion. This primary efficacy end point in a time-to-event analysis was the first documented clinical failure occurring more than 90 days after the index ablation procedure. Clinical failure was defined as documented recurrence of atrial fibrillation (lasting more than 30 seconds), documented occurrence of atrial flutter or atrial tachycardia, prescription of antiarrhythmic drugs (class I or III), or repeat ablation.

Recurrences of atrial fibrillation during the first 90 days after the index ablation (the so-called "blanking period") were not counted in the determination of the first clinical failure for the primary end point. Early recurrence of atrial fibrillation after ablation, resulting from inflammation or incomplete lesion healing, is common and may not predict long-term outcome.[1] Within the blanking period, recurrent arrhythmias could be managed with antiarrhythmic drugs (excluding amiodarone), cardioversion, or repeat ablation (with the same randomly assigned catheter type) without penalty with regard to the primary efficacy end point.

The prespecified secondary end points reported in this article include death from any cause, death from arrhythmia, total duration of the procedure, total fluoroscopy time, and first rehospitalization for cardiovascular causes. Additional prespecified secondary end points (for which results are not shown in this article) included the total number of hospitalizations for cardiovascular causes, time-to-event analyses of the components of the primary end point, time to recurrent atrial fibrillation, time to symptomatic atrial fibrillation, and quality of life.

The primary safety end point was a composite of death from any cause, stroke or transient ischemic attack from any cause, and serious adverse events. Serious adverse events included cardiac arrhythmias (apart from a recurrence of atrial fibrillation) that were causally related to the therapeutic intervention and procedure-related serious adverse events that were judged by the end-point review committee to be causally related to the treatment. All serious adverse events were prespecified. Physicians were required to report all adverse events.

STATISTICAL ANALYSIS

Assuming event-free 1-year survival rates of 70% in both groups and with a noninferiority margin of 10% (corresponding to a hazard ratio of 1.43), we calculated that 249 primary-end-point events would be required for the trial to have 80% power to test the noninferiority of cryoballoon ablation to radiofrequency ablation, at a one-sided alpha level of 0.025. A sample size of 549 patients was originally estimated. A prespecified blinded sample-size reestimation was performed before enrollment was fully complete. On the basis of the reestimation, we calculated that 768 patients would have to be enrolled to ensure that 249 primary-end-point events would be observed.

Two prespecified interim analyses and a final analysis were performed when 125, 187, and 249 primary-end-point events, respectively, had been observed. During the study, no early-stopping boundaries were met. Two analysis cohorts were prespecified (Fig. S2 in the Supplementary Appendix). The modified intention-to-treat cohort included all patients who underwent randomiza-

tion and their randomly assigned catheter ablation procedure. The per-protocol cohort consisted of patients who were treated and did not have a major protocol deviation. A major protocol deviation was defined as a deviation that confounded the efficacy end point; such deviations included amiodarone use, undergoing an ablation with a non–study-specified catheter, and undergoing an ablation with a catheter that was not in accordance with the randomly assigned treatment group.

The primary efficacy end point was evaluated with the use of a noninferiority log-rank test.[11] In addition, a noninferiority test based on a Cox proportional-hazards model was performed. The corresponding hazard ratio and 95% confidence interval were estimated with a Cox proportional-hazards model, after confirmation of the proportional-hazards assumption. If noninferiority was met in both the modified intention-to-treat cohort and the per-protocol cohort, then superiority could be tested in the modified intention-to-treat cohort with the use of a log-rank test. Cox proportional-hazards regression was used to estimate hazard ratios in the primary analysis, subgroup analyses, and primary safety analysis. The Kaplan–Meier method was used to calculate 12-month event-rate estimates. For each subgroup analysis, a Wald test for interaction was performed. Four separate types of catheter were used during the study: the first-generation and second-generation cryoballoon catheters, the combined first-generation radiofrequency catheters (there were two types; see the Methods section in the Supplementary Appendix), and the advanced-generation radiofrequency catheter. A log-rank test was used to analyze the primary efficacy end point according to catheter type.

Because of the blanking period defined above, 90 days was selected as the landmark (starting time) of time-to-event analyses for the primary efficacy end point. Analyses were conducted with SAS software, version 9.4 (SAS Institute), and the R statistical package, version 3.2.2 (www.r-project.org). Mean values are presented with standard deviations.

RESULTS

PATIENTS

Enrollment of patients started on January 19, 2012, and was completed on January 27, 2015. A total of 769 patients were enrolled (Fig. S2 in the Supplementary Appendix). The modified intention-to-treat population included the 750 patients who were randomly assigned to a treatment group (376 in the radiofrequency group and 374 in the cryoballoon group) and received treatment. Of those patients, 352 in the radiofrequency group and 341 in the cryoballoon group did not have a major protocol violation reported; these patients comprised the per-protocol cohort. The characteristics of the patients at baseline were balanced between the two groups, with the exception of the prevalence of chronic kidney disease and diabetes (Table 1). During the procedure, complete isolation was achieved in 97.9% of pulmonary veins in the radiofrequency group and in 98.9% of pulmonary veins in the cryoballoon group.

A total of 85% of the scheduled follow-up visits in the radiofrequency group (2007 of a total of 2372 visits) and 87% of the scheduled follow-up visits in the cryoballoon group (2006 of 2317 visits) were attended (Table S3 in the Supplementary Appendix). Patients transmitted transtelephonic ECGs for a mean of 60% of the weeks in which they were followed in the radiofrequency group and for 58% of the weeks in which they were followed in the cryoballoon group. In the radiofrequency group, 4 patients were lost to follow-up, and 32 patients withdrew from the trial or were withdrawn by the investigator; in the cryoballoon group, 5 patients were lost to follow-up, and 37 patients withdrew from the trial or were withdrawn by the investigator. In both groups, the maximum follow-up time was 33 months, and the mean follow-up time was 1.5 years.

EFFICACY END POINTS

The number of end-point events required to test the primary efficacy hypothesis was achieved on September 17, 2015, and data freeze occurred on January 29, 2016. In the modified intention-to-treat analysis, after the 90-day blanking period, the primary efficacy end point occurred in 138 patients in the cryoballoon group and in 143 patients in the radiofrequency group (1-year Kaplan–Meier event-rate estimates, 34.6% and 35.9%, respectively; hazard ratio, 0.96; 95% confidence interval [CI], 0.76 to 1.22; P<0.001 for noninferiority) (Table 2 and Fig. 2A). In the per-protocol analysis, the primary efficacy end point occurred

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Radiofrequency Group (N=376)	Cryoballoon Group (N=374)
Age — yr	60.1±9.2	59.9±9.8
Age >65 yr — no. (%)	117 (31.1)	113 (30.2)
Male sex — no. (%)	236 (63)	221 (59)
Years since first PAF diagnosis	4.7±5.3	4.6±5.1
Body-mass index†	27.8±4.5	28.0±4.7
Left atrial diameter — mm	40.6±5.8	40.8±6.5
Systolic blood pressure — mm Hg	134.8±18.9	133.6±18.0
Diastolic blood pressure — mm Hg	78.9±10.6	78.8±11.5
CHA_2DS_2-VASc score‡		
Mean	1.8±1.3	1.9±1.4
Distribution — no. (%)		
0	67 (17.8)	58 (15.5)
1	109 (29.0)	108 (28.9)
2	97 (25.8)	95 (25.4)
3	62 (16.5)	60 (16.0)
4	33 (8.8)	40 (10.7)
5	7 (1.9)	10 (2.7)
6	1 (0.3)	3 (0.8)
NYHA classification — no. (%)§		
No heart failure	277 (73.9)	263 (70.3)
Class I	40 (10.7)	47 (12.6)
Class II	58 (15.5)	64 (17.1)
Medical history — no. (%)		
Previous DCCV	88 (23.4)	86 (23.0)
Previous stroke	4 (1.1)	5 (1.3)
Previous TIA	10 (2.7)	11 (2.9)
Previous myocardial infarction	9 (2.4)	9 (2.4)
Previous CABG	4 (1.1)	2 (0.5)
Previous PCI	16 (4.3)	24 (6.4)
Coronary artery disease	32 (8.5)	31 (8.3)
LV hypertrophy — no. (%)¶	2 (0.5)	1 (0.3)
Chronic kidney disease — no. (%)‖	4 (1.1)	13 (3.5)
Hypertension — no. (%)**	221 (58.8)	215 (57.5)
Hyperlipidemia — no. (%)††	106 (28.3)	115 (30.9)
Type 2 diabetes — no. (%)‖	22 (5.9)	37 (9.9)
Medication use — no. (%)		
Antiarrhythmic drug	225 (59.8)	236 (63.1)
ACE inhibitor	89 (23.7)	73 (19.5)
Beta-blocker	253 (67.3)	235 (62.8)
Anticoagulation drug	274 (72.9)	282 (75.4)

* Plus–minus values are means ±SD. ACE denotes angiotensin-converting enzyme, CABG coronary-artery bypass graft, DCCV direct current cardioversion, NYHA New York Heart Association, PAF paroxysmal atrial fibrillation, PCI percutaneous coronary intervention, and TIA transient ischemic attack.
† Body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ The CHA_2DS_2-VASc score is a clinical estimation of the risk of stroke in patients with atrial afibrillation; scores range from 0 to 9, with higher scores indicating a greater risk of stroke.
§ Data were missing for one patient in the radiofrequency group.
¶ Left ventricular (LV) hypertrophy was defined as an LV wall thickness greater than 15 mm.
‖ The difference between the treatment groups was significant ($P<0.05$).
** Hypertension was defined as blood pressure higher than 140/90 mm Hg.
†† Hyperlipidemia was defined as a total cholesterol value higher than 300 mg per deciliter (7.76 mmol per liter). Data were missing for two patients in the radiofrequency group and two patients in the cryoballoon group.

Table 2. Efficacy End Points.*

End Point	Radiofrequency Group (N=376)	Cryoballoon Group (N=374)	Hazard Ratio (95% CI)†	P Value
Primary efficacy end point — no. of patients (%)‡	143 (35.9)§	138 (34.6)§	0.96 (0.76–1.22)	<0.001¶
Components of the primary efficacy end point — no. of patients				
Recurrent atrial arrhythmia	87	80	—	—
Antiarrhythmic drug treatment	49	51	—	—
Repeat ablation	7	7	—	—
Secondary efficacy end points				
Death from any cause — no. of patients	0	2‖	—	0.25**
Death from arrhythmia — no. of patients	0	0	—	—
Total procedure duration — min	140.9±54.9	124.4±39.0	—	<0.001††
Left atrial dwell time — min‡‡	108.6±44.9	92.3±31.4	—	<0.001††
Total fluoroscopy time — min§§	16.6±17.8	21.7±13.9	—	<0.001††
Rehospitalization for cardiovascular causes — no. of patients (%)	55 (13.5)§	44 (9.4)§	0.78 (0.53–1.16)	0.28**

* Plus–minus values are means ±SD.
† Time-to-event analyses use radiofrequency group as the reference (a hazard ratio <1 favors cryoablation, and a hazard ratio >1 favors radiofrequency ablation).
‡ The primary end point was a composite of documented recurrence of atrial fibrillation (lasting more than 30 seconds), documented occurrence of atrial flutter or atrial tachycardia, prescription of antiarrhythmic drugs (class I or III), or repeat ablation.
§ This value is the Kaplan–Meier estimate at 1 year.
¶ This P value is for noninferiority assessed by the log-rank test.
‖ One death (at day 366) was of unknown cause; one death (at day 95) was associated with sepsis and was determined by autopsy to be a noncardiac-related death.
** This P value was calculated by Fisher's exact test.
†† This P value was calculated by Student's t-test.
‡‡ Left atrial dwell time was a post hoc (nonprespecified) procedural end point and represents the length of time catheters were present in the left atrium during the procedure. This end point was evaluated in 357 patients in the radiofrequency group and in 354 patients in the cryoballoon group.
§§ Total fluoroscopy time was evaluated in 373 patients in the radiofrequency group and in 371 patients in the cryoballoon group.

in 118 patients in the cryoballoon group and in 131 patients in the radiofrequency group (1-year Kaplan–Meier event-rate estimates, 31.9% and 35.0%, respectively; hazard ratio, 0.91; 95% CI, 0.71 to 1.17; P<0.001 for noninferiority). A prespecified superiority test performed for the primary efficacy end point did not indicate a significant difference between the treatment groups (P=0.74). Prespecified subgroup analyses of the primary efficacy end point revealed no significant interactions (Fig. S3 in the Supplementary Appendix). A prespecified comparison of the primary efficacy end point among the four separate types of catheters revealed no significant heterogeneity (P=0.25) (Fig. 2B).

Results regarding the secondary efficacy end points are shown in Table 2. There were two deaths in the cryoballoon group; one death (at day 366) was of unknown cause, and the other death (at day 95) was associated with sepsis and was determined by autopsy to be a noncardiac-related death. The mean total procedure time was shorter in the cryoballoon group than in the radiofrequency group (124 vs. 141 minutes, P<0.001), as was the left atrial dwell time (the length of time the catheter was present in the left atrium during the procedure), which was a post hoc end point (92 vs. 109 minutes, P<0.001). The mean total fluoroscopy time was shorter in the radiofrequency group than in the cryoballoon group (17 vs. 22 minutes, P<0.001). The time to first rehospitalization for cardiovascular causes did not differ significantly between the groups.

SAFETY END POINTS

The primary safety end point occurred in 40 patients in the cryoballoon group and in 51 patients in the radiofrequency group (1-year Kaplan–Meier event rate estimates, 10.2% and 12.8%, respectively; hazard ratio, 0.78; 95% CI, 0.52 to 1.18;

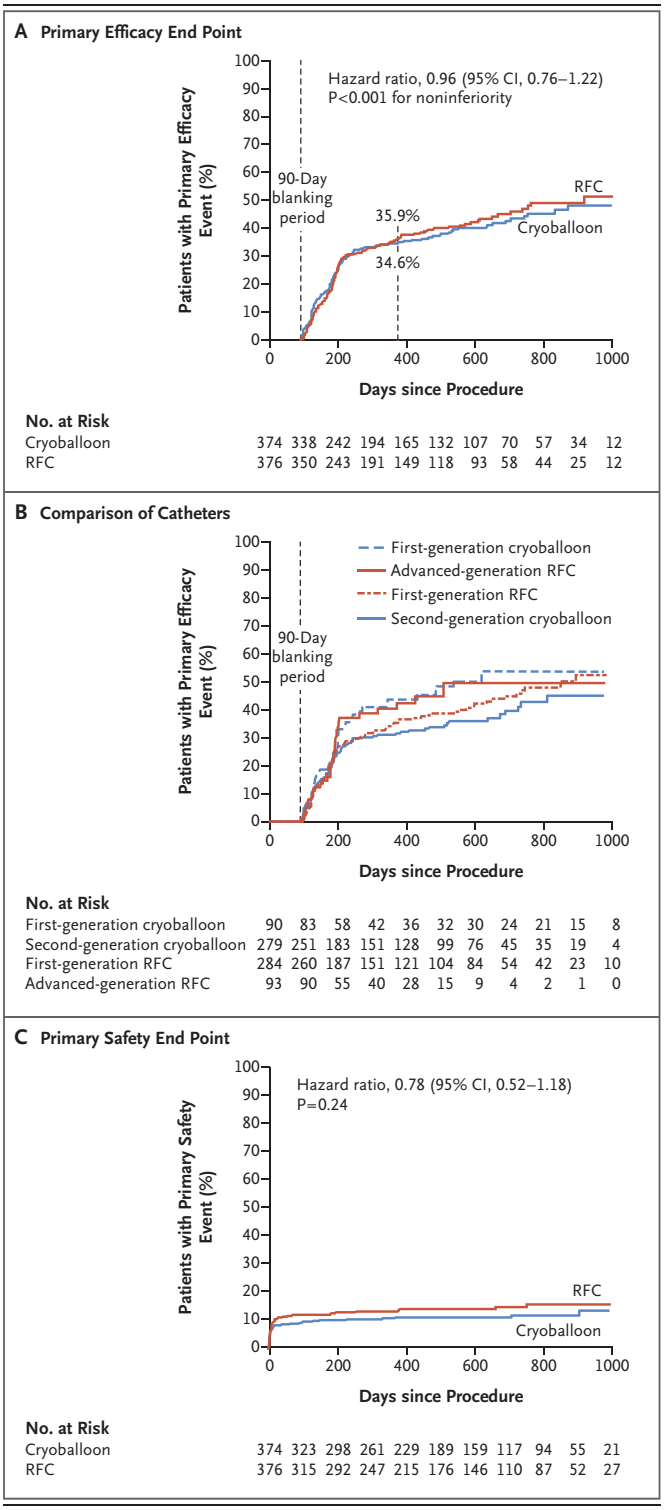

Figure 2. Event-free Survival for the Primary Efficacy and Safety End Points in the Modified Intention-to-Treat Cohort.

Panel A shows the 90-day landmark analysis of the primary efficacy end point. The trial confirmed the noninferiority of cryoballoon ablation to radiofrequency (RFC) catheter ablation. The first 90 days after the index ablation was the so-called "blanking period"; events during this period were not counted in the determination of clinical failure for the primary end point. Panel B shows the subgroup test of homogeneity across all four catheter categories; there was no significant difference among the catheters (P=0.25). The as-treated cohort was used for this analysis. Five patients were randomly assigned to the cryoballoon group but underwent radiofrequency ablation; they are included in the first-generation radiofrequency group; four patients who were randomly assigned to the radiofrequency group and were treated with nonstudy radiofrequency catheters are not included. Panel C shows the analysis of the primary safety end point. There was no significant difference between the cryoballoon and radiofrequency groups.

P=0.24) (Fig. 2C and Table 3). The most common safety events were groin-site complications (16 in the radiofrequency group and 7 in the cryoballoon group) and phrenic-nerve injury (10 in the cryoballoon group) (Table 3). No atrioesophageal fistulae, pulmonary-vein stenoses, or procedure-related deaths were observed. A full list of postprocedural adverse events is provided in Table S4 in the Supplementary Appendix.

DISCUSSION

The FIRE AND ICE trial was a randomized evaluation of catheter ablation in patients with paroxysmal atrial fibrillation, in which we examined the efficacy, safety, and procedural profiles of the two most commonly used ablation technologies. The characteristics of the patients were consistent with those in other trials[5-10,12,13] and are representative of patients with paroxysmal atrial fibrillation.[1] Cryoballoon ablation was found to be noninferior to radiofrequency ablation with regard to the primary efficacy end point, and superiority was not achieved in either group. There was no significant difference among the four types of ablation catheters with regard to the primary efficacy end point. There was also no significant difference in the primary safety end point between the radiofrequency group and the cryoballoon group.

Table 3. Safety End Points.

End Point	Radiofrequency Group (N=376)	Cryoballoon Group (N=374)	P Value*
	no. of patients (%)		
Primary safety end point†	51 (12.8)‡	40 (10.2)‡	
Death from any cause§	0	2 (0.5)¶	0.50
Stroke or TIA from any cause§	2 (0.5)	2 (0.5)	1.00
Atrial arrhythmia§‖	13 (3.5)	8 (2.1)	0.38
Atrial flutter or atrial tachycardia	10 (2.7)	3 (0.8)	0.09
Non–arrhythmia-related serious adverse events§	36 (9.6)	28 (7.5)	0.36
Groin-site complication**	16 (4.3)	7 (1.9)	0.09
Unresolved phrenic nerve injury††			
At discharge	0	10 (2.7)	0.001
At 3 months	0	2 (0.5)	0.25
At >12 months	0	1 (0.3)	0.50
Cardiac tamponade or pericardial effusion	5 (1.3)	1 (0.3)	0.22
Pulmonary or bronchial complication	4 (1.1)	2 (0.5)	0.69
Transient neurologic complication	3 (0.8)	1 (0.3)	0.62
Dyspnea	2 (0.5)	1 (0.3)	1.00
Gastrointestinal complication	2 (0.5)	1 (0.3)	1.00
Other, nonarrhythmia cardiac complications‡‡	0	3 (0.8)	0.12
Anxiety	0	1 (0.3)	0.50
Contrast media reaction	1 (0.3)	0	1.00
Contusion	1 (0.3)	0	1.00
Esophageal ulcer	0	1 (0.3)	0.50
Hematuria	1 (0.3)	0	1.00
Local edema	1 (0.3)	0	1.00
Atrioesophageal fistula	0	0	—
Pulmonary vein stenosis	0	0	—

* The P values were calculated with Fisher's exact test.
† In the time to event analyses, radiofrequency group was used as the reference; the hazard ratio was 0.78 (95% CI, 0.52–1.18; P=0.24) (a hazard ratio <1 favors cryoablation, and a hazard ratio >1 favors radiofrequency ablation).
‡ This value is the Kaplan–Meier estimate at 1 year.
§ This end point was a component of the primary safety end point, which was a composite of death from any cause, stroke or transient ischemic attack from any cause, and serious adverse events.
¶ The deaths were not related to the treatment or device; one death (at day 366) was of unknown cause; one death (at day 95) was associated with sepsis and was determined by autopsy to be a noncardiac-related death.
‖ Atrial arrhythmia includes palpitations, presyncope, the sick sinus syndrome, supraventricular extrasystoles, and syncope.
** Groin-site complications include vascular pseudoaneurysm, arteriovenous fistula, device-related infection, hematoma, puncture-site hemorrhage, and groin pain.
†† Phrenic nerve injuries included eight injuries that resolved by 3 months, one that resolved at 6 months, and one that was unresolved more than 12 months after the procedure. Two additional nonserious events of phrenic nerve injury were reported, and both resolved before hospital discharge.
‡‡ Other cardiac complications include atrial septal defect, coronary artery disease, and pericarditis.

Phrenic-nerve injury was the most common safety event in the cryoballoon group, although the 2.7% rate in our trial was substantially lower than the 13.5% rate reported in the Sustained Treatment of Paroxysmal Atrial Fibrillation (STOP AF) trial.[12] The most common safety events in the radiofrequency group were groin-site complications, which were unusually frequent in this trial (4.3%). Some groin injuries may be caused by the two-sheath system that is often used (a radiofrequency catheter and a separate circular mapping catheter).[1,13] Serious treatment-related adverse events of atrial arrhythmia occurred in 2.7% of the patients in the radiofrequency group and in 0.8% of the patients in the cryoballoon group (P=0.09). These new-onset arrhythmias may have been caused by incomplete pulmonary-vein isolation.

Six previous studies (which were smaller than the current trial, nonrandomized, or both) comparing radiofrequency ablation with cryoballoon ablation have been completed.[5-10] With regard to efficacy, four of these studies showed statistical equivalence between the two technologies,[5,6,9,10] whereas two studies showed a higher efficacy of cryoballoon ablation.[7,8] With regard to safety, five of the studies showed equivalent safety between the two technologies.[6-10] The FreezeAF trial showed a better safety profile with radiofrequency ablation; this result was driven by phrenic-nerve injuries associated with cryoballoon ablation.[5] However, the FreezeAF analysis included episodes of phrenic-nerve injury that resolved before discharge.[5] Also, the FreezeAF trial was primarily an examination of first-generation catheters.

In our trial, procedure duration and left atrial dwell time were shorter in the cryoballoon group, whereas fluoroscopy time was shorter in the radiofrequency group. Single-step circumferential ablations were probably key to the shorter duration of the cryoballoon procedure. Occlusion of the pulmonary vein by the cryoballoon is tested by means of contrast injection and fluoroscopic examination, and this testing contributed to prolonged fluoroscopy time. In contrast, radiofrequency ablation requires no occlusion angiography, and catheter steering is achieved by means of electroanatomical mapping.

The case-report form used in this trial did not record individualized secondary catheter performance characteristics. For the cryoballoon catheter, the study did not record pulmonary-vein occlusion scores, time to pulmonary-vein isolation, the duration of the freezing procedure, or the number of freezes. Similarly, in the radiofrequency catheter group, the study did not record application times, contact-force measurements, peak wattage, or three-dimensional mapping variables. During trial design, many of these catheter variables were not routinely reported.

The trial investigators attempted to plan and conduct this study so that the most advanced-generation catheters would be used on approximately the same date and at approximately equal distribution. However, because of an urgent field safety notice and voluntary field removal (i.e., recall by the manufacturer) in the European Union, the advanced-generation radiofrequency catheter became unavailable beginning in September 2013, with some reshipping started in January 2014. This interruption prohibited further statistical evaluation of efficacy according to individual catheter type.

Pulmonary-vein isolation is the cornerstone ablation strategy in the treatment of patients with paroxysmal atrial fibrillation.[1] However, achieving acute pulmonary-vein isolation does not guarantee long-term electrical isolation of the pulmonary veins.[14] The use of newer radiofrequency catheters with contact-force sensing has improved long-term pulmonary-vein isolation.[14-16] The second-generation cryoballoon catheter has also shown improvement in long-term pulmonary-vein isolation,[17] which may be attributable to the extensive wide-area circumferential ablation that is achieved.[18] Extensive wide-area circumferential ablation may have ablation-related benefits beyond pulmonary-vein isolation, including concomitant ganglionated plexus modification.[19] However, our trial was not powered to test the superiority of either the first-generation or the second-generation catheters.

In summary, in the FIRE AND ICE trial, we found that in the treatment of patients with drug-refractory paroxysmal atrial fibrillation, pulmonary-vein isolation by means of cryoballoon ablation was noninferior to pulmonary-vein isolation by radiofrequency ablation in terms of efficacy and safety.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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Esophageal Endoscopy Results After Pulmonary Vein Isolation Using the Single Big Cryoballoon Technique

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Esophageal Effects of Single Big Cryoballoon PVI. ***Introduction:*** **Reversible esophageal thermal lesions after cryoballoon pulmonary vein isolation (CB-PVI) have been reported when using variable balloon sizes. The aim of this study was to investigate (1) the incidence of esophageal thermal lesions, and (2) esophageal temperature changes associated with CB-PVI using the single big cryoballoon technique.**

Methods and Results: **Thirty-eight patients with atrial fibrillation underwent successful CB-PVI using only the 28 mm cryoballoon. Luminal esophageal temperature (LET) was continuously monitored by 3 thermocouples. Fluoroscopic distance from cryoballoon to esophagus probe was retrospectively evaluated in RAO 30° and LAO 40° projections. All patients underwent postprocedural esophageal endoscopy. Average minimal LET was lower during freezing at inferior PVs, when compared to superior PVs: 35.4 ± 0.9 (range: 32.6 to 37.4; RSPV); 31.5 ± 7.5 (2.5 to 37.6; RIPV); 32.9 ± 5.2 (8.5 to 36.5; LSPV); and 30.3 ± 8.4°C (−6 to 36.7°C; LIPV); P = 0.001. We found steep temperature gradients over distance (1) from the cryoballoon center (LETs < 10°C confined to a distance of < 15 mm in both RAO 30° and LAO 40° projections), and (2) along the esophagus long axis, underscoring the need for multiple measurement sites. None of the patients showed esophageal thermal lesions at endoscopy after 3 ± 1 (range 1–7) days. No AEF occurred during a follow-up of 125 ± 78 days.**

Conclusion: **In a cohort of AF patients treated by the single big cryoballoon technique, CB-PVI was not associated with thermal esophageal lesions.** *(J Cardiovasc Electrophysiol, Vol. 21, pp. 869-874, August 2010)*

atrial fibrillation, catheter ablation, esophagus, cryoballoon, pulmonary veins

Introduction

Atrioesophageal fistula (AEF) formation is the most feared complication associated with pulmonary vein isolation (PVI) using radiofrequency current (RFC) ablation due to its high mortality.[1-4] Cryoballoon-PVI (CB-PVI) is an emerging alternative technique with a favorable safety profile that has—as of now—not been reported as a cause of AEF.[5-11] Results from experimental studies suggest that cryothermal energy may be associated with less risk of esophageal ulceration when compared to RFC.[12] Nonetheless, clinical experience with this relatively new approach is limited, and esophageal ulcerations, albeit reversible and without clinical sequelae, have recently been reported in a series of patients utilizing different cryoballoon sizes for PVI.[8] The cryoballoon ablation technique varies among centers, particularly in the use of various balloon dimensions,[5-9] possibly impacting on esophageal lesion development. Here, we report the results of systematic postprocedural esophageal endoscopy in a series of patients with atrial fibrillation (AF) treated exclusively with the single big (28 mm) cryoballoon technique.[9]

Methods

Patients

A total of 38 consecutive patients with paroxysmal (n = 36) or persistent (n = 2) AF were included into the study between August 2008 and November 2009. All patients underwent preprocedural transesophageal echocardiography. Inclusion criteria were as follows: a history of symptomatic AF despite antiarrhythmic drug (AAD) treatment with ≥ 1 AAD and consent to undergo postprocedural esophageal endoscopy. Exclusion criteria were defined as a LA diameter > 55 mm, severe left ventricular hypertrophy (LV wall thickness ≥ 15 mm), LA thrombus, and decompensated heart failure. Patient baseline clinical characteristics are shown in Table 1.

§Both authors contributed equally to this manuscript.

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TABLE 1
Baseline Patient Characteristics (n = 38)

Age (years)	56 ± 12
Male (n)	27 (71%)
Paroxysmal AF	36 (95%)
Persistent AF	2 (5%)
Failed antiarrhythmics (n)	1.4 ± 0.9
AF duration (years)	6 ± 5
LA diameter (mm)	43 ± 5
Hypertension (n)	21 (55%)
Diabetes (n)	1 (3%)
CAD (n)	4 (11%)
GERD (n)	0

CAD = coronary artery disease; GERD = gastroesophageal reflux disease.

Cryoballoon Ablation

The concept of the "single big cryoballoon" technique for PVI (Arctic Front, 28 mm diameter, Medtronic CryoCath LP, Montreal, Quebec, Canada) has been described in detail previously.[9] No preprocedural imaging, such as CT or MRI, or intraprocedural imaging apart from angiography, such as transesophageal echocardiography,[13] was performed. All procedures were performed under deep sedation using boluses of midazolam and fentanyl as well as a continuous infusion of propofol. Following double transseptal puncture, intravenous heparin was repeatedly administered to maintain an activated clotting time of 250 to 300 seconds. Selective PV angiography was performed to identify the PV anatomy using standard projections (RAO 30°, LAO 40°). Baseline potentials of all PVs were recorded with a Lasso catheter (Biosense Webster, Inc., Diamond Bar, CA, USA). The 28 mm balloon was maneuvered to all PV ostia by use of a steerable 12F sheath (FlexCath, CryoCath) and either a guidewire (Amplatz Stiff Wire, Cook Inc., Bloomington, IN, USA) or a 6-pole spiral catheter (Promap, ProRhythm, Ronkonkoma, NY, USA)[14] inserted through the central canal of the balloon catheter. To assess the exact position of the inflated balloon in relation to the LA–PV junction, contrast medium was injected from the distal lumen of the cryoballoon catheter. Freezing at the LA–PV junction was performed for a target time of 300 seconds. The right phrenic nerve (PN) was constantly paced from the superior caval vein during freezing at the septal PVs. In case of loss of PN capture, freezing was immediately terminated. After each freeze, PV conduction was reevaluated by positioning the Lasso catheter at the same position within the PV as before the cryoballoon application. Alternatively, PV conduction was monitored in real-time by the spiral catheter (11 patients).[14] If the PV was not isolated, the cryoballoon was repositioned and balloon to LA–PV contact reevaluated by angiography before the next freeze. Safety (bonus) applications after PVI were performed with one application at each LA–PV junction in 28 patients or with 2 applications at each LA–PV junction in 10 patients. Ablation endpoint was the loss of all PV potentials as confirmed by the Lasso catheter after a waiting period of 30 minutes.

Esophageal Temperature and Fluoroscopic Distance Measurement

At the start of the procedure and before administration of the heparin bolus a temperature probe (ETP) with 3 thermocouples separated by 10 mm (SensiTherm, St. Jude Medical, Inc., St. Paul, MN, USA; Fig. 1) was inserted into the esophagus transorally under fluoroscopic guidance. In 2 patients the probe could not be placed. Its position was repeatedly adjusted to match the balloon position during freezing. For each cryoballoon application, baseline and minimal LET were recorded. Baseline LET was defined as the lowest temperature measured by any thermocouple before freezing. Minimal LET was defined as the temperature nadir occurring during or shortly after cryothermal energy deployment in any of the thermocouples. In a subgroup of patients (n = 6), temperature readings of all 3 thermocouples were recorded at baseline and at the time of LET nadir. To minimize a stacking effect, LET was allowed to recover before starting the next freeze. Temperature measurements were observational

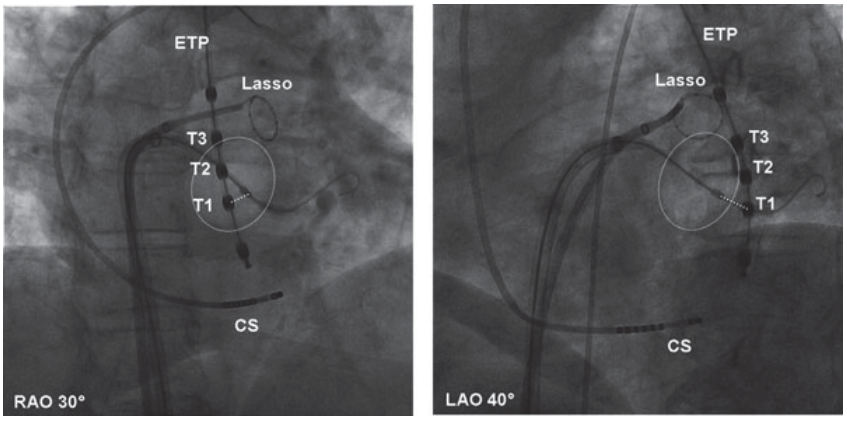

Figure 1. *Cryoballoon and esophageal temperature probe (ETP) position during freezing at the left inferior pulmonary vein in the patient with an LET nadir of −6.0°C. Fluoroscopic views in right anterior oblique (RAO) and left anterior oblique (LAO) projections are shown. The 3 thermocouples of the ETP separated by 10 mm (T1–3) can be seen. At the time of LET nadir, temperature readings were: 6.6 (T1), −6.0 (T2), and 20.0°C (T3). Punctuated lines represent fluoroscopic distance of the cryoballoon refrigerant injector to the thermocouple in closest proximity (RAO: 7 mm; LAO: 9 mm). Lasso = Lasso catheter in left superior pulmonary vein; CS = coronary sinus catheter.*

only and did not influence cryoballoon applications. The refrigerant injector near the distal cryoballoon pole was used as a fluoroscopic marker to measure the distance (mm) between the cryoballoon and the esophageal probe thermistor in closest proximity in RAO 30° and LAO 40° projections (Fig. 1).

Postprocedural Care and Follow-Up

All patients underwent postprocedural transthoracic echocardiography and chest X-ray to rule out pericardial effusion or pneumothorax. Patients were bridged with low molecular weight heparin (enoxaparin), and oral anticoagulation (phenprocoumon targeting an INR value of 2.0–3.0 for at least 3 months) was initiated the following day. Proton-pump inhibitor therapy was not routinely prescribed. All patients underwent gastroesophageal endoscopy within 7 days following ablation. In addition, patients were scheduled for outpatient clinic visits or contacted by telephone 1, 3 and 6 months after ablation.

Statistics

Continuous data were presented as mean ± standard deviation. The Friedman test was used to compare average minimal LETs measured during freezing at the 4 anatomical PVs (data on superior and inferior branches of a left common trunk were included into LSPV and LIPV group, respectively). Confidence intervals (CI) of proportions were calculated from the binomial distribution. A correlation coefficient was calculated to asses the relationship between minimal LET and maximum temperature difference measured between 2 thermocouples of the esophageal probe. A P-value of < 0.05 was considered statistically significant.

Results

Cryoballoon Ablation

In 38 patients a total of 149 PVs were identified including a short left common trunk (LCPV) in 3 patients. Mean angiographic diameters measured in RAO 30° (septal PVs) or LAO 40° (lateral PVs) were: 18 ± 3 (range: 12–24): RSPV, 17 ± 3 (10–25): RIPV, 18 ± 3 (10–23): LSPV, 17 ± 2 (12–21): LIPV, and 28 ± 4 mm (25–33 mm): LCPV. In the 2 patients with persistent AF, sinus rhythm was restored by external cardioversion before ablation. A total of 399 cryoballoon (including bonus) applications were applied; RSPV: 3 ± 1 (total: 97), RIPV: 3 ± 1 (total: 109), LSPV: 2 ± 1 (total: 84), LIPV: 3 ± 2 (total: 97), and LCPV: 4 ± 0 (total: 12). All PVs were successfully isolated using only the 28 mm balloon. Procedure duration was 176 ± 32 minutes, radiation time was 31 ± 11 minutes.

Esophageal Temperature Changes

Average minimal LET during freezing varied with treated PV, with lower LETs observed during freezing at inferior PVs when compared to superior PVs (Fig. 2, Table 2): 35.4 ± 0.9 (RSPV); 31.5 ± 7.5 (RIPV); 32.9 ± 5.2 (LSPV); and 30.3 ± 8.4°C (LIPV); $P < 0.001$ for comparison between all groups. The number of freezes with minimal LETs < 10°C was: 0 (RSPV), 3 (RIPV), 1 (LSPV), and 4 (LIPV). The absolute minimal LET achieved in any patient according to treated PV was as follows: 32.6 (RSPV), 2.5 (RIPV), 8.5 (LSPV), and −6.0°C (LIPV), which was the lowest LET and the only freeze with subzero LET observed in this study. The fluoroscopic position of the cryoballoon in relation to the esophageal probe during this application is shown in Figure 1 (7 mm in RAO 30°; 9 mm in LAO 40°). The first freeze at the LIPV in this patient resulted in a LET decrease from 36.8 to 14.6°C and the second freeze (bonus application) resulted in a LET decrease from 35.2 to −6.0°C.

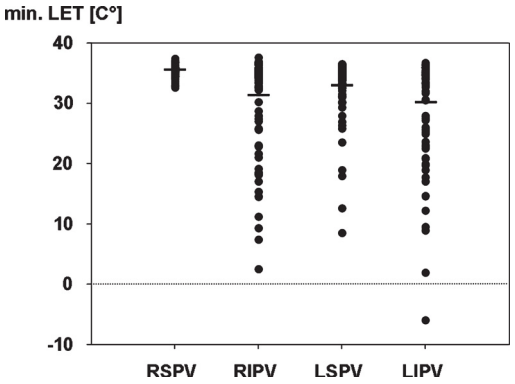

Figure 2. *Minimal luminal esophageal temperature (LET) measurements per vein treated. Solid bars indicate group means. RSPV = right superior pulmonary vein; RIPV = right inferior pulmonary vein; LSPV = left superior pulmonary vein (including data on 3 superior branches of a left common PV); LIPV = left inferior pulmonary vein (including data on 3 inferior branches of a left common PV).*

The temperature distribution among the 3 thermocouples at the time of absolute LET nadir in a subgroup of patients is shown in Table 3. The maximum temperature difference measured between 2 thermocouples correlated well with the absolute LET nadir ($r = -0.982$, $P < 0.001$); thus, differences were more pronounced when freezing near the esophagus. The highest temperature gradient (26°C) was measured in the patient with subzero LET between T2 (−6°C) and T3 (20.0°C). Thus, with the thermocouples spaced 10 mm apart, subzero LET was confined to a small area (Fig. 1, Table 3).

Average and absolute minimal LETs according to the fluoroscopic distance between the cryoballoon center (refrigerant injector) and the esophageal temperature probe during freezing at any PV are shown in Table 4. These data demonstrate a steep temperature gradient over distance from the cryoballoon with lowest LETs (< 10°C) confined to a distance of < 15 mm in both RAO 30° and LAO 40° projections (Table 4).

Gastroesophageal Endoscopy and Follow-Up

Endoscopy was performed 3 ± 1 (range 1–7) days following ablation. Thirty-seven out of 38 patients (including the patient with subzero LET during cryoablation) were free of any detectable lesion of the esophageal mucosa. In 1 patient, endoscopy at the first postprocedural day revealed 2 longitudinal, fissural lesions confined to the top of mucosal folds in a region beginning 35 cm from the incisor teeth and reaching down to the esophagogastric junction. These lesions were interpreted to be of mechanical origin by the investigator, possibly due to preprocedural transesophageal echocardiography or manipulation with the temperature probe. In this patient, proton-pump inhibitor therapy was initiated and a

TABLE 2
Luminal Esophageal Temperature Measurements

	RSPV	RIPV	LSPV	LIPV
Average minimal LET (°C)	35.4 ± 0.9*	31.5 ± 7.5*	32.9 ± 5.2*	30.3 ± 8.4*
Absolute minimal LET (°C)	32.6	2.5	8.5	−6.0
Minimal LET < 30°C (n)	0	21	10	25
Minimal LET < 10°C (n)	0	3	1	4
Average LET decrease (°C)	0.2 ± 0.9	2.7 ± 5.5	2.8 ± 5.3	5.3 ± 8.1

Data for LSPV and LIPV include 3 superior and inferior branches of a left common pulmonary vein, respectively. RSPV = right superior pulmonary vein; RIPV = right inferior pulmonary vein; LSPV = left superior pulmonary vein; LIPV = left inferior pulmonary vein; LET = luminal esophageal temperature; *$P < 0.001$ for comparison among all groups (Friedman test).

control endoscopy 6 days later showed a normal esophageal mucosa. In summary, the incidence of thermal esophageal lesions was 0% (95% CI: 0–9.3%). The incidence of any esophageal lesion was 2.6% (95% CI: 0.07–13.8%).

During a follow-up of 125 ± 78 days, no atrioesophageal fistula occurred.

In 2 patients, gastroesophageal endoscopy at day 3 after the procedure showed food retention despite overnight fasting. In patient 1, pyloric spasm was also shown. Both patients reported mild abdominal discomfort and distention, but were able to continue food intake. Repeat gastroesophagoscopy was performed 1 week after the procedure in both patients, demonstrating normal gastric emptying and pyloric function in patient 1, with complete resolution of symptoms. In patient 2, impaired gastric emptying was still demonstrated. However, with conservative treatment the patient was successfully discharged on almost normal diet at 1 week.

Complications

Right PN palsy (PNP) occurred in 2 patients despite immediate cessation of the cryoballoon application upon loss of PN capture. In 1 patient PNP occurred during the third cryothermal application (2nd bonus) at the RSPV (max. diameter: 22 mm). Thus, despite a relatively small PV diameter, cumulative tissue cooling ultimately led to PNP. This patient felt dyspnea on exertion, which resolved within 7 months after ablation. Repeat chest fluoroscopy demonstrated normal diaphragm movement at that time. In the other patient, PNP occurred during the first cryothermal application at a large RIPV (max. diameter: 25 mm) and persisted until discharge. This patient was asymptomatic and refused further chest fluoroscopy. No other complication occurred during procedure or follow-up.

TABLE 3
LET Measurements from 3 Thermocouples at the Time of Absolute LET Nadir

Vein	T1 [°C]	T2 [°C]	T3 [°C]	Δmax [°C]	Pt
LSPV	35.7	36	33.1*	2.9	39
LIPV	22.1*	25.6	32	9.9	37
LIPV	19.7*	23.9	31	11.3	31
LIPV	22.5*	26.6	33.9	11.4	32
RIPV	33.6	24.5	18.5*	15.1	38
LIPV	6.6	−6*	20	26	29

RIPV: right inferior pulmonary vein; LSPV = left superior pulmonary vein; LIPV = left inferior pulmonary vein; LET = luminal esophageal temperature; *absolute LET nadir; T1-T3 = individual thermocouples; Δmax = maximum temperature difference between 2 thermocouples; pt = patient number.

Discussion

The main new findings of this study are (1) the absence of esophageal thermal lesions in a cohort of 38 patients undergoing CB-PVI using only the big (28 mm) balloon, and (2) restriction of lowest LET to a small area as demonstrated by the use of multiple thermocouples, as well as a steep temperature gradient over the distance between cryoballoon center and temperature probe such that LET decreases to < 10° C occurred in a small subset of patients (n = 5) with a distance of < 15 mm in both RAO 30° and LAO 40° projections (Table 4).

Previous Studies

There is one previously published study reporting on postprocedural esophageal endoscopy following cryoballoon PVI. The authors found a 17% incidence (6 out of 35 patients) of reversible esophageal thermal ulcerations associated with CB-PVI.[8] The ablation technique differed from our approach in that both available balloon dimensions (23 and 28 mm) were employed for PVI, with the use of a 23 mm cryoballoon in 52% of patients.[8] The authors found no difference in mean LET decrease associated with the use of the 23 mm as opposed to the 28 mm balloon. However, a single thermocouple was used for LET measurement and esophageal thermal lesions in this cohort were observed over a wide range of minimal LETs (0–30.7°C), such that no temperature limit could be found to distinguish between patients with and without lesions.[8] On the other hand, we could show that minimal LET during LA cryoablation close to the esophagus is localized to a small area when using multiple thermocouples (Fig. 1, Table 3). Accordingly, measurement by a single thermocouple likely decreases sensitivity to detect maximum temperature changes in the esophagus.[15] Thus, it is currently not clear whether the use of a 23 mm cryoballoon may result in lower esophageal temperatures when compared to the use of a 28 mm balloon.

Possible Impact of Balloon Size

The use of a small as opposed to a big balloon at a given PV diameter may have several effects on collateral structures. A deeper position within the vein could result in the combined effect of (1) close proximity to adjacent tissue, and (2) deeper freezing temperatures due to less convective heating of the balloon by atrial blood flow.

TABLE 4
LET According to the Fluoroscopic Balloon-to-Esophagus Probe Distance

CB-ETP (mm)	CB-ETP (mm) RAO 30°								
LAO 40°	**0–4**	**5–9**	**10–14**	**15–19**	**20–24**	**25–29**	**30–39**	**40–49**	**50–59**
0–4	#	#	5.7 (1.9)	21.6 (19.7)	26.4 (25.8)	#	#	34.3 (34.3)	#
5–9	#	4.3 (−6.0)	#	21.5 (17.7)	31.4 (25.2)	33.5 (33.1)	35.2 (35.0)	#	#
10–14	10.8 (2.5)	26.3 (18.1)	#	18.8 (18.5)	#	33.0 (32.1)	34.5 (34.0)	34.8 (34.8)	#
15–19	27.2 (21.0)	27.0 (18.1)	#	#	#	33.1 (32.1)	35.0 (34.8)	35.2 (33.9)	#
20–24	35.6 (35.4)	#	#	34.8 (34.8)	#	34.8 (33.1)	35.5 (34.1)	35.0 (34.6)	36.1 (35.7)
25–29	34.9 (34.6)	34.2 (32.6)	#	#	35.7 (32.9)	35.1 (33.3)	35.5 (35.2)	34.7 (34.3)	#
30–39	34.0 (33.6)	31.7 (30.2)	35.8 (35.5)	#	34.2 (34.1)	35.3 (34.8)	34.8 (33.5)	36.2 (36.0)	35.1 (35.0)
40–49	#	#	#	35.0 (34.6)	35.4 (35.3)	36.0 (35.9)	34.9 (34.6)	35.9 (35.9)	36.1 (35.9)
50–59	#	#	#	#	35.5 (35.3)	#	34.9 (34.9)	35.9 (35.5)	#
60–69	#	#	#	#	#	#	35.9 (35.9)	#	34.5 (34.5)

Average and absolute minimal luminal esophageal temperature (LET [°C]) is shown as a function of fluoroscopic distance to the cryoballoon in both RAO 30° and LAO 40° projections. The refrigerant injector of the cryoballoon was used as a fluoroscopic marker. Values in parentheses represent absolute minimal LET. CB = cryoballoon; ETP = esophageal temperature probe.

Anatomical and imaging studies have shown that in ~60% of patients the esophagus passes close to the pulmonary venoatrial (VA) junction, most often on the left side.[16-18] In fact, the shortest distance between the LA endocardium and the esophageal wall was found at the left VA junction.[16] Due to the posterior course of the inferior PVs as opposed to the more anterior course of the superior PVs,[19] the shortest distance to the border of the esophagus has been described for the inferior PVs.[18] These anatomical findings are well reflected by our LET measurements during cryoablation at individual PVs (Fig. 2, Table 2). In some patients, the esophagus is crowded into a space surrounded by the LIPV, the spine, and the descending aorta.[18] Thus, especially during cryoablation at the LIPV, a relatively distal balloon position may result in close contact to the esophagus. Moreover, due to a steep temperature gradient in close proximity to the cryoballoon (Table 4), even a small difference in balloon-to-esophagus distance, such as might be brought about by the use of a small balloon, may greatly impact on LET when freezing near the esophagus.

In contrast, in this patient cohort treated exclusively with the 28 mm balloon, we did not observe thermal esophageal lesions. Thus, esophageal temperature measurement did not provide incremental safety benefit in this study. Further research is needed to confirm the study results in a larger cohort.

Complications

While reversible PNP is a well-recognized complication of cryoballoon ablation,[5-9,20] delayed gastric emptying has to the best of our knowledge not yet been reported in association with CB-PVI. Several cases of acute pyloric spasm and gastric hypomotility have been described following RFC ablation for AF,[21] probably due to damage of the periesophageal vagal plexus, some of which required corrective interventions. The 2 patients described in this study had mild or transient symptoms with successful conservative treatment. Further research is required to determine whether this complication takes a generally benign course following CB-PVI.

Limitations

This study has several limitations. (1) The study did not include a control group. Thus, the hypothesis that exclusive use of the 28 mm balloon is associated with a lower risk for esophageal lesions compared to ablation strategies involving the 23 mm balloon needs to be tested in a randomized trial. (2) Digital temperature readings were registered manually, thus exact LET-time curves could not be analyzed. (3) The relationship or time course between esophageal lesions detected at endoscopy and manifest AEF is unclear. Furthermore, it cannot be excluded that thermal esophageal lesions became manifest after endoscopy was performed. However, clinical and experimental studies indicate thermal esophageal lesion development by cryoablation well within the time frame of this study.[8,12]

Conclusions

In a cohort of AF patients treated by the single big (28 mm) cryoballoon technique, CB-PVI was not associated with thermal esophageal lesions. LET measurement by multiple thermocouples revealed high temperature gradients along the esophagus during cryoablation, underscoring the role of multiple measurement sites.

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Luminal esophageal temperature predicts esophageal lesions after second-generation cryoballoon pulmonary vein isolation

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BACKGROUND The novel second-generation cryoballoon (CB) facilitates pulmonary vein isolation (PVI) by improved surface cooling. The impact of this redesign on collateral damage is unknown.

OBJECTIVE To investigate the incidence of esophageal lesions after PVI using the second-generation CB and the role of luminal esophageal temperature (LET) measurement as a predictor of lesion formation.

METHODS Thirty-two consecutive patients underwent PVI using the second-generation 28 mm CB. Target application time was 2 × 240 seconds. Ninety-two percent of the PVs were isolated after 1 cryoenergy application. Complete PVI was achieved in all patients. LET with 3 thermocouples was continuously measured during cryoenergy application. Freezing was interrupted only if weakening/loss of phrenic nerve function or low LET (<5°C) was observed.

RESULTS The lowest measured LET was −12°C (despite cryoapplication interruption). Postprocedural gastroesophagoscopy was performed after 1–3 days in all patients and showed lesions in 6 of 32 (19%) patients. A minimum LET of ≤12°C predicted esophageal lesions with 100% sensitivity and 92% specificity (area under the receiver-operator characteristic curve 0.97; 95% CI 0.93–1.02; $P = .001$). Persistent phrenic nerve palsy occurred in 2 (6%) patients during ablation at the right inferior pulmonary vein. Repeat gastroesophagoscopy confirmed healing of lesions after 16 ± 14 days.

CONCLUSIONS Second-generation 28 mm CB PVI is associated with significant esophageal cooling, resulting in lesion formation in 19% of the patients. LET measurement accurately predicts lesion formation and may enhance the safety of the novel device.

KEYWORDS Ablation; Arrhythmia; Atrial fibrillation; Balloon; Electrophysiology

ABBREVIATIONS AF = atrial fibrillation; **CB** = cryoballoon; **INR** = international normalized ratio; **LCPV** = left common pulmonary vein; **LET** = luminal esophageal temperature; **PN** = phrenic nerve; **PNP** = phrenic nerve palsy; **PV** = pulmonary vein; **PVI** = pulmonary vein isolation; **ROC** = receiver-operator characteristic

Introduction

Cryoballoon (CB) ablation is increasingly used for pulmonary vein isolation (PVI) in patients with atrial fibrillation (AF) owing to its relative technical simplicity when compared to radiofrequency current ablation.[1–3] Recently, the second-generation CB has become available, featuring a redesigned refrigerant injection system. This modification results in a larger balloon surface area of optimal cooling, now comprising the entire frontal hemisphere, as well as an increased refrigerant flow of the 28 mm CB. Accordingly, improved procedural efficacy when compared to the first-generation 28 mm CB has been demonstrated.[4] Enhanced ice formation within the PV during freezing has been reported with the novel balloon,[5] which is indicative of enhanced heat removal from tissue when compared to the first-generation device. This may impact on an inadvertent lesion formation of contiguous structures. A rare but catastrophic complication of CB-PVI is atrio-esophageal fistula formation.[6] Prior studies of systematic postprocedural esophagoscopy following CB-PVI with the first-generation device have reported mixed results.[7–9] No discriminative value of luminal esophageal temperature (LET) could be found predicting lesion development.[7] Studies using a single 28 mm CB strategy reported a 0% incidence of esophageal lesions.[8,9] Thus, many operators do not measure LET routinely during CB ablation.[1,3] Here, we investigated the incidence of esophageal lesions after CB-PVI with the second-generation 28 mm CB and the role of LET as a predictor of lesion formation.

Methods

Patients

Thirty-two consecutive patients with symptomatic paroxysmal or short-lasting persistent AF were included in the study. Exclusion criteria were continuous AF for >6 months, a left

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atrium size >55 mm, intracardiac thrombi, and failure to provide written informed consent to undergo postprocedural gastroesophagoscopy. Baseline characteristics of the study cohort are shown in Table 1. Phenprocoumon was continued, aiming for an INR of 2–2.5 at the day of the procedure; dabigatran or rivaroxaban was discontinued 2 days before the procedure. Patients underwent transesophageal echocardiography to rule out left atrial thrombi immediately before the procedure. No further imaging was performed prior to PVI.

CB ablation

The design of the second-generation CB has been described previously.[4] Briefly, the refrigerant N_2O is injected into the balloon where it undergoes a liquid-to-gas phase change. The number of refrigerant injection ports has been increased from 4 to 8, and the injection coil has been repositioned 4.5 mm toward the distal pole, resulting in increased and more uniform refrigerant flow to the frontal hemisphere when compared to the first-generation 28 mm CB. All procedures were performed under conscious sedation using boluses of midazolam, fentanyl, and a continuous infusion of propofol. A temperature probe with 3 thermocouples separated by 10 mm (SensiTherm, St Jude Medical, Inc, St Paul, MN) was inserted into the esophagus transorally under fluoroscopic guidance (Figure 1). The position of the probe was adjusted to the fluoroscopic position of the balloon before each cryothermal application. For each application, minimal LET was recorded defined as the temperature nadir occurring during or shortly after cryothermal energy deployment in any of the thermocouples.[8] Fluoroscopic ostial PV diameters were measured from selective PV angiographies (right PVs: right anterior oblique 30°; left PVs: left anterior oblique 40°). The principles of single transseptal 28 mm CB-PVI have been described previously.[10] In brief, the second-generation CB (Arctic Front Advance, Medtronic, Inc, Minneapolis, MN) was inserted into the left atrium guided by an endoluminal spiral mapping catheter (Achieve, 15 or 20 mm, Medtronic, Inc). To assess

Table 1 Baseline characteristics of patients

Sex: male (%)	35
Age (y)	63 ± 12
Paroxysmal AF (%)	81
Persistent AF (%)	19
AF history (y)	4 ± 3
LA size (mm)	38 ± 13
CHA_2DS_2-VASc score	3 ± 2
PV diameter (mm)	
LSPV	17 ± 7
LIPV	16 ± 7
LCPV	24 ± 4
RSPV	16 ± 6
RIPV	17 ± 6
Comorbidities (%)	
Hypertension	69
Diabetes	9
Stroke/TIA	6
Heart failure	6
CAD	19
GERD	3

AF = atrial fibrillation; CAD = coronary artery disease; GERD = gastroesophageal reflux disease; LA = left atrium; LCPV = left common pulmonary vein; LIPV = left inferior pulmonary vein; LSPV = left superior pulmonary vein; PV = pulmonary vein; RIPV = right inferior pulmonary vein; RSPV = right superior pulmonary vein; TIA = transient ischemic attack.

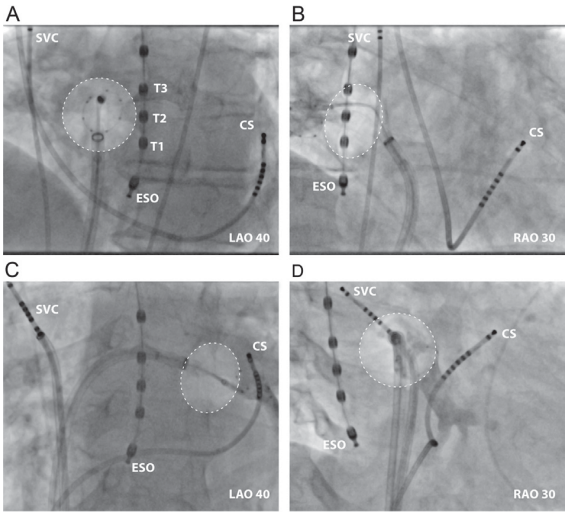

Figure 1 Fluoroscopic view during cryoballoon ablation. **A–B:** Ablation at the right inferior pulmonary vein (PV) in patient 29. Right anterior oblique (RAO; panel B) and left anterior oblique (LAO; panel A) projections are shown. The esophageal temperature probe (ESO) with 3 thermocouples (T1–T3) indicates a close relative position of the esophagus and cryoballoon in both projections. Minimum luminal esophageal temperature (LET) during this application was −4.3°C despite interruption of freezing at a LET of 5°C. A lesion was found at postprocedural esophagoscopy in this patient. **C–D:** Balloon position at the left common PV in patient 25 during angiography via cryoballoon tip, demonstrating occlusion of the PV. Esophageal probe and balloon are well separated. Minimum LET during this application was 33°C, and no lesion was found at postprocedural esophagoscopy in this patient. CS = coronary sinus; SVC = catheter at the phrenic nerve capture site in the superior caval vein.

the exact position of the inflated balloon in relation to the PV ostium, contrast medium was injected from the distal lumen of the CB catheter. Application time was set to 240 seconds. Following successful PVI, 1 bonus application was performed for each PV.[11] In the first 4 patients, our protocol did not include a LET cutoff to guide early interruption of cryothermal energy application. In patient 5, it became evident that LET may decrease rapidly to subzero temperatures by using the second-generation CB. Thus, a LET cutoff of 5°C was defined for the remaining patients and cryoenergy application was interrupted when this temperature was reached. In these cases, no additional bonus application was deployed. PVI was demonstrated by the loss or dissociation of the PV potential recorded by the spiral mapping catheter during freezing or, alternatively, after cryoenergy application by moving the mapping catheter to a position just distal to the angiographically defined ostium.[10] Only the 28 mm CB was used without touch-up lesions by a focal catheter. The right phrenic nerve (PN) was constantly paced from the superior caval vein during freezing at the right PVs. In the case of cessation or weakening of right hemidiaphragm contractions, freezing was stopped immediately. The ablation end point was the absence or dissociation of all PV potentials as confirmed by the spiral mapping catheter after a waiting period of 30 minutes.

Postprocedural care and gastroesophagoscopy

All patients underwent transthoracic echocardiography to rule out pericardial effusion after the procedure. Low-molecular-

weight heparin was administered starting 6 hours after ablation in patients with previous dabigatran or rivaroxaban treatment or an INR <2. The safety of systematic gastroesophagoscopy following PVI has previously been demonstrated in several studies.[7–9,12] Gastro-esophagoscopy was performed by experienced operators with particular awareness for possible esophageal lesions. The endoscope was introduced under continuous videoscopic surveillance. Gastroesophagoscopy was performed within 3 days after the procedure in all patients. Thereafter, phenprocoumon (with overlapping low-molecular-weight heparin until a therapeutic INR was achieved), dabigatran, or rivaroxaban was readministered according to the previous regimen and prescribed for at least 2 months. A proton pump inhibitor was administered for 2 weeks starting on the day of ablation. All patients were seen in the outpatient clinic or contacted via telephone 30 days after the procedure.

Statistical analysis

Continuous variables were expressed as mean ± SD and analyzed by using the Student *t* test. Nominal variables were expressed as frequencies or proportions and analyzed by using the χ^2 test. A receiver-operator characteristic (ROC) curve was constructed to evaluate the performance of LET as a predictor of esophageal lesion formation. The correlation between minimum balloon temperature and minimum LET was analyzed by using the Pearson correlation coefficient. A *P* value of $<.05$ was considered statistically significant.

Results

CB ablation

In 32 patients, a total of 124 PVs were identified, including 4 left common PVs (LCPV; Table 2). Among patients with an LCPV, the upper and the lower branch were treated as left superior pulmonary vein and left inferior pulmonary vein in 1 patient, whereas in 3 patients the LCPV was treated as a single PV. Procedural parameters are summarized in Table 2. Minimum CB temperatures are shown in Table 3. Isolation with a single application occurred in 92% of the PVs. Interruption of cryoenergy application was performed at 8 PVs after a mean of 176 ± 27 (range 122–200) seconds. The reasons for early interruption are listed in Table 4. Despite interruption of freezing before 240 seconds in a subset of PVs, complete PVI was achieved in all patients.

LET measurement

The temperature probe could be positioned in every patient without complications. In 1 patient, LET could not be measured owing to a technical problem with the probe. Minimum LET values during each balloon application according to anatomical PV are shown in Table 3 and Figure 2. We did not find significant correlations between minimum balloon temperature and minimum LET for any of the anatomical PVs. The lowest LET measured in the patient cohort was −12°C during the first ablation at the left inferior pulmonary vein in patient 5. PVI was demonstrated at 54 seconds, and a slow fall in LET was noted during the first 2 minutes, followed by a progressively rapid temperature drop. Cryoenergy delivery was interrupted after 170 seconds at 0°C LET, which continued to decrease for approximately 15 seconds to a minimum of −12°C. For subsequent patients, a LET cutoff of 5°C was defined, which was observed in 3 patients (Table 4).

Table 2 Procedural parameters

Total balloon applications per patient	7.6 ± 1.5
Procedure duration (min)	92 ± 25
Fluoroscopy exposure (min)	13 ± 4
Contrast medium (mL)	108 ± 40

Table 3 Luminal esophageal and balloon temperatures

	Minimum LET (°C)	LET range (°C)	Minimum balloon temperature (°C)
LSPV	28.6 ± 7.5	5.8 to 36.0	−51 ± 6
LIPV	28.5 ± 9.3	−12.0 to 35.5	−47 ± 5
LCPV	31.1 ± 6.8	20.9 to 34.6	−54 ± 6
RSPV	33.8 ± 1.2	29.1 to 35.3	−50 ± 7
RIPV	28.2 ± 9.6	−4.3 to 34.9	−49 ± 6

LC = left common; LET = luminal esophageal temperature; LI = left inferior; LS = left superior; PV = pulmonary vein; RI = right inferior; RS = right superior.

Gastroesophagoscopy

Gastroesophagoscopy was performed 2 ± 1 (range 1–3) days after the procedure. Esophageal lesions were found in 19% (6 of 32) of the patients (patients 1, 5, 11, 12, 13, and 29). The endoscopic aspect of esophageal ulcerations associated with second-generation CB ablation is shown in Figure 3. Lesions were found at the retrocardiac aspect of the esophagus. Repeat gastroesophagoscopy was performed in patients with esophageal lesions after 16 ± 14 (range 4–37) days and showed complete resolution in all patients. In patient 5 (LET −12°C), additional thoracic magnetic resonance imaging was performed, which did not show any abnormalities.

Performance of LET to predict lesions

Figure 4A shows the lowest LET measured in each patient according to the presence or absence of lesions in post-procedural esophagoscopy. Average minimum LET was 0.3 ± 8.9°C (lesion) and 22.3 ± 8.3°C (no lesion), respectively ($P < .001$). To test the performance of minimum LET as a predictor of esophageal lesion formation, an ROC curve was constructed (Figure 4B). The area under the curve was 0.97 (95% CI 0.93–1.02; $P = .001$). A minimum LET of ≤12°C predicted lesion formation with the highest

Table 4 Early interruption of cryoballoon applications

Patient	Vein	Appl. no.	Appl. duration (s)	Reason
4	RIPV	1	150	Loss of PN capture
5	LIPV	1	170	Low LET (<0°C)
11	RIPV	2	122	Low LET (<5°C)
16	RSPV	1	190	Transient PN weakening
20	RIPV	1	200	Loss of PN capture
24	RSPV	1	190	Transient PN weakening
29	RIPV	3	200	Low LET (<5°C)
30	RIPV	1	187	Low LET (<5°C)

Appl. = balloon application; LC = left common; LET = luminal esophageal temperature; LI = left inferior; LS = left superior; PV = pulmonary vein; PN = phrenic nerve; RI = right inferior; RS = right superior.

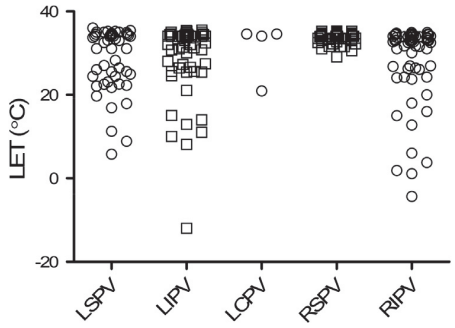

Figure 2 Minimum luminal esophageal temperature (LET) according to anatomical pulmonary vein. Each data point represents the lowest LET measured during 1 cryoballoon application. LCPV = left common pulmonary vein; LIPV = left inferior pulmonary vein; LSPV = left superior pulmonary vein; RIPV = right inferior pulmonary vein; RSPV = right superior pulmonary vein.

sensitivity (100%) and specificity (92%), negative predictive value (100%), and positive predictive value (71%).

Extraesophageal complications

Right PN palsy (PNP) occurred in 2 patients during the first application at the right inferior pulmonary vein despite interruption of freezing at 150 and 200 seconds upon loss of PN capture. Asymptomatic PNP was shown to persist at chest fluoroscopy on day 1. In 2 patients, transient weakening of right hemidiaphragm contraction was noted during the first application at the right superior pulmonary vein, which was interrupted at 190 seconds in both cases. Diaphragm function recovered completely during the procedure in both patients. The mean diameter of PVs associated with transient/persistent PNP was 16 ± 1 mm. No further complication occurred during procedure or follow-up.

Discussion

The main findings of this study are as follows: (1) The use of the novel 28 mm CB with improved surface cooling was associated with esophageal lesions in 19% of the patients. (2) The second-generation CB may lead to esophageal freezing with the lowest LET hitherto reported during CB ablation (−12°C), despite interruption of cryoenergy application at 0°C LET. (3) In contrast to prior observations with the first-generation CB, LET was an excellent predictor of lesion formation using the novel device. A LET of ≤12°C predicted lesion formation with 100% sensitivity and 92% specificity.

In prior studies, a 17% incidence of esophageal lesions was observed in 1 study using the smaller 23 mm CB in 52% of the patients,[7] whereas no thermal lesions were observed in 2 studies using exclusively the 28 mm CB.[8,9] The latter suggested the single 28 mm CB strategy to be relatively safe.[13] However, this is not applicable to the second-generation 28 mm CB for which we show a 19% incidence of esophageal ulcerations. Lesions healed without clinical sequelae in all patients, but it has to be emphasized that cryoenergy application was interrupted in 4 patients during rapid LET drop and no additional bonus application was applied. Thus, it may be speculated that continued and/or repeated energy application would have led to more severe lesions possibly with different outcomes. We therefore suggest routine LET monitoring using the second-generation CB.

Minimum LET provided high predictive performance of esophageal lesions with an area under the ROC curve of 0.98. No esophageal lesions were observed at a minimum LET of >12°C (negative predictive value of 100%). After interruption of cryoenergy delivery, LET may continue to decrease for a short period. Thus, the ideal LET to interrupt a CB application may have to account for this "overshoot." We used a temperature probe with 3 thermocouples, facilitating measurement of the lowest temperature. A different sensitivity to measure minimum LET when using a single thermocouple as well as different tissue-temperature distributions between first- and second-generation CB may have resulted in a lower performance of LET to predict esophageal lesions in a previous study using the first-generation CB.[7]

Among the anatomical PVs, interruption of freezing was most frequently necessary at the right inferior pulmonary vein, which may be in close anatomical contact with the right PN as well as the esophagus.[14,15] Because of its anatomical course, the esophagus is rarely contiguous to the right superior pulmonary vein[15]; hence, LET is less influenced during freezing at this vein.[8] In theory, interruption of cryoenergy application guided by LET may impact on acute and/or chronic PVI efficacy. However, PVI occurred rapidly using the second-generation CB after a mean ± SD of 46 ± 27 seconds in this study. In contrast, low LET (<5°C) leading to interruption of freezing was observed after 170 ± 42 seconds

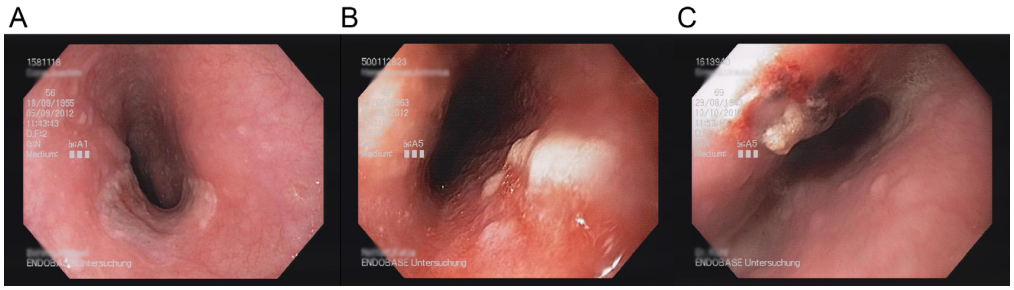

Figure 3 Endoscopic view of cryoballoon-induced esophageal lesions (ELs) in 3 different patients. **A:** EL at 30 cm from the incisor level at day 1. A shallow fibrin-coated lesion was found along an esophageal segment of 2 cm. **B:** EL at 36 cm from the incisor level at day 1. Multiple fibrin-coated lesions were found along an esophageal segment of 1 cm. **C:** EL at 28 cm from the incisor level at day 1. A single hemorrhagic ulceration was found.

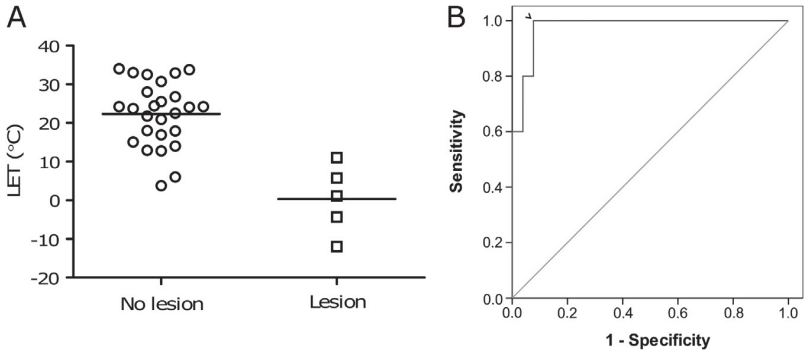

Figure 4 Minimum luminal esophageal temperature (LET) predicts esophageal lesion development. **A:** Minimum LET according to the presence or absence of esophageal lesions in postprocedural esophagoscopy. Each data point represents lowest LET measured in a patient during ablation. Horizontal bars indicate mean value. **B:** Receiver-operator characteristic curve constructed from the minimum LET per patient and the presence or absence of esophageal lesions. Arrowhead indicates point (LET of 12°C) with highest sensitivity and specificity.

when PVI had already occurred. Thus, a conventional application time of 240 seconds may not be necessary for every PV and may be titrated by safety and/or efficacy parameters such as LET and time to PVI[10] in future studies.

We observed a transient and persistent right-sided PNP rate of 6% each in this study despite continuous PN stimulation and palpation of diaphragmatic movement during ablation at right PVs. In a meta-analysis,[16] the overall PNP incidence in the published studies of first-generation CB ablation was 6.4%, with an immediate or delayed recovery in $>99\%$ of the patients. The incidence was lower when only a 28 mm CB was used (3.5%).[16] The latter observation may be explained by a relatively proximal position of the bigger 28 mm balloon in the PV antrum, more distant from the PN course. In a previous study, a PV-to-balloon diameter ratio of $\geq 26/28$ mm was found in patients with PN lesions by using the first-generation 28 mm CB.[2] Here, PNP occurred during ablation at relatively small PVs (16 ± 1 mm). This may indicate deeper penetrance of cryolesions by the second-generation CB also operative in esophageal lesion development.

Study limitations

A number of limitations apply to this study. (1) LET measurement was not purely observational but led to interruption of freezing in 4 patients. Three of these 4 patients exhibited esophageal lesions. Thus, the incidence of lesions without LET measurement may be higher than the reported 19% in this study. The proposed LET cutoff of 12°C needs to be validated in a prospective trial. (2) We investigated a relatively small group of patients. However, esophageal lesions were not rare and their association with LET statistically significant. Withholding the results until a larger group was studied was considered unethical in the opinion of the authors because the novel CB is approved for use in Europe and the United States and LET monitoring may avoid collateral damage in the treated patients. (3) Esophagoscopy was performed early after CB-PVI within 3 days. We cannot exclude delayed lesion development. Mechanical lesions due to preprocedural TEE or temperature probe manipulation cannot be completely excluded; however, lesions were found in loco typico in the retrocardiac area associated with low LET. (4) The relation of esophageal mucosal lesions to atrio-esophageal fistula formation is unknown. However, given the high mortality of this complication, it seems prudent possibly to avoid any esophageal collateral damage.

Conclusions

Second-generation 28 mm CB PVI is associated with significant esophageal cooling, resulting in lesion formation in 19% of the patients. LET measurement accurately predicts lesion formation and may enhance the safety of the novel device.

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Reduced incidence of esophageal lesions by luminal esophageal temperature–guided second-generation cryoballoon ablation

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BACKGROUND An increased incidence of esophageal lesions (EL) after pulmonary vein isolation (PVI) using the second-generation cryoballoon (CB2) has been described. We hypothesized that luminal esophageal temperature (LET)–guided PVI reduces the incidence of EL.

OBJECTIVE The aim of this study was to investigate the incidence of EL after LET-guided PVI using the CB2.

METHODS Ninety-four consecutive patients underwent CB2-PVI for paroxysmal or persistent atrial fibrillation. Target freezing time was 2 × 240 seconds. LET was continuously measured by a probe with 3 thermocouples. Early freezing interruption was performed when LET reached a prespecified cutoff temperature. A group of 32 patients who underwent CB2-PVI with observational LET measurement served as the control group. Postprocedural esophagoscopy was performed in all patients.

RESULTS Compared with observational LET measurement, a strategy of LET-guided CB-PVI significantly reduced the incidence of EL from 18.8% to 3.2% (P = .008). A progressive decline in the incidence of EL was observed with an increasing LET cutoff: 7.1% (2/28 patients, 12°C cutoff) and 1.5% (1/66 patients, 15°C cutoff, P = .005 vs control). Despite early freezing interruption at a single pulmonary vein in 27% (25/94) of patients, complete PVI was achieved in all patients using the 28 mm balloon. Repeat esophagoscopy confirmed healing of EL after 1 week. After a mean of 268 ± 119 days, 87% (76/87) of patients were free of recurrent atrial fibrillation or atrial tachycardia following a 90-days blanking period.

CONCLUSION LET-guided CB2-PVI significantly reduced the incidence of thermal EL. Interrupting cryoablation at 15°C LET was associated with the lowest incidence of esophageal injury.

KEYWORDS Ablation; Atrial fibrillation; Cryoballoon; Esophageal injury; Complication

ABBREVIATIONS **AEF** = atrioesophageal fistula; **AF** = atrial fibrillation; **AT** = atrial tachycardia; **CB** = cryoballoon; **CB1** = first-generation cryoballoon; **CB2** = second-generation cryoballoon; **CI** = confidence interval; **EFI** = early freezing interruption; **LET** = luminal esophageal temperature; **OR** = odds ratio; **PN** = phrenic nerve; **PV** = pulmonary vein; **PVI** = pulmonary vein isolation; **RIPV** = right inferior pulmonary vein

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Introduction

Cryoballoon (CB) ablation is increasingly used to perform pulmonary vein isolation (PVI) as an alternative to point-by-point radiofrequency ablation.[1] Recently, the second-generation cryoballoon (CB2) has become available and improved procedural[2,3] as well as clinical[4–7] performance of the CB2 has been demonstrated compared with the first-generation cryoballoon (CB1). The CB2 differs from the CB1 by a widened zone of minimum temperature as well as a higher refrigerant flow rate in the larger 28 mm balloon. This possibly affects collateral structures such as the esophagus. Atrioesophageal fistula (AEF) formation has been reported after CB-PVI.[8–10] We previously demonstrated an association of low luminal esophageal temperature (LET) with esophageal thermal ulcerations.[11] A LET value of ≤12°C predicted lesions with the highest sensitivity and specificity (100% and 92%, respectively).[11] On the basis of these results, we hypothesized that LET-guided CB-PVI with interruption of cryoenergy deployment at ≥12°C LET

Dr Fürnkranz, Dr Schmidt, Dr Bordignon, and Dr Chun have received honoraria for Medtronic educational lectures. Dr Fürnkranz has received congress travel support from Medtronic **Address reprint requests and correspondence:** Dr Alexander Fürnkranz, Cardioangiologisches Centrum Bethanien (CCB), Medizinische Klinik III, Markus Krankenhaus, Wilhelm-Epstein-Str 4, D-60431 Frankfurt, Germany. E-mail address: a.fuernkranz@gmail.com.

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reduces the incidence of esophageal lesions compared with observational LET measurement.

Methods

Patients

We conducted a prospective study in 94 consecutive patients with paroxysmal or persistent atrial fibrillation (AF). Exclusion criteria were as follows: a left atrial diameter of >55 mm, persistent AF for >6 months, intracardiac thrombi, and failure to consent to postprocedural gastroesophagoscopy. Patients underwent CB-PVI with interventional LET measurement, that is, early freezing interruption (EFI) at $\geq 12^{\circ}$C LET. Clinical baseline characteristics of the study patients are summarized in Table 1. The study protocol was approved by the local institutional review board. All patients provided written informed consent. A group of patients (n = 32) who underwent CB-PVI with observational LET measurement, that is, without a prespecified LET cutoff to guide freezing interruption, served as the control group. These results have been published previously.[11] The study cohort was treated consecutively to the control group.

CB ablation

We previously described the technique of CB2-PVI and LET measurement.[2,11] Briefly, vitamin K antagonists were continued, aiming for an international normalized ratio of 2–2.5 at the day of the procedure, and direct oral anticoagulants were discontinued 2 days before the procedure. Transesophageal echocardiography to rule out left atrial thrombi was performed immediately before the procedure. All procedures were performed under sedoanalgesia using boluses of midazolam and fentanyl and a continuous infusion of propofol. After single transseptal puncture, the CB2 (Arctic Front Advance, 28 mm, Medtronic, Inc, Minneapolis, MN) was introduced into the left atrium via a 12-F steerable sheath (FlexCath, Medtronic). Mapping of the pulmonary veins (PVs) was performed before, during, and after freezing with an endoluminal spiral mapping catheter (Achieve, Medtronic). To assess the exact position of the inflated balloon in relation to the PV ostium, contrast medium was injected from the distal lumen of the CB. Target application time was 240 seconds. After successful PVI, 1 "bonus" application was performed per PV unless low LET or right phrenic nerve (PN) dysfunction mandated freezing interruption. The ablation protocol consisted of CB-PVI only without additional ablation using a focal catheter. If necessary, sinus rhythm was restored by cardioversion during the procedure. A temperature probe with 3 thermocouples (SensiTherm, St Jude Medical, Inc, St Paul, MN) was inserted into the esophagus transorally under fluoroscopic guidance. The position of the temperature probe was adjusted to the position of the balloon before each cryothermal application. Minimum LET was defined as the temperature nadir occurring during or shortly after cryothermal energy deployment in any of the thermocouples. The right PN was paced from the superior caval vein during freezing at the septal PVs. In the case of cessation or weakening of right hemidiaphragm contractions, freezing was immediately stopped. The procedural end point was the absence or dissociation of all PV potentials as confirmed by the endoluminal spiral mapping catheter after a waiting period of 30 minutes.

Table 1 Baseline characteristics of patients

Sex: male	68
Age (y)	64 ± 10
AF history (y)	3 ± 3
Persistent AF	10
LA size (mm)	40 ± 5
LVEF (%)	62 ± 11
Hypertension	69
Diabetes	7
Stroke/TIA	4
CAD	17

Values are presented as mean ± SD and as percentages.AF = atrial fibrillation; CAD = coronary artery disease; LA = left atrial; LVEF = left ventricular ejection fraction; TIA = transient ischemic attack.

Analysis of LET and balloon temperature

In a subset of patients (n = 17), continuous videoscopic recordings of esophageal and CB temperature readouts were performed during the procedure. From these recordings, during each cryothermal application, LET and balloon temperature curves were constructed with a 5-second sampling interval. The distance between the temperature probe and the CB was measured fluoroscopically in right anterior oblique 30° and left anterior oblique 40° projections (Figure 1). If both structures overlapped, the distance was set to zero. The larger distance of the 2 fluoroscopic projections was used for the analysis.

Postprocedural care and esophagoscopy

Details of the postprocedural protocol and esophagoscopy have been described previously.[11] In short, low-molecular-weight heparin was administered starting 6 hours after ablation in patients with previous direct oral anticoagulant treatment or in patients receiving vitamin K antagonists if the international normalized ratio was <2. Gastroesophagoscopy was performed within 3 days of the procedure. The endoscope was introduced under continuous videoscopic surveillance. The gastroenterologist performing esophageal endoscopy was blinded to procedural parameters including LET measurement. Thereafter, oral anticoagulation was restarted according to the previous regimen and prescribed for at least 2 months. A proton pump inhibitor was administered for 2 weeks starting on the day of ablation. Patients were scheduled for outpatient clinic visits at 3, 6, 9, and 12 months at which time 72-hour Holter electrocardiogram recording was performed. In the case of symptoms suggestive of atrial tachyarrhythmia recurrence, additional visits were scheduled. Atrial tachyarrhythmia recurrence was defined as AF or atrial tachycardia (AT) lasting >30 seconds

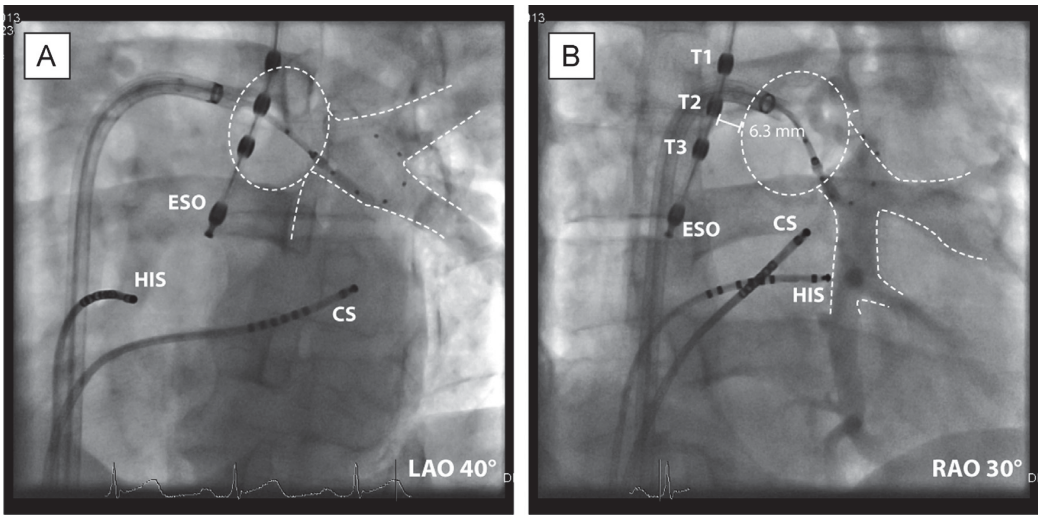

Figure 1 Fluoroscopic view during cryoballoon ablation at the left inferior pulmonary vein in LAO 40° (**A**) and RAO 30° (**B**) projections. A temperature probe (ESO) with 3 thermocouples (T1-T3) is positioned within the esophagus. An endoluminal spiral mapping catheter carrying 6 electrodes is positioned within the pulmonary vein outlined by the contrast medium that had been injected via the balloon tip. The fluoroscopic distance between the temperature probe and the balloon surface was 6.3 mm in RAO (panel B), while both structures overlapped in LAO (panel A). CS = diagnostic catheter positioned in the coronary sinus; HIS = diagnostic catheter at His position; LAO = left anterior oblique; RAO = right anterior oblique.

documented after a blanking period of 90 days after the procedure.

Statistical analysis

Continuous variables were expressed as mean ± SD and analyzed using the Student *t* test. Nominal variables were expressed as frequencies and proportions and analyzed using the χ^2 or Fisher exact test. Multivariate logistic regression was performed to determine independent predictors of esophageal lesion formation in patients with LET-guided PVI or observational LET measurement. Covariates entered into the model were age, sex, LA diameter, total CB applications, procedure time, and performance (or not) of LET-guided PVI. The correlation between minimum LET and balloon temperature or distance between the temperature probe and the balloon was analyzed using the Pearson correlation coefficient. A 2-sided *P* value of $<.05$ was considered statistically significant.

Table 2 Global procedural parameters

Parameter	LET-guided CB-PVI (n = 94)	Observational LET measurement (n = 32)	*P*
Procedure duration (min)	88 ± 25	92 ± 25	.40
Fluoroscopy exposure (min)	14 ± 9	13 ± 4	.61
Balloon applications	7.5 ± 2.0	7.6 ± 1.5	.79
Complete PVI	100	100	—
Time of esophagoscopy (d)	2 ± 1	2 ± 1	.27

Values are presented as mean ± SD and as percentages.

CB = cryoballoon; LET = luminal esophageal temperature; PVI = pulmonary vein isolation.

Results

LET-guided CB ablation

Global procedural parameters are summarized in Table 2. The mean procedure duration (groin puncture to sheath removal) and fluoroscopy exposure time were 88 ± 25 and 14 ± 9 minutes, respectively. A left common PV treated as a single vein was found in 11 (12%) patients. The cutoff LET to guide EFI was set to 12°C on the basis of the results of the evaluation study.[11] Because of the observation of 2 esophageal lesions in the first 28 patients and additional LET decrease after EFI, the cutoff LET was set to 15°C, starting with patient 29. EFI triggered by esophageal cooling was performed at 25 PVs in 25 of 94 patients (27%) (Table 3). In 9 patients, EFI at 12°C LET was performed after 180 ± 30 seconds, and in 16 patients, EFI at 15°C LET was performed after 164 ± 43 seconds. The minimum LET in patients with EFI was 10.5 ± 1.0°C (12°C cutoff) and 13.0 ± 1.3°C (15°C

Table 3 Procedural parameters in patients with EFI due to low LET

Parameter	Stop at 12°C	Stop at 15°C
No. of patients (%)	9 (9.6)	16 (17.0)
LSPV	1	—
LIPV	4	9
LCPV	—	—
RSPV	—	—
RIPV	4	7
Time to PVI (s)	40 ± 31	47 ± 30
Time to EFI (s)	180 ± 30	164 ± 43
Minimum LET (°C)	10.5 ± 1	13 ± 1.3

Values are presented as mean ± SD and as numbers.

EFI = early freezing interruption; LCPV = left common pulmonary vein; LET = luminal esophageal temperature; LIPV = left inferior pulmonary vein; LSPV = left superior pulmonary vein; PVI = pulmonary vein isolation; RIPV = right inferior pulmonary vein; RSPV = right superior pulmonary vein.

cutoff). The additional LET decrease during the thawing phase of the CB after EFI varied between 0 and 4.5°C (mean 1.9°C). EFI was performed in 21 patients at the first application, in 2 patients at the second application, and in 1 patient each at the third and the fourth application, respectively. Despite EFI in 27%, complete PVI was achieved in 100% of patients using the 28 mm balloon only. The mean time period from PVI to EFI was 121 ± 39 seconds (n = 16; in 7 patients, PV signals could not be recorded during freezing in the respective PV, and in 2 patients the LET cutoff was reached during a "bonus" freeze).

Loss or weakening of right PN function mandated freezing interruption at 4 PVs in 4 patients. In each case, the culprit PV was isolated after the balloon application. In 1 patient, PN function returned to normal during the procedure. In 3 patients, right PN palsy persisted until discharge. Vascular access complications occurred in 4 patients, groin hematoma in 1, and arteriovenous fistulas in 3, one of which required surgical intervention. All 4 patients recovered completely. One patient developed a transient ischemic attack within 1 hour after the procedure and recovered completely. No complication occurred because of the placement of the esophageal probe.

Esophageal endoscopy

Gastroesophagoscopy was performed in all patients 2 ± 1 days after the procedure. Lesions were found in 3 of 94 patients at the retrocardiac aspect of the esophagus, consisting of a submucosal hematoma in 1 patient (Figure 2A) and shallow fibrin-coated ulcerations in the 2 remaining patients (Figures 2B and 2C). None of these patients had symptoms such as dysphagia or retrosternal chest pain. Compared with observational LET measurement, a strategy of LET-guided CB-PVI significantly decreased esophageal lesion formation (18.8% vs 3.2%; odds ratio [OR] 0.14; 95% confidence interval [CI] 0.03–0.61; P = .008). In the multivariate analysis, a strategy of LET-guided PVI was the only independent predictor of esophageal lesion formation (adjusted OR 0.16; 95% CI 0.03–0.77; P = .02). In the 12°C LET cutoff group, lesions were observed in 2 of 28 patients (7.1%; unadjusted OR 0.33; 95% CI 0.06–1.81; P = .26 vs control). In the 15°C LET cutoff group, a lesion was observed in 1 of 66 patients (1.5%; unadjusted OR 0.07; 95% CI 0.01–0.58; P = .005 vs control; Figure 3). The time of esophagoscopy was not different between patients with LET-guided CB-PVI and those with observational LET measurement (Table 2).

In the 3 patients with esophageal lesions after LET-guided CB-PVI, EFI was performed in 2 patients after 140 and 190 seconds at 12°C LET and during freezing at the left inferior pulmonary vein (first application) and right inferior pulmonary vein (RIPV; fourth application), respectively. The LET nadir was 10.9 and 12.0°C, respectively. One patient in the 15°C cutoff group showing an esophageal lesion (Figure 2C) exhibited a minimum LET of 16.2°C after the second application at the RIPV and EFI was not performed. Repeat esophagoscopy after 1 week demonstrated healing in all 3 patients.

LET curve analysis

Balloon temperature and LET versus time curves of each cryothermal application were analyzed in 17 patients (Figure 4). The maximum temperature difference between 2 contiguous esophageal thermocouples at the end of freezing was 14.2°C (mean 1.4 ± 2.1°C). With a thermocouple spacing of 10 mm, a longitudinal LET gradient of up to 1.4°C/mm was observed. The time to the first LET decrease in any thermocouple was 76 ± 52 seconds. The mean esophageal cooling rate over the total freezing time was 0.8 ± 1.4°C/min. The maximum cooling rate observed at any time during freezing varied between 0.2 and 15°C/min (mean 1.9°C/min). Minimum LET was not correlated with minimum CB temperature (R^2 = 0.008; P = .61; Figure 4B). The relationship of minimum LET to the fluoroscopic distance between the esophageal temperature probe and the CB surface (D_{eso}) is shown in Figure 4C. The largest D_{eso} associated with a LET value of ≤30°C in at least 1 application was 19 mm. For distances <20 mm, minimum LET was significantly correlated with D_{eso} (R^2 = 0.36; P < .0001).

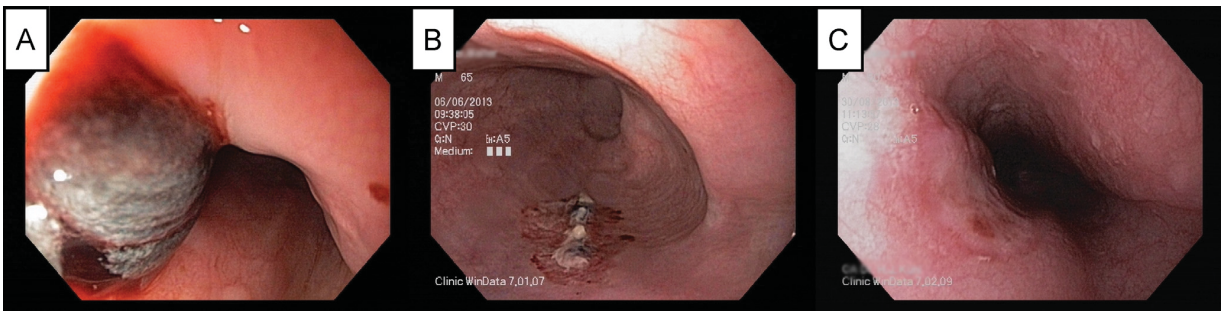

Figure 2 Endoscopic aspect of esophageal lesions. **A** and **B:** Lesions were found in 2 patients of the 12°C LET cutoff group: a submucosal hematoma (panel A) that drained into the esophageal lumen during endoscopy, leaving a small ulceration, and (panel B) a shallow fibrin-coated ulceration. **C**: A small, fibrin-coated ulceration was found in 1 patient in the 15°C LET cutoff group. Repeat esophagoscopy demonstrated healing of all lesions after 1 week. LET = luminal esophageal temperature.

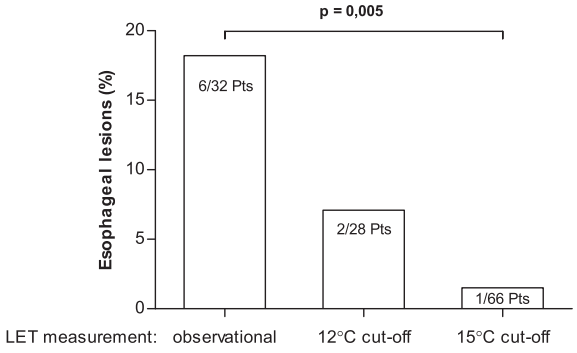

Figure 3 Luminal esophageal temperature (LET)–guided cryoballoon pulmonary vein isolation reduces the incidence of thermal esophageal lesions compared with observational LET measurement. A progressive decline in the incidence of esophageal lesions was observed with an increasing LET cutoff to trigger early freezing interruption. Pts = patients.

Follow-up

In 87 patients, follow-up beyond the 90-day blanking period was available (268 ± 119 days); 87.4% of these patients remained free from recurrent AF/AT, of whom 97.4% were off membrane-active antiarrhythmic drug treatment at the end of follow-up. Success rates were not different between patients in whom EFI due to low LET was performed (n = 22) and those in whom EFI due to low LET was not performed (n = 65): 95.5% vs 84.6%, respectively (P = .17). Of 11 patients with recurrent AF/AT, 5 patients underwent a second procedure using radiofrequency current ablation with 3-dimensional mapping. In none of these patients, EFI due to low LET had been performed during the index procedure. In 4 of these patients with recurrent AF PV reisolation was performed. Electrical reconnection of a single PV was found in 3 patients, and of the 2 lateral PVs in 1 patient. Of 5 PVs exhibiting electrical reconnection during the second procedure, freezing interruption at < 240 seconds had been performed in 1 PV during the index procedure (RIPV; freezing time 100 seconds) because of transient PN palsy. One patient presented with AT, which was diagnosed as perimitral flutter and terminated during ablation of an anterior line. All PVs were found to be isolated in this

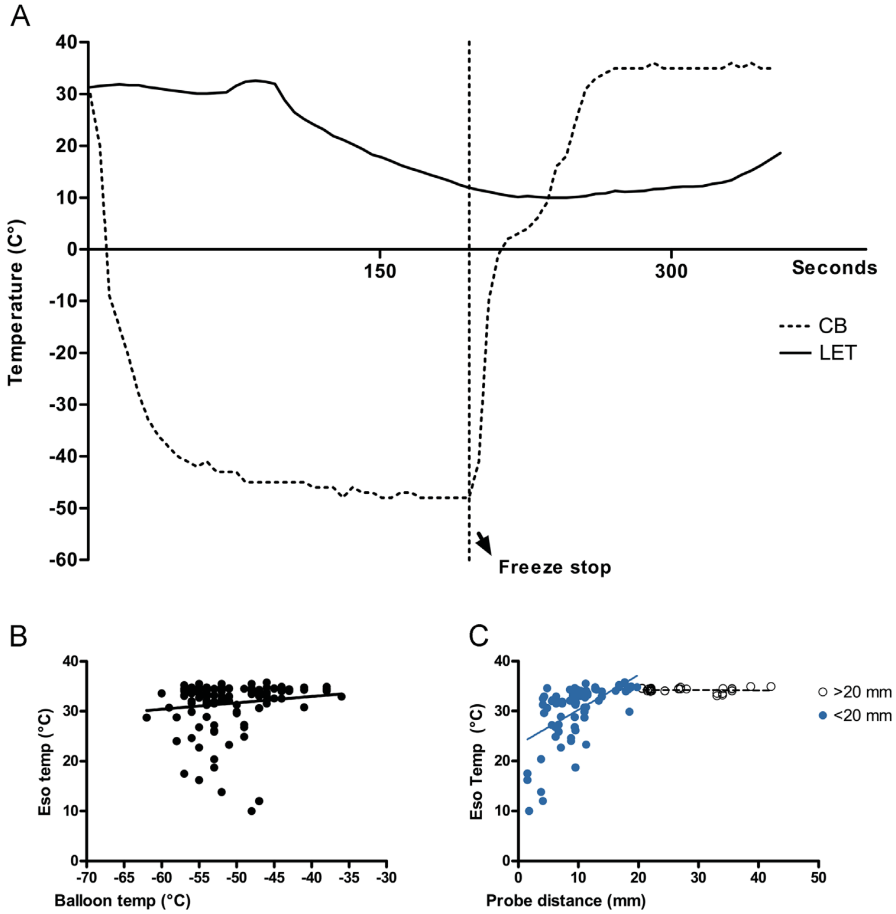

Figure 4 **A:** Luminal esophageal temperature (LET) during cryoballoon ablation with freezing interruption at 12°C LET. LET and cryoballoon (CB) temperature are shown. A constant decrease in LET was observed after 100 seconds. After cessation of cryoenergy delivery after 200 seconds, LET continued to decrease by 1.5°C, followed by slow rewarming. **B:** Minimum balloon temperature is not correlated with minimum LET ($R^2 = 0.008$; $P = .61$). **C:** Relationship of minimum LET to the fluoroscopic distance between the esophageal temperature probe and the CB surface. Distances < 20 mm were significantly correlated with minimum LET ($R^2 = 0.36$; $P < .0001$). Eso = esophagus.

patient. In patients with recurrent AF/AT who did not undergo a redo procedure, symptoms were well controlled with β-blocker or antiarrhythmic drug treatment.

In patients with persistent PN palsy, repeat chest fluoroscopy demonstrated complete restitution of PN function after 10 ± 1 months. No additional complication occurred during follow-up.

Discussion

The main results of the study are as follows: (1) LET-guided CB-PVI using the CB2 significantly reduced the incidence of thermal esophageal lesions. (2) A LET cutoff of 15°C was associated with the lowest incidence of esophageal lesions (1.5%). (3) EFI due to low LET did not affect the procedural end point of complete PVI. (4) At mid-term follow-up, clinical success was comparable to that observed in previously published studies without LET guidance.

AEF is a rare but catastrophic complication observed after PVI using various energy sources.[12] As of today, 5 cases of AEF after CB-PVI have been described in the literature: 3 cases with the CB1[9,10] and 2 cases with the CB2.[8,9] During all reported cases, continuous LET measurement was not, or could not, be performed because of temperature probe design or malfunction.[8–10]

Systematic postprocedural esophagoscopy results after CB-PVI have been reported in 3 studies using the CB1[13–15] and 2 studies using the CB2.[11,16] Collectively, these studies reported esophageal ulcerations in 6 of 116 (5.2%) and 11 of 82 (13.4%) patients, respectively. Among the 4 studies involving a 28-mm-balloon-only strategy, ulcerations were found in the 2 studies using the CB2,[11,16] but not in the studies using the CB1.[14,15] The higher incidence of esophageal ulcerations reported after PVI using the CB2 likely results from increased surface cooling of the 28 mm CB2.[17] Although the exact pathogenesis of AEF formation after cryoablation is unknown, it seems prudent to avoid endoscopically detectable damage of the esophagus. The present study demonstrates that LET measurement using a 15°C cutoff is a simple tool to significantly reduce the rate of this complication.

We set the target ablation time to 4 minutes,[4,6,7] a value that has been reported to be associated with improved clinical efficacy, as compared with 5-minute freezes using the CB1.[5,7] LET-guided CB-PVI reduced the application time to a mean of 180 and 164 seconds (12 and 15°C cutoff, respectively) at a single PV in patients with EFI. This did not result in a lower mid-term success rate compared with that observed in previously published studies without LET guidance.[4,5,7] The ideal application time using the novel CB2 is still under debate. In a canine model of CB2-PVI, the mean lesion depth was not different when comparing 2-minute with 4-minute ablation time.[18] In our study, EFI was performed in 3 patients (4%) within 2 minutes of freezing.

In the group of patients with a prespecified LET cutoff of 15°C, we observed 1 esophageal ulceration in a patient associated with a minimum LET of 16.2°C. This may be due to the interindividual variation in LET to predict lesions or, more probably, due to the limitation of LET measurement with a probe that can be longitudinally, but not transversally, adjusted to the balloon position. A multisensor probe with a sinusoidal shape has been investigated in the context of PVI using radiofrequency current ablation[19]; however, compared with a single-sensor probe, the use of a multisensor probe was associated with an increased incidence of esophageal lesions, possibly by increasing the width of the esophagus in contact with the left atrium.[19] Notwithstanding, we were able to demonstrate a high longitudinal LET gradient (>14°C/cm) during freezing, underlining the importance of multiple sensors in a longitudinal arrangement to identify the minimum LET.

Analogous to findings in the evaluation study,[11] minimum balloon temperature had no effect on minimum LET during LET-guided CB2-PVI. The analysis of the balloon-to-temperature probe distance revealed a linear correlation with minimum LET at distances ≤20 mm in both fluoroscopic planes (right anterior oblique 30° and left anterior oblique 40°). This result may help in identifying balloon positions at risk of LET decrease before the initiation of freezing. Careful alignment of the thermocouple(s) is therefore increasingly important at close distances to the balloon.

Study limitations

We investigated consecutive patients and the limitations of a nonrandomized design pertain to this study. However, in studies investigating esophageal lesions after CB-PVI, no effect of a learning curve has been found[11,13–16] and all operators were well trained in CB ablation at the beginning of the study. Esophageal endoscopy was performed within 3 days of the procedure. Therefore, we cannot exclude later lesion formation. Mechanical lesions by transesophageal echocardiography or temperature probe placement cannot be excluded; however, lesions were found in the retrocardiac area associated with low LET. Luminal temperature is only an approximation of temperatures in the outer esophageal layers, which are closer to the cryothermal source. It is currently not known whether endoscopically visual lesions precede AEF formation. However, because of the low incidence of this serious complication, surrogate lesions provide a basis for systematic research of CB-induced esophageal damage. Active deflation of the CB upon freezing interruption, that is, bypassing automatic deflation at 20°C balloon temperature, has been associated with a shorter thawing phase.[20] This technique could possibly have further decreased the incidence of lesions.

Conclusion

LET-guided CB-PVI using the CB2 significantly reduced the incidence of thermal esophageal lesions. Interrupting cryoablation at 15°C LET was associated with the lowest incidence of esophageal injury.

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CLINICAL PERSPECTIVES

Cryoballoon pulmonary vein isolation using the second-generation cryoballoon (CB2; Arctic Front Advance, 28 mm, Medtronic, Inc, Minneapolis, MN) has been associated with improved procedural and clinical performance but may lead to esophageal ulcerations demonstrated by postprocedural endoscopy. This is the first study to show a significant reduction in esophageal lesion formation by luminal esophageal temperature (LET)–guided CB2 ablation compared with observational LET measurement. Interrupting cryoablation at a LET value of 15°C was associated with the lowest incidence of esophageal injury. At mid-term follow-up (mean 9 months), 87% of patients were free from recurrent atrial fibrillation or atrial tachycardia, which is comparable to the published success rates of CB2 pulmonary vein isolation without LET guidance. We provide evidence that LET-guided pulmonary vein isolation improves the safety of cryoballoon ablation by reducing collateral injury of the esophagus. We therefore suggest the routine use of an esophageal temperature probe during second-generation cryoballoon ablation.

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Incidence and characteristics of phrenic nerve palsy following pulmonary vein isolation with the second-generation as compared with the first-generation cryoballoon in 360 consecutive patients

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Aims The second-generation cryoballoon (CB2) with increased surface cooling has recently become available. The aim was to investigate the incidence and characteristics of phrenic nerve palsy (PNP) during pulmonary vein isolation (PVI) using the CB2 as compared with the first-generation balloon (CB1).

Methods and results A total of 360 consecutive patients with atrial fibrillation underwent PVI with the CB1 (106 patients) or the CB2 (254 patients). Right PN function was monitored by continuous stimulation and palpation during septal PV ablation. Persistent PNP (present at discharge) occurred in 2.8 and 1.9% ($P = 0.63$) of patients, transient PNP (full recovery before discharge) in 5.9 and 3.8% ($P = 0.41$) of patients in the CB2 and CB1 group, respectively. Phrenic nerve palsy during ablation at the right inferior PV was observed in 0% (CB1) and 4.3% (CB2, $P = 0.03$) of patients. Using the CB2, a trend of reduced incidence of persistent PNP over quartiles of consecutive patients was observed [4.8% (Q1) vs. 0% (Q4); $P = 0.077$]. At the culprit PV, PNP occurred after 3.5 $\pm$ 2.1 (CB1) and 1.1 $\pm$ 0.4 applications (CB2; $P = 0.036$). Complete recovery of PN function occurred after 29 $\pm$ 11 (CB1) and 259 $\pm$ 137 days (CB2; $P = 0.004$).

Conclusions The rate of transient/persistent PNP associated with the use of the CB2 was 5.9 and 2.8%, respectively. Time to restitution of PN function was longer using the CB2.

Keywords Ablation • Arrhythmia • Atrial fibrillation • Balloon • Phrenic nerve

Introduction

The cryoballoon technology is increasingly used to perform pulmonary vein isolation (PVI) due to a short learning curve[1] and comparable long-term clinical efficacy as described for radiofrequency current ablation.[2,3] Recently, the second-generation cryoballoon (CB2) has been introduced, featuring a homogeneous distribution and an increased flow of refrigerant in the 28 mm variety. This results in increased procedural and clinical efficacy compared with the first-generation balloon (CB1).[4–8] However, increased surface cooling may also affect collateral structures. A higher incidence of reversible oesophageal ulcerations has been described after PVI using the 28 mm CB2 compared with the CB1.[9,10] The most frequent complication associated with cryoballoon PVI is right-sided phrenic nerve palsy (PNP) due to the anatomical course of the phrenic nerve (PN) close to the ostium of the septal pulmonary veins (PVs). In a previous analysis, the use of the smaller 23 mm cryoballoon was associated with a significantly higher rate of PNP.[11] Here, we describe incidence and characteristics of PNP following PVI using the 28 mm CB2 compared with the 28 mm CB1 in a large group of patients.

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What's new?

- In the largest study involving cryoballoon ablation with the second-generation device (CB2) hitherto reported, there was no statistically significant increase in the incidence of phrenic nerve palsy (PNP) compared with the first-generation balloon (CB1).
- The time to restitution of persistent PNP was longer when using the CB2.
- PNP associated with the CB2 frequently occurred at the right inferior pulmonary vein, which is in contrast to the CB1.
- With increased experience and introduction of immediate balloon deflation upon temporary PNP, a trend towards decreased incidence of PNP was observed using the CB2.

Methods

Patients

A total of 360 consecutive patients undergoing cryoballoon PVI between May 2010 and May 2014 for paroxysmal or short-term persistent (<6 months) atrial fibrillation were studied; 106 patients were treated with the CB1 group, and starting from May 2012, 254 patients were treated with the CB2 group. Clinical baseline characteristics of the study patients are shown in *Table 1*.

Table 1 Clinical baseline characteristics

	CB1 group ($n = 106$)	CB2 group ($n = 254$)	*P* value
Age (years)	64 ± 11	64 ± 12	0.62
Male (%)	71	59	0.04
Persistent AF (%)	16	14	0.55
LA diameter (mm)	40 ± 4	40 ± 5	0.55
Hypertension (%)	63	72	0.08
Diabetes (%)	9	9	0.91
Stroke/Transient ischemic attack (%)	5	5	0.96
Heart failure (%)	8	3	0.04
Coronary artery disease (%)	10	20	0.01

Cryoballoon ablation

We previously described the technique of cryoballoon PVI (28 mm, Arctic Front or Arctic Front Advance, Medtronic, Inc., 710 Medtronic Parkway, Minneapolis, MN, USA).[4,12] After transseptal access, selective PV angiographies were performed. If the angiographically defined ostial diameter of any septal PV in right anterior oblique (RAO) 30° projection was ≥26 mm, the patient was excluded from CB-based PVI and PVI was performed by radiofrequency current ablation. Pulmonary vein mapping was performed before, during, and after freezing with an endoluminal spiral mapping catheter (Achieve, Medtronic). We aimed for complete PV occlusion before initiating freezing. Balloon positions distal to the angiographically defined PV ostium were strictly avoided. Target application time was 300 s using CB1 and 240 s using CB2. The standard sequence of isolation was left superior PV(LSPV) – left inferior PV (LIPV) – right superior PV (RSPV) – right inferior PV (RIPV). In a subset of patients luminal oesophageal temperature was measured. In general, one bonus application was performed for each PV after successful PVI, unless PN or oesophageal temperature monitoring led to freezing interruption. In 31 patients in the CB2 group, the bonus application was omitted due to participation in a prospective study (ICE-Trial, DRKS-ID: DRKS00004937). The procedural endpoint was absence or dissociation of all PV potentials as confirmed by the endoluminal spiral catheter. The right phrenic nerve was paced from the superior caval vein during freezing at the septal PVs (12 V, 2.9 ms, and 1000 ms interval). Diaphragmatic contractions were palpated by hand. In case of cessation or weakening of diaphragm contractions, freezing was stopped by initiating the thawing phase, which is followed by automatic deflation at a balloon temperature of 20°C. Due to the report of Ghosh *et al.*[13] demonstrating safety and efficacy of immediate balloon deflation to prevent persistent PNP, this technique was systematically performed starting with patient 178 of the CB2 group. No further balloon application was applied to the culprit PV. Transient PNP was defined as weakening/loss of hemi-diaphragmatic motion with full recovery until discharge as demonstrated by chest fluoroscopy. Persistent PNP was defined as weakening/loss of hemi-diaphragmatic motion present at discharge. The ostial PV diameter was measured from selective PV angiographies in RAO 30° for septal PVs and left anterior oblique 40° for lateral PVs.

Post-procedural care

All patients underwent transthoracic echocardiography to rule out pericardial effusion after the procedure. Unless patients were on therapeutic phenprocoumon, low-molecular weight heparin (LMWH) was administered 6 h after ablation. Phenprocoumon (with overlapping LMWH if the international normalized ratio was <2), or dabigatran, or rivaroxaban was re-started according to the previous regimen and prescribed for at least 2 months. A proton pump inhibitor was administered for 2 weeks starting on the day of the procedure. Patients with persistent PNP were scheduled for chest fluoroscopy after 4 weeks and every 3 months thereafter until complete resolution of PNP was observed.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation and analysed with Student's *t*-test. Nominal variables were expressed as frequencies and proportions and analysed with the χ^2 test. A two-sided value of $P < 0.05$ was considered statistically significant.

Results

Cryoballoon ablation

Procedural data of cryoballoon PVI in both groups are shown in *Table 2*. In the CB1 group, the circular mapping catheter had to be switched to a stiff guidewire in two patients to achieve isolation. Complete PVI was achieved in 103 of 106 (97%) patients using only the CB1. In two patients touch-up lesions with an irrigated radiofrequency catheter were performed to ablate remaining conduction gaps at the RIPV and LIPV, respectively. In one patient, the RIPV could not be isolated despite five CB applications and no touch-up ablation was performed.

In the CB2 group, complete PVI was achieved using only the CB2 in 252 of 254 patients (99%). In one patient, transient PNP was observed during freezing at the RIPV, mandating early interruption after 156 s, at which time the RIPV was not isolated. No additional cryoablation

was applied to that PV. In the other patient, a left common PV could not be isolated after four CB applications and no further attempt was made to isolate the PV.

Phrenic nerve palsy

In total, PNP occurred in 22 of 254 (8.7%) patients in the CB2 group and 6 of 106 (5.7%) patients in the CB1 group ($P = 0.25$). Procedural and clinical characteristics of the patients with PNP are detailed in *Table 3*. Persistent PNP occurred in seven (2.8%) and two (1.9%) patients in the CB2 and CB1 groups, respectively ($P = 0.63$). Transient PNP occurred in 15 (5.9%) and 4 (3.8%) patients in the CB2 and CB1 groups, respectively ($P = 0.41$). Phrenic nerve palsy occurred exclusively during freezing at the RSPV in the CB1 group, while in 11 patients (4.3%) of the CB2 group, Phrenic nerve palsy occurred during freezing at the RIPV ($P = 0.03$). One patient in the CB2 group developed delayed left-sided PNP 1 day after the procedure with unimpaired intra-procedural PN function.

A subgroup analysis was performed analysing the incidence of PNP in the 31 patients of the CB2 group, in whom a systematic bonus freeze was not performed after PVI was achieved. In this subgroup, one persistent and one transient PNP was observed (patients 123 and 237, respectively; *Table 3*). When compared with the remaining 223 patients in the CB2 group, there was no statistically significant difference in the incidence of persistent (3.2 vs. 2.7%; $P = 0.87$) or transient (3.2 vs. 6.3%; $P = 0.50$) PNP.

The ostial diameter of the culprit PV was 18.5 ± 2.4 and 17.5 ± 4.6 ($P = 0.42$) in the CB1 and CB2 groups, respectively. The time to PNP did not differ between the two groups: 226 ± 92 (CB1) and 177 ± 56 (CB2) seconds ($P = 0.26$). In the CB1 group, PNP occurred after repeat cryoablation at the culprit PV in the majority of patients, after a mean of 3.5 ± 2.1 applications. In contrast, PNP occurred at

Table 2 Procedural parameters

	CB1 ($n = 106$)	CB2 ($n = 254$)	*P* value
Procedure duration (min)	132 ± 31	88 ± 26	<0.001
Fluoroscopy exposure (min)	20.4 ± 9.0	14.4 ± 9.8	<0.001
Balloon applications	10.2 ± 2.0	7.5 ± 2.1	<0.001
Complete isolation using only balloon (%)	97	99	n.s.

Table 3 Clinical and procedural characteristics of patients with PNP

Patient	Group	PV	PV size (mm)	Appl.	Time (s)	Type	Days to restitution
26	CB1	RSPV	19	2	155	Transient	
31	CB1	RSPV	16	6	266	Transient	
37	CB1	RSPV	23	3	71	Persistent	36
44	CB1	RSPV	17	3	292	Persistent	21
66	CB1	RSPV	18	6	293	Transient	
106	CB1	RSPV	18	1	281	Transient	
2	CB2	RSPV	15	1	160	Transient	
11	CB2	–	–	–	–	Persistent left	483
20	CB2	RIPV	20	2	210	Transient	
39	CB2	RIPV	15	1	150	Persistent	251
53	CB2	RSPV	17	1	190	Transient	
57	CB2	RIPV	14	1	200	Persistent	170
67	CB2	RIPV	13	1	240	Transient	
80	CB2	RSPV	23	1	160	Transient	
85	CB2	RIPV	23	1	156	Transient	
86	CB2	RIPV	14	1	210	Persistent	36
103	CB2	RIPV	15	1	240	Transient	
104	CB2	RIPV	18	2	240	Persistent	283
123	CB2	RSPV	18	1	185	Persistent	314
140	CB2	RIPV	19	1	120	Persistent	279
163	CB2	RSPV	20	1	199	Transient	
167	CB2	RSPV	16	1	144	Transient	
172	CB2	RIPV	15	1	205	Transient	
178	CB2	RIPV	18	1	178	Transient	
188	CB2	RSPV	18	1	109	Transient	
223	CB2	RSPV	19	1	198	Transient	
237	CB2	RSPV	20	1	143	Transient	
239	CB2	RSPV	18	1	90	Transient	

the first application in the majority of patients in the CB2 group (1.1 ± 0.4, $P = 0.036$ vs. CB1 group).

We investigated the influence of cumulative cases performed on the incidence of transient and/or persistent PNP by dividing the patient cohort in quartiles stratified by the use of CB1 or CB2 (*Figure 1*). Cumulative cases performed had no influence on the occurrence of transient/persistent PNP using the CB1 (*Figure 1*). Using the CB2, there was a trend of reduced incidence of persistent PNP with increasing case numbers [4.8% (Q1) vs. 0% (Q4); $P = 0.077$], while there was no influence on transient PNP [4.8% (Q1) vs. 4.7% (Q4); $P = 0.98$; *Figure 1*]. In the five patients of the CB2 group (two in quartile 3 and three in quartile 4) in whom immediate balloon deflation was performed upon transient PN injury, persistent PNP did not occur.

Follow-up

In the CB1 group, two patients with persistent PNP demonstrated complete recovery of PN function after 29 ± 11 days (*Table 2*). In the CB2 group, seven patients with persistent PNP demonstrated complete recovery after a mean of 259 ± 137 days (*Table 2*; $P = 0.004$ vs. CB1 group). In three patients of the CB2 group, freedom of symptoms occurred at a stage of partial PN functional restitution after 4 ± 3 months (4 ± 1 months before full recovery demonstrated by fluoroscopy).

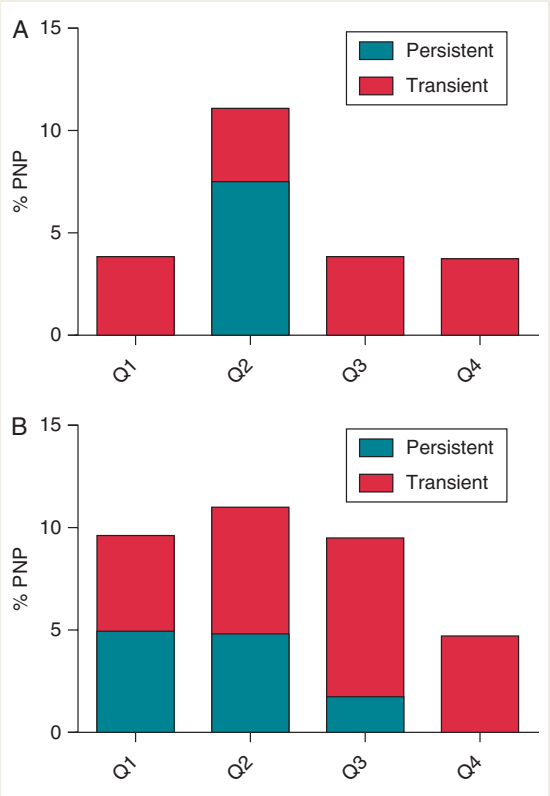

Figure 1 Incidence of transient/persistent PNP over quartiles of consecutively treated patients. (*A*) Patients treated with the first-generation cryoballoon. (*B*) Patients treated with the second-generation cryoballoon.

Discussion

To the best of our knowledge, this is the largest study investigating the incidence of PNP associated with cryoballoon ablation using the CB2. The main findings are as follows: (i) The incidence of transient and persistent PNP using the CB2 in 254 patients was 5.9 and 2.8%, respectively. (ii) The time to restitution of PN function was longer using the CB2 when compared with the CB1. (iii) In contrast to the CB1 group, PNP using the CB2 frequently occurred during freezing at the RIPV.

Prior studies

In previous studies of CB-PVI with the CB1, utilizing the 23 mm balloon was reported to be associated with a higher incidence of PNP.[11,14] This probably results from a relatively distal position of the smaller balloon at the PV ostium, and hence closer proximity to the PN. Regarding previous studies utilizing a 28 mm cryoballoon-only strategy, Kojodjojo *et al.*[15] reported a 1.6% incidence of persistent PNP after PVI with the CB1, which is in the magnitude of our findings. Casado-Arroyo *et al.*[16] reported on the incidence of PNP in 80 and 41 patients treated with the CB1 and CB2, respectively. A 6.3% (all transient) and 19.5% (persistent: 7%) incidence of PNP associated with CB1 and CB2 ablation, respectively, has been found. Martins *et al.*[17] investigated 66 and 81 patients treated with the CB1 and CB2, respectively. Only transient PNP was observed at a rate of 10.6% (CB1) vs. 24.4% (CB2). Metzner *et al.*[18] investigated 115 patients using the CB2. Only persistent PNP was observed at a rate of 3.5%. The reasons for these diverse results are not clear, but may involve: (i) Two of the prior studies included relatively few patients. (ii) Only Martins *et al.*[17] reported the systematic use of combined immediate stop of freezing and balloon deflation upon PN injury in all patients. (iii) Occurrence of PNP clustered in the initial patients treated with the CB2 in the study by Casado-Arroyo *et al.*,[16] suggesting an influence of ablation technique, which the authors subsequently changed by accepting non-occlusive balloon positions at the beginning of freezing. In our study, the cryoballoon technique was not changed and we always aimed for complete occlusion at the time of freezing initiation. However, we strictly observed an antral position of the balloon avoiding inflation/ablation within the PV. Despite this, we observed a trend in reduced incidence of persistent PNP with increasing case numbers using the CB2 (*Figure 1*). The most probable reason for this observation is the introduction of immediate balloon deflation upon PN injury[13] starting with patient 178. In addition, increased alertness for possible PN injury at the RIPV position may have resulted in intervention in the reversible phase.

Characteristics of cryoballoon-induced phrenic nerve palsy

In an experimental model of cryoballoon-induced PN injury, histopathological analysis showed Wallerian degeneration characterized by loss of large myelinated axons in a subperineural distribution, with the majority of animals showing signs of neuro-regeneration at 30 days.[19] In the current study, restitution of PN function typically took the course of progressive inspiratory caudal motion of the

right hemi-diaphragm during repeat fluoroscopy. This led to relief of symptoms before complete restitution in a subset of patients after an average of 4 months. Due to its anatomical course close to the septal PVs, CB-induced PN injury occurs almost exclusively on the right side. We observed one case of delayed left-sided PNP evident 24 h after the procedure. This patient had a left subclavian vein access for coronary sinus catheter placement. Since PN injury has been described as a complication of left subclavian vein puncture,[20,21] this mode of injury cannot be excluded. However, left-sided intra-procedural, but not delayed, PNP associated with CB-PVI has been reported.[22]

Clinical implications

In this retrospective analysis, we did not find a significant difference in the rate of PNP between the first- and second-generation devices. However, a longer time to restitution of PN function, PN injury predominantly following a single application and frequent PNP occurrence at the RIPV, which is in general located more distant to the course of the right PN than the RSPV, together may indicate a higher propensity for PN damage by the CB2 due to an enlarged volume of tissue freezing. An increased incidence of PNP during freezing at the RIPV using the CB2 compared with the CB1 was also observed in the study by Casado-Arroyo *et al.*[16] In this regard, the sequence of balloon positions may have an influence. Due to our standard approach, the RSPV was isolated before the RIPV. It may be speculated that in some cases an initially subclinical damage to the right PN (while freezing at the RSPV) may have become clinically overt by cumulative PN damage during freezing at the RIPV. The optimal time of freezing using the CB2 has to be still determined. In a prior experimental study of PVI using the CB2, no histopathological difference in the rate of circumferential transmural lesions has been found between 4 and 2 min of freezing time.[23] Studies in humans comparing different ablation times are ongoing. Of note, in this study only 4 of 28 (14%) PN injuries occurred after 120 s.

Limitations

The limitations of a retrospective analysis pertain to this study. An increased number of patients per group may have resulted in a difference in PNP incidence between the treatment groups within the level of significance. Phrenic nerve function was monitored by palpation. Measuring diaphragmatic electromyograms (compound motor action potential) may provide a more sensitive method to detect PN injury.[24]

Conclusion

The rate of transient/persistent PNP associated with the use of the CB2 was 5.9 and 2.8%, respectively. Time to restitution of PN function was longer using the CB2.

Conflict of interest: A.F., B.S., S.B., and K.R.J.C. received honoraria payment for Medtronic educational lectures; A.F. received congress travel support from Medtronic. All other authors have received none.

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