## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | A Randomized Clinical Trial of Cryoballoon vs. Irrigated Radiofrequency Catheter Ablation for Atrial Fibrillation: The effect of Double Short vs. Standard Exposure Cryoablation Duration During Pulmonary Vein Isolation (CIRCA-DOSE) - Methods and Rationale |
| **AUTHORS** | Andrade, Jason; Deyell, Marc; Badra, Mariano; Champagne, Jean; Dubuc, Marc; Leong-Sit, Peter; Macle, Laurent; Novak, Paul; Roux, Jean-Francois; Sapp, John; Tang, Anthony; Verma, Atul; Wells, George; Khairy, Paul |

## VERSION 1 – REVIEW

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| **REVIEWER** | Ugur Canpolat<br>Hacettepe University, Faculty of Medicine, Department of Cardiology, Ankara, Turkey |
| **REVIEW RETURNED** | 05-Jun-2017 |

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| **GENERAL COMMENTS** | The authors designed a well-organized study comparing 3 different ablation techniques (1 with RF vs other 2 with cryoballoon of different freezing time intervals). The methods have been defined clearly. I have some minor comments which have been included in the pdf format of the paper. Other than some grammar errors, I have an additional comment why the authors prefer to freeze 4 min rather than 3 min compared to 2 min group? Besides efficacy outcomes, what about the safety outcomes of the study? Please comment in the paper appropriately. |

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| **REVIEWER** | Giuseppe Ciconte<br>IRCCS Policlinico San Donato<br>San Donato Milanese, Milano, Italy |
| **REVIEW RETURNED** | 08-Jun-2017 |

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| **GENERAL COMMENTS** | The Authors describe the protocol of the CIRCA DOSE study which has been designed to evaluate the effectiveness of contact force catheter ablation (CFCA) vs second generation cryoballoon ablation.<br><br>The methodology is clear, well written and highlights some interesting points, representing the strength of the protocol: use of implantable cardiac monitors, sample size, statistical consideration and pre-clinical background.<br><br>- Regarding CF PVI group, I have no comments on this topic as it is clear and well designed. |

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| | - Regarding CB ablation I have some questions:<br><br>1. Some of the authors of this protocol have demonstrated the absence of differences in terms of PVI and transmurality of the lesion in the canine model among a 4 and 2 minutes freeze. However, I think it might be too early to propose the 2 minutes strategy per vein followed by an insurance freeze for every patient, without testing the 3 minutes strategy at all.<br>2. In addition, considering that a single freeze approach has been consistently reported as safe and effective as well as the double freeze strategy, I suggest to evaluate the opportunity to modify one of the group to a single freeze strategy, as both of the CB group will receive an insurance freeze even after a successful PVI with the first freeze.<br><br>Minor comment:<br>- Definition of arrhythmic recurrence: Are we sure that 30 or 120 seconds are the correct limit to evaluate a clinical success following ablation? Relatively recent studies demonstrate that AF episodes >5 minutes (measured using pacemakers) are related to cerebrovascular events.<br>Perhaps it might be the time to set another limit or to evaluate AF recurrences in terms of arrhythmia burden. Please comment. |

**VERSION 1 – AUTHOR RESPONSE**

Reviewer One
Comment:
Why the authors prefer to freeze 4 min rather than 3 min compared to 2 min group?

Response:
We thank the reviewer for their comment. At the time of study conception and grant submission the standard of care for cryofocal and cryoballoon ablation was to utilise 4 minute freezes. While discussions regarding the utility of three minute freezes were active in the cryoballoon ablation community, we did not feel the evidence base was mature enough to justify the use of three-minute freeze durations as the comparator group. It is for this reason that we used the four-minute freeze duration as our comparator.

Comment:
However, we do recognise that he landscape has changed as the evidence base on freeze durations has matured. Since our study was conceived and initiated several studies have evaluated the clinical utility of the three-minute freeze duration. While these non-randomised studies have demonstrated comparable clinical efficacy to longer 4-minute freeze durations it is our understanding that the prospective randomised multicenter pilot study on 3-minute freeze durations is ongoing (The Short Freeze study).

Response:
We have included the following on Page 7, Paragraph 3 – “Information regarding the safety and efficacy of shorter cryoballoon ablation durations are limited to 3 minute lesions, which have been suggested in several non-randomised studies to be of comparable efficacy to longer duration cryolesions.(Ciconte, Sieira-Moret et al. 2016, Miyazaki, Hachiya et al. 2016)”

Comment:
Besides efficacy outcomes, what about the safety outcomes of the study? Please comment in the paper appropriately.

Response:
We thank the reviewer for their observation. We had previously included a discussion on the safety benefits of cryoballoon ablation and shorter freezing durations. Specifically, we highlighted the theoretical benefits of cryothermy (1. freeze-mediated catheter adhesion resulting in less collateral damage to nearby structures, such as the PVs or esophagus; 2. the preservation of tissue ultrastructural integrity resulting in a lower risk of acute myocardial perforation and esophageal injury, as well as a lower incidence of late PV stenosis; 3. The minimal endocardial surface disruption associated with cryothermal ablation is less thrombogenic than those produced with RF energy; 4. The observation that cryoablation appears to activate platelets and the coagulation cascade to a lesser degree than RF ablation. As such, cryoablation is thought to be associated with a lower risk of thromboembolism, and post-procedural ischemic cerebral lesions. However, we felt it best to omit this discussion as the majority of perceived benefit is theoretical rather than definitively established. Specifically, other comparative trials of RF and cryoablation (the cited Jourda et al., Squara et al., Ciconte et al. and the recently published “Fire and Ice”) have not conclusively demonstrated significant benefit or harm with either technology.

Comment:
The evidence gap is even more prominent in the case of cryoablation freeze duration, where the majority of studies are either animal studies or retrospective single centre cohorts. In our previous pre-clinical animal model, we observed a reduction in late PV strictures in the 2 minute group (6/30 PVs with strictures in the 4-minute freeze duration vs. 0/29 PVs with strictures in the 2-minute freeze duration; p=0.024). Thus, while we feel this serves as a preliminary justification that shorter ablation durations with contemporary cryoballoon ablation systems may be safer, we felt the totality of information regarding the safety of shorter cryoablation durations are limited.

Response:
In response we have added the following statements regarding safety to the manuscript text.

Comment:
Page 6, Paragraph 2 – “While none of these studies demonstrated a significant difference in the incidence of complications a recent meta-analysis observed a lower incidence of pericardial effusion (OR 0.44; 95%CI 0.28-0.69; P<0.01) and tamponade (OR 0.31; 95%CI 0.15-0.64; P<0.01) with cryoballoon ablation in comparison to contact-force guided RF ablation, whereas transient phrenic nerve palsy was more frequent after cryoballoon (OR 7.40; 95%CI 2.56–21.34; P<0.01).(Cardoso, Mendirichaga et al. 2016)”
Page 8, paragraph 1 – “Although 4-minute lesions were associated with a thicker neointima than 2-minute lesions (223.8μm vs. 135.6μm; p=0.007), no differences were observed in the rates of procedural PVI, or the achievement of complete circumferentially transmural lesions at 30 days (78% overall; 86.2% for 2-min vs. 70% for 4-min; P=0.285). However, a reduction in late PV strictures was observed in the 2 minute group (6/30 PVs with strictures in the 4-minute freeze duration vs. 0/29 PVs with strictures in the 2-minute freeze duration; p=0.024).”

Reviewer Two:

Comment:
Some of the authors of this protocol have demonstrated the absence of differences in terms of PVI and transmurality of the lesion in the canine model among a 4 and 2 minutes freeze. However, I think it might be too early to propose the 2 minutes strategy per vein followed by an insurance freeze for every patient, without testing the 3 minutes strategy at all.
a. We thank the reviewer for their comment. As outlined above, we conceived this study several years ago. At the time of study conception and grant submission, the standard of care for both cryofocal and cryoballoon ablation was a 4-minute freeze duration. While discussions regarding the utility of three minute freezes were active in the cryoballoon ablation community, we did not feel the evidence base was mature enough to justify the use of three-minute freeze durations as the comparator group. Conversely, we felt that the emerging non-randomised evidence (such as those subsequently published by the reviewer) as well as the prospective randomised multicenter pilot “Short Freeze” study limited the use of the 3-minute freeze duration in the experimental group.

Response:
As such, we designed our study based on previous work our group conducted on focal and cryoballoon ablation:
• “In these studies, it was observed that the effect of a cryoablation lesion reached a plateau of three-minutes after the onset of ablation. Thereafter prolongation of exposure time beyond 3 minutes did not result in any further increase in lesion dimension or volume.”(Dubuc, Talajic et al. 1998, Dubuc, Roy et al. 1999);
• “PVI procedures were randomized to a single 2-minute vs. 4-minute cryoballoon application. Although 4-minute lesions were associated with a thicker neointima than 2-minute lesions (223.8μm vs. 135.6μm; p=0.007), no differences were observed in the rates of procedural PVI, or the achievement of complete circumferentially transmural lesions at 30 days (78% overall; 86.2% for 2-min vs. 70% for 4-min; P=0.285), however a reduction in late PV strictures was observed in the 2 minute group (6/30 PVs with strictures in the 4-minute freeze duration vs. 0/29 PVs with strictures in the 2-minute freeze duration; p=0.024)”(Andrade, Dubuc et al. 2013);
• With the focal cryocatheter: “Single 2-minute and 4-minute application times result in catheter ablation lesions of similar size using the modern cryoablation system with nitrous oxide as a refrigerant.”(Bessiere, Dubuc et al. 2017)

Comment:
In addition, considering that a single freeze approach has been consistently reported as safe and effective as well as the double freeze strategy, I suggest to evaluate the opportunity to modify one of the group to a single freeze strategy, as both of the CB group will receive an insurance freeze even after a successful PVI with the first freeze.

Response:
We thank the reviewer for their comment. Similar to the discussion regarding 3-minute freeze duration, we did not feel that the evidence supporting a single freeze approach was mature enough at the time of study conception and grant submission. As such we opted to modify only the freeze duration and retain the concept of insurance freeze. Unfortunately, the study has already enrolled patients and a modification to the protocol of this nature is not feasible.

Comment:
Definition of arrhythmic recurrence: Are we sure that 30 or 120 seconds are the correct limit to evaluate a clinical success following ablation? Relatively recent studies demonstrate that AF episodes >5 minutes (measured using pacemakers) are related to cerebrovascular events. Perhaps it might be the time to set another limit or to evaluate AF recurrences in terms of arrhythmia burden. Please comment.

Response:
We thank the reviewer for their comment, and we wholeheartedly agree with the sentiment. The steering committee spent a considerable amount of time debating the relative merits of the various definitions of arrhythmia recurrence. While we do not entirely agree that the “30 second cut-off” is necessarily an important clinical endpoint, we deemed it sensible to adhere to international recommendations on the conduct of clinical trials provided by an HRS consensus statement that defines arrhythmia recurrence as “AF/AFL/AT of at least 30 s duration that is documented by an ECG or device recording system and occurs following catheter ablation.”(Calkins, Kuck et al. 2012)

While the “primary end point and the 3-month blanking period adhere to the Heart Rhythm Society recommendations for reporting outcomes in AF ablation trials”(Calkins, Kuck et al. 2012), we structured secondary endpoints and planned analyses around other clinically meaningful outcomes such as AF Burden, and quality of life (listed in the supplemental appendix Table 4). It is our intention to use the evidence derived in this trial to question the utility of the current definition of arrhythmia recurrence.

REFERENCES
Andrade, J. G., et al. (2013). "Pulmonary vein isolation using a second-generation cryoballoon catheter: a randomized comparison of ablation duration and method of deflation." J Cardiovasc Electrophysiol 24(6): 692-698.

**VERSION 2 – REVIEW**

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| **REVIEWER** | Ugur Canpolat<br>Hacettepe University Faculty of Medicine, Department of Cardiology, Ankara, Turkey |
| **REVIEW RETURNED** | 12-Jul-2017 |

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| **GENERAL COMMENTS** | Thanks to authors for their revision, I have no further comments. |

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| **REVIEWER** | Giuseppe Ciconte<br>Department of Electrophysiology and Cardiac Pacing<br>IRCCS Policlinico San Donato<br>San Donato Milanese, Milano, Italy |
| **REVIEW RETURNED** | 08-Jul-2017 |

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| **GENERAL COMMENTS** | The authors have adequately replied to my comments. |