ONLINE FIRST

This is a provisional PDF only. Copyedited and fully formatted version will be made available soon.

CARDIOLOGY JOURNAL

ISSN: 1897-5593

e-ISSN: 1898-018X

Time to –30°C as a predictor of acute success during cryoablation in patients with atrial fibrillation

Authors: Carlos Antonio Álvarez-Ortega, Miguel Angel Ruiz, César Solórzano-Guillén, Alberto Barrera, Jorge Toquero-Ramos, Jesús Daniel Martínez-Alday, Carlos Grande, José M. Segura, Arcadio García-Alberola, Pablo Moriña-Vázquez, Ángel Ferrero-de-Loma-Osorio, Roger Villuendas, Cózar Rocío, Maria Fe Arcocha, Alicia Ibañez, Rafael Peinado

DOI: 10.5603/CJ.a2021.0135

Article type: Original Article

Submitted: 2021-06-29

Accepted: 2021-09-30

Published online: 2021-10-25

Time to –30°C as a predictor of acute success during cryoablation in patients with atrial fibrillation

Carlos Antonio Álvarez-Ortega et al., Time to –30°C predictor AF cryoablation

Carlos Antonio Álvarez-Ortega[1, 2], Miguel Angel Ruiz[3], César Solórzano-Guillén[1], Alberto Barrera[4], Jorge Toquero-Ramos[5], Jesús Daniel Martínez-Alday[6, 7], Carlos Grande[8], José M. Segura[9], Arcadio García-Alberola[10], Pablo Moriña-Vázquez[11], Ángel Ferrero-de-Loma-Osorio[12, 13], Roger Villuendas[14], Cózar Rocío[15, 16], Maria Fe Arcocha[17], Alicia Ibañez[18], Rafael Peinado[1]

[1]Arrhythmia Unit, Cardiology Department, University Hospital La Paz, Madrid, Spain

[2]Cardiology Department, University Hospital Torrejón, Spain

[3]School of Psychology, Universidad Autónoma de Madrid, Spain

[4]Hospital Clínico Universitario, Virgen de la Victoria, Málaga, Spain

[5]University Hospital Puerta de Hierro, Majadahonda, Madrid, Spain

[6]Basurto University Hospital, Bilbao, Spain

[7]Clínica IMQ Zorrotzaurre, Bilbao, Spain

[8]Hospital Universitario Son Espases, Palma, Spain

[9]Córdoba Hospital Universitario Reina Sofía, Córdoba, Spain

[10]Department of Cardiology, Hospital Universitario Virgen de la Arrixaca, Murcia, Spain

[11]Juan Ramón Jiménez Hospital, Huelva, Spain

[12]Hospital Clínico Universitario de Valencia, Valencia, Spain

[13]Hospital Quiron Valencia, Valencia, Spain

[14]Hospital Universitario Germans Trias i Pujol, Badalona, Spain

[15]Hospital Universitario Virgen Macarena, Sevilla, Spain

[16]Hospital Nisa Aljarafe, Sevilla, Spain

[17]Araba Hospital, Vitoria, Spain

[18]Alicante University Genaral Hospital, Alicante, Spain

Address for correspondence: Carlos Antonio Álvarez-Ortega, Arrhythmia Unit, Cardiology Department, Hospital Universitario La Paz, Instituto de Investigación Hospital Universitario La Paz (IdiPAZ), Paseo de la Castellana 261. 28046 Madrid. Spain, tel: +34 912 071 775, e-mail: calvarezo@gmail.com

Abstract

Background: Freezing rate of second-generation cryoballoon (CB) is a biophysical parameter that could assist pulmonary vein isolation. The aim of this study is to assess freezing rate (time to reach –30°C ([TT-30C]) as an early predictor of acute pulmonary vein isolation using the CB.

Methods: Biophysical data from CB freeze applications within a multicenter, nation-wide CB ablation registry were gathered. Successful application (SA), was defined as achieving durable intraprocedural vein isolation with time to isolation in under 60 s (SA-TTI<60) as achieving durable vein isolation in under 60 s. Logistic regressions were performed and predictive models were built for the data set.

Results: 12,488 CB applications from 1,733 atrial fibrillation (AF) ablation procedures were included within 27 centers from a Spanish CB AF ablation registry. SA was achieved in 6,349 of 9,178 (69.2%) total freeze applications, and SA-TTI<60 was obtained in 2,673 of 4,784 (55.9%) freezes and electrogram monitoring was present. TT-30C was shorter in the SA group (33.4 ± 9.2 vs 39.3 ± 12.1 s; $p < 0.001$) and SA-TTI<60 group (31.8 ± 7.6 vs. 38.5 ± 11.5 s; $p < 0.001$). Also, a 10 s increase in TT-30C was associated with a 41% reduction in the odds for an SA (odds ratio [OR] 0.59; 95% confidence interval [CI] 0.56–0.63) and a 57% reduction in the odds for achieving SA-TTI<60 (OR 0.43; 95% CI 0.39–0.49), when corrected for electrogram visualization, vein position, and application order.

Conclusions: Time to reach –30°C is an early predictor of the quality of a CB application and can be used to guide the ablation procedure even in the absence of electrogram monitoring.

Key words: cryoballoon ablation, second-generation cryoballoon, atrial fibrillation, pulmonary vein isolation, atrial fibrillation ablation

Introduction

Pulmonary vein isolation (PVI) using a second generation cryoballoon (CB) catheter (Arctic Front Advance, Medtronic Inc.) has become a widespread procedure for the treatment of patients with atrial fibrillation (AF) [1, 2]. Two cryoballoon-specific procedural guidelines were published with practical recommendations on operator-controlled parameters for dosing and monitoring [3, 4]. Important parameters related to tissue injury and procedure efficacy are balloon-to-vein occlusion, freezing rate, balloon nadir temperature (NT), visibility of vein potentials and real-time isolation monitoring, balloon thawing time, and total freezing time. Studies have observed that a longer time-to-isolation (TTI) during a freeze is a predictor of vein reconnection during follow-up [5–7], and a target of a TTI in under 60 s (TTI<60) is recommended [4]. A more specific evaluation determined that the time to reach –40°C balloon temperature (when longer than 60 s) is an independent multivariate predictor of vein reconnection [5]. Furthermore, the CIRCA-DOSE trial protocol recommends to stop an application after 60 s of freezing if no vein isolation is achieved or the CB has not reached –35°C [8]. Notably, the time to reach –30°C (TT-30C) is a parameter that indicates the rate of freezing and is potentially related to the quality of occlusion and vein reconnection [9]. Thus, the aim of this study was to assess if TT-30C could predict, at early stages, the quality of an application and guide decisions regarding it.

Methods

Study design

The Spanish Registry of Cryoballoon Ablation (RECABA) (NCT02785991) is a prospective registry used to monitor the treatment of patients with AF when undergoing a CB catheter ablation. This RECABA registry included 1,745 patients at 27 centers in Spain, from September 2016 to January 2019. Each center selected patients with an indication of AF ablation and followed their local CB ablation practice(s). The study protocol was validated by local ethics committees, and patients signed an informed consent upon inclusion. The study followed the general principles outlined in the Declaration of Helsinki. There were no predefined target ablation parameters nor established cryoablation dose(s) per application. The acute intraprocedural efficacy endpoint was the isolation of all pulmonary veins (PVs). Procedures were performed using an Arctic Front Advanced CB (Medtronic, Inc.), and only 28-mm cryoballoon procedures were included in this analysis (n = 1,733).

Cryoballoon ablation

The descriptions of a CB ablation have been previously described in detail [1, 2]. During the RECABA collection each center used their own standard-of-care practices during the procedure. In general, subjects were sedated by either general anesthesia or conscious sedation. A transseptal needle puncture for left atrial access was immediately followed by heparin bolus delivery. Subsequent heparin delivery was administered while monitoring activated clotting time. A purpose-built dedicated delivery sheath (FlexCath or FlexCath Advance; Medtronic, Inc.) was used to advance the CB catheter during the procedure. Cryoablations were conducted with a 28-mm CB which was delivered by an over-a-wire method in the left atrium. Freeze applications and length of individual freezes were determined by the center's standard-of-care usage. Operators were using a dedicated inner-lumen diagnostic catheter (Achieve or Achieve Advance; Medtronic, Inc.) to record real-time PV electrograms during freeze application. Post-ablation testing methods were left to the discretion of the operator; however, acute durable PVI was the intraprocedural endpoint which was consistently defined as electrical conduction isolation confirmed by pace-block testing.

Measured parameters

RECABA recorded several variables with regards to CB-related parameters utilized during PVI, including: 1) PV location, 2) TT-30C denoted as the time in seconds from the beginning of the freeze application until the cryoballoon reached –30°C, 3) visibility of electrogram which was recorded as the presence of a PV electrogram during the application, 4) TTI denoted as the time from the beginning of the freeze until the disappearance of PV electrograms, indicating entry block, 5) Temperature at isolation (TAI) which was the temperature (°C) of the CB when acute isolation was achieved, 6) balloon NT was recorded as the lowest temperature (°C) achieved by the CB during the application, 7) cryoballoon dose (CBD) was reported as the time from the beginning of the freeze until its termination, 8) balloon thaw time was denoted from the time of freeze termination until the balloon reached +20°C, and 9) acute PVI which was recorded as the elimination of PV electrograms at the end of the application. Data on continuous application parameters were cleaned by excluding values below and above the 1^{st} and 99^{th} percentiles, respectively. Application parameters with conflicting data (likely due to data entry errors) were excluded from evaluation in this study.

Successful applications (SA) were denoted as achieving durable vein isolation after a complete application with or without live electrogram monitoring which was confirmed by entrance and/or exit block. Conversely, failed applications (FA) were recorded as a failure to achieve vein isolation with or without electrogram monitoring. This category included acute reconnections, as applications where isolation was achieved but the cardiac-to-PV electrograms resumed after cryoballoon thawing. In some cases, a bonus freeze (one additional freeze beyond established and proven PVI) was used because of physician preference, but those were not taken into consideration in this analysis. Consequently, the first established endpoint was defined as SA or FA. Because TTI<60 is an established freeze parameter for predicting durable PVI, the RECABA study also evaluated this variable with regards to intraprocedural SA or FA. Thus, there were two categories of TTI<60. In SA-TTI<60 applications, a freeze had visible real-time electrograms, and TTI was achieved in under 60 s with durable intraprocedural PVI. In an FA-TTI<60, there was either a failure during real-time electrogram recording, or an acute isolation whereby TTI took longer than 60 s.

Statistical analysis

Associations between SA and SA-TTI<60 and biophysical parameters were investigated using logistic regression and building receiver operating characteristic (ROC) curves. Both SA and SA-TTI<60 were used as dichotomous criteria (success or failure). Biophysical variables (vein location, type of vein, etc.) and procedure parameters (TT-30C, NT, etc.) were used as possible explanatory predictors. Standard errors from regression models were adjusted clustering applications by patient. Differences in the model goodness-of-fit chi-square statistic ($\Delta\chi^2$) and resulting ROC curves and associated statistics were used to compare models. An all-possible-combination approach was used, while fixing TT-30C and selecting the model based on the area under the curve (AUC). AUC values between different models were compared seeking maximum parsimony without a significant decrease in the AUC in order to select the final model. A table with predicted probabilities for the endpoint was constructed for a set of values for the variables in the model. *T*-tests were used to analyze continuous data where appropriate. Associations between observed TT-30C and other continuous variables were assessed using the Pearson's correlation and linear regression models. Classical transformations were performed seeking the best fitting power.

Analyses were performed in STATA statistical software (StataCorp LLC) advised by an independent statistician. Statistical significance was assumed for two-sided p-values below 0.05.

Results

In total, 1,733 patients from 27 Spanish centers were included between September 2016 and January 2019. Within the data collection, 1,202 (68.9%) were men, and the mean age was 58.01 ± 10.41 years. Baseline characteristics are summarized in Table 1. A total of 12,448 CB applications were reported in 6,694 veins from 1,733 patients. Up to 376 (3%) were not classified due to inconsistent data, leaving 12,072 applications from 1,722 patients. The mean number of applications per procedure was 7.18 ± 2.7, and the mean freeze applications per vein was 1.9 ± 1.1.

Overall, 4,601 (37.4%) freezes applied a 180 s dose, and 3,740 (30.4%) freezes applied a 240 s dose. Operators applied 2,995 bonus freeze applications (CB application after achieving vein isolation) in 2,569 (38.4%) veins from 1,097 (63.3%) patients. Vein electrograms were monitored in 5,046 (53.31%) non-bonus applications, and TT-30C was recorded in 9,827 applications. A total of 6,349 of 9,178 freeze applications were successful (SA = 69.2%), and 2,673 of 4,784 applications achieved TTI<60 (SA-TTI<60 = 55.9%, Fig. 1). Overall, the mean TT-30C was 35.05 ± 10.4 s. In the SA group, the mean TT-30C was 33.4 ± 9.2 vs. 39.3 ± 12.1 s in the FA group (t test = –22.0, $p < 0.001$), and 31.8 ± 7.6 vs. 38.6 ± 11.5 s for the SA-TTI<60 and FA-TTI<60 groups, respectively (t test = –22.3, $p < 0.001$).

Time to reach –30°C did not differ between right or left-sided applications. From 9,827 applications, the average TT-30 for right veins was 34.8 ± 10.8 vs. 34.5 ± 10.2 s for left ones (t-test = 1.6, $p = 0.11$).

There was also no relationship between phrenic nerve palsy and TT-30C in RSPV. From 1,374 patients with TT-30C data on RSPV application, 36 presented phrenic nerve palsy. Mean TT-30 was 30.13 ± 8.9 s in the control group and 27.8 ± 6.1 seconds in the phrenic nerve palsy group, (t-test = 1.52, $p = 0.13$).

Univariate logistic regression models for different biophysical parameters showed different AUCs (Table 2). Thaw time and balloon NT were better predictors of SA ($\Delta\chi^2 = 479.8$, $p < 0.001$) than TT-30C. However, TT-30C tended to be a better predictor of SA-TTI<60 than the other two variables, but without statistically significant differences between the three variables ($\Delta\chi^2 = 4.9$, $p = 0.09$). Multivariate logistic models included TT-30C, visualization of PV electrograms, first vs. successive freeze applications in the same vein and the type of PV (superior, intermediate, inferior, or common trunk) as predictors for acute intraprocedural isolation success. Estimates for the multivariate models are shown in Figure 2.

Time to reach –30°C, PV electrogram visualization, first application, and inferior or intermediate vein were independent predictors for SA. In the multivariate model, a 10 s increase in TT-30C entailed an odds ratio (OR) of 0.58 (95% confidence interval [CI] 0.54–0.62) for SA. Compared to superior veins, inferior and intermediate veins had a statistically significant effect. This model was compared with a simplified one omitting the type of vein, finding no statistically significant differences between the AUCs (0.7332 [95% CI 0.72–0.75] vs. 0.7301 [95% CI 0.72–0.74]; $\Delta\chi^2 = 5.41$, $p = 0.02$).

Logistic regression models for predicting SA-TTI<60 included TT-30C, first vs successive applications in the same vein and the type of vein. Electrogram visualization was discarded since all applications considered had electrogram monitoring (Fig. 3). TT-30C, first application and common trunk were independent predictors of SA-TTI<60. A 10-s increase in TT-30C entailed an OR 0.43 (95% CI 0.39–0.49) for SA-TTI<60. The two-variable model achieved an AUC 0.7326 (95% CI 0.72–0.75). Figure 4 depicts the probability of achieving SA-TTI<60 for different values of TT-30C and applications. The optimal cutoff point based on the ROC curve was a predicted probability of 60.3% for SA-

TTI<60, with sensitivity = 68.6% (95% CI 66.7–70.5%) and specificity = 66.7% (64.4–68.9%).

The (TT-30C and balloon NT) scatter plot showed a non-linear relationship between TT-30C and NT (Fig. 5). Classical transformations showed an inverse relationship between TT-30C and balloon NT. A multivariable linear regression model predicting NT considered 9,453 freeze applications in 1,418 procedures (including SA, FA, and bonus applications). In the total examination, 1/TT-30C was the best single predictor of balloon NT. The final model reached an adjusted-R^2 = 0.53. Additionally, CB dose, vein type (inferior or intermediate vs. superior), first freeze application, bonus freeze application, and PV electrogram visualization were also independent predictors of balloon NT (Fig. 6). Figure 5 depicts the relationship between balloon NT, TT-30C, SA, and SA-TTI<60.

Discussion

According to available research, RECABA is the largest cryoablation registry that includes biophysical parameters for each CB freeze application. In the present analysis, the relationship was quantified between freezing rate (TT-30C) and established quality markers of a CB application, such as SA-TTI<60, and balloon NT. Specifically, a TT-30C of 30 s in a first freeze application predicted a 71.7% probability of SA-TTI<60 (95% CI 68.4–74.7%) with a sensitivity of 44.5%, specificity 80.9%, positive predictive value 82.0%, and negative predictive value of 42.7%. This finding could be of critical importance, since an early indicator of a poor-intraprocedural outcome may lead the operator to either perform a maneuver such as “pull-down” or to reposition the CB and continue with a new freeze attempt.

Since the early days of CB ablation, there has been an interest in optimizing the procedure by identifying biophysical parameters from an application and clarifying their relationship with the application’s effectiveness. In 2011, Fürnkranz et al. [10] established the relationship between balloon NT and acute vein isolation using the first-generation CB. In that study, a NT below –51°C was unequivocally associated with vein isolation. In the following years, studies have examined patients with AF recurrences that underwent a second AF ablation procedure. Those studies compared biophysical parameters between reconnected and isolated veins. Ghosh et al. [9] observed that thawing time, balloon NT, the grade of occlusion, and freezing rate (time from 0°C to –30°C) were all predictors of PV reconnection and that thawing time, vein diameter, and grade of occlusion were independent predictors in the multivariate model. Those procedures were performed using the first-generation CB, and for every 10 s of freezing from 0°C to –30°C, the OR for PV reconnection was 1.58 (1.03–2.43; $p < 0.037$).

With the second-generation CB and use of a spiral catheter (Achieve, Medtronic Inc.); researchers have found the of the quality of the freeze application rather than the quantity (cryoablation dose) to be of most importance. The TTI was proven to be a marker of the quality and related to less PV reconnections in repeat ablation procedures [5, 7, 10]. Thus, TTI < 60 s has traditionally been established as a general intraprocedural parameter target. Moreover, the CryoDosing study evaluated a TTI-guided protocol [12]. In the CryoDosing study, if a TTI under 60 s was achieved, then the total dose was TTI + 120 s. Additionally, if TTI was between 60 and 90 s, a bonus application took place. Finally, if the isolation was not achieved in 90 s, the application was stopped. This study proved that a uniform dosing strategy (using TTI) could be used successfully in a multicenter study, and it demonstrated that TTI-dosing could deliver long-term durable outcomes. In the CIRCA-Dose study, an application was interrupted if within 60 s neither vein isolation nor -35°C were reached [8]. Also, the ICE-T study protocol established that an application would be stopped if isolation was not achieved in 90 s [13]. Therefore, there exist quality standards from trials for freeze application termination which are widely used in clinical practice. However, an extensive evaluation of intraprocedural parameters that predict acute PVI has not been evaluated in a large registry format that encompasses several real-world cryoablation techniques in order to obtain vastly generalizable results.

Intraprocedural parameter finding in RECABA

The present study evaluated the relationship between TT-30C and the effectiveness of a CB freeze application(s). The model established the importance of freezing rate (TT-30C) as an early predictor of efficacy. Other biophysical parameters, such as thawing time and balloon NT, showed a stronger association with intraprocedural success. However, those are *final* parameters instead of predictive ones. Specifically, NT and thaw time cannot actively inform the quality of a freeze (early within the application).

The effect of TT-30C on intraprocedural acute efficacy can be explained by the close relationship between balloon-vein coupling, freezing rate, and NT. Another predictor of acute efficacy was the PV electrogram monitoring during the application. This could be explained by veins with no electrogram visualization tending to be more difficult to couple. Thus, the ablation requires a deeper progression of the spiral catheter to gain stability. Nevertheless, the OR for SA suggests that for every 10 s of TT-30C in the vein without electrogram visualization corrected by the application order was 0.64 (95% CI 0.58–0.70), which confirms this relationship (and validates TT-30C as a guidance parameter in veins lacking electrogram visualization). Therefore, in veins without the possibility of monitoring real-time isolation, TT-30C should be considered.

It is when predicting isolation under 60 s where TT-30C is more relevant. In the univariate analysis, TT-30C tends to be a better predictor of SA-TTI<60 than thawing time or NT. This can be explained by SA-TTI<60 and TT-30C both being variables that are time-driven. Furthermore, NT and thawing time are related to the success of an application, but their values are known only after the application is completed. This model allows us to establish cutoff points within TT-30C that could guide the operator during an application. If in a first application the CB has not reached –30°C in 40 s and 50 s, the probability to isolate the PV in under 60 s falls to 51% and 32%, respectively.

Cryoballoon ablation maneuvers such as “pull-down” are performed after 60 s of freezing and the recommendation is to stop the application if it fails to isolate or to drop temperature within 20 s [14]. The use of these techniques, particularly in difficult anatomies, fall out of our models and therefore the present recommendations do not apply.

Clinical implications

The freezing rate as TT-30C was shown to be an early biophysical parameter, together with isolation in under 60 s, that could be used to stop a low-quality application and guide the procedure. Its usefulness is even greater in veins without electrogram monitoring, where it could be used to stop a suboptimal application or even avoid a bonus freezing. This last consideration ought to be prospectively assessed before its implementation.

Limitations of the study

The main limitation of the current study is that the origin of the data is a multicenter registry, in which each center followed different protocols depending on its local practice and where some errors may have occurred during recording of the procedure data. Additionally, there was no access to the cryo-console data afterwards. Nevertheless, the registry enrolled an important number of patients and showed real-life data for each application. There are confounding variables that were not included in the model. The grade of the occlusion and the vein diameter were pointed out by Gosh et al. [9] as independent predictors of AF recurrence, but the present registry lacked those data. Moreover, another confounding factor is if the “pull-down” technique for achieving isolation was implemented. Those applications would reach a lower NT than predicted by the present model.

Conclusions

Freezing rate is an early predictor of the quality of a CB application. A time to reach –30°C after 40–50 s should prompt termination of the freeze application. The time to –30°C is closely related to balloon NT which is a well-established predictor of vein reconnection and AF recurrence.

Acknowledgments

We would like to thank I. Molina, S. Bello, and P. Pascual from Medtronic scientific department, who were responsible for the study’s national coordination and database. H. Lim from Medtronic for grammatical assistance on the manuscript.

Conflict of interest: Pablo Moriña-Vázquez received consulting honoraria from Medtronic Inc. and Abbott Inc.; Jesús Daniel Martínez-Alday received educational honoraria from Medtronic Inc. and Abbott Inc.; Arrhythmia Unit of Hospital Clínico Universitario of Valencia is a training center in the Arctic Front Training Program (AFTP), funded by Medtronic Inc. Ángel Ferrero-de-Loma-Osorio has received lecture honoraria from Medtronic Inc.; Hospital Virgen de la Arrixaca (Murcia) received grants/research financial support from Medtronic; Jorge Toquero-Ramos received lecture honoraria from Medtronic

Inc. and is a Member of the Medtronic European Advisory Board; Rafael Peinado declares educational and research grants from Medtronic Inc., the rest of the authors do not declare any potential conflict of interest.

References

1. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. Eur Heart J. 2021; 42(5): 373–498, doi: 10.1093/eurheartj/ehaa612, indexed in Pubmed: 32860505.

2. Chen S, Schmidt B, Bordignon S, et al. Atrial fibrillation ablation using cryoballoon technology: Recent advances and practical techniques. J Cardiovasc Electrophysiol. 2018; 29(6): 932–943, doi: 10.1111/jce.13607, indexed in Pubmed: 29663562.

3. Su W, Kowal R, Kowalski M, et al. Best practice guide for cryoballoon ablation in atrial fibrillation: The compilation experience of more than 3000 procedures. Heart Rhythm. 2015; 12(7): 1658–1666, doi: 10.1016/j.hrthm.2015.03.021, indexed in Pubmed: 25778428.

4. Su W, Aryana A, Passman R, et al. Cryoballoon Best Practices II: Practical guide to procedural monitoring and dosing during atrial fibrillation ablation from the perspective of experienced users. Heart Rhythm. 2018; 15(9): 1348–1355, doi: 10.1016/j.hrthm.2018.04.021, indexed in Pubmed: 29684571.

5. Ciconte G, Mugnai G, Sieira J, et al. On the quest for the best freeze: predictors of late pulmonary vein reconnections after second-generation cryoballoon ablation. Circ Arrhythm Electrophysiol. 2015; 8(6): 1359–1365, doi: 10.1161/CIRCEP.115.002966, indexed in Pubmed: 26527624.

6. Ciconte G, Velagić V, Mugnai G, et al. Electrophysiological findings following pulmonary vein isolation using radiofrequency catheter guided by contact-force and second-generation cryoballoon: lessons from repeat ablation procedures. Europace. 2016; 18(1): 71–77, doi: 10.1093/europace/euv224, indexed in Pubmed: 26445821.

7. Aryana A, Mugnai G, Singh SM, et al. Procedural and biophysical indicators of durable pulmonary vein isolation during cryoballoon ablation of atrial fibrillation. Heart Rhythm. 2016; 13(2): 424–432, doi: 10.1016/j.hrthm.2015.10.033, indexed in Pubmed: 26520204.

8. Andrade J, Champagne J, Dubuc M, et al. Cryoballoon or radiofrequency ablation for atrial fibrillation assessed by continuous monitoring. Circulation. 2019; 140(22): 1779–1788, doi: 10.1161/circulationaha.119.042622.

9. Ghosh J, Martin A, Keech AC, et al. Balloon warming time is the strongest predictor of late pulmonary vein electrical reconnection following cryoballoon ablation for atrial fibrillation. Heart Rhythm. 2013; 10(9): 1311–1317, doi: 10.1016/j.hrthm.2013.06.014, indexed in Pubmed: 23792110.

10. Fürnkranz A, Köster I, Chun KR, et al. Cryoballoon temperature predicts acute pulmonary vein isolation. Heart Rhythm. 2011; 8(6): 821–825, doi: 10.1016/j.hrthm.2011.01.044, indexed in Pubmed: 21315836.

11. Ciconte G, Chierchia GB, DE Asmundis C, et al. Spontaneous and adenosine-induced pulmonary vein reconnection after cryoballoon ablation with the second-generation device. J Cardiovasc Electrophysiol. 2014; 25(8): 845–851, doi: 10.1111/jce.12421, indexed in Pubmed: 24678900.

12. Aryana A, Kenigsberg DN, Kowalski M, et al. Verification of a novel atrial fibrillation cryoablation dosing algorithm guided by time-to-pulmonary vein isolation: Results from the Cryo-DOSING Study (Cryoballoon-ablation DOSING Based on the Assessment of Time-to-Effect and Pulmonary Vein Isolation Guidance). Heart Rhythm. 2017; 14(9): 1319–1325, doi: 10.1016/j.hrthm.2017.06.020, indexed in Pubmed: 28625929.

13. Chen S, Schmidt B, Bordignon S, et al. Impact of cryoballoon freeze duration on long-term durability of pulmonary vein isolation: ICE re-map study. JACC Clin Electrophysiol. 2019; 5(5): 551–559, doi: 10.1016/j.jacep.2019.03.012, indexed in Pubmed: 31122376.

14. Chen S, Schmidt B, Bordignon S, et al. Practical Techniques in Cryoballoon Ablation: How to Isolate Inferior Pulmonary Veins. Arrhythm Electrophysiol Rev. 2018; 7(1): 11–17, doi: 10.15420/aer.2018;1;2, indexed in Pubmed: 29686870.

Table 1. Baseline characteristics of all patients included in the analysis.

Baseline characteristic	**Overall (n = 1733)**
Age [years]	58.01 ± 10.41
Male sex	1202 (68.9%)
Weight [kg]	83,3 ± 15,52

Height [cm]	171.7 ± 10.24
Body mass index [kg/m^2]	28.0 ± 3.9
Atrial fibrillation type:	
Paroxysmal	1235 (71.2%)
Persistent	432 (24.9%)
Long-standing	37 (2.1%)
Short-standing	31 (1.8%)
Repeat procedure	80 (4.6%)
Heart disease	327 (18.9%)
Left-side pulmonary veins anatomy:	
2 veins	1448 (83.4%)
> 2 veins	5 (0.3%)
Common trunk	264 (15.2%)
Right-side pulmonary veins anatomy:	
2 veins	1571 (90.4%)
> 2 veins	114 (6.6%)
Common trunk	28 (1.6%)

Table 2. Odds ratio (OR) for univariate logistic models predicting successful application and successful application with time to isolation (TTI) < 60 s.

Predictor[†]	Endpoint: Successful application		Successful application and TTI < 60 s	
	OR	**AUC (n = 6,414)**	**OR**	**AUC (n = 3,638)**
Time to –30°C [s]	0.60	0.66	0.43	0.70
Nadir temp [°C]	5.27	0.80*	3.24	0.69
Thaw time [s]	2.23	0.80*	1.53	0.69

***Statistically significant χ^2 goodness of fit difference; [†]Measured in 10-unit steps; AUC — area under the curve**

Figure 1. Flowchart and classification of cryoballoon applications. Successful application refers to achieving vein isolation; TTI — time to isolation.

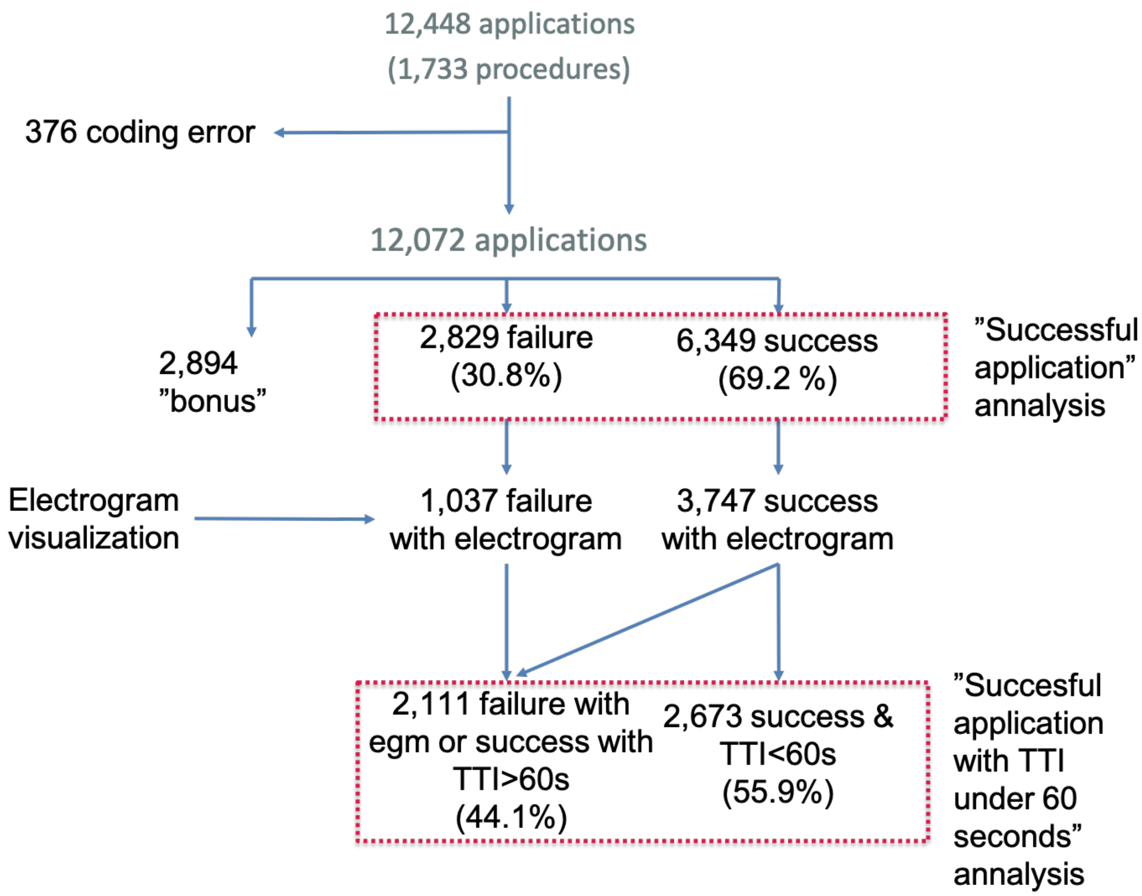

Figure 2. Multivariate logistic regression models predicting successful application.

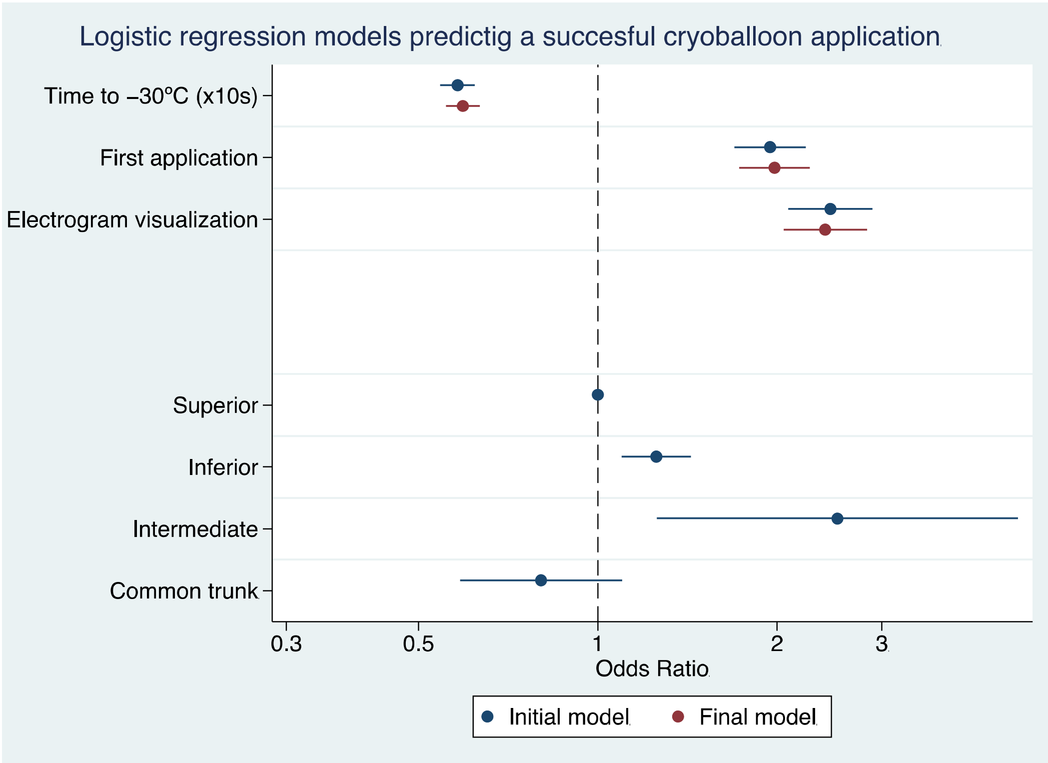

Figure 3. Multivariate logistic regression models predicting a successful cryoballoon application achieving vein isolation within 60 s.

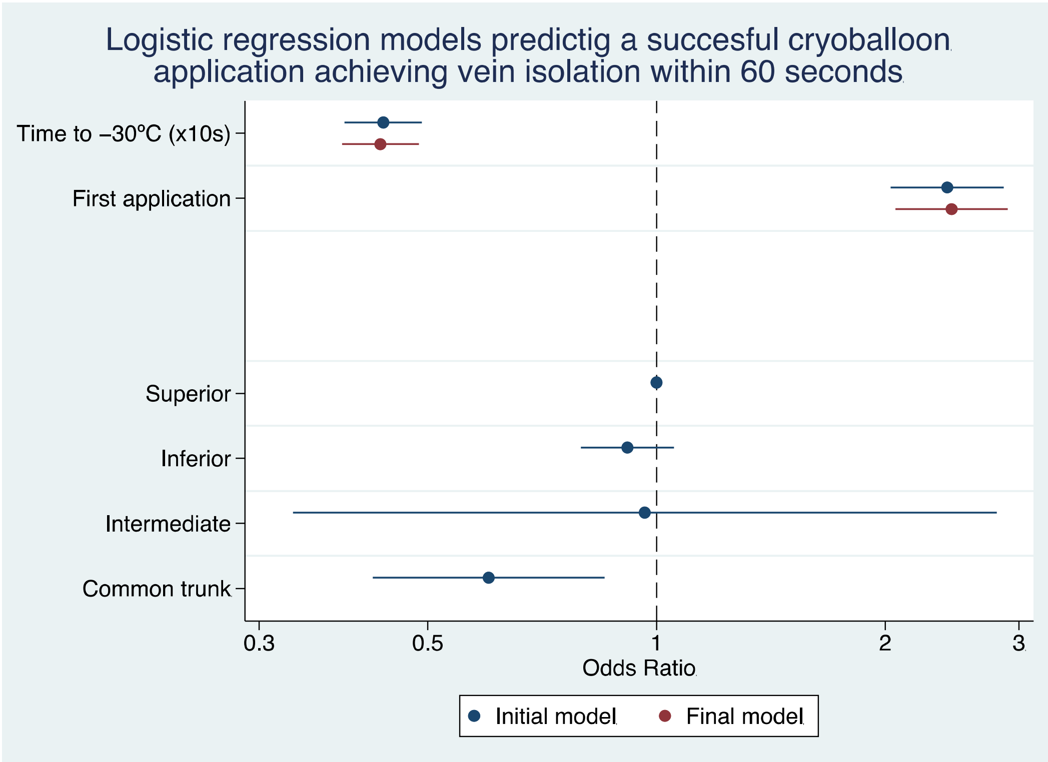

Figure 4.

Predicted probability of successful application with time to isolation (TTI) under 60 s for different times to reach –30°C (s). Data were derived from the logistic models.

Time to -30ºC (s)	Probability of succesful application with TTI <60 s (%)	
	Succesive application	First application
15	78	90
20	70	85
25	60	79
30	50	71
35	40	62
40	30	51
45	22	41
50	16	32
55	11	23
60	8	17
65	5	12
70	3	8
75	2	5
80	2	4
85	1	2

Figure 5. Scatter plot of recorded nadir temperature and time to –30°C; **A, B.** Green dots represent successful applications, and red dots represent failure to isolate; **C, D.** Green dots represent isolation under 60 s, and red dots depict failure to isolate under 60 s with electrogram monitoring.

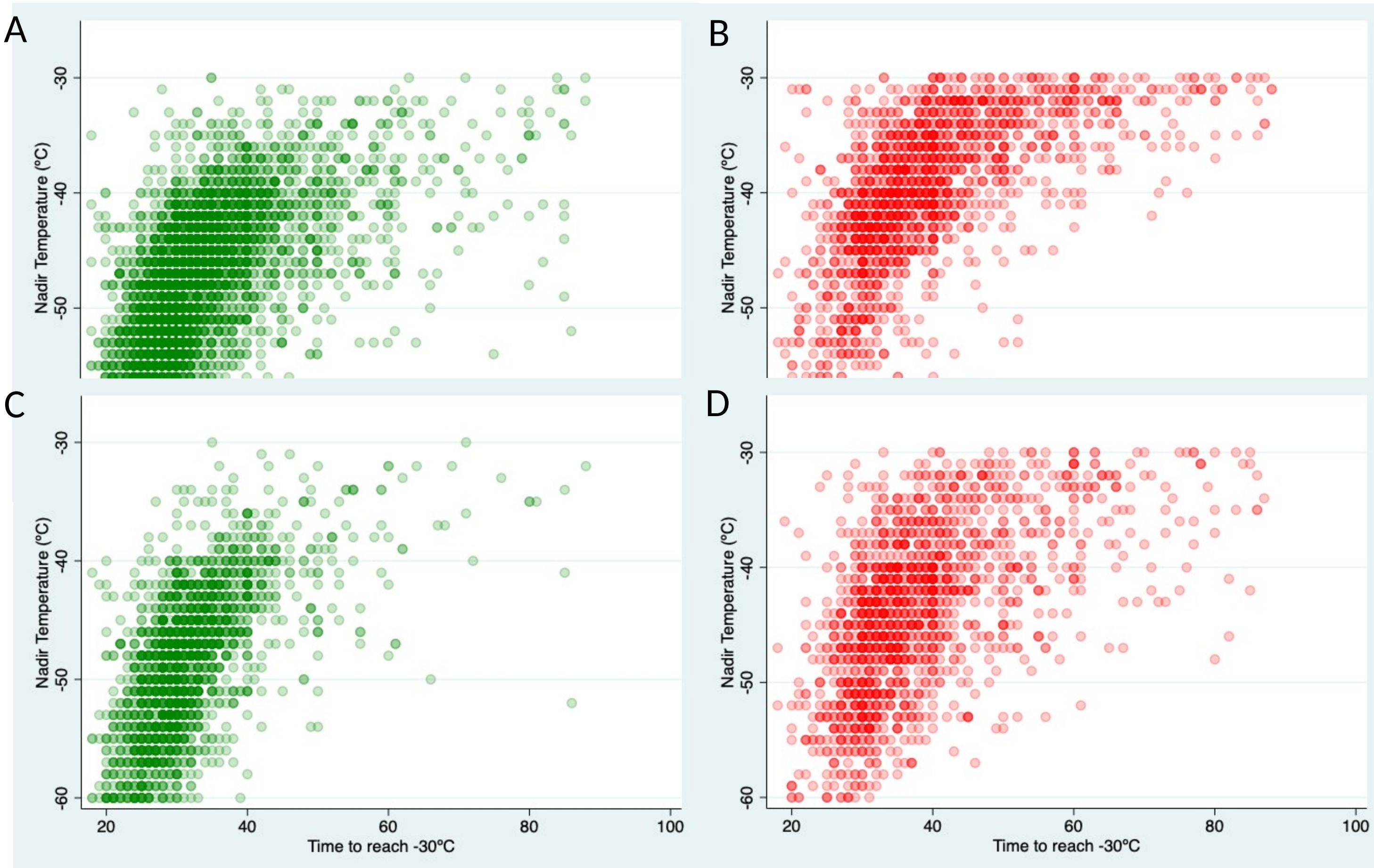

Figure 6. Multivariable linear regression model for nadir temperature.