PolarX cryoballoon parameters predicting acute and sustained pulmonary vein isolation: targets for ablation of atrial fibrillation.

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ABSTRACT

Background- Preliminary data suggests that the freeze profile for pulmonary vein isolation (PVI) using the novel PolarX Cryoballoon is very different to the Arctic Front Advance (AFA) meaning that ablation targets are not equivalent.

Methods- The study aim was to evaluate the PolarX Cryoballoon in AF catheter ablation and identify freeze parameters predictive of successful PVI. The temperature drop during the freeze, time to PVI (TTI), thaw time and nadir temperatures were recorded. Acute reconnection was assessed after a waiting period of 30 minutes and with adenosine.

Results- 60 patients were included and 238 veins were treated. A total of 305 freezes were performed (1.3±0.6 freezes per vein) to achieve initial PVI with 176 (73.9%) veins isolating with a single freeze. Of the 238 veins, 39 (16.4%) veins showed reconnection. Independent predictors for achieving initial PVI was temperature at 30s (OR 1.26; p=0.003) and time to reach -40 ℃ (OR of 1.88; p<0.001) with optimal cut-off of ≤-38.5 ℃ at 30s (AUC 0.79; p<0.001) and ≤-40 ℃ at ≤32.5s (AUC 0.77; p<0.001). Temperature at 30s (≤-39.5 ℃, OR 1.24; p=0.002), nadir temperature (≤-53.5 ℃, OR 1.35; p=0.003) and TTI (≤38.0s, OR 1.18; p=0.009) were independent predictors of sustained PVI. Combining 2 of these 3 targets was associated with reconnection in only 2-5% of PVs.

Conclusions- The PolarX Cryoballoon has a very different freeze profile and TTI to the AFA. Prospective testing of these proposed targets in large outcomes studies are required and equivalence to the AFA cannot be assumed.

Key Words- Cryoablation, Atrial fibrillation, Pulmonary vein isolation, Novel technology

INTRODUCTION

Pulmonary vein isolation (PVI) plays a fundamental role in the ablation strategy applied in atrial fibrillation (AF). In patients with symptomatic paroxysmal AF (PAF), PVI has played a primary role and is superior to medical therapy [1]. Ablation with the Medtronic Cryoballoon is an established technique to achieve PVI in patients with AF and has shown to be compatible to radiofrequency (RF) point by point ablation [2]. With the evidence from the STAR AFII trial [3], PVI has been shown not to be inferior to other ablation strategies in patients with persistent AF. PVI with the Medtronic Cryoballoon has produced similar results in persistent AF to those expected with RF ablation including in the context of structural heart disease [4, 5].

The Arctic Front Advance™ Cryoballoon (Medtronic, Min, US) has been in widespread use for over a decade and there is a wealth of data regarding procedural parameters, freeze metrics, intraprocedural targets and dosing, workflow and outcomes. The PolarX™ Cryoballoon (Boston Scientific, MA, US) has been designed to emulate the Medtronic system, but there remain important differences in the design and operation of the two systems [6, 7]. In particular, the temperature drop measured with the PolarX system is very different, with temperature differences during the freeze and at nadir being approximately 10°C lower with the PolarX system than with the Arctic Front Advance [7, 8].

Previous ablation targets used for the Arctic Front Advance in terms of temperatures reached or time to isolation (TTI), dosing in terms of duration and number of freezes, safety and of course efficacy in terms of achieving acute or sustained PVI may not apply to the PolarX system at all which means there is currently an evidence vacuum for operators using the PolarX system. This multi-centre study aimed to evaluate the PolarX system in terms of the temperature profile during the freeze and what parameters were associated with achieving PVI acutely. A waiting period of 30 minutes was then observed, and IV adenosine administered to look for acute PV reconnection,

enabling determination of temperature profile and TTI associated with sustained PVI. We hypothesized that novel targets could be derived for the PolarX system in terms of temperatures and TTI achieved that would differ to targets currently used for the Arctic Front Advance.

METHODS-

Study design-

This was a prospective multi-centre study across 3 UK centres that included patients that underwent a first ablation procedure for AF. Patients were consecutively enrolled between 2020-2021. All patients underwent cryoablation using the Polarsheath (15.5F deflectable sheath), PolarX 28-mm balloon catheter and the Polar map (eight electrodes, 20mm loop diameter and 3F shaft diameter).

All patients provided written informed consent before the procedure. The study complied with the Declaration of Helsinki and was registered and endorsed by the Barts Health NHS Trust Clinical Effectiveness Unit (registration ID: 11690). Prospective approval for the use of the PolarX system was obtained from the Barts Heart Centre New Technologies Committee.

Procedure protocol-

Patients underwent their procedure under conscious sedation or general anaesthetic depending on patient/operator preference. All procedures were performed with un-interrupted anticoagulation therapy and intravenous heparin administration to achieve an ACT of >300ms. Transeptal punctures were performed through the Polarsheath using a BRK or BRK1 89cm (Abbott, IL, US) and a safesept guidewire. Right sided PVs had cryoablation with phrenic pacing using a quadripolar catheter and monitoring diaphragmatic movement and compound motor action potentials for phrenic nerve compromise. Prior to the freeze application, the seal between the balloon and the vein ostium was

assessed with contrast injection to ensure no leak. If the seal was inadequate the balloon was repositioned to achieve a better seal.

Cryoablation was performed until PVI was achieved. Applications of the cryoballoon were standardised at 180 seconds. Attempts were made to visualize electrograms with the Polarmap at the start of the freeze. The metrics for the freeze and TTI were recorded. If PVI was not achieved, then further applications were performed with acute PVI as the endpoint. Once PVI was achieved no additional bonus freezes were performed.

Following a 30-minute waiting period after PVI, the veins were individually assessed for reconnection. If the vein remained isolated, isolation was assessed with IV administration of adenosine 18-24mg (as required to achieve atrioventricular block). If the vein showed reconnection with the waiting period or adenosine further cryoablation was performed to achieve isolation. Reconnection with either the waiting period or adenosine was recorded as failure to achieve sustained isolation. The waiting period and administration of adenosine was not repeated after the repeat applications(s).

Baseline characteristics and procedural metrics were collected which included the number of freezes required to achieve isolation, the temperature change over time, temperature at the time of isolation, time to isolation (TTI), nadir temperature for the freeze and thaw time (time to reach 0 ℃). Safety outcomes were also recorded.

Follow-up-

The focus of this study was acute PVI and determination of potential targets for the Boston Cryoballoon. Nevertheless, patients were followed up to determine any late complications and to describe the short-term follow-up data available. AF/AT recurrence was defined as documented

atrial arrhythmia lasting ≥ 30 seconds off antiarrhythmic drugs as per guidelines [9]. Given the short-term nature of the follow-up a blanking period was not observed.

Endpoints-

The end points studied were the association between the various freeze metrics studied and (1) achieving acute PVI, and (2) achieving sustained PVI after a waiting period and adenosine. Using this data, novel procedural targets for the PolarX system for achieving acute PVI and sustained PVI were determined.

Statistical analysis-

All statistical analyses were performed using SPSS (IBM SPSS Statistics, Version 25 IBM Corp, NY, USA). Continuous variables are displayed as mean ± standard deviation (SD) or median (IQR). Categorical variables are presented as a number and percentage. Fisher's exact test was used for the comparison of nominal variables. The student t-test, or its non-parametric equivalent Mann-Whitney was used for comparison of continuous variables. Anova was performed to compare cryofreeze parameters in accordance with vein type. Binary logistic regression was performed to identify specific cryofreeze parameters that were predictive of a successful initial and sustained PVI. Receiver Operating Characteristic (ROC) analysis was performed to determine the association between the continuous variables studied and the outcomes of acute PVI and sustained PVI. Area under the curve (AUC) was determined and optimal cut-off, sensitivity and specificity were determined manually from ROC plots. This was used to determine sensitivity and specificity for achieving acute PVI and sustained PVI using different cut-offs. Relative risk of PV reconnection was determined for individual and a combination of parameters that were shown to predict sustained PVI. A p-value of <0.05 was deemed significant.

RESULTS-

A total of 60 patients were included in this study (mean age 60.3±9.2 years and 38 male (63.3%)). Out of these patients, 40 (66.7%) patients underwent ablation for PAF and 20 (33.3%) for persistent AF. A majority of the procedures were performed under conscious sedation (n=50, 83.3%). The average procedure duration was 91.3±27.8 minutes (which included the 30 minutes waiting period) with a fluoroscopy duration of 10.9±7.1 minutes and a dose area product (DAP) of 282.2±421.5 $Gycm^2$. The baseline characteristics are described in Table 1. No procedural complications were encountered either acutely or within 30 days. All procedures were performed as day case procedures.

i) Initial PVI

In the 60 patients, a total of 238 veins underwent cryoablation to achieve initial PVI. In 2 patients it was deemed that the left sided veins were a common vein based on contrast injections. The average total freeze duration on a per patient basis was 918.3±232.7 seconds to achieve initial PVI of all the veins. On a per patient basis an average total number of freezes applied to achieve initial PVI of all the veins was 5.2±1.4 freezes.

A total of 305 freezes were applied to achieve initial PVI of the PVs. To achieve initial PVI, an average of 1.3±0.6 freezes were applied per vein with a range between 1-4 freezes in the whole cohort. Out of the 238 veins treated, 176 (73.9%) veins isolated with a single freeze. The average freeze duration (including the initial freeze and any subsequent applications) on a per vein basis was 232.1±110.1 seconds. On a per vein basis, a total of 3 freezes were applied to the LCPV (1.5±0.5), 76 freezes to the LUPV (1.3±0.7 freezes), 76 to the LLPV (1.3±0.6 freezes), 75 to the RLPV (1.3±0.5 freezes) and 75 to the RUPV (1.3±0.7 freezes) to achieve initial PVI. There was no significant difference in the average number of freezes applied per vein type to achieve initial PVI (p=0.43). Initial PVI was achieved in all patients.

The average nadir temperature achieved was -53.5±7.6 ℃. Initial PVI was on average achieved at a temperature of -42.8±5.3 ℃ at 43.3±25.7 seconds. The average temperature at 30 and 60 seconds was -38.5±9.2 ℃ and 48.2±6.5 ℃ respectively. A temperature of -40 ℃ and -50 ℃ was achieved on average at 33.7±10.9 seconds and 65.4±34.1 seconds. The average rate of temperature drop over 30 seconds was 2.4±0.2℃ per seconds. The average thaw time was 16.5±6.1 seconds.

ii) Predictors of initial PVI

Comparison was made to the cryofreeze parameters during the freezes that resulted in initial PVI in contrast to those freezes that did not result in initial PVI. Out of the total 305 freezes, 235 (77.0%) freezes resulted in PVI whilst 70 (23.0%) freezes did not. As shown in Table 2, a lower temperature was achieved at 30 seconds and 60 seconds with the freezes that resulted in PVI compared to the freezes that did not result in PVI (-39.5±10.0 ℃ PVI freezes vs. -35.4±4.9 ℃ non PVI freezes; p=0.002 at 30 seconds and -49.5±6.4 ℃ PVI freezes vs. -43.6±4.4 ℃ non PVI freezes; p<0.001 at 60 seconds). The time to reach -40 ℃ and -50 ℃ occurred quicker with the freezes that resulted in PVI compared to the freezes that did not. The rate of temperature drop between 0 and 30 seconds was greater with the freezes that resulted in PVI compared to the freezes that did not result in PVI (2.41±0.18 ℃/s PVI freezes vs. 2.24±0.16 ℃/s non PVI freezes; p<0.001). The nadir temperature was also lower and the thaw time was longer in the freezes that resulted in PVI compared to the freezes that did not (Table 2).

In a multivariate analysis temperature at 30 seconds and the time to reach -40 ℃ were independent predictors of achieving initial PVI. Table 3 summaries the findings of the multivariate analysis. A lower temperature at 30 seconds was shown to be an independent predictor of initial PVI with an odds ratio of 1.26 (95% CI 1.05-1.31; p=0.003) with an AUC of 0.79 (95%CI 0.73-0.86; p<0.001). The optimal cut off was ≤-38.5 ℃ at 30 seconds with a sensitivity of 73.6% (95%CI 71.2%-81.0%) and specificity of 78.6% (95% CI 72.4%-82.3%). Reaching -40 ℃ at an earlier

time was also shown to be an independent predictor of acute PVI with an odds ratio of 1.88 (95% CI 1.81-1.95; p<0.001) with an AUC of 0.77 (95%CI 0.71-0.84; p<0.001). The optimal cut off was ≤32.5 seconds with a sensitivity of 70.2% (95%CI 68.2%-76.2%) and specificity of 73.6% (95% CI 70.4%-78.3%).

iii) Sustained PVI

Following initial PVI, all veins were checked after a waiting period of 30 minutes and a bolus of adenosine to look for acute PV reconnection. Out of the 238 veins, 31 (13.0%) veins showed acute reconnection after the waiting period. An additional 8 (3.4%) veins showed acute reconnection following the waiting period after the IV administration of adenosine. Therefore, a total of 39 (16.4%) veins were reconnected following the waiting period and after adenosine administration. On a per vein basis 11 (28.2%) were LUPV, 11 (28.2%) LLPV, 8 (20.5%) RLPV and 9 (23.1%) RUPV. There was no significant difference in the reconnection rates between vein types (p=0.89). A total of 45 freezes were performed for the reconnected veins with an average of 1.1±0.4 freezes per vein to achieve PVI.

When comparing the veins that did not reconnect after the waiting period and adenosine with those that did reconnect, the differences in freeze parameters were consistent with the initial findings in terms of the freezes that resulted in initial PVI compared to those that did not (Table 4). When comparing PVs that reconnected to those that did not there was no difference in the number of freezes required to achieve initial PVI (1.4±0.8 reconnected veins vs. 1.3±0.6 not reconnected veins; p=0.29) or the temperature at which PVI occurred (-42.8±5.1 ℃ vs. -42.6±6.1 ℃; p=0.41). However, the TTI was significantly longer with the veins that reconnected versus those that did not (67.6±38.3 seconds vs. 39.3±18.5 seconds; p<0.001).

iv)Predictors of sustained PVI

In a multivariate analysis, the temperature at 30 seconds (odds ratio 1.24, 95%CI 1.08-1.42; p=0.002), nadir temperature (odds ratio 1.35, 95%CI 1.11-1.64; p=0.003) and the TTI during initial PVI (odds ratio 1.18, 95%CI 1.04-1.34; p=0.009) were independent predictors of sustained PVI with no reconnection after the waiting time and adenosine (Table 5). A lower temperature at 30 seconds showed an AUC of 0.80 (95%CI 0.72-0.88; p<0.001) with an optimal cut off of ≤-39.5 °C at 30 seconds with a sensitivity of 74.0% (95%CI 71.3%-80.1%) and specificity of 65.6% (95% CI 62.4%-72.4%). A lower nadir temperature showed an AUC of 0.83 (95%CI 0.76-0.90; p<0.001) with an optimal cut off of ≤-53.5 °C with a sensitivity of 70.7% (95%CI 68.3%-75.3%) and specificity of 75.0% (95% CI 71.2%-79.3%). Achieving PVI at an earlier freeze time showed an AUC of 0.73 (95%CI 0.63-0.84; p<0.001) with an optimal cut off of ≤38.0 seconds with a sensitivity of 71.9% (95%CI 68.7%-73.5%) and specificity of 66.0% (95%CI 64.3%-70.1%).

v*) Evaluation of potential targets*

Using whole (and preferably round) numbers that could feasibly be used as intraprocedural targets, achieving a TTI of ≤38 seconds was strongly predictive of sustained PVI with a significantly lower relative risk of PV reconnection (RR 0.26, 95%CI 0.13-0.50; p<0.001) (Table 6). Freezes with a TTI of 39-60 seconds were associated with a significantly higher PVI reconnection rate compared to freezes with a TTI of ≤38 seconds (21.6% vs. 8.3%; p=0.03). This was even higher with a TTI of >60 seconds (40.5% vs. 8.3%; p=0.002). Adding a temperature to the TTI target was beneficial, in that reaching temperature of ≤-40 °C at 30 seconds (RR 0.23 95%CI 0.07-0.79; p=0.02) or particularly nadir temperature of ≤ -54 °C (RR 0.12, 95%CI 0.03-0.55; p=0.006) in addition to achieving this TTI target resulted in a significantly lower relative risk of PV reconnection compared to TTI target alone. The combination of all of these 3 targets did not result in a significant lower rate of PV reconnection compared to the combination of 2 of these targets (p=0.22).

Defining targets for PVs without including TTI (as TTI is not always seen due to lack of signal) reaching temperature of ≤-40 ℃ at 30 seconds (RR 0.20, 95%CI 0.09-0.42; p<0.001) or nadir temperature of ≤-54 ℃ (RR 0.27, 95%CI 0.13-0.55; p<0.001) was associated with a significantly lower relative risk of PV reconnection (Table 6). Again, the combination of these two targets resulted in a significantly lower relative risk of PV reconnection compared to either of these targets alone (RR 0.11, 95%CI 0.02-0.53; p=0.006). Freezes with a temperature of -35 to -39 ℃ at 30 seconds were associated with a higher PV reconnection rate compared to freezes with a temperature of ≤-40 ℃ at 30 seconds (19.0% vs. 9.0%; p=0.08). The PV reconnection rate was even higher with freezes with a temperature of >-35 ℃ at 30 seconds (45% vs. 9.0%; p<0.001).

Figure 1 demonstrates proposed cryoablation targets with the PolarX system that would indicate an optimal freeze with sustained PVI.

v) Follow-up

All patients reached at least 3 months follow-up, and none had any late procedural complications. During an average follow-up 8.8±4.1 months, 49 (81.7%) patients remained free from AF/AT off anti-arrhythmic drugs. Out of the 11 (18.3%) patients that had AF/AT recurrence during follow-up, 3 (27.3%) had PAF prior to their procedure and 8 (72.7%) had persistent AF. The freedom from AF/AT during the follow-up in the PAF patients was 92.5% and in the persistent AF patients was 60.0%. Those with persistent AF were more likely to have AF/AT recurrence during follow-up (8/20, 40.0% vs. 3/40, 7.5%; p=0.004). The AF/AT recurrence rates during follow-up was not significantly different in those that had sustained PVI versus those that did not and required additional freezes after the waiting period and adenosine (3/39, 7.7% vs. 8/199, 4.0%; p=0.40).

DISCUSSION

This multicentre prospective study evaluated the novel PolarX Cryoballoon for PVI in AF. This is the first study that has identified specific freeze parameters with the PolarX system that were associated with acute and sustained PVI in order to derive targets for ablation. The main findings were:

- Safety, efficacy and procedural metrics for the PolarX system were comparable to that reported for the Arctic Front Advance, but the freeze profile, thaw times and TTI were markedly different.
- The temperature at 30 seconds and time to reach -40°C were strongly predictive of acute PVI. The temperature at 30 seconds, nadir temperature and TTI were predictive of sustained PVI.
- The overall rate of acute PV reconnection after a waiting period and adenosine was moderate at 16% of PVs without bonus applications. However, rates of acute PV reconnection were lower where TTI was ≤38 seconds (8.3%) and lower still when this endpoint was paired with a temperature of ≤-40°C at 30 seconds or a nadir temperature of ≤-54°C (4.8 and 2.6% respectively). If both of these temperature targets were met, then PV reconnection remained low at 2.2% irrespective of TTI.

Ablation using the PolarX system

The Arctic Front Advance has been used for PVI for over a decade. There is a wealth of data on safety and procedure metrics, targets in terms of temperatures and TTI, dosing in terms of extending or repeating freezes, and outcomes in practically every sub-group. Conversely, although the PolarX system has been designed to emulate the Arctic Front Advance, there is almost no data on its usage.

The overall procedure metrics with the PolarX system were similar to that reported many times using the Arctic Front advance. Procedure times were short at approximately 90 minutes which included a 30-minute waiting time and administration of adenosine. Fluoroscopy times were also

comparable to other reports using the Arctic Front Advance. Rates of PVI (100%) and the number of applications to achieve this were all comparable. Rates of acute PV reconnection with waiting periods and adenosine were similar to that reported with the Arctic Front Advance and contemporary reports using radiofrequency ablation [10, 11]. There was no signal of safety concern and indeed all cases were performed as day cases.

Preliminary data has shown that the temperature drop and freeze profile is very different with the PolarX Cryoballoon and is approximately 10°C lower at 30 seconds, 60 seconds and nadir temperature [7, 8]. This raises questions regarding procedural targets. There are differences in the balloon design and operation that may cause actual differences in the application of refrigerant but also differences in measurement [6, 7]. *Knecht et al.* [6] observed that on removing the balloon surrounding the catheters there were differences in the position and injection orientation of the nitrous oxide injection coil relative to the front of the balloon, different refrigerant flow and closer proximity of the thermocouple to the refrigerant outflow proximally (5mm with PolarX and 10mm with Arctic Front Advance). Furthermore, the higher compliance of the PolarX may allow the thermocouple to move towards the area of cooling on the front surface of the balloon. These factors could all affect the actual temperature achieved and how it is measured. With such a difference in the temperature profile and the temperatures achieved it is difficult for PolarX users to know how to ablate. Essentially none of the targets for the Arctic Front Advance can be assumed and it is unclear what temperature range encompasses the therapeutic window and what temperatures are too low. This means tried and tested algorithms using the Arctic Front Advance like that proposed by *Aryana et al*. [12] will need to be modified for the PolarX Cryoballoon.

Parameters associated with acute and sustained PVI

The temperature at 30 seconds and time to reach -40°C were strongly predictive of acute PVI. The temperature at 30 seconds and nadir temperature were strongly predictive of sustained PVI. This

is consistent with the findings demonstrated in studies using the Artic Front Advance Cryoballoon [13, 14]. However, the optimal parameters for predicting acute and sustained PVI were very different to that reported using the Arctic Front Advance (approximately 10°C lower) [13, 14]. It is reasonable therefore to presume that the therapeutic window is approximately 10°C lower with the PolarX system. TTI was also predictive of PV reconnection but was earlier using the PolarX system (≤38 seconds in those without PV reconnection) than is usually reported using the Arctic Front Advance (around 60 seconds) [13, 15], suggesting that there is a faster temperature drop and lower temperatures with the PolarX and not just a difference in measurement.

Potential targets for ablation

These are the first data to be reported with a full analyses of freeze parameters associated with acute and sustained PVI with the PolarX cryoballoon. These data therefore provide the opportunity to devise preliminary ablation targets. It is accepted that these require prospective testing and much remains unknown. Nevertheless, achieving a temperature of ≤-38 °C at 30 seconds means the vein is very likely to isolate and fairly likely to remain isolated (8.3% reconnected). If this is coupled with a TTI of ≤ 38 seconds, or if TTI is not visualised then a nadir temperature of ≤-54 °C, then the expected PV reconnection rate is very low (2-5%). If these targets are met then a single freeze is reasonable based on these data. There are no data on the "TTI +2 minutes" approach, but this too would seem reasonable.

If the temperature is >-35 °C at 30 seconds, then the vein is unlikely to isolate and consideration could be given to abandoning the freeze. Likewise, if TTI is not achieved by 1 minute then it is unlikely to do so and very unlikely to stay isolated, so abandoning the freeze would be reasonable. If a temperature between -35 to -38 °C is achieved at 30seconds and a TTI is visualised at 38-60 seconds then a "bonus" application ought to be considered. Accepting the limitations of the data

available, a modification of the flow chart for targets and dosing proposed by *Aryana et al.* is suggested for the PolarX in Figure 1.

Limitations

We have studied parameters associated with acute isolation to determine targets during the freeze likely to result in isolation. Likewise, we have studied parameters associated with sustained isolation despite a waiting period and adenosine. These are useful early data with which to derive preliminary targets. However, routine re-study procedures are desirable to confirm parameters associated with long term isolation and large outcome studies are required to test targets with respect to clinical outcomes.

This is a small study in terms of evaluating complications. Although these data are reassuring, large long-term registries are required to define the rate of infrequent adverse events.

The data regarding clinical outcomes should be regarded as pilot data. Large multicentre studies using a standardised approach with long term follow up are required to define outcomes, although theses can only test one strategy at a time. It is hoped that these data will useful in defining standardised target led approaches.

CONCLUSION

PVI using the novel PolarX Cryoballoon was similarly quick, safe and effective as with the Arctic Front Advance. However, the temperature drop was faster, the temperatures achieved were approximately 10°C lower at 30 seconds, 60 seconds and nadir temperature, and the TTI was 15-20 seconds earlier with the PolarX compared to that reported with the Arctic Front Advance. Achieving a temperature of ≤-39 °C within 30 seconds was predictive of acute PVI. Achieving a

temperature of ≤-40 ℃ at 30 seconds, a nadir temperature of ≤-54℃ and a TTI of ≤38 seconds were all associated with sustained PVI and a combination of 2 out of 3 of these predicted reconnection in 2-5% of PVs. Prospective testing of these targets and ultimately outcome studies are needed to define the best ablation approach with the PolarX and this cannot be assumed to be the same as with the Arctic Front Advance.

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Table 1- *Baseline characteristics*

Baseline characteristics	**Cohort n=60**
Age yrs. mean ± SD	60.3 ± 9.2
Male n (%)	38 (63.3)
Diabetes mellitus n (%)	6 (10.0)
Hypertension n (%)	25 (41.7)
TIA/CVA[T] n (%)	5 (8.3)
Ischaemic heart disease n (%)	9 (15.0)
Cardiac surgery n (%)	0 (0)
Cardiomyopathy n (%)	7 (11.7)
Left ventricular EF[Ŧ] ≥ 55% n (%)	46 (76.7)
LA size mm, mean ± SD	42.6 ± 4.7
AF type	
Paroxysmal	40 (66.7)
Persistent	20 (33.3)
Current antiarrhythmic or rate-controlling strategy	
Beta-blockers including Sotalol	52 (86.7)
Amiodarone	9 (15.0)
Flecainide	19 (31.7)
Current anticoagulation strategy	
Warfarin	1 (1.7)
Novel oral anticoagulants n (%)	59 (98.3)
Apixaban n (%)	22 (37.3)
Edoxaban n (%)	9 (15.3)
Rivaroxaban n (%)	28 (47.5)

[T]TIA/CVA- Transient ischaemic attack/Cerebrovascular attack

[Ŧ]EF- Ejection fraction

Table 2- *Demonstrates differences in the freeze parameters with the veins which isolated during the freeze compared to the veins that did not isolate during the freeze.*

Freeze parameters	**Vein isolated n= 235**	**Vein did not isolate n= 70**	**p-value**
Rate of temperature drop over 30 seconds, ℃/s mean ± SD	2.41±0.18	2.24±0.16	p<0.001
Temperature at 30 seconds, ℃ mean ± SD	-39.5±10.0	-35.4±4.9	0.002
Temperature at 60 seconds, ℃ mean ± SD	-49.5±6.4	-43.6±4.4	p<0.001
Time to reach -40 ℃, s mean ± SD	32.3±10.5	39.1±10.6	p<0.001
Time to reach -50 ℃, s mean ± SD	63.7±34.4	80.0±27.9	0.02
Nadir temperature, ℃ mean ± SD	-55.6±6.6	-46.8±6.6	p<0.001
Thaw time (to reach 0℃), s mean ± SD	17.7±6.2	12.5±3.7	p<0.001

Table 3- Demonstrates the findings of the multivariate analysis which shows the freeze parameters that were predictors of initial PVI.

	Univariate analysis		Multivariate analysis	
Freeze parameters	**P-value**	**Odds Ratio (95%CI)**	**P-value**	**Odds Ratio (95%CI)**
Rate of temperature drop over 30 seconds, ℃/s mean ± SD	<0.001	2.45 (1.64-3.21)		
Temperature at 30 seconds, ℃ mean ± SD	<0.001	1.20 (1.12-1.28)	0.003	1.26 (1.05-1.31)
Temperature at 60 seconds, ℃ mean ± SD	<0.001	1.21 (1.13-1.30)	-	-
Time to reach -40 ℃, s mean ± SD	0.001	0.95 (0.93-0.98)	<0.001	0.88 (0.81-0.95)
Time to reach -50 ℃, s mean ± SD	0.06	0.99 (0.98-1.00)	-	-
Nadir temperature, ℃ mean ± SD	<0.001	1.22 (1.15-1.30)	-	-
time (to reach 0℃), s mean ± SD	<0.001	1.27 (1.16-1.39)	-	-

Table 4- Demonstrates differences in the initial freeze parameters with the veins which remained isolated after the waiting period and IV administration of adenosine compared to the veins that reconnected during the waiting period and IV administration of adenosine.

Freeze parameters	**Vein remained isolated n=171**	**Veins acutely reconnected n=39**	**p-value**
Rate of temperature drop over 30 seconds, ℃/s mean ± SD	2.41±0.15	2.25±0.20	<0.001
Temperature at 30 seconds, ℃ mean ± SD	-40.3±10.5	-35.4±5.9	0.006
Temperature at 60 seconds, ℃ mean ± SD	-50.7±5.9	-43.6±5.0	<0.001
Time to reach -40 ℃, s mean ± SD	30.3±6.2	41.3±19.0	<0.001
Time to reach -50 ℃, s mean ± SD	61.5±34.8	81.8±24.1	<0.001
Nadir temperature, ℃ mean ± SD	-57.0±6.0	-49.3±5.0	<0.001
Thaw time (to reach 0 ℃), s mean ± SD	18.6±6.3	13.2±3.0	<0.001
Number of freezes to achieve initial PVI[T], n mean ± SD	1.3±0.6	1.4±0.8	0.29
Temperature at PVI, s mean ± SD	-42.8±5.1	-42.6±6.1	0.41
Time at PVI, s mean ± SD	39.3±18.5	67.6±38.3	<0.001

[T]PVI- Pulmonary vein isolation

Table 5- Demonstrates the findings of the multivariate analysis which shows the freeze parameters that were predictors of sustained PVI.

	Univariate analysis		Multivariate analysis	
Freeze parameters	**P-value**	**Odds Ratio (95%CI)**	**P-value**	**Odds Ratio (95%CI)**
Rate of temperature drop over 30 seconds, ℃/s mean ± SD	<0.001	2.25 (1.64-3.11)	-	-
Temperature at 30 seconds, ℃ mean ± SD	<0.001	1.33 (1.18-1.49)	0.002	1.24 (1.08-1.42)
Temperature at 60 seconds, ℃ mean ± SD	<0.001	1.27 (1.15-1.40)	-	-
Time to reach -40 ℃, s mean ± SD	<0.001	0.91 (0.87-0.96)	-	-
Time to reach -50 ℃, s mean ± SD	0.03	0.99 (0.98-1.00)	-	-
Nadir temperature, ℃ mean ± SD	<0.001	1.27 (1.16-1.38)	0.003	1.35 (1.11-1.64)
Thaw time (to reach 0℃), s mean ± SD	<0.001	1.31 (1.15-1.48)	-	-
Number of freezes to achieve initial PVI[T], n mean ± SD	0.46	0.81 (0.46-1.42)	-	-
Temperature at PVI, s mean ± SD	0.82	0.99 (0.92-1.07)	-	-
Time at PVI, s mean ± SD	<0.001	0.97 (0.95-0.98)	0.009	1.18 (1.04-1.34)

[T]PVI- Pulmonary vein isolation

Table 6- Demonstrates the PV reconnection rate and relative risk with individual and combination of parameters shown to be associated with a lower risk of PV reconnection.

Freeze parameters	**PV reconnection rate %**	**Relative Risk (95% CI)**	**P-value**
TTI ≤38 seconds	8.3	0.26 (0.13-0.50)	<0.001
Temperature at 30 seconds ≤-40 ℃	9.0	0.20 (0.09-0.42)	<0.001
Nadir temperature ≤-54 ℃	7.0	0.27 (0.13-0.55)	<0.001
TTI ≤38 seconds + Temperature at 30 seconds ≤-40 ℃	4.8	0.17 (0.06-0.46)	<0.001
TTI ≤38 seconds + Nadir temperature ≤-54 ℃	2.6	0.09 (0.02-0.38)	<0.001
Temperature at 30 seconds ≤-40 ℃ + Nadir temperature ≤-54 ℃	2.2	0.07 (0.02-0.27)	<0.001
TTI ≤38 seconds + Temperature at 30 seconds ≤-40 ℃ + Nadir temperature ≤ -54 ℃	1.6	0.06 (0.01-0.43)	0.005

FIGURES-

Figure 1- *Demonstrates a flow chart that proposes practical cryoballoon ablation dosing protocol when using the PolarX cryoballoon to achieve sustained PVI.*

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