Protocol:

Cryoballoon Isolation of CoMbined Posterior Wall and Pulmonary Veins VeRsus PulmOnary Veins AlonE for the Treatment of Paroxysmal Atrial Fibrillation (IMPPROVE–PAF) Study:

A Retrospective Analysis

Version 1.2 (August 8, 2021)

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1 STUDY INVESTIGATORS AND COORDINATOR CONTACT INFORMATION

PROJECT TITLE:	**Cryoballoon Isolation of CoMbined Posterior Wall and Pulmonary Veins VeRsus PulmOnary Veins AlonE for the Treatment of Paroxysmal Atrial Fibrillation (IMPPROVE–PAF) Study**
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2 OBJECTIVE

To examine the efficacy and safety of posterior wall isolation (PWI) within the region of the PV component in conjunction with pulmonary vein (PV) isolation (PVI) versus PVI alone using cryoballoon ablation for the treatment of patients with symptomatic paroxysmal atrial fibrillation (PAF) during long-term follow-up

3 STUDY ENDPOINTS

3.1 PRIMARY EFFICACY ENDPOINT

To investigate the recurrence of AF following PVI+PWI versus PVI alone using cryoballoon ablation in patients with symptomatic PAF

3.2 SECONDARY EFFICACY ENDPOINT

To investigate the recurrence of all atrial arrhythmias following PVI+PWI versus PVI alone using cryoballoon ablation in patients with symptomatic PAF

3.3 SAFETY ENDPOINTS

To examine the acute and long-term adverse event rates associated with PVI+PWI versus PVI alone using cryoballoon ablation in patients with symptomatic PAF, including but not limited to the following:

- Vagal nerve injury resulting in GI or esophageal dysmotility
- Heart failure
- Stroke or transient ischemic attack
- Esophageal injury or atrioesophageal fistula
- Vascular access complications (*e.g.* groin site issues, vascular injury)
- Cardiac perforation, tamponade or pericardial effusion
- Pericarditis
- Phrenic nerve injury (unresolved at discharge)
- Pulmonary vein stenosis
- Major bleeding
- Myocardial infarction
- Death

4 INTRODUCTION AND RATIONALE

Cryoballoon ablation has emerged as a safe and effective strategy for the treatment of atrial fibrillation (AF)[1,2], and based on growing evidence,[2,3,4] it recently received an initial rhythm control strategy ('first-line' therapy) indication by the Food and Drug Administration. Pulmonary vein (PV) isolation (PVI) guided typically by cryoballoon PV occlusion remains the cornerstone of cryoballoon ablation. Although single-procedure freedom from recurrent AF following such an approach has been reported to be as high as 82% at 12 months,[5,6] the success appears to be markedly diminished in the range of 50–60% during long-term follow-up.[7] This in part may be related to the inherent limitations of cryoballoon ablation which often yields an ostial (distal) level PVI.[8] Along these lines, prior investigations have found wide-area antral PVI encompassing the PV component (*i.e.,* the region of the posterior wall lying between the PVs) to be superior to ostial PVI.[9] Other more recent studies involving the cryoballoon have demonstrated marked improvements in clinical efficacy associated with concomitant PVI and posterior wall isolation (PWI) within the region of the PV component as compared to PVI alone, in patients with persistent AF.[10,11,12,13] Though widely-practiced, this approach has not been formally investigated in patients with symptomatic paroxysmal AF (PAF). Given the mechanistic similarities between persistent and PAF, we hypothesize that similar benefits may also be observed with PVI+PWI in the patients with PAF. Yet, given the relative infrequency of breakthrough/recurrent arrhythmias in patients with PAF, to detect a significant difference, large sample sizes and extended follow-up (>24 months) are likely needed. Hence, the aim of this retrospective, observational study is to examine the clinical efficacy and safety of PVI alone versus PVI+PWI using cryoballoon ablation **(Figure 1),** in a large cohort of patients with symptomatic PAF beyond 36 months of follow-up.

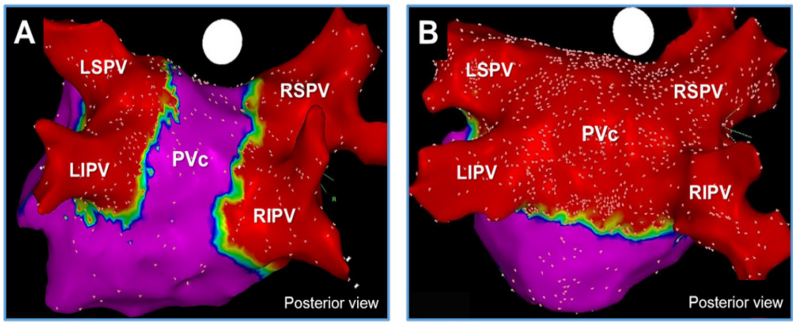

FIGURE 1. 3-D electro-anatomic maps created following cryoablation of AF illustrating the two proposed ablation strategies, including PVI **(A)** versus PVI+PWI to ablate and target the PV component **(B).** Voltage cutoff set to: 0.1 mV (the maps were created using CARTO; Biosense Webster, Inc, Irvine, CA). Areas shown in red correspond to ablated sites (voltage <0.1 mV) and those in pink correspond to unablated regions with normal voltage. *Abbreviations: LIPV, denotes left inferior pulmonary vein; LSPV, left superior pulmonary vein; PVc, pulmonary venous component; RIPV, right inferior pulmonary vein and RSPV, right superior pulmonary vein.*

4.1 EMBRYOLOGIC EVIDENCE

The PV component of the posterior left atrial wall shares a common primordial origin with the PVs.[14] The embryologic origin of the four PVs and the PV component can be traced back to the mediastinal myocardium derived from a mid-pharyngeal strand at 6 weeks of gestation.[15] Early on during development, a single primitive vein returns blood from the lungs to the common trabeculated atrium.[16] As the interatrial septum forms, the single vein divides twice to give rise to the four PVs. As the PV ostia migrate away from one another, the smooth tissue of the posterior left atrial wall forms.[16] Although this region is anatomically contiguous with the surrounding trabeculated tissue from the primitive left atrium, its embryologic origin results in electrophysiologic properties that are more similar to the muscular PV sleeves than the immediately adjacent atrial roof or floor ('true' posterior wall).[16]

During embryogenesis, the single vein and its surrounding tissue (in addition to the Bachmann's bundle and sinus venosus-derived structures) demonstrate the expression of genes responsible for development of cardiac conduction system.[17] Although expression of these genes decreases during embryogenesis, it is hypothesized that their continued low-level expression may explain why certain regions within the atria are more commonly the site of origin of focal ectopy.[17] These embryologic characteristics would certainly explain the well-accepted clinical observation that AF is frequently initiated by ectopic beats arising from the PVs[18] and the increasingly reported observation that ectopic beats from the left atrial posterior wall can similarly initiate AF.[19]

4.2 ANATOMIC EVIDENCE

A visual examination of the PV component and the orientation of its myofibrils suggests direct continuity between this region and the PV antra as does a gross anatomical assessment of certain left atrial morphologies **(Figure 2).** Meanwhile, underneath the smooth endocardial surface of the PV component, numerous subendocardial and subepicardial muscular bundles traverse with varying fiber orientation.[16] Fibers immediately surrounding the PVs typically encircle the veins, whereas those in the subepicardial aspect of the posterior wall are comprised of the septo-pulmonary bundle and display a more vertical or oblique orientation **(Figure 3).**[16] Immediately adjacent to the lateral aspect of the septo-pulmonary bundle are found transversely

oriented fibers which extend to the left PV ostia. It is this change in orientation that is believed to promote anisotropic conduction and therefore reentry.[16]

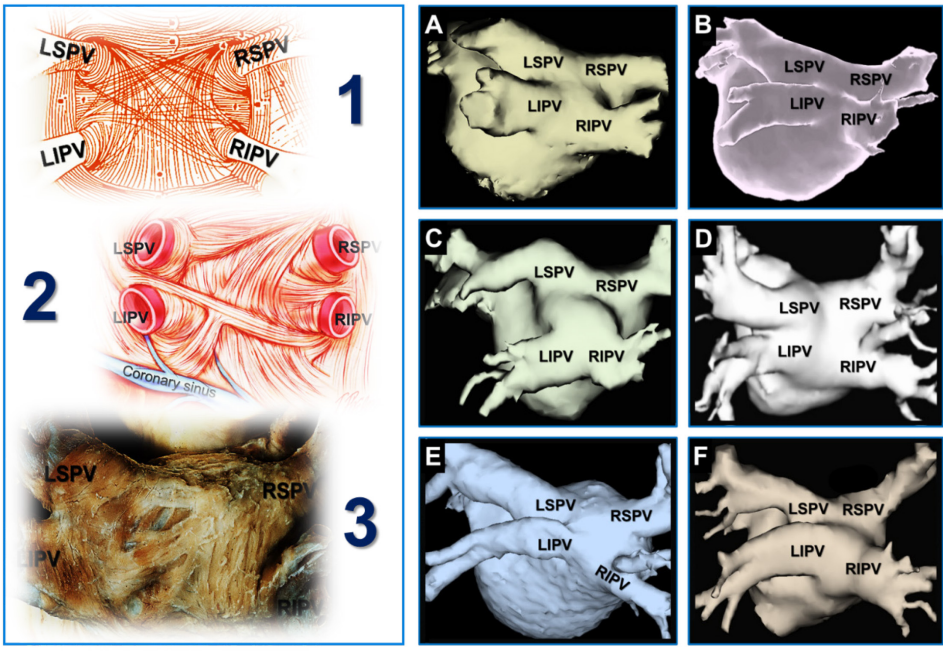

FIGURE 2. As shown in the left panel, a visual examination of the 'PV component of the posterior wall and the orientation of the myofibrils in this region strongly suggests direct continuity between this area of the posterior wall and the PV antra *(image borrowed from: [1]Nathan, et al. Circulation 1966; 34:412–22; [2]Illustration by Tim Phelps 2017 Johns Hopkins University, AAM; [3]Courtesy of Prof. Anton E. Becker, MD*), as does a gross anatomical assessment of certain left atrial morphologies seen in these computerized tomography scan images (right panel A–F). *Abbreviations: LIPV, denotes left inferior PV; LSPV, left superior PV; RIPV, right inferior PV and RSPV, right superior PV.*

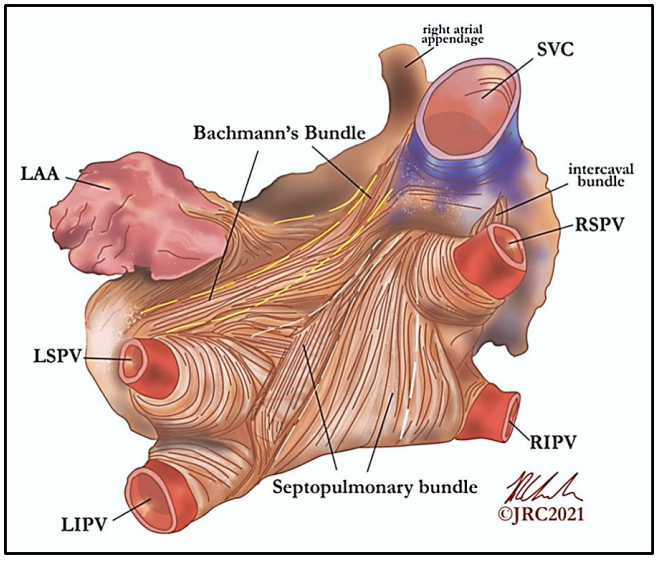

FIGURE 3. An illustration of the human inter-atrial and intra-atrial muscular bundles of the posterior left atria wall *(illustration borrowed from: Clarke, et al. J Cardiovasc Electrophysiol 2021 Jul 13. doi: 10.1111/jce.15164. Online ahead of print). Abbreviations: LAA, denotes left atrial appendage; LIPV, denotes left inferior PV; LSPV, left superior PV; RIPV, right inferior PV; RSPV, right superior PV and SVC, superior vena cava.*

Markides *et al.*[20] found that in patients with PAF, this juxtaposition of fiber orientations was associated with isochronal crowding and functional block depending on the direction of wave front propagation during sinus or paced rhythm. Similarly, mapping of fibrillatory waves during

cardiac surgery in patients with AF has revealed simultaneous propagation of longitudinally dissociated fibrillation waves which are separated by continuously changing lines of block.[21] These lines of block are once again most densely packed in the PV component, leading to the highest degree of block and dissociation and the lowest incidence of wave front boundaries formed by collision.[22]

4.3 ELECTROPHYSIOLOGIC EVIDENCE

As discussed, the PV component is derived from tissues other than the primitive cardiac tube.[14,23] Hence, the PV component is believed to be related more to PV versus atrial tissue. Some studies have suggested that these tissues share more in common with the sinoatrial nodal myocytes, displaying higher diastolic calcium contents and propensity to spontaneous depolarization.[24] Furthermore, the PV component exhibits increased conduction abnormalities,[25] a higher incidence of delayed after depolarizations and larger late sodium and intracellular and sarcoplasmic reticulum Ca++ contents, but a smaller inward rectifier potassium currents[20,26] and a reduced resting membrane potential.[26,27] The posterior wall and the PV myocytes are also characterized by shorter action potential durations and slower phase 0 upstroke velocities.[27] As such, the PV component is believed to be the site of collision of activation wave fronts as they sweep across the left atrial dome.[14] Along these lines, Mandapati *et al.* [28] found this region of the left atrium to be responsible for 80% of high-frequency rotors in an isolated sheep heart model.[29] Similarly, mapping in humans often localizes stable rotors or focal sources[29] as well as complex fractionated electrograms[30] in the posterior wall and the left atrial roof. The PV component has in fact been shown to be a common source of triggers accounting for up to ~40% of non-PV triggers in patients with AF.[31]

Lastly, the PV component is also the site of the main autonomic ganglionic plexi related to the left atrial dome (*i.e.,* the superior left atrial ganglionated plexus) which is believed to modulate extrinsic cardiac innervation and facilitate the occurrence of AF in a hyperactive autonomic state.[13,32] As such, it is believed that catheter ablation of the PV component also greatly attenuates the input of these plexi to the PVs, interrupting the vagosympathetic input to the ligament of Marshall and the inferior left ganglionated plexus which have been highly implicated in the pathogenesis of AF.[13,32]

5 STUDY DESIGN

All consecutive patients with an age >18 years and symptomatic PAF who underwent a first-time cryoballoon ablation using either PVI alone or PVI+PWI with at least 36 months of follow-up by a single operator (A. Aryana) between 1/2014 and 12/2018 at Mercy General Hospital, will be included in this retrospective, non-randomized study. Consistent with the current definitions,[33] all patients with persistent or long-standing persistent/permanent AF will be excluded from this analysis. Baseline patient demographics, procedural and clinical findings and outcomes will be exclusively obtained from retrospective chart reviews within the Cerner electronic medical record by the study investigator or sub-investigators listed on the protocol.

6 SAMPLE SIZE

The target sample size for this study is approximately 1,000 patients.

7 STATISTICAL METHODS

Baseline patient demographics, procedural and clinical characteristics will be recorded for the entire cohort. Continuous variables will be analyzed using the two-sample *t* test or Mann-Whitney test for parametric and non-parametric variables, respectively. The $\chi 2$ or Fisher exact test will be used for parametric or non-parametric categorical variables, respectively. For freedom from recurrent atrial arrhythmias, a Kaplan-Meier modeled analysis will be performed. For all analyses, P-values will be two-sided and a $P<0.05$ will be considered statistically significant. The analyses will be conducted with use of SPSS Version 20 (IBM SPSS Statistics, Chicago, IL).

8 DATA HANDLING

All Protected Health Information (PHI) will be confidential and each subject will be assigned a unique numerical identifier which will only be used by the members of the

research team to verify accuracy and completion of data collection. This unique numerical identifier, which will correspond to each subject's Medical Record Number (MRN), will be saved in a list called the Subject Key and will be the only link to each subject's identity. This Subject Key will be destroyed upon completion of the study. All variables will be entered into an electronic database. This electronic database will be saved separately from the Subject Key and both will be stored in a folder which is access restricted, encrypted and password protected. Only Institutional Review Board approved investigators will have access to this folder.

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