Risk of Coronary Artery Injury with Radiofrequency Ablation and Cryoablation of Epicardial Posteroseptal Accessory Pathways within the Coronary Venous System

Running title: Stavrakis et al.; coronary injury with EpiPSAP ablation

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Abstract:

**Background** - Ablation of epicardial posteroseptal accessory pathways (EpiPSAP) requires ablation within the coronary venous system. We assessed the risk of coronary artery (CA) injury with radiofrequency ablation (RFA) within the coronary venous system as a function of the distance between the CA and ablation site. We also examined the efficacy and safety of cryoablation close to a CA.

**Methods and Results** - Two-hundred-forty patients underwent ablation for EpiPSAP. Coronary angiography was performed prior to ablation in the last 169 patients and was repeated after ablation if performed in the coronary venous system within 5mm of a significant CA. The distance between the ideal ablation site and closest CA was <2mm in 100 (59%), 3-5mm in 28 (16%) and >5mm in 41 of 169 (25%) patients. CA injury was observed in 11 of 22 (50%) and 1 of 15 (7%) patients when RFA was performed within 2mm and 3-5mm of a CA, respectively. Cryoablation was performed in 26 patients with a significant CA located within 5mm. Cryoablation alone eliminated EpiPSAP conduction in 17 of 26 (65%) patients and in 8 patients with additional RFA without CA narrowing in any patient. Over a follow-up period of 3-6 months, single procedure success rates were 90% and 77% for RFA and cryoablation at the ideal site, respectively.

**Conclusions** - The risk of CA injury with RFA is correlated inversely with the distance from the ablation site. Cryoablation is a safe and reasonably effective alternative when a significant CA is located close to the ideal ablation site.

**Key words:** Wolff-Parkinson-White syndrome, ablation, coronary angiography, radiofrequency ablation, cryoablation
Epicardial posteroseptal and left posterior accessory pathways (EpiPSAP) comprise 19% of all posteroseptal and left posterior accessory pathways.1 These accessory pathways are formed by a connection between a sleeve-like extension of the coronary sinus (CS) myocardial coat (along the middle cardiac vein, posterior cardiac vein, another coronary vein, or the neck of a CS diverticulum) and the epicardial surface of the left ventricle (coronary sinus - ventricular accessory connection). 1-3 During anterograde accessory pathway (AP) conduction, endocardial mapping of the right and left ventricles identifies far-field activation (unipolar potential has a wide initial R wave), with the earliest far-field ventricular potential recorded at least 1cm apical to the tricuspid or mitral annulus. Local endocardial activation (rapid downstroke of the unfiltered unipolar electrogram) is recorded late, reflecting activation from epicardium to endocardium.1 Earliest ventricular activation is recorded epicardially, from the branch of the CS containing the myocardial extension (coronary vein, or neck of a CS diverticulum). Ventricular activation is preceded by a high frequency potential, similar to an anterograde AP potential,4 which is generated by activation of the CS myocardium extending along the venous branch (CSE potential in Figure 1).1

During retrograde AP conduction, the earliest high frequency potential (similar to a retrograde AP potential 4) is generated by the CS myocardial extension and is recorded from the same venous branch of the CS. This potential is followed by activation of the CS myocardium. The CS myocardial potentials propagate rapidly leftward, activating the left atrium 1-3 cm leftward of the vein,1 due to the oblique orientation of the fibers connecting the CS myocardial coat with the left atrium 5-7.

Attempts to ablate EpiPSAP conduction from the endocardium, close to the mitral annulus, by targeting the site of earliest retrograde activation generally fail to eliminate AP
conduction (but often produce a septal shift in the site of earliest retrograde atrial activation mimicking multiple APs) due to the extensive connections between the CS myocardium and the left atrium. Ablation also fails when endocardially targeting the site of earliest anterograde ventricular activation, which is often located 1 cm or more apical to the tricuspid or mitral annulus. The ideal ablation site is located within the branch of the CS containing the CS myocardial extension (coronary vein or neck of a CS diverticulum), at the site recording the sharpest CS myocardial extension potential (similar to an AP activation potential) on the unipolar electrogram recorded from the ablation electrode. However, in some patients, branches of the distal right coronary artery (posterolateral branch) or left circumflex coronary artery (posterior descending coronary artery) course between the vein and the ventricle, just below the CS, adjacent to the ideal ablation site. Early clinical experience and recent experimental studies suggest that delivering radiofrequency (RF) current close to a coronary artery can result in narrowing or occlusion of the artery. On the other hand, recent experimental evidence suggests that cryoablation within the coronary sinus and its branches can produce lesions in the CS and adjacent atrial or ventricular myocardium with a low risk of narrowing an adjacent artery.

The purpose of this study was to determine how often a significant branch of the distal right or left circumflex coronary artery is located close to the ideal ablation site in the coronary vein in patients with EpiPSAP, and assess the risk of injuring the coronary artery with RF ablation as a function of the distance from the ablation site. This study also examined the efficacy and safety of cryoablation when delivered at the ideal site within the coronary venous system, close to a coronary artery.
Methods

Study Population

Between 1989 and 2007, 716 patients were referred for catheter ablation of a posteroseptal or a left posterior AP at the University of Oklahoma Health Sciences Center. Of those, 306 (43%) had had one or more prior failed catheter or surgical ablation procedures. An EpiPSAP (CS - ventricular connection) was identified in 240 of 716 (34%) patients, including 88 of 410 (21%) of patients without prior ablation and 152 of 306 (50%) of patients with prior failed ablation.

Ablation

CS angiography (balloon occlusion technique) was performed in all patients at the beginning of the procedure to define the coronary venous anatomy as well as the presence or absence of a CS diverticulum. The ideal ablation site was defined as the location within a tributary of the CS (middle cardiac vein, posterior coronary vein, small cardiac vein, or other branch) or the neck or body of a CS diverticulum recording the largest, sharpest CS myocardial extension potential on the unipolar electrogram recorded from the distal (ablation) electrode on the ablation catheter (Figure 1).

Prior to 1994, RF ablation was performed using a 4mm or 8mm tip electrode (without irrigation), beginning at 5 W and increasing power gradually towards 15 W (25 W with 8mm electrode), using a temperature limit of 60-70°C. The power at which AP conduction blocked was held constant (no further increase) for 2 minutes or until impedance rise occurred. The RF application was terminated immediately in the event of an impedance rise (≥ 5 Ω above the lowest value). Beginning in 1994, RF ablation was performed using an investigational irrigated electrode catheter (ThermoCool, Biosense Webster, Inc), followed by use of the approved device after 2004. Using the irrigated electrode, the RF application was initiated at 15 W and the power
was increased slowly towards 25 W, until AP conduction block was achieved (no further increase). The RF application was maintained for 2 minutes or until an impedance rise occurred ($\geq 5 \, \Omega$). Beginning in 1994 (the last 169 patients), coronary angiography was performed prior to ablation, with the ablation catheter positioned at the ideal ablation site. The distance between the ablation electrode at the ideal ablation site and the closest significant artery (diameter $>1$mm) was measured at the point in the cardiac cycle where the electrode was located closest to the artery in the right anterior oblique and left anterior oblique projections. Coronary angiography was repeated following ablation (either RF or cryoablation) in all patients when ablation was performed within the coronary venous system at a site within 5mm of a significant coronary artery. Intra-coronary nitroglycerin was administered prior to contrast injection in both pre- and post-ablation angiography, to prevent (and exclude the diagnosis of) coronary spasm due to catheter manipulation or temperature changes.

Cryo-ablation was performed using an investigational 7Fr, 4mm cryo-electrode catheter beginning in late 2002 (Freezor Focal Ablation Catheter, CryoCath Technologies, Inc), followed by use of the approved device after 2004. Cryo-applications ($-75^\circ$C for 4 min) were delivered at ideal sites within the coronary venous system using the 7Fr, 4mm or 7Fr, 6mm cryo-electrode, when coronary angiography revealed a significant coronary artery within 5mm of the ideal site.

**Statistical Analysis**

Data are presented as mean $\pm$ standard deviation for normally distributed continuous variables, median and interquartile range for non-normally distributed discrete variables and as percentages with 95% confidence intervals (CI) for categorical variables. Comparison between discrete variables was performed using the Wilcoxon rank sum test. Categorical variables were compared using chi-square test. P-values $<0.05$ were considered statistically significant.
Results

Two hundred forty patients (mean age 31.7±15.5 years; 50% male) underwent catheter ablation for an epicardial postero-septal (222) or left posterior (18) EpiPSAP between 1989 and 2007 at our institution. CS angiography identified a CS diverticulum in 51 of 240 (21%) patients. The neck of the diverticulum inserted into the middle cardiac vein (rather than the CS) in 15 of the 51 (29%) patients. A CS myocardial extension potential (similar to an AP potential) was identified in 213 of 240 (89%) patients.

Coronary Angiography Results

Coronary angiography was performed prior to ablation in 169 of 240 (70%) patients. Of the 169 patients, 129 (76%) had a right dominant circulation, 28 (17%) had a left dominant circulation and 12 (7%) had a co-dominant circulation. The median distance between the ideal ablation site and the closest significant coronary artery was only 2mm (interquartile range 1mm to 5mm). In 100 of 169 (59%) patients, the distance of a significant coronary artery from the ideal ablation site was ≤2mm (Figure 2). This distance was 3mm to 5mm in 28 (16%) patients and >5mm in 41 (25%) patients (Table 1).

Coronary Artery Injury

Of the 100 patients with a significant coronary artery within 2mm of the ideal ablation site, RF ablation was performed at the ideal site in only 22 patients (Table 1). Due to the risk of RF ablation close to a coronary artery, in the remaining 78 patients: 1) RF ablation was attempted at a non-ideal site, outside of the coronary venous system (at the tricuspid or mitral annulus) in 48 patients; 2) ablation was not attempted in 8 patients prior to the availability of cryoablation (patients were referred for surgical ablation using the epicardial approach\textsuperscript{14}); and 3) cryoablation was performed in 22 patients. For the 28 patients with a coronary artery within

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3mm to 5mm of the ideal ablation site: 1) RF ablation was performed at the ideal ablation site in 15 patients; 2) RF ablation was attempted at a non-ideal site, outside of the coronary venous system in 8 patients; 3) ablation was not attempted in 1 patient; 4) and cryoablation was performed in 4 patients (Table 1). RF ablation was performed at the ideal ablation site within the coronary venous system in all 41 patients without a significant coronary artery located within 5mm (mean distance 10±3mm) (Table 1).

Coronary angiography after ablation revealed arterial stenosis in 11 of 22 (50%; 95% CI, 28% to 72%) patients who underwent RF ablation at the ideal site within 2mm of a significant coronary artery (Table 2 and Figures 3 and 4). Coronary artery stenosis ranged from 25% in 2 patients, to >50% in 9 patients, including complete occlusion in 3 patients. In 1 patient, complete occlusion was treated with balloon angioplasty. In the remaining 2 patients, complete occlusion occurred in a smaller branch, and angioplasty was not required. Of the 15 patients who underwent RF ablation at the ideal site located 3-5mm from a significant coronary artery, coronary artery injury was detected on repeat angiography in only 1 (7%; 95% CI, 0% to 32%) patient (70% stenosis). None of the 41 patients who underwent ablation at the ideal site >5mm from a coronary artery developed electrocardiographic or clinical evidence of coronary artery injury (Table 2). The number of RF applications was similar between patients with (median 5 RF applications; interquartile range 2 to 11) or without coronary artery injury (median 5 RF applications, interquartile range 2 to 9; p=0.81). A plot of coronary artery injury as a function of the distance from the ablation site is shown in Figure 5.

Angiography was repeated at 6 months in 8 of the 12 patients with coronary artery injury. All 6-month angiograms showed minimal arterial narrowing (<50% stenosis in all 8 patients tested), including the 2 patients who had had complete occlusion. Long-term follow up in these
patients is lacking, so it remains unknown whether these lesions became clinically significant or remained silent.

None of the 26 patients (0%; 95% CI, 0% to 13%) who underwent cryoablation within 5 mm of a significant coronary artery had new stenosis on angiography after ablation (Table 2).

**RF Ablation Success**

When RF energy was delivered at the ideal ablation site within the coronary venous system, EpiPSAP conduction was acutely eliminated in 142 of 143 (99%; 95% CI, 96% to 100%) patients, including patients with and without coronary angiography (Table 1). A median of 5 RF applications (interquartile range 1 to 8) were required in this group. When RF ablation was performed at a non-ideal site, EpiPSAP conduction was acutely eliminated in only 49 of 62 (79%; 95% CI, 67% to 88%) patients ($p<0.0001$ vs. RF ablation at ideal site). Over a follow-up period of 3 to 6 months, EpiPSAP conduction returned in 13 patients who underwent RF ablation at the ideal site, resulting in a long-term, single-procedure success rate of 90% (95% CI, 84% to 95%). When ablation was performed at a non-ideal site, the long-term, single-procedure success was only 56% (95% CI, 43% to 69%; $p<0.001$ vs. ablation at ideal site).

Of the 41 RF patients who had acute failure (14 patients) or recurrence of EpiPSAP conduction at follow-up (27 patients), 21 patients underwent a second catheter ablation at our institution, which was successful in 19, while a third procedure was required in the other 2 patients to achieve permanent elimination of the EpiPSAP. This results in a long-term success in 137 of the 143 patients (96%; 95% CI, 91% to 98%) in whom RF ablation was performed at the ideal ablation site and 48 of the 62 patients (77%; 95% CI, 65% to 87%) in whom RF ablation was performed outside of the ideal ablation site.
**Cryoablation Success**

Twenty six patients underwent cryoablation between late 2002 and 2007, due to the presence of a significant coronary artery close to the ideal ablation site. A CS myocardial extension potential (CSE, similar to an AP potential) was recorded from the venous branch of the CS (most often the middle cardiac vein) in 25 of the 26 patients. The distance between the ideal ablation site and the closest significant coronary artery was ≤2mm in 22 patients and 3-5mm in 4 patients.

Cryoablation alone successfully eliminated accessory pathway conduction in 17 of 26 (65%; 95% CI, 44% to 83%) patients (median 7 cryo-applications; interquartile range 4 to 9). In 8 of the 9 remaining patients, cryoablation within the coronary venous system blocked conduction between the vein and the CS, and therefore the left atrium (median 10 cryo-applications; interquartile range 9 to 21), but failed to completely eliminate AP conduction due to persistent epicardial connections between the AP and right atrium. The right atrial component of the EpiPSAP was eliminated in 7 of the 8 patients by multiple RF applications within the right atrium, away from the tricuspid annulus, at the site of earliest (far-field) retrograde atrial activation (median 8 RF applications; interquartile range 3 to 9). In the 8th patient, the combination of cryoablation within the coronary venous system and RF ablation in the right atrium failed to eliminate EpiPSAP conduction. In the one remaining patient, ablation at the posterolateral mitral annulus was required to completely eliminate EpiPSAP conduction. Thus, the overall acute success rate of cryoablation in eliminating EpiPSAP conduction was 65% (95% CI, 44% to 83%) with cryoablation alone and 96% (95% CI, 80% to 100%) with additional RF ablation (Table 1). The large number of cryo-applications reflects the fact that frequent recurrences of AP conduction were observed within 1 hour of the last successful cryoablation, necessitating waiting for up to 2 hours after the final “successful” cryo-ablation to ensure...
elimination of EpiPSAP conduction. Over a follow-up period of 3 to 6 months, 5 of the 25 patients with successful cryoablation had recurrence of EpiPSAP conduction. Thus, the long-term, single procedure success rate of cryoablation (with and without additional RF ablation) was 77% (95% CI, 56% to 91%).

Discussion

The main finding of this study is that RF energy delivered within coronary veins or the neck of CS diverticula in close proximity to a coronary artery is associated with a high risk of coronary artery injury. This is extremely important considering that most patients undergoing ablation of an EpiPSAP are young (average age 31 years in our cohort). Moreover, ablation within the coronary venous system may lead to disastrous complications, including lethal arrhythmias. Therefore, RF ablation within <5 mm of a significant coronary artery should be considered carefully, or avoided. The orientation of the ablation catheter may be an important determinant of the likelihood of coronary artery injury. Based on our experience, delivering RF energy with the electrode oriented perpendicular to a coronary artery (where the electrode in the vein compresses the artery) appears to carry a higher risk of coronary artery injury compared to an electrode oriented parallel to an artery (Figure 4).

Our results highlight the value of coronary angiography when ablation anywhere within the coronary venous system is contemplated. We found that it was often safer to perform ablation relatively deep in the middle cardiac vein (or other vein) than within the CS or just inside the vein, due to the frequent proximity of the posterolateral branch of the right coronary artery to the CS (Figure 4). The risk of injuring a coronary artery, as a function of the distance from the coronary artery, represents a continuum, rather than an all-or-none phenomenon. The risk diminishes significantly for distances >2 mm and is negligible for distances >5 mm. Although
the stenosis often appears to regress at 6 months, experimental studies have shown that the media, and frequently the intima, of the artery are destroyed \(^{10}\) and therefore the ability of the artery to dilate may be compromised.

Targeting ablation of an EpiPSAP outside the coronary venous system is associated with a significantly lower success rate compared to ablation within the coronary venous system (middle cardiac vein, posterior coronary vein, other coronary vein, or the neck of a CS diverticulum). This is due to the unique anatomy of the EpiPSAP, which represents an anatomical and electrical connection between an extension of the CS myocardial coat (along a coronary vein) and the epicardial surface of the left ventricle \(^1\). This places the entire CS myocardial coat within the connection between the left atrium and ventricle. While a typical atrioventricular AP connects the atrium and ventricles at the level of the tricuspid or mitral annulus, allowing successful ablation from the endocardium \(^{16}\), the extensive connections between the CS myocardial coat and the left atrium, compounded by the oblique course of the CS myocardial fibers and the absence of a clear endocardial location for the ventricular insertion of the AP, lead to frequent ablation failure of EpiPSAP from the endocardial aspect at the mitral annulus \(^1\). RF ablation of an EpiPSAP should be ideally attempted within the coronary vein or neck of a diverticulum, where the connecting fibers are narrowest. Cryoablation is the preferred option when a significant coronary artery is located close to the ideal ablation site. Surgical ablation, using the epicardial approach described by Guiraudon and co-workers, is another treatment option for these patients \(^{14}\).

Our results suggest that cryoablation is safe, as supported by the absence of coronary artery narrowing despite the close proximity of cryo-applications to a significant coronary artery. Given that coronary artery stenosis has been reported with epicardial cryoablation, both
clinically \(^{17}\) and in experimental models \(^{18}\), the risk of coronary artery stenosis with cryoablation close to a coronary artery, although significantly smaller compared to RF ablation, may not be zero. However, based on recent experimental data, the probability of vascular damage is inversely proportional to vessel diameter, with no evidence of vascular damage in vessels with diameters \(>0.7\text{mm}\) \(^{18}\). Cryoablation (alone or in combination with RF applications at endocardial sites) is associated with a reasonable acute success rate and should be considered when coronary angiography shows a significant coronary artery located close to the ideal ablation site, even though the long-term success rate of cryoablation is less optimal than RF ablation (Table 1). These results are consistent with prior studies of accessory pathway ablation showing that the recurrence rate with cryoablation is higher compared to RF ablation \(^{19,20}\). It should be noted that the success rate of cryoablation in our cohort may have been underestimated because of the use of \(4\text{mm}\) and \(6\text{mm}\) tip cryo-electrodes. In our subsequent experience, the acute success rate is somewhat improved with advances in cryo-electrode technologies (use of \(8\text{mm}\) tip cryo-electrodes), but the recurrence rate remains higher with cryoablation that with RF ablation. Notwithstanding this limitation, the significantly better safety profile of cryoablation compared to RF ablation makes it the treatment of choice for ablation of EpiPSAP located in close proximity to a coronary artery, in order to avoid coronary artery injury.

These results are consistent with recent experimental data, which suggested that cryoablation within \(2\text{mm}\) of a coronary artery was not associated with coronary artery narrowing, despite producing a similar incidence of necrosis of the media of the artery as RF ablation \(^{10}\). The type of medial necrosis is different between RF ablation and cryoablation. RF ablation causes coagulation necrosis, destroying the architecture of the vessel, while the medial necrosis produced by cryoablation is associated with fibroblast infiltration and relatively preserved
architecture. The exact mechanism of coronary artery narrowing produced by RF ablation has not been elucidated. Spasm is unlikely, because the narrowing occurred despite the presence of intracoronary nitroglycerin. It is possible that heat-induced shrinkage of collagen fibers associated with RF energy application is responsible for the coronary artery narrowing. Cryoablation was not associated with late intimal proliferation or narrowing of the coronary arteries up to six months post-ablation in a recent experimental study in young piglets. The clinical implication for this observation is that cryoablation can be safely used in both children and adults with little or no risk of acute or chronic injury to the coronary arteries.

Conclusion

The risk of injuring a coronary artery with RF ablation delivered within a coronary vein is inversely related to the distance of the artery from the ablation site, with very high (50%) risk of coronary artery injury for RF ablation within 2 mm of the artery. Cryoablation is a safe and reasonably effective alternative when a significant coronary artery is located close to the ideal ablation site.

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Conflict of Interest Disclosures: None

References:


**Table 1.** Distance between the ablation electrode at the ideal ablation site and the closest significant coronary artery, mode of ablation, and single procedure ablation success.

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Table 2. Risk of coronary artery injury with radiofrequency (RF) ablation vs. cryo-ablation at the ideal ablation site as a function of distance from a significant coronary artery

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Figure Legends:

Figure 1. During right atrial appendage (RAA) pacing, electrograms recorded from the ideal ablation site within the middle cardiac vein (MCV) exhibit a large, sharp coronary sinus myocardial extension potential (CSE, arrows) on both the distal bipolar (Bip 1-2) and distal unipolar (Uni I) electrograms. Note early antegrade ventricular activation (short vertical line represents local ventricular activation time). Earliest ventricular activation was recorded 3-5 mm deeper within the MCV. HB, His bundle; RV, right ventricle; Bip, bipolar electrogram; Uni, unipolar electrogram; p, proximal; d, distal; A, atrial potential; H, His bundle potential; V, ventricular potential; and S, pacing stimulus.

Figure 2. Radiographs in the right anterior oblique (RAO; A) and left anterior oblique (LAO; B) projections during right coronary artery angiography in a patient with an epicardial posteroseptal accessory pathway (EpiPSAP). The ablation catheter is positioned at the ideal site in the middle cardiac vein (MCV). The posterolateral branch of the right coronary artery (RCA) is located within 2 mm of the proximal edge of the ablation electrode at ideal ablation site. No
radiofrequency ablation was performed at that site. For size reference, note that the distal electrode of the ablation catheter is 2.5mm in diameter.

**Figure 3.** Radiograph in the LAO projection during right coronary artery (*RCA*) angiography in a patient with EpipSAP. **A.** Before radiofrequency (RF) ablation, the ablation catheter is positioned at the ideal site in the MCV (*arrow*), less than 2mm from the posterolateral branch of the RCA. **B.** After RF ablation, there is a 90% stenosis of the posterolateral branch of the RCA (*arrow*). For size reference, note that the distal electrode of the ablation catheter is 2.5mm in diameter.

**Figure 4.** RCA angiography (LAO projection) in a patient with an EpipSAP, showing the posterolateral branch of the RCA coursing directly behind the CS. Ablation was performed deep in the MCV, far from the posterolateral branch of the RCA, but close (<2mm) to a small artery running parallel to the ablation electrode. **A.** Before RF ablation, the ablation electrode is positioned at the ideal site, deep in the middle cardiac vein (*arrow*), less than 2mm from a small branch of the distal RCA. **B.** Angiography prior to ablation, showing the small arterial branch. **C.** After radiofrequency ablation, there is no change in the small arterial branch that was oriented parallel to the ablation electrode. For size reference, note that the distal electrode of the ablation catheter is 2.5mm in diameter.

**Figure 5.** Risk of coronary artery injury with radiofrequency ablation as a function of the distance from the ablation site. Note that no coronary artery injury was observed when the distance from the ablation site was >5mm (*dotted line*).
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