Published in final edited form as:
Heart Rhythm. 2011 December ; 8(12): 1975–1980. doi:10.1016/j.hrthm.2011.07.006.

CORONARY ARTERY PATHOPHYSIOLOGY AFTER RADIOFREQUENCY CATHETER ABLATION: REVIEW AND PERSPECTIVES

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Abstract

Radiofrequency ablation (RFA) has proven to be an effective and safe treatment in patients with ventricular and atrial tachyarrhythmias. Among complications arising after RFA, the incidence of coronary artery (CA) injury is exceedingly low. When CA injury does occur, however, it can be clinically devastating. The proximity of CAs to common ablation sites suggests that the relationship between RFA and CA perfusion pathophysiology is important. While others have described the presentation and outcomes of patients with CA injury after ablation, a review that consolidates the mechanisms of CA injury after RFA has yet to be presented in the cardiology literature. We conducted an extensive literature search of studies published over the past thirty years that relate the biophysics of RFA with CA perfusion pathophysiology and injury. From this, we present a review of the dynamic relationship between RFA and CA perfusion. We describe RFA lesion pathology, mechanisms of CA injury from RFA, and factors that influence lesion formation such as convective cooling and the 'shadow effect.' Finally, we summarize methods to mitigate CA injury after RFA and propose new research avenues to optimize lesion formation and safe arrhythmia treatments when tissue is ablated in the vicinity of CAs.

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Conflicts of Interest: The authors have no conflict of interests to disclose.

Keywords

Radiofrequency Ablation; Coronary Artery Injury; Lesion Formation; Coronary Artery Stenosis; Complications; Convective Cooling; Heat Sink; Shadow Effect

Introduction

Over three decades, the establishment of catheter RFA for the treatment of arrhythmias such as Wolff-Parkinson-White Syndrome, atrioventricular nodal reentrant tachycardia and cavotricuspid-dependent atrial flutter heralded its application to more complex arrhythmias such as atrial fibrillation (AF) and ventricular tachycardia (VT). In general, the use of RFA for the treatment of arrhythmias holds a high efficacy and an excellent safety record. Complication rates range from 1–5% according to recent surveys[1, 2] and vary depending on the tachycardia and myocardial volumes ablated. RFA procedural complications include pulmonary vein stenosis, pericardial effusion or cardiac tamponade, peri-procedural stroke or transient ischemic attack, atrioesophageal fistula, phrenic nerve paralysis, peripheral vascular complications including deep vein thrombosis, pseudoaneurysm, and catheter insertion site hematoma requiring transfusion or invasive intervention.

CA injury is among the rarest complications of RFA. In a cohort of patients undergoing 4655 procedures between 1998 and 2008, only 4 patients (0.09%) experienced coronary artery injury secondary to ablation.[3] However, the close proximity of common ablation sites to CAs would suggest that CA injury might occur more often than reported, as CA pathophysiology after RFA may go undetected.[4] In order to capture the full range of CA injury after RFA, we discuss general RFA lesion pathology, mechanisms of CA injury after RFA, and present several parameters that affect lesion formation such as convective cooling and the opposing ‘shadow effect’ on the arrhythmia treatment. We show how specific procedures and sub-groups of patients are associated with higher risk for CA injury. Finally, we propose areas for research and development of new ablation techniques to maximize safety and procedure efficacy.

Lesion pathology after RFA

An understanding of how tissue pathology at the RF lesion progresses over time is essential for planning safe and efficacious RFA. Changes at the lesion site can be observed immediately after RFA and continuously evolve over approximately 8 weeks (Figure 1). Instantaneous RF delivery results in tissue discoloration because of protein denaturation, principally myoglobin, which loses its red pigment.[5] Within hours of RFA, histological examination reveals a central zone of coagulation necrosis, nuclear pyknosis, and basophilic stippling indicating intracellular calcium overload.[5] This central area of necrosis is surrounded by a hemorrhagic transition zone (granulation tissue), with infiltrating mononuclear inflammatory cells associated with edema and increased tissue thickness.[6–8] Within 4–5 days, complete coagulation necrosis and early fatty changes are evident in the central lesion zone while the transition zone has disappeared.[5–7] By the end of the first week, fatty changes have developed and by week 8, fibrosis has completely replaced the lesion.[9]

In general, the extent of acute injury at the RF lesion is believed to determine success or failure of ablation at an arrhythmogenic focus, but other factors can also influence efficacy. First, thermal latency causes an increase in tissue temperature that may persist for over 30 seconds after cessation of RF delivery. This prolonged temperature increase explains how an arrhythmia may disappear permanently several hours after presumed unsuccessful RFA.[10, 11] Second, growth of the ablation lesion has been suggested to cause long-term

freedom from AF after early recurrence of the arrhythmia.[12, 13] Finally, arrhythmogenic substrate may return to function up to a few weeks following a presumed successful RFA as inflammatory and necrotic tissue regresses.[14, 15] Therefore, several phenomena affecting the RFA lesion influence RFA outcomes.

Mechanisms of RFA-induced coronary artery damage

Due to the proximity of CAs to commonly ablated sites, it is reasonable to hypothesize that in addition to affecting tissues, RFA also compromises vascular integrity and function. The presentation and outcomes of CA injury after RFA in adults is well described.[3] Specific mechanisms of CA injury vary from case to case as Roberts-Thomson et al. discuss, but a summary of these mechanisms has not yet been consolidated in the cardiology literature. Based on our review of case reports and case series, we describe how RFA causes CA injury acutely and subacutely (Figure 2).

In the acute setting, RF energy can result in coronary spasm, direct vessel trauma, and thromboembolism. Spasm is thought to be the most common mechanism of coronary injury due to RFA, especially if RF energy is delivered in the coronary sinus or on the epicardium.[16] Coronary spasm after RFA is supported by reports of presumed acute arterial occlusions responsive to nitrates yet with angiographically normal vessels.[17–20] The mechanism of spasm is thought to be due to RF-induced increases in autonomic activity at nerve terminals in the densely innervated left atrium.[21–24]

RF energy also causes functional and morphological damage to the CA media and endothelium. This direct damage compromises the vessel's ability to regulate vascular tone and coagulation, increasing the propensity for nidus formation leading to acute or subacute thrombosis. In a porcine model, epicardial RF lesions created near the major CAs were associated with both disruption of the vascular wall and severe modulation of vascular tone.[25] Application of RF 1 mm from the CA resulted in a significant decrease in endothelium- independent contraction to potassium chloride and a significant decrease in endothelium- dependent relaxation to bradykinin. On histological examination, these functional findings correlated with disruption of the vascular wall up to 5 mm from the RF application site. Accordingly, Sosa et al. have recommended that RF should not be applied to an epicardial site within 12 mm of a major CA.[26]

Another mechanism of RFA induced CA damage proposes heat-induced collagen shrinkage and subsequent vessel narrowing.[27] It is known that the extent of CA stenosis correlates with the amount of heat-induced denaturation of collagen fibers in the vessel wall.[28, 29] Replacement of the coronary arterial media with proliferating extracellular matrix, as shown in a study of 9 mongrel dogs, led to severe hyperplasia and intravascular thrombosis.[30] In these experiments investigators also compared the effects of RFA with the orientation of the lesion line and its proximity to CAs. The extent of injury to the vessel wall depended on how the ablation line crossed the CA: RFA delivered adjacent and parallel to the artery resulted in lesions that were limited to the media; however, RFA delivered directly and perpendicularly to the artery resulted in severe intimal hyperplasia and intravascular thrombosis. Therefore, heat from the catheter tip and its orientation in relation to the CA are important considerations for the ablationist to minimize intimal hyperplasia and intravascular thrombosis.

Convective cooling protects coronary arteries but may also complicate RF lesion formation: weighing the 'heat sink' against the 'shadow effect'

Lesion size, properties of RF energy, proximity and orientation to CAs are known parameters that determine the impact of RFA on CAs. Convective cooling is another important factor that influences lesion formation. Initially described in the setting of anti-malignancy hyperthermia treatments,[5] convective cooling results from the flow of intracardiac and microvascular blood, which creates a 'heat sink' (Figure 3). In general, the susceptibility of CAs to thermal damage is inversely proportional to the electrode-to-artery distance.[30] When RFA is delivered to a tissue through an electrode, temperature gradients are created as heat moves from the tip through the tissue. Because temperature decreases through tissue in a hyperbolic fashion,[31] the likelihood of thermal injury to CAs also decreases as distance from the catheter tip increases. This tissue temperature model is independent of the convective cooling phenomenon.[31] In the 'heat sink' effect, when an RF electrode is positioned close to a vessel, coronary blood flow within and surrounding the vessel provides a protective feature by preventing substantive heating of the vascular endothelium.[32] In fact, convective cooling may account for the paucity of reported CA complications or measurable changes in coronary arteriograms performed pre- and post-RFA.[33]

Protection conferred by convective cooling during RFA, however, may be limited by the brief duration of energy delivery and decreases in microvascular perfusion of ablated tissue.[31] Ablation in young or small hearts where narrower vessels yield a less pronounced cooling phenomenon may lead to increased susceptibility to CA injury.[34] Pre-existing narrowed atherosclerotic CAs in patients with coronary artery disease (CAD) are also at increased risk for thermal injury. In a patient who underwent RFA for atrial flutter, undocumented upstream right CA stenosis, which limited flow and decreased convective cooling, was believed to have been the mechanism of CA injury.[35]

The cooling effect of small coronary vasculature, though less protective from thermal injury than that of larger vessels, is at times sufficient to prevent RF lesion formation and decrease ablation efficacy. Fuller et al. demonstrated in a rabbit model that flow through even small intramyocardial vessels can prevent transmural lesion formation, preserve conduction through an RF lesion and thereby prevent complete conduction block.[36] Termed, the 'shadow effect', this phenomenon must be weighed against the benefit of the 'heat sink' in order to maximize the likelihood that an RF lesion eliminates aberrant electrical conduction.

Understanding the parameters involved in lesion formation and how they relate to coronary blood flow in large *and* small coronary vessels is essential to safe and effective ablation. For example, Fuller et al. elucidated that the amount of protected myocardium around the perfused vessel is related to arterial flow rate, intramural vascular diameter, and lesion temperature while electrical conduction through a lesion is dependent on arterial flow rate and volume of preserved myocardium. Application of such parameters to pre-ablation measurements and computational models of lesion formation could lead to safer and more efficacious ablation techniques.

Predicting lesion dimension to enhance safety and efficacy of RFA

We have discussed several phenomena that influence RF lesion formation and the success of RFA. Extensive modeling in experimental tissue systems supports the concept that some of these phenomena can be quantified prior to RF administration to predict lesion dimension.[37, 38] In a tissue model of myocardial electrical conductivity, convective cooling was approximated by maximum tip temperature increase and the slope of temperature decay.

These measurements correlated well with flow rate and predicted lesion dimension. Therefore, treatment planning for cardiac RFA could estimate RF lesion dimensions depending on target temperature, ablation time and blood flow.[39] It is conceivable that incorporation of other measures mentioned previously such as thermal latency, growth of the ablation lesion, healing, the shadow effect, and tip temperature into a computational model might lead to even more accurate predictions of lesion formation that could reduce the incidence of CA injury and enhance efficacy of RFA.

Prevention of Coronary Artery Injury from RFA

Several protocol improvements in addition to computational calculations can reduce CA injury (Figure 4). For example, minimizing RF energy delivery during ablation is advisable, especially in small patients in whom vital structures may lie close to the ablation site, or in patients with severe coronary artery stenosis.[28, 40, 41] Defining a patient's unique coronary anatomy is also essential. In epicardial ablations, the ablationist applies RF in the neighborhood of major coronary arteries susceptible to damage from RFA. Major coronary arteries also lie in close proximity to the right ventricular outflow tract (RVOT). The left main coronary artery, for example, courses within the penumbra of potential ablation sites in septal regions of the RVOT near the pulmonary valve. The electrophysiologist should therefore delineate the anatomic courses of major coronary arteries prior to ablation of VT arising from the RVOT.[42]

Chilled saline irrigation has been proposed as another strategy to counter injury to CAs during RFA. Thyer et al. demonstrated that intracoronary irrigation with chilled saline in an *in vitro* ovine heart model protected the CA endothelium from heat-induced damage and reduced the probability of the ablation lesion extending to the CA during epicardial RFA.[43] Follow-up *in vivo* animal studies and subsequent trials to assess the safety and efficacy of this technique are needed.

Fluoroscopic or electro-anatomic confirmation of catheter position and use of smaller tip catheters are straightforward procedures that can be employed prior to RFA to minimize CA complications.[44] In patients with known or suspected CAD, angiography could evaluate the extent[35] and determine the anatomic relationship between the catheter and coronary vessels.[3, 30, 44] It has been suggested that RF pulses should only be delivered if large diameter vessels are more than 4 mm away from the ablating electrode.[30]

Future Research Directions

Cryoablation energies may be safer in patients who demonstrated ST segment elevation during RFA.[45] In a canine model, cryoablation was compared to RF ablation within the coronary sinus near the circumflex coronary artery.[27] Histological analysis demonstrated medial necrosis within the CA with both modalities, however only after RF ablation was there disruption of elastic lamina and loss of intimal endothelial cells.[27] Intravascular echocardiography and angiography showed narrowing of the CA with RF ablation but not cryoablation. This suggests that cryoablation may be safer than RFA in certain settings when a CA is in close proximity.

High-intensity focused ultrasound (HIFU) is a newer, extracorporeal lesion-forming technology that could create thermal ablation within a defined focal volume without affecting neighboring tissues such as large blood vessels.[46] One of the advantages of HIFU is its precise focus in a targeted tissue region by a remote transducer. This induces molecular vibration and friction that results in rapid absorptive heating, thermal coagulation and ultimately necrosis of the targeted region.[47–50]

Other technologies and impact of alternate energies such as laser, microwave or beta irradiation on coronary arteries are under investigation.[46] Biological cell-based approaches, such as the injection of autologous fibroblasts, have been suggested as an alternate approach to create specific lesions and minimize distant injury.[51] Finally, new approaches to biological or chemical ablation of cardiac tissue may offer more targeted elimination of cardiac myocytes while sparing major vascular structures.

Altogether, a better understanding of CA pathophysiology after RFA is warranted to enhance safety and further refine current ablation approaches.

Acknowledgments

We thank Dr José Jalife for his advice to investigate coronary artery pathophysiology after radio-frequency ablation and Dr Fred Morady for valuable suggestions. We also thank Krishna Bandaru, Vamsi Korrapati and Auras R. Atreya for their contributions.

List of Abbreviations

AF	atrial fibrillation
CA	coronary artery
CAD	coronary artery disease
HIFU	High-intensity focused ultrasound
RFA	radiofrequency ablation
RV	right ventricle
RVOT	right ventricular outflow tract
VT	ventricular tachycardia

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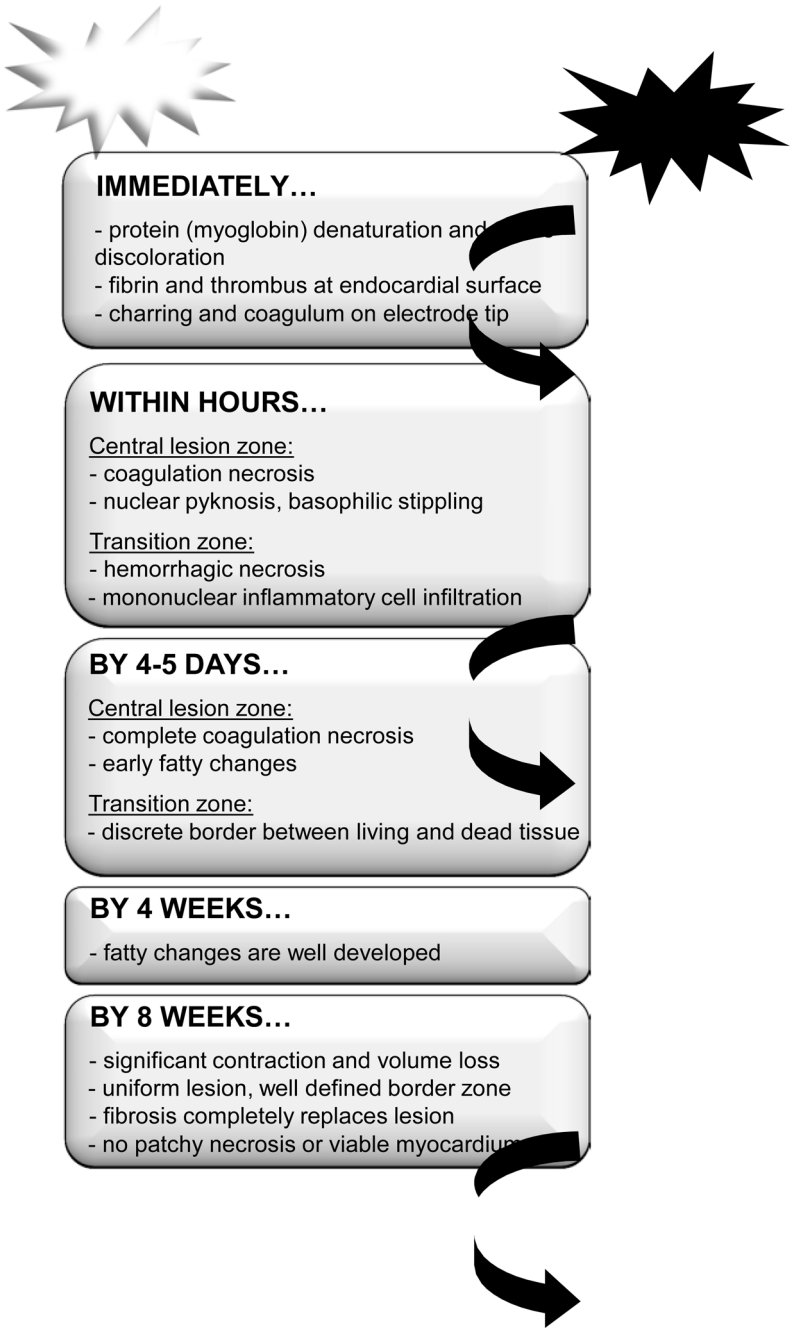

Figure 1. Time course of general lesion pathology following RFA

Pathologic changes occur in tissues after RFA immediately and can be observed up to 8 weeks post ablation.

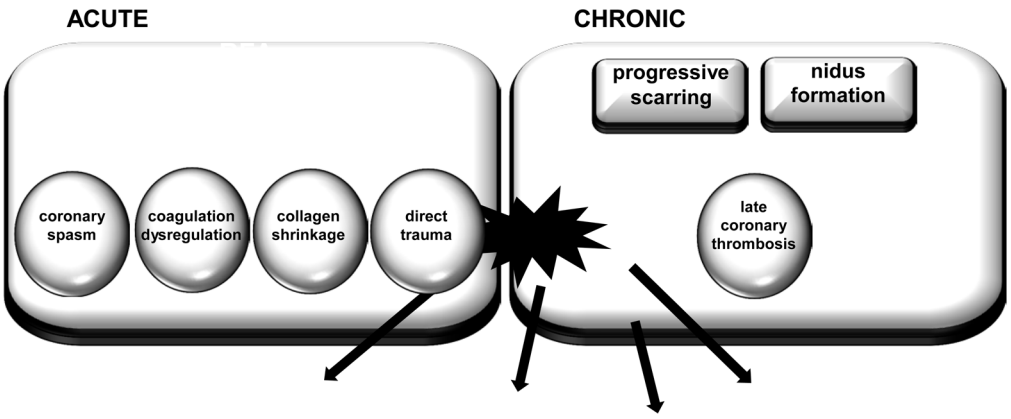

Figure 2. Mechanisms of coronary artery injury following RFA

Acutely, RFA can cause coronary spasm, coagulation dysregulation, collagen shrinkage, and direct vessel trauma that results in functional and morphological changes. Progressive scarring and nidus formation ensue and may lead to late coronary thrombosis.

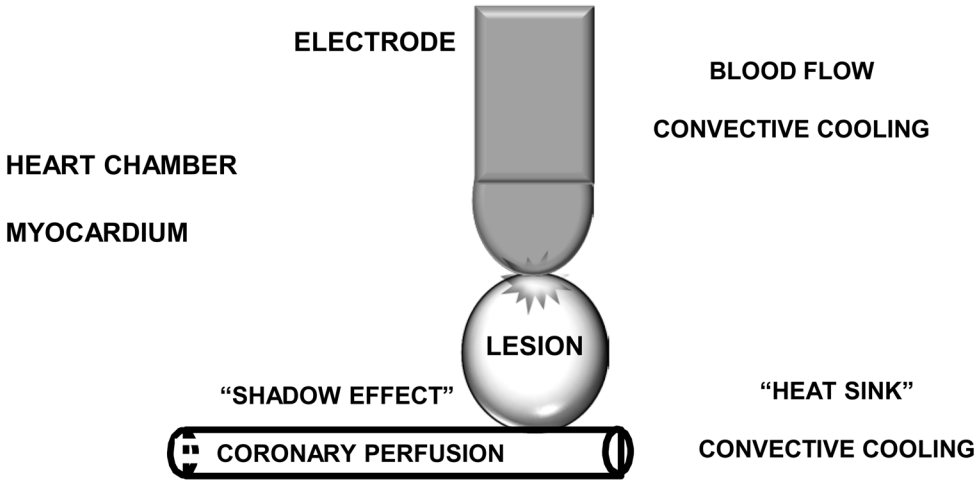

Figure 3. Convective cooling and the 'shadow effect' during RFA cause electrode-tissue temperature discrepancy

Convective cooling confers a protective effect for CAs against thermal energy from RFA. This phenomenon among others, must be weighed against the 'shadow effect', which can prevent transmural lesion formation, preserve conduction through an RF lesion, and thereby prevent complete conduction block

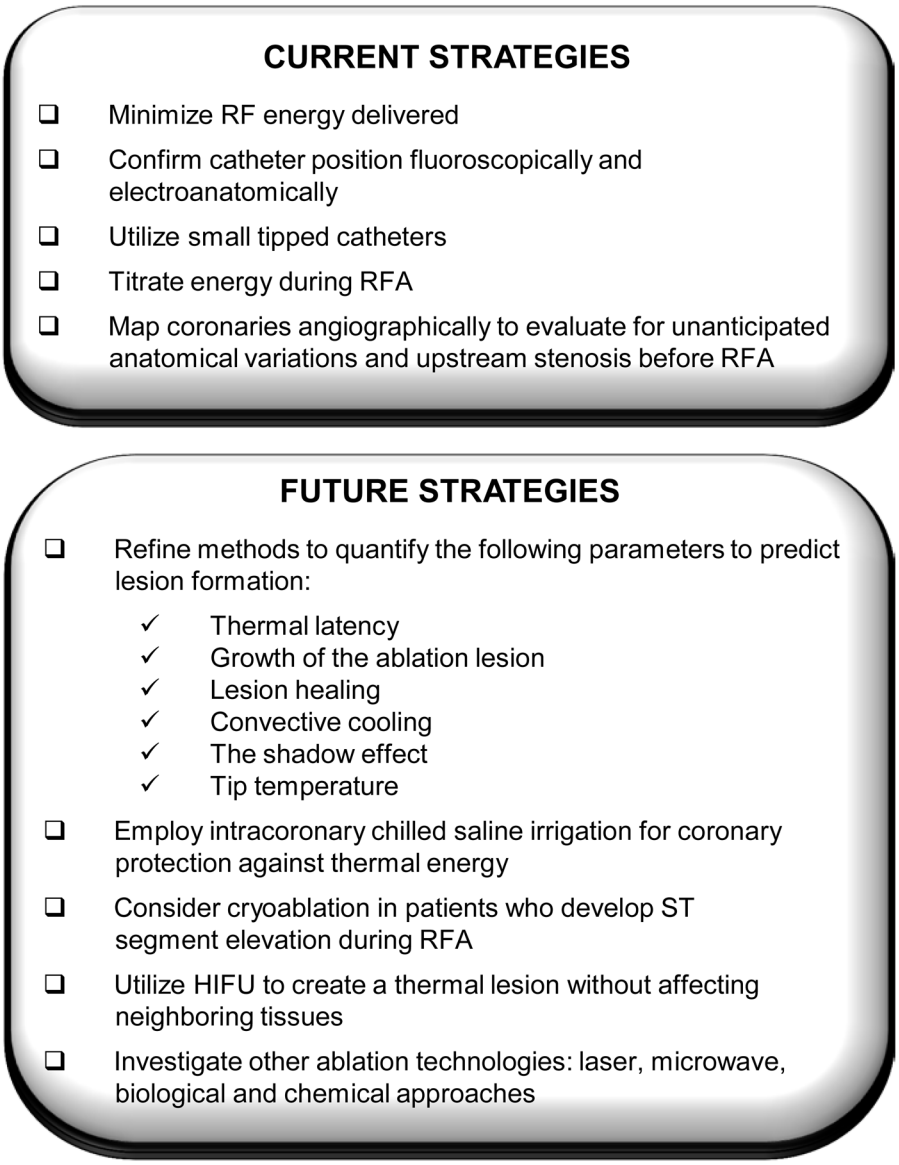

Figure 4.
Current and future strategies to mitigate CA complications from RFA and enhance procedure efficacy