Featured Review

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Is Cryo a Better Energy Source Than Radiofrequency for AF Ablation in Preventing Esophageal Injury?

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Introduction

Atrial fibrillation (AF) is by far the most common tachyarrhythmia in humans. Prevalence of this rhythm disorder is 0.3-0.4% of the adult population and increases with age from 2-4% in people over the age of 60 to 11.6 % in those over the age of 75.[1] In recent years, an increasing number of patients are subjected to catheter ablation in an effort to cure AF. It has been shown that a successful AF ablation results in improved quality of life as well as left ventricular function when compared to other treatment modalities including pharmacotherapy and pacemaker devices.[2, 3] Most ablation strategies today target electrical isolation of the pulmonary veins (PVs), which are believed to be the major site of major foci triggering AF.[4]

Radiofrequency (RF) is currently the most common energy source for catheter ablation procedures. Although RF ablation is significantly less invasive than surgery, it is still subject to complications including phrenic nerve injury, pulmonary vein stenosis, bronchial irritation, vagal excitation, hemopericardium, thromboembolism, and esophageal injury.[5] Among these, esophageal injury is a rare but devastating and often fatal complication. Multiple cases of esophageal perforation and atria-esophageal fistula have been reported in the literature with patients presenting usually days to weeks after their ablation with complaints of fever, odynophagia, chest pain, and hematemesis.[6-9] Currently, alternative energy sources such as cryoenergy, laser, ultrasound, and microwave have gained increasing attention to avoid certain RF related complications.[10-12] Among these alternatives, cryoenergy has evolved as the most promising energy source. In this review we will compare RF ablation to cryoablation in preventing esophageal injury (Fig. 1).

Radiofrequency Lesions

Radiofrequency energy is an alternating current (30 KHz to 300 MHz). The radiofrequency energy used (20 to 50 W) is generated usually from a 550 KHz electrosurgical unit and is delivered for 10 to 60 seconds [13]. RF energy is delivered through transvenous steerable electrode catheters with an irrigated or non-irrigated distal electrode 4-10 mm long. The ablative lesion is produced by tissue heating. Tissue temperatures of approximately 50°C and above are required to cause irreversible injury. Temperature above 45°C increases the calcium permeability of plasma membrane which induces an increase in cytostolic calcium concentration. Also activity of sarcoplasmic reticulum ATPase is inhibited at temparatures above 50o.[14-15]

Acute lesion created by RF consists of central zone

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Figure 1: Lesion Formation: Cryoablation versus Radiofrequency (RF)
Presents the gross appearance of in-vitro ablation with the RF lesion on the left showing pallor and volume loss. In contrast the cryolesion shown on the right is not perceptible (J Interv Card Electrophysiol (2007) 19:77–83- submitted with permission)

of coagulation necrosis. At 2 weeks, these areas develop inflammatory infiltrates and areas of hemorrhage; and by 4 weeks inflammatory infiltrates are replaced by fibrosis (Fig. 2).[16] Temperature above 60 degree causes the denaturation of collagen and loss of elasticity and compliance of pulmonary veins. Lesion diameter and depth depends on various factors such as electrode tissue contact, current density, temperature, duration of RF application.[13, 17] Cryothermal energy produces lesions through hypothermic exposure, with a very different mechanism of tissue injury from RF. Cryotechnology has been used for cardiac ablation for three decades, but cardiac catheter ablation has been a more recent development. Cryolesions are generated by applications of a cryoprobe cooled with liquid nitrous oxide for 2-5 minutes.[18] Progressive Cooling of cardiac tissue slows down conduction and eventually blocks electrical activity when temperature is reduced to 0 to -20 °C. Permanent lesions are created when temperatures are reduced to -60 to -80 °C.[19] Applying the cryoprobe to the tissue surface causes the formation of a hemisphere of frozen tissue, or iceball. Cells trapped in the iceball become irreversibly damaged and ultimately replaced by fibrous tissue.[25] The primary mechanism of cell death includes fatal changes in the structure of sub cellular organelles and mito-

Figure 2: Histological findings 2 to 4 weeks after RF energy application (GAFT staining). At 2 weeks, necrotic atrial myocardium (small arrow) is interspersed with RBCs, macrophages, and collagen fibrils (A). By 4 weeks, necrotic muscle has been replaced by collagen, but RBCs remain present. B, Disrupted internal elastic lamina (large arrow) and organizing vascular channels (small arrow). { GAFT- Gomori aldehyde fucbsin trichrome, RF- radiofrequency, RBC- red blood cells }(Circulation. (2000); 101:1736-1742-submitted with permission)

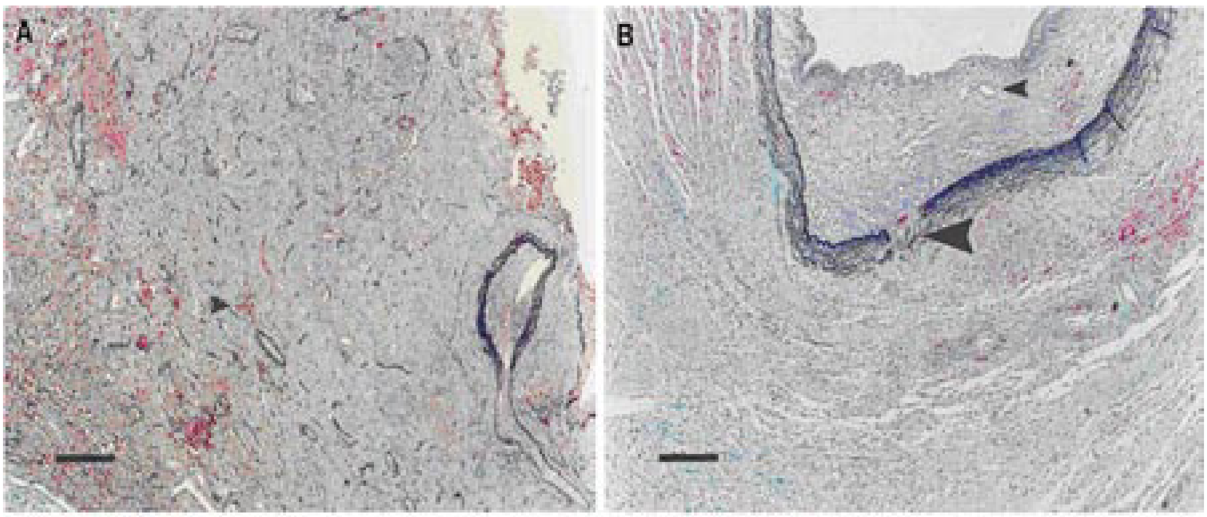
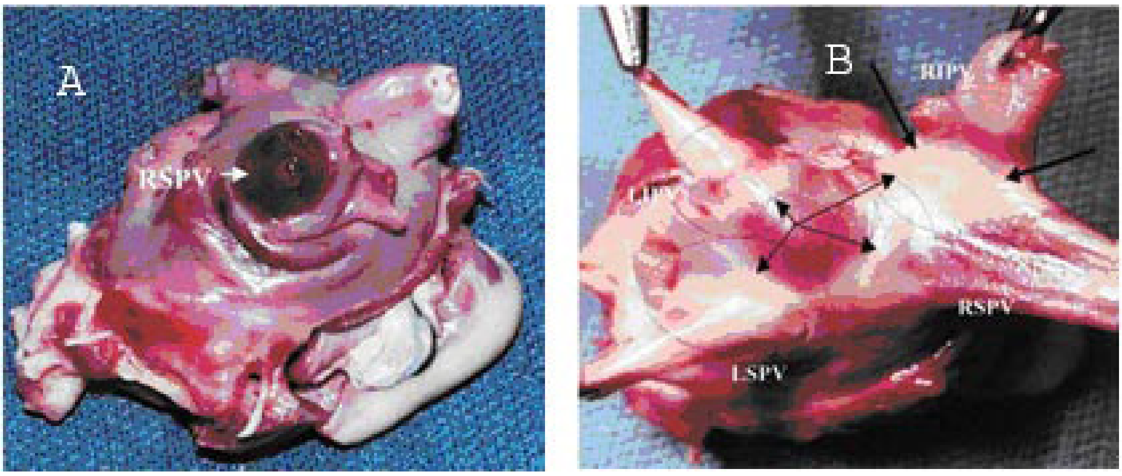


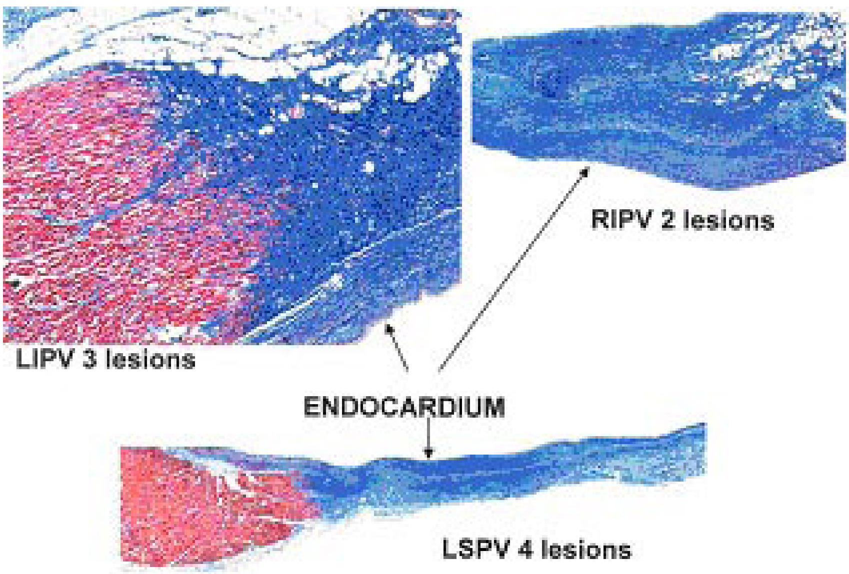
Figure 3: Gross pathology of cryolesions. A: Cryoablation of −70◦C was applied to the right superior pulmonary vein for 3 minutes. The heart was removed 2 hours later. The lesion is well demarcated and grossly hemorrhagic. B: Inverted atria and PVs showing the endocardial surfaces 3 months after cryoisolation of all PVs. The inverted left atrium (LA) and pulmonary veins (PVs) showing the endocardial surfaces of the atrial body and LA tissues extending into the PVs, forming the atrial tissue sleeves. Cryoablations of −60◦ to −70◦C were applied for 3 minutes. The tissues that were exposed to Cryoablation consisted of healed lesions with interconnected soft fibrous tissue rings at the PV-LA junctions, with no signs of hemorrhage, PV stenosis, or collagen.(J Cardiovasc Electrophysiol (March 2003)Volume 14 Issue 3, Pages 281 – 286- submitted with permission)



chondrial destruction.[26] Cryotherapy results in the formation of intracellular and extracellular ice crystals varying in shapes and sizes. These crystals do not penetrate the membrane but cause compression and distortion of adjacent cytoplasmic components and nuclei.[27]

The ice-crystal formation increases mitochondrial membrane permeability, which leads to disruption of the electron transport chain and irreversible mitochondrial de-energization, resulting in ischemic changes and coagulation necrosis. The cell membrane is then disrupted during the thawing phase. Furthermore, the microvascular network is disrupted and tissue hemorrhage is noted following the thawing of the ice ball. The inflammatory phase is characterized by the development of edema, coagulation, and inflammation. The final phase consists of dense fibrous tissue formation.[26]

Figure 4: Trichrome stain (40_ magnification) of longitudinal sections from 3 veins from the same atria, 3 months post–cryoablation. The histological sections illustrate the characteristics of typical Cryo lesions placed at the PV–atrial junction. As shown, regardless of the number of lesions applied to the veins, pure fibrous tissues are seen with no tissue thickening, collagen, or cartilage tissues. The fibrous tissue's transition with the atria is well demarcated.(Heart Rhythm ,(2004) Volume 1 , Issue 2 , Pages 203 – 209- submitted with permission)

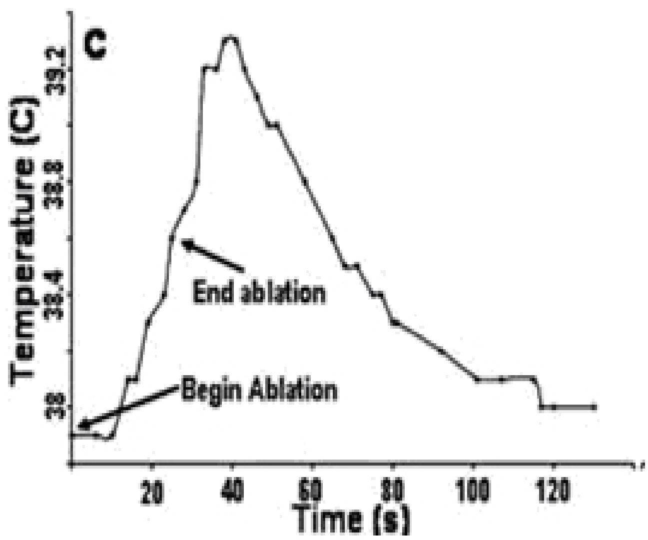


The effects of cryoablation are in part mediated by changes in the microvasculature (Fig. 3).[28] Effects on the microcirculation are characterized by endothelial cell damage, platelet aggregation and flow stasis, occlusion, and ultimately recovery of flow. On gross examination, the lesion is well demarcated, homogeneous and hemorrhagic immediately after the ablation procedure. By 12 weeks, the lesion appears small and fibrotic with no tissue thickening, collagen or cartilage tissue; there is normal distribution of the small and large blood vessels (Fig.4).[28] The size of the cryolesion is determined by a variety of factors including temperature, the size of probe used, and the duration of freeze cycles to which the tissue is subjected.

Esophageal Injury, Cryo vs. RF

With RF ablation, tissue heating decreases as a function of 1/r4, (r=distance from the RF ablation electrode) so deeper tissues are not heated as a result of dissipation of electrical energy, but are heated via conductive heating from the tissue near the electrode tissue interface.[17, 29] Conductive heating is the main cause of esophageal injury during RF ablation. The goal of achieving transmural lesions in an RF ablation procedure may sometimes lead to the application of excess energy, causing increased conductive heating to the esophagus. An engineering study by Enrique et al demonstrated that esophageal injury is significantly influenced by the thickness of the atrial wall and the connective tissue layer between the atrium and esophagus.[30] The results showed that the risk of esophageal perforation is very high when a temperature of 80°C is combined with adverse anatomic conditions, i.e, a thin atrial wall and very thin connective tissue layer. Another study demonstrated that real-time monitoring of the luminal esophageal temperature during left-atrial RF ablation can recognize the extent of esophageal heating such that RF application can be stopped when esophageal temperature increases by 2°C.[31] In order to prevent esophageal injury, the resultant RF pulse termination may not result in transmural lesion, leading to an unsuccessful procedure.

Figure 5: Graph shows that there is a rapid rise in luminal esophageal temperature when RF energy was delivered and continues to rise after the end of RF application.(J Cardiovasc Electrophysiol, (February 2006) Vol. 17,pp. 166-170- submitted with permission)



This study also demonstrated that esophageal temperature continues to rise even after RF pulse is delivered (Fig. 5). So repeated application of RF further enhances esophageal heating and increases the chances of esophageal injury. Cryothermal ablation also causes injury to esophagus when the iceball expands to entrap the esophagus, but the mechanism of tissue injury is benign and reversible. Cryothermal injury is distinguished from hyperthermic injury by preservation of basic underlying tissue architecture, thus making cryogenic lesions most ideally suitable for catheter based AF ablation in preventing esophageal injury. Evonich et al. conducted a randomized trial comparing effects of RF and cryoablation on the structural integrity of porcine esophageal tissue by direct application. On gross examination, esophageal lesions created with RF ablation showed a central zone of pallor with volume loss at the lesion center; in contrast, cryolesions were not detectable on gross examination.[32] Histopathological examination displayed the clear disruption of elastic fibers within RF lesions in comparison to normal appearing elastic fibers in cryolesions (Fig. 6). RF ablation significantly reduces tensile strength and tensile strength after cryoablation is not significantly different from normal tissue. This preservation of tensile strength during cryoablation prevents perforation or ulceration of esophageal tissue.[32] Another animal study demonstrated the fistula like lesions in the esophageal wall as a consequence of RF ablation while no such lesion developed as a result of cryoablation.[33]

Conclusion

Radiofrequency is currently the most widely used energy source used for catheter ablation in most arrhythmias but it may not be the ideal source for tissue ablation in all cases. Cryoenergy has emerged as the most promising alternative to RF, which has formidable safety and efficacy issues. RF tissue heating results in extensive tissue destruction and an intense inflammatory response. Conversely, cryoablation creates homogenous lesions preserving endocardial contours and tissue architecture. Cryoenergy has also gained increasing attention in relation to preventing other complications of ablative procedures. Several studies have demonstrated no pulmonary vein stenosis following pulmonary vein isolation using cryoablation.[28] Also, since cryotherapy preserves the endocardium which makes lesions less thrombogenic resulting in lower emboli risk.[34] Cryoenergy therefore demonstrates advantages to RF for AF ablation in preventing esophageal injury and other complicationsbecause of its benign mechanism of action. Studies are being conducted on new Cryoballoon technology and if successful it is likely to make pulmonary vein isolation more rapid and safe.[13]

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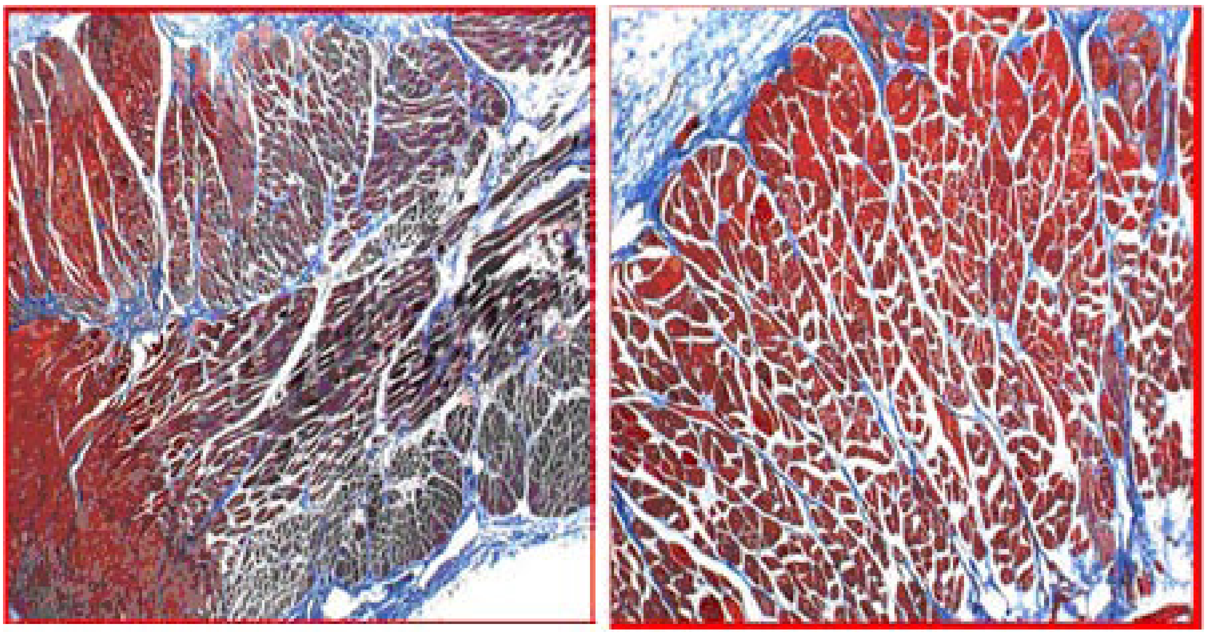
Figure 6: Masson's Trichrome staining of in-vitro esophageal lesions created using radiofrequency (RF) energy (left) and cryothermal energy (right). Note the dark staining of the entire muscularis propria within the RF lesion. In contrast, the cryolesion is not well demarcated from the surrounding normal tissue(J Interv Card Electrophysiol (2007) 19:77–83-submitted with permission)



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