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Histopathological Change Following Cox-Maze IV Procedure for Atrial Fibrillation

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Abstract

The prevalence of atrial fibrillation and the likelihood of undergoing concomitant surgical ablation at the time of open heart surgery are increasing. Currently, the conventional cut-and-sew Maze procedure has been predominantly replaced by Cox-Maze IV procedure, in which new energy sources such as radiofrequency energy and/or cryoablation are applied. Cox-Maze IV procedure has been associated with lower rate of complications than a cut-and-sew procedure. However, some previous studies reported the lower success rate of Cox-Maze IV procedure, possibly because radiofrequency ablation or cryoablation cannot always achieve transmural. For the success of surgical ablation, achieving transmural-ity, defined as complete atrial wall thickness of fibrotic changes, is of paramount importance. A review of previous articles regarding histopathological changes of the atrial tissue following surgical ablation is performed. The effectiveness of new energy sources such as radiofrequency and cryoablation in terms of histological transmural-ity is discussed.

Keywords: atrial fibrillation, Maze procedure, radiofrequency, cryoablation

1. Introduction

Surgical ablation for atrial fibrillation (AF) has been under continuous development for over two decades. The most recent guidelines for the surgical treatment of AF reported by the Society of Thoracic Surgeons (STS) state that surgical ablation for persistent AF can be performed without adding operative risk and is recommended at the time of concomitant mitral valve operations, isolated aortic valve operations, isolated coronary artery bypass grafting, and combined aortic valve and coronary artery bypass surgery (class I strength of recommendation) [1]. Surgical ablation is also recommended to symptomatic AF refractory to medical or catheter-based therapy in the absence of structural heart disease (class II strength of recommendation) [1].

Cox Maze Procedure

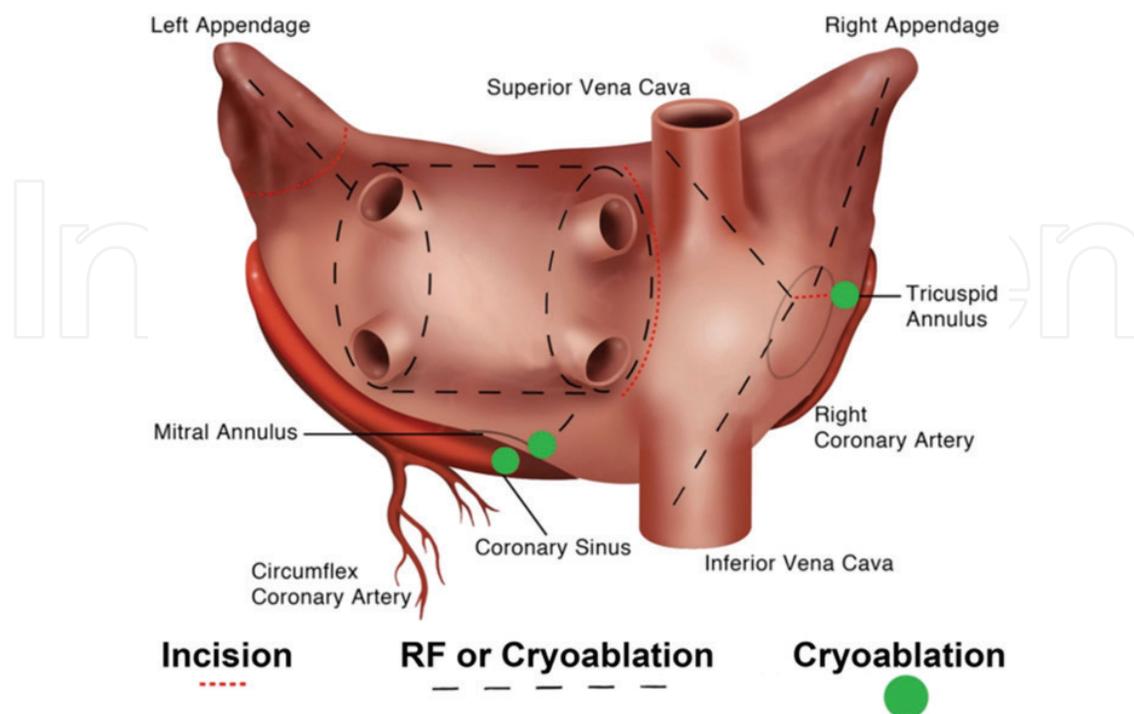


Figure 1. Scheme of the bi-atrial Cox-Maze procedure IV utilizing radiofrequency (RF) or cryoablation energy sources.

The first clinical surgical ablation for AF was introduced by Dr. James Cox in 1987, and was termed the Cox-Maze I. The successful 22 cases were reported in 1991 [2]. Over the subsequent years, the operation evolved into the Cox-Maze III or the cut-and-sew Maze [3], which has been applied extensively in clinical practice [4]. In the meantime, the introduction of ablation technology has significantly changed the attitude. Damiano et al. employed a combination of radiofrequency energy and cryoablation to replace several of the Cox-Maze III cut and sew lesions and termed this procedure as the Cox-Maze IV [5, 6]. Finally, the lesion sets of the Cox-Maze IV have evolved to its current form [7, 8] (**Figure 1**).

Khargi et al. reported that conventional cut-and-sew Cox-Maze III procedure is getting less frequently performed, and alternative sources of energy were predominantly used in all surgical ablation cases (92.0%), and almost always (98.4%) in concomitant procedures [9]. Cryoablation is employed as an alternative source of energy [10–12]. As compared to radiofrequency and cryoablation, other energy sources such as microwave, laser, and high-frequency ultrasound have proven less effective, and are not commercially available now [13–18].

2. Electrophysiologic basis of atrial fibrillation

It was documented that all AF is characterized by the presence of two or more large macroreentrant circuits in the atria simultaneously [19]. Haïssaguerre et al. first detected the focal triggers of atrial ectopic beats [20]. They noted that the ectopic foci are mainly (>90%) located in and

around the orifices of the pulmonary veins and the remaining are located in other sites such as right atrium, left atrium, crista terminalis, and left atrial appendage. The findings of their paper, which reported that the triggers were successfully treated with radiofrequency ablation, led to an explosion of efforts by a number of cardiologists and cardiac surgeons to treat AF with catheter ablation and surgical techniques, respectively. The concept of treating AF was originally focused on isolating the pulmonary veins, either by catheters or surgical devices.

However, AF produces unfavourable changes in atrial function and structure, which is called remodeling [21]. After many years of paroxysmal AF, the macroreentrant circuits of AF can become self-perpetuating. At this point, paroxysmal AF can become long-standing or persistent AF, and the underlying electrophysiologic culprit is no longer the focal triggers, but rather the macroreentrant circuits themselves. Therefore, for long-standing or persistent AF, simple isolation of pulmonary veins is not an effective treatment because the focal triggers do not account for onset of AF for this type of AF. In these patients, it is necessary to interrupt the macroreentrant circuits by placing additional linear lesions in the atria. This concept has led to a surgical ablation technique called Cox-Maze procedure.

3. Cryoablation

3.1. Introduction of cryoablation

The era of cryosurgery began with the development of automated cryosurgical equipment in the 1960s. Cooper et al. described cryosurgical resection of parenchymal organs using liquid nitrogen-refrigerated clamp in 1966 [22]. Cryosurgery has been an integral part of the surgical treatment of cardiac arrhythmias since the 1970s. With the recent technological development of cryoablation devices, the use of cryotherapy in the treatment of cardiac arrhythmias is increasing.

Cryoablation is effective in producing electrical silent ablation lines, and can be used judiciously safely without injuring surrounding structures such as coronary arteries and valve tissue.

3.2. Mechanisms of tissue injury in cryoablation

Gage et al. described the mechanisms of tissue injury in cryosurgery [23]. The adverse effect of low temperature on cells begins as temperature falls into the hypothermic range. The function and structure of cells are stressed, and cell metabolism progressively fails. As the temperature goes further down and falls into the freezing range, water is crystallized, which causes more serious consequences than the earlier cooling. Ice crystal formation first occurs in the extracellular spaces, and with further cooling, it occurs within the cell. Intracellular ice formation requires temperatures colder than -40°C . Once intracellular ice is formed, it disrupts organelles and cell membranes, and cell death is practically certain.

The progress to a stable lesion can be divided into three phases: (1) freeze/thaw phase, (2) haemorrhagic and inflammatory phase, and (3) replacement fibrosis phase [24].

1. Freeze/thaw phase.

Intracellular and extracellular ice formation vary in size and location depending on tissue type, proximity to the cryoprobe, and the presence of blood flow during cryoablation. Ice crystals, themselves, do not cause mechanical disruption. They do not penetrate the cell membrane, but induce compression and distortion of adjacent cytoplasmic components [25, 26]. Irreversible injury to mitochondria is a consequence of increased membrane permeability during the thaw phase [27]. The damage to the mitochondrial membrane leads to membrane lipid peroxidation and enzyme hydrolysis. At this point, mitochondria become irreversibly deenergized [28]. In the heart, the application of cryoprobe to myocardium results in the formation of an elliptical hemispheroid lesion [29]. During the thawing, the myocytes get swollen and the myofilaments are extremely stretched.

2. Haemorrhagic and inflammatory phase.

The second phase of myocardial injury following cryoablation is characterized by the development of haemorrhage [29], oedema, and inflammation [30], which are found within 48 hours after thawing. Harrison et al. reported the histologic changes following cryoablation to the atrioventricular node [31]. One week after the procedure, microscopy showed necrosis of myocardial cells and conduction fibres, a polymorphonuclear leukocytic infiltrate and marked haemorrhage in the peripheral lesion.

3. Replacement fibrosis phase.

The last phase in the evolution of a stable cryolesion is detected at 2–4 weeks after the cryoablation. At this point, the cryolesions consist of dense collagen and fat infiltration along with many small blood vessels. Harrison et al. reported that, 1 month after the procedure, the lesion had been replaced by dense fibrotic connective tissue [31].

3.3. Electrophysiologic effects of cryoablation on the heart

Jensen et al. developed an experimental myocardial injury model using cryoinjury in dogs [32]. Their histologic examination showed that the cellular pattern or healing myocardial cryolesions was similar to that of a healing myocardial infarction, but with less variability. Several papers reported that cryolesions have low arrhythmogenic potential in canine models [33–35].

Holman et al. reported the decrease of electrogram amplitude in cryolesions [33]. The decrease in amplitude reflects epicardial ice insulation or inhibition of myocardial electrical potential. More than 70% decrease in absolute amplitude from control potentials was predictive of cellular death. Klein et al. demonstrated that the cryolesions are sharply demarcated from normal myocardium and does not disrupt the surrounding anatomy [34]. The chronic cryolesion behaves electrophysiologically like an inert plug with no disruption of surrounding activation. Ventricular ectopic activity disappeared in cryolesions after 1 week of the cryoablation.

In conclusion, the cryothermal energy can create discrete, structurally intact, and electrically inert foci in the myocardium. That is, the electrophysiologic mechanism for a cryoablation is considered to be a useful therapeutic modality in the treatment of cardiac arrhythmias.

3.4. Cryoablation device

Cryothermal energy is delivered to myocardial tissue by using a cryoprobe. Cryoablation devices create an inflammatory response (cryonecrosis) that blocks the electrical conduction pathway by freezing target tissues.

There are two commercially available cryoablation probes for surgical treatment of cardiac arrhythmias. AtriCure Inc. (Mason, OH) has provided cryoICE probe, which uses a 10 cm malleable probe on a 20 cm shaft. It utilizes nitrous oxide (N_2O) to create continuous transmural lesions that block propagation of atrial activation. The cryoFORM is a latest generation of cryoablation probe, which is made from stainless steel and has a corrugated surface, a design that provides a high flexibility [36] (**Figure 2**).

Medtronic Inc. (Minneapolis, MN) has developed Cardioblade CryoFlex surgical ablation probes, which utilize argon-powered cryoablation (**Figure 3**). This is a malleable probe easily shaped by hand, and reaches temperature of approximately $-150^{\circ}C$. This device is currently approved for use in surgical ablation for AF in Europe but not in the United States.

3.5. Transmurality of cryoablation

Kettering et al. created a successful, a right atrial septal linear lesion with cryocatheter in pigs [37]. The bipolar voltage map demonstrated very low potentials along the ablation line and a sharply demarcated ablation area. However, they concluded that creating a transmural lesion and a complete conduction block remains an unsolved problem. Wadhwa et al. reported that successful transmural was achieved with catheter cryoablation in the canine ventricle [38]. Masroor et al. reported that endocardial hypothermia was achieved with epicardial



Figure 2. Illustration of the flexibility of the cryoFORM ablation probe. The length of the active site of the malleable probe surface is adjustable by the movable shaft cover (Reproduced with permission from AtriCure, Inc.).



Figure 3. Illustration of the Cardioblade CryoFlex ablation device (Reproduced with permission from Medtronic, Inc.).

cryoablation on a beating heart model in pigs [39]. Schill et al. reported that the latest cryoablation probe produced transmural lesions in 97% of the arrested heart in an ovine model [40].

However, the transmurality created by surgical cryoablation in the human tissue has not been well studied.

4. Radiofrequency ablation

4.1. Introduction of radiofrequency ablation

Since Haissaguerre et al. demonstrated the efficacy of radiofrequency ablation for paroxysmal atrial fibrillation [20], radiofrequency has become the standard treatment for both catheter-based ablation and surgical ablation for cardiac arrhythmias. Chiappini et al. reported the efficacy of radiofrequency ablation in the patients who had chronic atrial fibrillation, and it was as effective as cut-and-sew Maze procedure [41, 42].

However, lesions created by hyperthermia have a potential risk of tissue disruption that can result in perforation of surrounding tissue, pulmonary stenosis, and thromboembolic stroke [43, 44].

4.2. Bipolar versus unipolar radiofrequency

Bugge et al. compared the transmurality of ablated lesions in ovine hearts using irrigated bipolar and unipolar radiofrequency ablation [45]. They reported that bipolar radiofrequency was superior in creating transmurality, but both devices failed to produce consistent transmurality using the epicardial beating heart technique. Gonzalez-Suarez et al. also demonstrated that bipolar is more effective than unipolar in achieving transmurality in vitro [46]. However, the superiority of bipolar over unipolar in human has not been established.

AtriCure Inc. (Mason, OH) has provided bipolar radiofrequency ablation device, which has stainless steel shaft and jaws to maintain consistent tissue pressure and precise electrode alignment across the entire length of the jaws (**Figure 4**).

Medtronic Inc. (Minneapolis, MN) has provided Cardioblade system, which utilizes irrigated bipolar radiofrequency energy to ablate tissue transmurally (**Figure 5**).



Figure 4. Illustration of the bipolar radiofrequency clamp (Reproduced with permission from AtriCure, Inc.).



Figure 5. Illustration of the Cardioblade clamp, which utilizes bipolar radiofrequency energy source (Reproduced with permission from Medtronic, Inc.).

4.3. Histopathological changes after radiofrequency ablation

Heat propagation is based on both resistive and passive mechanisms. In the early phase of radiofrequency ablation, tissue is heated to 50–60°C resulting in coagulation and irreversible destruction of cell and collagen structures. Ablation of the peripheral part of the lesion results from passive heating with the same effect of irreversible damage. Both resistive and passive heating propagate in all directions so that the tissue lesion becomes similar in depth and width [41]. Once the transmural is achieved with radiofrequency ablation, there is no proarrhythmic activity found in the scar tissue [47].

Aupperle et al. reported the histological findings in experimental atrial ablation in sheep [48]. They reported that epicardial bipolar radiofrequency resulted in intensive endocardial necroses and severe sharply demarcated transmural myocardial necroses. Similarly, endocardial unipolar radiofrequency resulted in severe endocardial necroses as well as intense, transmural, and well demarcated myocardial necroses. Ba et al. also reported that radiofrequency resulted in myocyte necrosis in sheep, and radiofrequency was as effective as cryotherapy [49]. Gaynor et al. performed surgical ablation using bipolar radiofrequency energy source in pigs [50]. They reported histological assessment that showed all lesions created by bipolar radiofrequency were transmural and there were no stenosis of the coronary vessels or injuries to the valves.

4.4. Transmurality of radiofrequency ablation

Although bipolar radiofrequency produces transmural linear lesions in the animals [51, 52], transmural is not always achieved in human, as several papers reported [53, 54]. Deneke et al. reported that transmural of the ablated lesions could only be found in 75% in human atria [55]. Kasirajan et al. reported the histopathological findings in three human patients who had autopsy after surgical ablation [53]. Their microscopic examination showed that (1) surgically ablated lesions showed not only transmural but also nontransmural lesions (**Figure 6**), (2) chronic ischemic and fibrotic changes existed in the myocardium of the patients who had long-standing persistent AF and mitral regurgitation, and (3) acute bi-directional electrical conduction block did not guarantee transmural of ablation lesions. They assumed that the underlying disease process prevented the creation of transmural lesions. The wall thickness

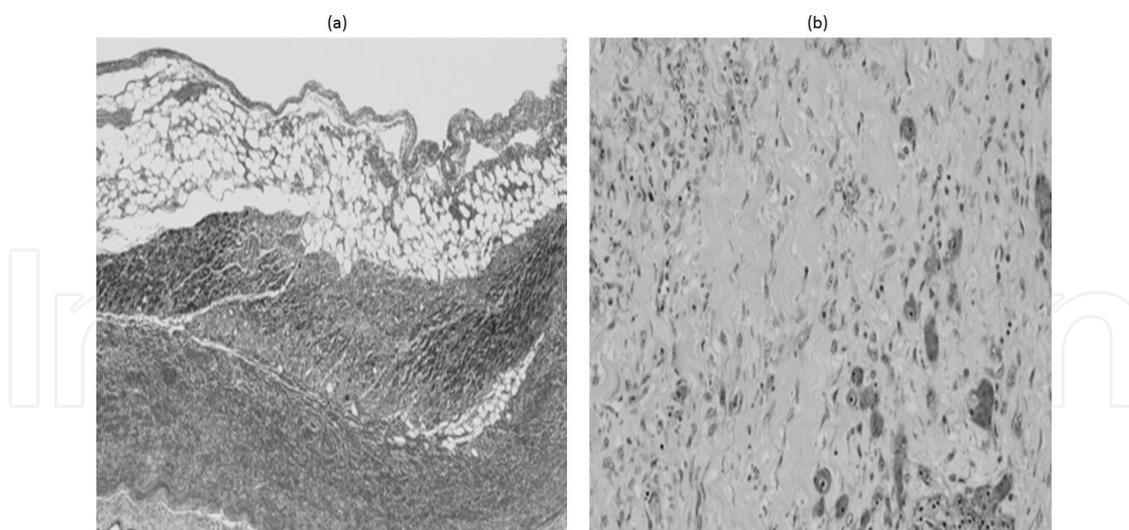


Figure 6. (a) Day 6 of surgical ablation. Extensive fibrosis in atrial tissue (blue) with necrotic myocardium (purple), and viable muscle (red). (Mason trichrome stain: magnification $\times 40$.) (b) Day 18 of surgical ablation. Healing with coagulative necrosis and wavy bundles of collagen with few viable cells in between (hematoxylin and eosin: magnification $\times 100$).

of the atrium has been known to affect the transmural [45]. Therefore, repeated radiofrequency ablation is recommended, especially in thick lesions [56, 57].

Ventosa-Fernandez et al. reported the histologic evidence of transmural 4 years after bipolar radiofrequency ablation [58].

5. Conclusions

Recently, the conventional cut-and-sew Cox-Maze procedure has been replaced by alternative energy sources in the surgical treatment of atrial fibrillation. Cryoablation and radiofrequency ablation have been playing an important role in this field. Both energy sources have been shown to be effective in treating atrial fibrillation. However, despite the technological advancement, there remains uncertainty of transmural in human tissue, especially when patients have underlying disease. Lack of transmural may result in failure of surgical ablation. Further histopathological studies will be necessary in assessing the effectiveness of using alternative energy sources. Moreover, a further technological advancement in achieving reliable transmural should be warranted in the future.

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