

Effects of Inflammatory Cell Death Caused by Catheter Ablation on Atrial Fibrillation

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Abstract: Atrial fibrillation (AF) poses a serious healthcare burden on society due to its high morbidity and the resulting serious complications such as thrombosis and heart failure. The principle of catheter ablation is to achieve electrical isolation by linear destruction of cardiac tissue, which makes AF a curable disease. Currently, catheter ablation does not have a high long-term success rate. The current academic consensus is that inflammation and fibrosis are central mechanisms in the progression of AF. However, artificially caused inflammatory cell death by catheter ablation may have a significant impact on structural and electrical remodeling, which may affect the long-term prognosis. This review first focused on the inflammatory response induced by apoptosis, necrosis, necroptosis, pyroptosis, ferroptosis and their interaction with arrhythmia. Then, we compared the differences in cell death induced by radiofrequency ablation, cryoballoon ablation and pulsed-field ablation. Finally, we discussed the structural and electrical remodeling caused by inflammation and the association between inflammation and the recurrence of AF after catheter ablation. Collectively, pulsed-field ablation will be a revolutionary innovation with faster, safer, better tissue selectivity and less inflammatory response induced by apoptosis-dominated cell death.

Keywords: atrial fibrillation, inflammatory cell death, radiofrequency ablation, cryoballoon ablation, electroporation

Introduction

Atrial fibrillation (AF) is a common arrhythmia with high morbidity and mortality.¹ Without proper intervention, this arrhythmia may develop into a permanent condition. Current therapeutic regimens include catheter ablation and drug therapy. Although antiarrhythmic drugs can help maintain sinus rhythm, most of them are ineffective and associated with intolerable side effects. AF and heart failure are closely related and mutually reinforcing. Evidence supported that catheter ablation reduces all-cause mortality in patients with AF combined with heart failure compared with drug therapy.²

Since Haissaguerre identified the pulmonary veins as the main trigger of AF,³ isolation of the electrical activity of the pulmonary veins by utilizing various form of energy (radiofrequency, cryoballoon, laser, ultrasound, pulsed-field) has become the cornerstone of catheter ablation. The primary goal of catheter ablation is to eliminate the symptoms associated with AF and improve quality of life. However, numerous clinical evidences have shown that the success rate of catheter ablation is not very high. After weighing complications such as atrioesophageal fistula, cardiac tamponade, phrenic nerve injury, esophageal injury, and pulmonary vein contracture, catheter ablation is not a routine choice as a first-line option.⁴ This awkward positioning of catheter ablation suggests that there is much room for improvement and optimization.

Catheter ablation leads to the membrane-breaking cell death of localized cardiomyocytes, releasing diverse bioactive substances. Undoubtedly, the local pro-inflammatory microenvironment may create a substrate for structural and electrical remodeling. This review will focus on the possible inflammatory response induced by cell death as well as

arrhythmias, and attempt to clarify the differences in catheter ablation induced cell death at a microscopic level, with a view to translate the available evidence into clinical guides.

Cell Death and AF

Excessive cardiomyocytes death with limited regenerative capacity leads to a variety of cardiac diseases, including myocardial infarction, malignant arrhythmia, heart failure, and sudden cardiac death. Currently, known modes of cell death include, but are not limited to, apoptosis, necrosis, necroptosis, pyroptosis, and ferroptosis, which occur independently and interact with each other. Dead cells can exhibit features of autophagy, apoptosis, pyroptosis, and necrosis simultaneously.⁵ Except for apoptosis, all other membrane-breaking cell deaths (necrosis, necroptosis, pyroptosis, and ferroptosis) all occur in conjunction with an inflammatory response. More importantly, the loss of cardiomyocytes may not only imply diminished systolic function, but also activate the cascade of inflammatory responses, which may further contribute to the development of arrhythmia (Figure 1). Additionally, arrhythmia can exist as a single or cardiomyopathy-related disorder, and myocardial injury associated with arrhythmia is usually accompanied by a temporary or permanent inflammatory response.⁶

Apoptosis and AF

Apoptosis is required for the clearance of damaged or senescent cells. Since 1972, the ultra-structural features of apoptosis have been characterized as the integrity of the cell membrane structure and the absence of a significant inflammatory response.⁷ Apoptosis has been shown to be associated with ischemia/reperfusion (I/R) injury, heart failure, and atherosclerosis. In 1994, evidence of apoptosis in the I/R myocardial tissue of rabbits was obtained by transmission electron microscopy and DNA gel electrophoresis.⁸ Apoptosis was present in the sinoatrial node, atrioventricular node, and conduction tissues during embryonic development and the postnatal weeks of development. Excessive, insufficient, or delayed apoptosis can cause arrhythmia.⁹ James et al observed typical apoptosis in surgically resected sinus nodes in patients who were recurrent ventricular arrhythmia combined with syncopal long Q-T syndrome, suggesting that

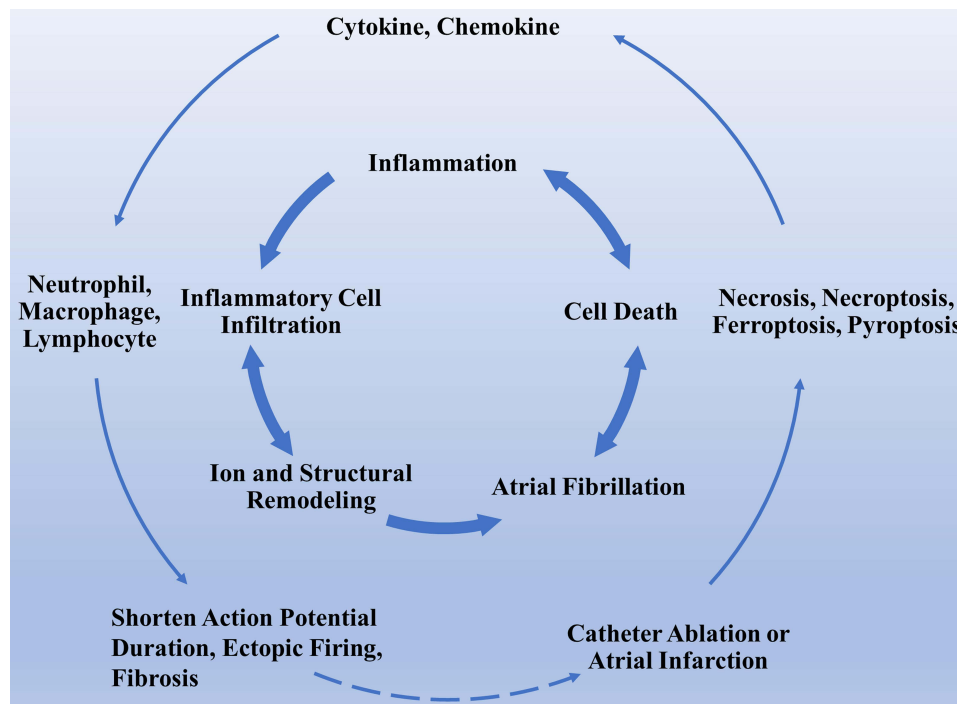


Figure 1 The association between inflammatory cell death and AF. This figure briefly recapitulates the association between inflammatory cell death and AF induce inflammatory cell death. Inflammatory cell death caused by artificial therapeutic regimens releases inflammatory factors that lead to structural and electrical remodeling, thereby contributing to the permanent progression of the arrhythmia. The cross-link between AF and inflammatory cell death creates a vicious loop.

Abbreviation: AF, atrial fibrillation.

arrhythmia is implicated in apoptosis, with limited, non-inflammatory degeneration in the sinus node.¹⁰ Thus, an imbalance of apoptosis may underlie the pathogenesis of some arrhythmia.

Sustained tachycardia and rapid pacing promote cardiomyocytes apoptosis, which have been corroborated by extensive clinical data.^{11–13} Knocking down caspase-3 in a porcine AF model could prevent intra-atrial conduction delay and inhibit the development of sustained AF.¹⁴ Additionally, ATG5 and M30, which are associated with autophagy and apoptosis, were elevated in the serum of patients with paroxysmal AF.¹⁵ Besides, epicardial isolation of pulmonary veins also reduced the apoptosis indicators in AF.¹⁶

Apoptosis may be the ultimate culmination of various unfavorable stimuli. However, how apoptosis without inflammatory response contributes to the progression of AF has not been investigated clearly. A possible explanation is that widespread apoptosis of cardiomyocytes or conduction system implies a weakening of atria contractile function which causes the atria to enlarge, ultimately leading to structural remodeling and electrical remodeling.

Necrosis and AF

Necrosis is usually considered a non-programmed, unregulated cell death process resulting from exposure to external violent stimuli or severe imbalance in the homeostasis of the internal environment. Necrosis is characterized by cell swelling, rupture, and spillage of cell contents, which triggers an inflammatory response.

Necrotic myocardium can trigger innate and adaptive immunity.¹⁷ Damage-associated molecular patterns (DAMP) bind to pattern recognition receptors to induce activation of downstream signaling pathways on cardiomyocytes or resident immune cells (Figure 2). Many DAMPs have been identified, including high-mobility group box 1 (HMGB1), uric acid, double-stranded DNA, amyloid- β -peptide, heat shock proteins (HSP), interleukin-1 α (IL-1 α), and IL-33. Ultimately, the cascade leads to the upregulation of chemokines and cytokines.¹⁸ The inflammatory response is also

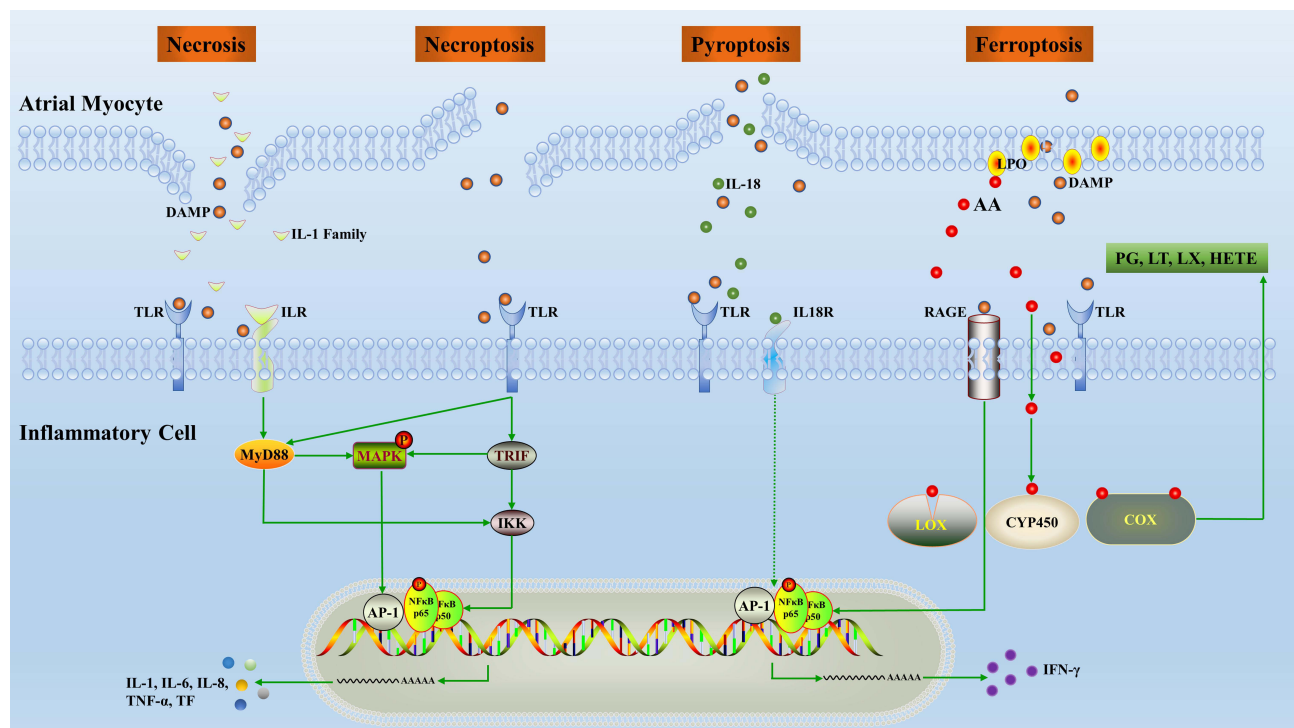


Figure 2 Overview of the inflammatory pathways induced by inflammatory cell death. Release of inflammatory factors, mainly DAMPs, following cardiomyocytes death promotes polarization and chemotaxis of inflammatory cells. In turn, inflammatory cells secrete inflammatory factors which alter the structure and electrical conduction activity of the local microenvironment.

Abbreviations: AA, arachidonic acid; TF, tissue factor; AP, activating protein; NF, nuclear factor; IFN, interferon; IL, interleukin; PG, prostaglandin; LT, leukotriene; LX, lipoxin; CYP450, cytochrome P450; MyD, myeloid differentiation factor; LOX, lipoxygenase; COX, cyclooxygenase; TNF, tumor necrosis factor; IKK, inhibitor of kappa B kinase; TLR, toll-like receptors; LPO, lipid hydroperoxide; DAMP, damage-associated molecular patterns; RAGE, the receptor of advanced glycation end products; HETE, hydroxyeicosatetraenoic acid; MAPK, mitogen-activated protein kinase; TRIF, TIR-domain-containing adaptor inducing interferon β .

exacerbated because of elevated fibrinogen, fibronectin, bilirubin, metalloproteinase 2 (MMP-2), tissue inhibitors of metalloproteinase 2 (TIMP-2), and thrombospondin 2 in neutrophils or polarized macrophages.¹⁹⁻²¹

There are few direct studies of necrosis on arrhythmia, but we can draw an analogy to myocardial infarction as a more severe form of myocardial necrosis. Studies have found that larger infarct sizes in the heart are more prone to arrhythmia.²²⁻²⁴ The cumulative morbidity of AF over 5 years after acute myocardial infarction is 6%-21%, compared to 3% in the general population.²⁵ Recent studies have shown that the morbidity of supraventricular tachycardia in atrial infarction patients is 27%.²⁶ A prospective cohort study has shown that artificial atrial coronary occlusion causes atrial arrhythmias and delayed intra-atrial conduction.²⁷ Moreover, the more atrial branches are blocked, the higher morbidity of AF.^{28,29} It has been verified that atrial infarction is associated with slower atrial conduction velocity, increased conduction heterogeneity, increased susceptibility to AF, and a longer duration of AF.³⁰ Coincidentally, in the canine model of chronic atrial infarction, researchers found an approximately 50-fold increase in spontaneous atrial ectopic activity and conduction abnormalities, and significant fibrosis at the border of the atrial infarct region. Patch-clamp implied that the initiating activity of atrial myocytes in infarct boundary areas was enhanced, with faster decay of caffeine-induced Ca^{2+} transients and enhanced Na^+ - Ca^{2+} exchange currents.³¹ A refined study by Uma et al reported that ligation of the atrial branch of the left anterior descending coronary artery resulted in spontaneous AF. Optical mapping observed focal spontaneous discharges and conduction delays at the border of the ischemic/normal zone, which provided substrates for reentry. The possible mechanism involved is that the physiological binding of calmodulin to ryanodine receptor type 2 (RyR) is altered by hypoxic and inflammatory responses.³² Taken together, these results suggest that local myocardial tissue necrosis has profound effects on electrophysiology. However, little is known about whether catheter ablation of the pulmonary veins and extensive linear ablation in the atria could cause atrial infarction by damaging the corresponding arteries and whether it has any effect on the recurrence of AF after the procedure.

Of course, researchers have also conducted a series of mechanistic explorations to find interventions. Previous research prompted that C1q/TNF-related protein 9 may reduce atrial inflammation and fibrosis effectively and reduce the incidence of concomitant AF after myocardial infarction through its inhibitory effects on TLR4/NF- κ B and Smad2/3 signaling pathways.³³ Relaxin exerts beneficial anti-fibrotic and anti-inflammatory effects and reduces the susceptibility of AF after myocardial infarction.³⁴

Necroptosis and AF

Necroptosis is a newly discovered mechanism of cell death that combines the features of necrosis and apoptosis.³⁵ A cascade of physicochemical factors stimulates the activation of autophosphorylation of receptor-interacting serine/threonine protein kinase. It leads to the release of DAMPs, which promote the inflammatory response (Figure 2).

Several studies have shown that necroptosis plays an accelerating role in myocardial infarction, I/R injury, and heart failure.³⁶⁻³⁸ Inhibition of necroptosis was found to reduce the susceptibility to CaCl_2 -acetylcholine or high lipid-induced AF and reverse structural remodeling of the atria.³⁹ TGF- β activated kinase 1 acts as a key survival factor by antagonizing necroptosis directly, which is essential for maintaining myocardial homeostasis and preventing unfavorable myocardial remodeling.⁴⁰ A recent study demonstrated that tumor necrosis factor receptor-associated factor 2-mediated NF- κ B independent pro-survival pathway inhibited necrotic signaling, and it could be used as a therapeutic target for ventricular remodeling and heart failure.³⁷ More studies are needed to gain a better understanding of the relationship between necroptosis and arrhythmia.

Ferroptosis and AF

Ferroptosis is a regulated cell death characterized by iron-dependent lipid peroxidation (LPO) accumulation.⁴¹ Ferroptosis has been shown to release mitochondrial and intranuclear material,⁴² but the study of inflammation in ferroptosis is still in the early stage.⁴³

Ferroptotic cells were found to be extremely pro-inflammatory by recruiting macrophages through chemokine ligand 2.⁴⁴ Ferroptotic cells release HMGB1⁴⁵ and anti-HMGB1-neutralizing antibodies mitigated the inflammatory response of macrophages.⁴⁶ Inhibition of ferroptosis has been reported to inhibit leukocyte extravasation.⁴⁷ The activation of the toll-like receptors (TLR) inflammatory response led to neutrophil accumulation and myocardial

injury in cardiac transplantation, and Ferrostatin (selective ferroptosis inhibitor) reversed this alteration.⁴⁸ 4-hydroxynonenal, which is the LPO product, is a ligand for the TLR4 receptor and triggers an inflammatory response.⁴⁹ In addition, LPO drives an increase in modified low-density lipoprotein, which promotes inflammation through macrophage polarization.⁵⁰ Reducing glutathione peroxidase 4 (GPX4) expression up-regulates the expression of 12-lipoxygenase (ALOX12) and cyclooxygenase 1 (COX-1).^{51,52} (Figure 2) In contrast, GPX4 activation inhibits ferroptosis and inflammatory responses by attenuating arachidonic acid oxidation and NF- κ B pathway activation.⁵³ Arachidonic acid is an unsaturated fatty acid that is metabolized by COX, LOX, cytochrome P450, and monooxygenases to synthesize biologically active inflammatory mediators such as prostaglandins, leukotrienes, epoxyeicosatrienoic acid, and hydroxyeicosatetraenoic acid.⁵⁴ Excessive reactive oxygen species (ROS) and iron overload are strongly associated with arrhythmia.^{55,56} A recent study reported that SARS-CoV-2 induced ferroptosis, leading to the dysfunction of human embryonic stem cell-derived sinoatrial node-like pacemaker cells.⁵⁷ AF is a common cause of death in β -thalassemia patients, and it can be hypothesized that the presence of ferroptosis in β -thalassemia patients promotes the development of AF.⁵⁸ Basic research hinted that rapid pacing cardiac fibroblast-derived exosomes exacerbated cardiomyocytes ferroptosis, and AF could be prevented by intervening in exosomal miRNAs.⁵⁹ In addition, LPS-induced endotoxemia,⁶⁰ excessive alcohol consumption,⁶¹ and obesity-related gut flora dysbiosis⁶² could increase AF susceptibility through ferroptosis.

Pyroptosis and AF

Pyroptosis is an inflammatory form of programmed cell death involving the activation of caspase-1 by the inflammasome. Pyroptosis exhibits a plasma membrane blistering morphology and therefore is usually considered a monocyte-specific form of apoptosis. However, the recent discovery of Gasdermin-D of pore-forming activity, which is a key executor of pyroptosis, has redefined pyroptosis as a necrotic form of cell death.

Pyroptosis is a type of pro-inflammatory cell death that is closely associated with the activation of NOD-like receptor thermal protein domain associated protein 3 (NLRP3) inflammasome and is intensively involved in AF.⁶³ A previous report claimed the NLRP3 inhibitor glibenclamide reversed atrial remodeling partially and prevented AF in diabetic rabbits.⁶⁴ Yao et al found that NLRP3 inflammasome activity was enhanced significantly in atrial myocytes from AF patients and dogs with atrial tachycardia pacing.⁶³ Over activation of the NLRP3 signaling pathway promotes the expression of apoptotic mechanisms mediated by RyR2 and caspase-1, resulting in increased Ca^{2+} release from the sarcoplasmic reticulum and increased secretion of inflammatory cytokines.^{63,65} At the same time, enhanced transcription of *Kcna5* leads to an increase of *Kv1.5*-current, shortening the effective refractory period and forming a reentry substrate.⁶³ Cold exposure increased trimethylamine N-oxide by enhancing gut-derived trimethylamine production, which promoted M1 macrophage infiltration, induced the pyroptosis of cardiomyocytes in rats, exacerbates atrial structural remodeling, and ultimately led to AF.⁶⁶ LncRNA *x*-inactive specific transcript (XIST) may promote *Arl2* expression through the uptake of miR-214-3p to blunt the pyroptosis of cardiomyocytes, providing encouraging insights for XIST-based AF-targeted therapy.⁶⁷

Pulsed-Field Ablation (PFA) versus Conventional Catheter Ablation

Catheter ablation has formed a scenario in which radiofrequency ablation (RFA) is the mainstay, supplemented by cryoballoon, laser, and ultrasound ablation during the past decades. The success rates of RFA, cryoballoon ablation (CBA), and PFA for paroxysmal AF within 1 year are 61.1%–92%, 51.7%–88% and 66.2%–90% respectively (Table 1). Although a shoulder-to-shoulder comparison of the effectiveness of RFA and PFA is not yet available, the published data from small samples of PFA is worth envisioning. Unlike RFA and CBA, which use extreme temperatures to destroy myocardial tissue, PFA utilizes strong electric fields to disrupt the phospholipid bilayer integrity of cell membranes or organelles to induce cell death.⁶⁸ Cardiomyocytes have the lowest electroporation threshold of all tissues, which makes this technique particularly appropriate for cardiac ablation.⁶⁹ This difference in sensitivity between cardiomyocytes and other non-target tissues may reduce the risk of collateral damage to the esophagus and phrenic nerve.

Table 1 Summary of Success Rate After Different Ablation Procedures of Atrial Fibrillation

Reference	Total Number	Age (Year)	LVEF%	Type of AF	Treatment Method	1-Year Success Rate	Follow-Up Time (Success Rate)
[70]	150	63.4±9.9	60.3±4.8	Par	PFA	66.2%	–
[71]	121	57.4±10.3	62.5±5.7	Par	PFA	78.5%	–
[72]	186	59.4±10.2	60.8±5.8	Par	PFA	78.9%	–
[73]	1568	64.5±11.5	60	Par/Per	PFA	78.1%	–
[74]	52	65±10	56±11	Par/Per	PFA	–	0.5 years (85%)
[75]	200	71 (62–77)	–	Par/Per	PFA	80.3%(Par)/66.8%(Per)	–
[76]	191	69±12	60±10	Par/Per	PFA	–	0.5 years (94.2%)
[77]	138	67±12	52±10	Par/Per	PFA	90%(Par)/60%(Per)	–
[70]	150	66.0±9.0	57.6±6.4	Per	PFA	55.1%	–
[78]	45	67.1±10	56.5±11.2	Per	PFA	–	0.3 years (80%)
[79]	253	61±9	65.8±4.4	Par	RFA	82.7%	2.1 years (79.6%)
[80]	25	59±9	58±6	Par	RFA	92%	–
[81]	100	60.0±10.1	58.9±8.0	Par	RFA	61.1%	–
[82]	260	58.3±8.7	–	Par	RFA	–	1.9 years (57.3%)
[83]	66	54.3±1.3	60.8±7	Par	RFA	–	2 years (45.5%)
[84]	146	56±9	–	Par	RFA	82.2%	2 years (84.9%)
[85]	159	60 (54–67)	–	Par	RFA	70.7%	–
[86]	121	59.8±9.7	–	Par	RFA	–	4.8 years (46.6%)
[87]	210	56.6±10	61.8±6.1	Par/Per	RFA	80.6%	–
[88]	61	63.4±10.5	67.1±6.6	Par/Per	RFA	96.7%	3 years (88.5%)
[89]	136	58.2±10.8	–	Par/Per	RFA	57.4%	–
[90]	63	56.0±7.2	55.5±8.2	Par/Per	RFA	38.1%	7 years (13%)
[91]	150	58.2±10	57.±10.8	Par/Per	RFA	84%	–
[92]	356	59 (51–65)	60 (57–62)	Par/Per	RFA	~67.5%	5 years (45%)
[93]	100	55.7±9.6	70±11	Par/Per	RFA	40%	5 years (29%)
[94]	229	–	–	Par/Per	RFA	77.3%	–
[95]	50	62.4±9.5	56.3±4.1	Per	RFA	54%	–
[96]	83	65±8	27.8±9.5	Per	RFA	73.5%	–
[97]	25	60±7	55 (50–60)	Per	RFA	68%	–
[98]	49	64.0±8.7	56.8±8.1	Per	RFA	61.2%	–
[99]	67	58±10	55±11	Per	RFA	–	1.5 years (59%)
[100]	61	62.1±9.9	–	Per	RFA	54%	–
[101]	202	61±9	60±7	Per	RFA	35.1%	4.6 years (20.3%)
[102]	191	58.2±12.9	57±11	Per	RFA	–	1.1 years (32%)
[103]	104	60.4±11.2	60.9±0.6	Par	CBA	74.6%	–
[104]	154	57.7±12.3	59.6±7.0	Par	CBA	57.1%	–
[105]	116	58.6±9.2	59.1±6.6	Par	CBA	51.7%	–
[106]	163	57±9	60±6	Par	CBA	69.9%	–
[107]	107	50.5±13.1	62.8±5.4	Par	CBA	82.2%	–
[79]	247	60.8±10.0	65.9±5.4	Par	CBA	79.8%	2.2 years (70.9%)
[108]	163	58 (50, 64)	62 (57, 65)	Par	CBA	69%	5 years (53%)
[80]	25	58±9	60±5	Par	CBA	88%	–
[109]	55	62.9±8.7	61.7±5.4	Par/Per	CBA	61.8%	–
[81]	101	62.9±8.9	58.0±9.0	Par	CBA	60.3%	–
[82]	136	57±13.3	–	Par	CBA	–	1.9 years (63.2%)
[110]	120	61.9±9.3	55.9±8.5	Par/Per	CBA	74.2%	–
[111]	1742	58.0±10.4	–	Par/Per	CBA	78.5%	–
[112]	100	66.5±9.4	61.5±5.6	Par/Per	CBA	80%	–
[113]	80	66±10	57±10	Par/Per	CBA	68%	–

(Continued)

Table 1 (Continued).

Reference	Total Number	Age (Year)	LVEF%	Type of AF	Treatment Method	1-Year Success Rate	Follow-Up Time (Success Rate)
[114]	256	58±10.9	65±6.5	Par/Per	CBA	85.5%	5 years (59.4%)
[87]	200	57.5±9.8	61.1±7.1	Par/Per	CBA	72.7%	–
[115]	299	60±11	59±8	Par/Per	CBA	83.9%(Par)/61.6%(Per)	–
[88]	70	64.1±10.1	68.0±9.1	Par/Per	CBA	82.8%	3 years (70.0%)
[116]	236	54.6±10.45	64.5±5.8	Par/Per	CBA	–	1.5 years (74.5%)
[89]	133	59.7±9.9	–	Par/Per	CBA	75.2%	–
[117]	133	66±10	51±8	Per	CBA	67%	–
[118]	49	63±10	–	Per	CBA	69%	1.1 years (69%)
[119]	100	63±10	57.6±6.4	Per	CBA	–	0.9 years (67%)
[95]	50	62.4±9.8	57.5±3.7	Per	CBA	56%	–
[120]	69	59.4±8.1	–	Per	CBA	59%	1.7 years (50%)
[121]	917	–	–	Per	CBA	–	1.4 years (68.9%)

Abbreviations: AF, atrial fibrillation; RFA, radiofrequency ablation; PFA, pulsed field ablation; CBA, cryoballoon ablation; Par, Paroxysmal; Per, Persistent.

Cell Death in RFA and CBA

RFA uses radiofrequency currents to generate high temperature to cause damage to the target tissue, while CBA uses argon to absorb surrounding heat as it expands rapidly to cause a rapid drop in the temperature of the surrounding tissue. Both RFA and CBA are energy-based ablations that utilize extreme temperatures, resulting in irreversible cellular damage.

RFA causes a high temperature and then transmits it to the surrounding tissues, forming the main characteristic lesion centered on coagulative necrosis. When the temperature exceeds 60 °C, the time to reach irreversible damage decreases exponentially. The inactivation of important enzymes is the initial feature of the damage, and proteins are denatured quickly and followed by cytotoxicity causing coagulative necrosis (Figure 3). At temperatures around 40–45 °C, irreversible cellular damage only occurs with prolonged exposure (30–60 minutes). Temperature gradients caused by catheter can induce apoptosis and lead to the progression of injury. Besides, stimulation of apoptosis can be triggered by various cytokines and can induce direct alterations in the tissue microenvironment.¹²² In particular, endothelial pyroptosis after RFA of liver tissue has been reported to

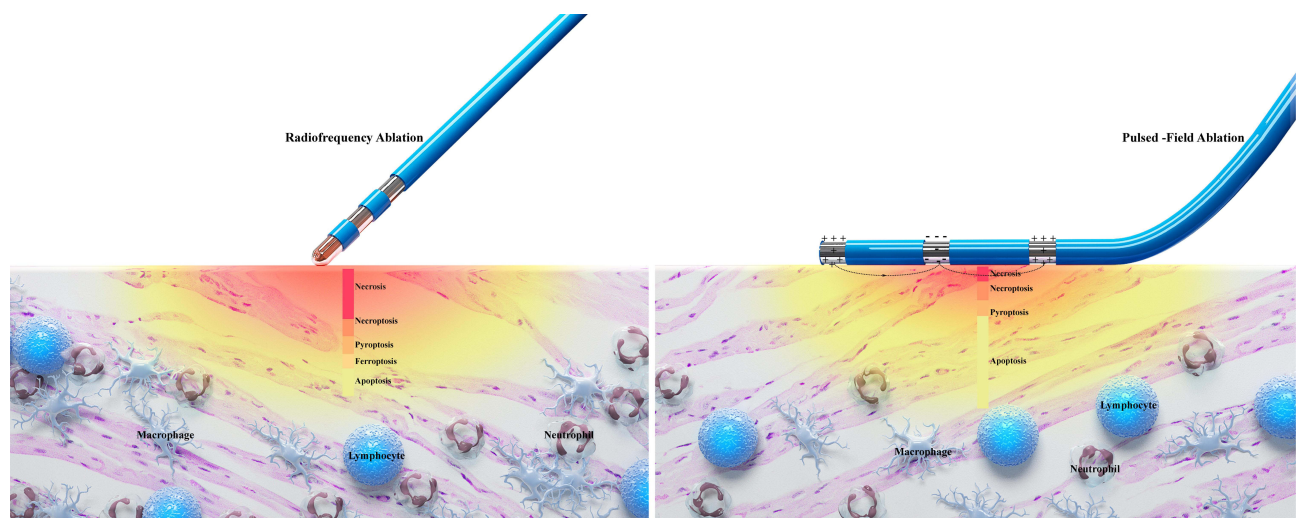


Figure 3 Comparison of cell death patterns due to RFA and PFA. RFA causes damage by localized cell necrosis, whereas PFA causes damage by apoptotic cell death. By comparing the schematic diagrams, RFA causes widespread necrosis, and the area of necrosis may contain patterns of death including necrosis, necroptosis, pyroptosis, and ferroptosis. A large accumulation of inflammatory cells such as neutrophils, monocytes and lymphocytes are chemotactic to the migrated area, which in turn induces a strong inflammatory response. Whereas the necrosis by PFA is limited to the area close to the catheter, the wider damage is predominantly apoptotic. There is also relatively little infiltration of inflammatory cells in the migratory zone.

Abbreviations: RFA, radiofrequency ablation; PFA, pulsed field ablation.

be closely associated with systemic inflammatory response syndrome, confirming that pyroptosis occurs with thermal injury.^{123,124} There is little ferroptosis reported from RFA or thermal injury. However, ferroptosis mediated alkali burn-induced corneal injury has been reported in ophthalmology.¹²⁵ In sum, cell death in the injury zone is a complex process and various types of cell death may need to be further explored.

CBA creates an injury similar to RFA, a pattern of injury centered on necrosis.¹²⁶ Ice crystals can form inside and outside the cells during CBA and are accelerated by nucleation. Spontaneous nucleation of cells can occur at -5°C to -15°C .¹²⁷ The percentage of intracellular ice increases during rapid temperature reduction. Cell damage occurs due to shearing, and the damage caused during rapid temperature reduction is lethal.¹²⁸ Animal studies verified that the sublethal temperature in the peripheral zone causes cells to activate apoptosis.^{129,130} Regrettably, the existence of other types of cell death in the migratory region has not yet been reported clearly.

Cell Death in PFA

Unlike RFA and CBA, which are energy-based ablations, PFA uses multiple strong pulses to generate an electric field that causes irreversible cell membrane damage.¹³¹ Electric fields are most commonly generated by a high-voltage direct current delivered between two or more electrodes. When a sufficiently strong electric field is applied to a cell and increases the permeability of its membrane, electroporation occurs, leading to increased ion transport and overall membrane instability.¹³² Its nonthermal mechanism of ablation allows PFA to ablate the atrial myocardium because it has a lower threshold for injury compared to the phrenic nerve and esophagus which are close to the heart. At a certain distance from the electrode, there will be an area of tissue at the PFA threshold that forms the edge of the lesion. With the use of higher voltages or increasing other exposure metrics (including pulse duration and the number of pulses), the lesion volume will increase. Cell death due to field exposure above the PFA threshold and permanent hyperpermeability is attributed to adenosine triphosphate depletion, ion channel failure, calcium overload, and a general loss of intracellular homeostasis.^{133–135}

This non-thermal damage maintains the integrity of the extracellular matrix and thus reduces structural remodeling. Apoptosis has been reported widely as the most common form of cell death by PFA.¹³⁶ (Figure 3) Animal models showed that the injury zone is delineated well and bounded by the surrounding tissue clearly.¹³⁷ This ensures that tissues outside the lesion are less affected during ablation and reduces the occurrence of inflammation. The PFA delivery energy is determined by the voltage, the pulse duration, and the number of pulses. In the region close to the electrodes, where the electric field reaches high amplitude, cells may undergo thermal damage.^{138,139} Sometimes, PFA-ablated tissues experience necrosis, pyroptosis, or necroptosis rather than apoptosis.^{140–142} Therefore, appropriate electroporation parameters could mitigate the degree of necrosis and the inflammatory response.

Inflammation and AF

The inflammatory response in local myocardial tissue leads to structural remodeling, which slows down atrial myocardial conduction velocity and prolongs the effective induction period, ultimately leading to the AF toward permanent arrhythmia. In patients with an acute systemic inflammation such as sepsis, the morbidity of AF can be up to 23%.¹⁴³ In patients with more severe septic shock, the morbidity of new-onset AF can be up to 46%.¹⁴⁴ Other chronic systemic inflammatory diseases such as rheumatoid arthritis,¹⁴⁵ psoriasis,¹⁴⁶ and inflammatory bowel disease¹⁴⁷ have all reported high incidences of AF. In addition, AF can lead to the release of inflammatory factors. Elevated IL-6 and tumor necrosis factor (TNF) were detected in both atrial tissue and peripheral blood in canines with atrial rapid pacing.¹⁴⁸ Recent studies have shown that T-cell-mediated inflammation can be regulated by modulating gut flora, which reduces atrial structural remodeling in turn and the development of age-related AF.¹⁴⁹

In addition to elevated serum inflammatory factors in AF, the local inflammatory status of myocardial tissue was also validly assessed. Epicardial adipose tissue from persistent AF patients expressed IL- 1β in large abundances at the transcriptional level.¹⁵⁰ High expression of tissue factors was produced by inflammatory stimuli in the left atrial appendage obtained from AF patients.¹⁵¹ Narducci et al showed high expression of CRP in atrial septum specimens from patients with paroxysmal AF.¹⁵² Local inflammation produces abundantly pentraxin 3. Markedly elevated pentraxin 3 expression by serology and immunohistochemistry confirmed an increased local inflammatory burden in AF.¹⁵³

Inflammation and Electrical Remodeling

Inflammatory cytokines such as platelet derived growth factor (PDGF), IL-2, and TNF- α regulate cellular ion channels and calcium homeostasis. PDGF from myofibroblasts can reduce the action potential duration and Ca²⁺ transients.¹⁵⁴ TNF- α can increase the potential for pulmonary veins to cause arrhythmogenesis and induce abnormalities in calcium homeostasis, leading to inflammation-associated AF.¹⁵⁵ It has been shown that mice overexpressing TNF- α have prolonged action potentials and Ca²⁺ transients, higher diastolic Ca²⁺ currents, and lower systolic Ca²⁺ currents.^{156,157}

Inflammation, in addition to regulating cellular ion channels and calcium homeostasis, has been associated with the heterogeneity of atrial conduction. Heterogeneous conduction may be the result of altered expression or distribution of connexin (Cx) 40, Cx43, or atrial fibrosis. In a canine model of aseptic pericarditis, reduced expression and transmural gradients of Cx40 and Cx43 (both absent in the epicardium, reduced in the pericardium, and normal in the endocardium) were associated with marked atrial conduction abnormalities and the induction and maintenance of AF.¹⁵⁸ One study found that the serum IL-6 level is negatively correlated with the expression level of Cx43. The expression of Cx40 and Cx43 decreased rapidly after direct exposure of IL-6 to HL-1 cells, and their expression recovered rapidly after the cessation of IL-6 exposure.¹⁵⁹ Ishii et al found that the degree of atrial inflammation was associated with the atrial conduction heterogeneity and the duration of AF.¹⁶⁰ Topical application of arachidonic acid to the atria of canines produced heterogeneous conduction, whereas methyl-prednisolone reversed it.¹⁶¹ Additionally, endurance athletes have increased risk for AF, and a longitudinal study of athletes participating in marathons found that prolonged signal-averaged P-wave duration was accompanied by transient increases of high-sensitivity C-reactive proteins (hs-CRP), pro-inflammatory cytokines, leukocytes, neutrophils, pro-cardiac natriuretic peptide, and high-sensitivity troponin, suggesting that acute changes in inflammatory cytokines are associated with atrial electrical conduction and susceptibility to AF.¹⁶²

Inflammation and Structural Remodeling

Inflammation is also closely related to structural remodeling of the heart, and clinical and experimental studies of AF have revealed that atrial fibrosis is the most important histopathological change in AF.¹⁶³ PDGF-A promotes cell proliferation and collagen expression in cardiac fibroblasts and increases susceptibility to atrial fibrosis and AF, which can be reversed by mast cell stabilizers and PDGF-A blockers.¹⁶⁴ PDGF and its receptors are expressed in atrial fibroblasts more strongly compared to ventricular fibroblasts. Whereas induction of HSPs, especially HSPA1A, attenuates the remodeling of atrial substrates.¹⁶⁵ TNF- α /TGF- β signaling pathway could increase secretion of MMPs which is involved in the pathogenesis of mouse atrial fibrosis.¹⁶⁶ In contrast, anti-TNF- α treatment reduced the activation of MMP-2 and MMP-9 and prevented collagen synthesis and deposition.¹⁶⁷ Recruitment of macrophages is critical for tissue fibrosis. Macrophages can stimulate IL-6 in cardiac fibroblasts, which leads to TGF- β 1 in cardiac fibroblasts and the phosphorylation of Smad3, stimulating cardiac fibrosis.¹⁶⁸ In clinical studies, high levels of CRP, IL-6, and IL-18 and low levels of HSP27 were associated with increased atrial size and susceptibility to AF, which further supports the role of inflammation in atrial remodeling.^{169–171}

Inflammatory Response After Ablation Procedures

There is no doubt that invasive catheter ablation procedures impart inflammatory response to the tissue, but this inflammatory response may be intimately correlated with the form of energy.

The ablated tissue or cells and extracellular matrix may release pro-inflammatory cytokines.¹⁷² Serum levels of IL-1 β , IL-6, IL-8, and TNF- α are shown to be elevated after RFA.^{173–175} Infiltration of inflammatory cells such as neutrophils, macrophages, dendritic cells, and natural killer cells has been reported in migratory zone.^{176–178} There is controversy regarding the cellular damage and inflammatory response produced after CBA. Some studies have shown a weak systemic inflammatory response after CBA,¹⁷⁹ while others have shown comparable cellular damage and inflammatory response between CBA and RFA.¹⁸⁰ Antolić et al found that myocardial damage was more pronounced with CBA than RFA. However, there was no significant difference between the two ablation techniques in terms of inflammatory

response and coagulation activation.¹⁸¹ Nonetheless, Shinsuke et al found that RFA and CBA groups had comparable peak blood hs-CRP and produced comparable inflammatory responses, and CBA caused greater myocardial damage.¹⁸²

The inflammatory response after PFA has been less studied. Massimo et al reported a detailed histological analysis of atrial lesions after PFA and performed the first comparative study of the histological findings at 7 and 30 days, finding that the degree of tissue inflammation was evident at 7 days and reduced with almost no inflammatory cells observed at 30 days, indicating a shorter duration of the inflammatory response.¹⁸³ Another study found that significant ablation-related necrosis, inflammation and fibrosis were seen in all tissue sections of RFA compared with PFA, and they speculated that RFA causes a greater inflammatory burden compared with PFA.¹⁸⁴ Comparing the inflammatory response generated by the organism after PFA and RFA in patients with hepatocellular carcinoma, it was found that the serum of macrophage migration inhibitory factor was elevated immediately after PFA, while this phenomenon was not observed in the RFA group, which may promote the early repair process after PFA and lead to a significant reduction of the ablation zone and alleviate the inflammatory burden in the organism.¹⁸⁵ Further studies are still needed regarding the strength of the inflammatory response after different ablation procedures for AF.

There is little direct histological evidence of inflammation in local myocardial tissue post catheter ablation, mainly due to concerns about the safety of invasive myocardial biopsy procedures. However, advances in imaging technology have made it possible to assess atrial inflammation in a non-invasive manner. Xie et al proposed that ¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography (PET-CT) would reflect favorably the degree of inflammatory burden after catheter ablation.¹⁸⁶ Late-gadolinium enhancement magnetic resonance imaging (LGE-MRI) is superior for assessing fibrosis as the final terminus of local inflammation. Clinical studies have reported that the higher the grade of fibrosis appraised by LGE-MRI after catheter ablation, the increased the rate of recurrence. In addition, enhanced CT assessment epicardial adipose tissue associated with local inflammation has been extensively utilized in clinical practice.^{187–189} Artificial intelligence algorithms can effectively predict the recurrence of AF after catheter ablation. By evaluating patient data, artificial intelligence algorithms can select the most effective AF treatment based on the patient's unique characteristics.¹⁹⁰ These tools considerably enrich the means of objectively appraise the local inflammatory response after catheter ablation. Early identification of excessive inflammatory responses and interventions facilitate a better prognosis.

Relationship Between Inflammation and Recurrence After Ablation Procedures

The primary goal of catheter ablation is to eliminate triggers that cause fibrillation, such as reentry, or to eliminate areas that lead to multiple depolarization, but it does not address the underlying process of myocardial remodeling.

The report published by Andrade et al suggested that early recurrence is thought to be due to inadequate early structural remodeling after pulmonary vein isolation (PVI), leading to leakage of the electrical impulses. Late recurrence may be the ectopic foci shifting from the pulmonary veins to other sites.¹⁹¹ In addition to other comorbidities, there is a fact that the levels of markers associated with myocardial injury like creatine kinase, creatine kinase-MB and troponin are high after catheter ablation.¹⁹² Troponin has been shown to be the most sensitive marker for detecting myocardial injury.¹⁹³ A systemic review found that the level of troponin was closely associated with AF recurrence after RFA.¹⁹⁴ During PVI, both radiofrequency ablation and cryoballoon ablation indiscriminately damage myocardial tissue, including blood vessels, nerves and myocardium. Complete PVI inevitably damages the left coronary artery branch, and stenosis with thrombosis causes myocardial tissue damage to extend from the ablation line to other areas. As mentioned above, ectopic foci activity is enhanced by subsequent atrial infarction and inflammation. The increase of local inflammation after catheter ablation may contribute to recurrence.

Several studies identified lymphocytes/neutrophils as a reliable predictor of recurrence after catheter ablation.^{195,196} Galectin-3 is a biomarker of AF that mediates atrial inflammation and may reflect progressive atrial fibrosis in AF. More studies have shown that galectin-3 is an independent predictor of recurrence after catheter ablation of AF,^{197–199} and Takemoto et al demonstrated that inhibition of galectin-3 could improve outcomes in persistent AF treated with catheter ablation.²⁰⁰ Besides, it has been reported that uric acid/albumin,²⁰¹ myeloperoxidase,^{202,203} monocyte/HDL,²⁰⁴ TLR4,²⁰⁵ MMP-2 and TNF- α ,²⁰⁶ and CRP²⁰⁷ were associated with higher recurrence after catheter ablation. The inhibitory effects of anti-inflammatory drugs such as steroids, colchicine, angiotensin-converting enzyme inhibitor/angiotensin receptor

blocker, and statins on AF are summarized in a review by Kensuke et al in detail.²⁰⁸ In addition, the AntaEP study indicated that antazoline may be suitable for pharmacological cardioversion of AF occurring during PVI, hinting the potential participation of histamine in the progression of AF.²⁰⁹

Conclusion

Inflammatory cell death is strongly associated with the development and recurrence of AF. Therefore, avoiding inflammatory and unnecessary cell death in myocardial tissue is essential to prevent the recurrence of AF. In the current review, PFA, a new energy source of non-thermal irreversible electroporation, has great advantages over traditional catheter ablation. From the cellular perspective, catheter ablation uses extreme temperatures to cause necrosis of diseased tissues and cells, and the inflammatory response generated places a certain burden on the organism. In contrast, PFA benefits patients by protecting adjacent tissues and inducing apoptosis with a less inflammatory response on the organism while ensuring significant efficacy of durable PVI. However, different parameters cause different types of cell death in the tissues. There is still a lack of clinical trials on PFA, and further research is needed to investigate its safety and effects.

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