CURRENT STATUS AND FUTURE DIRECTION OF PULSED FIELD ABLATION: HOW TO PREVENT ALH SYNDROME

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Introduction

Pulsed field ablation (PFA) has rapidly emerged as an important advancement in catheter ablation for atrial fibrillation (AF). By inducing irreversible electroporation through high-voltage, short-duration electrical pulses, PFA produces myocardial injury with less dependence on conventional thermal mechanisms. Its potential tissue selectivity has generated considerable enthusiasm, particularly because of the reduced risk of certain complications associated with radiofrequency (RF) and cryothermal ablation, including esophageal injury and pulmonary vein stenosis.

However, clinical studies have shown that PFA is noninferior, rather than clearly superior, to conventional thermal ablation in long-term efficacy. More importantly, accumulating clinical experience has revealed a new spectrum of potentially life-threatening complications, including severe hemolysis-related acute kidney injury (AKI), cerebral embolic events, coronary vasospasm, myocardial ischemia, ventricular fibrillation (VF), and sudden cardiac death.[1-4] These observations challenge the assumption that PFA is inherently safe simply because it is predominantly nonthermal. They also raise a fundamental question: Are we delivering more PFA energy than is necessary to produce durable myocardial lesions?

We have proposed the term **“ALH Syndrome” (Ablate Like Hell Syndrome)** as a conceptual framework highlighting the potential consequences of excessive or unnecessary PFA delivery.[1] ALH Syndrome is not an established clinical diagnosis, but rather a hypothesis-generating concept intended to promote safer, more rational PFA strategies.

Emerging Life-Threatening Complications of PFA

Hemolysis and acute kidney injury

Intravascular hemolysis has emerged as an important PFA-specific safety concern. High-voltage electric fields can disrupt red blood cell membranes, releasing plasma-free hemoglobin (Hb). Clinical studies have demonstrated that repeated PFA applications are associated with increased plasma-free Hb, hemoglobinuria, elevated serum creatinine, and, in severe cases, AKI requiring hemodialysis. Importantly, the extent of hemolysis appears to depend not only on the number of PFA applications but also on electrode–tissue contact, waveform characteristics, electrode configuration, and energy-delivery strategy. When PFA energy is delivered without adequate electrode–tissue contact, a greater proportion of the electric field may interact with circulating blood rather than myocardium. Consequently, unnecessary PFA applications may increase hemolysis without producing effective irreversible myocardial lesions.

Cerebral embolic events

Although PFA has been thought to avoid conventional RF-induced coagulation necrosis, silent cerebral lesions detected by diffusion-weighted magnetic resonance imaging remain a concern.[2] Potential mechanisms include microbubble formation, thrombus formation related to electrode-tissue interface overheating, and direct interactions between high-voltage electric fields and blood components. Importantly, these complications appear to be influenced by waveform design, electrode geometry, and saline irrigation strategies.

Coronary vasospasm, myocardial ischemia, and ventricular fibrillation

Perhaps the most concerning emerging observations involve delayed myocardial ischemia and malignant ventricular arrhythmias. In a recent international multicenter analysis involving 6,721 patients undergoing PFA for AF, 11 life-threatening delayed or prolonged ischemic and arrhythmic adverse events were reported.[1-4] These included delayed ST-segment elevation, intraprocedural VF requiring resuscitation, prolonged vagal reactions, and sudden cardiac death. Of particular concern, delayed diffuse coronary vasospasm and VF have been reported even when PFA was not delivered directly adjacent to the coronary arteries.[4] Although the precise mechanisms remain uncertain, these observations suggest that PFA-related cardiovascular complications may involve not only direct local tissue injury but also systemic vascular and autonomic effects.

Potential Mechanisms of PFA-Related Complications

1. Hemolysis, nitric oxide depletion, and endothelial dysfunction

Intravascular hemolysis may represent a potentially important link among several emerging PFA complications. Following red blood cell membrane disruption, cell-free Hb enters the circulation and rapidly scavenges nitric oxide (NO), an essential mediator of vascular relaxation and endothelial homeostasis. Reduced NO bioavailability may promote vasoconstriction, endothelial dysfunction, platelet activation, and microvascular impairment.[1,5] In addition, free heme and iron can induce oxidative stress and inflammatory responses, potentially contributing to renal and vascular injury. These mechanisms provide a biologically plausible explanation for why extensive hemolysis could contribute to systemic complications beyond AKI.

We hypothesize that PFA-induced hemolysis and subsequent endothelial dysfunction may contribute to delayed diffuse coronary vasospasm, myocardial ischemia, and malignant ventricular arrhythmias in susceptible patients.[1] However, a direct causal relationship has not yet been established and requires further experimental and clinical investigation.

2. Electrode–tissue interface heating and microbubble formation

Although PFA is predominantly nonthermal, high-voltage electrical pulses can produce localized Joule heating, particularly at the electrode–tissue interface. The degree of heating depends on waveform characteristics, current density, electrode configuration, pulse duration, repetition frequency, and saline irrigation flow rate.[2]

Microbubble formation during PFA may result from electrochemical reactions, localized heating, and cavitation-related mechanisms. Importantly, experimental observations demonstrate that waveform optimization can markedly reduce microbubble generation while preserving myocardial lesion formation. These findings indicate that PFA waveform design should be optimized not only for lesion efficacy but also for minimizing electrode–blood interactions and embolic risk.

3. Direct coronary vascular injury and autonomic effects

Experimental studies have demonstrated that PFA delivered near coronary arteries can produce acute vasospasm and, under certain conditions, vascular wall injury involving the intimal and medial layers. Although nitroglycerin can attenuate PFA-associated coronary narrowing, cases of clinically significant coronary vasospasm despite nitroglycerin administration have been reported.[3,4]

Furthermore, stimulation of cardiac autonomic ganglionated plexi during PFA may contribute to prolonged vagal responses and potentially arrhythmic complications. The relative contributions of direct vascular injury, hemolysis-related endothelial dysfunction, and autonomic mechanisms remain incompletely understood.

How Can We Prevent ALH Syndrome?

1. Avoid unnecessary and excessive PFA applications

The most immediate preventive strategy is to minimize PFA applications that do not contribute to durable lesion formation. Unlike conventional RF ablation, PFA produces a relatively broad zone of reversible electroporation surrounding the central irreversible lesion. Consequently, acute disappearance of intracardiac electrograms or achievement of conduction block does not necessarily indicate durable myocardial lesion formation. This creates a procedural dilemma: insufficient PFA may result in lesion recovery and arrhythmia recurrence, whereas excessive PFA may increase hemolysis and other complications. The objective should therefore be to deliver the minimum effective PFA dose required to achieve durable irreversible lesion formation, rather than simply minimizing the total number of applications.

2. Ensure adequate electrode–tissue contact

Our experimental studies have demonstrated that electrode–tissue contact is a critical determinant of irreversible PFA lesion formation.[6,7] In swine beating-heart models, lesion depth increased significantly with increasing contact force and the number of delivered PFA pulses. In contrast, no irreversible lesion formation was observed when the ablation electrode was positioned only 1–2 mm away from the myocardial surface, despite repeated pulse delivery. [6,7] These findings challenge the assumption that PFA lesion formation is relatively independent of catheter contact. Importantly, delivering high-voltage energy without adequate tissue contact may increase blood exposure to electrical fields while providing little or no therapeutic benefit.

3. Optimize waveform, electrode configuration, and saline irrigation

PFA systems differ substantially in waveform characteristics, electrode geometry, and energy-delivery strategies. Consequently, efficacy and safety observations from one platform should not automatically be generalized to others. Waveform optimization may reduce microbubble formation, degree of hemolysis, and electrode–tissue interface heating without compromising lesion formation.

Saline irrigation is another potentially important modifiable factor. In a clinical study using a variable-loop PFA catheter, increasing irrigation flow from 4 to 30 mL/min was associated with a reduction in MRI-detected silent cerebral lesions from 33.3% (6/18 patients) to 4.8% (1/21 patients).[2] These findings emphasize that irrigation strategy may significantly influence the embolic safety profile of PFA. However, the optimal irrigation flow rate should be established for each catheter and waveform configuration.

4. Develop real-time prediction of irreversible lesion size

A major limitation of current PFA technology is the lack of a reliable real-time indicator of durable myocardial lesion formation.

Our experimental studies demonstrated that conventional procedural markers, including electrogram attenuation, impedance changes, and electrode temperature, correlate poorly with irreversible PFA lesion size.[6,7] To address this limitation, we developed a novel PF Ablation Index integrating contact force and the number of PFA applications to predict irreversible lesion depth.[6,7] In a prospective swine beating-heart validation study, predicted lesion depth was within ±1.0 mm of actual lesion depth in 97 of 106 lesions (92%). These findings provide proof of concept that quantitative, real-time lesion prediction may improve the precision of PFA delivery. Importantly, such technology could potentially reduce unnecessary applications, improve lesion durability, and minimize blood exposure to excessive electrical energy. Whether PF Ablation Index-guided strategies can improve clinical outcomes and reduce serious complications remains to be established in prospective clinical studies.

Future Directions: From Rapid Ablation to Precision PFA

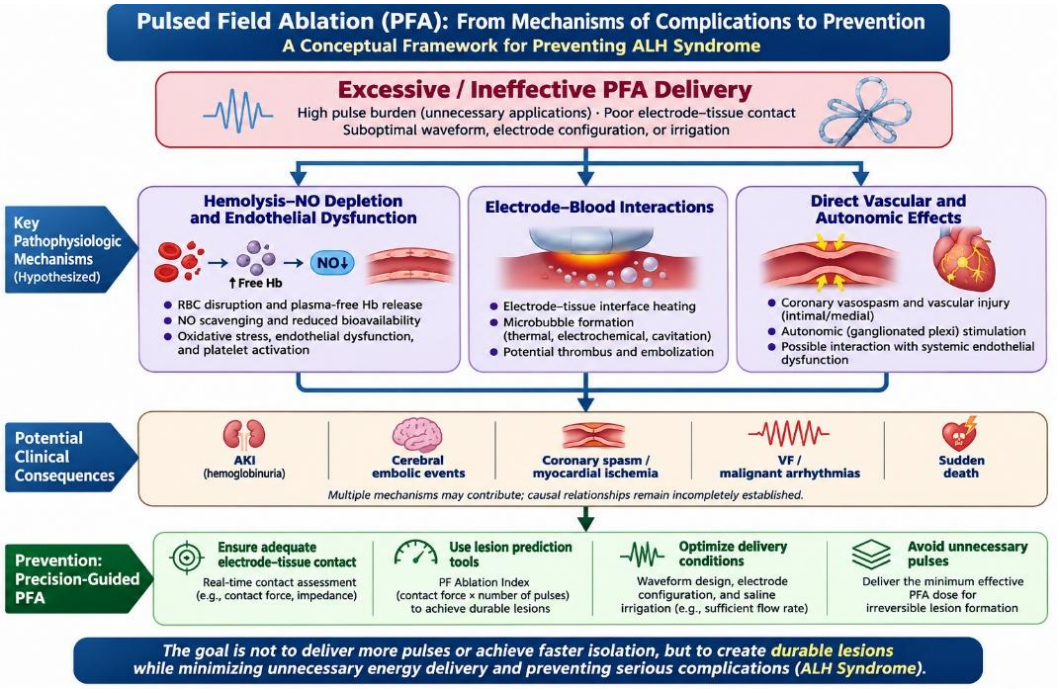
The next generation of PFA should focus on three interconnected objectives: predictable lesion durability, reduced systemic toxicity, and improved procedural safety.[1]

First, PFA systems should incorporate real-time assessment of electrode–tissue contact, electric field distribution, and irreversible lesion size. These capabilities may enable operators to deliver an appropriate energy dose for each anatomical target.

Second, systematic evaluation of PFA-induced hemolysis and endothelial dysfunction is needed. Measurements of plasma-free Hb, NO bioavailability, vascular endothelial function, and markers of platelet activation may help clarify the mechanisms underlying renal, vascular, and arrhythmic complications.

Third, waveform design, electrode configuration, and irrigation strategies should be optimized through rigorous preclinical and comparative clinical investigations. The goal should be to minimize unwanted blood and vascular interactions while preserving effective myocardial electroporation.

Finally, prospective multicenter studies and long-term surveillance are essential to determine whether emerging serious complications relate to specific PFA systems, procedural strategies, patient characteristics, or combinations of these factors.



Proposed Mechanisms of Complications Related to PFA.

Conclusions

PFA represents a major technological advancement in catheter ablation, but its rapid adoption has revealed important limitations and previously underrecognized complications. The concept of ALH Syndrome highlights the risks of excessive or unnecessary PFA delivery and the importance of balancing lesion efficacy with systemic and vascular safety. The future of PFA should move from empirical, repetitive energy delivery toward precision-guided ablation based on real-time prediction of irreversible lesion formation. Our ultimate goal should not simply be faster pulmonary vein isolation, but safer, more effective, and more durable catheter ablation. Preventing ALH Syndrome may be an essential step toward realizing the full clinical potential of PFA.

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