

## Editorial

### From atrium to ventricle - evolving evidence for extracardiac complications from non-thermal but not risk-free pulsed field ablation platform

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Heart, Vessels and Transplantation

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#### Summary of key evidence: Extracardiac complications across PFA and thermal ablation modalities

Aspect	Mulder et al. 2025	Venier et al. 2023	MANIFEST-17K 2024	Ghajar et al. 2025	MANIFEST-US 2026
Complication focus	Hemoptysis / AKI post-PFA	Severe hemolysis-AKI	Registry-wide PFA safety	Hemolysis (moderate dose)	Real-world US PFA safety
PFA applications (approx.)	40	High (>100)	Median 143 in AKI cases	48	Varied (registry)
AKI severity	Dialysis required	Severe AKI	0.03%; some dialysis	AKI without dialysis	AKI in <0.03%
Esophageal injury	Not reported	Not reported	None in 17,642 pts	Not applicable	None in 41,968 pts
Key message	Risk even at moderate dose	Hemolysis-AKI is real	Low incidence, dose-linked	Moderate dose still carries risk	Favourable profile; no AEF or PVS

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**Key words:** Pulse field ablation, complication, atrial fibrillation ablation, hemoptysis, hemolysis, extracardiac injury (Heart Vessels Transplant 2026; 10: doi:10.24969/hvt.2026.649)

#### Highlights

- Hemoptysis, hemolysis and AKI could occur after PFA for atrial fibrillation
- Close monitoring for complications is essential
- Energy delivery frequency should be taken in account in presence of renal disease

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We read with interest the recent European Heart Journal – Case Reports publication by Mulder et al. (1) describing hemoptysis following atrial fibrillation (AF) ablation using pulse field ablation (PFA). The case is timely and clinically meaningful, drawing attention to a complication that, while uncommon, carries the potential for serious morbidity. Hemoptysis following AF ablation has classically been attributed to pulmonary vein (PV)-related injury, encompassing venous stenosis, bronchopulmonary vascular trauma, and inflammatory pulmonary hemorrhage. Our own group has previously documented hemoptysis arising days to weeks after cryoballoon ablation—a complication reported both in a peer-reviewed case report (2) and in subsequent communications in the Pakistan Journal of Cardiology (3, 4)—underscoring the capacity for subacute pulmonary injury to manifest in delayed fashion across thermal energy modalities. The present case extends this concern to PFA, reinforcing that the evolution toward non-thermal energy sources does not in itself eliminate the risk of extracardiac pulmonary injury.

PFA achieves myocardial cell death through irreversible electroporation, delivering ultrashort high-voltage electrical pulses that selectively disrupt cardiomyocyte membranes while largely sparing adjacent structures such as the esophagus, phrenic nerve, and pulmonary vein walls (5). This tissue selectivity underpins the strong safety profile observed in large registries (Table 1). The MANIFEST-17K study, encompassing over 17,000 patients, reported no instances of atrio-esophageal fistula, pulmonary vein stenosis, or persistent phrenic nerve injury (6). The more recent MANIFEST-US study—the largest post-approval PFA dataset to date, including 41,968 patients from 102 United States centers—confirmed a major adverse event rate of only 0.63%, again with no cases of esophageal fistula, PV stenosis, or persistent phrenic paralysis (7). Taken together, these data confirm a favorable overall safety profile; nevertheless, they also reflect the limits of aggregate registry reporting when it comes to infrequent pulmonary complications.

Mild or self-limited hemoptysis, if attributed to anticoagulation alone or unreported, would not be captured. Early cross-sectional imaging—ideally contrast-enhanced computed tomography—remains essential in any post-ablation patient presenting with hemoptysis, irrespective of energy modality used.

Beyond pulmonary complications, PFA has been associated with a distinct pattern of systemic extracardiac injury: intravascular hemolysis with

resultant hemoglobin-mediated nephrotoxicity and acute kidney injury (AKI). Severe hemolysis requiring dialysis has been described in individual case reports (8, 9) and was quantified in MANIFEST-17K at an incidence of 0.03% (5 of 17,642 patients). A recently published narrative review (March 2026) has clarified the mechanistic basis and procedural determinants of this complication, confirming that risk correlates with peak output voltage, the total number of energy applications delivered, and catheter-tissue contact quality (10). Critically, the threshold for clinically significant hemolysis appears to rise substantially when PFA applications exceed 90–100; patients with pre-existing renal impairment may reach this threshold at lower application counts. Separate work using tissue proximity indication software has further established that energy discharged from non-contact electrodes—irrespective of total pulse count—independently amplifies hemolysis markers, suggesting that catheter positioning discipline is as important as limiting the number of applications (11). The pathophysiological mechanisms underlying hemoptysis and hemolysis differ fundamentally; however, both complications serve as evidence that high-voltage electrical energy delivered within the left atrium can exert clinically meaningful effects at sites remote from the target myocardium.

Post-marketing surveillance data broaden the spectrum of extracardiac concern. A Medical Device Report submitted to the United States Food and Drug Administration documents a fatal atrio-esophageal fistula associated with PFA—a complication not captured in either MANIFEST registry—underscoring that rare but catastrophic outcomes may require longer follow-up and more granular reporting frameworks to surface reliably (12). A separate FDA MAUDE report describes a single episode of ventricular fibrillation occurring after the 11th pulsed field application during a PFA procedure, requiring emergency resuscitation. While individual adverse event reports cannot establish causality, they represent a critical adjunct to controlled registry data and should inform ongoing post-market surveillance protocols. Furthermore, gastroparesis has recently been identified as a potential extracardiac autonomic complication of pentaspline PFA even in the absence of endoscopically detectable esophageal injury, suggesting that vagal plexus modulation during posterior wall energy delivery may produce clinically relevant gastrointestinal effects not reflected in standard safety endpoints (13).

**Table 1. Summary of key evidence: Extracardiac complications across PFA and thermal ablation modalities**

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This observation expands the catalogue of PFA-specific extracardiac effects and warrants prospective study. Contextualizing these findings within the broader catheter ablation literature is instructive.

A systematic review and meta-analysis of catheter ablation for valvular atrial fibrillation has demonstrated that procedural efficacy and safety outcomes differ meaningfully across structural substrates, with concomitant valvular pathology modifying both arrhythmia recurrence risk and the probability of procedural complications (5). This is directly relevant to PFA adoption, since real-world practice increasingly involves patients with structural heart disease, hypertensive cardiomyopathy, and impaired renal function—precisely the cohorts in whom hemolysis-related AKI may be most consequential and in whom post-ablation hemoptysis is least likely to be attributed to an ablation-related mechanism. The PFA-SHAM trial (7), presented at the American Heart Association 2025 Scientific Sessions, provided the first randomized placebo-controlled evidence that PFA reduces AF recurrence and improves quality of life compared with a sham procedure, with no major safety signals observed—strengthening the efficacy case while reinforcing that ongoing complication surveillance remains warranted as indications broaden.

The present report by Mulder et al. (1), read alongside our prior experience with cryoablation-related hemoptysis, and the emerging data on PFA-specific systemic complications, point to several practical conclusions. First, post-ablation hemoptysis must not be reflexively attributed to anticoagulation; early contrast-enhanced CT of the chest is essential regardless of

energy source. Second, the risk of hemolysis-induced AKI should be anticipated prospectively in patients undergoing high-application-count PFA, particularly those with reduced baseline renal reserve, and procedural protocols should aim to minimize non-contact electrode energy delivery. Third, uncommon complications—whether pulmonary, renal, autonomic, or cardiac—are unlikely to be fully characterized within the observational follow-up windows of existing registries, and dedicated adverse event reporting, inclusive of delayed presentations, should be embedded within all post-approval PFA programs. As PFA platforms proliferate and indications expand, a rigorous and systematic approach to extracardiac safety remains indispensable to ensuring that the real-world experience matches the promise of pre-clinical and early registry data.

The emerging application of PFA to ventricular tachycardia (VT) ablation introduces a distinct and amplified complication landscape that warrants dedicated consideration. Unlike the thin-walled atrium, ventricular targets—particularly scar-related substrates—require deeper lesion penetration into fibrotic, heterogeneous myocardium, necessitating higher energy densities and greater application counts. This elevates the risk of hemolysis-induced AKI well beyond what is observed in AF ablation, while simultaneously raising concerns about coronary artery proximity, conduction system injury (including bundle branch block and atrioventricular block), and acute hemodynamic decompensation in patients who already carry severely impaired ventricular function.

A systematic review of PFA for VT identified vascular complications, cardiogenic shock, and conduction system damage as the principal risks in early-experience cohorts (14). The first-in-human VCAS trial, evaluating high-voltage focal PFA for scar-related VT, reported primary safety events in 11.5% of patients within 180 days—including cardiogenic shock and heart failure hospitalization—though no energy-related strokes or phrenic nerve injuries were observed, and hemolysis, while biochemically detectable, did not necessitate renal replacement therapy in any patient (15).

As VT PFA programs scale, prospective complication surveillance strategies must be specifically designed for the ventricular context, recognizing that the safety benchmarks established in AF cannot be directly extrapolated.

It will be worth monitoring once PFA will be used even for supraventricular tachycardia arrhythmias too.

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