



# Pericardial Blood as a Trigger for Postoperative Atrial Fibrillation After Cardiac Surgery

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**Background.** Prevention strategies have long been sought to reduce the incidence and burden of postoperative atrial fibrillation (POAF) after heart surgery. However, none has emerged as a dominant and widely applicable prophylactic measure. The purpose of this review is to consider the biological mechanisms by which shed mediastinal blood leads to oxidation and inflammation within the postoperative pericardial environment and how this might trigger POAF in susceptible persons, as well as how it could represent a new target for prevention of POAF.

**Methods.** We conducted a structured research of literature using PubMed and MEDLINE databases to May 2016. Biomolecular and clinical articles focused on assessing the contribution of pericardial blood, or the resulting inflammation within the pericardial space and its potential role in triggering POAF, were included in this review.

**Results.** Evidence suggests that shed mediastinal blood through breakdown products, activation of coagulation cascade, and oxidative burst contributes to a highly pro-oxidant and proinflammatory milieu found within the pericardial space that can trigger postoperative atrial fibrillation in susceptible persons. The extent of this reaction could be blunted by reducing the exposition of pericardium to blood either through posterior pericardiotomy or improved chest drainage.

**Conclusions.** Shed mediastinal blood undergoing transformation within the pericardium appears to be an important contributing factor to POAF. Strategies to prevent shed mediastinal blood from pooling around the heart might be considered in developing future paradigms for prevention of POAF.

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Postoperative atrial fibrillation (POAF) is the most common complication after cardiac surgery, occurring in 19% to 30% of patients according to modern surgical series [1, 2]. The risk for postoperative atrial fibrillation is highest in the first 48 hours after surgery, followed by a slow decline over the following 4 to 7 days [3]. POAF is associated with a higher incidence of subsequent postoperative complications, including cognitive changes and stroke, renal dysfunction, and infection [4]. POAF has been linked to longer hospital stays and to more readmissions and deaths during recovery after surgery [1, 5].

Given the high incidence and important consequences of POAF in this population, prevention strategies have long been sought. Common approaches for prophylaxis for POAF have relied on targeting the sympathetic nervous system, atrial conduction, and refractory periods with administered systemic drugs such as beta-blockers, digoxin, and amiodarone [6, 7]. Because most of these strategies work by attenuating neurohormonal activation

or conduction, adverse side effects, including hypotension and bradycardia, can limit broader use [8]. Combining these agents with magnesium does not reliably improve efficacy, and may increase adverse events [9]. Furthermore, potassium and magnesium supplementation alone does not protect against POAF after cardiac surgery [10].

Beyond neurohormonal activation, increasing evidence points to an additional inflammatory component in the genesis of POAF [11–14]. This recognition was primarily driven by the measurement of increased biomarkers of inflammation in the systemic circulation in patients with POAF, as well as the ability to induce atrial fibrillation with surface inflammation in the laboratory [11, 12]. Systemic efforts to blunt the responses (fish oil, polyunsaturated fatty acids, statins, N-acetylcysteine, and colchicine) as a prophylactic pharmacologic measure have been largely ineffective, however, and therefore none has been uniformly adopted [13, 15]. Although

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steroids have shown some promise in reducing the incidence of POAF, the risks due to side effects are considered too high for general use as a widely applied preventative measure [16, 17]. The failure of any systemic pharmacologic approach to emerge as a dominant prophylactic strategy to prevent POAF helps to explain why the incidence of POAF has remained stable in the last decades [18, 19].

A growing body of literature details the unique features of the local intrapericardial postoperative inflammatory milieu after cardiac surgery as a possible contributor to POAF [11, 13]. In particular, increasing evidence suggests that shed mediastinal blood may be a significant source for this inflammation [20–22]. The purpose of this review is to detail the intrapericardial biologic mechanisms by which shed mediastinal blood may set in motion an inflammatory response that contributes to the development of POAF in susceptible persons, and examine how prophylactic strategies might evolve to better address this common problem by minimizing retained blood and subsequent pericardial inflammation.

## Material and Methods

### Search Strategy

We aimed to evaluate all studies examining the etiologic role of pericardial blood in triggering of POAF after cardiac surgery. A structured review of literature was performed using PubMed and MEDLINE databases. The search strategy involved combinations of the (MESH) terms “atrial fibrillation,” “cardiac surgical procedure,” “postoperative complication,” “oxidative stress,” “inflammation,” “hemolysis,” “pericardium,” “mediastinum,” “pericardial effusion,” “etiology,” and “prophylaxis.” The last search was conducted in May 2016. Once an abstract’s general information had been identified as useful to the reader and worth further investigations, full articles were assessed and additional research was initiated. Reference lists of skimmed articles were hand-searched for relevant studies, and tangential electronic explorations of related investigations were performed.

### Evaluation of Evidence

Although a multitude of factors may contribute to POAF, the evaluation of the resources remained focused on the contribution of pericardial blood, or the resulting inflammation within the pericardial space that ensues when blood is broken down and its potential role in triggering POAF. Studies not published as full-text articles, single case reports, opinion articles, and articles not written in English were excluded. No article was excluded based on date of publication. Hard copies of all relevant articles were obtained and read in full. Two independent reviewers had to agree to select an article for inclusion in our review.

## Comment

### POAF Is Triggered in Susceptible Persons

Any arrhythmia requires a susceptible electrophysiologic substrate (usually nonuniform recovery) and a depolarizing trigger to be initiated [23]. POAF occurs when persons with susceptible atrial substrate are exposed to certain triggers at the time of surgery, and these triggers push them temporarily past the atrial fibrillation threshold [24]. At the atrial tissue level, susceptibility to triggers occurs in patients who present with long standing structural changes in the electrophysiologic atrial substrate [24, 25]. These physical changes in the structure of the atrium occur after long-standing myocardial stress and damage from various forms of structural heart disease, yet their proarrhythmic changes are insufficient to engender paroxysmal, persistent, or chronic atrial fibrillation before surgery [24]. Several studies have implicated predisposing chronic factors such as advanced age, hypertension, obesity, myocardial infarction, valvular heart disease, left atrial enlargement, left ventricular dysfunction, periatrial fat volume, electrolyte imbalance, and other forms of structural heart disease [4, 26, 27]. These chronic cardiac conditions can lead to abnormal (heterogeneous) dispersion of refractoriness that leaves the atrium vulnerable to the development of fibrillation [23, 28]. Once surgery is performed, acute transient factors, layered on the preexistent vulnerable atrial substrate, can exceed the fibrillation threshold and trigger POAF [24]. This transient alteration in the chronically damaged atrial tissue goes away in a vast majority of patients during the subsequent weeks or months of recovery from heart surgery, explaining why most patients eventually return to sinus rhythm [2].

Several potential triggers for POAF have been considered and include ischemia reperfusion injury, sympathetic activation, and the systemic inflammatory response to cardiopulmonary bypass [13]. In addition, direct trauma to the atrium during cannulation may be a trigger of POAF, as evidenced by the histologic findings in dog models demonstrating a role in neutrophils infiltration and inflammation within the atrial wall around atriotomy correlated with inhomogeneities and alteration in action potential duration in the atrial substrate that are essential to trigger reentrant circuits rotating around the atriotomy responsible for POAF [29, 30].

Generally, the more complex and invasive the operation, the higher the incidence of POAF. As an example, coronary artery bypass graft surgery (CABG) combined with valve or complex aortic procedures is associated with a significantly higher rate of POAF than is CABG alone [1]. Conversely, in less complex surgeries, less POAF is encountered. Advances in technique that enable heart surgery to be performed through minimally invasive incisions, off pump, without cooling, and even without opening the chest all provide a window into the mechanisms of POAF. For example, performing the procedure through a sternotomy but not placing the patient on cardiopulmonary bypass modestly reduces the incidence of POAF [31]. Reducing the size of the surgical

incisions diminishes the incidence of POAF in valve surgery patients, but again only to a modest extent [32].

Recent investigations demonstrated a marked difference in the incidence of POAF between procedures involving the opening of the pericardium and the exposition of the postoperative intrapericardial environment to blood, and those when the pericardium is not entered to perform a valve replacement. In one report, POAF occurred in 60% of patients who underwent surgical aortic valve replacement, in 53% after minimally invasive transapical transcatheter aortic valve replacement, in 33% after open transaortic transcatheter aortic valve replacement, and in only 14% after transfemoral transcatheter aortic valve replacement. These data demonstrate that procedures without pericardiectomy and intrapericardial blood exposure had an 82% risk reduction of POAF compared with procedures with pericardiectomy [33, 34]. In addition, many studies have shown that the more the patient bleeds postoperatively, the higher the risk of POAF [19, 35, 36]. Although these clinical impressions do not point to a single root cause, they raise the possibility that an increased exposure to pericardial blood postoperatively, superimposed on the intrinsic myocardial inflammation induced by surgical incision, may cause a higher incidence of POAF.

#### *Shed Mediastinal Blood Is Potent Trigger for POAF by Inducing Both Inflammatory and Oxidative Damage to Heart Surface*

A considerable body of literature now exists linking oxidative stress with the development of atrial fibrillation [37]. Oxidative stress occurs when excess production of reactive oxygen species overwhelms endogenous antioxidant defenses, resulting in tissue injury through lipid peroxidation at the cell surface level [38]. Oxidative stress in large part comes when recruited leukocytes are activated to release  $O_2^-$  (superoxide) by the reduction of oxygen at the expense of nicotinamide adenine dinucleotide phosphate (NADPH), producing  $H_2O_2$  (hydrogen peroxide) [39]; NADPH oxidase is the major enzymatic source for reactive oxygen species in neutrophils and monocytes [37]. Reactive oxidant species cause lipid peroxidation, a process that breaks down tissue cell membranes, leading to decreased mitochondrial function, cellular calcium overload, and apoptosis or cell death [40].

Recent evidence supports that a highly inflammatory and prooxidant milieu develops within the pericardium after heart surgery, and that this may serve as an important trigger of POAF [40]. Consistent with these theories, inflammatory cells infiltration is prominent in the atrial myocardium of patients with AF [14]. Atrial fibrillation can be induced by surface inflammation in animal studies, with the degree of atrial oxidative inflammation associated with a proportional increase in atrial damage, cardiac myocyte dysfunction, electrical and structural remodeling, inhomogeneity of atrial conduction and atrial fibrillation duration [38, 41, 42]. Shed mediastinal blood within the pericardium is a major

source of this intrapericardial oxidative stress and inflammation that triggers POAF through several pathophysiologic steps.

#### *Blood and Blood Breakdown Products in Pericardial Space May Trigger POAF*

Surgery that involves pericardiectomy allows bleeding into the pericardial space; hence, all patients require chest tubes to evacuate shed mediastinal blood in the early hours of recovery. However, if blood loss or clotting is excessive chest tubes often fail because of blockade. Indeed, nearly 1 in 3 patients have chest tube occlusion, which, because of ensuing stasis and sustained blood loss due to high fibrinolytic activity, can lead to retained blood around the heart and has been associated with higher rates of POAF [43–45] (Fig 1). When not adequately evacuated, the volume of retained blood can be large, in which case mechanical compression of the heart becomes clinically obvious; alternatively smaller collections of unevacuated blood may go unnoticed or untreated by the care providers managing the patient postoperatively but still have an important biologic impact within the pericardium, resulting in oxidative stress [44]. Nearly 1 in 5 patients have enough retained blood to require a drainage intervention, and that results in worse outcomes, including a significantly higher incidence of POAF [46].

It has been extensively characterized that shed mediastinal blood undergoes substantial procoagulant and proinflammatory modifications starting at the time of surgery because of various factors including cardiopulmonary bypass and operative trauma [20, 21]. These modifications continue and multiply in the hours and days after surgery [22] (Fig 2). Activation of the clotting cascade in the intrapericardial blood produces both thrombin and fibrin, two powerful activators of the inflammatory response [47, 48]. The local generation of thrombin recruits and activates platelets and increases fibrin generation. Thrombin-activated platelets quickly express P-selectin, an adhesion molecule that initiates translocation of neutrophils from the vasculature lining the pericardium and surface of the heart to the pericardial space [49, 50]. Both platelets and neutrophils generate inflammatory cytokines, including interleukin (IL)-1, and IL-8, which heighten the recruitment of leukocytes, and IL-6, a potent stimulator that primes neutrophils for oxidative burst and release of reactive oxygen species into the local environment. The highly concentrated fibrin binds to the activated neutrophils, localizing them to the area of clot to maximize damage, which further potentiates the release of cytokines, and expands recruitment, activation, and priming of additional neutrophils in the local environment [22].

An additional driver of postoperative inflammation in the pericardial space from shed mediastinal blood is hemolysis, which occurs postoperatively as part of the resolution process of a hematoma. When hemolysis occurs, cell free hemoglobin is released from the red blood cells and is quickly oxidized to methemoglobin, the protein that gives clot its bluish, chocolate brown

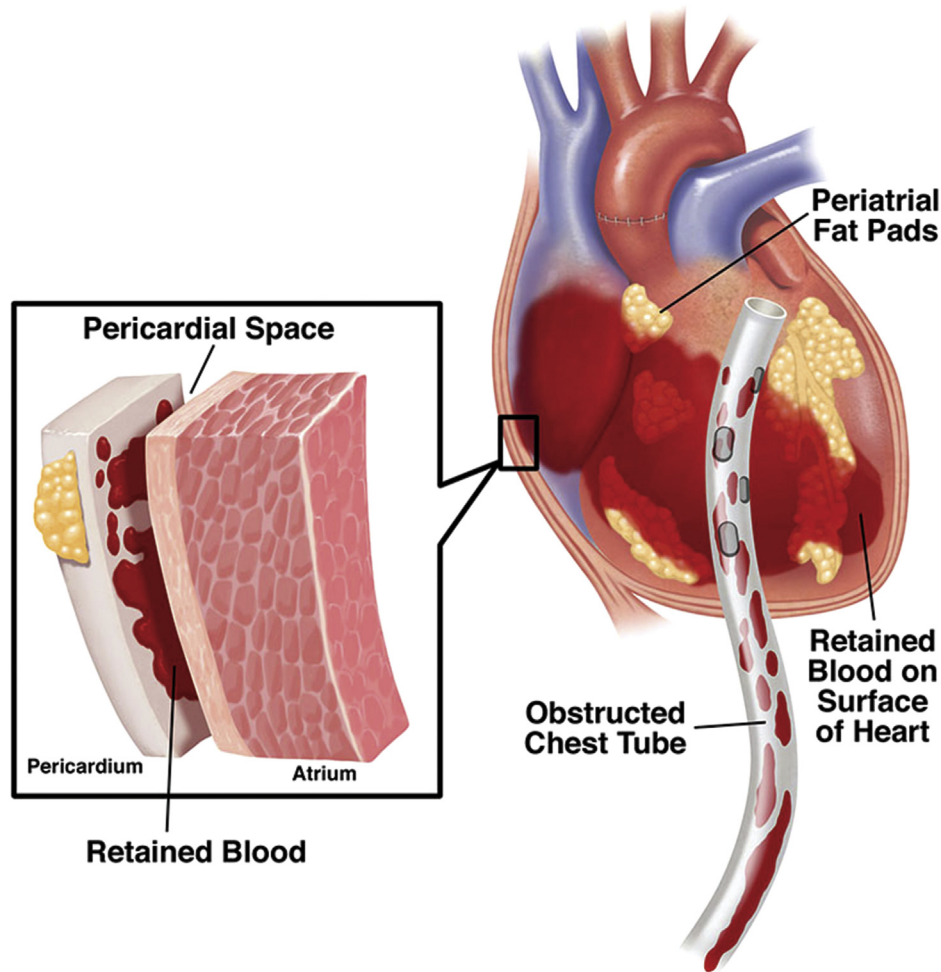


Fig 1. Chest tube clogging results in retained blood within the pericardium.

appearance [51] (Fig 2). Methemoglobin is a potent activator of endothelial cells through nuclear factor-kappa B-mediated upregulation of cell adhesion molecule, such as E-selectin, and expression of chemokines and cytokines, such as IL-6 and IL-8, all of which aid in the recruitment of neutrophils into the pericardial space from the surrounding vasculature [52]. Like the generation of thrombin, this has the effect of promoting migration of neutrophils from the vasculature into the postoperative pericardial space, where they undergo activation subsequent oxidative burst of reactive oxygen species. The net effect of these mechanisms is the induction and propagation of a local leukocyte-mediated inflammatory response that sets up an intensely prooxidative environment within the pericardium during the early postoperative period [53].

As part of the oxidative burst by white cells, hydrogen peroxide is released through NADPH oxidase-2 activity [22] (Fig 3). Hydrogen peroxide, in the presence of methemoglobin and myoglobin from hemolyzed red cells, promotes lipid peroxidation of cellular fat and myocardial tissue either directly or from the generation of ferrylhemoglobin. The formation of lipid radicals ultimately

results in bioactive or electrophilic lipids capable of modifying nucleophilic protein residues such as cysteine, tyrosine, arginine, and histidine, and subsequent cell damage [22]. That was shown in the pericardial fluid by Kramer and colleagues [22] who demonstrated high levels of lipid breakdown products, myoglobin, creatine kinase-myocardial band, and troponin-1 rising many fold in the pericardial space over the subsequent 48 hours after heart surgery when POAF is most likely to develop.

Whereas it is well established that oxidative stress can trigger POAF, it is unclear whether oxidative stress and inflammation act through damage of the surface of the atrium, or possibly even the surrounding fatty tissue, which may help modulate the atrial rhythm through autonomic regulation [54]. Traditionally, the pulmonary vein orifices have been regarded as the source of reentrant rhythms that drive chronic atrial fibrillation; however, prospective data suggest that pulmonary veins may be unrelated to the etiology of POAF after heart surgery. In a clinical trial by Kiaii and colleagues [55], patients undergoing CABG were randomly assigned to undergo adjuvant bilateral radiofrequency pulmonary vein ablation in addition to CABG. They found no



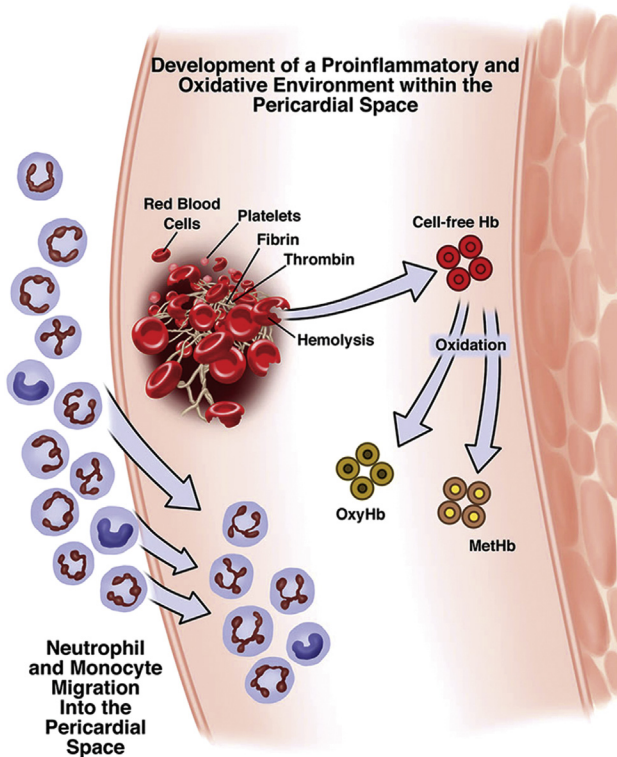


Fig 2. Retained blood ultimately clots and the red cells undergo hemolysis, initiating an inflammatory process that recruits neutrophils to the pericardial space. (Hb = hemoglobin; MetHb = methemoglobin; OxyHb = oxyhemoglobin.)

difference in POAF with prophylactic pulmonary vein isolation, suggesting that might not be the anatomic source of POAF.

In contrast, periatrial fat may be a significant target of inflammation induced from shed mediastinal blood that could trigger POAF. The periatrial fat and its inflammatory activity have recently been closely tied to new-onset atrial fibrillation [56, 57]. Pericardial fat is autonomically innervated and highly metabolically active, allowing it to act as an important source of several adipokines and cytokines that can impact the development of POAF [58, 59]. One hypothesis is that the paracrine secretion of cytokines and adipokines associated with atrial fat pad inflammation might interact with the closely located atrial ganglionated plexuses. The stimulation of these plexuses could create electrophysiologic modifications promoting POAF, such as shortened action potential and increased calcium transient in the atrial substrate [59, 60]. Removing or preserving these fat pads does not reduce POAF [61]. However, ameliorating the inflammatory or vagal output of these fat pads does in fact reduce POAF [62, 63]. Inflammation and oxidative stress as a result of shed mediastinal blood within the pericardium may directly inflame the pericardial fat pads around the atria, triggering POAF in some persons. Additional studies are needed to quantify the impact of retention of shed mediastinal blood, for example, when shed blood is incompletely evacuated from the pericardium due to chest tube

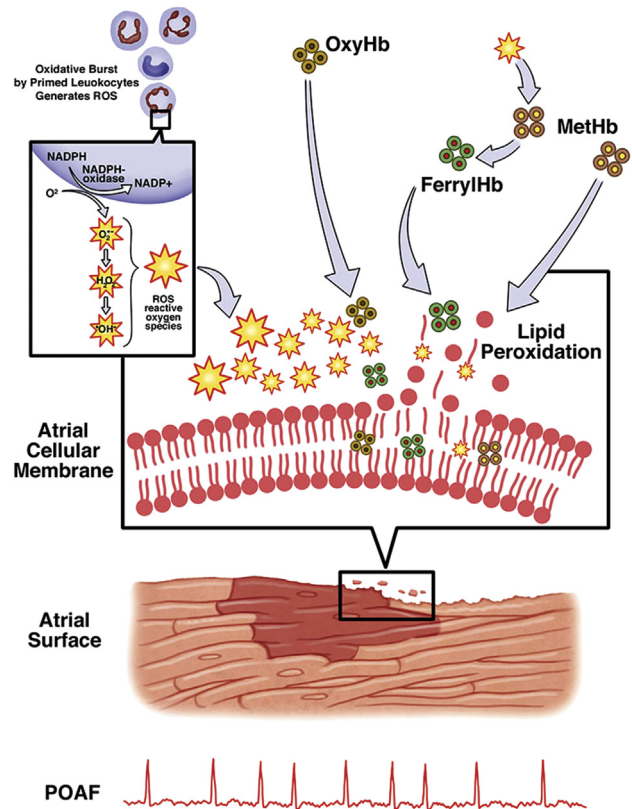


Fig 3. Oxidative damage by reactive oxygen species (ROS) leads to lipid peroxidation that damages the atrial surface and periatrial epicardial fat pads, triggering postoperative atrial fibrillation (POAF) in susceptible persons. (FerrylHb = ferrylhemoglobin; Hb = hemoglobin; MetHb = methemoglobin; NADPH = nicotinamide adenine dinucleotide phosphate; OxyHb = oxyhemoglobin.)

clogging or other contributors to inadequate drainage. Correlation of the amount of retained blood and the degree of ensuing intrapericardial inflammation is needed.

#### Minimizing Retained Pericardial Blood Reduces POAF

Evidence exists that supports the idea that reducing the exposure of the pericardium to shed mediastinal blood consistently reduces POAF [64, 65]. Various posterior pericardiectomy approaches have been studied, all of which rely on shunting blood from the pericardium to pleural spaces through large, surgically created incisions [66]. A meta-analysis of 19 randomized studies involving 3,425 patients showed reduced the odds of POAF by 58% [67]. There are downsides and risks to routine prophylactic pericardiectomy, including the risk of heart and bypass graft herniation, adhesion formation, and contribution to the development of pleural effusions that limit recovery because the blood is simply moved from the pericardial to the pleural space where it can contribute to pleural effusions [7, 65]. That has not become routine practice for most surgeons, but these studies provide a strong rationale for further efforts to identify practical ways to reduce retained pericardial blood during early recovery after cardiac surgery.

Attempts—including stripping, squeezing, milking, and open suction of chest tubes [68–70]—have long been made at maintaining chest tube patency at the bedside in an effort to prevent retained shed mediastinal blood. These evidence for approaches have been reviewed and found these techniques to be ineffective, even potentially harmful, and therefore are not generally recommended [69]. Recent efforts have focused on more effective external blood evacuation methods, rather than internal shunting to the pleural space using posterior pericardiectomy.

Active clearance of chest drains utilizing the PleuraFlow (ClearFlow Inc, Anaheim, CA) device to mechanically break up clot and keep chest tubes lumen clear during the first 24 hours after surgery may offer a simple, easy to adopt approach to not only reduce the incidence of POAF, but also reduce the need for reinterventions for pericardial and pleural effusions [71–75]. In preclinical studies, this approach was effective in reducing retained blood [73]. In one clinical trial, propensity matched patients treated with active clearance of chest drains had a statistically significant 33% reduction in POAF by adopting a protocol to keep the mediastinal chest tubes free of clot during the first 24 hours after surgery [74]. In another clinical study, the odds of POAF developing was reduced by 50% with active clearance of chest tubes [75]. Although this approach shows promise as a simple and safe approach to further reduce complications associated with POAF by maintaining chest tube patency and maximally evacuating shed blood in the early hours after surgery, further prospective studies are needed to validate these findings.

Blake drains (Ethicon, Somerville, NJ) are small, soft silastic channeled drainage tubes believed to promote fluid drainage and cause less pain because of their flexibility and smaller size, and are not uncommonly used after cardiac surgery. One study assessing the impact of these chest tubes demonstrated a significantly smaller volume of pericardial effusion, evaluated by transthoracic echocardiography, as well as a 52% reduction in the rate of POAF associated with the use of Blake drains [76]. However, in more recent studies, including a randomized control trial, prolonged mediastinal drainage using silastic tubes showed no advantage over standard chest drainage catheters in regard of significant effusion or tamponade, or in the incidence of POAF [77, 78]. Therefore, the evidence remains unclear regarding this chest tube design.

Additional studies should be considered as to how chest tubes strategies can be evolved to better evacuate shed mediastinal blood, such as adding a posterior pericardial chest tube, more mediastinal chest tubes, and using different materials or designs. Efforts should also be oriented toward reducing postoperative bleeding in the first place, as changes in surgical procedures or bleeding management could impact on the quantity of retained blood and intrapericardial clotting, for example point-of-care coagulation testing [79].

### Conclusion

Postoperative atrial fibrillation is one of the most common complications of heart surgery and is associated with

significantly worse outcomes. The development of effective prophylactic strategies to prevent POAF have been elusive, perhaps because the etiologic mechanisms have been poorly understood. As it is impossible to eliminate the atrial substrate that renders patients susceptible to POAF, investigators should focus on identifying targetable common root cause triggers such as pericardial inflammation or oxidative stress derived from retained blood that might allow broad preventative strategies to be developed and tested. Studies where retained blood is minimized have shown promising reductions in POAF. That supports the notion that approaches that limit postoperative exposure to shed pericardial blood might more effectively prevent POAF after cardiac surgery than do systemic drugs [79]. Adjustment of actual surgical techniques or modification of temporary drainage devices already in use to prevent retained blood have considerable advantages in terms of safety and cost when compared with pharmacologic approaches. We advocate further studies to elucidate the mechanisms of how shed mediastinal blood might trigger POAF and fill the gap of evidence by correlating the degree of inflammation of shed mediastinal blood from postoperative chest tubes with the quantity of retained pericardial blood, as well as studies to evaluate preventive strategies that aim to reduce retained blood as a more applicable prophylactic strategy for prevention of POAF.

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