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