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REVIEW

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Retained blood syndrome after cardiac surgery

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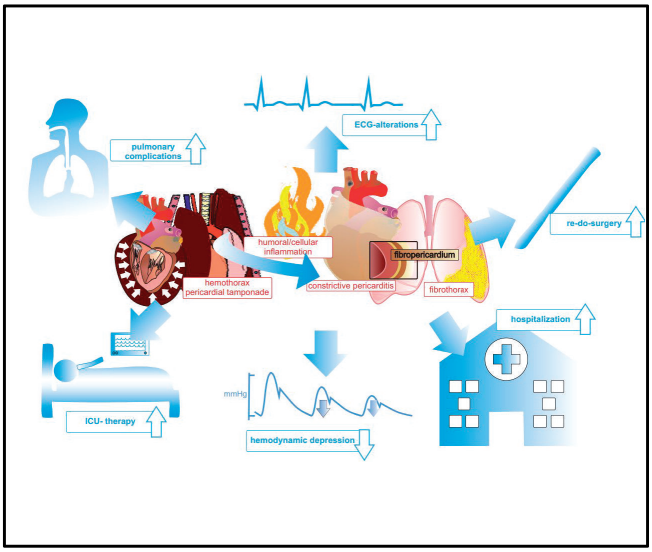
Retained Blood Syndrome After Cardiac Surgery

Summary

The retained blood syndrome is a relevant complication after surgical procedures, includes mechanical impairment of the heart and the lung and its function, induces inflammatory processes and impairs prognosis after surgery.

Results: Prevention is a priority of surgical care anti-inflammatory and surgical therapy should avoid long-term complications.



Abstract

OBJECTIVES: Retained blood syndrome (RBS) is defined as the postoperative retention of blood within the thoracic cavity. In addition to the mechanical impacts on cardiac and pulmonary function, RBS triggers inflammatory processes. It is associated with increased morbidity following cardiac surgery. The goal of this non-systematic review was to summarize the current understanding of the pathophysiology, consequences and both prophylactic and therapeutic measures related to RBS.

METHODS: The subjects to be covered were defined in advance. A literature search was conducted in PubMed and Google Scholar using relevant search terms and MeSH terms.

CONCLUSIONS: RBS is a significant complication following cardiac surgical procedures. It is associated with a poorer prognosis due to mechanical suppression of haemodynamics and the amplification of inflammatory processes. Therefore, preventing pericardial and pleural effusions should be a priority in cardiac surgical care. If RBS occurs, aggressive anti-inflammatory therapy should be initiated to prevent the development of long-term complications.

Keywords: Retained blood syndrome • Chest tubes • Drainage • Inflammation • Bleeding

ABBREVIATIONS

ACT	active clearance technology
RBS	retained blood syndrome
ROS	reactive oxygen species

INTRODUCTION

Effective evacuation of intrathoracic fluids (exudate, blood) following cardiac surgical procedures is essential and is typically achieved through the placement of chest tubes. The postoperative retention of intrathoracic (pericardial and/or pleural) is collectively termed *retained blood syndrome* (RBS) [1]. Approximately one-fifth of all cardiac surgery patients develop RBS [2]. RBS can lead to mechanical consequences such as cardiac tamponade and pulmonary atelectasis. Besides these evident sequelae, RBS also appears to trigger significant inflammatory responses [3]. Clinically, RBS may result in increased postoperative complication rates, including increased ventilation time, increased need for re-explorations, prolonged hospital stays and even increased mortality [2, 4, 5] (Fig. 1). Therefore, a comprehensive understanding of RBS and its consequences, as well as the implementation of prophylactic measures, is crucial for improving patient recovery after cardiac surgery. The goal of this non-systematic narrative review was to summarize the pathophysiology and clinical consequences of RBS. Additionally, prophylactic measures are briefly discussed.

METHODS

To prepare this narrative, non-systematic review, the subjects to be covered were defined in advance. A literature research was conducted in PubMed and Google Scholar using appropriate search terms and MeSH terms. Our review focuses on the inflammatory processes initiated and perpetuated by RBS. We provide a brief overview of clinical symptoms and therapeutic considerations associated with RBS.

Pathophysiology of retained blood syndrome

RBS leads to an inflammatory disease of the pericardium and promotes the formation of long-lasting pericarditic effusions, which can compromise cardiac function even in the long term (Fig. 2).

Inflammatory activations can be initiated and maintained by fibrin clot deposits themselves, but can also be triggered by inflammatory diseases such as pericarditis, myocarditis, Dressler syndromes and postcardiotomy syndrome, infections, inflammatory and ischaemic abdominal diseases and drug complications [6]. The 5-acetylsalicylic acid derivatives (sulfasalazine, mesalamine and balsalazide) can potentially cause pericarditis. Drug-induced pericarditis has also been reported with infliximab and azathioprine therapy, possibly due to IgE-mediated allergic reactions or direct cardiotoxicity. RBS is also characterized by bloody effusions in the early phase and fibrin clots in the later phase.

In addition, substrate modifications caused by inflammatory processes and reactive oxygen species (ROS) can directly induce atrial fibrillation in the surgical environment [7]. Within the pericardium, different proinflammatory cytokines, thrombin and fibrin clots themselves are identified as proinflammatory substrate modifiers (Fig. 3). Thrombin and fibrin are highly potent inducers of the inflammatory response [8]. Thrombin, activated by tissue factor, can influence inflammatory recruitment by activating downstream mediators. Inflammatory expression in smooth muscle cells can also promote further vascular damage. Leukocytes are bound by chemokine receptors. The activation of thrombin can initiate both autocrine and paracrine signalling. Auto-amplification occurs through further local activation of thrombin by tissue factor. Thrombin also cleaves fibrinogen to fibrin, which is further degraded by plasmin through multiple splicing to X and Y fragments, D-dimers, D and E fragments, Bβ15–42 and smaller fragments, mostly from the α chain. Fibrin, fibrinopeptides and fragments further contribute to inflammatory activation and leucocyte migration (Fig. 3). Fibrin itself increases proinflammatory expression in endothelial cells, and fibrin fragments such as D-dimers are inflammatory activators and perpetuators [9].

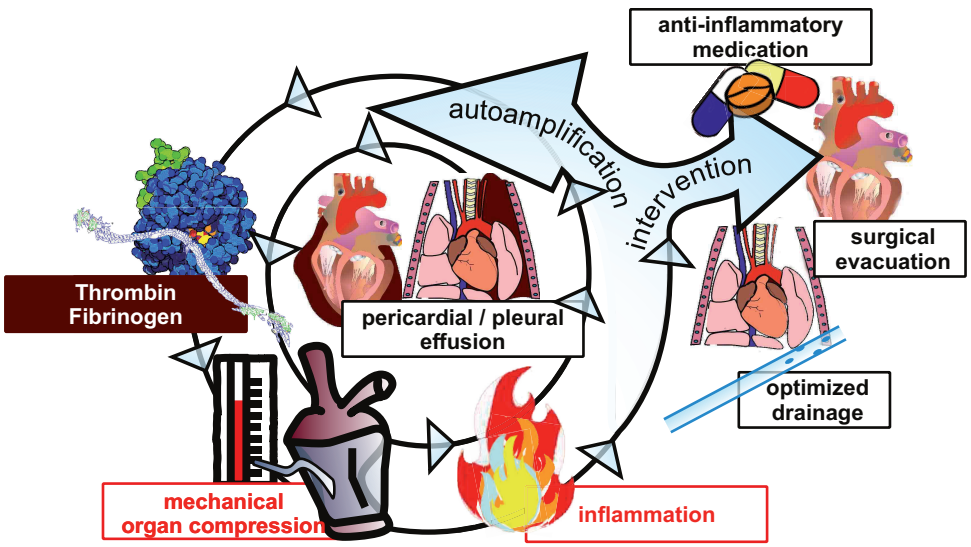


Figure 1: Thrombin and fibrin lead to activation of inflammation and fibrosis.

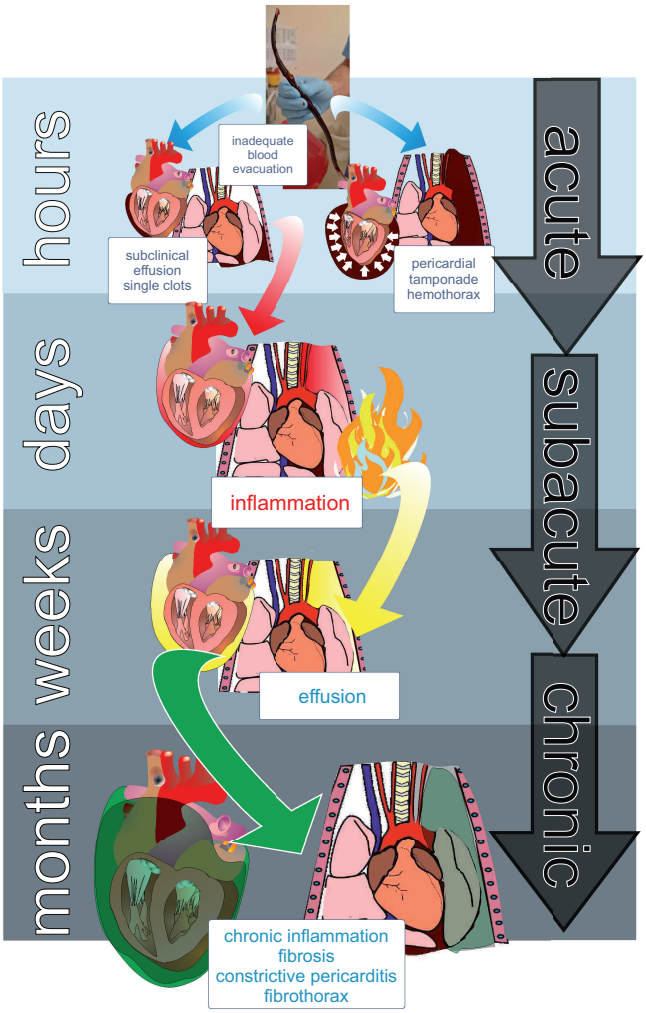


Figure 2: Time course of acute and chronic pathology of pericardial and pleural haematoma. In addition to the haemodynamic significance of an effusion and the acute need for drainage in cases of tamponade, the indication of subacute and chronic inflammation over weeks and months is important in the sense of structurally scarring remodelling of the effusion cavity and the adjacent organs.

Thrombin also leads to the recruitment of platelets, which interact with neutrophils via adhesion molecules, initiating their translocation from the epicardium into the pericardial space. Both platelets and neutrophils generate inflammatory cytokines that enhance leucocyte recruitment and the oxidative response of neutrophils. Oxidative damage and ROS accumulation are promoted by disruptions in the mitochondrial respiratory chain of cardiomyocytes, leading to an inflammatory vicious circle. Oxidative stress results from an attack of ROS that overwhelms endogenous antioxidant defences, resulting in lipid, protein and DNA oxidation and peroxidation. Lipid peroxidation leads to calcium overload in cells, ultimately inducing apoptosis and necrosis [10]. The epicardium can be viewed as a reactive gland that enables communication with the myocardium and the pericardium without fascia and produces and secretes inflammation-modifying adipocytokines. This process further modulates leucocyte recruitment signalling cascades and haemostasis matrix-modulating proteins. In addition to clot formation, clot degradation also activates inflammatory processes besides the effects of fibrin-breakdown products. Free haemoglobin resulting from haemolysis is immediately converted into methaemoglobin, a potent inducer of endothelial adhesion molecules that further recruit neutrophils [11]. These effects are particularly evident postoperatively in the pericardial fluid of cardiac surgery patients [12]. Signs of pericardial inflammatory activation include release of troponin, creatine kinase and myoglobin. The use of heart–lung machines leads to a pro-inflammatory shift similar to that of systemic inflammatory response syndrome and lowers the response threshold to stimuli.

Clinical consequences of retained blood syndrome

The clinical consequences of RBS have been investigated in numerous clinical studies. Chronic symptoms of RBS can lead to fibrosis and calcification, resulting in inflammation-driven tissue remodelling and even constrictive pericarditis or the pleural formation of a fibrothorax. RBS results in an increased need for postoperative re-explorations that are associated with increased lengths of stay in the intensive care unit and the hospital [13]. Several studies have identified postoperative bleeding requiring re-exploration as an independent risk factor for death [14, 15]. Ranucci *et al.* demonstrated that, aside from the surgical re-exploration itself, a significant determinant of increased deaths associated with postoperative bleeding is the amount of packed red cell transfusions required [16]. A meta-analysis by Biancari *et al.*, which included 557,923 patients, found that re-exploration for bleeding is associated with a 3.27-fold increased risk of death. Additionally, the risks of stroke, acute kidney injury, sternal wound infection and prolonged mechanical ventilation were higher in patients who required re-exploration [5]. It has been repeatedly shown that atrial fibrillation coincides with cardiac inflammation. Manifest isoforms of atrial fibrillation have a proven mechanistic inflammatory pathway that initiates and perpetuates atrial fibrillation in obesity, diabetes and ROS overload, leading to electrophysiological and later on to structural remodelling. This situation represents a complex interplay of pathophysiological pathways and regulators that may not be adequately addressed or explained by a single drainage tube or a pericardial incision, but rather through an understanding of calcium handling, connexin modulation and anti-inflammatory counter-regulation. Moreover, the mechanisms involved in RBS do not appear to lead to manifest isoforms of atrial fibrillation. Long-term electrical and structural remodelling, as seen in paroxysmal and persistent atrial fibrillation, has not been shown for RBS. Furthermore, postoperative atrial fibrillation can also occur without RBS [17–20].

Nevertheless, some authors, including us, describe a positive or neutral effect on reducing atrial fibrillation following the relief of sanguinous and non-sanguinous pericardial effusions through drainage procedures [21], operative re-explorations or intraoperative drainage of pericardial effusions into the left pleural space by posterior pericardiotomy [22–25].

Although clinical relief of the effusion appears to be effective, there is currently no evidence regarding the exact pathophysiological mechanisms, which may differ from those of manifest atrial fibrillation. Nonetheless, understanding the pathophysiological inflammatory mechanisms remains crucial for anticipating and managing inflammation and its autoregulation. Operating in a manner that prevents blood accumulation and thereby avoids triggering an excessive inflammatory response seems to be an optimal preventive strategy.

In summary, RBS and its consequences—namely, the transfusion of blood products and re-explorations and, to a certain extent, non-

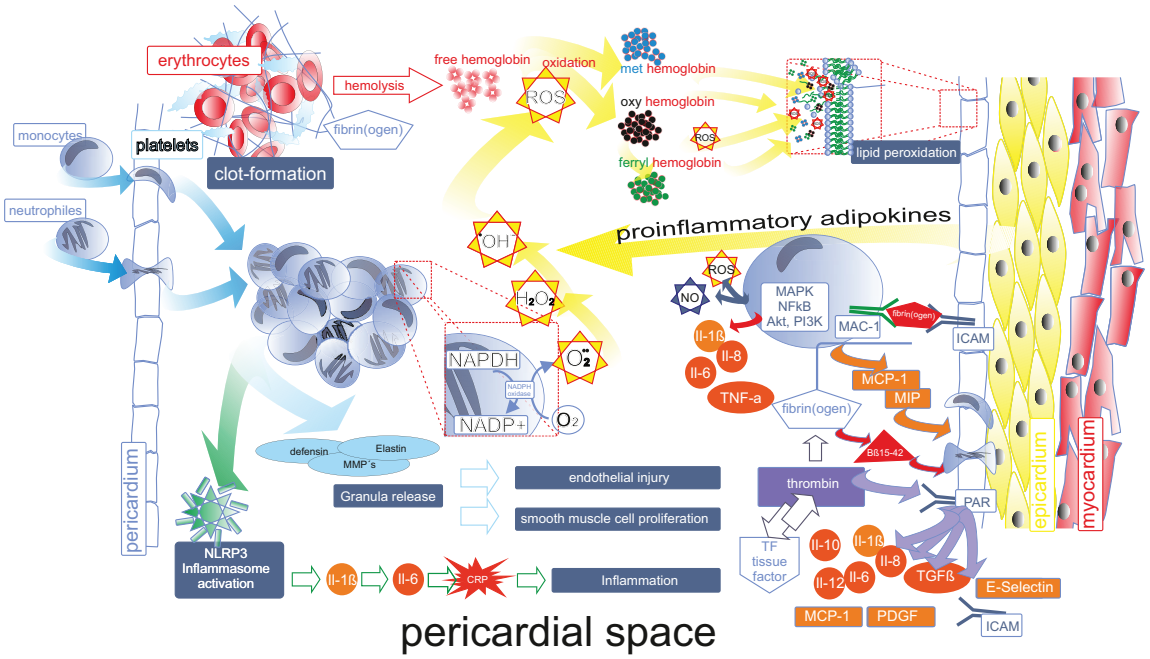


Figure 3: Inflammatory activation during retained blood syndrome. act: protein kinase B; CRP: C-reactive protein; H_2O_2: hydroxine peroxide; IL: interleukin; MAPK: mitogen-activated protein kinase; MCP-1: CC chemokine ligand-2; MIP-1: macrophage inflammatory protein; MMP: matrix metallo proteinase; NfkB: nuclear factor 'kappa-light-chain-enhancer' of activated B-cells; NLRP3: NLR family pyrin domain containing 3 protein; NO: nitric oxide; O_2: oxygen; OH-: hydroxide ion; PAR: protease-activated receptors; PDGF: platelet derived growth factor; PI3K: phosphoinositide 3-kinases; ROS: reactive oxygen species; TF: tissue factor; TGFß: tumour growth factor beta; TNFa: tumour necrosis factor alpha.

persisting atrial fibrillation—significantly impact postoperative outcomes and perioperative morbidity, such as prolonged stays in the ICU and prolonged ventilation requirements. Therefore, both prophylactic and therapeutical measures for RBS are highly relevant.

Prophylaxis of retained blood syndrome

The mainstay of RBS therapy is to avoid its occurrence. Therefore, meticulous surgical technique, haemostasis and intraoperative/perioperative measures to optimize blood coagulation are essential to minimize perioperative intrathoracic bleeding. Chest tubes should be placed to ensure effective drainage of intrathoracic fluids from all cavities. Timely removal of chest tubes is also important to reduce their role as potential inflammatory stressors in the pericardium. Maintaining the patency of chest tubes postoperatively might play a crucial role in avoiding RBS. Chest tube clogging has been reported in 36% of patients after cardiac surgery [26]. Traditionally, milking and stripping of chest tubes are routinely used to maintain their patency. However, although these techniques increase chest tube volumes, they do not reduce the incidence of bleeding complications and the need for re-explorations [27]. Because milking and stripping induce acute strong negative pressures in the thoracic cavities, one can speculate that these manoeuvres might not only mobilize fluid retention but also dislodge freshly formed blood clots, potentially inducing further bleeding [28]. However, the available data, summarized in a systematic review by Wallen *et al.*, are insufficient to draw generalizable conclusions regarding the benefit or harm of chest tube manipulations [29].

Another approach to reduce RBS involves the use of novel, potentially more effective chest tube systems, such as those equipped with active clearance technology (ACT) [30–32]. However, the data on the effect of ACT in reducing the occurrence of RBS or RBS-related interventions/complications are conflicting. Sirch *et al.* reported a significant reduction of RBS-related interventions in their propensity score matched prospective study including 1849 patients using ACT systems [33]. Similarly, Maltais *et al.* observed a decrease of re-exploration rates after left-ventricular assist device implantation in their retrospective analysis of 252 patients [34]. In our own prospective non-randomized propensity score matched study of 444 patients undergoing elective or urgent cardiac surgical procedures, we found an association between the use of ACT systems and reduced re-exploration rates, but no significant reduction in the occurrence of RBS or RBS-related interventions/complications [21]. Conversely, a recent propensity score matched retrospective study by Ntinopoulos *et al.* involving 2461 patients undergoing cardiac surgical procedures showed no difference in the occurrence of RBS or its components in patients receiving either conventional chest tubes or ACT systems in the retrosternal position [35]. Shifting the inflammatory response by draining the pericardial effusion into the pleura using a postoperative pericardiotomy prevents the mechanical consequences of a pericardial effusion but relocates the effusion to the pleura and leads to inflammatory activation there and to the induction of a postcardiotomy syndrome through systemic mechanisms. However, whereas some groups have reported reduced rates of atrial fibrillation with this approach, others have reported neutral efficacy in preventing atrial fibrillation [23, 24, 36–43].

Treatment of retained blood syndrome

Once RBS occurs, the therapeutic goal should focus on evacuating the retained fluid through methods such as chest tube or pericardial drainage tube placement, or if necessary, by surgical re-exploration. Additionally, drug therapy targeting the inflammation associated

with RBS can be considered. Various strategies are available, including stage-appropriate therapy with adequate drainage, non-steroidal anti-inflammatory drug (NSAID)-based therapy, corticosteroid-assisted therapy and immunoglobulin therapy. NSAIDs and colchicine are commonly used to address the early development of the inflammatory reaction postoperatively rather than as preventive measures. Colchicine specifically inhibits neutrophil chemotaxis to inflammatory foci and their adhesion to endothelial cells by reducing the expression of L-selectin and adhesion molecules [44]. Detailed information is given elsewhere [45–49]. These effects lead to a reduced inflammatory response, as evidenced by decreased levels of CRP and interleukin-6, and may inhibit the transdifferentiation of fibroblasts into myofibroblasts as well as the proliferation of smooth muscle cells, thereby reducing structural remodelling and fibrosis. According to European Association of Cardio-Thoracic Surgery guidelines, colchicine is currently recommended for postoperative prophylaxis of inflammation [50–53]. Another approach involves antibody-based therapies that target inflammatory mediators upstream. Canakinumab, for example, is a monoclonal antibody that intercepts interleukin-1beta and suppresses further inflammatory activation [54–58].

CONCLUSION

RBS is a significant complication following cardiac surgical procedures, characterized by mechanical impairment of heart and lung function. Additionally, RBS triggers inflammatory processes that further exacerbate its impact. RBS is associated with a poorer prognosis after cardiac surgery, highlighting the importance of preventive measures against RBS. If RBS occurs, prompt therapeutic interventions are necessary to mitigate the development of subsequent complications.

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Conflict of interest: The authors declare that there are no conflicting financial or non-financial interests relevant to this manuscript. All authors confirm that they had full control of the design and the methods of the review, the data analysis, and the production of the written report.

DATA AVAILABILITY

All data and sources used in the review are listed in the reference list. Furthermore, no original data or analyses of external data or meta-analyses of pooled data from the literature were used. Data and materials can be provided upon relevant request.

Author contributions

Bernd Niemann and Philippe Grieshaber screened the literature in equal parts, conceived, wrote and corrected the manuscript.

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