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To my family

ABSTRACT

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University of Turku, Faculty of Medicine, Department of Cardiology and Cardiovascular Medicine, Doctoral Programme in Clinical Research

Annales Universitatis Turkuensis, Medica-Odontologica, Turku, Finland, 2019

Postpericardiotomy syndrome (PPS) is a common complication after cardiac surgery. In most cases it develops within two to three weeks after the surgery and the typical symptoms include dyspnea, chest pain, and fever. An immunological mechanism is suspected as the cause of the disease. The disease process is usually self-limiting. Even though PPS occasionally requires invasive interventions, the prognosis of the disease is considered to be benign. This thesis investigated the incidence of clinically significant PPS, the risk factors for the disease, and the effect of operation type on the occurrence of the disease. Furthermore, the mortality of PPS patients was investigated.

The results suggest that although the course of PPS is mostly benign, PPS requiring invasive interventions is associated with increased mortality. The syndrome had no significant impact on the occurrence of atrial fibrillation, cerebrovascular events, or bleeding episodes. The results also demonstrate that the incidence of clinically significant PPS is markedly lower compared to the diagnoses included in previous studies concerning the medical treatment of the disease. The use of red blood cell units, female sex, and younger age were identified as predisposing factors for PPS. Valve procedures and especially aortic procedures represented higher occurrence of the disease when compared to coronary artery bypass surgery. Moreover, PPS was less common in patients with diabetes.

The results demonstrate that the majority of the PPS diagnoses included in recent studies are clinically irrelevant. The knowledge concerning the predisposing factors, such as younger age, female sex, and specific operation types, may be useful for the targeting of prophylactic methods. In contrast with the previous conception, PPS requiring the evacuation of pericardial or pleural effusion is associated with higher mortality. The results suggest that PPS patients requiring invasive interventions are in the need of more intensive follow-up and treatment.

Keywords: postpericardiotomy syndrome, risk factors, mortality, adverse events, epidemiology, cardiac surgery, pericardium

TIIVISTELMÄ

Joonas Lehto

POSTPERIKARDIOTOMIAOIREYHTYMÄN RISKIREKIJÄT JA ENNUSTE

Turun yliopisto, Lääketieteellinen tiedekunta, Kardiologia ja kardiovaskulaarilääketiede, Turun kliininen tohtoriohjelma

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Postperikardiotomiaoireyhtymä (PPS) on yleinen sydänleikkauksen jälkeinen komplikaatio. Taudin tyypilliseen oireistoon kuuluu kahdesta kolmeen viikkoa sydänleikkauksen jälkeen ilmaantuva hengenahdistus, rintakipu ja lämpöily. Taudin aiheuttajaksi epäillään immunologista mekanismia. Tautiprosessi rajoittuu yleensä itsestään. Vaikka PPS:n hoito vaatii joissain tapauksissa kajoavia hoitotoimenpiteitä, on sen ennustetta pidetty hyvänlaatuisena. Tässä väitöskirjassa tutkittiin kliinisesti merkittävän PPS:n ilmaantuvuutta ja riskitekijöitä sekä leikkaustyypin vaikutusta taudin ilmaantuvuuteen. Lisäksi tutkittiin PPS:n vaikutusta potilaiden ennusteeseen.

Tämä tutkimus osoittaa, että vaikka PPS:n ennuste on pääosin hyvänlaatuinen, kajoavaa hoitoa vaativa PPS on yhteydessä lisääntyneeseen kuolleisuuteen. Oireyhtymä ei ollut merkittävästi yhteydessä eteisvärinän, aivotapahtumien tai vuototapahtumien ilmaantuvuuteen. Tulokset osoittavat myös, että kliinisesti merkittävän PPS:n määrä on selvästi pienempi kuin taudin määrä viimeaikaisissa PPS:n lääkehoitoa koskevissa tutkimuksissa. Verituotteiden käytön, naissukupuolen ja nuoremman iän todettiin altistavan taudin kehittymiselle. Leikkaustyypeistä läppäleikkaukset ja erityisesti aortan toimenpiteet olivat yhteydessä taudin lisääntyneeseen ilmaantuvuuteen sepelvaltimoiden ohitusleikkaukseen verrattuna. Lisäksi diabeteksen todettiin merkittävästi vähentävän taudin ilmaantuvuutta.

Tulokset osoittavat, että valtaosa viimeaikaisten tutkimusten PPS-diagnooseista on kliinisesti merkityksettömiä. Tieto taudille altistavista tekijöistä, kuten nuorempi ikä, naissukupuoli ja tietyt leikkaustyypit, voi olla hyödyllistä, kun valitaan kohteita taudin ennaltaehkäiseville toimille. Aiemmasta käsityksestä poiketen PPS on yhteydessä lisääntyneeseen kuolleisuuteen. Vaikka löydöksen syitä on tutkittava vielä lisää, tulosten perusteella kajoavaa hoitoa vaativat PPS-potilaat ovat kuolemanvaarassa ja tarvitsevat siksi nykyistä intensiivisempää hoitoa ja seurantaa.

Avainsanat: postperikardiotomiaoireyhtymä, riskitekijät, kuolleisuus, haittavaikutukset, epidemiologia, sydänkirurgia, perikardium

TABLE OF CONTENTS

ABBREVIATIONS

AEA = anti-endothelial antibody

AFA = anti-fibrillary antibodies

AHA = anti-heart antibody

AIDA = anti-intercalated disc antibodies

ASA = anti-sarcolemmal antibodies

ASD = atrial septal defect

AVR = aortic valve replacement

BCKD-E2 = branched chain alpha-ketoacid dehydrogenase dihydrolipoyl transacylase

BMI = body mass index

CABG = coronary artery bypass grafting

CCI = Chalson Comorbidity Index

CI = confidence interval

CIC = circulating immune complexes

CECC = conventional extra-corporeal circulation

CPB = cardiopulmonary bypass

ECG = electrocardiography

ESC = European Society of Cardiology

GEA = gastroepiploic artery

HR = hazard ratio

ICD-10 = International Classification of Diseases, Tenth Revision

IRR = incidence rate ratio

IVIG = intravenous immunoglobulin

LAD = left anterior descending artery

LITA = left internal thoracic artery

MEFV = Mediterranean fever

MiECC = minimal invasive extracorporeal circulation

MVR = mitral valve replacement

NLR = neutrophil-to-lymphocyte ratio

NNT = number needed to treat

NSAID = non-steroidal anti-inflammatory drug

NYHA = New York Heart Association classification

OR = odds ratio

PCIS = post-cardiac injury syndromes

PET = positron emission tomography

POAF = postoperative atrial fibrillation

PPS = postpericardiotomy syndrome

RBS = retained blood syndrome

RITA = right internal thoracic artery

SAVR = surgical aortic valve replacement

TGA = transposition of great arteries

TIA = transient ischemic attack

VSD = ventricular septal defect

WBC = white blood cell

LIST OF ORIGINAL PUBLICATIONS

I Lehto J, Gunn J, Karjalainen P, Airaksinen J & Kiviniemi T. Incidence and risk factors of postpericardiotomy syndrome requiring medical attention: The Finland postpericardiotomy syndrome study. *J Thorac Cardiovasc Surg*. 2015;149(5):1324–1329.

II Lehto J, Kiviniemi T, Gunn J, Mustonen P, Airaksinen J, Biancari F, Rautava P, Sipilä J & Kytö V. Occurrence of postpericardiotomy syndrome admissions: A population-based registry study. *Ann Med*. 2016;48(1–2):28–33.

III Lehto J, Kiviniemi T, Gunn J, Airaksinen J, Rautava P & Kytö V. Occurrence of Postpericardiotomy Syndrome: Association With Operation Type and Postoperative Mortality After Open-Heart Operations. *J Am Heart Assoc*. 2018;7(22): e010269.

IV Lehto J, Gunn J, Björn R, Malmberg M, Airaksinen J, Kytö V, Nieminen T, Hartikainen J, Biancari F & Kiviniemi T. Adverse events and mortality after postpericardiotomy syndrome in patients with surgical aortic valve replacement. *Manuscript.*

1 INTRODUCTION

Postpericardiotomy syndrome (PPS) is a common complication after cardiac surgery. The syndrome is a subgroup of post-cardiac injury syndromes (PCIS) together with postmyocardial infarction syndrome (Dressler's syndrome) and post-traumatic pericarditis (Imazio *et al.*, 2013d). The typical clinical picture consists of pleuritic chest pain and fever appearing few days to several weeks after cardiac surgery (Imazio, 2012). Even though the syndrome was first described in the 1950s (Janton *et al.*, 1952; Soloff *et al.*, 1953), the etiology of the syndrome has remained obscure. Currently, PPS is presumed to be an immune-mediated process initiated by pericardial and/or pleural damage and pericardial bleeding but the role of viral infections and other possible acquired factors is not well understood (Imazio, 2012).

In previous studies, the incidence of PPS has varied between 10 and 40% (Imazio *et al.*, 2013d). In recent prospective studies the reported incidences have been between 21 and 29 % (Imazio *et al.*, 2010, 2014c). The large variability between the studies has evolved mostly from the differences in diagnostic criteria, patient populations, and procedure types (Imazio, 2012; van Osch *et al.*, 2017b). Standardized criteria for the syndrome were first described in 2015 in the European Society of Cardiology Guidelines with an objective to reduce the variability between studies (Adler *et al.*, 2015). The recommended criteria have, however, already received criticism due to their weak correlation with the clinical picture, overflowing sensitivity, and non-specificity (van Osch *et al.*, 2017b).

The current guidelines recommend the use of non-steroidal anti-inflammatory drugs (NSAIDs) combined with colchicine in more severe cases in the treatment of the syndrome (Adler *et al.*, 2015). Even though PPS occasionally requires invasive interventions, such as pericardial or pleural draining, as well as longer hospital stays and readmissions (Imazio *et al.*, 2011b), the prognosis of the syndrome is considered to be benign (Bucekova *et al.*, 2012; Imazio, 2012; Imazio *et al.*, 2013d). However, this perception is mainly based on clinical experience rather than appropriate epidemiological studies concentrating on the long-term prognosis of the syndrome.

This thesis focuses on the occurrence, risk factors, and prognosis of PPS requiring medical attention. The recent prospective studies have included PPS patients with a broad spectrum resulting in a high apparent incidence of the syndrome. However, the clinical relevance of the diagnoses is uncertain. Several approaches are used to evaluate the aforementioned issues which are crucial to the assessment of appropriate clinical approach to the syndrome in the "real world" practice.

2 REVIEW OF LITERATURE

2.1 Cardiovascular surgery

The term “cardiovascular surgery” covers all open-heart procedures, including procedures for congenital heart disease, ischemic heart disease, valvular heart disease, aortic disease, atrial and ventricular arrhythmia, myotomies, the installation of mechanical circulatory support devices, and cardiac transplantations. The following sections detail the four cardiac procedure types included in the present investigation.

2.1.1 Coronary artery bypass graft surgery

Typical anesthesia for cardiac surgery includes inhalational anesthetics (sevoflurane or desflurane) in conjunction with muscle relaxants and modest dosage of opioids for analgesia. Additionally, the maintenance of anesthesia typically includes intravenous antibiotics with gram-positive pathogen coverage (typically cefuroxime) 30–60 minutes before the skin incision, intraoperative blood glucose control with insulin, acid-base management, heparinization for cardiopulmonary bypass (CPB), hypothermia, hemodynamic adjustment after the separation from CPB (vasopressors, vasodilators, catecholaminergic agents, phosphodiesterase inhibitors), and possible mechanical support devices (e.g., an intra-aortic balloon pump) (Sellke *et al.*, 2010).

The progress of cardiac surgery procedures follow a fairly uniform scheme as described in textbooks (Sellke *et al.*, 2010). The most widely used exposure is the midline sternotomy with the skin incision made from the manubrium of the sternum to the xiphoid process. After a slight mobilization of the subcutaneous fat the sternum is divided with a saw. Meticulous hemostasis is ensured at all stages. A pericardial incision is performed in the extent needed according to the procedure type. Coronary artery bypass graft (CABG) is performed on CPB in the majority of cases. CPB is most often established with ascending aortic or arch cannulation and right atrial venous cannula drainage. The extracorporeal circulation can be executed by conventional extracorporeal circulation (CECC) or minimal invasive extracorporeal circulation (MiECC). MiECC consist of a centrifugal pump–driven, closed and minimized circuit without open venous reservoir, whereas CECC exploits conventional roller pumps or centrifugal pumps and open venous reservoir (Ellam *et al.*, 2019). The aorta is cross-clamped, and venting (i.e., de-airing and

suction of blood) is performed via the proximal ascending aorta by using the antegrade cardioplegia delivery catheter. After the first dose of cardioplegia has been delivered, the construction of distal coronary anastomoses begins. In the vast majority of cases the LAD is grafted with the LITA while additional anastomoses are grafted with saphenous vein or radial artery grafts and the right internal thoracic artery (RITA). The epicardium is incised over the intended area of the coronary artery, the anterior wall of the artery is opened longitudinally, and the anastomoses are attached using 7-0 or 8-0 polypropylene suture. Most proximal anastomoses are made on the ascending aorta, and alternative sites such as end-to-side anastomoses to the LITA can be used as needed or convenient.

During the weaning from CPB, the patient is slowly rewarmed, the aortic cross-clamp is removed, atrial and ventricular epicardial pacing wires are affixed to the heart when necessary, and the heart rhythm and rate are optimized using cardioversion or pacing as necessary. The venous cannula is removed, protamine is administered, chest tubes are inserted in the posterior pericardium, the anterior mediastinum, and each pleural cavity entered, and aortic cannula is removed. The pericardium is sometimes, mainly depending on local custom, partially reapproximated over the anterior left ventricle, and the sternum and skin incision are closed.

Alternatively, coronary surgery can be performed “off-pump” without CPB with a beating heart (Trapp *et al.*, 1975). Off-pump coronary surgery is performed nowadays in approximately one sixth of the cases (Bakaeen *et al.*, 2014). Surgical exposures are for the most part similar to “on-pump” surgery, but the anastomotic epicardial sites are stabilized and the heart is positioned with suction stabilizers (Borst *et al.*, 1996) and gauze harnesses and no aortic or venous cannulation is employed. Myocardial perfusion can be maintained using temporary intracoronary shunts.

2.1.2 Surgical aortic valve replacement

Surgical aortic valve replacement (SAVR) is most commonly performed to treat aortic valve stenosis, but it is also indicated in other pathologies such as aortic regurgitation, combined stenosis and regurgitation, and infective endocarditis (Baumgartner *et al.*, 2017). The procedure is typically performed via median sternotomy similar to the CABG procedure as specified above. Cannulations are similar to those used in CABG, but the left ventricle is often directly vented via a cannula inserted through the right upper pulmonary vein and cardioplegia can be administered retrogradely through coronary venous cannulation via the coronary sinus. Once the heart is arrested, the aortic valve may be approached through a

transverse or oblique aortotomy. The incision is typically carried out into the non-coronary sinus if root enlargement is contemplated. The valve is lifted with the help of traction sutures to improve visualization, if necessary. The native valve is removed using scissors and rongeurs.

Possible valve replacements include a bioprosthesis, a mechanical valve, sometimes a homograft, and in rare cases in children and young adults an autograft (Ross procedure). Most commonly, the valve is implanted using pledgeted horizontal mattress sutures of braided polyester. Aortotomy closure is then accomplished with running polypropylene suture. The weaning from CPB is accomplished similarly as specified above.

2.1.3 Mitral valve repair and replacement

Mitral valve surgery is most commonly performed due to mitral valve regurgitation, in addition to the nowadays relatively rare cases of mitral stenosis (Baumgartner *et al.*, 2017). Mitral valve procedures are also typically approached via median sternotomy. The procedure is classically performed with cardioplegic arrest, but in a selected group of patients, alternative techniques, such as beating heart and ventricular fibrillatory arrest, are available. The three most commonly used approaches for the exposition of the mitral valve include: the interatrial approach through Sondergaard's groove, the horizontal biatrial trans-septal approach, and the superior biatrial trans-septal approach. The most commonly used approach is the interatrial approach through Sondergaard's groove which includes the incision of the interatrial groove and the dissection and dividing of the two atria up to the fossa ovalis. The roof of the left atrium is then opened close to the mitral valve.

The repair of the mitral valve is preferred over replacement with a prosthesis in most indications (Baumgartner *et al.*, 2017). Mitral valve repair techniques are numerous but almost always include remodeling ring annuloplasty complemented by techniques aimed at re-establishing leaflet function such as quadrangular resection of a prolapsed posterior leaflet area, triangular resection of the prolapsed anterior leaflet area, choral transfer, chordal transposition, chordal shortening, artificial chordoplasty, and papillary muscle sliding plasty and shortening. In patients for whom mitral valve repair is not suitable, mitral valve replacement (MVR) with either a bioprosthesis or a mechanical prosthesis is performed. The anterior leaflet is detached, and the posterior leaflet is typically left intact. The mitral prosthesis is inserted most commonly using horizontal mattress sutures. After the closure of the atrium, the weaning from CPB is started.

2.1.4 Ascending aortic surgery

Ascending aortic surgery is typically performed to treat the enlargement of the aortic root or ascending aorta, or, emergently, to treat aortic dissection or rupture (Pan *et al.*, 2018). Procedures are performed via median sternotomy, and they require an extensive preparation of the pericardial reflection. The CPB is established by arterial cannulation of the transverse aortic arch, right axillary artery or femoral artery, and venous cannulation through the right atrium or femoral vein. Deep or moderate hypothermia is employed to protect from end-organ ischemia as a brief circulatory arrest is often necessary to complete the anastomoses to the arch or supra-aortic vessels. The ascending aorta is replaced using a tubular vascular graft. Patients with aortic valve disease not amenable to repair are treated by AVR and supracoronary replacement of the ascending aorta. If only the noncoronary aortic sinus is dilated, AVR with a graft extension into the noncoronary sinus can be performed. Composite replacement of the aortic valve and ascending aorta with the reimplantation of the coronary arteries is performed if two or more aortic sinuses are dilated. When the aortic valve cusps are not calcified, aortic valve sparing techniques such as the David reimplantation (David *et al.*, 1992) or Yacoub remodeling procedure (Yacoub *et al.*, 1983) can be performed. After all the sutures are sealed, the patient is slowly rewarmed and the weaning from CRP is accomplished as specified above.

2.2 Pericardium

The pericardium consists of visceral and parietal components. The visceral component, layering the surface of the heart, is a monolayer of mesothelial cells adhering firmly to the epicardium via fibrous tissue containing elastic fibers. The parietal layer consists of dense collagen bundles with interspersed elastic fibers that form a tough sac enveloping the heart surfaced with a serosal layer of mesothelial cells. Outside the fibrous pericardium is a variable amount of adipose tissue layered with mesothelial cells (Cremer *et al.*, 2016; Hoit, 2017). The parietal component of pericardium is continuous with the visceral pericardium tethering around the origin of the great vessels. Between the two serosal layers encloses the pericardial space that normally contains up to 50 ml of plasma ultrafiltrate (Spodick, 1992; Hoit, 2017). Besides the roots of the great vessels, the parietal component is attached to diaphragm, sternum, and vertebral bodies by ligamentous attachments neutralizing the effects of respiration and change of body position and preventing the torsion and displacement of the heart (Troughton *et al.*, 2004). The arterial supply of the pericardium comes from small aortic branches in the posterior part and from internal thoracic arteries in the superior, lateral, and inferior proportions

of the parietal pericardium. The anterior and posterior parietal pericardium as well as visceral pericardium all contain lymphatics draining to anatomically corresponding mediastinal nodes (Spodick, 1992).

The pericardium is not an essential structure, although it has many advantageous functions. The pericardial fluid reduces friction, equalizes forces directed to the heart (i.e., gravitation and accelerations) hence minimizing the pressure changes in the cardiac muscle, and works as a mechanical barrier to infection. The fibrous layer limits cardiac distention and maintains the pressure-volume relations of the cardiac chambers. Also, the mesothelial layer is metabolically active modulating numerous immunologic, vasomotor, and fibrinolytic functions and modulates the sympathetic neurotransmission and contractility (Spodick, 1992; Hoit, 2017).

Pericardial heart diseases include infectious (viral, bacterial, fungal, and parasitic) and non-infectious pericardial diseases (autoimmune, neoplastic, metabolic, traumatic and iatrogenic, drug-related, congenital, and other diseases, including aortic dissection and amyloidosis), in addition to the complications of pericarditis, including constriction and acute tamponade (Adler *et al.*, 2015). The inflammatory states damage the visceral pericardium, also interfering with epicardial venous and lymphatic flow, leading to loss of interstitial fluid from the myocardium to the pericardial space (Spodick, 1983). This leads to pericardial effusion accompanied with the accumulation of inflammatory cells and increased fibrin production (Hoit, 2017). Rapid increases in the volume can cause tamponade even if the pericardial effusion was relatively small. However, slowly developing effusions may not produce tamponade even in large volume (Imazio *et al.*, 2013a). The healing process may result in pericardial adhesions between the visceral and parietal layers and later calcification (Hoit, 2017).

2.3 Postpericardiotomy syndrome

2.3.1 Epidemiology of PPS

The first descriptions of PPS date back to 1950s, shortly after the establishment of the first surgical cardiac valve procedures, when Janton and colleagues reported the results of their first 100 consecutive commissurotomies for mitral stenosis (Janton *et al.*, 1952). The authors observed unpredictable pleuropericardial pain unresponsive to salicylates, antibiotics, and ordinary doses of narcotics in about 30 percent of the patients. The symptoms occurred typically during the second postoperative week. The episodes were considered to be possible manifestations of

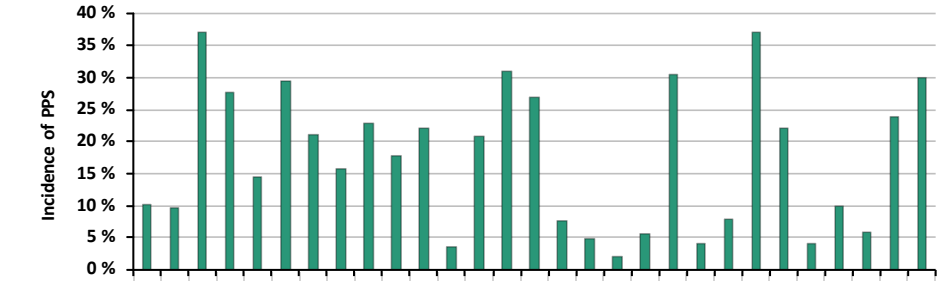
smoldering rheumatic activity, even though only one sixth of all patients had microscopic evidence of active rheumatic infection in the left auricular appendage. Soloff and colleagues investigated the syndrome further and observed an incidence of 24% after consecutive mitral commissurotomies (Soloff *et al.*, 1953). Because of the misunderstood causality, the syndrome was named "postcommissurotomy syndrome" until 1958, when an identical state was detected following cardiac surgery in patients without rheumatic heart disease (Ito *et al.*, 1958). The syndrome was only observed when the pericardial cavity was entered, and therefore it was renamed "postpericardiotomy syndrome".

The reported incidences of the syndrome have varied largely. During the first years after the discovery of the syndrome the incidence varied from 4% to 63% after mitral commissurotomy with an average of 17% (Janton *et al.*, 1952; Soloff *et al.*, 1953; Wood, 1954; January *et al.*, 1954; Julian *et al.*, 1954; Fell *et al.*, 1955; Dresdale *et al.*, 1956; Papp *et al.*, 1956; Hall *et al.*, 1958; Likoff *et al.*, 1958; Lisan *et al.*, 1959; Bain *et al.*, 1961). Besides the differences in diagnostic criteria, which were not reported in most of the studies, this exceptionally large variety illustrates the lack of effective differential diagnostic equipment, especially the heart echocardiography. After the inclusion of different procedure types, the syndrome was detected in 27–31% of patients (Drusin *et al.*, 1965; Engle *et al.*, 1980). Studies requiring good response to steroid therapy for the diagnosis reported incidences of 6–7% (Louhija *et al.*, 1971; Ikäheimo *et al.*, 1988).

Engle concluded that the incidence of PPS, according to their quite comprehensive prospective studies, was 27% in children and 18% in adults aged 21 years or older (Engle, 1982). After the age of 70 years the incidence decreased to 10%. Furthermore, patients aged under 2 years presented very few cases of PPS (3.5%) and infants under the age of six months did not seem to present with the syndrome at all. Later, consistent with the aforementioned study, a large prospective epidemiological study by Miller *et al*. observed an incidence of 24% in patients under 54 years, 18% in patients 55–64 years, and 11% in patients over 65 years after careful differential diagnostic procedures (Miller *et al.*, 1988).

In the major PPS studies during the last decades, the reported incidences have been the following: 10–28% in children (Wilson *et al.*, 1994; Mott *et al.*, 2001; Webber *et al.*, 2001; Heching *et al.*, 2015; Rabinowitz *et al.*, 2018) and 15–21% in adults (Horneffer *et al.*, 1990; Imazio *et al.*, 2010; Bunge *et al.*, 2014) with a median of 16% in adult patients (van Osch *et al.*, 2017b). In the recent COPPS-2 trial (Imazio *et al.*, 2014c), the incidence in adult patients was as high as 29% in elderly patients, although the time limit of fever was abandoned resulting in a markedly higher occurrence during the first postoperative days compared to the COPPS trial (Imazio

et al., 2010). The reported incidences of PPS and details of major PPS studies are presented in Figure 1.



	Gabaldo et al., 2019	Rabinowitz et al., 2018	Sevuk et al., 2016b	Heching et al., 2015	Bunge et al., 2014	Imazio et al., 2014c	Imazio et al., 2010	Mott et al., 2001	Webber et al., 1992	Miller et al., 1988	Ikäheimo et al., 1988	Englom et al., 1985	De Scheerder et al., 1985b	Kaminsky et al., 1982	Engle et al, 1980	Ikäheimo et al., 1979	Livelli et al., 1978	Asanza et al., 1976	Louhija et al., 1971	Drusin et al., 1965	Bain et al., 1961	Likoff et al., 1958	Larson, 1957	Papp et al., 1956	Fell et al., 1955	Wood, 1954	Julian et al., 1954	Soloff et al., 1953	Janton et al., 1952
Prospective	–	–	–	–	–	+	+	+	+	+	+	–	+	–	+	+	–	+	–	–	NA	NA	NA	+	NA	NA	NA	–	NA
Retrospective	+	+	+	+	+	–	–	–	–	–	–	+	–	+	–	–	+	–	+	+	NA	NA	NA	–	NA	NA	NA	+	NA
CABG	+	–	+	–	+	+	+	–	NA	+	+	+	+	–	–	–	+	+	NA	–	–	–	–	–	–	–	–	–	–
Aortic valve	+	–	–	–	+	+	+	+	NA	+	+	–	+	–	–	+	+	NA	+	+	–	–	–	–	–	–	–	–	–
Mitral valve	+	–	–	–	+	+	+	+	NA	+	+	–	+	–	–	+	+	NA	+	+	+	+	+	+	+	+	+	+	+
ASD	–	+	–	+	–	NA	NA	+	+	NA	NA	–	–	–	+	+	NA	NA	+	+	–	–	–	–	–	–	–	–	–
VSD	–	–	–	–	–	NA	NA	+	+	NA	NA	–	–	–	+	+	NA	NA	NA	+	–	–	–	–	–	–	–	–	–
Aorta	+	–	–	–	–	+	+	+	+	NA	NA	–	–	–	+	–	NA	+	+	+	–	–	–	–	–	–	–	–	–
Other	–	–	–	–	+	NA	NA	+	+	+	+	–	–	+	+	–	NA	+	+	+	–	–	–	–	–	–	–	–	–
Combined	+	–	–	–	+	+	+	+	+	+	+	–	+	–	+	+	+	+	NA	+	–	–	–	–	–	–	–	–	–
Adults	+	+	+	–	+	+	+	–	–	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Children	NA	+	–	+	–	–	–	+	+	–	–	–	–	+	+	+	–	NA	–	+	NA	NA	NA	–	+	+	NA	NA	+
	N = 461	N = 207	N = 100	N = 97	N = 822	N = 180	N = 180	N = 246	N = 149	N = 944	N = 150	N = 441	N = 129	N = 161	N = 400	N = 194	N = 147	N = 200	N = 690	N = 262	N = 100	N = 200	N = 137	N = 100	N = 100	N = 150	N = 139	N = 179	N = 100

Figure 1. Reported incidences of PPS and study specifications in major previous studies. Artwork by Joonas Lehto. ASD: atrial septal defect; CABG: coronary artery bypass grafting; PPS: post-pericardiotomy syndrome; VSD: ventricular septal defect.

After pacemaker implantation the incidence of PPS has been reported to be 1.8%, with a higher risk after the insertion of epicardial leads (2.5%) compared to transvenous leads (1.0%) (Zeltser *et al.*, 2004), although markedly lower incidences (<0.2%) have also been reported (Gatzoulis *et al.*, 2014). It appears that the incidence is roughly 2–5% after the implantation of active-fixation leads and notably lower after passive-fixation leads (Sedaghat-Hamedani *et al.*, 2014). After radiofrequency ablation complicated by cardiac perforation, the incidence is 28.6%, in other words similar to that after cardiac procedures (Liu *et al.*, 2013).

2.3.2 Clinical features of PPS

PPS typically occurs within one months after the surgery, and an initial onset after six months is rare (Lisan *et al.*, 1959; McGuinness *et al.*, 1962; Ikäheimo *et al.*, 1979; Nishimura *et al.*, 1983; Imazio *et al.*, 2011b; Alraies *et al.*, 2014; Gabaldo *et al.*, 2019). In children, the onset is slightly earlier, typically within 1 to 2 weeks (Engle *et al.*, 1980; Mott *et al.*, 2001; Heching *et al.*, 2015). The median duration of the syndrome is 2–3 weeks (Drusin *et al.*, 1965; Nishimura *et al.*, 1983; Heching *et al.*, 2015), and possible relapses tend to occur within 2–11 weeks after the initial onset (McGuinness *et al.*, 1962).

The most characteristic symptom of PPS is pleuritic or pericarditic chest pain, referring to a stabbing pain often radiating to precordial region, neck, back, shoulders, arms, lower chest, and abdomen, made worse by coughing, deep breathing, swallowing, or any movement, and in severe cases leading to a fast and shallow respiration easily confused with the dyspnea of congestive heart failure (Papp *et al.*, 1956; Lisan *et al.*, 1959; Gore, 1960; Uricchio, 1963; Maisch *et al.*, 1979; Nishimura *et al.*, 1983). The reported incidences of the symptom have varied largely, but according to a recent prospective study, pleuritic chest pain occurs in over a half of the PPS episodes (Imazio *et al.*, 2011b). An intermittent, low grade fever is another common feature of PPS, and it occurs in approximately a half of the PPS cases (Imazio *et al.*, 2011b; Gabaldo *et al.*, 2019). The fever is usually the first manifestation. It may merge with the early postoperative temperature elevations so that the patient has a prolonged febrile course, but more often the fever recurs as a delayed reaction after a distinct afebrile period (Engle *et al.*, 1961). Another characteristic clinical finding is pericardial friction rub detected in the heart auscultation. The reported incidences of the friction rub have varied tremendously. According to recent studies it is detected in 20 to 30% of patients (Imazio *et al.*, 2011b; Alraies *et al.*, 2014), although it has been suggested that it could probably be heard at some time in all patients but due to the transient nature a serial auscultation strategy is necessary (Engle *et al.*, 1961). The start of medical treatment, especially corticosteroids, offers a prompt relief of symptoms, typically within 24 to 48 hours (Kaminsky *et al.*, 1982).

C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are elevated in most PPS patients (Soloff *et al.*, 1953; Elster *et al.*, 1954; Fell *et al.*, 1955; Ito *et al.*, 1958; Tabatznik *et al.*, 1961; Urschel *et al.*, 1976; Nishimura *et al.*, 1983; Alraies *et al.*, 2014; Gabaldo *et al.*, 2019), although their specificity is poor during the first weeks after cardiac surgery (Bartels *et al.*, 1994; Köhler *et al.*, 2003). Other typical laboratory findings include neutrophilic leukocytosis (Soloff *et al.*, 1953; Ito *et al.*, 1958; Tabatznik *et al.*, 1961; Uricchio, 1963; Urschel *et al.*, 1976; Maisch *et al.*, 1979). If pericardiocentesis is performed, the pericardial effusion is

clear, straw-colored fluid or serosanguineous fluid and sterile on culture (Papp *et al.*, 1956; Ito *et al.*, 1958; Engle *et al.*, 1961; Tabatznik *et al.*, 1961; Bortolotti *et al.*, 1981; Ofori-Krakye *et al.*, 1981; Meyers *et al.*, 1997; Karatolios *et al.*, 2013). The fluid is exudate containing high counts of lymphocytes and red blood cells and relatively high counts of granulocytes (Ofori-Krakye *et al.*, 1981; Meyers *et al.*, 1997; Karatolios *et al.*, 2013). The specifications of pleural effusions are similar to the ones in pericardial fluid (Papp *et al.*, 1956; Bielsa *et al.*, 2016).

The thoracic X-ray reveals unilateral (usually left) or bilateral pleural effusion in most of the patients with PPS (Elster *et al.*, 1954; Ito *et al.*, 1958; McGuinness *et al.*, 1962; Maisch *et al.*, 1979; Nishimura *et al.*, 1983; Imazio *et al.*, 2011b; Bielsa *et al.*, 2016; Gabaldo *et al.*, 2019). The separation of the pleuritic effusions from the normal surgery-related effusions is however complicated, as >80% of patients have at least minor effusions during the postoperative period (Bunge *et al.*, 2014). ECG findings, including low voltage of the QRS, T-wave inversion, or ST-segment elevation or depression, can be detected in approximately half of the patients. (Elster *et al.*, 1954; Papp *et al.*, 1956; Johnson, 1959; Tabatznik *et al.*, 1961; Uricchio, 1963; Nishimura *et al.*, 1983). However, these findings as well seem to be relatively nonspecific and thus only marginally helpful (Miller *et al.*, 1988), and ECG changes suggestive of pericarditis appear only in <¼ of cases (Imazio *et al.*, 2011b).

The pericardial effusion can often be detected on chest x-ray as an enlargement of the cardiac silhouette. However, it is often difficult to tell whether this enlargement is cardiac or pericardial or both (Engle *et al.*, 1961; Kaminsky *et al.*, 1982; Nishimura *et al.*, 1983). According to recent studies, pericardial effusion can be detected as often as in 89% of the episodes (Imazio *et al.*, 2011b; Alraies *et al.*, 2014). The effusion is typically mild (<10 mm), and moderate (10–20 mm) and large (>20 mm) effusions are detected in 13% and 4%, respectively (Imazio *et al.*, 2011b). Most patients (>80%) have combined pleuropericardial involvement (Imazio *et al.*, 2011b). The typical echocardiographic finding is presented in Figure 2.

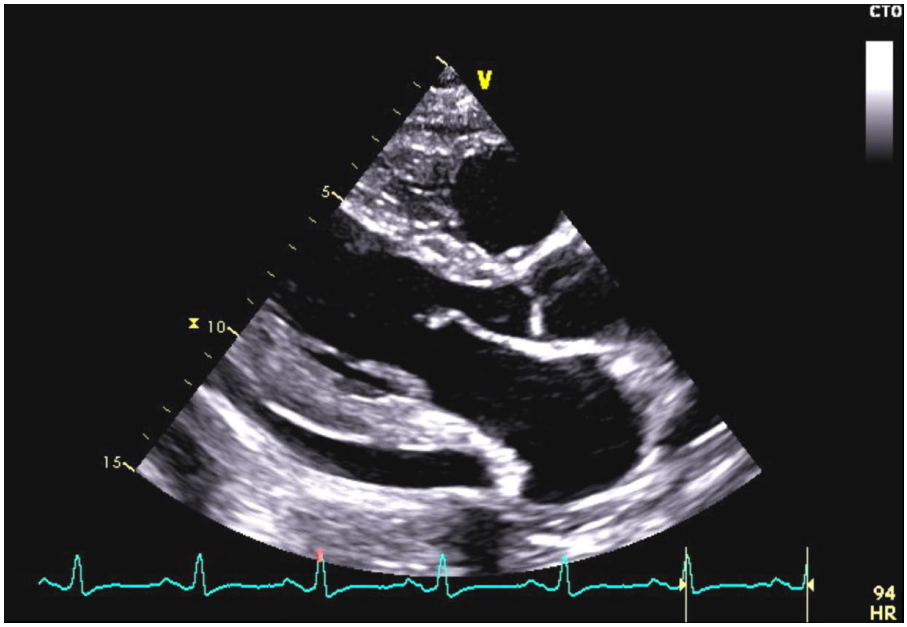


Figure 2. An echocardiographic image taken in the parasternal long axis view demonstrates moderate pericardial effusion in the posterior pericardium. Artwork by Joonas Lehto.

2.3.3 Diagnostic criteria

PPS is a diagnosis of exclusion. Since there are no specific tests with which to establish the diagnosis, it is made by excluding other diseases potentially producing similar symptoms. The main diagnoses to exclude are incisional pain, pneumonia, mediastinitis, congestive heart failure, atelectasis, bacterial endocarditis, sepsis, myocardial or pulmonary infarction, pulmonary embolism, and aortic dissection (Kirsh *et al.*, 1970; Barnhorst, 1973). The evaluation of a patient with a suspected PPS includes a focused physical examination to detect pleural or pericardial rubs, laboratory tests (blood count and markers of inflammation and myocardial necrosis), ECG, chest X-ray, and transthoracic echocardiography to detect the presence, size, and hemodynamic importance of the pericardial effusion (Imazio *et al.*, 2013d; Adler *et al.*, 2015).

Since the first description of PPS, numerous different diagnostic criteria have been used in research with a striking inconsistency between one another (van Osch *et al.*, 2017b). Engle *et al*. were the first to specify the diagnostic criteria for PPS (Engle *et al.*, 1974). Patients were diagnosed with PPS when there was either the persistence or appearance of the following combination of findings beyond the first postoperative week: fever not otherwise explained, together with signs of pericardial reaction on physical examination and serially obtained electrocardiograms and

roentgenograms. At that time, the one week boundary was in general use, as it is usually safe to assume that symptoms occurring before the seventh day are part of the normal postoperative course (Lessof, 1976). In fact, fever early in the first postoperative week is virtually universal (Livelli *et al.*, 1978), and benign, surgery-related pleural effusion appear in 50% of the patients without PPS during the first postoperative days (Kaminsky *et al.*, 1982). Besides fever and pleural effusions, benign, surgery-related leukocytosis, pericardial effusion, pericardial friction rub, and electrographic changes of pericarditis diminish after the 1st postoperative week enabling the diagnosing of PPS (Engle *et al.*, 1978).

Table 1. Definition and diagnosis of postopericardiotomy syndrome (PPS) according to the ESC Guideline (Adler *et al.*, 2015).

1. Fever without alternative causes
2. Pericarditic or pleuritic chest pain
3. Pericardial or pleural rubs
4. Evidence of pericardial effusion
5. Pleural effusion with elevated CRP

At least 2 of 5 criteria should be fulfilled.

In the year 2015, European Society of Cardiology (ESC) published the first guideline recommending diagnostic criteria for PPS which are the following: 1) fever without alternative causes, 2) pericarditic or pleuritic chest pain, 3) pericardial or pleural rubs, 4) evidence of pericardial effusion and/or 5) pleural effusion with elevated CRP (Table 1). Two of the criteria should be fulfilled for the diagnosis, and the demonstration of inflammatory activity should be essential to establish the diagnosis (Adler *et al.*, 2015). Neither the a time limit for the fever often used in the earlier studies nor the "new or worsening" term of pericardial or pleural effusion included in the review concerning the diagnostic criteria (Imazio *et al.*, 2013c) were included in the criteria for a reason not specified. The criteria have been recently criticized accordingly (van Osch *et al.*, 2017b), although any sort of universal recommendations should reduce the variety of employed diagnostic criteria in future PPS studies. Although not included in the ESC guideline, exclusive criteria for children have been also proposed by Heching and colleagues (Heching *et al.*, 2015).

2.3.4 Risk factors for PPS

Numerous previous studies have evaluated the risk factors for PPS to both clarify the cause of the syndrome and to identify the patients with the highest risk of developing the disease. One of the few risk factors several studies have agreed upon

is female gender (Larson, 1957; Webber *et al.*, 2001; Imazio *et al.*, 2011b), although contradicting reports have also been published (Miller *et al.*, 1988; van Osch *et al.*, 2017a). It has been suggested that this finding might reflect a different predisposition to autoimmune pathogenesis, as it is known that women are more susceptible to a variety of autoimmune diseases (Voskuhl, 2011).

Another factor most certainly influencing the occurrence of PPS is age. According to previous studies, the incidence of PPS decreases above the age of thirty (Drusin *et al.*, 1965), is minimal in children under two years, and is the highest immediately after that, at the age of two years (Engle *et al.*, 1980). The absence of the syndrome in infants has been hypothesized to be related to the short period of experience with exposure to viruses, so that these patients do not react immunologically to the new stress by developing PPS (Engle, 1982). Furthermore, infants under the age of six months did not develop PPS at all, possibly due to protection by transplacental transfer of maternal antibody and the absence of contact with people with respiratory or gastrointestinal infections. Engle also discussed that a certain degree of maturity of the immunological system might be required before the infant can mount the kind of autoimmune response and anti-viral reaction that can be tested by measurements of AHA and titers of anti-viral agents. It needs to be taken into consideration, however, that infants are generally unable to express themselves concerning chest pain and other subjective findings. The incidence of PPS seems to decrease steadily from early adulthood to old age, and the incidence in patients aged 70 years falls to 10% (Engle, 1982; Köhler *et al.*, 2003). This may be due to the acquired protection over many years of exposure to viral illnesses and, on the contrary, less frequent recent exposure to viral infections because of the alterations in lifestyle. Also, with aging, possibly comes some immunosenescence, so that they are less capable of mounting an immune response against the intrapericardial trauma and possible exposure to viruses in the hospital (Engle, 1982). Negative results concerning the association of PPS and age has also been reported (Maisch *et al.*, 1979; Imazio *et al.*, 2011b; Jaworska-Wilczyńska *et al.*, 2014; Heching *et al.*, 2015; Sevuk *et al.*, 2015, 2016c, 2016b; van Osch *et al.*, 2017a), although typically in cohorts with a highly delineated age distribution. Moreover, a nonsignificant trend towards higher PPS occurrence in younger patients is detectable in most of the studies.

During the first decades after the description of PPS, the research payed attention to seasonal changes in PPS occurrence. McGuinness and colleagues found a summer peak of incidence (McGuinness *et al.*, 1962). Drusin *et al.* suggested that the incidence of PPS was higher during the consecutive six-month period from February through July (Drusin *et al.*, 1965). These findings were later confirmed in a large prospective epidemiological study, as summer months (May, June, and July) presented a significant seasonal peak the lowest incidence occurring during early

fall months (August, September, and October) (Miller *et al.*, 1988). This seasonal peak suggested the possibility that a pre-existing virus is activated by the operation and produces the syndrome. The pathogenetic involvement of viruses is discussed below.

A retrospective analysis by Alraies *et al*. assessed the predictors of PPS leading to procedural intervention due to the pericardial effusion or pericardial constriction (Alraies *et al.*, 2014). Independent predictors of invasive interventions included younger age (OR 1.03, 95% CI 1.01–1.05), early onset of PPS (OR 1.03, 95% CI 1.01–1.05), and constrictive physiology (OR 6.23, 95% CI 2.04–19.07) when compared to PPS patients not requiring invasive interventions. The higher incidence within younger individuals is presumably related to the more aggressive immune response discussed above. However, the results have been challenged, as the older patients also received a somewhat more aggressive medical treatment for the disease (Chhabra *et al.*, 2015). No other studies assessing the risk factors for adverse outcomes of PPS have been previously published.

The type and/or extent of the procedure has also been reported to influence the incidence of PPS. Engle *et al*. found PPS occurring at a higher frequency in procedures for the tetralogy of Fallot and ventricular septal defect (VSD) accompanied by some other anomaly compared those entailing less damage to the cardiac muscle (ASD, isolated VSD, TGA, pulmonary stenosis) (Engle *et al.*, 1980). De Scheerder *et al*. also found that PPS was more common after valve replacement operation as compared to after CABG (De Scheerder *et al.*, 1984, 1991). In an epidemiological setting containing only adult patients, AVR patients were at greater risk for PPS and mitral valve replacement patients appeared to have a reduced risk (Miller *et al.*, 1988). Other procedures presented relatively high incidence. The lower incidence in patients undergoing MVR remained equivocal but it was presumed that the underlying cause of the valvular disease may play a role. The number of grafts in CABG was not associated with the incidence of PPS. Overall, it seems that the procedure type has an impact on the occurrence of PPS, although it was observed already during the first years after the description of the syndrome that it can appear also after exploratory pericardiotomies in whom no further surgical procedures are attempted (Ito *et al.*, 1958).

Although PPS most commonly occurs after cardiac surgeries and especially frequently after the most extensive procedures, numerous case reports concerning more unusual triggers of PPS have been previously published. A picture similar to PPS has followed penetrating injuries of the chest (Segal *et al.*, 1960; Tabatznik *et al.*, 1961; Loughlin *et al.*, 1987), gunshots of the thoracic area (Tabatznik *et al.*, 1961; Zeft *et al.*, 1965; Akdemir *et al.*, 2003), nonpenetrating trauma to the chest (Goodkind *et al.*, 1960; Gunnar *et al.*, 1962; Sikes, 1963; Goldstein *et al.*, 1965),

left ventricular puncture (Stewart *et al.*, 1962; Peter *et al.*, 1966), pulmonary embolism (Jerjes-Sanchez *et al.*, 1987), pacemaker implantation with epicardial leads (Dressler, 1962; Wang *et al.*, 1983; Terada *et al.*, 1995), transvenous pacemaker implantation (Kaye *et al.*, 1975; Snow *et al.*, 1987; Lau *et al.*, 1992; Hargreaves *et al.*, 1994; Miller *et al.*, 1996; Bajaj *et al.*, 1999; Spindler *et al.*, 2001; Sasaki *et al.*, 2001; Turkie *et al.*, 2005; Cevik *et al.*, 2009; Tsai *et al.*, 2012; Sedaghat-Hamedani *et al.*, 2014; Gatzoulis *et al.*, 2014; Salih *et al.*, 2015; Kumar *et al.*, 2018), coronary artery perforation during balloon angioplasty (Escaned *et al.*, 1992), uncomplicated coronary angioplasty and stenting (Hearne *et al.*, 2003; Setoyama *et al.*, 2006; Gungor *et al.*, 2008; Park *et al.*, 2010; Kawase *et al.*, 2015; Gurunathan *et al.*, 2016; Elbaz-Greener *et al.*, 2017; Paiardi *et al.*, 2017; Gavrielatos *et al.*, 2018), percutaneous mitral balloon valvuloplasty (Demirtas *et al.*, 1998), atrial radiofrequency ablation (Turitto *et al.*, 1998; Wood *et al.*, 2003; Koller *et al.*, 2004; Tang *et al.*, 2007; Zheng *et al.*, 2007; Yukumi *et al.*, 2015), diagnostic transdiaphragmatic pericardial window (King *et al.*, 2009), thymectomy (Santos *et al.*, 1992; Yukumi *et al.*, 2012; Nishimura *et al.*, 2019), accidental opening of the pericardium during lung lobectomy (Eguchi *et al.*, 2010), and Nuss procedure (Muensterer *et al.*, 2003; Berberich *et al.*, 2004).

In the case reports of nonpenetrating traumas to the chest, the pericardiocentesis and/or thoracocentesis revealed either blood in the pleural or pericardial cavities during the initial trauma or serosanguineous fluid during the pleuropericarditis by rule. Therefore, according to these reports, the only required trigger for the syndrome seems to be the presence of pericardial hematoma and/or a compressing injury of the heart during a car accident, although laceration or contusion of the pericardium cannot be ruled out. Atrial or ventricular wall perforation with bleeding into the pericardial sac occurring without recognition is a possible complication of transvenous pacemaker implantation, and it has been discussed to be the possible etiology of the relatively rare cases resulting to PPS (Sedaghat-Hamedani *et al.*, 2014). This hypothesis is strengthened by the observations that only leads placed on the lateral or anterolateral wall seem to provoke acute pericarditis (Greene *et al.*, 1994) and that active-fixation leads seem crucial for the development of the disease (Gatzoulis *et al.*, 2014; Sedaghat-Hamedani *et al.*, 2014). Direct irritation of the pericardium by slightly protruding electrodes might be another possible trigger for the inflammatory response (Wolk *et al.*, 2013; Gatzoulis *et al.*, 2014; Sedaghat-Hamedani *et al.*, 2014). Hemopericardium is also a rare but possible complication of percutaneous mitral balloon valvuloplasty (Tuzcu *et al.*, 1992). An unrecognized perforation of a coronary artery causing small bleeding into the pericardial space is a potential complication of percutaneous coronary intervention (Setoyama *et al.*, 2006; Park *et al.*, 2010; Elbaz-Greener *et al.*, 2017), although also prolonged endothelial trauma (Gungor *et al.*, 2008) combined with negative remodeling due to the myocardial damage (Gavrielatos *et al.*, 2018) has

been suggested to be the inducing factors. In one of the percutaneous coronary intervention cases, PPS required pericardiocentesis, and erythrocytes were identified in the evacuated fluid (Park *et al.*, 2010). In the seven cases of atrial radiofrequency ablation, the authors suggested either the extensive transmural atrial or pericardial injury (Wood *et al.*, 2003; Yukumi *et al.*, 2015) or a possible cardiac perforation (Turitto *et al.*, 1998; Koller *et al.*, 2004) to be the triggering factors for the syndrome. In contrast to the typical onset of PPS, the symptoms generally appeared either immediately after the procedure or during the first postoperative day. The outstandingly early onset was also presented in a study assessing the incidence of PCIS after radiofrequency ablation complicated by cardiac perforation (Liu *et al.*, 2013), supporting the perforation-based etiology in the aforementioned cases. A study containing 303 patients undergoing Nuss procedure, pericarditis occurred in 7 (2.3%) patients (Croitoru *et al.*, 2002). However, no new PPS cases were detected after the substitution of the introducer into a new model allowing gentle dissection of the pericardium away from the underside of the sternum. Overall, according to the previous case reports concerning PPS-like states after different procedures, penetrating pericardial incision or injury does not seem to be necessary for the development of PPS. Instead, PPS appears to require pericardial haemorrhage and/or intensive pericardial manipulation as a minimum trigger.

Besides the younger age, operation type, and summer months, a large prospective epidemiological study performed in adult population by Miller and colleagues also identified the following as independent risk factors for PPS: lower preoperative platelet count, history of prednisone treatment (past or present), history of pericarditis, lower weight, and halothane anesthesia (Miller *et al.*, 1988). Preoperative prednisone was given to patients for variety of reasons, but in general the drug was used to suppress an inflammatory response, suggesting that these patients may be more immunoreactive compared to patients not developing PPS. The fact that PPS patients more often had a history of pericarditis suggests that trauma to the pericardium might trigger a recurrence or that these patients are prone to pericarditis. Also, despite the number of subjects in this group was low, blood type B– represented notably higher PPS occurrence. The authors suggested that even though PPS was represented in patients with all blood types, certain blood types may predispose to developing PPS.

A more recent retrospective study by van Osch and colleagues including 822 patients undergoing valve surgery found higher BMI to be an independent protective factor for PPS (OR per point increase 0.94, 95% CI 0.89–0.99, p=0.028) (van Osch *et al.*, 2017a). Treatment for pulmonary disease without corticosteroids was associated with a higher risk of PPS (OR 2.55, 95% CI 1.25–5.20, p=0.010). In addition, contrary to the results of Miller and colleagues (Miller *et al.*, 1988), the uni-

variable model identified mitral valve surgery as a predisposing factor and preoperative corticosteroid use as a protective factor for PPS, in addition to prior stroke. The authors suggested that the protective effect of higher weight, also identified by Miller *et al*. (Miller *et al.*, 1988), could be related to the immunomodulatory effects of obesity, referring to the higher levels of anti-inflammatory ILs (IL-4 and IL-13) (Zampieri *et al.*, 2015). The higher incidence of PPS in patients with pulmonary disease without corticosteroid treatment was presumed to be related to the vulnerability of these patients to develop systemic and pericardial inflammation.

In a substudy of the COPPS trial assessing the risk factors for PPS, besides female sex, pleural incision also was found to be an independent predisposing factor for the syndrome (Imazio *et al.*, 2011b). In cardiac surgery, pleural incision may be either part of the surgical plan or accidental. If the pleural cavity is entered, it is advised to insert a chest tube accordingly (Sellke *et al.*, 2010) which causes pleural irritation. The intended or unintended opening of the pleura may also lead to the drainage of pericardial fluid through pleural drains via pleural cavity possibly triggering pleuritis and/or PPS which might offer an additional explanation for the finding.

A systematic review published by van Osch and colleagues investigated the risk factors for PPS (van Osch *et al.*, 2017b). The review included all major studies concerning the risk factors and representing adequate quality. A total of 7 studies met the quality requirements. The discrepancy of identified risk factors between different studies was striking. Authors presumed this to be due to different definitions of PPS as well as the evolution of surgical techniques during the past 50–60 years which make it rather impossible to compare the findings of all the studies available. Overall, the authors concluded that both the inflammatory response and perioperative bleeding and coagulation may play a role in the development of PPS, suggesting a multifactorial etiology of the syndrome. The variability in the observed risk factors led to the same conclusions also decades earlier, as Kirsh *et al*. suggested that the syndrome may be a symptom-complex with multiple etiological factors (Kirsh *et al.*, 1970).

2.3.5 Peri- and postoperative characteristics

Besides the operation type discussed above, many other factors related to the peri- and postoperative period have been associated with PPS. As mentioned above, halothane anesthesia has been associated with a twofold increase in the incidence

of PPS (Miller *et al.*, 1988). The authors presumed this to be mediated by lymphocyte stimulation which has been described before in patients with hepatitis (Paronetto *et al.*, 1970).

Only two previous studies have reported the amount of blood transfusions given perioperatively in patients with and without PPS (Maisch *et al.*, 1979; van Osch *et al.*, 2017a). In the study by Maisch *et al*. containing overall 65 subjects, patients developing definite PPS received 6.3±2.3 units of transfused blood compared to 5.2±2.4 units given to patients with incomplete PPS and 4.2±2.1 units to patients without PPS. In the study by van Osch *et al*. patients developing PPS also seemed to receive more units of packed red cells although it did not reach statistical significance (transfusion of ≥2 units packed red cells 23.1% vs. 17.0%, p=0.164). It is possible that either the greater amount of perioperative bleeding or the immunological aspects related to blood transfusions affect the development of PPS, but this finding needs to be confirmed before further speculations.

No laboratory test has been proven to reliably predict the onset of PPS during the perioperative period. However, some associations between the laboratory tests and PPS have been detected. Miller *et al*. found that PPS patients had significantly lower mean platelet count preoperatively compared to patients not developing PPS (Miller *et al.*, 1988). Also, higher mean % lymphocyte cell count was associated with PPS after adjustment for age and sex although it did not reach statistical significance in the overall multivariable model. A retrospective study by Sevuk *et al*. investigated pre- and postoperative laboratory data in 72 patients with PPS and 100 control patients who had underwent isolated CABG (Sevuk *et al.*, 2016c). There were no differences in the preoperative WBC, neutrophil count, lymphocyte count, or neutrophil-to-lymphocyte ratio (NLR). In the postoperative values measured in the first postoperative day, patients with PPS had significantly higher WBC (14.1 vs. 12.0, p<0.001) as well as neutrophil count (11.0 vs. 9.6, p<0.001) with no changes in the lymphocyte count (1.2 vs. 1.2, p=0.7) leading to higher NLR (8.7 vs. 7.6, p=0.01). The results were also significant in the multivariable model (WBC: OR 1.6, 95% CI 1.36–2.03, p<0.001; NLR: OR 3.3, 95% CI 1.56–7.01, p=0.002; neutrophil and lymphocyte counts not tested separately). The authors suggested the higher postoperative neutrophil count to be a consequence of the IL-8-mediated chemotaxis which has been associated with PPS (Snefjellå *et al.*, 2012; Jaworska-Wilczyńska *et al.*, 2014). The ROC analysis observed a sensitivity of 60% and specificity of 59% for NLR when using a cut-off value of 8.34. Therefore, postoperative NLR or neutrophil count could be useful in the prediction of the syndrome, although further studies are needed to confirm these results. The studies investigating more specific immunological markers of PPS are detailed below.

Heching and colleagues investigated the incidence and risk factors of PPS in pediatric patients following surgical closure of secundum ASD (Heching *et al.*, 2015). 27 (27.8%) of the included 97 patients developed PPS. A small pericardial effusion during the time of discharge was identified in 17 (63.0%) PPS patients, whereas only 19 (27.1%) of patients in the non-PPS group presented the effusions (p=0.001). The median length of hospital stay was 4 days. Therefore, although some of the patients could have developed an active PPS before the discharge, it seems that echocardiogram at the time of discharge could have predictive value for the syndrome.

2.3.6 Pathophysiology of PPS

Soon after the exclusion of the rheumatic etiology, the hypothesis of blood-induced delayed hypersensitivity phenomenon, the one also currently believed, was introduced (Engle *et al.*, 1961). It was hypothesized that the syndrome represents a delayed hypersensitivity reaction to the presence of damaged tissue in the pericardial cavity, whether this was blood, traumatized pericardium, or necrotic muscle (Kirsh *et al.*, 1970). Consequently, this material becomes "foreign" protein and thus induces the production of auto-antibody for which the myocardium, red blood cells, or the myocardial or pericardial tissues are "target" organs. The immunological characteristics were first studied in 1963 (Robinson *et al.*, 1963). Preoperative and postoperative hemagglutination tests were performed in 36 patients undergoing mitral valvotomy in comparison with 12 patients undergoing non-cardiac thoracotomy, 6 patients undergoing laparotomy, and 35 healthy controls. PPS developed in 6 (16.7%) patients entering the mitral procedure, and the postoperative hemagglutination test was positive in 5/6 PPS patients, 1/30 non-PPS patients, and 0/53 of the patients in the control groups. Therefore, a circulating antibody-like substance reacting with heart tissue was suggested to be the pathophysiological mechanism of PPS. The results strengthened the theory of an autoimmunological reaction and underlined the influence of individual susceptibility to developing the disease.

A year later, van der Gled *et al.* reported the association of anti-heart antibodies (AHA) and PPS (van der Geld, 1964). AHA were detected in the sera of thirteen out of fifteen patients with PPS and in eight out of fourteen patients with the Dressler's syndrome. The number of false positives was reported to be minimal. However, patients undergoing cardiac procedure without developing PPS were not included in the analyses. A prospective double-blind analysis a decade later containing overall 400 patients confirmed these results (McCabe *et al.*, 1973; Engle *et al.*, 1974, 1975, 1976, 1980). High rise of AHA was found in 95.4% of PPS cases

appearing typically 0–3 days after the clinical signs of the syndrome. Again, the specificity as well as sensitivity were excellent. No effect of AHA on the viability or growth characteristics of the human heart cells could be seen, and therefore, the effect seemed to be either indirect (e.g., via phagocytic function or lymphocyte activation) or produced in combination with other blood elements, such as a virus. Maisch *et al*. later reported fairly similar results and also evaluated the appearance of three different types of striated muscle antibodies: anti-sarcolemmal antibodies (ASA), anti-fibrillary antibodies (AFA), and anti-intercalated disc antibodies (AIDA) from which myocardial and skeletal ASA predominated in the complete PPS group presenting all the included diagnostic criteria (Maisch *et al.*, 1979). The difference was equal in ASA antibodies against heart and skeletal muscle, and thus no organ-specificity could be detected. In addition, antibodies against the endothelium of small vessels (AEA) were markedly higher in patients with PPS. The autoimmune hypothesis was further strengthened by De Scheerder and colleagues, after they observed all the patients with complete PPS (all 3 diagnostic criteria met, 20.9%) having positive AHA postoperatively, while incomplete and no-PPS groups together presented 31.4% of positive AHA (De Scheerder *et al.*, 1985b). Moreover, the highest intensity titers were only present in patients with complete PPS. It was also found that complete PCIS was associated with the higher ratio of postoperative titres of anti-actin and anti-myosin antibodies (De Scheerder *et al.*, 1985b, 1986, 1991). Because of a large number and extent of different circulating antibodies, a general polyclonal hyperimmune response was suggested to have a major pathogenetic role in the development PPS (De Scheerder *et al.*, 1991). However, this hypothesis was soon belied, as no generalized autoantibody production was detected in PPS patients (Webber *et al.*, 1992).

2.3.6.1 Immunology and virology

A more recent study investigating pre- and postoperative inflammatory markers found an association between PPS and lower preoperative IL-8 concentrations (Jaworska-Wilczyńska *et al.*, 2014), but the incidence of PPS was 49/75 (65.3%) reflecting inappropriate diagnosing and/or insufficient differential diagnostics, and therefore these results cannot be applied directly to PPS. Nevertheless, a result of higher postoperative level of IL-8 has also been published in another small trial (Snefjellå *et al.*, 2012). Therefore, IL-8 might play a role in the pathogenesis of PPS. However, a wide range of cells secrete and respond to this chemokine (Qazi *et al.*, 2011), and therefore, the deduction of a specific pathogenetic pathways via this finding is complicated. The authors suggested that the lower IL-8 concentration could be related to younger age, as elderly patients may be adapted to an increased level of the cytokines and thus develop less PPS as a consequence to the

proinflammatory IL-8 rise resulting from the surgical injury (Jaworska-Wilczyńska *et al.*, 2014). It is possible that the IL-8 rise results in a chemotactic response of neutrophils, as patients with PPS also appear to represent higher neutrophil counts in the first postoperative day compared to patients without PPS (Sevuk *et al.*, 2016c). This collaboration could possibly be the main pathway the prophylactic effect of colchicine is based on, as colchicine, among its numerous other functions, inhibits the neutrophil chemotactic response to and production of IL-8 (Leung *et al.*, 2015). Also prednisolone seems to have a reducing effect on the IL-8 immediately after the operation, although the effect is less substantial than the effect on IL-6 and IL-10 (Amanullah *et al.*, 2016). This could explain the prophylactic effect of prednisolone detected in some studies (Dresdale *et al.*, 1956; Sevuk *et al.*, 2016b). Further studies are needed to confirm the involvement and mechanism of IL-8 in the pathogenesis of PPS.

Driven by the detected annual changes in PPS occurrence (McGuinness *et al.*, 1962; Drusin *et al.*, 1965), interest in the participation of viruses in the pathogenesis of PPS arose. In the study mentioned above by Engle and colleagues, viral titers of adenovirus, coxsackie B1–6, and cytomegalovirus were also tested in 280 patients. Titers for one or more of the viruses were positive in 69.9% of PPS patients with positive AHA, whereas in patients with negative AHA and no PPS only 7.8% of patients represented positive results (Engle *et al.*, 1980). Coxsackie B4 was the most prevalent virus but all viruses tested were presented and the authors also observed remarkable annual changes in the viral titers. More than a half of the patients with PPS and positive AHA had no detectable viral titers preoperatively and then had a rise. Consequently, the hypothesis by Engle and colleagues for the pathophysiology was as follows: PPS is the result of an immune response to traumatized myocardium with the "neighbourhood" involvement of the pleura. Heart-reactive antibody (AHA) appears in high titer in the individuals who, because of their age and previous immunologic experience, react to the epicardial and myocardial injury incurred at pericardiotomy. The reaction may also be triggered by a latent or recent viral illness, or the viral illness may be acquired in connection with the operation, perhaps in the operating room while the pericardium is open. Virus invasion of the myocardial cells transforms self into non-self, and the AHA is produced against the neoantigen (Engle *et al.*, 1976, 1980). It has been also suggested that immune complexes are formed between the foreign material and the antibody engenders. This, in turn, may trigger the complement cascade resulting in the release of inflammatory agents causing the clinical signs and symptoms (Lessof, 1976). This hypothesis was strengthened by the study of De Scheerder and colleagues, who observed higher rate of positive circulating immune complexes (CIC) in patients with PPS (De Scheerder *et al.*, 1984) and by Meri and colleagues, who found higher levels of C3 breakdown products during the syndrome (Meri *et al.*, 1985). As discussed before, it is however possible that the elevation of AHA as

well as antiviral antibodies are related to the greater amount of myocardial injury presented in more extensive procedures which are also followed by the higher incidence of PPS (Engle *et al.*, 1980). Then again, the higher degree of myocardial injury provides higher number of binding sites for antigen-antibody reactions as well as higher amount of traumatized tissue for viral invasion. Nevertheless, it has to be kept in mind that also conflicting results of the correlation of viral titers (Maisch *et al.*, 1979; De Scheerder *et al.*, 1984) as well as AHA (Bufalino *et al.*, 1983; Baker *et al.*, 1986; Akl *et al.*, 1992; Bartels *et al.*, 1994) and PPS have been published, although in markedly smaller settings and often representing differences in assay techniques and questionable incidences of PPS. In a small prospective study including only 3 PPS patients, AHA was negative at the time of PPS onset but was detected 14 days after the appearance of the symptoms (Hoffman *et al.*, 2002). Therefore, AHA appeared to be an epiphenomenon rather than a cause. In a prospective study containing 149 children, no correlation was found between PPS and the detection of enteroviral genome (Webber *et al.*, 2001). The authors discussed that the use of IgG serology for the diagnosing of acute viral infections is problematic and can be influenced by many factors, including perioperative blood transfusions performed to all patients in majority of the previous studies. Therefore, the isolation of the virus itself is necessary, with which no correlation was detected in the aforementioned study. Nevertheless, even with the most modern techniques, the detection of the underlying viruses can be problematic (Maisch, 2005).

The participation of B-cell mediated humoral immune system in the pathophysiology of PPS is challenged by the fact that the syndrome has been observed also in patients receiving immunosuppressants (Cabalka *et al.*, 1995). Most of the children received triple-drug immunotherapy with cyclosporin A, azathioprine, and corticosteroids after cardiac transplantation. Regardless of this, 7 out of 15 patients developed PPS appearing 9 to 26 days after the operation. PPS was associated with significantly higher proportion of activated helper T cells (CD4+/25+) during the 2nd month after transplantation when compared to patients without PPS in addition to a rise in the activated cytotoxic T cells (Leu-7+/CD8+). The results suggested a role for T-cell-mediated immunity in the development of PPS. It was hypothesized that initial T-cell activation results in the release of cytokines, which promote inflammatory mediator production by local effector cells, such as monocytes and macrophages. This secondary release of inflammatory mediators could then lead to the clinical manifestations of PPS.

2.3.6.2 Other investigations and theories

The first study assessing the effects of genetics in the development of PPS was published in 2017 (Dechtman *et al.*, 2017). The study included overall 45 patients with PPS and 41 patients who did not develop the syndrome for 3 months following the surgery. The authors determined the three most common MEFV (Mediterranean fever) gene mutations (M694V, V726A, and E148Q) and found no significant differences between patients with and without PPS. However, when comparing mild to moderate (n=24) and severe PPS (n=21), the patients with severe PPS had significantly less carriage of MEFV mutation (4.8% vs. 25%, $p<0.05$). The authors suggested that this could be mediated by the elevation of the inflammatory markers in patients carrying MEFV mutations leading to protective role against PPS. Another offered hypothesis was the diversion of balance between inflammation and apoptosis towards the latter eventually leading to T cell-mediated changes in inflammatory reaction. However, the study did not report either the diagnostic criteria, the incidence of PPS, or the baseline data in mild-moderate PPS and severe PPS separately, and patients with PPS were outstandingly more often female (82.3% vs. 42.0%, $p=0.0001$). Therefore, these results need to be confirmed before further speculation.

Only a few case reports of patients undergoing pericardiectomy due to PPS or the autopsy findings of the pericardial space during active recurrent PPS have been published (Goodkind *et al.*, 1960; Engle *et al.*, 1961). In these severe cases of PPS, an intense pericardial reaction on the epicardium and pericardium was observed, in addition to pericardial thickening, loculated blebs of serous pericardial fluid, and fibrinous adhesions between the pericardium and epicardium. Previous reports of pericardial biopsy in PPS patients are mainly from patients who have undergone non-surgical procedures of the heart or non-cardiac procedures. In these cases, the histology of the pericardium has been non-specific inflammatory changes by rule, featured by fibrous hyperplasia and inflammatory cell invasions (Cevik *et al.*, 2009; Li *et al.*, 2011; Bialy *et al.*, 2017; Nishimura *et al.*, 2019). Similar changes have been detected in the biopsy specimen of pleura (Yukumi *et al.*, 2015; Bujarski *et al.*, 2016; Sinha *et al.*, 2016; Nishimura *et al.*, 2019). When specified, the inflammatory cells have presented macrophage and lymphocyte predominance (Cevik *et al.*, 2009; Yukumi *et al.*, 2015). In a one case report of PPS following transdiaphragmatic pericardial window, the pericardium was thickened, contained fibrinous lesions, and the histology revealed abundant lymphoid infiltrations staining heavily for CD138, with rare IgG4 patterns (King *et al.*, 2009). CD138 refers to plasma cell infiltrations (Calame, 2001), and IgG4 is usually produced as a response to chronic exposure to antigens “blocking” the pathogenic effector mechanisms of other antibody species (Koneczny, 2018). These findings support strongly the hypothesis of antigen revelation as the triggering factor for PPS.

Bufalino and colleagues studied the use of gallium-67 scan in the diagnosing of PPS (Bufalino *et al.*, 1983). They found that patients developing PPS during the early postoperative period presented negative scanning, whereas patients developing PPS after 2 weeks presented positive scanning. This led the authors to the conclusion that latent PPS might represent the "classic" immune-mediated syndrome, whereas the patients with early PPS appearing within 8 days postoperatively may have traumatic pericarditis, or less dense inflammatory response and thus a negative gallium-67 uptake. Later, the scan was found to be negative in patients with Dressler's syndrome, suggesting separate etiologies also for the two diseases (Hutchison *et al.*, 1987).

Besides the prevailing view of the pathophysiological mechanism of PPS, other less-investigated hypotheses have been suggested. One of the theories was proposed by Osborne *et al*., who suggested that starch pericarditis, induced by the starch powder used in the surgical gloves, could be one of the several mechanisms of PPS (Osborne *et al.*, 1974). Although the starch could, theoretically, be one of the etiological agents, this mechanism would not quite explain the cases following intravenous pacemaker implantations and other non-surgical procedures. CPB has been also discussed to be a contributory factor in the pathogenesis of PPS (Tárnok *et al.*, 2001). A major involvement of CPB as well as the factors related to it is unlikely, as during the first descriptions of the disease, CPB was an unestablished part of cardiac procedures and not a part of common practice (Sellke *et al.*, 2010). Moreover, in the patients undergoing cardiac surgery involving the heart-lung machine, PPS develops just as in the patients without (Engle *et al.*, 1978; Kaminsky *et al.*, 1982; Jaworska-Wilczyńska *et al.*, 2014).

2.3.6.3 Retained blood theory

The concept of retained blood syndrome (RBS) was first established in the year 2015 (Boyle *et al.*, 2015). RBS covers a spectrum of mechanical and inflammatory complications related to drainage system failure to adequately evacuate blood after cardiac surgery. According to the aforementioned article, the diagnostic criteria for the syndrome are specified as at least one of the following: 1) pleural effusion/hemothorax requiring drainage, 2) pericardial effusion requiring drainage, 3) re-exploration for washout of blood, 4) interventions for postoperative pericardial constriction, and 5) interventions for postoperative fibrothorax. Therefore, there is an obvious overlap within the entities of PPS and RBS. The authors went on to state that RBS is the root cause of PPS via the acute, subacute, and chronic inflammatory response the retained blood triggers. It was suggested that once the retained

blood clots within the pericardium or pleural space, thrombin and fibrin are generated. These products are powerful chemoattractants of inflammatory cells that can stimulate the mesothelial cells of the pericardium and pleura to release inflammatory cytokines. As stated above, it seems that PPS requires pericardial haemorrhage and/or intensive pericardial manipulation as a minimum trigger. Therefore, the hypothesis of Boyle and colleagues seems logical, although the inadequate blood evacuation does not seem necessary for the onset of PPS, as no previous studies have reported excessive pericardial blood collections to be in association with PPS. It needs to be taken into consideration, however, that the accuracy of transthoracic echocardiography, the examination typically included in the diagnostic evaluation of PPS, in detecting pericardial effusion/hematoma is limited (Floerchinger *et al.*, 2013). Nevertheless, it seems likely, that even minimal amount of pericardial blood can serve as a trigger for the syndrome, and even though the active techniques to enhance the surgical drainage appear to reduce the development of postoperative new-onset AF (Sirch *et al.*, 2016), it is unlikely that they would eliminate the entity of PPS. Still, the pathophysiological mechanism suggested by the authors seems conceivable. Also, according to previous studies, it seems plausible that the extended chest tube drainage as well as posterior pericardiotomy could reduce late tamponade related to PPS (Gozdek *et al.*, 2017; Khan *et al.*, 2019).

2.4 Management of PPS

2.4.1 Medical treatment

The investigations concerning possible methods for the treatment and prevention of PPS started rapidly after the first description of the syndrome. The value of corticosteroids in the treatment of PPS was shortly observed (Soloff *et al.*, 1953; Dresdale *et al.*, 1956). Also NSAIDs were found to be efficacious (Elster *et al.*, 1954), and later they were recommended as the first-line treatment for the milder presentations of PPS (Uricchio, 1963; Engle, 1983; Nishimura *et al.*, 1983; McClendon *et al.*, 1986; Engle *et al.*, 1987), whereas corticosteroids were recommended for the most severe clinical presentations (McClendon *et al.*, 1986; Engle *et al.*, 1987).

Later, both NSAIDs and corticosteroids, in addition to colchicine, have been investigated in double-blind, placebo-controlled settings. In a trial including overall 149 PPS patients, both ibuprofen and indomethacin administered for 10 days relieved symptoms and shortened the duration of the illness without considerable

side effects (Horneffer *et al.*, 1990). Another trial including 21 patients with PPS found that a two-week corticosteroid treatment increased the one-week remission rates and fastened the time to symptom relief (Wilson *et al.*, 1994). However, the use of corticosteroids in the treatment of pericarditis is no longer recommended as it has been associated with higher recurrence rate (Artom *et al.*, 2005; Imazio *et al.*, 2005a, 2005b, 2005c, 2013b; Adler *et al.*, 2015). As stated before, however, evidence against their use in postsurgical pericardial syndromes are scarce (Cantinotti *et al.*, 2014). In most of the aforementioned studies, the number of patients using corticosteroids were small, the drug was only administered in case of aspirin contraindications or failure, and the durations of the treatments were relatively short. Moreover, the notably effective response during the treatment leading to too rapid tapering is a typical pitfall of corticosteroid use, and rather than abandoning the drug it should be used with awareness and slow tapering, and routine administration during the first episode should be avoided (Adler *et al.*, 2015; Imazio *et al.*, 2019). Colchicine has been found to be effective in the most persistent cases of PPS (Tenenbaum *et al.*, 2004), and it has been also associated with a decreased need for invasive interventions (Alraies *et al.*, 2014). The ICAP trial focused on the benefits of first-line use of colchicine in the treatment of acute pericarditis including overall 48 (20.0%) PCIS patients found a significant reduction in the rate of symptom persistence at 72 hours (19.2% vs. 40.0%, $p=0.001$), the number of recurrences (16.7% vs. 37.5%, $p<0.001$), and the hospitalization rate (5.0% vs. 58.3%, $p<0.001$) and increased remission rate at one week (85.0% vs. 58.3%, $p<0.001$) (Imazio *et al.*, 2013b). Multiple meta-analyses have confirmed the efficacy of colchicine both in the first-line treatment of pericarditis as well as in the secondary prevention of recurrent episodes (Alam *et al.*, 2012; Imazio *et al.*, 2012, 2014b; Agarwal *et al.*, 2015; Li *et al.*, 2016; Wang *et al.*, 2016; Papageorgiou *et al.*, 2017).

According to the current guidelines, the treatment of PPS is based on the use of NSAIDs and colchicine, with the occasional addition of corticosteroids. Although symptomatic effusions require medical treatment, the management of asymptomatic effusions is controversial. Recommended doses for uncomplicated cases include aspirin 750–1000 mg or ibuprofen 600 mg every 8 hours with a duration of 1–2 weeks followed by tapering. Colchicine should only be used in the presence of systemic inflammation, and the recommended dose is 0.5 mg once (<70 kg) or twice (≥70 kg) daily for 3 months with an optional halving of the dose in the last weeks of the treatment. Corticosteroids should be considered as a second option in patients with contraindications and the failure of NSAIDs with low to moderate doses (i.e., prednisone 0.2–0.5 mg/kg/day or equivalent) (Adler *et al.*, 2015).

According to few case reports, methotrexate (Zucker *et al.*, 2003), azathioprine (Marcolongo *et al.*, 1995; Vianello *et al.*, 2011), as well as high-dose intravenous

immunoglobulin (Wendelin *et al.*, 2008; Moretti *et al.*, 2013; del Fresno *et al.*, 2014; Imazio *et al.*, 2016), may be effective if a patient with PPS develops dependency on steroids. In chronic recurrent pericarditis, also anakinra, a recombinant IL-1β receptor antagonist (Lazaros *et al.*, 2014, 2016) as well as cyclophosphamide (Marcolongo *et al.*, 1995) have been successfully used. Moreover, intrapericardial triamcinolone has been used in the treatment of chronic autoreactive pericardial effusion (Maisch *et al.*, 2002), and it is also mentioned in the ESC guideline as well as azathioprine, intra-venous immunoglobulin, and anakinra (Adler *et al.*, 2015).

2.4.2 Interventional treatment

If the patient has evidence of clinical tamponade or if the symptoms persist regardless of the medical treatment and an alternative diagnosis is suspected, the evacuation of pericardial effusion is required (Engle *et al.*, 1978; Adler *et al.*, 2015). In the presence of tamponade, the needle pericardiocentesis is preferred, whereas surgical approach might be safer when the pericardial fluid is not free, it is located in a lateral or posterior position, or the effusion is mild (<10 mm). The pericardiocentesis should be performed under guidance either by fluoroscopy or echocardiography and under local anesthesia. The ideal entry site in the echocardiography-guided procedure is the point where the effusion is closest to the transducer and the fluid collection is maximal and the liver or pleura are not on the way, whereas in the fluoroscopy-guided procedure the subxiphoid route is more common. If there is a need for pericardial biopsy for the differential diagnostics, the surgical approach is the gold standard, classically through a subxiphoid incision. In this procedure, a small drain is left in place to evacuate any remaining effusion (Adler *et al.*, 2015). In the presence of extensive pleural effusions, a pleural drainage or thoracocentesis may be required, and they should be preferably performed on ultrasound-guidance. The drain should be inserted in the “triangle of safety”, referring to the area bordered by the lateral edge of the latissimus dorsi, the lateral border of the pectoralis major muscle and superior to the horizontal level of the fifth intercostal space (Havelock *et al.*, 2010).

In the most persistent cases of pericardial effusion, pericardiectomy may be considered (Adler *et al.*, 2015). Fortunately, this is needed only in extremely rare cases (Engle *et al.*, 1978). Other possible interventional treatments include prolonged pericardial drainage, the aforementioned intrapericardial triamcinolone treatment, and pericardial window (Adler *et al.*, 2015). The pericardial window can be performed either by conventional heart surgery, by thoracoscopy, or by balloon pericardiotomy by inserting a deflated single catheter or double balloon catheters into

the pericardial space (Imazio *et al.*, 2017). If the surgery is performed, pericardiectomy is the procedure of choice, because pericardial window may not relieve loculated pericardial fluid or may close soon after being performed (Ofori-Krakye *et al.*, 1981; Adler *et al.*, 2015). If the persistent PPS manifests as large, symptomatic pleural effusions continuing despite several thoracocenteses, thoracoscopy should be considered. At thoracoscopy, any fibrous tissue coating the visceral pleura should be removed and either the parietal pleura should be abraded or talc should be used to create a pleurodesis (Light, 2002; Paull *et al.*, 2003). In addition, a single case report has been published of the use of indwelling pleural catheter for the recurrent pleural effusions secondary to PPS (Bujarski *et al.*, 2016).

2.4.3 Prevention

The first study concerning PPS prophylaxis was published in 1956 (Dresdale *et al.*, 1956). A prophylactic 3–8 weeks cortisone treatment postponed the development of PPS and resulted in a less stormy immediate postoperative course, although the incidence of PPS was similar after drug withdrawal (29 vs. 31%). Later, a double-blind placebo-controlled study including 246 children found no effect of short-term prophylactic intravenous methylprednisolone (1 mg/kg before CPB plus four additional doses within 24 hours) on the incidence of PPS (Mott *et al.*, 2001). Instead, a greater proportion of the treatment group developed PPS leading to hospital admission (6.3% vs. 0.8%). A substudy of the DECS trial investigated the effect of intraoperative dose of 1 mg/kg dexamethasone in 822 adults and found no benefits in either the occurrence of PPS or complicated PPS (Bunge *et al.*, 2014). On the other hand, a retrospective study including overall 200 adult patients reported significant PPS reduction in patients receiving a single intraoperative dose of 1 mg/kg methylprednisolone (22.0% vs. 37.0%, $p<0.026$) (Sevuk *et al.*, 2016b). It has been suggested that the positive result conflicting with previous studies could be due to the strict exclusion criteria used (Wamboldt *et al.*, 2018). Further large-scale studies are needed to assess the possible value of corticosteroids in the prevention of PPS maintaining special focus on the exact timing and route of the drug administration (Wamboldt *et al.*, 2018).

A prospective study evaluating the effect of one week aspirin prophylaxis (60 mg/kg/day) in children found no significant reduction in the size of postoperative pericardial effusions (Béland *et al.*, 1990). This finding has been supported by later studies in children and young adults (Gill *et al.*, 2009; Rabinowitz *et al.*, 2018). By contrast, a retrospective study evaluating the effect of diclofenac treatment for postoperative analgesia during the hospital admission in 100 adult patients found

a significant reduction in PPS occurrence when compared to patients not administered to NSAIDs (20.0% vs. 43.0%, p=0.001) (Sevuk *et al.*, 2015). However, no prospective trials have yet confirmed this finding.

The first trial reporting the possible value of colchicine for the prevention of PPS was published in 2002 (Finkelstein *et al.*, 2002). After that, two randomized, placebo-controlled trials have been published accordingly. The COPPS trial included overall 360 adult cardiac surgery patients, from which 180 received placebo and 180 received colchicine for a month postoperatively. Colchicine significantly reduced the incidence of PPS (8.9% vs. 21.1%, p=0.002, NNT=8) and PPS-related hospitalization, cardiac tamponade, constrictive pericarditis, and relapses (0.6% vs. 5.0%, p=0.024). A few years later the COPPS-2 trial included another 360 adult cardiac surgery patients, from which 180 received colchicine starting two to three days preoperatively and continuing until 1 month after the surgery. Again, the administration of colchicine resulted in a significant reduction of PPS (19.4% vs. 29.4%, NNT=10). The effect was significantly higher in patients with systemic inflammation, specified as an elevation of C-reactive protein (CRP) during the hospital admission. This time, no significant reduction in the PPS-related secondary end points was detected. The three aforementioned studies have been also analysed using meta-analytic pooling that has shown a relative risk reduction of 44–52% in PPS incidence (Agarwal *et al.*, 2015; Briasoulis *et al.*, 2015; Wang *et al.*, 2016; Papageorgiou *et al.*, 2017). Therefore, colchicine seems effective in the prevention of PPS, although its use is limited by the gastrointestinal side effects. According to previous studies, colchicine causes an increment of 8–10 percentage points in gastrointestinal side effects compared to placebo but serious side effects have not been observed (Finkelstein *et al.*, 2002; Imazio *et al.*, 2005a, 2010, 2012, 2013b, 2014b; Alam *et al.*, 2012; Agarwal *et al.*, 2015; Wang *et al.*, 2016; Li *et al.*, 2016; Papageorgiou *et al.*, 2017). The effect is worsened if the drug is started preoperatively (Imazio *et al.*, 2014c).

Currently, because of the relatively good outcome of PPS patients and the adverse effects of colchicine, instead of the primary prevention, clinicians are advised to consider early recognition and treatment of the syndrome (Adler *et al.*, 2015; Imazio, 2015). However, according to the ESC Guideline, a one-month colchicine prophylaxis should be considered after cardiac surgery for the prevention of PPS if there is evidence of systemic inflammation, there are no contraindications, and the drug is tolerated (class IIaA recommendation).

2.5 Prognosis after PPS

According to previous studies, PPS is associated with a prolonged hospital stay (Engle *et al.*, 1975; Maisch *et al.*, 1979; Imazio *et al.*, 2011b; van Osch *et al.*, 2017a) and readmissions (Mott *et al.*, 2001; Imazio *et al.*, 2011b; Bunge *et al.*, 2014). The reported recurrence rates have varied between 4% and 21% and typical timing of the repeating episodes is from 1 to 3 months after the first episode (Drusin *et al.*, 1965; Nishimura *et al.*, 1983; Imazio *et al.*, 2011b). The incidence of PPS-related cardiac tamponade is 0.8–1.3% after the first week after cardiac surgery, making PPS the most common etiology of delayed cardiac tamponade (Bortolotti *et al.*, 1981; Ofori-Krakye *et al.*, 1981). The tamponade can occur anywhere between 7 and 180 days after the operation. In a recent study, PPS was associated to an over 15-fold risk of reoperation for tamponade (van Osch *et al.*, 2017a).

Apart from the aforementioned complications, the previous knowledge of PPS-related adverse events is limited. A study including 100 patients undergoing mitral valvotomy found no association between PPS and new-onset AF (Papp *et al.*, 1956). Another retrospective study including 60 patients developing postoperative atrial fibrillation (POAF) and 142 patients without POAF after CABG found a significant association between POAF and PPS (incidence of PPS after POAF (61.7%) vs. no-POAF (45.8%), OR 1.9, 95% CI 1.03–3.5, p=0.04) (Sevuk *et al.*, 2016a). However, there were multiple baseline differences between the study groups, and the incidence of PPS was strikingly high (overall incidence 51%) reflecting either selection bias or problems with the differential diagnostics of PPS and also questioning the main results.

Constrictive pericarditis has been suggested to be a complication of PPS appearing during long-term follow-up (Imazio, 2012). An analysis including 37 constrictive pericarditis patients with adequate clinical information, PPS was observed in 23 (62.2%) patients (Killian *et al.*, 1989). Similar results have been reported in several studies (Rice *et al.*, 1981; Miller *et al.*, 1982). However, another analysis including 5207 cardiac surgery patients, 11 cases of constrictive pericarditis were observed, but only one presented acute pericarditis during the postoperative period (Kutcher *et al.*, 1982). According to the aforementioned studies, constrictive pericarditis occurs in a broad time frame of 1 month to 17 years postoperatively, typically within 24 months, with an overall incidence of 0.2–0.3%. Assuming 60% of constrictive pericarditis would be of PPS-related etiology, approximately 0.5% of the patients with PPS would develop constrictive pericarditis during long-term follow-up. This incidence is similar to idiopathic/viral pericarditis (Imazio *et al.*, 2011a). However, markedly higher incidences of constrictive pericarditis have also been reported (Alraies *et al.*, 2014), although possibly reflecting the selection bias of the original

patient selection as stated also by the authors themselves. Only one prospective study has evaluated the rate of constrictive pericarditis after PCIS (Imazio *et al.*, 2011a). However, even though PCIS was combined with connective tissue diseases, the number of patients was insufficient (n=36) to draw any conclusions. Another study including 119 PPS patients with a follow-up of one year found no constrictive pericarditis cases (van Osch *et al.*, 2017a). Therefore, the question of whether constrictive pericarditis is associated to the development of PPS or to a common pathophysiological trigger, e.g., surgery related hemopericardium, is controversial. Either way, the presence of PPS should serve as a warning signal to clinicians, as a theoretical risk of constriction exists (Adler *et al.*, 2015).

Symptomatic treatment of PPS has been associated with a higher incidence of venous graft occlusion when compared to patients receiving NSAIDs and prednisolone for a time period of 6 weeks (Urschel *et al.*, 1976). The patients were observed to have diffuse adhesions between the pericardium and epicardium, often obliterating the pericardial space. The venous grafts had microscopical fibrinoid degeneration and infiltration by chronic inflammatory cells suggesting external compression rather than intimal hyperplasia as the cause of the stenosis or occlusion. However, similar results have not been reported since apart from a single case report of a patient developing rapid coronary artery occlusion after PPS (De Scheerder *et al.*, 1985a). Other reported possible complications include the extrusion of the pulse generator from the pacemaker pocket (Wang *et al.*, 1983) and the thickening and scarring of autogenous pericardial baffle (Luken *et al.*, 1986).

Van Osch *et al*. have published the largest study focusing on the prognosis of PPS (van Osch *et al.*, 2017a). This retrospective subanalysis of the DECS trial included 822 patients undergoing valve surgery followed up to a year postoperatively. Overall 119 (14%) patients developed PPS. Patients with PPS presented markedly more reoperations for tamponade at one year (20.9% vs. 2.5%, OR 15.49, 95% CI 7.14–33.58, $p<0.001$) with the difference appearing within two months after the surgery in addition to longer hospital stay (13 vs. 11 days, $p=0.001$). However, the one-year prognosis was interpreted excellent: 4/119 (4.2%) of PPS patients and 37/703 (5.5%) of patients without PPS died during the first year after the surgery (OR 0.63, 95% CI 0.22–1.79, $p=0.497$). Also, no significant associations were observed between PPS and reoperation for surgical bleeding, pleural puncture, postoperative AF, stroke, myocardial infarction, or readmissions.

The aforementioned study is the only study evaluating the effect of PPS on mortality. Therefore, the previous knowledge of the benignity of PPS is somewhat uncertain. Despite the limited published data, the prognosis of PPS has been considered to be benign (Bucekova *et al.*, 2012; Imazio *et al.*, 2013d; Adler *et al.*, 2015).

3 AIMS OF THE STUDY

The principal aims of the study were to:

1. Evaluate the incidence and risk factors for PPS requiring medical attention.

2. Investigate the effect of sex, age, and procedure type on the occurrence of PPS.

3. Examine the prognosis after PPS.

4. Estimate the role of PPS-related adverse events in the higher mortality after PPS.

4 MATERIALS AND METHODS

4.1 Patient populations

In the study I, the study population included a consecutive series of 699 patients who had undergone an isolated CABG between 2008 and 2010. All operations were performed in Turku University Hospital, Turku, Finland. The follow-up was complete for 688 (98.4%) patients.

The study II included all patients admitted to a hospital with PPS as a primary cause of admission between May 2000 and October 2009 in 29 hospital in Finland nationwide. Only patients aged 20–79 years were included resulting in 760 PPS patients.

The population of the study III included overall 28,761 consecutive adult patients entering CABG, AVR, MVR, or ascending aortic surgery in Finland between January 2005 and December 2013. The data included cardiovascular admissions from 131 health care units nationwide. Overall 493 PPS episodes severe enough to require hospital admission or contributing to death were identified. The study population flow chart is presented in Figure 3.

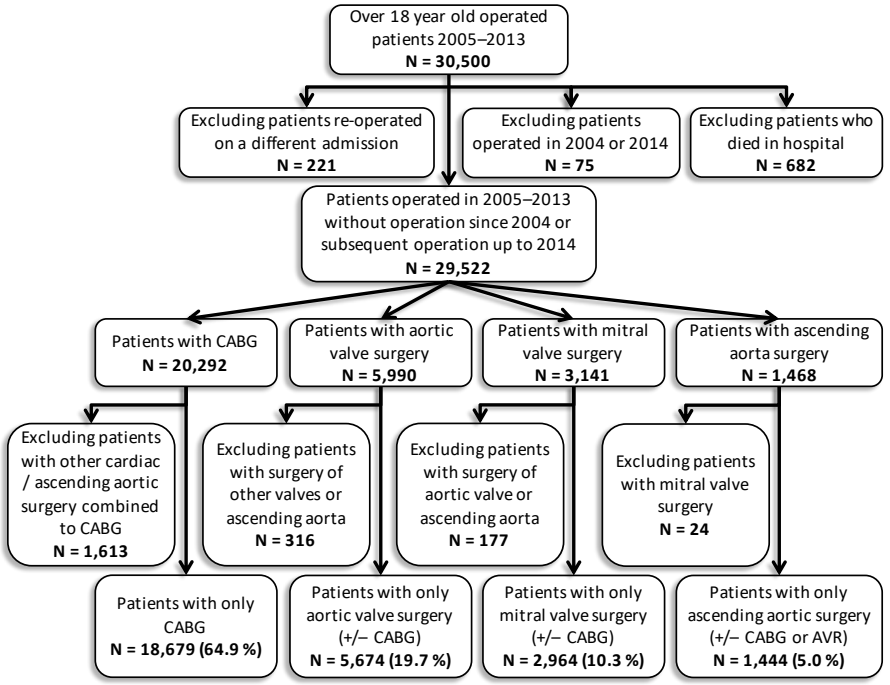


Figure 3. Study population flow chart for the study III. Modified from the original publication III, Figure 1. AVR: aortic valve replacement; CABG: coronary artery bypass grafting.

The study IV contained patients from two separate databases. Majority of the patients (n=622) were from the multicenter (university hospitals of Turku, Oulu, and Kuopio), retrospective CAREAVR database and the remaining patients (n=49) were from the prospective, single-center (Turku University Hospital) CAREBANK database resulting in a combination database of 671 patients. The patients underwent an isolated SAVR with a bioprosthesis (n=361) or a mechanical prosthesis (n=310) over the period of 2002–2014 (CAREBANK: 2016–2018).

4.2 Study designs

The study I was a retrospective cohort study. The data on baseline and perioperative characteristics, discharge medication, and postoperative outcomes were collected from electronic patient records. Follow-up data were retrieved from the catchment areas of Turku University Hospital, Turku City Hospital, and Satakunta Central Hospital. The median follow-up time was 5.3 years. The causes and timing of death were derived from Statistics Finland.

The studies II and III were retrospective cohort studies using data collected from the nationwide Care Register for Healthcare database, maintained by the Finnish National Institute for Health and Welfare. This database contains basic baseline data (e.g., age and sex), data on the length of hospital stay, performed procedures, and International Classification of Diseases, Tenth Revision (ICD-10) diagnostic codes for all hospital admissions in Finland nationwide. In the study II, age- and gender-matched population data from Statistics Finland was also used to specify the incidence rates in the overall Finnish population. In addition, the numbers of cardiac procedures were estimated using the Blood Products in Cardiac Surgery (BiCS) database, maintained by Finnish Red Cross Blood Service. In the study III, the data on causes and timing of death were derived from Statistics Finland.

The study IV contains data from two separate databases included in the CAREFIB Consortium: CAREAVR (Consortium of Studies in the Field of Atrial Fibrillation, Stroke, and Bleeding in Patients Undergoing Aortic Valve Replacement; ClinicalTrials.gov Identifier: NCT02626871) and the CAREBANK (Cardiovascular Research Consortium - a Prospective Project to Identify Biomarkers of Morbidity and Mortality in Cardiovascular Interventional Patients; ClinicalTrials.gov Identifier: NCT03444259). The CAREAVR is a Finnish multicenter retrospective study containing patients undergoing isolated SAVR in four Finnish university hospitals (Helsinki, Turku, Oulu, and Kuopio). Helsinki was excluded from the study IV due to incomplete follow-up data for PPS. The electronic patient records were reviewed with a standardized structured data collection protocol for pre- and perioperative data, discharge data, and long-term follow-up events, including POAF, stroke, transient ischemic attacks (TIA), bleeding events, and mortality. The CAREBANK is an ongoing Finnish prospective cohort study assessing the associations between the features of cardiac tissue samples and clinical phenotypes in patients undergoing cardiac procedures in Turku University Hospital. In the study IV, only patients undergoing isolated SAVR were included. The data were collected from electronic patients records and by follow-up phone calls at 3, 12, 24, and 60 months. A standardized structured data collection protocol similar to the CAREAVR study was used allowing the combination of the two databases. The data on causes and timing of death were derived from Statistics Finland. In the combination database, the median follow-up time was 9.0 years for survival and 5.1 years for the other adverse events.

4.3 Outcomes

Study I

The primary outcome of the study I was PPS requiring medical attention. PPS was

defined by the presence of at least 2 of the following: 1) fever without alternative causes, 2) pleuritic chest pain, 3) friction rub, 4) evidence of new or worsening pleural effusion, and 5) evidence of new or worsening pericardial effusion, based on the previously proposed criteria for scientific purposes (Imazio *et al.*, 2013c). Secondary outcomes included PPS relapse defined by the worsening of pericardial or pleural effusion while on medication or after the withdrawal of medication, the evacuation of pleural or pericardial effusion due to PPS, and all-cause death.

Study II

The primary outcome of the study II was PPS leading to hospital admission. Patients with PPS as the primary cause of admission were identified by ICD-10 code I97.0. Readmissions due to PPS were also included. The data of the study I were used to evaluate the pre-, peri-, and postoperative factors between patients included in the study II and the remaining PPS patients to assess the possible selection bias. Validation showed no significant differences between the PPS patients included in the study II and the remaining PPS cases.

Study III

In the study III, the primary outcome was PPS severe enough to require hospital admission or contributing to death. Postoperative admissions with PPS as the primary, secondary, or tertiary cause of admission, or as any cause of death were identified using ICD-10 code I97.0. The secondary outcome was 1-year all-cause mortality.

Study IV

The primary outcome of the study IV was PPS requiring medical attention defined by the presence of at least two of the following criteria: 1) fever without alternative causes, 2) pericarditic or pleuritic chest pain, 3) pericardial or pleural rubs, 4) evidence of pericardial effusion, and 5) evidence of pleural effusion with elevated C-reactive protein (CRP), based on the criteria recommended by the ESC guideline (Adler *et al.*, 2015). PPS was categorized into two subgroups according to the severity of the syndrome: moderate PPS which did not require invasive interventions, i.e., the evacuation of pleural or pericardial effusion, and severe PPS which required invasive interventions such as pericardial or pleural drainage. Secondary outcomes included new-onset AF, stroke, major stroke, TIA, major bleeding, and all-cause death. Stroke was defined as a permanent focal neurological deficit adjudicated by a neurologist and confirmed via computed tomography or magnetic resonance imaging. Major stroke was defined as a stroke other than lacunar-type (< 20 mm in diameter). TIA was defined as a transient (< 24 hours) focal neurological deficit adjudicated by a neurologist. Major bleed was defined as an overt, actionable sign of haemorrhage requiring diagnostic studies, hospitalization, or treatment by a health care professional.

4.4 Statistical analysis

The statistical analyses were performed using SPSS software, SAS, and R software. In the study I, SPSS statistical software version 22.0 (IBM SPSS Inc, Armonk, NY) was used for all the statistical analyses. The analyses of the studies II and III were conducted using SAS system version 9.4 (SAS Institute Inc, Cary, NC), in addition to SPSS version 24.0 (IBM SPSS Inc, Chicago, IL) in the study III. All the statistical analyses of the study IV were conducted with R software version 3.3.3 (https://www.R-project.org/).

Continuous variables were reported as mean ± standard deviation if normally distributed and as median (25^{th} – 75^{th} percentiles) if skewed. The data were tested for normal distribution using Shapiro-Wilk and Kolmogorov-Smirnov tests. Categorical variables were described as counts and percentages. In all studies, p-values < 0.05 were considered statistically significant.

Study I
Chi-square test, Mann-Whitney test, and Cox regression were used to analyse the baseline differences and mortality between patients with and without PPS. The multivariable analysis was performed using the Cox regression backward stepwise selection procedure. The multivariable model was performed by including variables of relevance with a p-value < 0.10 in the univariable analyses. Metformin was excluded due to its association with diabetes, and abnormal use of red blood cell units was excluded due to its association with the use of 1 or more red blood cell units. The Kaplan-Meier method was used to present survival curves.

Study II
The data of the study II was analysed by using negative binomial regression models. In the model for incidence rates and in the model for estimating the amount of PPS compared to the number of cardiac surgeries, the logarithms of age- and gender-specific population and number of cardiac surgeries were used as offset parameters. Analyses were adjusted for study year. Total incidence rates were standardized with the European 2013 standard population by using a direct method.

Study III
Cox regression univariable and multivariable models were used for studying the hazard of PPS and the association between PPS and mortality. The multivariable model was performed by including age, sex, Chalson Comorbidity Index (CCI), the urgency of the procedure, procedure type, and resternotomy. The associations between concomitant CABG in valve and aortic procedures, the use of LITA in CABG, and the use of a mechanical valve in AVR and the occurrence of PPS were studies by subgroup analyses.

Study IV

Unpaired t-test, Mann-Whitney test, and Cox regression were used for the univariable analyses of the baseline differences between patients with and without PPS. The independency of the predictors of PPS was evaluated using Cox regression model with interaction terms. The multivariable Cox regression models of the secondary outcomes were performed by including variables of relevance with a p-value < 0.10 in the univariable analyses. Survival analyses were adjusted for EuroSCORE II (European System for Cardiac Operative Risk Evaluation) (Nashef *et al.*, 2012). Cause-specific competing risk hazard models accounting for death were used for analyses of other outcomes than mortality.

4.5 Ethics

Studies I-IV were conducted according to the principles of the Declaration of Helsinki. The study protocols were approved by the local ethics committees and the ethics committee of the National Institute for Health and Welfare in Finland. An informed consent was obtained from the participants of the CAREBANK study. Because of the retrospective, observational nature of the remaining studies, an informed consent was not required.

5 RESULTS

5.1 Risk factors and incidence of PPS requiring medical attention (study I)

In the study I, overall 61 of 688 patients (8.9%) undergoing CABG developed PPS leading to delayed hospital discharge, readmission, or medical therapy due to symptoms. The median latency between the operation and PPS onset was 21 (11–52) days. The freedom from PPS after isolated CABG is detailed in Figure 4.

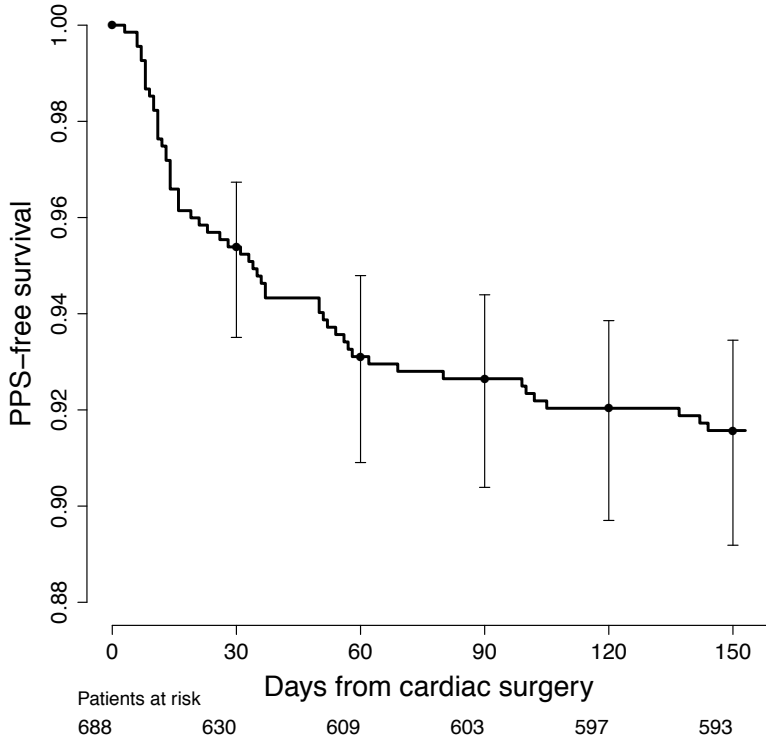


Figure 4. Freedom from PPS in patients undergoing isolated CABG. Reproduced from the original publication I, Figure 1. PPS: postpericardiotomy syndrome.

The symptoms of PPS occurred according to the following: pleuritic chest pain 20%, dyspnea 44%, and fever 41%. Typical clinical findings included pericardial effusion (93%), positive chest x-ray (pleural effusion or cardiac silhouette enlargement, 93%), abnormal erythrocyte sedimentation rate (90%), abnormal CRP (84%), and positive electrocardiogram (widespread ST-segment elevations, 45%). Friction rub was detected in only 6.9% of the PPS patients.

Baseline characteristics and operative data in patients with and without PPS are detailed in Table 2. Patients with PPS had less often diabetes and were less often taking metformin treatment. Postoperative characteristics of patients with and without PPS are detailed in Table 3. Patients with PPS had more often red blood cell units transfused in addition to a nonsignificant trend towards more postoperative bleeding. Although also the abnormal use (1–2 units) of red blood cell units was significantly associated with higher PPS occurrence, the use of one or more units had a stronger presumption against null hypothesis.

Table 2. Baseline characteristics and operative data in patients with and without PPS. Modified from the original publication I, Table 1.

	PPS N=61	***No-PPS N=627***	***P-value***
Age (years)	67 (59–74)	67 (60–73)	0.95
Females	13 (21%)	141 (23%)	0.83
BMI	28 (25–30)	28 (25–31)	0.32
Diabetes	7 (12%)	190 (31%)	0.002
Hypertension	58 (95%)	590 (94%)	0.83
Pulmonary disease	3 (4.9%)	49 (7.8%)	0.41
Atrial fibrillation	3 (4.9%)	49 (7.8%)	0.41
Extracardiac arteriopathy	1 (1.6%)	50 (8.0%)	0.071
Prior stroke or transient ischemic attack	3 (4.9%)	44 (7.0%)	0.54
Prior percutaneous coronary intervention	10 (16%)	110 (17%)	0.92
Prior cardiac surgery	0 (0.0%)	14 (2.2%)	0.24
Recent AMI	14 (23%)	130 (21%)	0.76
Two or three-vessel disease	57 (93%)	600 (96%)	0.34
Left main stenosis	32 (53%)	280 (44%)	0.20
Left ventricular ejection fraction <30%	5 (8.2%)	43 (6.9%)	0.70
Emergency operation	7 (12%)	94 (15%)	0.46
Urgent or emergency operation	33 (54%)	320 (51%)	0.65
Preoperative IABP	2 (3.3%)	5 (0.8%)	0.065
Off-pump surgery	8 (13%)	71 (11%)	0.68
At least one mammary artery graft	60 (98%)	600 (95%)	0.28
Radial artery graft	4 (6.6%)	47 (7.5%)	0.79
No. of distal anastomoses	3.0 (2.0–3.0)	3.0 (2.0–3.0)	0.84
Preoperative labs:			
INR	1.0 (1.0–1.1)	1.1 (1.0–1.1)	0.054
Hemoglobin	140 (130–150)	140 (130–150)	0.72
EGFR	70 (62–83)	77 (65–90)	0.069
Preoperative medical treatment:			
Aspirin	60 (98%)	580 (95%)	0.20
Clopidogrel	14 (23%)	100 (17%)	0.22
LMWH	13 (21%)	160 (27%)	0.34
Warfarin	5 (8.2%)	52 (8.5%)	0.93
Statin	61 (100%)	590 (95%)	0.074
GP IIa/IIIb –inhibitors	2 (3.3%)	24 (3.8%)	0.83
Thrombolysis	0 (0.0%)	17 (2.7%)	0.19
Metformin	2 (3.3%)	130 (20%)	0.001
Sulphonylurea	1 (1.6%)	47 (7.5%)	0.086
Gliptin	0 (0.0%)	8 (1.3%)	0.37
Glitazone	0 (0.0%)	6 (1.0%)	0.44
Insulin	4 (6.6%)	85 (14%)	0.12
Aortic cross-clamping time (min)	61 (46–71)	59 (47–70)	0.61
CPB time (min)	80 (71–97)	80 (67–94)	0.80
Operation length (min)	180 (150–220)	180 (160–210)	0.58

Continuous variables are reported as median (25th – 75th percentiles). Values in parentheses are percentages. AMI: acute myocardial infarction; BMI: body mass index; CPB: cardiopulmonary bypass; eGFR: estimated glomerular filtration rate using modification of diet in renal disease formula; GP: glycoprotein; IABP: intra-aortic balloon pump; INR: international normalized ratio; LMWH: low molecular weight heparin; PPS: postopercardiotomy syndrome.

Table 3. Postoperative characteristics after isolated CABG in patients with and without PPS. Modified from the original publication I, Table 2.

	PPS N=61	***No-PPS N=627***	***P-value***
IABP	5 (8.2%)	47 (7.5%)	0.85
Atrial fibrillation	11 (18%)	140 (23%)	0.41
Stroke or transient ischemic attack	1 (1.6%)	29 (4.6%)	0.28
Pneumonia	3 (5.7%)	19 (3.4%)	0.39
Mediastinitis	1 (1.9%)	7 (1.2%)	0.69
Red blood cell			
≥1 units used	37 (61%)	270 (43%)	0.008
Abnormal use (1-2 units)	19 (31%)	120 (19%)	0.019
Major use (>2 units)	18 (30%)	150 (24%)	0.36
Fresh frozen plasma			
≥1 units used	11 (18%)	99 (16%)	0.61
Abnormal use (1-4 units)	11 (18%)	88 (14%)	0.40
Major use (>4 units)	0 (0.0%)	11 (1.8%)	0.30
Platelets			
≥1 units used	7 (12%)	70 (11%)	0.95
Abnormal use (1-8 units)	7 (12%)	56 (8.9%)	0.51
Major use (>8 units)	0 (0.0%)	14 (2.2%)	0.24
Bleeding (ml)	980 (670–1300)	830 (620–1200)	0.099
Resternotomy for bleeding	4 (6.6%)	58 (9.3%)	0.48
Surgical bleeding	5 (8.2%)	25 (4.0%)	0.12
ICU stay (days)	1.0 (1.0–2.0)	1.0 (1.0–2.0)	0.89
In-hospital stay (days)	7.0 (6.0–8.0)	7.0 (5.0–8.0)	0.36

Continuous variables are reported as median (25^{th} – 75^{th} percentiles). Values in parentheses are percentages. IABP: intra-aortic balloon pump; ICU: intensive care unit; PPS: postopericardiotomy syndrome; Surgical bleeding: a significant bleeding from any anastomosis, graft, or vessel in the surgical field (pericardial artery, mammary vessels, Keynes' veins).

The Cox regression multivariable model identified the use of 1 or more red blood cell units as an independent predictor of PPS (HR 1.9, 95% CI 1.1–3.2, p=0.017). Diabetes was detected to be an independent protective factor (HR 0.32, 95% CI 0.15–0.71, p=0.005).

The relapse of PPS occurred in 23 of 61 (38%) PPS patients. PPS patients developing relapse were more obese (BMI 29 vs. 26, p=0.024) and had significantly shorter in-hospital stay after the index surgery (7.0 vs. 8.0 days, p=0.017) when compared to PPS patients without relapse. No significant differences in the first-line medications for PPS were detected between patients with relapsed and non-relapsed PPS. Although not reaching statistical significance, emergency operations (22% vs. 5.3%, p=0.050), NSAIDs as first-line medication for PPS (35% vs. 16%, p=0.087), and longer delay between the index operation and PPS onset (34 vs. 15 days, p=0.094) had a nonsignificant trend towards higher occurrence of PPS relapses.

First-line medical treatment for PPS was glucocorticoids in 43%, NSAIDs in 23%, and colchicine in 15% of patients. PPS required the evacuation of pleural effusion in 13 (22%) patients and the evacuation of pericardial effusion in 3 (4.9%) patients. One patient (1.6%) developed cardiac tamponade due to PPS. No differences in the mortality rates were detected between patients with and without PPS.

5.2 The impact of age and sex on the occurrence of PPS admissions (study II)

During the study period of the study II, PPS was the primary cause of 760 hospital admissions. Most of the patients with PPS were male (67.8%). The median age of PPS patients was 63 (56–71) years, and the number of PPS patients increased by an estimated 82% (95% CI 66–98%) with every 10-year increment in age. Women with PPS were slightly older compared to men (63.4±11.6 vs. 61.1±11.3 years, p=0.007) and the number of female PPS patients increased steadily from 20 to 79 years of age, whereas the number of male PPS patients increased more steeply from 40 to 60–70 years. The age distribution of PPS patients divided by sex is detailed in Figure 5. The median length of hospital stay was 6 (4–8) days, and 17.3% of PPS patients had two or more admissions due to the syndrome.

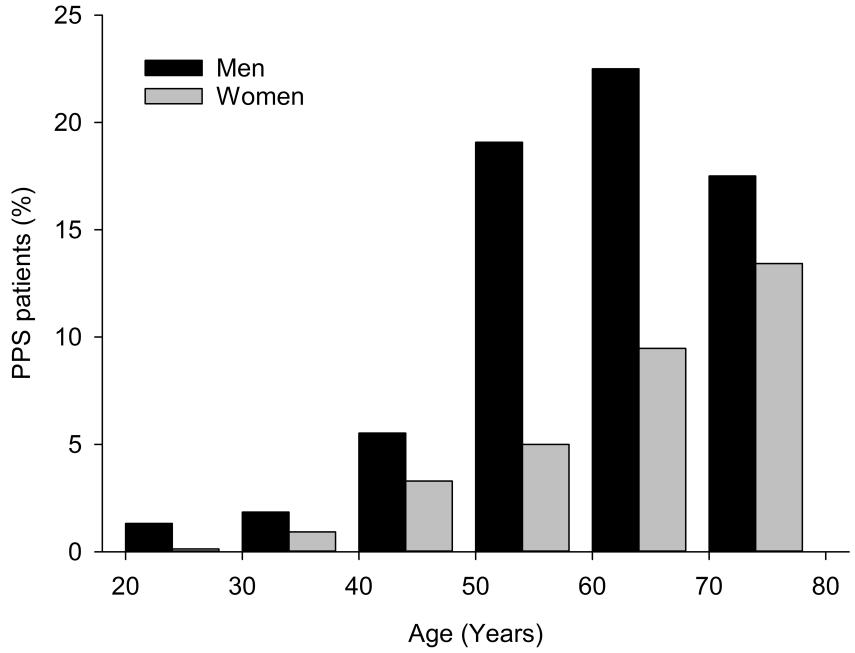


Figure 5. The age distribution of PPS patients divided by sex. From the original publication II, Figure 1B. PPS: postpericardiotomy syndrome.

The total standardized incidence rate of PPS leading to hospital admission was 2.22/100,000 person-years. The gender-adjusted incidence rate increased by an estimated 106% (95% CI 92–121%) with every 10-year increment in population age, and the rate and pattern of increase was similar for both sexes. The age-adjusted incidence rate of PPS was significantly higher in men compared to women (IRR 2.49, 95% CI 2.05–3.02, p<0.0001). The gender-bias was not age-dependent

(p=0.49 for interaction). The incidence rate of PPS admissions is detailed in Figure 6.

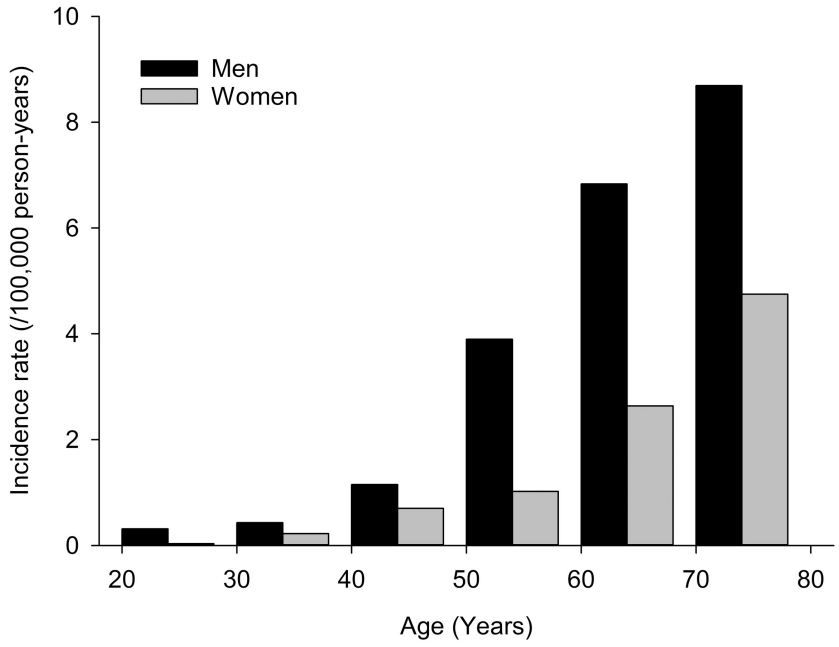


Figure 6. Sex-specific incidence rate of PPS admissions in general population. From the original publication II, Figure 2B.

Between 2002 and 2008, overall 22,373 cardiac surgery procedures in adults were identified in the participating hospitals in Finland. The median age of the patients was 67 (59–74) years and 73.4% of the patients were male. During the period in question, 550 admissions due to PPS were recorded resulting in an annual PPS rate of 2.46% (95% CI 2.25–2.67%) in the total study population. The rate of PPS was the highest in the youngest patients (11.5%) followed by a gradual decrease of 41% with every 10-year increment in age (RR 0.59, 95% CI 0.55–0.65, $p<0.0001$ per 10-year increment in age). The occurrence of PPS in relation to cardiac surgeries is detailed in Figure 7. The rate of PPS in relation to the number of cardiac surgeries was significantly higher in women (2.99% vs. 2.28%; RR 1.78, 95% CI 1.45–2.19, $p<0.001$). No significant interaction between sex and age was detected (p=0.87 for interaction). No significant annual changes were detected during the study period.

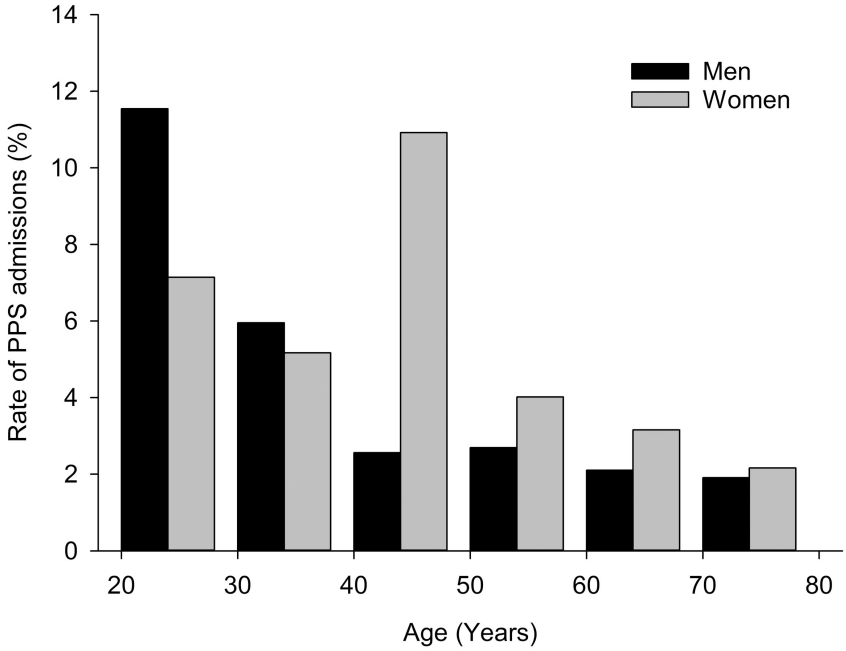


Figure 7. Sex-specific occurrence of PPS in relation to cardiac surgeries. From the original publication II, Figure 3B. PPS: postpericardiotomy syndrome.

5.3 The impact of procedure type and mortality of PPS patients (Study III)

The final patient cohort of the study III included 28,761 patients undergoing open-heart surgery, from which 64.9% (n=18,679) underwent isolated CABG, 19.7% (n=5,674) underwent AVR ± CABG, 10.3% (n=2,964) underwent MVR ± CABG, and 5.0% (n=1,444) underwent ascending aortic surgery ± CABG and/or AVR. Within these patients, overall 493 PPS episodes were identified. PPS was the primary, secondary, or tertiary cause of admission in 99.4% of the PPS cases and 0.6% were identified post-mortem. Median latency between the operation and PPS was 22 (12–49) days.

The predictors of PPS are detailed in Table 4. In the univariable analysis, younger age was associated with higher PPS occurrence. No differences were detected in sex distribution and CCI between patients with and without PPS. The occurrence of PPS was significantly higher after AVR, MVR, and ascending aortic surgery when compared to CABG. Urgent or emergency procedures were also associated with higher PPS occurrence. No significant differences in the rate of PPS were detected in patients with and without resternotomy.

Table 4. Predictors of PPS leading hospital admission or contributing to death. Modified from the original publication III, Table 2.

	Univariable Analysis		Multivariable Analysis	
	HR (95% CI)	**P-Value**	**HR (95% CI)**	**P-Value**
Age class		<0.001		0.006
18–40 years vs. ≥71 years	2.51 (1.56–4.04)	<0.001	1.61 (0.98–2.64)	0.062
41–50 years vs. ≥71 years	1.93 (1.38–2.69)	<0.001	1.77 (1.25–2.50)	0.001
51–70 years vs. ≥71 years	1.22 (1.00–1.48)	0.050	1.27 (1.03–1.55)	0.024
Female sex	1.06 (0.87–1.29)	0.566	1.04 (0.84–1.27)	0.744
Charlson Comorbidity Index (CCI)		0.739		0.833
Mild risk (CCI 1) vs. low risk (CCI 0)	1.00 (0.82–1.21)	0.965	0.93 (0.75–1.14)	0.698
Moderate risk (CCI 2) vs. low risk (CCI 0)	0.86 (0.63–1.16)	0.308	0.89 (0.66–1.21)	0.618
High risk (CCI ≥ 3) vs. low risk (CCI 0)	0.91 (0.63–1.32)	0.620	1.00 (0.68–1.46)	0.992
AVR (± CABG) vs. CABG	1.91 (1.54–2.36)	<0.001	1.97 (1.58–2.46)	<0.001
MVR (± CABG) vs. CABG	1.76 (1.33–2.32)	<0.001	1.62 (1.22–2.15)	<0.001
Aortic surgery (± AVR or CABG) vs. CABG	3.49 (2.63–4.63)	<0.001	3.06 (2.24–4.16)	<0.001
Urgent or emergency procedure	1.54 (1.16–2.05)	0.003	1.36 (1.00–1.83)	0.047
Resternotomy	1.37 (0.92–2.05)	0.127	1.24 (0.82–1.88)	0.299

AVR: aortic valve replacement; CABG: coronary artery bypass graft; CI: confidence interval; HR: hazard ratio; MVR: mitral valve replacement.

The Cox regression multivariable model identified AVR, MVR, and ascending aortic surgery as independent predictors of higher PPS occurrence when compared to CABG. Urgent or emergency procedure also increased the risk, whereas an advanced age decreased the risk of PPS after the multivariable adjustment. The cumulative rate of PPS stratified by operation type and the urgency of the procedure is detailed in Figure 8. The occurrence was equally higher in those undergoing AVR and MVR procedures when compared to those undergoing CABG, but clearly the highest occurrence appeared after aortic surgery. Concomitant CABG in valve and aortic procedures (HR 1.27, 95% CI 0.94–1.71, p=0.120), the use of LITA in CABG (HR 1.06, 95% CI 0.67–1.68, p=0.795), and the use of a mechanical valve in AVR (HR 1.26, 95% CI 0.89–1.79, p=0.192) had no effect on the occurrence of PPS.

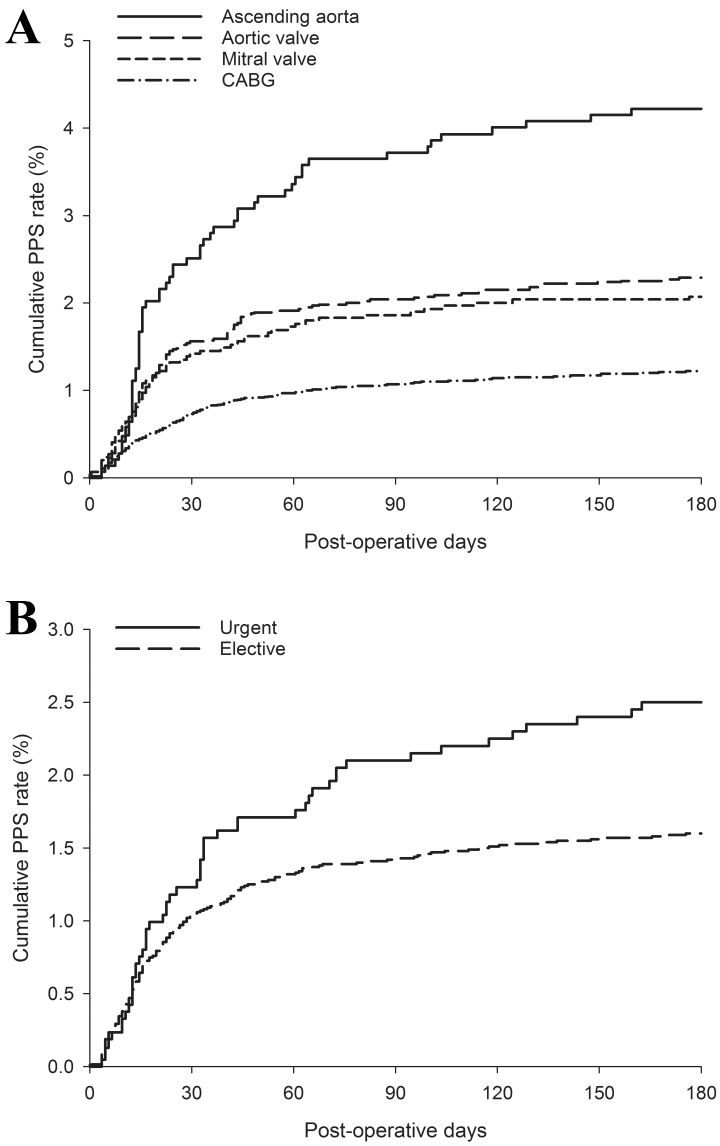


Figure 8. Cumulative PPS occurrence stratified by procedure type (A) and urgency of the procedure (B). From the original publication III, Figures 2B and C. CABG: coronary artery bypass grafting.

Overall 907 (3.2%) patients died within the first year after the surgery. The patients who died within the first 30 days after the surgery (244, 0.8%) were excluded from the mortality analyses to minimize the false-negative diagnoses of PPS. After the multivariable adjustment, PPS was associated with a 78% increase in the risk of death within the first year after the surgery. Survival after cardiac and ascending

aortic surgery in patients with and without PPS is detailed in Figure 9. Of the patients who died within the first year after the surgery, 10.5% had the diagnosis of PPS included in the death certificate. The mean delay between the initial PPS admission and death was 137±102 days. The causes of death in the patients who died within the first year after the surgery were similar between patients with and without PPS, with ischemic heart disease (ICD-10 codes I20-I25) being the most common cause of death.

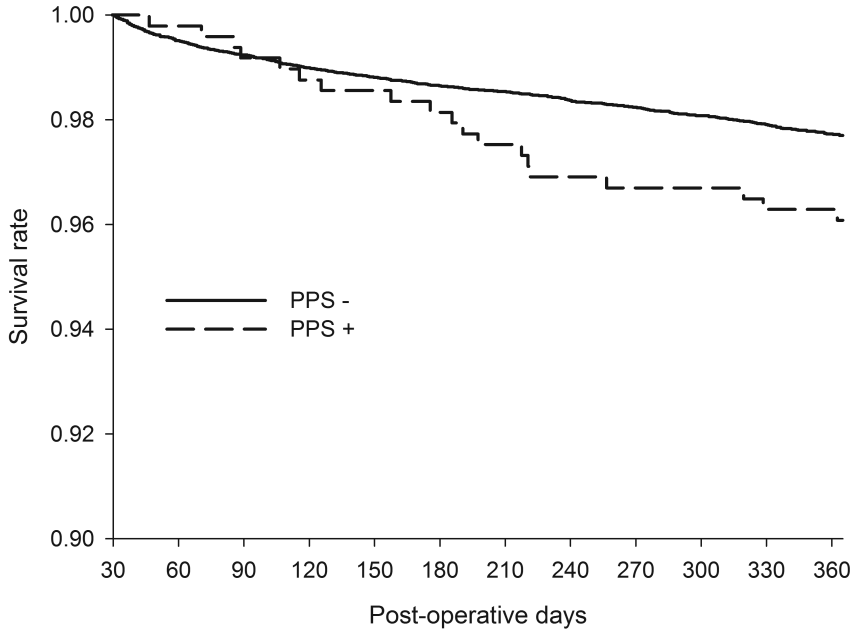


Figure 9. Survival after cardiac and ascending aortic surgery in patients with and without PPS. From the original publication III, Figure 3. Patients who died within the first 30 days after the surgery were excluded. PPS: postpericardiotomy syndrome.

5.4 Adverse events and mortality after moderate and severe PPS (study IV)

In the study IV, a total of 75 (11.2%) patients developed PPS leading to delayed hospital discharge, readmission, or medical therapy due to the symptoms. The median latency between the operation and PPS onset was 16 (11–36) days. PPS required the evacuation of pericardial effusion in 15 (20.0%) patients, the evacuation of pleural effusion in 11 (14.7%) and led to cardiac tamponade in 7 (9.3%) patients. Thus, the incidences of moderate and severe PPS were 51 (7.6%) and 24 (3.6%), respectively.

The baseline characteristics and in-hospital events in patients with and without PPS are detailed in table 5. Patients with PPS were more often male, were more often diagnosed with postoperative pneumonia, and underwent more frequently a reoperation due to valve problem during the index hospitalization. Male patients with PPS were significantly younger compared to their female counterparts (69.0 vs. 77.5 years, p=0.002), although no statistically significant interaction was detected (sex*age groups interaction p=0.493). The multivariable model identified male sex (HR 1.78, 95% CI 1.08–2.96, p=0.025) and pneumonia during the index hospitalization (HR 2.73, 95% CI 1.38–5.43, p=0.004) as independent predictors of PPS. No significant differences between patients with moderate and severe PPS were detected except that patients with severe PPS presented more often a history of permanent AF (20.8% vs. 2.0%, p=0.001) and heavy alcohol consumption (33% vs. 5.3%, p=0.039).

Table 5. Baseline characteristics and in-hospital events after isolated AVR in patients with and without PPS. From the original publication IV, Table 1.

	PPS N=75	***No-PPS N=596***	***P-value***
Age	72.0 (59.5–77.0)	70.0 (60.0–77.0)	0.887
Females	22 (29.3%)	272 (45.6%)	0.016
Diabetes	8 (10.7%)	89 (15.0%)	0.420
Dyslipidemia	42 (56.0%)	276 (46.5%)	0.134
Hypertension	55 (73.3%)	403 (67.6%)	0.351
Peripheral arterial disease	1 (1.3%)	19 (3.2%)	0.384
Coronary artery disease	21 (28.0%)	144 (24.2%)	0.522
Paroxysmal atrial fibrillation	7 (9.3%)	62 (10.4%)	0.578
Permanent atrial fibrillation	6 (8.0%)	54 (9.1%)	0.991
Chronic lung disease	10 (13.3%)	83 (13.9%)	0.969
Active Smoking	7 (11.7%)	58 (12.7%)	0.796
Active or ex-smoker	26 (44.1%)	171 (37.8%)	0.330
Body mass index (kg/m2)	26.7 (24.7–29.5)	27.5 (24.3–30.9)	0.757
Heavy alcohol consumption	4 (14.3%)	22 (9.0%)	0.392
Previous stroke	4 (5.3%)	31 (5.2%)	0.987
Previous myocardial infarction	6 (8.0%)	27 (4.5%)	0.359
Previous percutaneous coronary intervention	8 (10.7%)	47 (7.9%)	0.495
Previous cardiac surgery	2 (2.7%)	37 (6.2%)	0.317
Active endocarditis	3 (4.0%)	28 (4.7%)	0.878
Previous endocarditis	3 (4.0%)	17 (2.9%)	0.631
Previous venous thromboembolism	2 (2.7%)	11 (1.8%)	0.496
EuroSCORE II (%)	1.4 (0.9–2.1)	1.5 (0.9–2.4)	0.211
Pulmonary artery hypertension:			
Moderate to severe (systolic ≥31 mmHg)	13 (23.6%)	120 (29.0%)	0.500
Severe (systolic >55 mmHg)	3 (5.5%)	21 (5.1%)	0.754
NYHA Class III or more	34 (45.3%)	313 (52.5%)	0.343
Preoperative eGFR (mL/min/1.73 m²)	76.0±22.4	77.0±20.5	0.596
Urgent, emergency or salvage procedure	3 (4.0%)	64 (10.7%)	0.105
In-hospital events:			
New-onset atrial fibrillation*	27 (43.5%)	192 (40.1%)	0.635
Deep wound infection	1 (1.3%)	4 (0.7%)	0.496
Mediastinitis	0 (0.0%)	5 (0.8%)	0.995
Pneumonia	11 (14.7%)	30 (5.0%)	<0.001
Delayed ventilation	8 (10.8%)	70 (11.8%)	0.922
Acute de novo dialysis	1 (1.3%)	7 (1.2%)	0.778
Reoperation due to bleeding	9 (12.0%)	53 (8.9%)	0.295
Reoperation due to infection	1 (1.3%)	3 (0.5%)	0.340
Reoperation due to valve problem	2 (2.7%)	5 (0.8%)	0.045
Reoperation any	11 (14.7%)	59 (9.9%)	0.128
Length of hospital stay (days)	8.0 (7.0–13.0)	8.0 (7.0–10.0)	0.197

Continuous variables are reported as median (25^{th} – 75^{th} percentiles) or mean ± standard deviation (SD). Values in parentheses are percentages. EGFR: Estimated Glomerular Filtration Rate; EuroSCORE: European System for Cardiac Operative Risk Evaluation; NYHA: New York Heart Association; PPS: postpericardiotomy syndrome. * Patients with preoperative paroxysmal or chronic atrial fibrillation excluded.

No association was observed between PPS and all-cause mortality in the overall study cohort. However, severe PPS was associated with increased all-cause mortality (unadjusted analysis: HR 1.91, 95% CI 1.01–3.62, p=0.046; EuroSCORE II

-adjusted analysis: HR 2.06, 95% CI 1.08–3.95, p=0.029), whereas patients with moderate PPS had similar survival that of the patients without PPS (unadjusted analysis: HR 0.67, 95% CI 0.36–1.27, p=0.220; EuroSCORE II -adjusted analysis: HR 0.78, 95% CI 0.41–1.49, p=0.454). Survival after isolated SAVR in patients with severe and moderate PPS and in patients without PPS is detailed in Figure 10. The difference in mortality of the patients with severe PPS appeared within the first 24 months after the surgery, and the median time from PPS to death was 460 (83–1,300) days. Of the PPS patients who died within the first 24 months after the surgery (n=7), only one had PPS registered as the underlying cause of death and one as the intermediate cause of death. Pneumonia was registered as the immediate cause of death in half of the deaths, including the two deaths with PPS included in the death certificate.

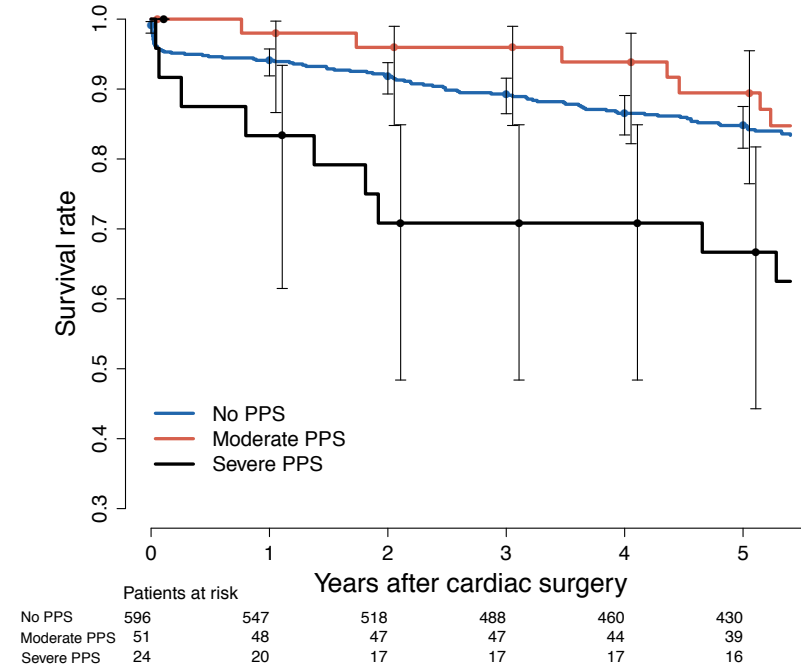


Figure 10. Survival after isolated SAVR in patients with moderate PPS (i.e., PPS not requiring the evacuation of pleural or pericardial effusion), patients with severe PPS (i.e., PPS requiring the evacuation of pleural or pericardial effusion), and patients without PPS. From the original publication IV, Figure 1. PPS: postpericardiotomy syndrome.

The Cox regression univariable and multivariable models of the impact of PPS on adverse outcomes are detailed in Table 6. PPS had no significant impact on the adverse events. However, in both univariable and multivariable analyses there was a nonsignificant trend towards higher occurrence of new-onset AF after hospital discharge in patients with PPS. As illustrated in the Figure 11, this effect appeared

within one month after the surgery. No significant associations were detected between severe PPS and the higher occurrence of new-onset AF after hospital discharge (HR 1.23, 95% CI 0.55–2.78, p=0.614), major stroke (HR 0.61, 95% CI 0.09–4.44, p=0.629), stroke or TIA (HR 0.34, 95% CI 0.05–2.46, p=0.287), or major bleeding (HR 1.67, 95% CI 0.61–4.54, p=0.318).

Table 6. The association of PPS and adverse outcomes after isolated SAVR. From the original publication IV, Table 2.

	Univariable analysis (PPS vs. no-PPS)		*Multivariable analysis (PPS vs. no-PPS)*	
	HR (95% CI)	***P-value***	***HR (95% CI)***	***P-value***
AF new onset	1.46 (0.97–2.19)	0.072	1.52 (0.95–2.45)	0.081
Major stroke	0.45 (0.14–1.43)	0.174	0.46 (0.14–1.48)	0.526
Stroke or TIA	0.60 (0.28–1.29)	0.188	0.63 (0.29–1.36)	0.432
Major bleeding	0.95 (0.49–1.82)	0.868	1.03 (0.53–2.00)	0.901
Death	0.99 (0.62–1.56)	0.989	1.13 (0.71–1.81)	0.361
Death (alive after 30 days)	1.06 (0.65–1.73)	0.816	1.16 (0.71–1.91)	0.498

AF: atrial fibrillation; CI: confidence interval; HR: hazard ratio; PPS: postpericardiotomy syndrome; TIA: transient ischemic attack.

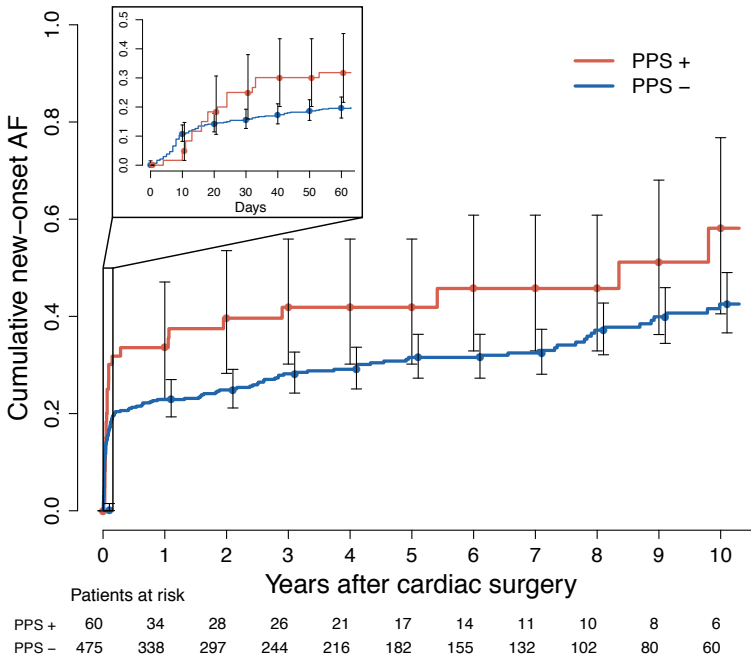


Figure 11. Cumulative new-onset AF occurrence after hospital discharge in patients with and without PPS. From the original publication IV, Figure 3. AF: atrial fibrillation; PPS: postpericardiotomy syndrome.

6 DISCUSSION

6.1 Incidence of PPS

The main finding of the study I was that the incidence of PPS requiring medical attention was markedly lower compared to the incidences reported in recent clinical trials (Imazio *et al.*, 2010, 2014c). The result was later confirmed by study IV presenting a similar incidence in a different patient population, therefore ruling out the possible dependency on operation type and patient population. This finding suggests that majority of the PPS diagnoses included in the previous prospective studies are clinically irrelevant.

In previous studies, the reported incidences have varied largely. This is most likely attributed to the lack of standardized diagnostic criteria until recent years (Adler *et al.*, 2015). It may also refer to improvements in surgical and CPB techniques (e.g., smaller bypass circuit and avoidance of cardiotomy suckers) or changes in blood transfusion protocols and blood conservation strategies (Brand, 2000). However, these changes cannot explain the discrepancy between the studies during the last few decades.

The standardized criteria for PPS were first published in the year 2015 (Adler *et al.*, 2015). The criteria included significant changes compared to, for instance, the criteria proposed a few years earlier by Imazio *et al*. (Imazio *et al.*, 2013c). The most important change was the removal of time limit from the criterion "fever without alternative causes". Either a one-week or a 24-to-72-hour limit has been included in the diagnostic criteria in majority of the previous PPS studies, including the recent COPPS trial (Imazio *et al.*, 2010). In the COPPS-2 trial, however, the time limit was discarded (Imazio *et al.*, 2014c). As can be observed in the survival plots of the COPPS and COPPS-2 trials, the inclusion of fever without a time limit results in a markedly higher incidence of PPS during the first days after the surgery. Another important change in the criteria recommended by the ESC guideline was the removal of the subcomponent "new or worsening" from the criterion "evidence of pericardial effusion" as well as from the criterion "pleural effusion with elevated CRP" (Adler *et al.*, 2015).

Fever early in the first postoperative week is virtually universal and in most cases remains for several days after the surgery (Livelli *et al.*, 1978). It is usually caused by complement activation by CPB, early stasis atelectasis, and sensitivity reactions to drugs, transfusions, etc. (Gay, 2004). Pleural effusions are also a very common finding in the immediate postoperative period. The effusions may results from a variety of reasons related to the postoperative state, including atelectasis following

diaphragm dysfunction, hemorrhagic effusions following internal mammary artery harvesting, congestive heart failure, decreased chest wall compliance, pulmonary embolism, and pneumonia (Heidecker *et al.*, 2006). According to Kaminsky *et al*., benign, surgery-related pleural effusions appear in 50% of the patients without PPS within the first 3 postoperative days (Kaminsky *et al.*, 1982). Furthermore, small pericardial effusions during the time of discharge are also a common finding in patients without PPS (Heching *et al.*, 2015). Considering the non-specificity of the diagnostic criteria, the explanation for the variability in the PPS incidences between previous studies is obvious. If one evaluates patients critically, most patients with cardiac trauma will meet the criteria for PPS. There is probably a continuum of responses to post-cardiac trauma ranging from mild fever and pericardial effusion to a complete syndrome with intermittent fever, notable pericardial and/or pleural effusion, and pleuritic chest pain.

In prospective trials, the detection of the benign, surgery-related findings is extremely sensitive because the follow-ups are mostly performed by PPS researchers. If the diagnostic criteria of the ESC guideline (Adler *et al.*, 2015) are interpreted without criticism, this will result in an erroneously high incidence of PPS. Although the criteria have been slightly different compared to the ones currently recommended, it is likely that a large part of the PPS diagnoses included in recent prospective trials are a result of the process ahead. This process also allows the diagnosing of asymptomatic pericardial and pleural effusions as PPS. This is possible even if the demonstration of inflammatory activity is required for the diagnosis because of the high frequency of fever and inflammatory marker rise during the postoperative era. It is questionable, whether a completely asymptomatic patient fulfills the classic definition of a postpericardiotomy "syndrome". In the studies I and IV, these borderline cases were excluded due to the "clinically relevant" requirement, consequently leading to more usable risk factors in clinical practice.

During the first decade after the discovering of PPS, patients were considered to have the disease if they were toxic and extremely enervated (Gore, 1960). In the past decades, however, the inclination of research has intentionally focused more and more on the sensitivity of the diagnosing of PPS (Imazio, 2012), also reflecting in the current guideline-recommended diagnostic criteria. It would presumably be more objective and specific to use the criteria introduced by Bunge *et al*.: at least two of the following: 1) new significant (>10 mm) pericardial effusion on echocardiography, 2) new significant (above the highest level of the diaphragm) pleural effusion on chest x-ray, 3) unexplained fever >72 hours postoperatively, 4) pleuritic chest pain, and 5) the presence of pericardial or pleural rubbing on physical examination (Bunge *et al.*, 2014). This would likely discard the early post-traumatic effusions and enable the separation of the patients with the "classic" im-

mune-mediated PPS. An even more sophisticated approach would be the one introduced by De Scheerder *et al*. (De Scheerder *et al.*, 1984, 1985b, 1986, 1991), including the concepts of "complete PPS" and "incomplete PPS". The integration of the two aforementioned methods would allow the comparison of the most certain positive PPS patients with the most certain negative PPS patients. This is particularly important in the studies assessing the pathophysiological mechanisms of PPS, as it is uncertain whether the borderline PPS cases, especially the ones within the first few days after the surgery, share the same pathophysiological mechanism with the delayed, more certain cases. The hypothesis of two separate mechanisms is strengthened by the fact that although colchicine is effective in the prevention of PPS, it does not seem to be effective in the treatment of early postoperative pericardial effusions (Izadi Amoli *et al.*, 2015; Meurin *et al.*, 2015).

6.2 Predictors of PPS

The study I provided evidence that patients receiving red blood cells during the periprocedural period are at a higher risk for PPS. This effect did not appear to be connected to the number of red blood cell units transfused but to the overall use. Only two previous studies have investigated the frequency of blood product transfusions in PPS patients (Maisch *et al.*, 1979; van Osch *et al.*, 2017a). In line with the study I results, in both studies, patients with PPS received more blood transfusions during the periprocedural period, although not reaching statistical significance in the study by van Osch *et al*. (transfusion of ≥ 2 units packed red cells 23.1% vs. 17.0%, p=0.09). The effect of blood products may be associated either to the immunological aspects related to blood transfusions themselves or to the greater amount of perioperative bleeding. Transfusions of red blood cells stimulate IL-8 gene expression in neutrophils (Escobar *et al.*, 2007) which may induce inflammation. Moreover, PPS has been previously associated with lower preoperative IL-8 concentrations (Jaworska-Wilczyńska *et al.*, 2014) and higher postoperative IL-8 concentrations (Snefjellå *et al.*, 2012) suggesting the participation of IL-8 in the pathogenesis of PPS. On the other hand, pericardial bleeding is one of the previously presumed triggers for the syndrome (Imazio, 2012), and it also plays a central role in the recently established concept of retained blood syndrome (RBS) (Boyle *et al.*, 2015). Besides, in the study I, there was a nonsignificant trend towards more postoperative bleeding in patients with PPS. Therefore, the latter mechanism seems the most logical, although there is also a possibility of the two aforementioned mechanisms having a combined influence on the development of PPS.

In the study I, diabetes was found to be a protective factor for PPS. In the study IV, however, no significant association was detected, although a nonsignificant trend towards lower diabetes incidence within PPS patients was observable. The previous studies have reported inconsistent results concerning the effect of diabetes. Contrary to the results of the study I, Imazio *et al*. reported a nonsignificant trend towards higher diabetes rate within PPS patients (28% vs. 23%, p=0.390). However, the data consisted of the patients of the COPPS trial that includes cardiac surgeries for any reason. Diabetes is a commonly known, extremely potent risk factor for numerous cardiac diseases, especially coronary artery disease (Oktay *et al.*, 2018). Therefore, the evaluation of the influence of diabetes is complicated in settings including a wide variety of different procedure types. In a study by van Osch *et al*., a nonsignificant trend towards lower diabetes rate in PPS patients was noticeable (10.9% vs. 14.2%, p=0.79) (van Osch *et al.*, 2017a). The study included only patients undergoing valve procedure with or without concomitant CABG, resulting in a more restricted patient population compared to the COPPS trial. Overall, although needing further confirmation, it seems that while diabetes has somewhat of a protective influence against PPS in valve procedures, the protection is markedly more efficient in patients undergoing CABG.

Diabetes and the obesity often related to it are known to lead to a proinflammatory state via numerous pathways as well as maladaptive immune responses (Oktay *et al.*, 2018). It is therefore unlikely that diabetes itself would protect against PPS. After going through the diabetes medications, metformin appeared to be the protective factor for PPS, although all the other medications also had a nonsignificant trend towards lesser PPS frequency. According to previous studies, high-dose metformin potentiates lymphocyte-suppressing and systemic anti-inflammatory effects of simvastatin and fenofibrate in patients with early glucose metabolism abnormalities (Krysiak *et al.*, 2012, 2013). Therefore, it seems probable that the protective effect of diabetes is mediated by metformin treatment, although further studies are needed to ensure the finding and possibly to evaluate the effect in patients without diabetes. Moreover, considering the existing literature, patients undergoing CABG seem to be more sensitive for the possible PPS-protective effect of the drug.

The study II showed that the rate of PPS in relation to the number of performed operations was significantly higher among women and younger patients. These results confirmed the previously reported associations between PPS and younger age (Drusin *et al.*, 1965; Engle *et al.*, 1980; Engle, 1982; Köhler *et al.*, 2003) as well as PPS and female gender (Larson, 1957; Webber *et al.*, 2001; Imazio *et al.*, 2011b). It has been previously suggested that the female predominance might reflect the different predisposition to autoimmune pathogenesis, as it is known that women are more susceptible to a variety of autoimmune diseases (Voskuhl, 2011)

possibly due to the effects of sex hormones on the immune system, genetic factors, and sex-specific behaviors and exposures (Gubbels Bupp, 2015). Even though the study II presented no statistically significant interaction between sex and age, the high incidence of PPS within women at the age group 40–49 years jumped out of the overall pattern (Figure 7). This could be explained by the hormonal changes related to menopause. In the study III, however, no significant association between PPS and sex was detected. The exclusion of complex combination procedures in the study III could possibly account for the discrepancy. A previous prospective study identifying female sex as an independent risk factor for PPS also included patients undergoing cardiac surgery for any reason (Imazio *et al.*, 2011b). It is therefore possible that the effect of female sex is mediated by differences in procedure types, possibly by complex combination procedures in female aged 40–70 years. Surprisingly, in the study IV, male sex was identified as an independent predictor of PPS. Male patients with PPS were, however, significantly younger compared to their female counterparts, even though the interaction analysis showed no significant interactions between age groups and sex. Regardless of the negative result, it is possible that the impact of male sex is indirect and due to differences in the age distributions of PPS patients in combination with the differences in procedure types. This hypothesis is strengthened by the fact that in the study IV only 1.0% of the female patients were 40–49 years of age which, according to the study II, is the group with the highest difference in PPS occurrence between sexes. Overall, the effect of sex still remains somewhat unclear and needs further clarification.

Although the studies II and III presented conflicting results of the effect of female sex, the results considering the effect of younger age were consistent in both studies. While the overall incidence of autoimmune diseases increases with age (Gubbels Bupp, 2015), different autoimmune diseases can affect a specific age group predominantly (Ramos-Casals *et al.*, 2015) which could possibly explain the higher occurrence of PPS within younger patients. Considering the hypothesis of viral participation in the pathogenesis of PPS, aging leads to less frequent exposure to viral infections because of the alterations in the mode of life. Moreover, acquired protection due to the many years of exposure to viral illnesses may lead to the lesser PPS frequency with aging. It has been also discussed that the immunosenescence related to aging might decrease the capability of mounting an immune response against the intrapericardial trauma and possible exposure to viruses in the hospital (Engle, 1982). In particular, the aging-related activity reduction of T and B cells might play a central role in the aforementioned mechanism (Simon *et al.*, 2015).

The study III implicated that the incidence of PPS is markedly higher in those undergoing AVR, MVR, and aortic procedures when compared to patients undergoing CABG. Overall, previous studies have identified higher PPS occurrence after tetralogy of Fallot and VSD plus some other anomaly procedures compared to ASD, VSD only, TGA, and pulmonic stenosis procedures (Engle *et al.*, 1980), valve replacement operations compared to CABG (De Scheerder *et al.*, 1984, 1991), and AVR compared to other open-heart operations (Miller *et al.*, 1988; Gabaldo *et al.*, 2019). Combination procedures have been also associated with the higher incidence of PPS, although it did not reach statistical significance in the multivariable analysis (Imazio *et al.*, 2011b). In addition, mitral valve replacement has been associated with lower PPS occurrence (Miller *et al.*, 1988). Nevertheless, a more recent study reported a significantly higher PPS frequency after mitral valve surgery compared to other valve procedures in the univariable analysis (van Osch *et al.*, 2017a). Considering the results of the study III and the previous literature, more traumatic procedures seem to be related to the higher incidence of PPS. The effect is presumably mediated by more extensive pericardial trauma rather than myocardial trauma, as the degree of myocardial injury, at least assessed by circulating cardiac enzymes and sarcomeric proteins, seems to be unrelated to the occurrence of PPS (Nomura *et al.*, 1994). These findings support the previously presumed mechanism of direct pericardial trauma acting as a trigger for the immune-mediated process leading to PPS. That being said, it needs to be kept in mind that the syndrome can appear also after exploratory pericardiotomies in whom no further surgical procedures are attempted (Ito *et al.*, 1958). According to previous literature, isolated valve procedures present lower postoperative bleeding within the first 12 hours after the operation compared to CABG procedure (Ranucci *et al.*, 2009). Therefore, pericardial bleeding alone is unlikely to be responsible for the higher occurrence of PPS after valve procedures, although it may still play a role in the pathophysiological mechanism of PPS. Besides the more extensive pericardial trauma, a more complex procedure usually means longer time in CPB (Salis *et al.*, 2008) and longer pericardial exposure to air and other unphysiological materials. These hypothetical causative factors should be investigated in further research to evaluate their participation in the pathophysiology of PPS.

Besides the pathophysiological considerations, the determination of the risk factors predisposing to PPS is crucial to provide effective targeting of possible preventive strategies minimizing the number of adverse events related to the methods used. According to the present results and previous literature, younger patients entering valve or ascending aortic procedure and the patients receiving blood product transfusions due to the perioperative bleeding would be the best targets for the prophylactic methods. In addition, the methods might be considered in women aged 40–49 years. However, if the patient has metformin medication for diabetes

and is undergoing CABG, the risk of PPS is low and thus no prophylactic methods are needed.

6.3 Etiology of PPS

The results of the studies I–IV are consistent with the hypothesis of immune-mediated process being behind the pathogenesis of PPS. Furthermore, the higher occurrence of the syndrome after more extensive procedures and more periprocedural bleeding supports the view that pericardial trauma and pericardial bleeding act as triggers for the immune reaction. However, the role of perioperative and latent viral infections and perioperative exposure to air and other nonphysiological materials still remains obscure. The proposed pathogenesis of PPS, according to the present results and previous literature, is detailed in Figure 12. The pleuropericardial trauma leads to the release of antigens, including most likely at least actin, myosin, troponin I and T, tropomyosin, and branched chain alpha-ketoacid dehydrogenase dihydrolipoyl transacylase (BCKD-E2) (Wehlou *et al.*, 2009). The reaction against the released antigens may be mediated by two possible mechanisms: 1) the pericardium and pleura are immunologically privileged spaces, and once the antigens release, they become autoreactive, or 2) the exposure of the pericardium and pleura to exogenous factors, such as concurrent viral infections or air, lead to the denaturation of the released proteins so that they become "foreign" material and thus induce the production of autoantibodies. The production of the autoantibodies leads to a hypersensitivity reaction mediated by either direct antibody-mediated (AHA) reaction, cell-mediated autoreactive reaction, or complement cascade activation. This delayed hypersensitivity reaction involves the epicardial layer of the pericardium, often accompanied with the "neighbourhood" involvement of the pleura even if the pleural space was not entered during the surgery. The early pericardial effusions, typically appearing within the first days after the surgery, are a result of pericardial bleeding and posttraumatic effusions. Thus, no immune-mediated reaction is required for their development. However, if the blood effusions retain, it may lead to clot formation releasing thrombin and fibrin. These products act as chemoattractants either strengthening or inducing the hypersensitivity reaction via the increased release of inflammatory cytokines from the mesothelial cells of the pericardium and pleura. Blood product transfusions may also contribute to the chemotactic response via the stimulation of IL-8 gene expression in neutrophils.

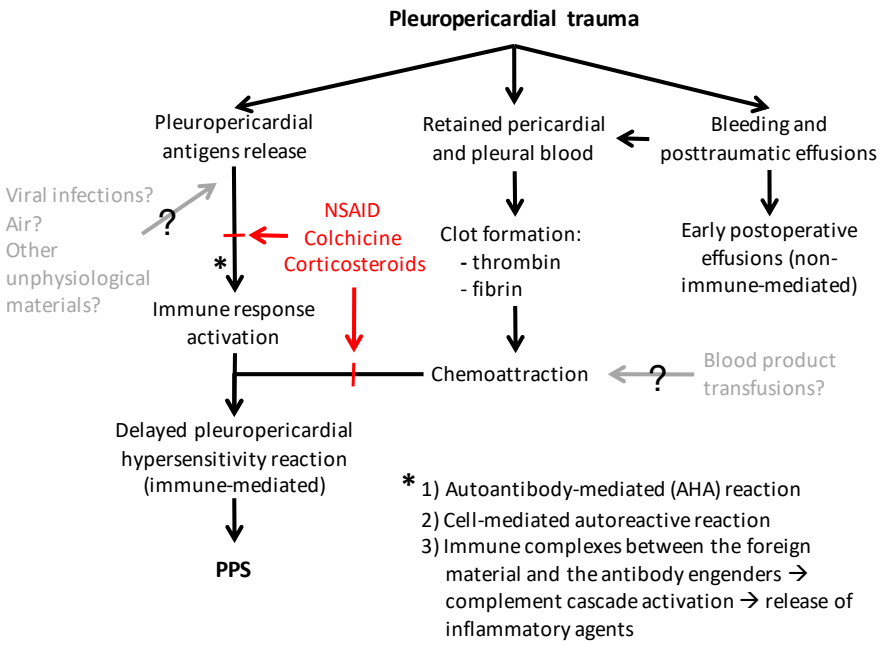


Figure 12. Proposed pathogenesis of PPS. Artwork by Joonas Lehto. AHA: anti-heart antibody; NSAID: non-steroidal anti-inflammatory drug; PPS: postpericardiotomy syndrome.

The pharmacological actions of the medical therapies of PPS, especially colchicine, closely intertwine with the presumed pathophysiological mechanism of PPS. The main effects of the medical therapies are most likely mediated by two different pathways: 1) the inhibition of the immune response activation against autoantigens and 2) the inhibition of the chemoattraction induced by the clot formation products and possibly by blood product transfusions. Even though the exact mechanism of colchicine action is not fully understood, most of the effects on inflammatory cells appear to be related to its capacity to disrupt microtubules. This leads to the downregulation of multiple inflammatory pathways and the modulation of innate immunity. One of the main effects of colchicine is the reduction of neutrophil-mediated immune reaction via, inter alia, the inhibition of neutrophil chemotaxis, adhesion, mobilization, recruitment, and superoxide production. Other important effects include macrophage downregulation and thus the modulation of innate immune response (Leung *et al.*, 2015). The therapeutic and preventive effects of colchicine are largely related to its rapid redistribution to leukocytes, as the disruption of microtubules is dose-dependent (Molad, 2002).

6.4 Relapses of PPS

In the study I, overall 38% of the PPS patients had a relapse defined by worsening of pericardial or pleural effusion while on medication or after the withdrawal of medication. In the study IV, the relapse rate was markedly lower (16%). PPS patients of the study IV were more often treated with glucocorticoids (64% vs. 43%) and less often with NSAIDs (5% vs. 23%). Therefore, the possible increased recurrence rate related to glucocorticoid treatment (Artom *et al.*, 2005; Imazio *et al.*, 2005a, 2005b, 2005c, 2013b; Adler *et al.*, 2015) is unlikely to explain the difference between the studies. In previous studies, the recurrence rates have varied between 4% and 21% (Drusin *et al.*, 1965; Nishimura *et al.*, 1983; Imazio *et al.*, 2011b). The higher recurrence rate especially in the study I is most likely related to the fact that only more severe PPS cases, referring to the PPS cases requiring medical attention, were included. However, it does not explain the difference between the studies I and IV. It therefore appears that patients undergoing isolated AVR are at lower risk of PPS recurrences compared to CABG, most likely due to the numerous baseline differences between the populations.

6.5 Prognosis of PPS

Although PPS is known to cause prolonged hospital stay, readmissions, and invasive interventions, the prognosis of the syndrome has been considered to be benign (Bucekova *et al.*, 2012; Imazio *et al.*, 2013d; Adler *et al.*, 2015). However, this perception has been mainly based on clinical experience rather than adequate epidemiological studies. Only one previous study has evaluated the mortality of PPS patients (van Osch *et al.*, 2017a). In the aforementioned study, patients with PPS represented an excellent 1-year prognosis (1-year mortality 4.2% vs. 5.5%, p=0.497). However, the study included only 119 patients with PPS and fewer patients with complete follow-up for death, of whom only 4 died within the first year after the surgery (expected value 5). Therefore, no clear conclusions can be driven from these results.

The study III provided evidence that PPS is associated with a >1.7-fold increase in the risk of death within the first year after the index surgery. None of the causes of death was overrepresented in patients with PPS who died within the first year after the surgery. Instead, the patients had an equal rise in all causes of death which from ischemic heart disease was the most common. The study IV further evaluated the reasons for the higher mortality. Severe PPS was found to be associated with a twofold all-cause mortality while moderate PPS presented similar survival to that of patients without PPS (Figure 10). Of the severe PPS patients who died within

the first 24 months after the surgery (n=7), only one had PPS registered as the underlying cause of death and one as the intermediate cause of death. Again, the underlying cause of death was often registered as atherosclerotic heart disease or aortic valve stenosis. Pneumonia was registered as the immediate cause of death in half of the deaths, including the two deaths with PPS included in the death certificate. In both the study III and IV, the incremental deaths appeared with a delay of several months after the syndrome. Therefore, a direct link to the hemodynamic problems caused by the syndrome was unlikely.

According to the results of the study IV, the increased mortality associated with severe PPS is unlikely to be related to new-onset AF, cerebrovascular events, or major bleeds. Considering the safety of the medical treatment for PPS, colchicine has no significant effect on the overall mortality (Imazio *et al.*, 2014c, 2014a). The effect of short-term corticosteroids on mortality in the presence of heart disease is poorly documented. Although long-term use of high-dose corticosteroids is associated with an increased risk of cardiovascular disease and mortality (Wei *et al.*, 2004), the effect appears within several years rather than months (Ajeganova *et al.*, 2014) and in high cumulative exposure (Davis *et al.*, 2007; del Rincón *et al.*, 2014). The use of NSAIDs is also associated with myocardial infarctions and higher mortality attributable to coronary heart disease (Coxib and traditional NSAID Trialists' (CNT) Collaboration *et al.*, 2013), but the effect is insignificant in therapies with a length of <1 month (García Rodríguez *et al.*, 2008), which is typical in the treatment of PPS. Therefore, the medical therapies for PPS are also unlikely to be responsible for the higher mortality.

Given the results of the studies III and IV, the higher mortality is most likely caused by the incremental disease burden of PPS and its sequelae, and especially the required interventions. It seems unlikely that PPS itself is the cause of the incremental deaths after cardiac surgery. Instead, PPS is likely to complicate previously weak and vulnerable patients, thus increasing mortality with a delay. However, even though the relationship with the underlying immunological changes caused by or resulting in PPS seems unlikely, further studies are needed to rule it out completely.

The association with an increased mortality supports the use of relatively aggressive prophylactic methods to prevent PPS. Therefore, for example, the increased risk of gastrointestinal adverse effects of colchicine should not be interpreted as an insuperable obstacle for the preventive use of the drug. According to the present results, the one-month colchicine prophylaxis, also recommended for consideration in the ESC Guideline (Adler *et al.*, 2015) (class IIaA recommendation), should be adopted in the current clinical practice. If necessary, the preventive treatment could be targeted to the patients in the highest risk of developing PPS, as detailed

above. It needs to be taken into consideration, however, that the evidence of whether the preventive therapies diminish the risk of mortality is lacking (Imazio *et al.*, 2014c). Nevertheless, the adoption of the prophylactic colchicine treatment would also allow the execution of large epidemiological studies evaluating the effect of the drug on mortality in long-term follow-up.

Considering the other complications related to PPS, only one patient had PPS leading to clinical cardiac tamponade in the study I. In the study IV, however, altogether 7 patients had PPS leading to tamponade resulting in a notably higher incidence of tamponade compared to the study I (9.3% vs. 1.6%). PPS required the evacuation of pericardial effusion in 20.0% and 4.9% and the evacuation of pleural effusion in 14.7% and 22% of the PPS patients in the studies IV and I, respectively. It therefore appears that although AVR patients experience less PPS recurrences, the syndrome itself is more severe compared to after CABG procedure. This conclusion is supported by the study by van Osch *et al*. including patients undergoing valve procedures, in which PPS patients had an over 15-fold risk of reoperation for all-cause tamponade within the first year after the surgery (20.9% vs. 2.5%). In the study by Imazio *et al*., the incidence of PPS-related tamponade was 1.9% after cardiac surgery for any reason (Imazio *et al.*, 2011b). However, half of the patients were receiving prophylactic colchicine potentially affecting the number of adverse events related to PPS. Delayed cardiac tamponade, referring to tamponade after the first postoperative week, has been reported to occur in 0.8–1.3% of PPS patients (Bortolotti *et al.*, 1981; Ofori-Krakye *et al.*, 1981).

The study IV provided evidence that PPS is not associated with major stroke, stroke or TIA, or major bleeding episodes. Importantly, PPS did not have a significant impact on the occurrence of new-onset AF during long-term follow-up. However, patients with PPS had somewhat (although nonsignificant) higher occurrence of new-onset AF within the first month after the surgery (Figure 11). It is therefore possible that the pericardial irritation caused by PPS provokes AF paroxysms during the first months after the surgery, but the effect is most likely transient. This result is consistent with the few previous studies assessing the impact of PPS on new-onset AF (Papp *et al.*, 1956; van Osch *et al.*, 2017a). Only one study has reported a significant association between PPS and POAF (Sevuk *et al.*, 2016a), but because of the multiple baseline differences between the study groups and the strikingly high PPS occurrence, these results cannot be considered reliable. The previous knowledge concerning other adverse events related to PPS is limited to a single study (van Osch *et al.*, 2017a). In line with the study IV results, van Osch *et al*. found no significant associations between PPS and stroke or reoperation for surgical bleeding. Also, PPS had no significant impact on the incidence of myocardial infarctions or readmissions (any reason) within one year or the incidence of pleural punctures performed within one month after the surgery.

The study IV introduced the concepts of moderate and severe PPS. The higher mortality in severe PPS patients supports the view that severe PPS should be considered as an end point in the future clinical trials. In addition, the classification into the subgroups might be useful in the treatment of PPS patients, as it reflects the prognosis of the patients. Patients with moderate PPS can be safely treated with symptomatic therapies in the outpatient clinics, while severe PPS patients require more intensive follow-up and treatment.

6.6 Strengths and limitations

The present research offers novel findings concerning the risk factors and prognosis of PPS. All of the studies only include the PPS cases severe enough to require medical attention making the results more clinically relevant and usable in practice. The study I includes numerous unexplored risk factors for PPS and factors that have only been investigated in small studies. The studies II and III are the largest studies concerning PPS to date and the first studies to offer epidemiological nationwide data. Moreover, the study III is the first study large enough to provide adequate evidence concerning the prognosis of PPS. In addition, before the study IV, the possible adverse events related to PPS have been only investigated in single studies.

The main limitation of the studies I–IV, apart from the prospective CAREBANK data included in the study IV, is the retrospective nature of the data. The small size of the studies I and IV is another limitation. Therefore, the results should be considered as hypothesis-generating except for mortality increase seen in both nationwide material and multicenter setting. Also, all tests leading to the diagnosis of PPS (e.g., chest x-ray and echocardiography) were not performed in every patient, so the underdiagnosing of asymptomatic PPS is conceivable. Nevertheless, the tests were performed as clinically indicated, reflecting the “real world” feature of the studies.

Although the studies II and III included all hospitals that perform cardiac operations in Finland, in addition to all central hospitals and largest regional hospital nationwide, it is possible that some of the PPS patients were treated in the smaller regional hospital not included in the data collection. Also, only patients admitted to a hospital were included. Because patients with mild symptoms can be treated at outpatient clinics, they were not included in these studies. Besides, there is also a possibility of underdiagnosing in the presence of one or few mild PPS-related symptoms, when the physician treats the symptoms (e.g., by anti-inflammatory medications), but the exact PPS diagnosis is not set. Therefore, the results can be directly applied only to PPS cases severe enough to result in hospital admission.

In both the studies II and III, the treating physicians made the diagnoses. Ideally, this would mean better differential diagnostic procedures and more certain diagnoses. However, the lack of nationwide criteria was unavoidable, because there were no standardized criteria for the syndrome until 2015 (Adler *et al.*, 2015). It is also possible that the assignment of PPS diagnosis became disturbed in the presence of other more dominant conditions, such as stroke or death. This would, however, only further strengthen the conclusion of increased mortality observed in the study III.

6.7 Future aspects

In the studies presented, we have explored the incidence, risk factors, and prognosis of medically relevant PPS using multiple research methods and populations. We have also brought out the problems in the currently recommended diagnostic criteria and recent prospective trials. As the etiology of PPS still remains uncertain, there is a need for further studies concentrating especially to the immunopathological mechanisms leading to the onset of the syndrome. However, these investigations should be focused on comparing the most certain or severe PPS cases to the ones without any significant signs of the syndrome. This would allow the more specific investigation of the "classic" immune-mediated PPS and hence the pathophysiology could be eventually unraveled. To achieve this and to reduce the heterogeneity between future studies, the currently recommended diagnostic criteria for PPS should be reconsidered. Moreover, future clinical trials assessing the prophylactic methods to prevent PPS should include severe PPS, referring to PPS requiring invasive interventions, as a separate endpoint to better evaluate the prognostic value of, i.e., the prophylactic administration of colchicine. This more pragmatic approach enables the improvement of patient care and recovery and the identification and avoidance of the factors leading to higher mortality.

7 CONCLUSIONS

The following conclusions may be drawn from the present investigation:

PPS has no significant impact on the occurrence of new-onset AF, cerebrovascular events, or major bleedings. Nevertheless, severe PPS, defined as PPS requiring the evacuation of pericardial or pleural effusion, is associated with higher all-cause mortality within the first 24 months after the surgery. These patients are in need of more intensive follow-up and treatment.

The incidence of PPS requiring medical attention is markedly lower compared to the incidences in earlier reports implicating that most of the diagnoses included especially in the recent prospective trials are clinically irrelevant. Therefore, the currently recommended diagnostic criteria need to be reconsidered and clarified.

PPS is more common in younger patients, in patients receiving blood product transfusions due to the perioperative bleeding, and after more traumatic procedures. These patients would be the best targets for the prophylactic methods against the syndrome. In addition, female sex is associated with higher PPS occurrence, although the effect seems to be procedure- and/or age-dependent. Diabetes, potentially mediated by the metformin treatment, is a protective factor against PPS especially in CABG procedures reducing the need for the disease prophylaxis.

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