INFLAMMATION RELATED CARDIAC COMPLICATIONS OF HEART SURGERY

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INFLAMMATION RELATED CARDIAC COMPLICATIONS OF HEART SURGERY

INFLAMMATIE GERELATEERDE CARDIALE COMPLICATIES VAN HARTCHIRURGIE

(met een samenvatting in het Nederlands)

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Dirk van Osch

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te Naarden

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Chapter 1

GENERAL INTRODUCTION

Cardiac surgery is among the most frequently performed surgical procedures in the developed world, and the numbers are expected to increase over the next decade, mainly due to the increasing and aging population (1). Cardiac surgery carries a substantial risk of postoperative complications and mortality. Major postoperative complications include myocardial infarction, stroke, renal failure and respiratory failure, with reported incidences ranging from 1-10% (2, 3). The incidence of overall hospital mortality after cardiac surgery was 3.9% in 2010, compared to 4.6% in 1995, despite a higher risk profile of patients who were operated in 2010 (older patients with more comorbidity). This reduction is the result of significant improvements both in cardiac surgical/anesthetic techniques and in perioperative patient care (4, 5). However, despite these improvements, the incidence of major postoperative complications still remains relatively high.

The inflammatory response after cardiac surgery

The systemic inflammatory response is an important contributor to the risk of postoperative complications after cardiac surgery. The use of cardiopulmonary bypass (CPB), where blood is exposed to artificial material, leads to activation of the systemic inflammatory response, in which both the humoral and cellular components of the immune system are activated. Ischemia-reperfusion injury, the surgical trauma, and perioperative transfusions of blood products are among factors that further contribute to the magnitude of the inflammatory response (6). The severity of the inflammatory response varies significantly between individuals. In some patients inflammation only presents as fever and leucocytosis, while in other patients it may lead to a systemic inflammatory response syndrome (SIRS), which may predispose the patient to serious postoperative complications such as myocardial dysfunction, atrial fibrillation (AF), post pericardiotomy syndrome, bleeding disorders, respiratory failure, renal dysfunction, neurologic dysfunction, liver dysfunction, vasoplegia and multiple organ failure (7, 8).

Corticosteroids to attenuate the inflammatory response

Since the 1960s, it has been hypothesized that prophylactic pharmacologic treatment with corticosteroids, to attenuate the inflammatory response after cardiac surgery, could reduce postoperative complications. Since that time, many small studies (both randomized and observational) have investigated this question. The studies mainly investigated surrogate endpoints (biochemical markers of inflammation) and showed that corticosteroids are potent inhibitors of the systemic inflammatory response that is associated with cardiac surgery (9). Until recently however, studies were never powered to investigate the protective effect of corticosteroids on important clinical endpoints such as mortality because of limited sample sizes (ranging from 13-295 patients). Furthermore, all studies investigated different types of corticosteroids, in variable dosages and with varying moments of administration. Because of this heterogeneity between studies, an adequately powered randomized controlled trial was needed in order to investigate the protective effect of corticosteroids on clinical important endpoints (10).

The first large trial on this subject, the DExamethasone for Cardiac Surgery (DECS) trial, was published in 2012. The DECS trial was a multicenter, randomized, double-blind, placebo-controlled trial of a single intraoperative dose of 1 mg/kg dexamethasone in 4,494 patients undergoing

cardiac surgery with use of CPB. The DECS trial showed no protective effect of dexamethasone on the primary outcome, which was a composite of death, myocardial infarction, stroke, renal failure or respiratory failure, within 30 days after randomization. However, the study found a reduction in the incidences of respiratory failure and pneumonia, and a shorter duration of postoperative mechanical ventilation, Intensive Care Unit (ICU) and hospital stay, suggesting an improved postoperative pulmonary outcome (2).
In 2015, the second large trial concerning this subject was published; the Steroids In caRdiac Surgery (SIRS) trial. The SIRS trial was a multicenter, randomized, double-blind, placebo-controlled trial comparing methylprednisolone (500 mg in total) with placebo treatment in 7,507 patients undergoing cardiac surgery with use of CPB. Besides the use of a different drug, the main difference between the SIRS and DECS trials was the fact that the SIRS trial only included high-risk patients (EuroScore ≥ 6). The SIRS trial showed no protective effect of methylprednisolone on the two co-primary outcomes, which were 30-day mortality and a composite of death, myocardial injury, stroke, renal failure or respiratory failure within 30 days after cardiac surgery. However, patients treated with methylprednisolone had an increased risk of myocardial injury (3).

Inflammation related cardiac complications of heart surgery

The two aforementioned trials, which investigated a large group of adult patients undergoing routine cardiac surgery, primarily focused on the effects of steroid treatment on major cardiovascular outcomes and mortality. More specific cardiac complications that are associated with the inflammatory response were not the primary focus of the studies. However, the populations of these trials create an ideal opportunity for studies into these complications as well. The studies included in this thesis therefore focus on inflammation related cardiac complications of heart surgery, specifically the post pericardiotomy syndrome and dexamethasone prophylaxis of several inflammatory cardiac complications.

Post Pericardiotomy Syndrome (PPS)

The post pericardiotomy syndrome is a common complication of cardiac surgery, with reported incidences up to 40% (11). The syndrome is characterized by the postoperative presence of at least two of the following five symptoms: fever without alternative causes, pleuritic chest pain, pleural/pericardial rubbing, new or worsening pleural effusion and new or worsening pericardial effusion (12). The syndrome is associated with life-threatening complications such as cardiac tamponade and constrictive pericarditis. The incidence of these complications varies significantly (2-31%) between studies (13, 14). Inflammation is believed to play a pivotal role in the development of PPS. Use of CPB, surgical trauma, residual blood in the pericardium, and ischemia-reperfusion injury are all believed to have a role in inducing both a local and systemic inflammatory response that can lead to PPS (15). However, the exact etiology of PPS remains unclear. As a result, optimal treatment and prevention strategies still need to be determined.

Dexamethasone prophylaxis of inflammation related cardiac complications

Besides PPS, there are several other postoperative cardiac complications of heart surgery that are related to inflammation. Inflammation in cardiac tissue has previously been associated with

the development of postoperative AF (16) and increased perioperative myocardial injury (17). Furthermore systemic inflammation is associated with postoperative bleeding disorders (8), possibly leading to more reoperations. Prior studies investigated whether corticosteroid prophylaxis could prevent these complications, however these studies have some important shortcomings or unexpected findings that justify further investigation.

Several meta-analyses have shown a protective effect of corticosteroid prophylaxis on the incidence of postoperative AF. Limitations were relatively small sample sizes of included studies and the short duration of follow-up (72 hours) (10, 16, 18, 19). In contrast to these meta-analyses, both the DECS and SIRS trial found no protective effect of dexamethasone treatment on postoperative AF (2, 3). The DECS trial however, did not investigate new-onset postoperative AF. Therefore, a potential protective effect of dexamethasone could have been missed.

Furthermore, prior studies investigating the effects of corticosteroids on perioperative bleeding have shown conflicting results, indicating both an increased as well as a decreased bleeding risk in cardiac surgical patients treated with corticosteroids (20). A meta-analysis on this topic found a reduced chest tube output in patients receiving corticosteroids, although no difference in the overall number of red blood cell transfusions could be demonstrated (21). Therefore, the effect of corticosteroids on perioperative bleeding disorders and reoperations remains controversial.

Also, prior studies showed that systemic inflammation may aggravate perioperative myocardial injury (17) through complement activation via increased C-Reactive Protein (CRP) (22, 23). A similar process occurs in cardiac surgery (24), however the association between inflammation and myocardial injury has not been studied extensively in cardiac surgery patients. Surprisingly, the SIRS trial showed that patients receiving methylprednisolone had an increased risk of myocardial injury (3). Therefore, it is unclear whether inflammation has a detrimental or beneficial effect on the extent of perioperative myocardial injury.

In the studies included in this thesis, each of the aforementioned cardiac complications is studied and the effect of dexamethasone treatment on each of these complications is investigated.

Thesis outline

This thesis focuses on the gaps in evidence around the post pericardiotomy syndrome and dexamethasone prophylaxis of postoperative cardiac complications after heart surgery. **Chapter 2** provides a systematic overview of existing literature around determinants of PPS to identify risk factors of PPS in order to better understand the syndrome. In **chapter 3**, risk factors and the long-term prognosis of PPS are investigated. **Chapters 4-7** focus on the effect of dexamethasone versus placebo treatment on the incidence of PPS (**chapter 4**), postoperative (new-onset) AF (**chapter 5**), rethoracotomies (**chapter 6**) and the extent of perioperative myocardial injury (**chapter 7**). **Chapter 7** also describes the association between the systemic inflammatory response and perioperative myocardial injury. **Chapter 8** provides a general discussion of the presented results and gives future perspectives.

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Chapter 2

Determinants of the Post Pericardiotomy Syndrome: a systematic review

Submitted

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ABSTRACT

Background

Post Pericardiotomy Syndrome (PPS) is a common complication following cardiac surgery, however the exact pathogenesis remains uncertain. Identifying risk factors of PPS might help to better understand the syndrome. The aim of this study was to provide an overview of existing literature around determinants of PPS in adult cardiac surgery patients.

Methods

Two independent investigators performed a systematic search in MEDLINE, EMBASE and the Cochrane Central Register. The search aimed to identify studies published between January 1950 and December 2015, in which determinants of PPS were reported.

Results

19 studies met the selection criteria. In these studies, 14 different definitions of PPS were used. The median incidence of PPS was 16%. After quality assessment, 7 studies were considered eligible for this review. Lower preoperative Interleukin-6 levels and higher postoperative complement conversion products where associated with a higher risk of PPS. Among other clinical factors, a lower age, transfusion of red blood cells and lower preoperative platelet and haemoglobin levels were associated with a higher risk of PPS. Colchicine use decreased the risk of PPS.

Conclusion

We found 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. Due to a lack of a uniform definition of PPS in the past, study comparability was poor across the studies.

INTRODUCTION

Post Pericardiotomy Syndrome (PPS) is a common complication after cardiac surgery, with reported incidences of 10-40% (1). PPS usually has an onset within several days up to three months after cardiac surgery (2) and is associated with serious complications, including acute and chronic cardiac tamponade and constrictive pericarditis (3). Furthermore, PPS is associated with prolonged hospital stay, more readmissions and higher costs (2).
Several definitions of PPS have been used in the past. The currently accepted diagnostic criteria for PPS are the presence of at least two of the following 5 symptoms: new or worsening pleural effusion, new or worsening pericardial effusion, fever without alternative causes, pleuritic chest pain, and pleural or pericardial rubbing (4). The pathogenesis of PPS is still not well understood; however inflammation seems to play a key role. It is believed that surgical trauma to the pericardium and pleura, residual blood in the pericardial sac, the use of cardiopulmonary bypass (CPB) and ischemia-reperfusion injury, may induce a local and systemic inflammatory reaction that can result in PPS (1, 5). PPS has also been shown to be associated with an underlying autoimmune process (6). Anti-inflammatory agents can be used to prevent or treat the syndrome, supporting the hypothesis that the inflammatory response following cardiac surgery plays an important role in the development of PPS. However, the exact pathophysiology and thus optimal treatment strategies remain unknown. The aim of this systematic review was to provide an overview of the existing literature concerning determinants of PPS in adult cardiac surgery patients.

METHODS

Search strategy

This systematic review was performed according to the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) statement criteria (7). A systematic literature search of MEDLINE via PubMed (coverage: 1809 to present), EMBASE (coverage: 1980 to present) and the Cochrane Database of Systematic Reviews (coverage: 1898 to present) was performed on 15 December 2015. The full search syntax is presented in table 1. Duplicates were removed using RefWorks software (ProQuest, Bethesda, MD, USA). Reference lists from retrieved articles (including meta-analyses and systematic reviews) and the 'Related Articles' section of PubMed were screened to identify additional relevant publications.
The search aimed at all articles published from January 1950 (implementation of cardiac surgery in clinical practice) up to December 2015. No language restrictions were applied. If there was no abstract or full text publication available, we tried to obtain the full-text article via the corresponding author and/or the Dutch university libraries.

Selection criteria

Inclusion criteria:

- Study focuses on PPS (either as domain or as outcome)
- Type of study: prognostic or etiologic (cross-sectional, patient-control and retrospective/ prospective cohort studies)
- Domain of the study is adult patients (≥ 18 years) undergoing cardiac surgery through sternotomy.

Exclusion criteria:
- No data about possible determinants of PPS
- No full-text available
- Studies in non-human subjects

Study selection
Two authors (DvO and KJ) independently screened all references that were obtained from the initial search, using predefined in- and exclusion criteria. After screening based on title and abstract, the two authors independently judged the remaining publications based on the full-text publication. If an article was excluded, this was motivated on the selection form. When two studies by the same institution reported similar data, the study that contained more informative data was included and the other publication was considered a duplicate.

Assessment of validity of included studies
After completion of full-text assessment, publications that both authors agreed to select were assessed on validity using a methodological quality assessment form (Table 2). The individual items that were scored on this form were based on methodological guidelines (8, 9) and judged six areas of potential study bias (study population, determinant, outcome, follow-up, confounding and statistical analysis). The authors rated overall study quality (categories: poor, intermediate, good), based on the individual criteria of this form. Discrepancies were discussed by both authors (DvO and KJ). Selection of articles was based on consensus between the reviewers. When no consensus was reached, a third author (JD) decided on selection of articles. Articles that were of poor quality were excluded from this review.

Data extraction
Among the included studies, a large variety of investigated determinants were to be expected due to the large period across which the studies were conducted. Therefore, we aimed at giving a systematic overview of the most important study characteristics and results, rather than performing a pooled analysis. Two authors independently extracted predefined data from each article using a standardized form (Table 3).

Table 1. Search syntax

Database	Search*
PubMed	#1: postpericardiotomy syndrome OR post-pericardiotomy syndrome OR postcommissurotomy syndrome OR post-commissurotomy syndrome OR post cardiac injury syndrome OR post-cardiac injury syndrome OR postpericardial injury syndrome OR post-pericardial injury syndrome OR dressler #2: cardiac surgery OR heart surgery OR thoracic surgery OR cardiovascular surgery OR heart surgical procedure OR cardiac surgical procedure OR thoracic surgical procedure OR cardiovascular surgical procedure OR sternotomy OR sternotomies OR thoracotomy OR thoracotomies OR valve surgery OR valvular surgery OR bypass OR CABG #3: #1 AND #2, Field: title/abstract
Embase	('postpericardiotomy syndrome':ab,ti OR 'post-pericardiotomy syndrome':ab,ti OR 'postcommissurotomy syndrome':ab,ti OR 'post-commissurotomy syndrome':ab,ti OR 'post cardiac injury syndrome':ab,ti OR 'post-cardiac injury syndrome':ab,ti OR 'postpericardial injury syndrome':ab,ti OR 'post-pericardial injury syndrome':ab,ti OR 'dressler':ab,ti) AND ('cardiac surgery':ab,ti OR 'heart surgery':ab,ti OR 'thoracic surgery':ab,ti OR 'cardiovascular surgery':ab,ti OR 'heart surgical procedure':ab,ti OR 'cardiac surgical procedure':ab,ti OR 'thoracic surgical procedure':ab,ti OR 'cardiovascular surgical procedure':ab,ti OR 'sternotomy':ab,ti OR 'sternotomies':ab,ti OR 'thoracotomy':ab,ti OR 'thoracotomies':ab,ti OR 'valve surgery':ab,ti OR 'valvular surgery':ab,ti OR 'bypass':ab,ti OR 'CABG':ab,ti)
Cochrane	#1: "postpericardiotomy syndrome":ti,ab,kw OR "post-pericardiotomy syndrome":ti,ab,kw OR "postcommissurotomy syndrome":ti,ab,kw OR "post-commissurotomy syndrome":ti,ab,kw OR "post cardiac injury syndrome":ti,ab,kw OR "post-cardiac injury syndrome":ti,ab,kw OR "postpericardial injury syndrome":ti,ab,kw OR "post-pericardial injury syndrome":ti,ab,kw OR "dressler":ti,ab,kw #2: "cardiac surgery":ti,ab,kw OR "heart surgery":ti,ab,kw OR "thoracic surgery":ti,ab,kw OR "cardiovascular surgery":ti,ab,kw OR "heart surgical procedures":ti,ab,kw OR "cardiac surgical procedures":ti,ab,kw OR "thoracic surgical procedures":ti,ab,kw OR "cardiovascular surgical procedures":ti,ab,kw OR "sternotomy":ti,ab,kw OR "sternotomies":ti,ab,kw OR "thoracotomy":ti,ab,kw OR "thoracotomies":ti,ab,kw OR "valve surgery":ti,ab,kw OR "valvular surgery":ti,ab,kw OR "bypass":ti,ab,kw OR "CABG":ti,ab,kw #3: #1 AND #2

*Searches were performed on 15 December 2015

Table 2. Quality assessment

Criteria*	Lehto *et al.* (2015) (10)	Jaworska- Wilczyńska *et al.* (2014) (11)	Snefjella *et al.* (2012) (12)	Imazio *et al.* (2011) (13)	Köhler *et al.* (2003) (14)	Hoffman *et al.* (2002) (15)	Kocazeybek *et al.* (1998) (16)	Bartels *et al.* (1994) (17)	Miller *et al.* (1988) (18)	De Scheerder *et al.* (1987) (19)	De Scheerder *et al.* (1986) (20)	Meri *et al.* (1985) (21)	De Scheerder *et al.* (1984) (22)	Engle *et al.* (1981) (23)	Maisch *et al.* (1979) I (24)	Maisch *et al.* (1979) II (25)	Drusin *et al.* (1965) (26)	Van Der Geld (1964) (27)	Robinson *et al.* (1963) (28)
Study design	±	+	+	+	±	+	+	+	+	±	+	+	+	+	+	+	±	NS	+
Study population																			
- Definition	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	-
- In- and exclusion	-	+	-	+	+	-	-	+	+	-	-	-	-	-	-	-	-	-	-
- Selection procedure	+	+	+	+	+	-	-	+	+	-	-	+	+	+	-	-	+	-	-
- Selection bias	+	+	±	±	±	±	±	±	+	±	±	+	+	+	±	±	±	±	±
- Sample size	688	75	50	360	96	20	100	57	944	129	62	45	82	142	56	56	262	30	36
Determinant																			
- Definition	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
- Standardization	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
- Valid method	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
- Blinding	-	-	-	-	-	-	+	+	-	-	+	+	+	+	-	-	-	-	-
Outcome																			
- Definition	+	+	-	+	+	+	+	+	+	+	+	+	+	-	+	+	+	-	-
- Standardization	-	-	-	-	+	+	-	+	+	-	-	+	-	+	-	-	+	-	-
- Valid method	+	-	-	+	+	+	-	+	+	+	+	+	+	-	-	-	+	-	-
- Blinding	-	-	-	-	-	-	+	+	-	-	+	+	+	+	-	-	-	-	-
Follow-up																			
- Duration	+	-	-	+	+	+	+	+	+	NS	+	+	+	+	+	+	+	+	+
- Loss-to-follow-up	+	+	+	+	±	+	NS	NS	NS	NS	NS	NS	+	NS	NS	NS	NS	NS	+
- Reason	-	NA	NA	NA	+	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	+
Analyses																			
- Confounders	+	+	-	+	+	-	-	+	+	-	-	-	-	-	+	+	+	-	-
- Univariable	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-
- Multivariable	+	+	-	+	-	-	-	+	+	-	-	-	-	-	-	-	-	-	-
Overall quality†	±	±	-	+	±	-	-	+	+	-	-	±	-	-	-	-	-	-	-

Abbreviations: NS: not specified; NA: not applicable.

(see also the next page ▶)

RESULTS

Study selection

The study selection process is shown in the flowchart (Figure 1). A total of 363 references were identified through database searching. After screening on title and abstract, 51 references remained for full-text screening. After detailed screening on full-text, 32 references were excluded from this review. The remaining 19 references were eligible for quality assessment (10-28).

Quality assessment

We assessed the quality of the remaining 19 articles using predefined criteria (table 2). After independently assessing the articles and discussing discrepant cases, the authors agreed to exclude 12 articles because of poor quality. The remaining 7 articles, scored as intermediate or good, were included in this review (10, 11, 13, 14, 17, 18, 21). The majority of the studies (12/19) were at high risk of bias because measurement of the outcome PPS was often unclear or not standardized. Also, the procedure for selecting patients was unclear in many studies (possibly leading to selection bias). Furthermore, investigators were often not blinded and confounders were often not studied or corrected for. Detailed information on study quality and reasons for exclusion can be found in supplement 1.

Definition and incidence of PPS

The definition of PPS was compared between all 19 articles that were eligible for quality assessment. 4 studies did not give a definition of PPS. An overview of the different definitions used to diagnose PPS in the remaining 15 articles is given in supplement 2. From 1965 until 2015, 14 different definitions were used to diagnose PPS. The incidence of PPS in these 15 articles ranged from 9-65%, with a median incidence of 16% (Interquartile Range 13-23%).

▶ Table 2 *continued*

*Individual criteria used for assessment of studies:
Study design: + prospective cohort, ± retrospective cohort, cross-sectional study or case-control study, - other.
Study population: *Definition*: + clearly defined, - not or unclear defined. *In- and exclusion*: + in- and exclusion criteria clearly described, - not clearly described. *Selection procedure*: + well described, - unclear. *Selection bias*: + no, ± possible, - yes.
Determinant: *Definition:* + well defined, - not well defined. *Standardization:* + measurement of the determinant was standardized, - not standardized or unclear. *Valid method:* + a valid method was used to measure the determinant, - measurement of the determinant was not valid or unclear. *Blinding:* + exposure to the determinant was measured without knowledge of the outcome, - with knowledge of the outcome or unclear.
Outcome: *Definition:* + well defined, - not well defined. *Standardization:* + measurement of the outcome was standardized, - not standardized or unclear. *Valid method:* + a valid method was used to measure the outcome, - measurement of the outcome was not valid or unclear. *Blinding:* + the outcome was measured without knowledge of exposure to the determinant, - with knowledge of exposure to the determinant or unclear.
Follow-up: *Duration:* + ≥ 1 week, - < 1 week or unclear. *Loss-to-follow-up:* + minimal and not selective (<5%), ± intermediate (5-10%) and not selective, - large (> 10%) or selective. *Reason:* + reasons for loss-to-follow-up are given, - are not given.
Analyses: *Confounders:* + the study studied potential confounders, - did not study potential confounders or unclear. *Univariable:* + the study provided univariable analysis, - did not. *Multivariable:* + the study provided multivariable analysis, - did not.
†**Overall quality:** The investigators judgment concerning overall study validity: - poor, ± intermediate, + good.

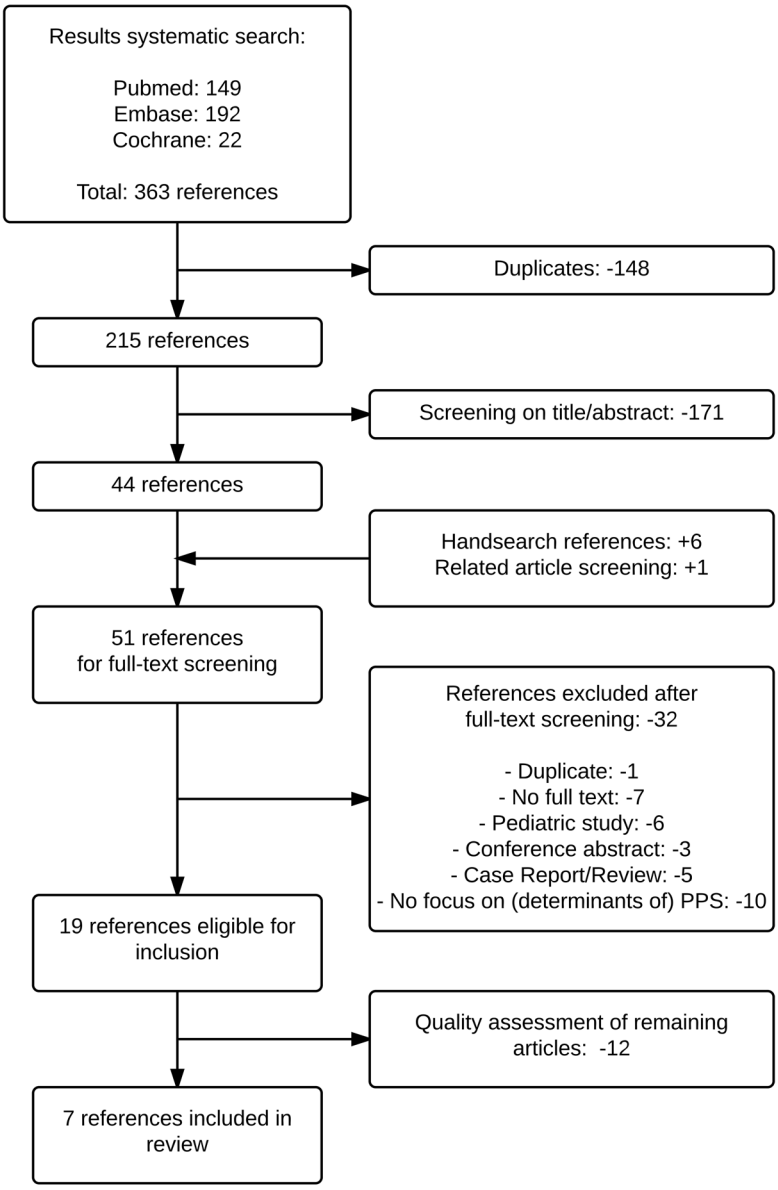

Figure 1. Study Flowchart
Abbreviations: PPS: Post Pericardiotomy Syndrome

Table 3. Included studies

Author (year)	Study design	Incidence PPS	Follow up time	Type of surgery	Definition of PPS	Study aim	Determinant of PPS studied	Principal finding
Lehto et al. (2015) (10)	Retrospective cohort	61/688 (8.9%)	Mean: 5.3 years	CABG	COPPS criteria*	To investigate predictors of PPS leading to prolonged hospital stay, readmission or medical therapy	Clinical, surgical and laboratory variables	Use of ≥1 red blood cell units was independently associated with a higher risk of PPS, whereas medically treated diabetes was independently associated with a reduced risk of PPS. A higher BMI and shorter hospital stay after index CABG were independently associated with a higher risk of relapsed PPS.
Jaworska-Wilczyńska et al. (2014) (11)	Prospective cohort	49/75 (65.4%)	6 months	CABG	COPPS criteria†	To investigate inflammatory markers of PPS	Clinical variables and IL-8, IL-6, IL-1β, IL-10, TNF-α, IL-12p70	Lower IL-8 concentration and lower haemoglobin levels before surgery were independently associated with a higher risk of PPS.
Imazio et al. (2011) (13)	Prospective cohort	54/360 (15.0%)	Mean: 19.8 months	Any type of cardiac surgery	COPPS criteria‡	To investigate risk factors of PPS.	Clinical, surgical and laboratory variables	Female gender and pleura incision were independently associated with a higher risk of PPS, whereas colchicine use was associated with a lower risk of PPS.
Köhler et al. (2003) (14)	Prospective/ retrospective cohort (unclear)	12/96 (12.5%)	1 month	Any type of cardiac surgery	Other§	To investigate the association between myocardial injury and inflammatory markers with PPS	Clinical variables and CK, CK-MB, cTnI, CRP, TNF-α, ESR	Patients with PPS were significantly younger than patients without PPS. Serum markers for tissue injury and inflammation were not significantly different between PPS and no PPS patients.
Bartels et al. (1994) (17)	Prospective cohort	10/57 (17.5%)	21 days	Any type of cardiac surgery	Other¥	To test the sensitivity and specificity of AHA and ACLA for the diagnosis PPS	AHA, ACLA, CRP, ESR, WBC	There was no difference in the level of AHA, ACLA, CRP, ESR and WBC between patients with and without PPS.

Table 3. *Continued*

Miller et al. (1988) (18)	Prospective cohort	168/944 (17.8%)	Median 9 days	Any type of cardiac surgery except ICD	Other¶	To identify factors associated with PPS	Clinical, surgical and laboratory variables	Lower age, history of prednisone treatment, blood type B-, halothane anesthesia, lower platelet count, lower weight and history of pericarditis were independently associated with a higher risk of PPS, whereas mitral valve replacement and fall season were independently associated with a decreased risk of PPS.
Meri et al. (1985) (21)	Prospective cohort	6/45 (13.3%)	± 12 days	Any type of cardiac surgery	Other#	To investigate the correlation between levels of complement components and PPS	C3, C4, factor B antigen, total haemolytic complement activity, C3b, C3bi, C3c, C3d	Mean C3 conversion products (C3bi, C3c) were significantly higher in PPS patients versus no PPS patients.

Abbreviations : ACLA: Anti-Cardiolipin Antibodies; AHA: Anti-Heart Antibodies; BMI: Body Mass Index; C3/4/3b/3bi/3c/3d: Complement 3/4/3b/3bi/3c/3d; CABG: Coronary Artery Bypass Grafting; CK: Creatinine Kinase; CK-MB: Creatinine Kinase isoenzyme MB; CRP: C-reactive protein; cTnI: Cardiac Troponin I; ESR: Erythrocyte Sedimentation Rate; ICD: Implantable Cardioverter Defibrillator; IL: Interleukin; PPS: Post Pericardiotomy Syndrome; TNF: Tumor Necrosis Factor; WBC: White Blood Cell Count.

Definition of PPS:

*COlchicine for the Prevention of the Post-pericardiotomy Syndrome (COPPS) criteria: Presence of ≥2 of 5 criteria; 1. fever without alternative cause, 2. pleuritic chest pain, 3. friction rub, 4. evidence of new or worsening pleural effusion, 5. evidence of new or worsening pericardial effusion.

†Diagnosis based on COPPS criteria*, however not only new/worsening pleural or pericardial effusions, but any pleural or pericardial effusion after surgery was accounted for.

‡Diagnosis based on COPPS criteria*, however fever without alternative cause only counted when lasting beyond the first postoperative week.

§Diagnosis PPS when all of the following criteria are present after the 7th postoperative day: 1. Initial or increased thoracic pain, 2. malaise/weakness, fever, or all of these, 3. the presence of pericardial or pleuropericardial rub

¥Diagnosis PPS if 2 major criteria and 1 minor criterion was present. Major criteria: 1. pericardial friction, 2. pleural friction, 3. chest pain after the 7th postoperative day, 4. fever after the 7th postoperative day. Minor criteria: 1. CRP > 10 mg/L after the 7th postoperative day, 2. ESR >40 mm/h after the 7th postoperative day, WBC >11000·mm-3

¶Diagnosis PPS if ≥2 of 3 criteria: 1. fever > 37.8º Celsius lasting > 8 hours, 2. significant anterior chest pain suggestive of pericardial inflammation, 3. a two- or three-component pericardial friction rub.

#Diagnosis PPS if 2 of 2 criteria (after the first postoperative week): 1. fever > 37.6º Celsius, 2. pericardial friction rub and/or effusion with/without pleural signs.

Table 4. Clinical variables associated with PPS

Variable	Lehto *et al.* (2015) (10)	Jaworska-Wilczyńska *et al.* (2014) (11)	Imazio *et al.* (2011) (13)	Köhler *et al.* (2003) (14)*	Bartels *et al.* (1994) (17)	Miller *et al.* (1988) (18)
Lower age	-	-	-	+	-	+
Female gender	-	-	+	-	-	-
Lower BMI	-	-	NS	NS	NS	+
Diabetes treatment	+	-	-	NS	NS	NS
Pulmonary disease	-	NS	-	NS	NS	NS
Renal insufficiency	-	-	-	NS	NS	NS
Atrial fibrillation	-	NS	NS	NS	NS	NS
Preoperative INR	-	NS	NS	NS	NS	NS
Preoperative Hb	-	+	NS	NS	NS	NS
Preoperative platelet count	NS	NS	NS	NS	NS	+
Anticoagulant therapy	-	NS	-	NS	-	NS
Anti-platelet therapy	-	NS	NS	NS	NS	NS
Use of packet red cells	+	-	NS	NS	NS	NS
Off-pump surgery	-	-	NS	NS	NS	NS
Type of cardiac surgery	NS	NS	-	-	-	+
Surgery duration	-	-	NS	-	NS	NS
Pleural incision	NS	NS	+	NS	NS	NS
Colchicine use	NS	NS	+	NS	NS	NS
Prednisone use	NS	NS	NS	NS	NS	+
History of pericarditis	NS	NS	NS	NS	NS	+
Blood type B-	NS	NS	NS	NS	NS	+
Halothane anaesthesia	NS	NS	NS	NS	NS	+
Fall season	NS	NS	NS	NS	NS	+

Abbreviations: BMI: Body Mass Index; Hb: Hemoglobin; INR: International Normalized Ratio; NS: Not Studied; PPS: Post Pericardiotomy Syndrome.
+ : The study found an association between the clinical variable and PPS
– : The study found no association between the clinical variable and PPS
* : The study only performed univariable analysis.

Inflammatory markers

Of the 7 included studies, 4 studies evaluated the association between inflammatory markers and PPS (table 3). The study of Jaworska-Wilczyńska *et al.* (11) evaluated the pro-inflammatory cytokines Interleukin (IL) -6, IL-8, IL-1β, IL-12p70, Tumor Necrosis Factor (TNF) -α and anti-inflammatory cytokine IL-10. A lower IL-8 concentration before cardiac surgery was independently associated with a higher risk of PPS. There was no association between the other cytokines and PPS in multivariable analysis. No other study that was included in this review investigated interleukins. The study of Köhler *et al.* (14) also evaluated TNF-α and did not find an association with PPS. Furthermore, C-Reactive Protein (CRP) and Erythrocyte Sedimentation Rate (ESR) levels were not associated with PPS. Bartels *et al.* (17) also investigated CRP, ESR, White Blood Cell Count (WBC), Anti-Heart Antibodies (AHA) and Anti-CardioLipin Antibodies (ACLA) and found no correlation with PPS. Meri *et al.* (21) evaluated complement components (C3, C4 and factor B), complement conversion products (C3b, C3bi, C3c, C3d) and total haemolytic complement activity. The study demonstrated that C3bi and C3c levels (complement conversion products that appear after complement activation by either pathway) were significantly higher in patients with PPS.

Markers of myocardial injury

One study by Köhler *et al.* (14) investigated the correlation between markers of myocardial injury and PPS, and found no association between Creatinine Kinase (CK), Creatinine Kinase isoenzyme MB (CK-MB), Cardiac Troponin I (cTnI) and PPS.

Clinical variables associated with PPS

Of the 7 included studies, 6 studies investigated the association between clinical variables and PPS (10, 11, 13, 14, 17, 18). Results of these studies can be found in table 4. The studies reported different variables that were associated with PPS. In the study of Lehto *et al.* (10), transfusion of ≥1 red blood cell unit was associated with a higher risk of PPS, whereas treatment for diabetes was independently associated with a reduced risk of PPS. This was not confirmed by the other studies, however in the study of Jaworska-Wilczyńska *et al.* (11), a lower preoperative hemoglobin level was associated with a higher risk of PPS and the number of red blood cell transfusions was not. Imazio *et al.* (13) found female gender and pleural incision to be risk factors for PPS, and colchicine use to be protective against PPS. Köhler *et al.* (14) found an association between younger age and PPS. This finding was confirmed by Miller *et al.* (18), who also found the following determinants as risk factor for PPS: history of prednisone treatment, blood type B-, halothane anesthesia, lower platelet count, lower weight and history of pericarditis. Mitral valve replacement and fall season decreased the risk of PPS in the study of Miller *et al.*

DISCUSSION

PPS has been studied for nearly 60 years now and the exact pathophysiology still remains unclear. In this review, we have provided a systematic overview of the existing literature on determinants of PPS in adult cardiac surgery patients. In this way, we aimed to identify all factors that are associated with PPS, in order to better understand the syndrome.

The inconsistency of the definition of PPS that has been used in various studies between 1965 until now is striking (supplement 2). Fourteen different definitions of PPS have been used in the past 50 years. In earlier studies (roughly before 2000), PPS could only be diagnosed after the first postoperative week, whereas in later studies, there was no time criterion for the diagnosis of PPS anymore. The latter definition effectively means that patients with early postoperative effusions and fever (which are not uncommon the first postoperative days) are considered to have PPS, and are not judged differently from patients who develop effusions and fever after the first postoperative week. It is possible that early and late postoperative effusions are the result of different pathophysiologic mechanisms (bleeding-related versus inflammation-related). Furthermore, the criterion 'new or worsening pericardial or pleural effusion' includes all postoperative effusions (irrespective of the size) and ignores the fact that mild effusions after cardiac surgery are not uncommon. This criterion inevitably leads to the diagnosis PPS in many patients, while it may not always be clinically relevant. Another problem with the definition of PPS is the rather subjective component of 'pleuritic chest pain', which is difficult to distinguish from common postoperative wound pain. In the past, inflammatory markers (WBC, CRP, ESR) have also been part of the diagnosis PPS, however these markers have not been used as criterion for the diagnosis PPS anymore in publications after 2002 (supplement 2), possibly because these markers are non-specific. Since we still do not know how to define PPS, and therefore do not have a reference standard to diagnose the syndrome against, it is difficult to correlate it with a clinical picture. The fact that so many definitions of PPS have been used in the past, makes it impossible to compare the findings of all the available studies. This problem was noted earlier by Imazio *et al.* in 2013 (4), which led these authors to propose new criteria to avoid this problem in the future. However, these proposed criteria still have the problem of being very broad, and thus non-specific. The current guideline on pericardial diseases have adopted most of the criteria as proposed by Imazio et al, however the criterion 'new or worsening pleural effusion' has been changed in 'pleural effusion with elevated CRP'. The reasons for this change are not given by the authors of the guideline. However they state that signs of inflammation should be essential for the diagnosis, which could be a reason (29). Yet another definition of PPS originated. Further research on this subject should use this uniform definition, in order to improve future study comparability.

In this systematic review, a lower IL-8 level before surgery and higher complement conversion (C3bi and C3c) product levels after surgery were associated with PPS, suggesting that the inflammatory response may play a role in the development of PPS. Other cytokines (IL-6, IL-1β, IL12p70, TNF-α), inflammatory markers (WBC, ESR, CRP) and cardiac specific antibodies (AHA, ACLA) were not associated with PPS, not supporting the hypothesis of an inflammatory etiology. We also attempted to summarize the associations between clinical variables and PPS (table 4). Inflammation might explain why a lower age, a lower Body Mass Index (BMI) and a history of pericarditis were associated with a higher risk of PPS. The inflammatory response is thought to be attenuated in older patients, due to an increasingly senescent immune system (18). Also, a higher BMI might protect against PPS, given the immunomodulatory effects of excessive visceral fat (30, 31). The finding that colchicine use decreases the risk of PPS supports this hypothesis. The finding that the use of ≥ 1 red blood cell unit postoperatively and lower platelet and haemoglobin levels preoperatively increased the risk of PPS might be an indication that

perioperative bleeding also plays a role in the development of PPS. Another possibility is that blood transfusions induce inflammation and therefore play a role in the development of PPS. A limitation of the abovementioned overview of clinical and laboratory variables associated with PPS is that these associations were mostly found in single studies and were never investigated nor confirmed by other studies. Various studies reported different variables to be associated with PPS. This is most likely due to the different definitions of PPS that have been used in the past and therefore the poor comparability of studies. Furthermore, cardiac surgical techniques evolved enormously during the past 50-60 years, also leading to poor comparability between the earliest and the latest studies. This is also the reason why we were not able to perform a pooled analysis in this study.

Anti-inflammatory agents can be used to attenuate the inflammatory reaction that occurs after cardiac surgery. Several interventional studies for the prevention of PPS have been performed, showing variable results. Only long-term colchicine treatment has demonstrated promising results in preventing PPS (32-35). However, it remains difficult to determine who to treat and what the duration of preventive treatment is. Postoperative aspirin treatment (36) and perioperative treatment with corticosteroids (methylprednisolone and dexamethasone) did not prevent from PPS (37, 38), however a recent study investigating a single intraoperative dose of methylprednisolone showed a significantly lower incidence of PPS and pericardial effusions (39). The fact that chronic treatment with colchicine is able to prevent PPS supports the hypothesis of an ongoing inflammatory etiology. In more recent literature it has been suggested that specifically retained blood in the pericardial and pleural space after cardiac surgery may be an important mechanism in the development of PPS (40, 41). Retained blood and coagulation are believed to induce a local inflammatory response that can manifest as acute, subacute or chronic effusions (40). Active chest tube clearance was associated with a reduction of reinterventions and postoperative atrial fibrillation (41), further supporting this hypothesis.

In this review, we found 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. Therefore, it is important that future studies around PPS should thus include data on inflammation and retained blood. Furthermore, more fundamental research on PPS is needed to reveal the exact mechanism behind PPS, in order to optimize prevention and therapeutic strategies in the future.

Conflict of interest

All authors report no conflicts of interests.

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SUPPLEMENT

Supplement 1. Quality assessment comments

Author (year)	Comments	Study quality
Lehto et al. (2015) (10)	Retrospective cohort study. In- and exclusion criteria are not described. Investigators were not blinded for determinant/outcome. X-rays and echocardiograms were not available in all patients (because of the retrospective study design), therefore measurement of the outcome was not standardized. Reasons for loss-to-follow-up were not given.	Intermediate
Jaworska-Wilczyńska et al. (2014) (11)	The time period in which the study was conducted was not described. The component fever of the outcome PPS was not well enough defined. It was not clear how and when the outcome was measured. The outcome PPS at 6 months after surgery was measured by a phone call, possibly resulting in less validity. It was unclear whether investigators were blinded for determinant/outcome or not. Follow-up was 5 days (and 6 months, however possibly less valid).	Intermediate
Snefjella et al. (2012) (12)	The study population, in- and exclusion criteria and the time period in which patients were included are unclear. Therefore, selection bias is possible. No baseline characteristics were given. It was unclear which determinants were studied and how determinants were measured. Investigators were not blinded for determinant/outcome. The outcome (fever and pericardial effusion) was not well enough defined and it was unclear how and when this was measured. Follow-up duration was undefined. The study did not study confounders and performed no multivariable analyses.	Poor
Imazio et al. (2011) (13)	In- and exclusion criteria and loss-to-follow up were not described in the article, however were well described in the COPPS trial of which this study was a substudy. Because the study population consists of patients included in the COPPS trial, there could have been selection bias. There was no blinding, however baseline characteristics were objective, therefore not affecting the outcome. The definition of fever was not given in the article. It was unclear how often and when the patients were assessed for PPS.	Good
Köhler et al. (2003) (14)	It was unclear whether the diagnosis of PPS was measured prospectively or retrospectively. Patients were selected from another cohort, so there could have been selection bias. The definition of fever was not given. Investigators were not blinded for determinant/outcome. Loss-to-follow-up was 10%. Only univariable analyses were performed.	Intermediate
Hoffman et al. (2002) (15)	In- and exclusion criteria and patient selection were unclear, therefore selection bias might have been possible. The definition of individual components of the outcome was not well enough described; fever and elevated erythrocyte sedimentation ratio were not further defined. Investigators were not blinded for determinant/outcome. Loss-to-follow-up was not described. Only univariable analyses were performed. No baseline characteristics were given. Confounders were not studied.	Poor
Kocazeybek et al. (1998) (16)	No in- and exclusion criteria were described. Discrepancies about patient selection were present in the abstract and main text, i.e. consecutive versus random, respectively. Hence, selection bias might have been present. The individual components of the outcome PPS were not well enough described; the exact definition of the components pericarditis, fever, leukocytosis, high sedimentation rate and CRP was unclear. Also, it was uncertain how and when the outcome was measured. Loss-to-follow-up was undefined and only univariable analyses were performed. Only few baseline characteristics were given, no confounders were studied.	Poor
Bartels et al. (1994) (17)	The patient selection procedure was well described, however it was unclear if consecutive patients were included. Therefore, selection bias might have been possible. Loss-to-follow-up was not described. Univariable analyses were performed, however no p-values are given. Only few baseline criteria were given.	Good
Miller et al. (1988) (18)	There was no blinding in the study, however the determinants of the study were objective, therefore it is not likely that this affects the study outcome. Loss-to-follow-up was not described.	Good
De Scheerder et al. (1987) (19)	Retrospective study. In- and exclusion criteria were not mentioned. Patient selection was unclear, selection bias was thus possible. Investigators were not blinded for determinant/outcome. The outcome PPS was not well enough defined: fever, pericarditis and laboratory evidence of inflammation were criteria, however these criteria were not further specified. It was not evident how and when these criteria were measured. Few baseline criteria were given. Duration of follow-up and loss-to-follow up was unclear. Only univariable analyses were performed. Confounders were not studied.	Poor

Supplement 1. *Continued*

De Scheerder *et al.* (1986) (20)	In- and exclusion criteria were not mentioned. Patient selection was not well described (were consecutive patients included?), therefore there could have been selection bias. The outcome PPS was not well enough defined: fever, pericarditis and laboratory evidence of inflammation were criteria, however these criteria were not further specified. It was unclear how and when these criteria were measured. Few baseline criteria were given. Loss-to-follow-up was not described. Only univariable analyses were performed. Confounders were not studied.	Poor
Meri *et al.* (1985) (21)	In- and exclusion criteria were not mentioned. Loss-to-follow-up was not described. Only univariable analyses were performed. Few baseline characteristics were given. Confounders were not studied.	Intermediate
De Scheerder *et al.* (1984) (22)	In- and exclusion criteria were unclear. The definition of PPS was not well described: pericardial inflammation on physical examination, electrocardiography, echocardiograms and X-rays was a criterion, however it was not discussed what signs of pericardial inflammation on the several examinations were used for diagnosis. Few baseline characteristics were given. Only univariable analyses were performed.	Poor
Engle *et al.* (1981) (23)	No in- and exclusion criteria were mentioned. No information was given about the completeness of follow-up data and loss-to-follow-up. The most important limitation was that no definition of the outcome PPS was given.	Poor
Maisch *et al.* (1979), study I (24)	The article provided no information about in- and exclusion criteria and the selection procedure was unclear. Therefore, there might have been selection bias in this study. Investigators were not blinded for determinant/outcome. The definition of PPS was not well defined: pericarditis and leukocytosis were both a criterion for PPS, however no definition of pericarditis and leukocytosis was given. It was unclear whether measurement of the outcome was standardized or not, or if a valid method was used to measure the outcome. Loss-to-follow-up was unclear. The study did not perform multivariable analyses. Only a few baseline characteristics were given.	Poor
Maisch *et al.* (1979), study II (25)	See above comments on the study of Maisch et al. 1979, study I.	Poor
Drusin *et al.* (1965) (26)	Retrospective cohort study, partially in children, but also in adult patients. The study investigated 'survivors' of intrapericardial surgery, but it was not clear what the definition of a survivor was (e.g. survival of the surgical procedure only or patients that survived at least x days/weeks after surgery?). In- and exclusion criteria were unclear. Because of the unclear definition and no in- and exclusion criteria, there could have been selection bias in this study. The study was not blinded. PPS was well defined, however it was not defined how and when the outcome was measured and if it was measured well in all patients (if enough data was available to diagnose PPS retrospectively). The study also did not state how complete follow-up data was. The study did not perform multivariable analyses. No baseline characteristics are given.	Poor
Van Der Geld *et al.* (1964) (27)	The study design and study population were unclear. No information about the in- and exclusion criteria and selection procedure was given, so selection bias was possible. No baseline characteristics were given. Investigators were not blinded for determinant/outcome. The definition of PPS and how and when this was measured was not evident. Loss-to-follow-up was not specified. No statistical analyses were performed.	Poor
Robinson *et al.* (1963) (28)	The definition of the population that was studied was unclear. No information about in- and exclusion criteria and selection procedure was given, so selection bias was possible. Investigators were not blinded for determinant/outcome. The definition of PPS, and how and when this was measured was undefined. No baseline characteristics were given. No statistical analyses were performed.	Poor

Abbreviations: COPPS: COlchicine for the Prevention of the Post-pericardiotomy Syndrome; CRP: C-reactive protein; PPS: Post Pericardiotomy Syndrome

Supplement 2. Historical overview of the definition of PPS

Author (year)	Definition of PPS
Lehto *et al.* (2015) (10)	COPPS criteria: Presence of ≥2 of 5 criteria; 1. fever without alternative cause, 2. pleuritic chest pain, 3. friction rub, 4. evidence of new or worsening pleural effusion, 5. evidence of new or worsening pericardial effusion.
Jaworska-Wilczyńska *et al.* (2014) (11)	COPPS criteria, however not only new/worsening pleural or pericardial effusions, but any pleural or pericardial effusion after surgery was accounted for.
Snefjella *et al.* (2012) (12)	Fever unresponsive to antibiotics and pericardial effusion
Imazio *et al.* (2011) (13)	COPPS criteria, however fever without alternative cause only scored when lasting beyond the first postoperative week.
Köhler *et al.* (2003) (14)	Diagnosis PPS when all of the following criteria were present after the 7th postoperative day: 1. Initial or increased thoracic pain, 2. malaise/weakness, fever, or all of these, 3. the presence of pericardial or pleuropericardial rub
Hoffman *et al.* (2002) (15)	Diagnosis PPS if ≥3 of 5 criteria (after excluding other conditions with similar features): 1. fever, 2. chest pain, 3. pericardial and/or pleural friction rub, 4. pericardial and/or pleural effusion, 5. elevated ESR.
Kocazeybek *et al.* (1998) (16)	Diagnosis PPS if pericarditis, fever, leucocytosis, high ESR and high CRP.
Bartels *et al.* (1994) (17)	Diagnosis PPS if 2 major criteria and 1 minor criterion was present. Major criteria: 1. pericardial friction, 2. pleural friction, 3. chest pain after the 7th postoperative day, 4. fever after the 7th postoperative day. Minor criteria: 1. CRP > 10 mg/L after the 7th postoperative day, 2. ESR >40 mm/h after the 7th postoperative day, WBC >11000·mm^{-3}
Miller *et al.* (1988) (18)	Diagnosis PPS if ≥2 of 3 criteria: 1. fever > 37.8º Celsius lasting > 8 hours, 2. significant anterior chest pain suggestive of pericardial inflammation, 3. a two- or three-component pericardial friction rub.
De Scheerder *et al.* (1987) and De Scheerder *et al.* (1986) (19, 20)	Diagnosis PCIS if 3 of 3 criteria (after the first postoperative week): 1. fever, 2. pericarditis, 3. laboratory evidence of inflammation. If 2 of 3 criteria were present, this was defined as incomplete PCIS.
Meri *et al.* (1985) (21)	Diagnosis PPS if 2 of 2 criteria (after the first postoperative week): 1. fever > 37.6º Celsius, 2. pericardial friction rub and/or effusion with/without pleural signs.
De Scheerder *et al.* (1984) (22)	Diagnosis PPS if 3 of 3 criteria (after the first postoperative week): 1. pericardial inflammation on physical examination/electrocardiograms/x-rays/echocardiograms, 2. unexplained fever, 3. elevated ESR and leucocytosis. If 2 of 3 criteria were present, this was defined as incomplete PPS.
Maisch *et al.* (1979) (24)	Diagnosis PPS if 3 of 3 criteria (after the first postoperative week): 1. pericarditis, 2. Fever > 37.5º Celsius, 3. leucocytosis. If 1 or 2 of 3 criteria were present, this was defined as incomplete PPS.
Drusin *et al.* (1965) (26)	Diagnosis PPS if fever ≥39 º Celsius persisting beyond the first postoperative week (without evidence of infection) and at least 1 of the following criteria: 1. pericardial chest pain, 2. pericardial friction rub or effusion, 3. pleural effusion, 4. Serial electrocardiographic changes consistent with pericarditis.

Abbreviations: COPPS: COlchicine for the Prevention of the Post-pericardiotomy Syndrome; CRP: C-reactive protein; ESR: Erythrocyte Sedimentation Rate; PCIS: Post Cardiac Injury Syndrome; PPS: Post Pericardiotomy Syndrome; WBC: White Blood Cell Count.

Chapter 3

Risk Factors and Prognosis of Post Pericardiotomy Syndrome in patients undergoing valve surgery

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ABSTRACT

Objective

The study aim was to investigate the long-term prognosis and risk factors of postpericardiotomy syndrome (PPS).

Methods

We performed a single center cohort study in 822 patients undergoing nonemergent valve surgery. Risk factors of PPS were evaluated using multivariable logistic regression analysis. We also compared the incidence of reoperation for tamponade at 1 year between patients with and without PPS. Main secondary outcomes were hospital stay and mortality.

Results

Of the 822 patients, 119 (14.5%) developed PPS. A higher body mass index (odds ratio (OR) per point increase, 0.94; 95% confidence interval (CI), 0.89-0.99) was associated with a lower risk of PPS, whereas preoperative treatment for pulmonary disease without corticosteroids (OR, 2.55; 95% CI, 1.25-5.20) was associated with a higher risk of PPS. The incidence of reoperation for tamponade at 1 year in PPS versus no PPS was 20.9% versus 2.5% (OR 15.49, 95% CI 7.14-33.58). One year mortality in PPS versus no PPS was 4.2% versus 5.5% (OR 0.68, 95% CI 0.22-2.08). Median hospital stay was 13 days (interquartile range, 9-18 days) versus 11 days (interquartile range, 8-15 days) (P=.001), respectively.

Conclusion

Despite longer hospital stays and more short-term reoperations for tamponade, patients with PPS had an excellent 1-year prognosis.

INTRODUCTION

Postpericardiotomy syndrome (PPS) is a common complication of cardiac surgery (1). The syndrome is associated with early postoperative problems such as prolonged hospital stay and cardiac tamponade (2, 3). The long-term prognosis of PPS has not been studied extensively. PPS is thought to be related to inflammation and autoimmune phenomena in response to surgical trauma and use of cardiopulmonary bypass (CPB) (1, 4). In a subanalysis of the DECS (DExamethasone for Cardiac Surgery) trial (5), we found no protective effect of 1.0 mg/kg dexamethasone on the incidence of PPS (6). In the present study, we investigated the short-term (one month) and long-term (one year) prognosis of PPS. Furthermore, we searched for risk factors of PPS, to better identify patients who are at risk of PPS and to be more alert on adverse events in these patients.

METHODS

Study design and population

The study population consisted of 822 patients enrolled in the DECS trial. The DECS trial was a double blind, randomized, placebo-controlled trial investigating the effect of an intraoperative dose of 1 mg/kg dexamethasone on a composite endpoint of death, myocardial infarction, stroke, renal failure, or respiratory failure, in 4494 adult patients undergoing cardiac surgery (5). The population of the present study consists of a subgroup of 822 patients, undergoing valve surgery at a single center (University Medical Center Utrecht, Utrecht, The Netherlands) and who were included in the earlier published DECS PPS substudy (6). In the DECS PPS substudy, 852 DECS patients initially underwent valve surgery. 30 patients (3.5%) were excluded, because no postoperative echocardiography was available (n=20) or other follow-up data needed to establish the diagnosis of PPS were missing (n=10). The remaining 822 patients were included for data analyses. The study consisted of patients undergoing valve surgery only, because of the availability of routine surveillance echocardiography, usually on postoperative days 4 to 6.
PPS was diagnosed if two out of five of the following symptoms were present: pericardial rubbing, fever >72 hours postoperative, pleuritic chest pain, new significant pleural effusion on chest radiograph (above the highest level of the diaphragm), or significant pericardial effusion (≥10 mm). In the main study, all patients provided written informed consent before randomization. The Research Ethics Committee at each participating center approved the protocol, which contained the protocol of the present substudy.

Clinical outcomes

The primary outcome was the incidence of reoperation for tamponade in patients with and without PPS at one year. Reoperation for tamponade was defined as a resternotomy or subxiphoid incision because of excessive pericardial fluid causing echocardiographic or clinical features of cardiac tamponade.
Long-term secondary outcomes at one year were mortality, stroke, myocardial infarction and readmissions (for any reason). Myocardial infarction was defined according to the criteria of the

Universal Definition of Myocardial Infarction (7). Stroke was defined as a neurologic deficit lasting >24 hours, with increased invalidity (Rankin scale increase: ≥1 point) and signs of a new ischemic cerebral infarction on computed tomography or magnetic resonance imaging scan.
Short-term secondary outcomes were total hospital stay in days and at one month the incidences of postoperative atrial fibrillation, reoperation for tamponade, reoperation for surgical bleeding and percutaneous pericardial or pleural puncture. Postoperative atrial fibrillation (AF) was defined by the occurrence of any episode of AF postoperatively (during ≥10 seconds on a 12 channel electrocardiogram or three channel rhythm recording), regardless of a medical history of AF.

Data collection

Mortality, stroke and myocardial infarction within 1 year after cardiac surgery and total hospital stay in days were collected prospectively as part of the original DECS trial. Data concerning postoperative AF, reoperations, and pleural and pericardial puncture were collected by examining all surgical reports, medical records, discharge letters and postoperative electrocardiograms. Detailed information regarding data collection on postoperative AF and reinterventions can be found in the earlier published DECS postoperative AF study (8) and the DECS rethoracotomy study (9). All participants were followed for one year after their initial surgery. In case of a hospital readmission, medical reports were collected retrospectively and assessed by an investigator, who was blinded regarding diagnosis of PPS.

Postoperative anticoagulant therapy and chest tube management

The standard postoperative anticoagulation regimen was as follows: The first moment that drain output was <50 mL in the past hour and <100 mL in the past 3 hours, all patients received low molecular weight heparin (LMWH) 2500 IU subcutaneously (s.c.). If the patient also underwent a coronary artery bypass grafting (CABG), a single intravenous dose of 450 mg acetylsalicylic acid was added. On the first postoperative morning, all patients received 2500 IU LMWH s.c. and in case of a CABG (or preoperative acetylsalicylic acid use), a daily oral dose of acetylsalicylic acid 100 mg was (re)started. From the evening of the first postoperative day, daily thrombosis prophylaxis was started: LMWH 2500 IU s.c. for for patients weighing <80 kg and 5000 IU s.c. for patients weighing > 80 kg. Also coumarin therapy was initiated, with target international normalized ratios (INR) of 2.5-3.5. If the INR was >2.0, LMWH therapy was stopped. Coumarin therapy was continued for 3 months in patients receiving a bioprosthetic valve or valve repair and lifelong for patients receiving a mechanical valve prosthesis. Chest tubes were removed if the production was decreasing to <60 mL over the past 3 hours, usually on the first postoperative day.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation (SD) or as median with interquartile range (IQR), where appropriate. Dichotomous variables are expressed as the number of cases followed by a percentage (n, %). We used the Kolmogorov-Smirnov test to determine whether the variables were normally distributed or not. For the comparison of categorical variables we used the $\chi 2$ test or Fisher exact test (in variables with a small sample size) and we

calculated Odds Ratios (ORs) with 95% Confidence Intervals (CIs). For the comparison of continuous variables we used the Student t test for normally distributed data and the Mann-Whitney U test for data that were not normally distributed.
To identify independent perioperative risk factors of PPS, baseline variables that may clinically be associated with inflammation (age, sex, body mass index (BMI), arterial vascular disease (defined as a medical history of: stroke, peripheral artery disease or significant coronary artery disease), diabetes, treatment for pulmonary disease without corticosteroid use, preoperative corticosteroid or aspirin use, intraoperative use of dexamethasone (DECS trial medication), CPB time, units of packed red cells transfused, reoperation for surgical bleeding) and all other baseline variables with a p-value < 0.10 in univariable analysis, were entered in multivariable analysis using logistic regression.
We also used multivariable logistic and linear regression analysis to adjust the association between PPS and primary and secondary outcomes for the following confounders: European System for Cardiac Operative Risk Evaluation score (as an overall measure of operative risk), treatment with intraoperative use of study medication (dexamethasone) and other baseline characteristic differences with a p-value <0.10. Freedom of reoperation for tamponade was compared using Kaplan-Meier survival analysis with log rank analysis. The incidences of one-year outcomes are the Kaplan-Meier estimate of the rate of the endpoint. IBM SPSS version 21 (IBM-SPSS Inc, Armonk, NY) was used for all analyses.

RESULTS

PPS occurred in 119 (14.5%) of the 822 patients. PPS was usually diagnosed on postoperative day 4-6, because at that time, a routine postoperative chest radiograph and echocardiography (needed to establish the diagnosis of PPS) were performed. However, if there was a clinical indication to perform additional investigations at a later moment in the postoperative course, PPS could also be diagnosed afterward. Baseline characteristics of the patients with and without PPS are listed in table 1. BMI, the rate of preoperative corticosteroid use and the rate of prior stroke were significantly lower in patients with PPS. The incidence of treatment for pulmonary disease without corticosteroids and mitral valve surgery was higher in patients with PPS.

Risk factors of PPS

In univariable analyses of baseline characteristics (table 1), a higher BMI (OR per point increase: 0.93, 95% CI 0.88-0.98, p=0.001), prior stroke (OR 0.31, 95% CI 0.11-0.85, p=0.015) and preoperative corticosteroid use (OR 0.24, 95% CI 0.08-0.79, p=0.007) were associated with a lower risk of PPS, whereas mitral valve surgery (OR 1.64, 95% CI 1.11-2.43, p=0.018) and treatment for pulmonary disease without corticosteroids (OR 2.42, 95% CI 1.27-4.63, p=0.011) were associated with a higher risk of PPS. After multivariable logistic regression analysis (table 2), a higher BMI (OR per point increase: 0.94, 95% CI 0.89-0.99, p=0.028) remained as an independent protective factor of PPS. Treatment for pulmonary disease without corticosteroids (OR 2.55, 95% CI 1.25-5.20, p=0.010) was independently associated with a higher risk of PPS.

Table 1. Baseline characteristics

Characteristic	PPS (n=119)	No PPS (n=703)	P-value
Patient characteristics			
Age, median (IQR), years	66.0 (54.0-74.0)	67.5 (59.0-75.0)	0.090
Male sex, n (%)	77 (64.7)	441 (62.7)	0.757
BMI, median (IQR)	24.3 (22.6-26.9)	25.7 (23.5-28.6)	0.001
*Euroscore, median (IQR)	5 (3-7)	6 (3-8)	0.067
Medical history, n (%)			
Diabetes	13 (10.9)	100 (14.2)	0.411
Hypertension	57 (47.9)	346 (49.2)	0.867
Preoperative creatinine, median (IQR), mg/dL	1.04 (0.92-1.22)	1.05 (0.90-1.21)	0.939
Treatment for pulmonary disease	18 (15.1)	88 (12.5)	0.524
- treatment without corticosteroids	14 (11.9)	37 (5.3)	0.011
- treatment with corticosteroids	3 (2.5)	50 (7.1)	0.068
Vascular disease, n (%)			
Prior stroke	4 (3.4)	72 (10.2)	0.015
Peripheral artery disease	6 (5.0)	58 (8.3)	0.306
Coronary artery disease	46 (38.7)	283 (40.4)	0.801
Left ventricular function, n (%)			
Normal, LVEF >50%	94 (79.0)	511 (72.7)	0.105
Moderate, LVEF 35-50%	18 (15.1)	164 (23.3)	
Poor, LVEF <35%	7 (5.9)	28 (4.0)	
Preoperative anti-inflammatory drugs, n (%)			
Corticosteroids	3 (2.5)	68 (9.7)	0.007
Aspirin	38 (31.9)	254 (36.1)	0.435
Intraoperative anti-inflammatory drugs, n (%)			
Dexamethasone	57 (47.9)	364 (51.8)	0.494
Cardiac surgery type, n (%)			
Isolated valve surgery	68 (57.1)	375 (53.3)	0.386
Valve surgery + CABG	34 (28.6)	190 (27.0)	
Other surgery	17 (14.3)	138 (19.6)	
Valve surgery characteristics, n (%)			
Aortic valve only	47 (39.5)	339 (48.2)	0.096
Mitral valve only	53 (44.5)	231 (32.9)	0.018
Tricuspid or pulmonic valve only	1 (0.8)	17 (2.4)	0.496
Multiple valve surgery	18 (15.1)	111 (15.8)	0.962
Perioperative parameters (OR and ICU)			
CPB time, median (IQR), min	141 (96-195)	133 (100-182)	0.435
Aortic cross-clamp time, median (IQR), min	108 (76-148)	101 (76-143)	0.275
No transfusion of packed red cells	78 (66.7)	515 (73.4)	0.104
Transfusion of 1 unit packed red cells	12 (10.3)	68 (9.7)	0.889
Transfusion of ≥ 2 units packed red cells	27 (23.1)	119 (17.0)	0.164

Abbreviations: BMI: Body Mass Index; CABG: Coronary Artery Bypass Grafting; CPB: Cardiopulmonary Bypass; ECG: Electrocardiogram; ICU: Intensive Care Unit; IQR: Interquartile Range; LVEF: Left Ventricular Ejection Fraction; OR: Operation Room; PPS: Post Pericardiotomy Syndrome
*European System for Cardiac Operative Risk Evaluation

Table 2. Multivariable logistic regression analysis of risk factors of PP

Variable	Beta	Odds Ratio (95% CI)	p-value
Age	-0.01	0.99 (0.97-1.02)	0.63
Female sex	0.01	1.02 (0.64-1.60)	0.95
Body Mass Index	-0.06	0.94 (0.89-0.99)	0.03
Arterial Vascular Disease	0.07	1.07 (0.64-1.78)	0.80
Diabetes	-0.09	0.91 (0.46-1.80)	0.79
Treatment for pulmonary disease without corticosteroids	0.94	2.55 (1.25-5.20)	0.01
Preoperative corticosteroid use	-1.03	0.36 (0.11-1.18)	0.09
Preoperative aspirin use	0.01	1.01 (0.62-1.63)	0.97
Dexamethasone treatment	-0.11	0.90 (0.60-1.35)	0.61
CPB time	<0.01	1.00 (0.99-1.01)	0.56
Reoperation for surgical bleeding	0.44	1.55 (0.45-5.36)	0.49
Prior stroke	-0.98	0.38 (0.13-1.10)	0.07
EuroScore*	-0.06	0.94 (0.84-1.05)	0.28
Aortic valve surgery	0.16	1.17 (0.60-2.29)	0.64
Mitral valve surgery	0.37	1.44 (0.78-2.67)	0.24
Transfusion of 1 unit packed red cells	0.20	1.22 (0.59-2.51)	0.59
Transfusion of ≥ 2 units packed red cells	0.50	1.65 (0.93-2.91)	0.09

Abbreviations: CPB: cardiopulmonary bypass; PPS: post pericardiotomy syndrome. Dependent variable: PPS. *European System for Cardiac Operative Risk Evaluation

Effects of PPS on clinical outcomes

The clinical outcomes are listed in table 3. Follow-up data were complete in all 822 patients, except for duration of hospital stay (12 cases missing, 1.5%).

The estimated incidence of a reoperation for tamponade within 1 year after cardiac surgery was 20.9% in patients with PPS versus 2.5% in non PPS patients (OR 10.19, 95% CI 5.28-19.67, p<0.001). A survival curve of reoperation for tamponade is depicted in Figure 1. All reoperations for tamponade occurred in the first 65 days after surgery and in all cases, PPS was diagnosed before the rethoracotomy for tamponade took place. Of the 41 patients who underwent a reoperation for tamponade, 11 patients underwent a subxiphoid drainage, 6 patients initially underwent a pericardial puncture and afterwards a resternotomy (5 patients) or subxiphoid drainage (1 patient) and 24 patients underwent a resternotomy as initial choice. The pericardial puncture in the 6 patients that required an additional surgical procedure afterwards was unsuccessful in 1 patient, complicated by right ventricular puncture in 2 patients and 3 patients had recurrence of pericardial fluid after the puncture.

Median duration of hospital stay was 13 days (IQR 9-18) in the PPS group and 11 days (IQR 8-15) in the non PPS group (p=0.001). Patients with PPS underwent significantly more reinterventions within 30 days after cardiac surgery compared with the non PPS group;

reoperation for tamponade occurred in 17.6% versus 2.4% of the patients respectively (OR 8.65, 95% CI 4.41-16.96, p<0.001) and pericardial puncture in 7.6% versus 0.6% respectively (OR 14.30, 95% CI 4.33-47.23, p<0.001). There were no significant differences in the incidence of reoperation for surgical bleeding, pleural puncture, postoperative AF, mortality, stroke, myocardial infarction and readmissions between the two groups. Of the 15 patients who underwent an early reoperation for surgical bleeding, 4 patients developed PPS afterwards.

Regression analyses

We adjusted the association between the presence of PPS and the primary and secondary outcomes for the following variables using multivariable regression analysis: age, BMI, history of stroke, treatment for pulmonary disease without corticosteroids, preoperative corticosteroid use, dexamethasone treatment, European System for Cardiac Operative Risk Evaluation score, aortic valve surgery and mitral valve surgery. Adjusted ORs and p-values are listed in table 4. After adjustment, the risk of reoperation for tamponade (at one month and one year after cardiac surgery), pericardial puncture at one month, and the total length of hospital stay remained significantly higher in the PPS group.

Table 3. Clinical outcomes

	PPS (n=119)	No PPS (n=703)	p-value	OR (95% CI)
Primary outcome				
Reoperation (tamponade) < 1 year, n (%)*	24 (20.9)	17 (2.5)	<0.001	10.19 (5.28-19.67)
Secondary outcomes				
Short term outcomes (1 month)				
Total hospital stay, days, median (IQR)	13 (9-18)	11 (8-15)	0.002	NA
Reoperation (tamponade), n (%)	21 (17.6)	17 (2.4)	<0.001	8.65 (4.41-16.96)
Reoperation (rebleed), n (%)	4 (3.4)	11 (1.6)	0.325	2.19 (0.69-6.99)
Pericardial puncture, n (%)	9 (7.6)	4 (0.6)	<0.001	14.30 (4.33-47.23)
Pleural puncture, n (%)	7 (5.9)	21 (3.0)	0.181	2.03 (0.84-4.89)
Postoperative AF, n (%)	71 (59.7)	423 (60.2)	0.997	0.98 (0.66-1.46)
Long term outcomes (1 year)				
Death, n (%)*	4 (4.2)	37 (5.5)	0.497	0.63 (0.22-1.79)
Stroke, n (%)*	2 (2.0)	13 (2.0)	1.000	0.91 (0.20-4.07)
Myocardial infarction, n (%)*	2 (2.1)	15 (2.3)	1.000	0.78 (0.18-3.47)
Readmission (any reason), n (%)*	23 (22.7)	153 (23.4)	0.632	0.86 (0.53-1.40)

Abbreviations: AF: Atrial Fibrillation; CI: Confidence Interval; IQR: Inter Quartile Range; NA: Not Applicable; OR: Odds Ratio; PPS: Post Pericardiotomy Syndrome. *The percentage is the Kaplan-Meier estimate of the rate of the endpoint

Table 4. Unadjusted and adjusted odds ratios for the association between PPS and the primary and secondary study outcomes

Variable	Univariable		Multivariable*	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Primary outcome				
Reoperation (tamponade) < 1 year	10.19 (5.28-19.67)	<0.001	15.49 (7.14-33.58)	<0.001
Secondary outcomes				
Short term outcomes (1 month)				
Total hospital stay	NA	0.002	NA	0.001
Reoperation (tamponade)	8.65 (4.41-16.96)	<0.001	13.52 (6.08-30.05)	<0.001
Reoperation (rebleed)	2.19 (0.69-6.99)	0.325	2.02 (0.61-6.67)	0.250
Pericardial puncture	14.30 (4.33-47.23)	<0.001	20.43 (5.25-79.58)	<0.001
Pleural puncture	2.03 (0.84-4.89)	0.181	2.42 (0.96-6.05)	0.060
Postoperative AF	0.98 (0.66-1.46)	0.997	1.01 (0.66-1.55)	0.965
Long term outcomes (1 year)				
Death	0.63 (0.22-1.79)	0.497	0.68 (0.22-2.08)	0.494
Stroke	0.91 (0.20-4.07)	1.000	0.90 (0.19-4.27)	0.893
Myocardial infarction	0.78 (0.18-3.47)	1.000	0.87 (0.19-3.99)	0.861
Readmission (any reason)	0.86 (0.53-1.40)	0.632	0.93 (0.56-1.54)	0.765

Abbreviations: AF: Atrial Fibrillation; CI: Confidence Interval; IQR: Inter Quartile Range; NA: Not Applicable; OR: Odds Ratio; PPS: Post Pericardiotomy Syndrome. *Adjusted for: PPS, EuroScore, Age, Body Mass Index, history of stroke, treatment for pulmonary disease without corticosteroids, preoperative corticosteroid, dexamethasone treatment, aortic valve surgery and mitral valve surgery.

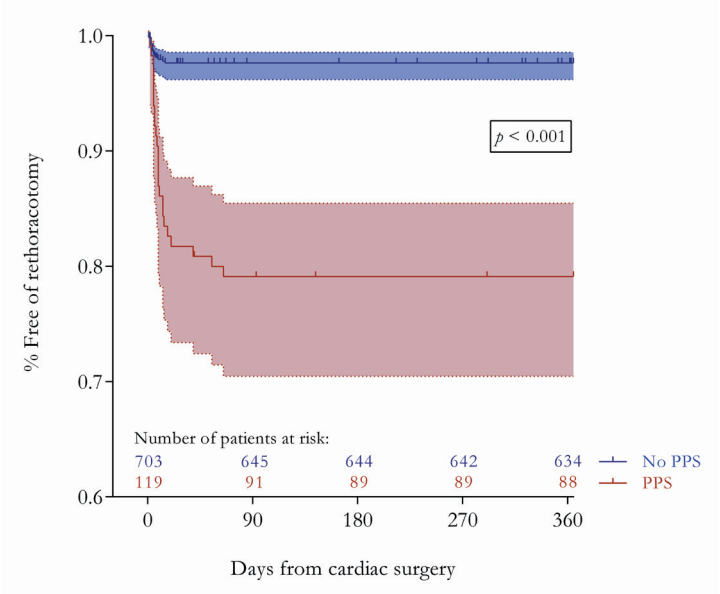

Figure 1. Survival free from reoperation for tamponade in PPS versus no PPS patients
Abbreviations: PPS: Post Pericardiotomy Syndrome

DISCUSSION

The present study is among the largest cohort studies of PPS, investigating both risk factors and long-term prognosis of PPS in valve surgery patients. In our study, PPS was associated with an increased incidence of reinterventions for tamponade. PPS was also associated with significantly longer postoperative hospitalization. There was no difference in the number of reoperations for tamponade in the first five postoperative days. Most likely, reoperations for tamponade that occur in the first five postoperative days, represent common bleeding related complications after cardiac surgery. After five days, the incidence of reoperations for tamponade in PPS patients increased significantly compared with patients without PPS, suggesting a different underlying mechanism of early versus late tamponade. The higher incidence of reinterventions in patients with PPS did not lead to differences in long-term outcome. Survival and readmissions at one year after cardiac surgery did not differ between the two study groups. The findings of the present study partially correspond with results of prior reports on the prognosis of PPS. Differences in study design, study population and definition of PPS may explain these discrepancies.

The most recent study, performed by Lehto and colleagues, investigated the prognosis of PPS in 688 patients undergoing coronary artery bypass grafting (CABG). There were no differences in total hospital stay and the incidence of resternotomy between patients with and without PPS (10). Chest radiograph and echocardiography results were not available for all of the 688 patients. Furthermore, no thresholds for minimal amounts of pleural and pericardial effusion were used. This and the difference in study population (CABG versus valve surgery) may be a reason for the different findings. A study by Imazio and colleagues in 360 patients undergoing any type of cardiac surgery found longer hospital stays in patients with PPS, which is confirmed by our study. In contrast to our study, that study also reported significantly more readmissions in the PPS group. The incidence of tamponade was remarkably lower than in our study: 1.9% in patients with PPS (3). Another study by Alraies and colleagues, which investigated 239 patients with PPS found a higher incidence of reinterventions, namely 31% (2). In our study, the rate of reoperation for tamponade was 20.9% in the PPS group. In the main study of 4494 patients, dexamethasone treatment was associated with an increased rethoracotomy risk (9). However, in the present study there was no difference in baseline dexamethasone use in patients with and without PPS. Furthermore, we investigated dexamethasone treatment in the multivariable analysis, therefore it is unlikely that this is the reason for the high incidence of reoperations in PPS patients. To perform a full resternotomy or a less invasive approach was at the discretion of the attending surgeon and was based on factors such as: expected active bleeding, the location of the pericardial effusion and presence of intrapericardial thrombus. Pericardial puncture has the advantage of being less-invasive and can be performed with local anesthetics only. However, in some cases this approach might be unsuccessful and an additional surgical intervention might be required. Furthermore, pericardial puncture has been associated with higher recurrence rates due to incomplete fluid evacuation and carries the risk of a complicated ventricular puncture (11, 12). These findings were confirmed in our study. Given the high incidence of reoperations for tamponade, we believe that PPS is an important complication of cardiac surgery, leading to prolonged hospital stay. Preventing PPS might thus be worthwhile, in particular for patient comfort and cost-effectiveness. For this reason, we aimed to identify preoperative risk factors of PPS.

Remarkably, a higher BMI was independently associated with a lower risk of PPS. The finding that a higher BMI was negatively associated with PPS has been reported before (13), however in more recent studies a lower BMI was not associated with PPS (10, 14). A possible explanation for higher BMI as protective factor of PPS can be the immunomodulatory effects of obesity. Excessive visceral fat is associated with increased interleukin-6 (IL-6) production and chronic, subclinical, systemic inflammation (15, 16). On the other hand, a higher BMI is also associated with higher levels of anti-inflammatory interleukins (17), which might protect against PPS.

Although we did not demonstrate a protective effect of a single intraoperative dose of 1 mg/kg dexamethasone on the occurrence of PPS (6), chronic corticosteroid use was associated with a reduced incidence of PPS in univariable analysis. This finding supports the hypothesis of a postoperative ongoing inflammatory process. Corticosteroids inhibit the synthesis of IL-8 and other pro-inflammatory mediators, and may therefore protect against PPS (14). However, after multivariable analysis there was no significant association between chronic corticosteroid use and PPS anymore, questioning the potential efficacy of corticosteroid treatment for the prevention of PPS. Earlier trials investigating corticosteroid treatment for the prevention of PPS also do not show convincing evidence in favor of corticosteroids (6, 18, 19).

In our study, treatment for pulmonary disease was defined as pulmonary disease requiring daily inhaled maintenance treatment with bronchodilators and/or corticosteroids. Because there was a strong relation between treatment for pulmonary disease and corticosteroid use, we only included treatment for pulmonary disease without corticosteroids in the multivariable model. After multivariable logistic regression analysis, treatment for pulmonary disease without corticosteroids was associated with a higher risk of PPS. A possible explanation could be that patients with chronic pulmonary inflammation are more vulnerable to develop systemic and pericardial inflammation, however, this finding has never been reported before.

An earlier study showed that transfusion of 1 or more units of red blood cells was associated with a higher risk of PPS (10), suggesting that bleeding may play a role in the development of PPS. Retained blood in the pericardial and pleural space is believed to induce a local inflammatory response that can lead to effusions (20-22). However, in our study transfusion of packed red cells was not associated with an increased risk of PPS. It has been suggested that increasing age is associated with a lower risk of PPS, due to a senescent immune system in the elderly (13, 23-25). In other studies and in our study, this protective effect of aging could not be confirmed (3, 10). Use of CPB has also been suggested as a possible etiologic factor of PPS and might lead to more reoperations (26), although duration of CPB was not associated with PPS in our study.

A strength of our study is the relatively large size of the study population and the fact that investigators were blinded to the diagnosis of PPS during data collection. A limitation of this study is that some data were collected retrospectively. Therefore, it was not possible to collect all clinically important variables, such as colchicine use, pericardial closure and use of a pleural window. Also no long-term data were available to evaluate the development of constrictive pericarditis, however no patient underwent a reoperation because of constrictive pericarditis in the first year after surgery. We thoroughly collected all other available data and used the prospectively available dataset of the DECS trial. We therefore believe that there is a low risk of having missed important clinical outcomes. Another limitation is the study population that

consisted of valve surgery patients only, because of the availability of routine postoperative echocardiography in these patients. Furthermore, because of the current definition of PPS, it is likely that some patients may fall within the definition of PPS, without having clinically relevant PPS. By only scoring pericardial effusions ≥10 mm and pleural effusions above the level of the diaphragm, we aimed to minimize this probability.

CONCLUSION

Despite longer hospital stays and more short-term reoperations for tamponade, patients with PPS had an excellent one-year prognosis.

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Conflict of interest

All authors report no conflicts of interests.

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Chapter 4

Dexamethasone for the prevention of postpericardiotomy syndrome: a DExamethasone for Cardiac Surgery (DECS) substudy

Am Heart J. 2014 Jul;168(1):126-31

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ABSTRACT

Background

The postpericardiotomy syndrome (PPS) is a common complication following cardiac surgery. The pathophysiology remains unclear, although evidence exists that surgical trauma and the use of cardiopulmonary bypass (CPB) provoke an immune response leading to PPS. We hypothesized that an intraoperative dose of dexamethasone decreases the risk of PPS, by reducing this inflammatory response.

Methods

We performed a sub-analysis of the DExamethasone for Cardiac Surgery (DECS) study, which is a multicenter, double-blind, placebo controlled, randomized trial of 4.494 patients undergoing cardiac surgery with use of CPB. The aim of the DECS study was to investigate whether a single intraoperative dose of 1 mg/kg dexamethasone reduced the incidence of a composite of death, myocardial infarction, stroke, renal failure, or respiratory failure, within 30 days of randomization. In this substudy, we retrospectively analyzed the occurrence of PPS in 822 patients who were included in the DECS trial and underwent valvular surgery. PPS was diagnosed if two out of five listed symptoms were present: Unexplained fever, pleuritic chest pain, pericardial or pleural rub, new or worsening pericardial or pleural effusion. All medical charts, X-rays and echocardiograms were reviewed. Secondary endpoint was the occurrence of complicated PPS, defined as PPS with need for evacuation of pleural effusion, pericardiocentesis, tamponade requiring intervention or hospital readmission for PPS. This is a blinded, single center, post-hoc analysis.

Results

PPS occurred in 119 (14.5%) patients. The incidence of PPS after dexamethasone compared with placebo was 13.5% vs 15.5%, (RR 0.88, 95% CI 0.63-1.22). For complicated PPS, the incidence was 3.8% vs 3.2% (RR 1.17, 95% CI 0.57-2.41, p=0.66) respectively.

Conclusion

In patients undergoing valvular cardiac surgery, high dose dexamethasone treatment had no protective effect on the occurrence of PPS or complicated PPS.

INTRODUCTION

Cardiac surgery using cardiopulmonary bypass (CPB) has been successfully implemented in clinical practice since the 1950s. Although these operations are nowadays among the most frequently performed surgical procedures, there is still a substantial risk of developing perioperative complications.

The combination of surgical trauma and CPB provokes a systemic inflammatory response in humans, and some complications may be related to this process (1). To attenuate the inflammatory response, it is routine practice in many European countries to give a single dose of long acting corticosteroids during the operation, although definitive evidence of its efficacy is lacking (2). The recently published DExamethasone for Cardiac Surgery (DECS) trial was designed to quantify the effect of a single intraoperative high dose (1.0 mg/kg) dexamethasone on the incidence of major adverse events in patients undergoing cardiac surgery (3). The study showed no statistical significant benefit of dexamethasone on the primary outcome, which was a composite of death, myocardial infarction, stroke, renal failure, or respiratory failure at 30 days, but the use of dexamethasone was associated with a decrease in duration of mechanical ventilation, length of intensive care unit and hospital stay, and a lower risk of infection.

The Post Pericardiotomy Syndrome (PPS) is characterized by prolonged fever, pleuritis and/or pericarditis, with an onset usually around postoperative day 4-5, although widespread intervals of onset have been reported (4). The syndrome may cause serious complications such as cardiac tamponade, need for readmission and recurrent pleural effusions. Although it is not a well-defined entity, and several definitions have been used in the past, lately some research groups have worked with the following definition, diagnosing PPS in the presence of at least two out of five listed symptoms: new pericardial effusion, new pleural effusion, fever, pleuritic chest pain, and pericardial or pleural rubbing on physical examination (5). PPS is thought to be related to inflammation and auto-immune phenomena (6-8). Only a few studies on pharmaceutical prophylaxis to reduce the incidence of PPS have been performed thus far, most of them with negative results (9-12). In contrast, the COlchicine for the Prevention of the Post-pericardiotomy Syndrome (COPPS) study showed a significant reduction in PPS after a postoperative regime of colchicine (13). The aim of the present post hoc analysis of the DECS trial was to investigate whether a single high-dose of dexamethasone reduces the incidence of PPS in patients undergoing valvular surgery.

METHODS

Study design and population

The DECS study was a multicenter, randomized, double-blind, placebo controlled trial comparing a single intraoperative dose of 1 mg/kg dexamethasone with placebo in 4494 patients undergoing cardiac surgery, between April 13, 2006, and November 23, 2011 in 8 centers in The Netherlands (trial registration: ClinicalTrials.gov, number NCT00293592). Inclusion criteria were age older than 18 years and elective or urgent cardiac surgery requiring CPB. Exclusion criteria were emergency and off-pump procedures.

For the current analysis, we analysed all patients who were included at the University Medical Center Utrecht (UMCU), and underwent valvular surgery with or without Coronary Artery Bypass Graft (CABG). We chose only valvular surgery patients from a single center because of the availability of all relevant parameters, including routine echocardiography, which was usually performed around day 4-6 postoperatively. For this additional analysis, we formulated the following exclusion criteria: other surgery than valvular surgery, no postoperative echocardiography available, and other missing follow-up data needed to establish the diagnosis of PPS. This was a blinded post-hoc analysis.

Intervention

Patients were randomized to receive an intravenous injection with dexamethasone (1.0 mg per kg, with a maximum dose of 100 mg) or placebo, immediately after induction of anesthesia, but before initiation of CPB.

Outcome

Primary endpoint of the present substudy was the occurrence of PPS. The diagnosis of PPS was established when at least two out of five diagnostic criteria were present: new significant pericardial effusion on echocardiography, new significant pleural effusion on chest X-ray, unexplained fever > 72 hour postoperatively, pleuritic chest pain, and presence of pericardial or pleural rubbing on physical examination.

Apart from the incidence of PPS, we monitored the incidence of complicated PPS in both subgroups as a secondary endpoint. The definition of complicated PPS was PPS plus one of the following: need for evacuation of pleural effusion, pericardiocentesis, (threatening) tamponade requiring intervention, or hospital readmission for PPS.

Assessment of outcome

We investigated the five individual components of the earlier proposed definition of PPS, by reviewing all medical records, and re-examining all chest X-rays and echocardiograms. The presence of fever was obtained from the nursing observations charts. For this analysis we only recorded patients with a temperature rise of ≥38° Celsius, with an onset on postoperative day 3 or later (≥72 hours postoperatively), in absence of other explanations of fever e.g. infection. All medical charts were screened for the presence of pericardial or pleural rubbing and signs of typical chest pain.

We decided to record the amounts of pleural and pericardial effusions, rather than just presence or absence, using semi-quantitative scales, because most of all postoperative patients will have some effusions. In this way we intended to record only clinically relevant effusions, and formulated cut-off values to categorize effusions in a more objective way. All X-rays from postoperative day 4 onwards were reviewed for amounts of pleural effusion. Effusions were scored using the following semi-quantitative scale: 0: no effusion, 1: minor effusion, not above the highest level of the diaphragm, 2: moderate effusion, above the highest level of the diaphragm but less than 25% of chest height, and 3: large effusion, more than 25% of chest height, or need for pleural tap. The postoperative day of maximum effusion and unilateral versus bilateral effusion were recorded as well. For the diagnosis of PPS, an effusion grade 2 or higher was considered significant.

Echocardiograms were reviewed for the presence of pericardial effusions. The postoperative day of the echocardiogram was recorded, as well as any pericardiocentesis or tamponade. Pericardial effusion was measured end-diastolic using the minimum amount in all available ultrasound windows and was recorded in the following categories, in line with American Society for Echocardiography recommendations: 0: no effusion, 1: < 10 mm, 2: 10-20 mm, 3: ≥ 20 mm. For the diagnosis of PPS, an effusion > 10 mm was considered significant. After obtaining the 5 components of PPS, it was decided for all individual cases whether PPS was present. To limit observer bias, this was done by two independent, blinded, researchers. Mismatched cases were discussed and judged together. Apart from the 5 components of PPS, all readmissions, need for pericardiocentesis, drainage of pleural effusions and re-operation for cardiac tamponade were documented as well.

Randomization and blinding

Detailed information about the randomization procedure can be found in the main study article (3). Patients, attending physicians, and all study personnel including the co-authors JB and DvO who evaluated the outcomes of the present analysis, were blinded for treatment allocation.

Statistical analysis

Data analyses were performed by intention to treat. Continuous variables are expressed as mean +/- SD or as median with interquartile range (IQR). Dichotomous variables are expressed as the number of cases followed by a percentage (n, (%)). For the comparison of the proportions of patients with the primary study outcomes, we used the $\chi 2$ test. We calculated relative risks with 95% Confidence Intervals (CIs) for the primary outcome and its individual components. Comparisons between treatment groups were performed using the Student t test or Mann-Whitney U test for continuous variables (as appropriate) and a $\chi 2$ analysis for categorical variables. We used logistic regression to adjust the outcome for possible baseline differences between study groups. A value of $p<0.05$ was considered to show statistical significance. IBM SPSS version 20 (SPSS Inc) was used for all analyses.

Funding

The DECS trial was supported by grants 80-82310-98-08607 from the Netherlands Organization for Health Research and Development (ZonMw) and 2007B125 from the Dutch Heart Foundation. No extramural funding was used to support this substudy. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the manuscript and its final contents.

RESULTS

Baseline characteristics

Of the 852 patients undergoing valvular surgery, 30 (3.5%) were excluded because of missing echocardiograms (n=20), or missing clinical data (n=10). The flowchart of patients in the present study is depicted in Figure 1. 401 patients were randomized to receive placebo treatment and 421 patients received dexamethasone. The baseline characteristics are listed in Table 1.

Table 1. Baseline characteristics

Characteristic	Dexamethasone (n=421)	Placebo (n=401)
Patient characteristics		
Age (mean±SD), years	65.5±13.1	64.7±12.7
Male sex, n (%)	268 (63.7)	250 (62.3)
EuroScore*, median (IQR)	5 (3-7)	6 (3-8)
Medical history, n (%)		
Hypertension	211 (50.1)	192 (47.9)
Diabetes	60 (14.3)	53 (13.2)
Preoperative use of: n (%)		
Corticosteroids	48 (11.4)	23 (5.8)
Aspirin	162 (38.5)	130 (32.4)
Left ventricular function, n (%)		
Good, EF >50%	303 (72.0)	302 (75.3)
Moderate, EF 30-50%	104 (24.7)	78 (19.5)
Poor, EF <30%	14 (3.3)	21 (5.2)
Cardiac surgery type, n (%)		
Isolated valvular surgery	281 (66.7)	284 (70.8)
Valvular surgery + CABG	140 (33.3)	117 (29.2)
Bypass type, n (%)		
LIMA	98 (23.3)	77 (19.2)
RIMA	4 (1.0)	2 (0.5)
LIMA + RIMA	8 (1.9)	9 (2.2)
Saphenous Vein	30 (7.1)	29 (7.2)
Intraoperative parameters		
CPB time (mean±SD), minutes	149±75	151±66
Aortic crossclamp time (mean±SD), minutes	115±54	116±50

Abbreviations: SD, standard deviation; IQR, interquartile range; EF, ejection fraction; CABG, coronary artery bypass graft; LIMA, left internal mammary artery; RIMA, right internal mammary artery; CPB, cardiopulmonary bypass.
*EuroScore preoperative risk estimate

The study groups were similar with respect to all demographic, clinical and surgical characteristics, except for a higher percentage of patients already using corticosteroids pre-operatively for clinical indications in the dexamethasone group (11.4% vs 5.8%). These patients received the full dose of dexamethasone or placebo according to their randomization status. In addition, baseline characteristics of this subgroup were comparable to baseline characteristics of the original DECS cohort. An important difference was, however, that no patients undergoing isolated CABG were included in the present sample.

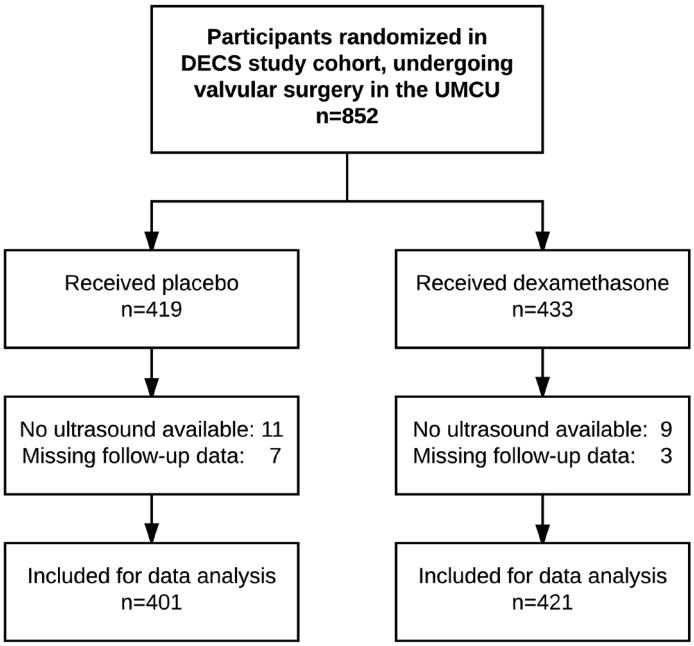

Figure 1. Study Flowchart
Abbreviations: DECS: DExamethasone for Cardiac Surgery; UMCU: University Medical Center Utrecht

Main outcomes

Results for the primary and secondary outcomes are listed in table 2. PPS occurred in 119 (14.5%) patients. A total of 29 patients (3.5%) developed complicated PPS. The risk of patients with PPS to develop complicated PPS was 24.4% (95% CI 0.17-0.33).

The incidence of PPS in the dexamethasone group was 13.5% versus 15.5% in the placebo group (RR 0.88, 95% CI 0.63-1.22, p=0.43). Complicated PPS occurred in 3.8% in the dexamethasone group versus 3.2% with placebo (RR 1.17, 95% CI 0.57-2.41, p=0.66). No significant differences were found between groups for the individual components of PPS, except for pleural effusions. Patients treated with dexamethasone had more often no pleural effusions compared with the placebo group: respectively 19.7% vs. 14.3% (RR 1.37, 95% CI 1.01-1.87, p=0.04).

We could not identify patients suffering pleuritic chest pain, because this was not recorded specifically enough in the medical charts. As a consequence, the diagnosis of PPS was established when two of four criteria (pleural effusions, pericardial effusion, fever and pericardial or pleural rubbing) were present.

Logistic regression

We corrected the primary and secondary outcome for the baseline difference in preoperative use of corticosteroids, using logistic regression. The corrected odds ratio for developing the primary outcome was 0.88 (95% CI 0.59-1.30, p=0.52) and 1.11 (95% CI 0.52-2.38, p=0.78) for the secondary outcome (dexamethasone vs. placebo).

Table 2. Results

Outcome	Dexamethasone (n=421)	Placebo (n=401)	RR (95% CI)
Primary study end point, n (%)			
PPS	57 (13.5)	62 (15.5)	0.88 (0.63-1.22)
Individual components of PPS, n (%)			
Pericardial effusions*			
<10 mm	399 (94.8)	387 (96.5)	0.98 (0.95-1.01)
10-20 mm	15 (3.6)	11 (2.7)	1.30 (0.60-2.79)
>20 mm	7 (1.7)	3 (0.7)	2.22 (0.58-8.54)
Pleural effusions			
None	82 (19.7)	56 (14.3)	1.37 (1.01-1.87)‡
Below level of diaphragm	237 (56.8)	231 (59.1)	0.96 (0.86-1.08)
<25% of the thorax	74 (17.7)	84 (21.5)	0.83 (0.62-1.09)
≥25% of the thorax	24 (5.8)	20 (5.1)	1.13 (0.63-2.00)
Unexplained fever†≥ day 3	56 (13.3)	64 (16.0)	0.83 (0.60-1.16)
Pericardial rubbing	102 (24.2)	87 (21.7)	1.11 (0.87-1.44)
Secondary end point			
Complicated PPS, n (%)	16 (3.8)	13 (3.2)	1.17 (0.57-2.41)
Pericardiocentesis or rethoracotomy for (threatening) tamponade§	11 (2.6)	8 (2.0)	1.31 (0.53-3.22)
Evacuation of pleural effusion§	5 (1.2)	4 (1.0)	1.18 (0.32-4.36)
Readmission for PPS§	3 (0.7)	8 (2.0)	0.36 (0.10-1.34)

Abbreviations: CI: Confidence Interval; PPS: Post Pericardiotomy Syndrome; RR: Relative Risk. *Minimal amount of effusion, measured end-diastolic on transthoracic/subcostal echocardiogram. †Definition of fever: temperature ≥ 38.0° Celsius. ‡Significant difference ($p<0.05$). §Occurrence of tamponade, evacuation of pleural fluid and readmissions in individuals with established PPS

DISCUSSION

The present study is the largest trial investigating the potential beneficial effect of corticosteroids on the incidence of PPS after cardiac surgery. We found no protective effect of a single high intraoperative dose of dexamethasone on the occurrence of PPS or complicated PPS in a cohort of adult patients undergoing valvular surgery.

The etiology of PPS is not exactly known, but multiple factors related to inflammation are involved. First, it has been hypothesized that surgical trauma may provoke an auto-immune based inflammatory reaction (6, 7). Second, the use of CPB has been shown to aggravate a systematic inflammatory response and this may enhance the development of PPS (1).

However, there are several reports of complicated PPS after off-pump procedures as well (14, 15). Established PPS can be treated with anti-inflammatory drugs such as NSAID's, steroids, and colchicine (12, 16-19). It is obvious that PPS and its complications can have a deleterious

effect on the rehabilitation process. This is why prophylactic treatment with anti-inflammatory drugs for the prevention of PPS has been investigated as well.
A few studies on the prevention of PPS were retrieved from the literature with variable outcomes. We could not find any studies investigating the preventive role of corticosteroids in adult patients. The results of the present study are in agreement with the study by Mott et al (11), in which a prophylactic regimen of methylprednisolone in children undergoing cardiac surgery failed to reduce the incidence of PPS, using a slightly different definition. Noteworthy, in contrast to this study, they reported a higher proportion of patients with complicated PPS in the methylprednisolone group. Another smaller study in children treated with prednisone for established PPS, suggested earlier clinical recovery, but also showed a tendency towards larger pericardial effusions in the methylprednisolone treated group (12). In contrast to these earlier, smaller studies in children, we did not find such a difference in the amount of the effusions in our study in adult patients. Earlier data suggest that the risk for full-blown PPS decreases with age, and that the immune system and its reaction to insults such as pericardiotomy may differ between adults and children (20).
As opposed to the results with corticosteroids, colchicine was found to be effective in preventing PPS in a pilot trial, and in the larger COPPS trial (9, 13). This study showed a remarkable reduction of more than 50% in the incidence of PPS with a prophylactic regimen of colchicine treatment starting on postoperative day 3 and lasting for one month.
Given our results and earlier negative trials, we conclude that currently there is no role for corticosteroid therapy for the prevention of PPS. Nevertheless, different steroid regimens, that is starting some days before operation, or repeated administration after operation, could further inhibit the inflammatory reactions involved in the development of PPS, and may therefore be more effective than the investigated single dose. Because corticosteroid therapy seemed safe in the DECS trial, there may be a rationale to investigate different steroid regimens. To date, the only positive trial on prevention of PPS is the COPPS trial. Recently, the design of the COPPS-2 trial was published, which may generate further evidence for colchicine to prevent PPS (21).
The strength of the current study is its big sample size. It represents a large group of adult patients undergoing daily practice valvular surgery with or without CABG. The randomization protocol resulted in a comparable distribution of baseline characteristics between the treatment groups. The difference in chronic pre-operative use of corticosteroids did not affect the outcome as was shown by logistic regression analysis.
Clinical data, daily recordings of temperature measurement and auscultated heart and lung sounds were well documented, and the same holds for the availability of chest X-rays and echocardiograms. The incidence of PPS found in our study, corresponds to incidences mentioned in earlier studies (4, 20). A problem that we encountered is the lack of a universal and clear definition of PPS. Several definitions have been used in the literature. In our population, the character of the pain patients suffered, was not described well enough to distinguish pleuritic chest pain from common postoperative pain after sternotomy (e.g. wound pain). This may be due to the fact that this was not a pre-specified item that was to be recorded in the DECS trial. In the end, we chose to leave out this component of PPS. Another problem with the various definitions of PPS is not defining a threshold for pleural or pericardial effusions. As we have shown, most patients have some minor pleural or pericardial effusion, which is not surprising

after thoracotomy and pericardiotomy, and usually has no clinical relevance. We used standardized measurements of pericardial effusions and a semi-quantitative analysis for pleural effusions on chest X-rays, giving more objective criteria for PPS. In addition, earlier concerns regarding a possible increase of pericardial or pleural fluids by steroids warrant the need for quantification of fluids, rather than only stating its presence or absence.

Limitations

This study has some limitations. The present analysis is a retrospective analysis, as occurrence of the individual components of PPS or complicated PPS was not a predefined outcome measure in the DECS study. The retrospective study design prevented us from collecting meaningful data on pleuritic pain. However, even in a prospective setting, distinction between wound pain and pleuritic pain in the post-operative phase is very difficult while using strong painkillers. The incidence of pericardial and pleural rubbing may have been underreported, although physical examination results were recorded daily. In addition, we only included patients who underwent valvular surgery with or without CABG, because of the availability of routine postoperative echocardiograms in these patients. Therefore the results cannot be generalized to patients undergoing isolated CABG.

Finally, we evaluated a single intraoperative dose of dexamethasone. Therefore, no conclusions can be made for other steroid regimes, that is starting preoperatively, or repeating doses in the postoperative phase

CONCLUSION

Prophylactic dexamethasone treatment was not able to reduce the occurrence of PPS or complicated PPS. A useful preventive strategy for PPS as a common complication after cardiac surgery remains to be defined, as patients who develop PPS are at risk for complications.

Conflict of interest

All authors report no conflicts of interests.

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Chapter 5

Dexamethasone for the prevention of postoperative atrial fibrillation

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ABSTRACT

Background

Postoperative atrial fibrillation (AF) is a common complication after cardiac surgery. Inflammation is believed to play a pivotal role in the etiology of postoperative AF. There is a suggestion from small studies that perioperative treatment with corticosteroids may reduce postoperative AF. The DExamethasone for Cardiac Surgery (DECS) study was a large randomized trial showing no protective effect of dexamethasone on major adverse events. The aim of this study was to investigate the effect of dexamethasone treatment on the occurrence of AF after cardiac surgery.

Methods

The DECS study compared intra-operative dexamethasone (1 mg/kg) or placebo treatment in 4,494 adult patients undergoing cardiac surgery. AF was defined by the occurrence of any reported AF within 30 days after surgery. We also performed an in-depth analysis of a subset of 1,565 patients on new-onset AF. Relative risks (RRs) with 95% confidence intervals (CIs) were calculated.

Results

The incidence of any AF in the main study of 4494 patients was 33.1% in the dexamethasone and 35.2% in the placebo group (RR 0.94, 95% CI: 0.87–1.02, p=0.14). In the substudy of 1565 patients, the incidence of new-onset AF was 33.0% vs. 35.5% (RR 0.93, 95% CI: 0.81–1.07, p=0.31), respectively. There was no protective effect of dexamethasone across clinically important patient subgroups.

Conclusion

Intraoperative administration of dexamethasone had no protective effect on the occurrence of any or new-onset atrial fibrillation after cardiac surgery. Therefore, the use of dexamethasone for the reduction of postoperative AF should not be recommended.

INTRODUCTION

Postoperative atrial fibrillation (AF) is a common complication after cardiac surgery, with reported incidences ranging from 10% up to 65%, depending on the type of surgery. A review of Maisel *et al.* (1) reported the lowest incidences in patients undergoing heart transplantation (11%), and isolated coronary artery bypass grafting (CABG) (23-33%). The highest incidences were found in patients undergoing isolated valve replacement (33-49%) and valve replacement combined with CABG (36-63%). Most frequently, postoperative AF has an onset between postoperative day 1 and 4 (1, 2). Postoperative AF is associated with an increased risk of mortality, stroke, prolonged hospital stay (intensive care unit and ward) and higher costs (3-5).

The pathophysiology of AF after cardiac surgery is not well understood and is believed to be multifactorial. Possible mechanisms leading to AF are structural and electrical remodeling, due to (pre)operative atrial injury. This remodeling leads to a change in conduction properties of the heart and could be a new focus for re-entry arrhythmias. Furthermore, changes in chemical and metabolic milieus and an increased adrenergic tone are possible mechanisms underlying postoperative AF (6).

There is also data suggesting that postoperative myocardial inflammation might be an etiological factor (7). It has been shown that the use of cardiopulmonary bypass (CPB) induces a major postoperative inflammatory response through complement activation (8, 9). Surgical trauma and reperfusion injury also contribute to this inflammatory reaction (10). Supportive to this hypothesis is the finding that higher, postoperative C-reactive protein levels are associated with an increased risk of postoperative AF and atrial biopsies of patients with postoperative AF show signs of inflammation (8). Steroids are potent inhibitors of the inflammatory cascade and their perioperative use may reduce morbidity after cardiac surgery. There are multiple studies showing that an intraoperative dose of dexamethasone reliably reduces postoperative CRP, leukocytes and other inflammatory markers (8, 11-13). Several meta-analyses evaluated the effect of corticosteroids on postoperative AF (8, 14-17) and reported a reduction of AF in patients treated with corticosteroids. Corticosteroids that have been investigated are dexamethasone, methylprednisolone, prednisolone and hydrocortisone. Limitations of these meta-analyses however, were the heterogeneity of the included studies and their small sample size. The largest study so far, however, is a well-designed randomized clinical trial in 294 patients, evaluating the effect of hydrocortisone 100 mg during 3 postoperative days on atrial fibrillation. In this trial, the incidence of AF was reduced from 48% to 30% (p=0.004) (18).

We recently published the main outcome of the DExamethasone for Cardiac Surgery (DECS) trial (10). There was no protective effect of dexamethasone on the primary outcome composed of death, myocardial infarction, stroke, renal failure and respiratory failure. In contrast to the aforementioned meta-analyses, in the DECS trial we did not observed a protective effect of dexamethasone on any postoperative AF. However in the DECS trial data regarding AF was not systematically collected and AF was considered present if mentioned in discharge letters. Data on new-onset AF was not collected at all. We hypothesized that the unexpected lack of a positive effect of dexamethasone observed in the DECS trial, might be explained by underreporting any postoperative AF or by neglecting new-onset AF.

In the present study, we thoroughly evaluated the occurrence of any or new-onset postoperative AF by reviewing all medical files and ECGs in a subsample of 1,565 patients. We also analyzed the effect of dexamethasone in clinically relevant subgroups of patients.

METHODS

Study design and population

The design of the DExamethasone for Cardiac Surgery (DECS) study, which is a large double-blind, randomized, placebo-controlled, multicenter trial, investigating the effects of preoperative administration of dexamethasone intravenously (1 mg/kg) on major complications within the first 30 days after surgery, was published elsewhere (10). Briefly, all adult patients (18 years or older) undergoing elective or urgent, on-pump cardiac surgery between April 2006 and November 2011 were included. Patients needing an emergency operation (in whom there was not sufficient time to consider participation), a re-operation within the same admission or with a life expectancy of less than 6 months were excluded. In the main study, all patients provided written informed consent before randomization. The research ethics committee at each participating center approved the protocol. A total of 4,494 patients were included in the DECS study and postoperative AF was defined as a secondary endpoint. Data regarding AF were not collected systematically and AF was considered present if mentioned in discharge letters. Therefore, we conducted a post-hoc in-depth substudy to systematically collect all occurrences of any episode of AF or new-onset AF in a subsample of 1,565 participants undergoing cardiac surgery at the University Medical Center Utrecht. At this site, we had access to a complete set of electronically stored electrocardiograms and relevant pre-, intra- and post-operative data related to postoperative AF. In addition, we also performed subgroup analyses in the entire DECS study population (4,494 patients) and in the substudy (1,565 patients) to investigate whether there are potential patient groups who may or may not benefit from dexamethasone therapy.

Intervention

Patients were randomized to receive an intravenous injection dexamethasone (1 mg/kg, with a maximum total dose of 100 mg) or placebo, immediately after the induction of anesthesia, but before the initiation of CPB.

Outcomes

The outcomes of interest were the occurrence of any postoperative AF or postoperative new-onset AF. Any postoperative AF was defined by the occurrence of any episode of AF within 30 days after cardiac surgery regardless of a medical history of AF. The definition of postoperative new-onset AF was as follows: any episode of AF within 30 days following cardiac surgery in patients without a history of paroxysmal or permanent AF. To determine whether a patient had a history of AF, we manually searched and examined the medical records, discharge letters and preoperative ECGs for previous episodes of AF. In order to determine the occurrence of postoperative AF, we manually searched the medical records, ICU discharge letters and ward discharge letters for postoperative heart rhythm information. Furthermore, we examined all the

postoperative ECGs until the date of discharge from the hospital. The following criteria were used to confirm the diagnosis of AF: 1) absence of P-waves in combination with irregular ventricular beats during ≥10 seconds on a 12 channel ECG or three channel rhythm recording; 2) any type of AF (paroxysmal, persistent or permanent); 3) any therapeutic intervention (medication, cardioversion, none).

Randomization and blinding

Detailed information about the randomization procedure has been published elsewhere (10). The randomization was stratified by each participating center. Patients and attending physicians and nurses were blinded for treatment allocation. The analysis of the ECGs, patient charts and patient letters for the present substudy was performed by two independent investigators (DvO and KJ), who were also blinded for randomization.

Perioperative procedures

Surgical access to the heart was achieved via midline sternotomy. Patients received either total intravenous anesthesia or a combination of intravenous opioids and muscle relaxants combined with volatile anesthetics. Techniques for cardioplegia, myocardial protection, and CPB were left at the discretion of the attending team. Use of corticosteroid-containing solutions for cardioplegia or initiation of CPB was not allowed (10). All of the patients received a postoperative β-blocker as AF prophylaxis (metoprolol 25 mg, twice a day), if hemodynamically tolerated. Treatment of postoperative AF varied across the participating hospitals. When postoperative AF was associated with hemodynamic instability it was treated with electrical cardioversion, whereas in more stable patients it was treated with medication in order to achieve rate or rhythm control. Typically, digoxin, metoprolol or amiodarone was used, in combination with therapeutic anticoagulation.

Subgroup analyses

We also performed subgroup analyses in the main study and in the substudy. The following subgroups were evaluated: female sex, older age (≥65 years), higher body mass index (>25), reduced left ventricular ejection fraction (≤50%), higher EuroScore (≥5), higher CPB-time (>150 min) and valve surgery.

Sample size and statistical analyses

Based on the meta-analysis of Marik and Fromm (8), the incidence of postoperative AF in the placebo group was estimated to be 42%. This meta-analysis showed an incidence of postoperative AF in the corticosteroid treated group of 25%, which is an absolute risk reduction of 17%. To detect such a difference in a subgroup of patients with a power of 80%, using a two sided p=0.05 test, we needed 276 patients, or 138 in each treatment arm. Data analyses were performed according to the intention to treat principle. Continuous variables are expressed as mean +/- standard deviation (SD) for normally distributed data and as median and interquartile range (IQR) if not. Dichotomous variables are expressed as the absolute number of cases followed by a percentage (n, (%)). For the comparison of dichotomous variables, we used the Chi-square test and calculated associated relative risks (RR) with 95% confidence intervals (CIs). For comparison of mean and median values of continuous variables, we used the Student *t* test

or the Mann-Whitney U test, as appropriate. A value of p<0.05 was considered to show statistical significance. We used logistic regression to assess heterogeneity in the preplanned subgroup analyses, with a *p*<0.10 threshold for significance. IBM SPSS version 20 (SPSS Inc.) was used for all analyses.

RESULTS

Main study encompassing 4,494 patients

The flowchart depicting inclusion of patients is depicted in Figure 1. There were no differences in baseline characteristics between the study groups (Table 1). There was no protective effect of dexamethasone across the following patient subgroups: female sex, older age (≥65 years), higher EuroScore (≥5), prolonged CPB time (>150 minutes) or surgery type (valve surgery vs. other surgery). Dexamethasone treatment had a protective effect on postoperative AF only in patients with a preserved left ventricular function (RR 0.88 95% CI: 0.80-0.97, *p*=0.02) (Figure 2).

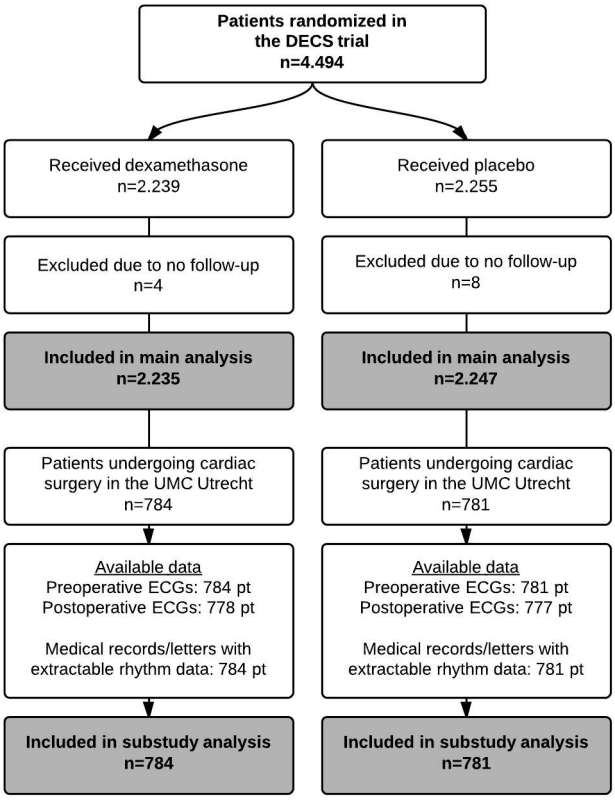


Figure 1. Flow of patients.
Abbreviations: DECS: DExamethasone for Cardiac Surgery; UMC: University Medical Center

Table 1. Baseline characteristics

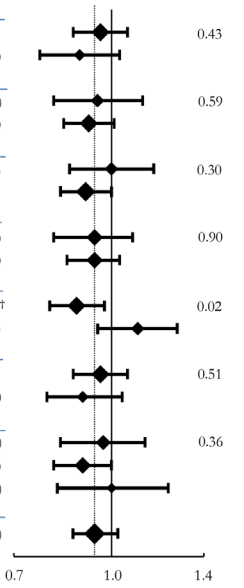
	DECS main study n=4,482		DECS substudy n=1,565	
Characteristic	Dexamethasone n=2,235	Placebo n=2,247	Dexamethasone n=784	Placebo n=781
Patient characteristics				
Age, mean (SD), years	66.2 (11.0)	66.1 (10.7)	65.4 (11.7)	65.4 (11.3)
Male sex, n (%)	1,622 (72.6)	1,628 (72.5)	562 (71.7)	542 (69.4)
BMI, mean (SD)	27.3 (4.1)	27.2 (4.2)	26.8 (4.1)	26.7 (4.2)
EuroScore*, median (IQR)	5 (3-7)	5 (3-7)	4 (3-7)	4 (3-7)
Medical history, n (%)				
Hypertension	1,179 (54.7)	1,180 (54.8)	427 (54.5)	433 (55.4)
Diabetes	415 (18.6)	436 (19.4)	158 (20.2)	143 (18.3)
Permanent atrial fibrillation	-	-	82 (10.5)	72 (9.2)
Paroxysmal atrial fibrillation	-	-	43 (5.5)	52 (6.7)
Preoperative use of: n (%)				
β-Blocker	1,485 (68.4)	1,479 (68.2)	530 (67.6)	520 (66.6)
Digoxin	-	-	57 (8.9)	48 (7.6)
Amiodarone	-	-	12 (1.9)	11 (1.7)
Flecainide	-	-	4 (0.6)	4 (0.6)
Corticosteroids	130 (7.2)	98 (5.4)	69 (8.8)	45 (5.8)
Aspirin	1,292 (59.5)	1,256 (57.8)	468 (59.7)	446 (57.1)
Left ventricular function, n (%)				
Normal, EF >50%	1,616 (72.7)	1,587 (70.9)	571 (72.8)	583 (74.6)
Moderate, EF 30-50%	503 (22.6)	534 (23.9)	180 (23.0)	164 (21.0)
Poor, EF <30%	103 (4.6)	117 (5.2)	33 (4.2)	34 (4.4)
Cardiac surgery type, n (%)				
Isolated CABG	884 (39.7)	903 (40.4)	330 (42.1)	332 (42.5)
Isolated valvular surgery	664 (29.9)	657 (29.4)	227 (29.0)	235 (30.1)
CABG and valvular surgery	377 (16.9)	365 (16.3)	124 (15.8)	108 (13.8)
Other cardiac surgery	301 (13.5)	310 (13.9)	99 (12.6)	102 (13.1)
Intraoperative parameters				
CPB time, mean (SD), minutes	125 (68)	124 (64)	119 (67)	118 (63)
Aortic crossclamp time, mean (SD), min	87 (47)	85 (44)	89 (50)	89 (49)
Postoperative use of: n (%)				
Prophylactic β-Blocker	-	-	350 (94.3)	339 (93.6)
Amiodarone	-	-	44 (11.9)	34 (9.4)
Corticosteroids	-	-	44 (5.6)	41 (5.3)

Abbreviations: BMI: Body Mass Index; DECS: DExamethasone for Cardiac Surgery; SD: standard deviation; IQR: interquartile range; EF: ejection fraction; CABG: Coronary Artery Bypass Grafting; CPB: CardioPulmonary Bypass. *EuroScore preoperative risk estimate
The baseline characteristics of the main study have been published earlier in JAMA (2012 Nov 7; 308(17):1761-7)

Substudy encompassing 1,565 patients

There were no baseline differences between the study groups except for a higher preoperative use of corticosteroids in the placebo group. The incidence of any AF in the dexamethasone vs. placebo group was 45.7% vs. 48.5% (RR 0.94, 95% CI: 0.85-1.05, p=0.26, Table 2). Thus, the incidence of any postoperative AF as retrieved in the substudy was higher than in the main study (34.1% vs. 47.0%, p<0.01). The incidence of postoperative new-onset AF in the dexamethasone vs. placebo group was 33.0% vs. 35.5% (RR 0.93, 95% CI: 0.81-1.07, p=0.31, Table 2). The subgroup analysis for postoperative new-onset AF showed no protective effect of dexamethasone (Figure 3). Of the 95 patients (6.1%) who had a medical history of paroxysmal AF, 27 patients (28%, 95% CI: 20-38%) remained in sinus rhythm during the postoperative hospital stay. Of the 154 patients (9.8%) who had a medical history of permanent AF, 21 patients (14%, 95% CI: 9-20%) did not have AF during the postoperative hospital stay. We corrected the outcomes for the baseline difference in preoperative use of corticosteroids, using logistic regression analysis. The corrected odds ratio for developing any postoperative AF was 0.89 (95% CI 0.76-1.62, p=0.26) and for new-onset postoperative AF 0.90 (95% CI 0.73-1.11, p=0.34), respectively.

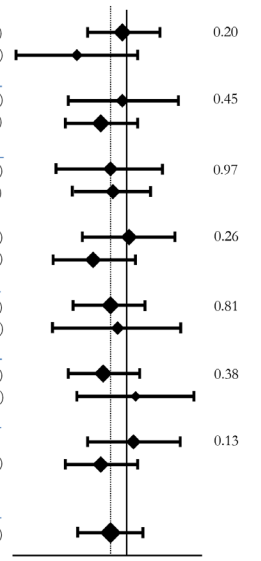
	Number of patients		Number of any postoperative AF			
Subgroup	Dexamethasone	Placebo	Dexamethasone	Placebo	Relative Risk (95% CI)	P for trend
Sex						
Men	1.622	1.628	524 (32.3)	547 (33.6)	0.96 (0.87-1.06)	0.43
Women	613	619	215 (35.1)	243 (39.3)	0.89 (0.77-1.03)	
Age						
<65	914	962	221 (24.2)	244 (25.4)	0.95 (0.81-1.12)	0.59
≥65	1.321	1.285	518 (39.2)	546 (42.5)	0.92 (0.84-1.01)	
Body mass index						
≤ 25	711	722	234 (32.9)	238 (33.0)	1.00 (0.86-1.16)	0.30
> 25	1.517	1.513	502 (33.1)	550 (36.4)	0.91 (0.83-1.00)	
EuroScore*						
<5	1.030	1.064	269 (26.1)	297 (27.9)	0.94 (0.81-1.08)	0.90
≥5	1.180	1.147	457 (38.7)	475 (41.4)	0.94 (0.85-1.03)	
Left ventricular function						
Good (>50%)	1.616	1.587	506 (31.3)	563 (35.5)	0.88 (0.80-0.97)†	0.02
Impaired (≤50%)	606	651	228 (37.6)	223 (34.3)	1.10 (0.95-1.27)	
CPB time						
≤150 min	1.674	1.659	517 (30.9)	535 (32.2)	0.96 (0.87-1.06)	0.51
>150 min	548	571	219 (40.0)	251 (44.0)	0.90 (0.79-1.04)	
Surgery type						
Isolated CABG	884	903	225 (25.5)	238 (26.4)	0.97 (0.83-1.13)	0.36
Valvular surgery +/- CABG	1.041	1.022	394 (37.8)	430 (42.1)	0.90 (0.81-1.00)	
Other	301	310	117 (38.9)	120 (38.7)	1.01 (0.82-1.23)	
Total	2.235	2.247	739 (33.1)	790 (35.2)	0.94 (0.87-1.02)	



Abbreviations: AF: atrial fibrillation; CABG: Coronary Artery Bypass Grafting; CPB: CardioPulmonary Bypass.
*EuroScore preoperative risk estimate; † Significant difference

Figure 2. Forest plot of subgroup analyses – Any postoperative atrial fibrillation in the main study

Subgroup	Number of patients		Number of new-onset AF		Relative Risk (95% CI)	P for trend
	Dexamethasone	Placebo	Dexamethasone	Placebo		
Sex						
Men	562	542	196 (34.9)	192 (35.4)	0.98 (0.84-1.16)	0.20
Women	222	239	63 (28.4)	85 (35.6)	0.80 (0.61-1.05)	
Age						
<65	317	341	86 (27.1)	94 (27.6)	0.98 (0.77-1.26)	0.45
≥65	467	440	173 (37.0)	183 (41.6)	0.89 (0.76-1.05)	
Body mass index						
≤25	288	294	90 (31.3)	99 (33.7)	0.93 (0.73-1.17)	0.97
>25	496	486	169 (34.1)	177 (36.4)	0.94 (0.79-1.11)	
EuroScore*						
<5	393	411	122 (31.0)	127 (30.9)	1.01 (0.82-1.24)	0.26
≥5	391	370	137 (35.0)	150 (40.5)	0.86 (0.72-1.04)	
Left ventricular function						
Good (>50%)	571	583	193 (33.8)	213 (36.5)	0.93 (0.79-1.08)	0.81
Impaired (≤50%)	213	198	66 (31.0)	64 (32.3)	0.96 (0.72-1.27)	
CPB time						
≤150 min	616	593	192 (31.2)	205 (34.6)	0.90 (0.77-1.06)	0.38
>150 min	158	185	64 (40.5)	72 (38.9)	1.04 (0.80-1.35)	
Surgery type						
Isolated CABG	335	339	95 (28.4)	93 (27.4)	1.03 (0.84-1.27)	0.13
Valvular surgery +/- CABG	439	425	164 (37.4)	178 (41.9)	0.89 (0.76-1.05)	
Other	10	17	0 (0.0)	6 (35.3)	NA	
Total	784	781	259 (33.0)	279 (35.5)	0.93 (0.81-1.07)	



Abbreviations: AF: atrial fibrillation; CABG: Coronary Artery Bypass Grafting; CPB: CardioPulmonary Bypass.; NA: Not apllicable due to small number of patients. *EuroScore preoperative risk estimate

Figure 3. Forest plot of subgroup analyses – Postoperative new-onset atrial fibrillation in the substudy

Table 2. Outcome of the main- and substudy

Outcome	DECS main study n=4,482			DECS substudy n=1,565		
	Dexa n=2,235 n, (%)	Placebo n=2,247 n, (%)	RR, 95% CI, p-value	Dexa n=784 n, (%)	Placebo n=781 n, (%)	RR, 95% CI, p-value
Any postoperative AF, n (%)	739 (33.1)	790 (35.2)	0.94 (0.87-1.02) *p*=0.14	358 (45.7)	379 (48.5)	0.94 (0.85-1.05) *p*=0.26
Postoperative new-onset AF, n (%)	NA	NA	NA	259 (33.0)	277 (35.5)	0.93 (0.81-1.07) *p*=0.31

Abbreviations: AF: Atrial Fibrillation; DECS: DExamethasone for Cardiac Surgery; Dexa: dexamethasone; RR: relative risk; CI: confidence interval; NA: not applicable. *Data concerning any postoperative AF in the main study have been published earlier in JAMA (2012 Nov 7; 308(17):1761-7)*

DISCUSSION

The present study is the largest randomized controlled trial evaluating the effect of dexamethasone on postoperative AF in cardiac surgery. In contrast to previous studies and meta-analyses, we conclude that there is no protective effect of a single dose of dexamethasone on the incidence of postoperative AF. There was also no benefit of dexamethasone in clinically important subgroups of patients.

Atrial fibrillation is a common complication following cardiac surgery. The incidence in the present study was between 25-28% for patients undergoing an isolated CABG and 37-42% for patients undergoing valvular surgery.

Despite of the huge amount of circumstantial evidence in favor of inflammation, we still do not have a proven gold standard definition of inflammation in the postoperative setting. The question remains however how to interpret the positive results of corticosteroids from previous reports and meta-analyses. A major limitation of these meta-analyses is the heterogeneity of the included studies. Previous studies were small in sample size (18 to 294 patients) and investigated various types of corticosteroids in multiple doses at different time points of administration. In contrast, we have investigated the role of dexamethasone in a large group of patients in a placebo-controlled, double blind, randomized trial. Any clinically important effect of corticosteroid therapy on postoperative AF should thus have been evidenced in our study. Given the outcome of the present study we should also reconsider the importance of the role of inflammation in the pathophysiology of postoperative AF, despite the fact that previous studies have demonstrated an association between levels of inflammatory markers and postoperative AF (8, 19).

There are several reasons that might explain why we could not demonstrate any protective effect of dexamethasone on postoperative AF. A possible reason for the lack of effect might be the dose of dexamethasone administration in the DECS study as compared to previous reports. Previous meta-analyses investigating the effect of steroids in preventing postoperative AF showed that low- and high-dose corticosteroids were ineffective in preventing AF in contrast to moderate doses (8, 16). Therefore, a lower dose of dexamethasone than 1 mg/kg bodyweight as given in the DECS study could have been more effective, although the optimal dosage remains unclear.

Another possible reason why no effect was found is the moment and duration of dexamethasone administration. In prior studies that investigated perioperative dexamethasone treatment (11, 20-23), dexamethasone was administered at various perioperative moments. Two out of three previous studies demonstrating a protective effect of dexamethasone treatment on postoperative AF (20-22) administered dexamethasone not only preoperatively, but also on the first postoperative day. Perhaps the moment of dexamethasone administration in the DECS study, a single shot shortly after induction of anesthesia, was not the optimal moment to induce an optimal counter-effect on inflammation of the atrial tissue. However, also the optimal timing of drug delivery and the frequency of administration remain unclear.

It is also conceivable that the inflammatory response of dexamethasone on the atrial tissue is not powerful enough to counteract other AF promoting factors after cardiac surgery. One could imagine that patients with a history of AF would not benefit from corticosteroids because of the presence of a longstanding advanced negative remodeling process on the atria prior to surgery.

However, dexamethasone was not effective to reduce postoperative new-onset of AF either. There was also no effect of dexamethasone in almost all clinically relevant subgroups of patients, except for those with a preserved left ventricular function. Maybe, the negative remodeling of the atria in patients with a preserved left ventricular function is less distinct enabling reduction of postoperative AF by dexamethasone. No firm conclusions can be drawn here, because of the limitations of the subgroup analysis. Visceral abdominal obesity is an important modulator of postoperative inflammation (24, 25). We did not collect baseline waist circumference as a possible modulator of the effect of dexamethasone on AF. A subgroup analysis of patients with high versus low body mass index, however, revealed no difference in the effect of dexamethasone.

Other types of corticosteroids might be more effective in inhibiting the inflammatory cascade. Maybe, methylprednisolone (22) or hydrocortisone (18) could be better candidates as demonstrated previously. Also other non-steroidal anti-inflammatory drugs such as colchicine in the management of post-operative atrial fibrillation could provide an alternative (26).

Strengths of our study are the large sample size, the appropriate study design and the availability of detailed clinical relevant data. By manually examining all pre- and postoperative ECGs, patient letters and medical records, we were able to present accurate data regarding postoperative AF. As a result, a 13% higher incidence of any AF was retrieved in the substudy as compared to the main study. However, this increased detection of AF did not change the effect size estimates. This study also has some limitations. The most important limitation is that the substudy was a retrospective analysis of chart data and diagnostic test results, with the inherent potential for information bias. However, since the study was randomized and the assessors were blinded to the treatment allocation at the time of data collection, any underreporting will likely have been evenly distributed across the treatment groups. The incidences of any AF and new-onset AF in our study are in agreement with the literature, which makes it unlikely that these have been significantly underestimated.

CONCLUSION

In conclusion, intraoperative administration of a single high dose dexamethasone had no protective effect on the occurrence of any or new-onset AF after cardiac surgery. There was also no benefit of dexamethasone in clinically important subgroups of patients. Therefore, the use of dexamethasone for the reduction of postoperative AF should not be recommended.

Conflict of interest

None.

Funding

The DECS trial was supported by grants 80-82310-98-08607 from the Netherlands Organization for Health Research and Development (ZonMw) and 2007B125 from the Dutch Heart Foundation, both located in Den Haag, the Netherlands. No extramural funding was used to support this additional study.

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Chapter 6

Intraoperative High-Dose Dexamethasone in Cardiac Surgery and the Risk of Rethoracotomy

Ann Thorac Surg. 2015 Dec;100(6):2237-42

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ABSTRACT

Background

Cardiac surgery with use of cardiopulmonary bypass (CPB) is associated with a systemic inflammatory response. Intraoperative corticosteroids are administered to attenuate this inflammatory response. The recent DExamethasone for Cardiac Surgery (DECS) trial could not demonstrate a beneficial effect of dexamethasone on major adverse events in cardiac surgical patients. Previous studies suggest that corticosteroids may affect postoperative coagulation and blood loss and therefore could influence the risk of surgical reinterventions. We investigated the effects of prophylactic intraoperative dexamethasone treatment on the rate of rethoracotomy after cardiac surgery.

Methods

We performed a post-hoc additional data collection and analysis in the DECS trial. A total of 4,494 adult patients undergoing cardiac surgery with use of CPB were randomized to intravenous dexamethasone (1.0 mg/kg) or placebo. The primary endpoint for the present study was the incidence of any rethoracotomy within the first 30 postoperative days. Secondary endpoints included the reason for rethoracotomy, and the incidence of perioperative transfusion of blood products.

Results

In the dexamethasone group 217 (9.7%) patients underwent a rethoracotomy, and in the placebo group 165 (7.3%) patients (RR 1.32; 95% CI 1.09-1.61; p=0.005). The most common reason for rethoracotomy was tamponade: 3.9% versus 2.1%, respectively (RR 1.84, 95% CI 1.30-2.61, p<0.001).

Conclusion

Intraoperative high-dose dexamethasone administration in cardiac surgery was associated with an increased rethoracotomy risk.

INTRODUCTION

Cardiac surgery with use of cardiopulmonary bypass (CPB) is associated with intense activation of the immune system, leading to a postoperative systemic inflammatory response syndrome (SIRS) in many patients (1-3). SIRS may lead to postoperative organ dysfunction, and even multi-organ failure (1-5). Moreover, through parallel activation of the coagulation system through tissue factor and NF-κB, the systemic inflammatory response may induce perioperative coagulation disorders that commonly occur after cardiac surgery.

Corticosteroids can be administered during cardiac surgery to attenuate systemic inflammatory activation, typically as a high dose of dexamethasone or methylprednisolone (6). The use of high-dose dexamethasone has been shown to reduce the incidence of postoperative respiratory complications as well as the length of postoperative stay in the intensive care unit (ICU) and the hospital (7).

The effect of prophylactic corticosteroid administration on bleeding-related complications has not been studied extensively. Meta-analyses of small randomized studies that reported outcomes related to bleeding, have not shown a clinically important effect of corticosteroids on rethoracotomy or blood transfusions between patients receiving corticosteroids or placebo treatment (6, 8). However, in one meta-analysis postoperative chest tube output was reduced in patients receiving corticosteroids (8).

We recently conducted the DExamethasone for Cardiac Surgery (DECS) trial. The trial did not demonstrate a beneficial effect of dexamethasone on major adverse events in cardiac surgical patients, but found fewer postoperative infections and shorter hospitalization in patients randomly assigned to dexamethasone. Rethoracotomy was not part of the predefined study outcomes. To explore the hypothesis that high-dose dexamethasone may reduce the risk of rethoracotomy, we conducted a post-hoc study involving all 4,494 patients who were included in the DECS trial.

METHODS

Study design and population

The present study was a post-hoc analysis of both existing and additionally collected data of patients who were included in the DECS trial, which has been described in detail elsewhere (7). Briefly, this trial was a multicenter, double-blind, randomized, placebo-controlled study, comparing high-dose intravenous dexamethasone with placebo treatment of 4,494 patients undergoing cardiac surgery between April 2006 and November 2011. Adult patients (aged 18 years or older) undergoing elective or urgent on-pump cardiac surgery were eligible for inclusion in this trial. Patients needing an emergency operation and patients with a life-expectancy of less than 6 months, were excluded. The primary outcome of the study was a composite of major adverse events in the first 30 days.

In the present study, we retrospectively analyzed the incidence of rethoracotomy. In the main study, all patients provided written informed consent before randomization. The research ethics committee at each participating center approved the protocol.

Intervention

Patients were randomly assigned to receive an intravenous injection of dexamethasone (1 mg/kg, with a maximum of 100 mg) or placebo, after induction of anesthesia, but before initiation of CPB.

Outcome

The primary outcome of interest for the present analysis was the incidence of any rethoracotomy within the first 30 postoperative days. Secondary study endpoints included the primary reason for rethoracotomy (categorized as bleeding, tamponade, wound or sternal problems, and other reasons), early versus late rethoracotomy (<24 hours vs ≥24 hours), freedom of surgical reinterventions, the incidence of transcutaneous interventions (pericardial or pleural puncture), and the exposure to transfusion of blood products during the operation and during the ICU stay.

Data collection

For the present study, we used data from the DECS study database, as well as additionally collected data from the patients' charts. The prospectively collected data registered in the case record forms of the trial included baseline characteristics, intraoperative characteristics, and use of blood products in the operation room and intensive care unit. Reoperations were reported as in the case record form, but were not a predefined endpoint of the DECS trial and were therefore possibly underreported. Therefore, discharge letters, readmission letters, letters from referring centers and surgical reports of all patients included in the DECS trail were retrospectively retrieved and checked (DvO and MB) for rethoracotomies, subxiphoidal incisions and pericardial and pleural punctures. Causes and timing of rethoracotomies and punctures were recorded on a dedicated form. After data collection, all reports were independently assessed by a cardiothoracic surgeon (JK). Discrepant assessments were discussed and scored after consensus was reached. All assessors were blinded to the treatment allocation of the patients during data collection and scoring.

Statistical analyses

Data analyses were performed according to the intention to treat principle. Continuous variables are expressed as mean +/- standard deviation (SD), or as median and interquartile range (IQR) where applicable. Dichotomous variables are expressed as the absolute number of cases followed by a percentage (n, (%)). For the comparison of dichotomous variables, relative risks (RRs) with 95% confidence intervals (CIs) were calculated and analyzed using the chi-square test. For comparison of mean and median values of continuous variables, the Student t test or the Mann-Whitney U test were used, as appropriate. Freedom of reinterventions was compared using Kaplan-Meier survival analysis with log-rank analysis. Hazard ratios (HRs) with 95% CIs were calculated using Cox-regression analysis. A value of $p<0.05$ was considered to show statistical significance. The software IBM SPSS, version 20 (IBM Corporation, Armonk, NY), was used for all analyses.

Funding

The DECS trial was supported by grants 80-82310-98-08607 from the Netherlands Organization for Health Research and Development (ZonMw) and 2007B125 from the Dutch Heart Foundation.

No extramural funding was used to support this additional data collection and analyses.
The authors are solely responsible for the design of this substudy, including the data collection, data analysis, and the drafting and editing of the paper and its final contents.

RESULTS

Study population

Of 4,494 randomized patients, 4,482 (99.9%) completed 30 days of follow-up. Data concerning reinterventions and transfusions were available for these 4,482 patients. A flow diagram of the study is given in Figure 1. Baseline characteristics of the study population are listed in Table 1. There were no differences in baseline characteristics between the two treatment groups.

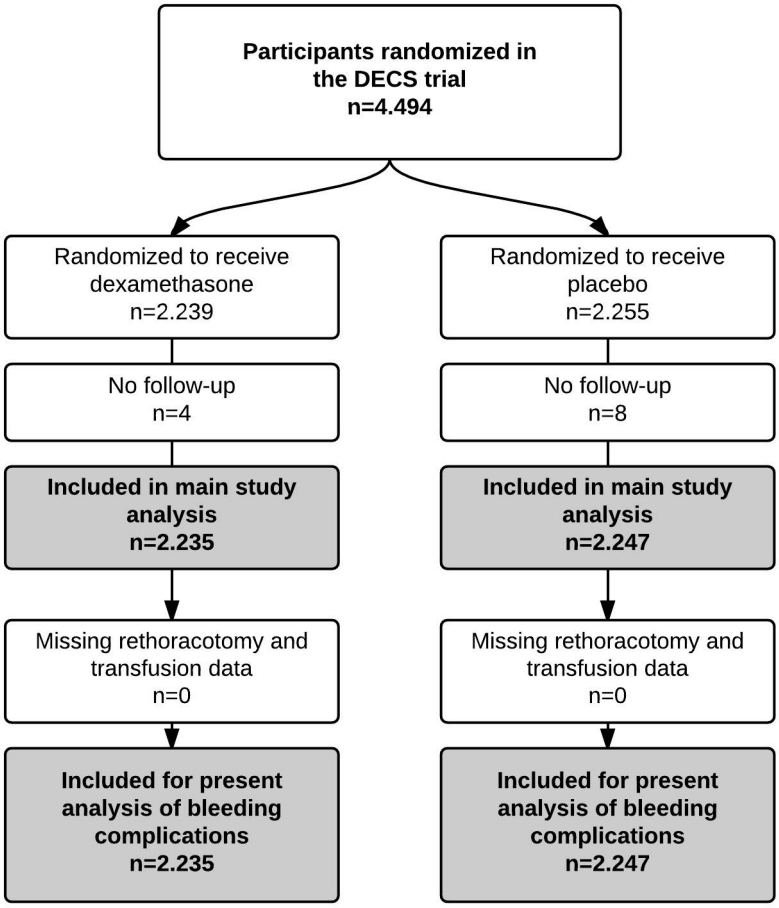

Figure 1. Study Flowchart
Abbreviations: DECS: DExamethasone for Cardiac Surgery

Table 1. Baseline characteristics

Characteristic	Dexamethasone (n=2.235)	Placebo (n=2.247)	P-value
Patient characteristics			
Age (mean±SD), years	66.2 (11.0)	66.1 (10.7)	0.69
Male sex, n (%)	1,622 (72.6)	1,628 (72.5)	0.93
EuroScore*, median (IQR)	5 (3-7)	5 (3-7)	0.65
Medical history, n (%)			
Hypertension	1,179 (54.7)	1,180 (54.8)	0.98
Diabetes	415 (18.6)	436 (19.4)	0.47
Preoperative use of, n (%)			
Corticosteroids	130 (7.2)	98 (5.4)	0.03
Aspirin	1,292 (59.5)	1,256 (57.8)	0.26
LMWH/Warfarin	537 (24.6)	554 (25.4)	0.57
Left ventricular function, n (%)			
Normal, EF >50%	1,616 (72.2)	1,587 (70.9)	0.21
Moderate, EF 30-50%	503 (22.6)	534 (23.9)	0.32
Poor, EF <30%	103 (4.6)	117 (5.2)	0.35
Cardiac surgery type, n (%)			
Isolated CABG	884 (39.7)	903 (40.4)	0.67
Valvular surgery +/- CABG	1,041 (46.6)	1,022 (45.5)	0.44
Intraoperative parameters			
CPB time (mean±SD), minutes	125 (68)	124 (64)	0.54
Aortic crossclamp time (mean±SD), minutes	87 (47)	85 (44)	0.16
Use of cell-saving device, n (%)	1151 (51.8)	1104 (49.4)	0.12
Use of tranexamic acid†, (%)	1834 (82.4)	1835 (81.8)	0.64

Abbreviations: CABG: Coronary Artery Bypass Grafting; CPB: CardioPulmonary Bypass. EF: ejection fraction; IQR: interquartile range; LMWH: Low Molecular Weight Heparin; SD: standard deviation. *EuroScore preoperative risk estimate. †The typical tranexamic acid dose was 6.25 mg/kg/hour after a loading dose of 12.5 mg/kg. Dowd NP, Anesthesiology 2002, Aug;97(2):390-9.
The baseline characteristics of the main study have been published earlier in JAMA (2012 Nov 7; 308(17):1761-7)

Outcomes

The incidence of rethoracotomy for any reason was 9.7% in the dexamethasone treated group, versus 7.3% in the placebo group (RR 1.32, 95% CI 1.09-1.61, p=0.005) (Table 2). There was a significantly higher incidence of rethoracotomy for tamponade in the dexamethasone treated group compared with the placebo group; 3.9% versus 2.1% respectively (RR 1.84, 95% CI 1.30-2.61, p<0.001).

Table 2. Primary and secondary study endpoints

Outcome	Dexamethasone (n=2.235), n (%)	Placebo (n=2.247), n (%)	Relative Risk (95% CI)	P-value
Primary study endpoint				
Rethoracotomy	217 (9.7)	165 (7.3)	1.32 (1.09-1.61)	<0.01
Secondary study endpoints				
Reason for rethoracotomy*				
Tamponade	88 (3.9)	48 (2.1)	1.84 (1.30-2.61)	<0.01
Rebleed	89 (4.0)	80 (3.6)	1.12 (0.83-1.50)	0.46
Wound problems	20 (0.9)	18 (0.8)	1.12 (0.59-2.11)	0.73
Other	20 (0.9)	19 (0.8)	1.06 (0.57-1.98)	0.86
Rethoracotomy ≤24 hours	81 (3.6)	70 (3.1)	1.16 (0.85-1.59)	0.35
Rethoracotomy >24 hours	136 (6.1)	95 (4.2)	1.44 (1.12-1.86)	<0.01
Pericardial puncture	25 (1.1)	20 (0.9)	1.26 (0.70-2.26)	0.44
Pleural puncture	113 (5.1)	81 (3.6)	1.40 (1.06-1.85)	0.02
Any blood product transfusion	871 (39.0)	946 (42.1)	0.93 (0.86-0.99)	0.03
Any packed red cells	711 (31.8)	763 (34.0)	0.94 (0.86-1.02)	0.13
Any fresh frozen plasma	434 (19.4)	459 (20.4)	0.95 (0.85-1.07)	0.40
Any platelets	359 (16.1)	397 (17.7)	0.91 (0.80-1.04)	0.15

All the study endpoints were measured within 30 days after cardiac surgery. *In case of multiple (>1) rethoracotomies, the reason for the first rethoracotomy was used as the primary reason. CI: confidence interval.

There were more late rethoracotomies (≥24 hours postoperatively) in the dexamethasone group than in the placebo group: 6.1% vs 4.3% respectively (RR 1.44, 95% CI 1.12-1.86, p=0.005). Incidences of rethoracotomies for postoperative bleeding or wound problems, as well as early rethoracotomies (<24 hours postoperatively) were comparable between the groups (Table 2). Survival analysis showed a significantly lower freedom from surgical reinterventions in the dexamethasone group (Figure 2), with a hazard ratio of 1.34 (95% CI 1.09-1.64, p=0.005).

Of the transcutaneous interventions, there was no difference in pericardial punctures; 1.1% vs. 0.9% respectively (RR 1.26, 95% CI 0.70-2.26, p=0.44). However, the incidence of pleural puncture was higher in the dexamethasone group compared with the placebo group: respectively 5.1% versus 3.6% (RR 1.40, 95% CI 1.06-1.85, p=0.017). Of the 2,235 dexamethasone patients, 1,364 (61.0%) remained free of transfusion of blood products, as compared with 1,301/2,247 patients (57.9%) in the placebo group (absolute risk reduction (ARR) 3.1%; 95% CI 0.3 to 6.0%; p=0.03).

There was no difference in the number of transfused blood products (fresh frozen plasma, thrombocytes or erythrocytes). The median number of transfused blood products was 3 (IQR 2-6) in the placebo group and 3 (IQR 1-6) in the dexamethasone group (p=0.44).

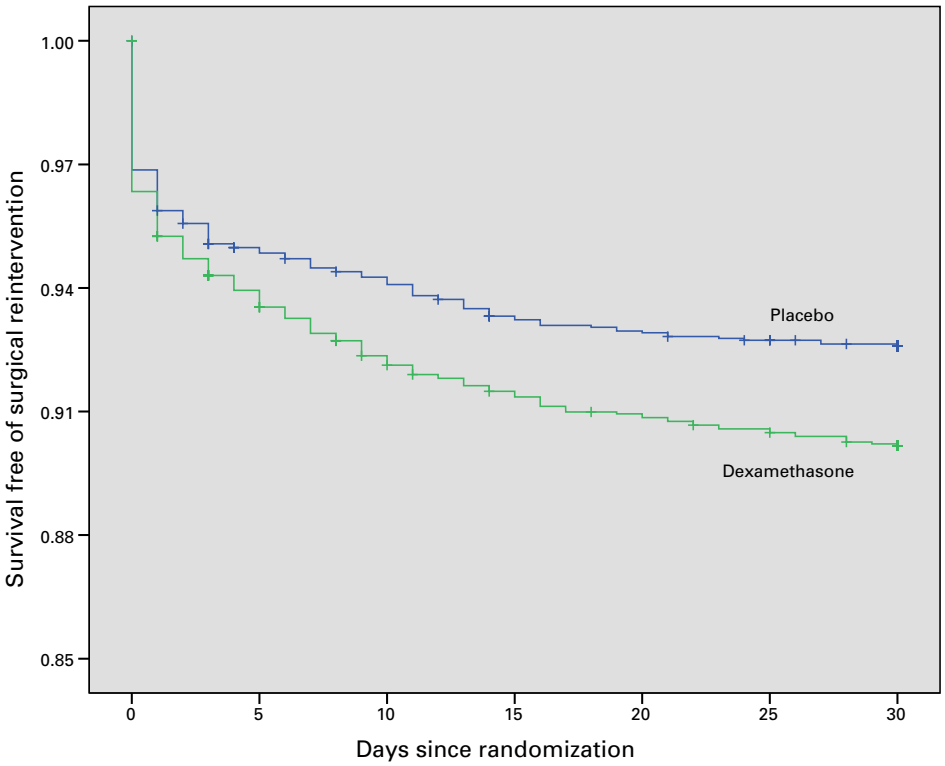

Figure 2. Survival curves for freedom from surgical reintervention
Abbreviations: DECS: DExamethasone for Cardiac Surgery

COMMENT

This study aimed to quantify the effect on rethoracotomy risk of intraoperative high-dose dexamethasone administration during cardiac surgery. We found a significant increase in the incidence of rethoracotomy among patients who received dexamethasone, particularly late interventions for tamponade.

This has been the first study with sufficient statistical power to examine the effect of high-dose dexamethasone on rethoracotomy after cardiac surgery. A few very small studies on corticosteroids in cardiac surgery have reported these outcomes previously. Meta-analyses of these studies have not been able to show any effect of corticosteroid administration on these complications, although there was a significant reduction in blood loss in the steroid treated group (mean difference -204.2 mL; CI -287.4 mL to -121 mL; $p<0.0001$) (9). The latter is consistent with our finding of an increased proportion of patients who remained free of perioperative transfusion in the dexamethasone group (6, 8, 9).

There are several potential mechanisms that may explain the increased rethoracotomy risk caused by dexamethasone. One possible mechanism could be an increased bleeding tendency caused by dexamethasone. In multiple pre-clinical studies the effects of dexamethasone on coagulation were investigated. These studies found varying effects of dexamethasone on different components of coagulation (platelet aggregation, fibrinogen, factor VIII, von Willebrand Factor, soluble P-selectin), indicating both an increased and a decreased bleeding risk (10-13).
There are also several clinical studies available that have specifically looked at the effects of dexamethasone on coagulation variables and on postoperative bleeding after surgical procedures (9, 11, 14-16). Most of these studies have been performed with noncardiac surgery patients. The effects of corticosteroids in these studies have also been variable, with an increased bleeding risk in some patients, and a decreased bleeding risk in others, depending on the circumstances and variables measured.
Another explanation for the increased incidence of need for (late) reinterventions in the dexamethasone group may relate to impaired recovery as a result of an actual lack of inflammatory response. As some level of inflammation is probably required to aid recovery from the major trauma of cardiac surgery, 'over-suppression' may delay recovery and thereby increase the risk of complications, such as impaired wound healing. This concept of over-suppression is also consistent with the differential effects of corticosteroids that have been demonstrated between younger and elderly patients after cardiac surgery (7), which may be based on the same principle of over-suppression of a relatively senescent immune system in the elderly. In several studies, corticosteroids have been shown to impair the healing of surgical skin wounds, and that may be related to a similar mechanism (17, 18). However, an important difference is that these effects have mainly been demonstrated for chronic use of steroids, rather than for a single dose as it was used in our study (17, 19, 20).

Our other finding of an increased proportion of patients remaining free of perioperative transfusion of blood products in the dexamethasone group, needs some consideration as well. Although administered to improve oxygen transport capacity or to treat coagulopathy, transfusion of blood products carries substantial adverse risks. Numerous studies have shown that transfusion of allogeneic blood is independently associated with an increased risk of infections, and even with a higher long-term mortality (21, 22). A limitation of the study is that we only recorded the use of blood products during the operation and the ICU admission, but not after ICU discharge. That might explain the unexpected combination of a lower rate of transfusion and a higher rate of rethoracotomy in the dexamethasone group. The survival curves (Figure 2) show that the higher rate of rethoracotomy in the dexamethasone group develops after the first postoperative day and gradually increases during the first postoperative weeks. It is conceivable that a decreased transfusion rate during operation and ICU stay, and an increased late rethoracotomy rate reflect separate mechanisms. At 30 day follow-up, the difference in blood transfusion favoring dexamethasone may have disappeared, or even changed in direction, because the rethoracotomies after ICU discharge were probably associated with additional, but unrecorded transfusions of blood products. Furthermore, despite the increased proportion of patients remaining free of perioperative transfusions in the dexamethasone group, the number of transfused blood products did not differ statistically significantly between the two groups.

There is always the possibility that the statistically significant differences in either the incidence of rethoracotomy or the reduced transfusion rate have been a play of chance. Evaluating several secondary outcome measures, may potentially lead to false positive results. The Steroids In caRdiac Surgery (SIRS) trial, which evaluated the effect of high-dose methylprednisolone in 7,507 cardiac surgical patients found no effect of corticosteroids on transfusions (23).

Strengths and limitations

One of the strengths of our study is that it has a very large sample size, representing a broad selection of patients undergoing any form of elective on-pump cardiac surgery. The randomized design of this study ensures an equal distribution of factors that could possibly influence the outcome and the blinding minimized the risk of observer bias.

An important limitation of the present study is that this was a post-hoc analysis. Rethoracotomy data were based on information obtained from discharge letters and surgical reports. Reporting of rethoracotomies, pericardial punctures and pleural punctures (and their respective reasons) in discharge letters was not standardized. Furthermore, the distinction between bleeding and tamponade in the early postoperative phase is difficult to make. Another limitation is the lack of transfusion data beyond the initial postoperative ICU admission.

CONCLUSION

Intraoperative high-dose dexamethasone administration in cardiac surgery was associated with an increased rethoracotomy risk.

Conflict of interest

All authors report no conflicts of interests.

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Chapter 7

The association between inflammation and myocardial injury following cardiac surgery

Submitted

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ABSTRACT

Objective

The primary study aim was to investigate the association between the intensity of the inflammatory response and the extent of myocardial injury after cardiac surgery. The second study aim was to evaluate the effect of dexamethasone treatment on postoperative myocardial injury.

Methods

We performed a post-hoc analysis of laboratory data in 985 patients undergoing cardiac surgery and who were randomized to dexamethasone or placebo treatment in the DExamethasone for Cardiac Surgery (DECS) trial. The relationship between postoperative peak C-reactive protein (CRP) and creatinine kinase isoenzyme MB (CK-MB) was investigated in the placebo group using multivariable linear regression analysis. Furthermore the extent of myocardial injury (measured in CK-MB) and the CRP response were compared between dexamethasone and placebo treated patients.

Results

There was no significant association between peak CRP and peak CK-MB (beta 0.06, 95% CI -0.01-0.13, p=0.12). The median peak CK-MB value was 36 U/L (IQR 25-65) in the dexamethasone group vs. 36 U/L (IQR 26-59) in the placebo group (p=0.84). The median peak CRP value was 84 mg/L (IQR 49-145) in the dexamethasone group vs. 167 (IQR 87-237) in the placebo group (p<0.001).

Conclusion

The intensity of the inflammatory response after cardiac surgery was not associated with the extent of postoperative myocardial injury. Furthermore, dexamethasone treatment effectively reduced postoperative CRP, however had no effect on myocardial injury.

INTRODUCTION

Cardiac surgery with use of cardiopulmonary bypass (CPB) leads to a significant systemic inflammatory response in many patients, while some develop a systemic inflammatory response syndrome (SIRS). SIRS is associated with an increased risk of postoperative complications. Contact of blood with artificial material, ischemia-reperfusion injury, the surgical trauma, aortic cross-clamping, perioperative transfusion of blood products and hypothermia are several factors that contribute to this inflammatory response (1-4). Furthermore, in each patient undergoing cardiac surgery, myocardial injury occurs to a certain extent. This injury results from periods of perioperative myocardial ischemia and reperfusion injury (1). It has previously been hypothesized that systemic inflammation may enhance myocardial injury. Evidence exists that complement activation via increased C-reactive protein (CRP) levels, enhances myocardial injury in patients with acute myocardial infarction (5) and in patients undergoing an elective percutaneous coronary intervention (PCI) (6). This CRP-mediated complement activation also occurs in cardiac surgery (7). However, the association between systemic inflammation and the extent of myocardial injury has not been studied extensively in cardiac surgery patients. Furthermore, it is unclear what the effect of anti-inflammatory therapy is on the extent of myocardial injury. Prior trials investigating anti-inflammatory treatment show conflicting results. A trial comparing pexelizumab (a C5 complement inhibitor) with placebo treatment showed a reduction of a composite of myocardial infarction and death 30 days after cardiac surgery in the pexelizumab treated group (8). On the other hand, the Steroids In caRdiac Surgery (SIRS) trial, showed an increased incidence of myocardial injury in methylprednisolone treated patients (9). However, in the SIRS trial, myocardial injury was defined as cardiac biomarker increase alone. Therefore, the study detected many subclinical myocardial injuries, while other studies investigated myocardial infarction, defined as cardiac biomarker increase in combination with ECG abnormalities (new Q-waves or new left bundle branch block). The aim of this study was to investigate the association between the intensity of the inflammatory response after cardiac surgery and the extent of perioperative myocardial injury. Furthermore, the effect of dexamethasone versus placebo treatment on the extent of perioperative myocardial injury was investigated.

METHODS

Study design and population

The present study was a post-hoc analysis of data derived from the DExamethasone for Cardiac Surgery (DECS) trial. The DECS trial was a multicenter, randomized, placebo-controlled trial in 4494 adult patients undergoing non-emergent cardiac surgery between 2006 and 2011. The trial investigated the effect of a single, intraoperative dose of dexamethasone on postoperative clinical outcomes. Patients were randomized to receive an intravenous injection dexamethasone (1 mg/kg, with a maximum total dose of 100 mg) or placebo, immediately after the induction of anesthesia, but before the initiation of CPB. Patients, attending physicians and all other study personnel were blinded for treatment allocation. Detailed information about the randomization procedure has been described elsewhere (10). In the main study, all patients provided written

informed consent before randomization. The local medical ethics committee approved the study protocol of the present study. The need for informed consent was waived, as only routinely collected patient data were used and data were anonymized before analysis (UMC Utrecht Medical Research Ethics Committee 16-100/C). The present study population consisted of a subgroup of 985 patients undergoing cardiac surgery with use of CPB in a single center (Isala Clinics, Zwolle, The Netherlands). We chose patients from this particular center because of the availability of routine postoperative surveillance of both CRP and creatinine kinase isoenzyme MB (CK-MB). Of the 985 patients, 490 patients were randomized to dexamethasone treatment and 495 patients were randomized to placebo treatment. For our first analysis, we investigated the association between the intensity of the inflammatory response following cardiac surgery (measured in CRP) and the extent of perioperative myocardial injury (measured in CK-MB) in the placebo treated group. We chose placebo treated patients only, because of the potential interference of dexamethasone treatment with the inflammatory response. In the second analysis, we looked at the effect of dexamethasone versus placebo treatment on the extent of perioperative myocardial injury (measured in CK-MB) and the intensity of the inflammatory response (measured in CRP) in the entire group of 985 patients. If there is indeed an association between the intensity of the inflammatory response and the extent of myocardial injury, one would expect a difference between patients who did and those who did not receive dexamethasone.

CRP and CK-MB measurement

Data from routine postoperative laboratory surveillance were used to obtain postoperative peak CK-MB and peak CRP values. Immediately after cardiac surgery, when the patient arrived at the Intensive Care Unit (ICU), the first CK-MB sample was obtained (time point 0). Every 3 hours thereafter, a new CK-MB sample was obtained until the value was decreasing. When the CK-MB value started to decrease, no additional samples were obtained, except when there was a clinical indication to assess CK-MB. CK-MB activity was measured by Roche UV assay based on immunological inhibition of CK-M by a Roche/Hitachi 917 Modular P analyzer. The normal range was <24 U/L in accordance with the manufacturer's instructions.

Postoperative CRP was routinely measured on postoperative day 1, 3 and 6, or at an additional moment in the postoperative course if there was a clinical indication to assess CRP. If a patient was discharged to another hospital, no additional samples could be obtained. CRP was measured using the immunoturbidimetric CRP assay on a Roche/Hitachi 917 Modular P analyzer. The normal range was <5 mg/L in accordance with the manufacturer's instructions.

Statistical analyses

Continuous variables are expressed as mean ± SD or as median with interquartile range (IQR). Dichotomous variables are expressed as the number of cases followed by a percentage (n, %). We used the Student t test or Mann-Whitney U test (as appropriate) for comparisons between continuous variables and the $\chi 2$ or Fisher's exact test (in variables with a small sample size) for comparisons between categorical variables. In our first analysis, investigating the association between the inflammatory response and the extent of myocardial injury in the placebo group, we log-transformed all peak CRP and peak CK-MB values to normalize their distribution.

We used univariable linear regression to analyse the association between postoperative peak CRP and peak CK-MB. Furthermore, we used multivariable linear regression to adjust the association between peak CRP and peak CK-MB for the following confounders: age, preoperative creatinine in mg/dL, EuroScore, hypertension, peripheral artery disease, recent myocardial infarction (<90 days), preoperative aspirin, β-blocker and statin treatment, left ventricular ejection fraction (LVEF), valve surgery and CPB time. Aortic crossclamp time was not included in the multivariable model, because this variable is strongly correlated with CPB time. Multicollinearity among variables included in the model was assessed using the variance inflation factors (VIFs). If the VIF exceeded the value of 10, a variable was removed from the model based on the correlation matrix. For our second analysis, we compared the extent of myocardial injury and the intensity of the inflammatory response in the dexamethasone versus placebo group using a Mann-Whitney U test, conducting an intention-to-treat analysis. A p-value of < 0.05 was considered to show statistical significance. IBM SPSS version 21 (SPSS Inc., Chicago, IL) was used for all analyses.

RESULTS

Baseline characteristics

Baseline characteristics of the study population are listed in Table 1. Baseline characteristics were similar between the two groups, except for a higher proportion of patients with a moderate left ventricular ejection fraction and peripheral artery disease in the placebo group.

Association between peak CRP and peak CK-MB in the placebo group

CRP and CK-MB data were not normally distributed unless transformed into log. Univariable linear regression analysis showed a significant association between peak CRP and peak CK-MB (beta 0.15, 95% CI 0.07-0.22, p<0.001, R^2 0.03). After adjustment for confounders, there was no significant association between peak CRP and peak CK-MB (beta 0.06, 95% CI -0.01-0.13, p=0.12). Results of the analysis are shown in Table 2. A lower LVEF (beta 0.11, 95% CI 0.01-0.20, p=0.02), valve surgery (beta 0.27, 95% CI 0.12-0.41, p<0.001) and longer CPB time (beta 0.003, 95% CI 0.002-0.004, p<0.001) were associated with a higher peak CK-MB value.

Dexamethasone versus placebo treatment in all patients

The median peak CK-MB value was 36 U/L (IQR 25-65) in the dexamethasone group vs. 36 U/L (IQR 26-59) in the placebo group (p=0.84). The median peak CRP value was 84 mg/L (IQR 49-145) in the dexamethasone group vs. 167 mg/L (IQR 87-237) in the placebo group (p<0.001) (Table 3). Figure 1 and Figure 2 show a graph of the median CRP and median CK-MB values at the different postoperative time points. The highest median CK-MB levels were measured 18 hours postoperatively. The highest median CRP levels were measured on postoperative day 3 in the placebo group and day 4 in the dexamethasone group. In 61% of the patients, peak CK-MB was detected directly after cardiac surgery.

Table 1. Baseline characteristics

Characteristic	Dexamethasone (n=490)	Placebo (n=495)	p-value
Patient characteristics			
Age (mean±SD), years	65.7 ± 10.2	66.4 ± 10.0	0.28
Male sex, n (%)	387 (79.0)	394 (79.6)	0.87
BMI, median (IQR)	26.9 (24.8-30.2)	27.3 (25.0-29.8)	0.75
Creatinine, median (IQR), mg/dL	0.96 (0.83-1.11)	0.97 (0.84-1.10)	0.60
EuroScore*, median (IQR)	4 (2-6)	5 (3-7)	0.06
Medical history, n (%)			
Hypertension	253 (51.6)	236 (47.9)	0.26
Diabetes	89 (18.2)	100 (20.5)	0.42
Stroke/TIA	26 (5.3)	40 (8.1)	0.10
Peripheral artery disease	40 (8.2)	61 (12.4)	0.04
Recent MI (<90 days)	34 (6.9)	39 (7.9)	0.65
Preoperative use of: n (%)			
Aspirin	320 (65.3)	324 (65.7)	0.95
Corticosteroids	20 (4.1)	25 (5.1)	0.56
Statin	284 (58.0)	273 (55.4)	0.45
β-blocker	348 (71.0)	365 (74.0)	0.32
Left ventricular function, n (%)			
Good, EF >50%	340 (69.8)	306 (62.2)	0.04
Moderate, EF 30-50%	118 (24.2)	152 (30.9)	
Poor, EF <30%	29 (6.0)	34 (6.9)	
Cardiac surgery type, n (%)			
Isolated CABG	242 (49.4)	246 (49.7)	0.97
Valve surgery +/- CABG or other surgery	248 (50.6)	249 (50.3)	
Intraoperative parameters			
CPB time, median (IQR), minutes	119 (86-165)	116 (89-166)	0.97
Aortic crossclamp time, median (IQR), minutes	82 (59-109)	78 (57-106)	0.27

Abbreviations: CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; EF, ejection fraction; IQR, interquartile range; MI: myocardial infarction; SD, standard deviation; TIA: transient ischemic attack.
*EuroScore preoperative risk estimate

Table 2. Multivariable linear regression analysis in the placebo treated group (n=495).

	Multivariable analysis		
Characteristic	Unstandardized Beta	95% CI	p-value
Log peak CRP	0.057	-0.014-0.128	0.12
Age	<0.001	-0.008-0.007	0.92
Preoperative creatinine	0.001	<0.001-0.002	0.24
EuroScore*	-0.022	-0.055-0.012	0.20
Hypertension	-0.041	-0.136-0.055	0.40
Peripheral artery disease	0.127	-0.047-0.302	0.15
Recent MI	0.080	-0.119-0.279	0.43
Aspirin	-0.115	-0.235-0.004	0.06
β-blocker	0.056	-0.062-0.175	0.35
Statin	-0.011	-0.121-0.099	0.85
LVEF	0.105	0.014-0.196	0.02
Valve surgery	0.268	0.123-0.414	<0.001
CPB time	0.003	0.002-0.004	<0.001

Dependent variable: log peak CK-MB.
Abbreviations: CPB: cardiopulmonary bypass; CRP: C-reactive protein; LVEF: left ventricular ejection fraction; MI: myocardial infarction. *EuroScore preoperative risk estimate

Table 3. The effect of dexamethasone on postoperative CK-MB and CRP values

Outcome	Dexamethasone (n=490)	Placebo (n=495)	p-value
Peak CK-MB, median (IQR), U/L	36 (25-65)	36 (26-59)	0.84
Peak CRP, median (IQR), mg/L	84 (49-145)	167 (87-237)	<0.001

Abbreviations: CRP: C-reactive protein; CK-MB: Creatinine Kinase isoenzyme MB.

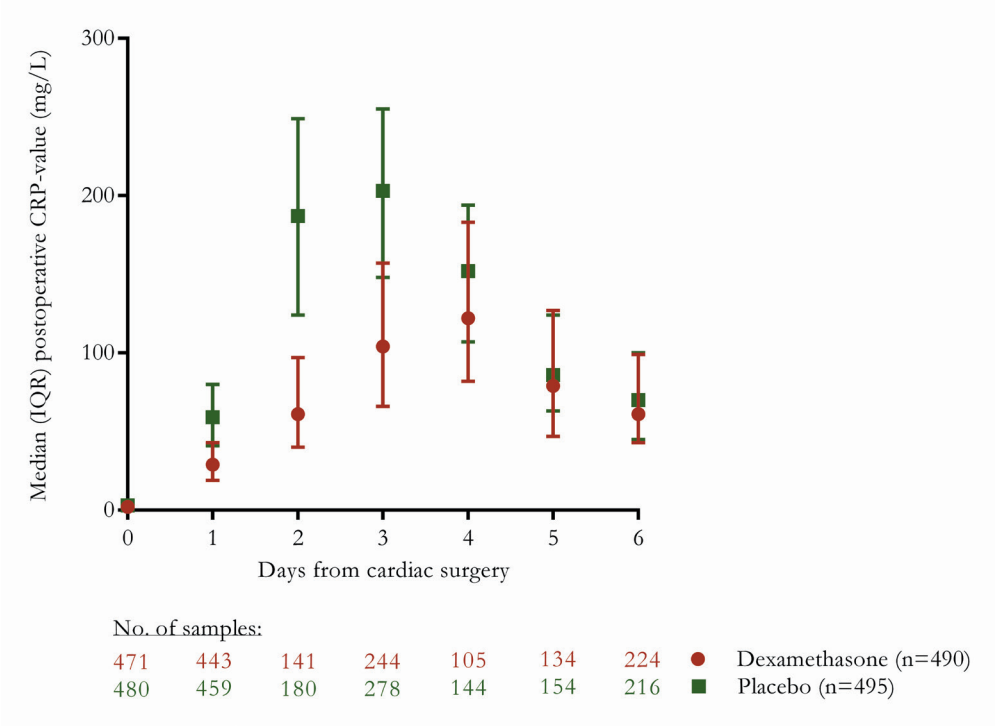

Figure 1. Median postoperative CRP values

DISCUSSION

In the present study, postoperative peak CRP was not associated with postoperative peak CK-MB. This indicates that the intensity of the inflammatory response after cardiac surgery is not associated with the extent of postoperative myocardial injury. The finding that postoperative peak CRP is not associated with postoperative peak CK-MB after cardiac surgery is supported by findings from prior studies. Min et al investigated the relationship between postoperative CRP elevation and major adverse cardiovascular events (MACE) in 1046 patients undergoing off-pump CABG. They found no association between postoperative maximum CRP and postoperative maximum troponin I levels. However, postoperative maximum CRP was related to an increased body temperature and heart rate at the end of surgery, peak lactate levels and transfusion of packed red cells. Furthermore maximum CRP levels after cardiac surgery predicted long-term postoperative MACE (11). Another study by Corral et al investigated the correlation between postoperative CRP and ICU outcomes in 216 patients undergoing on-pump cardiac surgery. They also did not find a relation between postoperative CRP and peak troponin I or CK-MB. However, they found an association between postoperative CRP and CPB time, peak lactate and need for norepinephrine treatment, suggestive of hypoperfusion and vasodilatation (12). Therefore, it seems that patients with a worse perioperative status, have a more pronounced inflammatory response. However, this inflammatory response was not associated with more

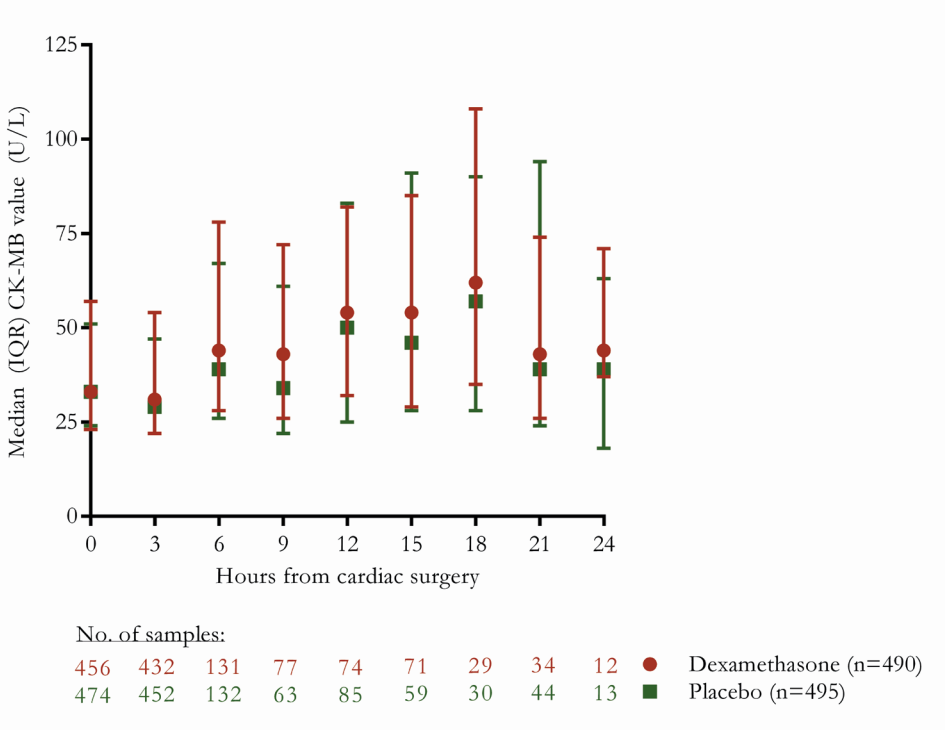

Figure 2. Median postoperative CK-MB values

myocardial injury. When interpreting Figure 1 and 2, one should be aware that the rise in CK-MB typically occurs earlier in time than the peak CRP values occur. Due to the fact that the analyses were not prespecified in the DECS trial, no simultaneous CRP and CK-MB measurements were drawn and most of the CRP samples were drawn after the CK-MB measurements. Therefore, it was impossible to investigate a causal relationship between postoperative CRP and CK-MB. This is a limitation. Another limitation was that CRP was not measured at all time-points after cardiac surgery in all patients, because some patients were transferred to another hospital before postoperative day 3 or discharged home before postoperative day 6. This might have introduced some form of bias, because in contrast to patients who are doing well after cardiac surgery, patients with a poor clinical condition are not likely to be discharged early after cardiac surgery. 71 patients in the placebo group (14.3%) were discharged to another hospital before postoperative day 3. Therefore, we only had a single postoperative CRP value available for these patients. This value is not likely to be the maximum postoperative CRP value, given the fact that maximum CRP values were most frequently measured on postoperative day 3. To assess to which extent this influenced the results of our study, we performed an additional multivariable linear regression analysis in which we left these patients out. The results of this analysis did not significantly change the results as reported in the present study.

We found that other factors than CRP, such as longer CPB time, lower LVEF and valve surgery were associated with an increased peak CK-MB after cardiac surgery. Prior studies support our finding that longer CPB time and valve surgery were associated with more postoperative myocardial injury. The increased enzyme release is likely due to increased complexity of the operation and more myocardial damage due to the surgical trauma and longer ischemia time (13, 14). The finding that lower LVEF is associated with increased myocardial injury has also been reported before in a study investigating patients undergoing CABG with use of CPB (15). The ability to counteract ischemia–reperfusion induced oxidative myocardial damage was inversely correlated with LVEF. As a result, the extent of myocardial injury was higher in patients with a decreased LVEF (15). We did not find protective factors of myocardial injury. Myocardial damage due to the surgical trauma leads to local inflammation in cardiac tissue and activation of platelets (16). Aspirin inhibits platelet aggregation and might therefore prevent from small vessel obstruction and microembolization. Furthermore, aspirin has anti-inflammatory effects and is able to reduce oxidative stress. It is possible that these effects attenuate the extent of myocardial injury (17), however in our study we found no association between aspirin use and lower CK-MB levels.

In contrast to findings from the SIRS trial, dexamethasone treatment had no effect on the extent of perioperative myocardial injury in our study. Dexamethasone effectively reduced the postoperative peak CRP value. This supports the finding of our study that the inflammatory response was not associated with the extent of myocardial injury. There are several factors that may have contributed to the different results between the SIRS trial and our study. First the SIRS trial used methylprednisolone instead of dexamethasone. Corticosteroids induce insulin resistance, which blocks glucose entry into the myocyte and therefore might impair recovery of the myocytes (9). However, the effects of dexamethasone are similar to methylprednisolone, therefore it is unlikely that this explains the difference between the two studies. Second, the SIRS trial used CK-MB thresholds to diagnose myocardial injury, while we investigated median peak CK-MB levels. Unfortunately, preoperative CK-MB levels were not available in our study, therefore it was not possible to investigate the effect of dexamethasone treatment on myocardial injury exactly as it was defined by the SIRS trial. However, if we define myocardial injury as a postoperative peak CK-MB activity ≥40 U/L for CABG patients and ≥120 U/L for patients undergoing valve or other cardiac surgery (largely in line with the definition in the SIRS trial), we would find no difference in the proportion of patients with myocardial injury in the dexamethasone versus placebo treated group: 85/483 (17.6%) versus 86/489 (17.6%) ($p>0.99$), respectively. The incidence of myocardial injury was higher than in the SIRS trial, likely due to the fact that the SIRS trial also took preoperative CK-MB into account in diagnosing myocardial injury and we were not able to do this. The extent of postoperative myocardial injury has been associated with an increased intermediate- and long-term risk of mortality. Therefore myocardial injury after cardiac surgery may be prognostically important (18), however its additional treatment consequences remain uncertain. A similar association has been found in non-cardiac surgery (19) and in patients undergoing a percutaneous coronary intervention (PCI) (18). Given the similar findings in patients undergoing cardiac surgery, a PCI or non-cardiac surgery, the extent of myocardial injury seems to be more important than the way in which damage was inflicted to the heart. Though, the underlying mechanism how myocardial injury leads to a reduced survival

remains unclear and this association may just be an epiphenomenon. It is possible that postoperative elevated cardiac biomarkers (as well as CRP) are an expression of a poor clinical condition rather than a primary cardiac event.

CONCLUSION

The intensity of the inflammatory response after cardiac surgery was not associated with the extent of postoperative myocardial injury. Furthermore, dexamethasone treatment effectively reduced postoperative CRP, however had no effect on myocardial injury.

Conflict of interest

All authors report no conflict of interests.

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Chapter 8

GENERAL DISCUSSION

The research described in this thesis has been focused on inflammation related cardiac complications in patients undergoing heart surgery. More specifically, we have investigated the evidence gaps around the Post Pericardiotomy Syndrome (PPS), as well as the effects of inflammatory prophylaxis with dexamethasone on cardiac complications.

POST PERICARDIOTOMY SYNDROME

As stated in **chapter 2**, it is remarkable that after more than 60 years of research on PPS, the mechanisms underlying PPS are still poorly understood. As a result, optimal treatment and prevention strategies remain unclear. An important reason why so little progress has been booked in PPS research, is poor comparability between the available studies. Cardiac surgical techniques, preservation methods, and perioperative patient care have improved dramatically throughout the years, making it impossible to compare the earliest reports (from the 1950s) with more recent studies. Another reason for poor study comparability is the lack of consistency in the definition of PPS that has been used over time. In the past decades, the definition of PPS has changed many times and the current definition still has important shortcomings.

In the available literature on PPS, the syndrome is considered to be an inflammatory complication of cardiac surgery. However, the most commonly used definitions of PPS do not solely include inflammatory causes. With the current definition, PPS can be diagnosed at any time in the postoperative course. In this way, both early and late postoperative pericardial effusions fall within the diagnosis of PPS, while the etiology may be entirely different. Early postoperative effusions may be the result of surgical bleeding, which is common after cardiac surgery in general, while late postoperative effusions may be inflammation mediated. In earlier studies (roughly before the year 2000), PPS could only be diagnosed after the 7th postoperative day, making it unlikely that the effects of prolonged postoperative bleeding were considered to be PPS. For unknown reasons, this criterion was abandoned in studies after 2000. This led to a much broader definition of PPS, resulting in a discrepancy in what PPS is considered to be in literature (an inflammation mediated complication) and how it is defined (a bleeding or inflammation mediated complication). Supportive to this hypothesis are the findings presented in **chapter 3**. The Kaplan Meier curves of reoperation for tamponade in PPS versus no PPS patients are similar during the first 5 postoperative days. However, after 5 days the curves diverge, showing a higher incidence of 'late' reoperations for tamponade in PPS patients. This result suggests a different underlying mechanism of early and late tamponades; common surgical bleeding versus inflammation, respectively. If inflammation is becoming increasingly important in the development of pericardial effusions at a later stage after surgery, there has to be a transition phase where both bleeding and inflammation contribute (Figure 1). However, the exact duration of this transition phase is difficult to determine based on the available evidence. Furthermore, bleeding itself may induce inflammation (1).
With the current definition, many patients without inflammation will fall within the diagnosis PPS and that might be one of the reasons why dexamethasone was not shown to reduce the incidence of PPS (**chapter 4**). Another reason might be the timing of drug administration.

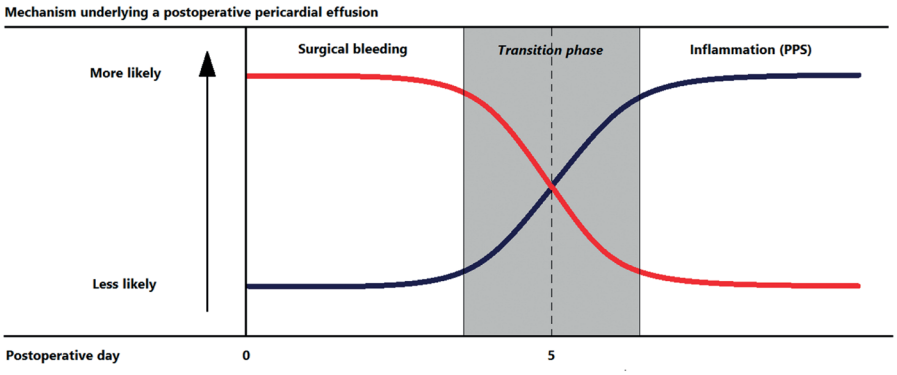

Figure 1. Mechanism underlying postoperative pericardial effusions

A single intraoperative dose dexamethasone is likely to be less effective if inflammation only contributes to the development of pericardial effusions from day 5 postoperatively. Prophylactic administration of corticosteroids might thus be more effective to prevent PPS at a later moment in the postoperative course. The biological half-life of dexamethasone is 36-72 hours (2). Therefore, dexamethasone also has an effect beyond the first postoperative week, however the anti-inflammatory effects are likely to be less pronounced than directly after injection.

There are some other shortcomings of the current definition of PPS. First, no minimal amounts of pericardial and pleural effusions, necessary to diagnose PPS, are defined. Therefore, many patients with small effusions fulfil the criteria for the diagnosis of PPS without having clinically relevant PPS. Furthermore, pericardial chest pain and a pericardial or pleural rub are components of the diagnosis, however it is unclear why for example pericarditis characteristics on the ECG are not. All these symptoms imply pericardial inflammation and might thus be PPS. Fever without alternative cause is a non-specific symptom of inflammation and is a component of the diagnosis, while other non-specific laboratory markers of inflammation (C-reactive protein, white blood cell count) are not. The currently used criteria were published in 2013 and are largely based on the (at that moment) two largest prevention trials on PPS (3). However, the reasons why the current criteria were chosen are not further clarified by the authors. Because of the aforementioned shortcomings of the current diagnosis, we should consider refining the diagnosis. The uncertainty about the mechanism underlying PPS, might be a reason why the definition of PPS has changed so many times in the past decades. If we can increase our understanding about the mechanism underlying PPS, it would be easier to determine what characteristics/symptoms are specific for PPS.

It has been hypothesized before that retained blood in the pericardial space might be the trigger for the development of pericardial effusions past the immediate postoperative period; the retained blood syndrome (RBS). Boyle *et al.* suggest that surgical bleeding causes acute and subacute tamponade (during the first postoperative days) and retained blood leads to local,

chronic inflammation and therefore causes late tamponades (1). Supportive to this hypothesis are the findings from prior studies in which active chest tube clearance and continuous postoperative pericardial flushing reduced reinterventions for retained blood (4, 5). The findings presented in **chapter 6** further support the hypothesis of retained blood. Dexamethasone treatment was associated with significantly more reoperations for 'late' tamponade (>24 hours postoperatively) as compared to placebo treatment. A possible explanation is that retained blood in the pericardial space leads to a localized inflammatory response, which is necessary to clear blood from the pericardial space. Too much suppression of this local inflammatory reaction by dexamethasone impairs this process, leading to an increased amount of retained blood in the pericardium, which is less likely to resolve spontaneously (6). This idea of over-suppression of the immune system has also been proposed in the DExamethasone for Cardiac Surgery (DECS) trial in which a possible harmful effect of dexamethasone was seen in elderly patients who already have a senescent immune system (7).
Retained blood however is not the only trigger for pericardial inflammation. Many other factors contribute to this local inflammatory reaction. The surgical trauma, the presence of intrapericardial drains and the effects of the systemic inflammatory response all contribute to the development of a local response in the pericardium. Prior studies have shown that cardiac surgery inflicts damage to mesothelial cells of the pericardium and leads to inflammation. Inflammatory changes in pericardial biopsies have been demonstrated to occur within 30 minutes following pericardial incision (8, 9). Furthermore, preliminary results of a PPS cohort that we are currently establishing, show that some patients without a pericardial effusion on the postoperative echocardiogram (without retained blood), can develop PPS afterwards. Although it is possible that small amounts of retained blood are not well detectable with echocardiography, this supports the hypothesis that the etiology of PPS is multifactorial and that retained blood is not the only determinant of pericardial inflammation and PPS.

FUTURE PERSPECTIVES

If we aim to significantly improve our understanding of PPS, there are two main issues that we should focus on in the future. On the one hand, more fundamental research on PPS is needed in order to better understand the mechanisms. On the other hand, we need to refine the clinical definition of PPS.

Many clinical studies have been performed on PPS, however it is remarkable that, to our knowledge, no prior studies have investigated large series of pericardial fluid and pericardial tissue in patients with and without PPS. Therefore, the composition of postoperative pericardial effusions in PPS patients, as well as the underlying processes that play a role in the pericardial cells, are largely unknown. If we want to gain more insight in the mechanism of PPS development, it is important that we take a step back and think of study designs that answer the following questions:

1. Are there histological differences in pericardial cells between patients that are considered to have PPS versus patients without PPS?

2. Is there a difference in the composition of pericardial fluid in patients that are considered to have PPS versus patients without PPS?
3. Are there histological differences in pericardial cells in patients with early versus late postoperative effusions?
4. Is there a difference in the composition of pericardial fluid between patients with early versus late postoperative pericardial effusions.

To answer the first two questions, one ideally would obtain pericardial fluid and tissue samples in all patients that are considered to have PPS, and compare those to samples of matched controls without PPS. However, it would be unethical to perform a second, unnecessary surgical procedure (with all the associated risks) on patients with an uncomplicated postoperative course. The only opportunity to obtain pericardial tissue or fluid in a patient after cardiac surgery is when the patient needs to undergo a reoperation (resternotomy, subxiphoid drainage or pericardial puncture) at some point in the postoperative course. Therefore, we designed the PEricardial Tissue and the Post Pericardiotomy SYndrome (PEPPSY) study, that is now recruiting patients in the University Medical Center Utrecht, The Netherlands. The study is designed as a 'case-control' study. In a first pilot, in 30 patients undergoing a resternotomy (for any reason, >24 hours after cardiac surgery and within 90 days after cardiac surgery), a pericardial tissue sample, a pericardial fluid sample and a blood sample will be obtained. We will retrospectively examine whether the patient had PPS before the reoperation or not and compare tissue and fluid characteristics between the two groups. Furthermore, similar samples will be obtained in 10 consecutive patients undergoing cardiac surgery for the first time, in order to compare tissue and fluid characteristics of the pericardium at initial surgery with postoperative pericardial tissue characteristics (at time of the rethoracotomy). Sections of the pericardial tissue will be stained with hematoxylin and eosin and assessed by a pathologist who is blinded for the diagnosis PPS. The pathologist will assess the morphology of the mesothelial cells and will in particular look for signs of inflammation, including edema, margination and the presence of infiltration. Presence of macrophages, B- and T-lymphocytes will be assessed by CD68, CD20 and CD3 staining. Pericardial fluid and peripheral blood will be saved in a biobank and the materials will be investigated after the results from histology studies will be available. Considering prior literature, it will be important to investigate markers of coagulation, fibrinolysis, inflammation, fibrosis and vascular endothelial growth factor (a permeability inducing agent of mesothelial cells) (1, 10, 11). The study has the potential to generate new hypotheses on the pathogenesis of PPS. Furthermore, it will be particularly interesting to compare characteristics of pericardial effusions that were obtained before and after postoperative day 5, given the findings of **chapter 3** of this thesis. If we are able to gain more insight in the mechanism underlying PPS, this will be an important opportunity for the development of more targeted treatment and prevention strategies in the future.

Another important challenge for the future is to refine the definition of PPS. We believe that only patients with inflammation should be able to meet the criteria for the diagnosis PPS. Most important herein is the return of a time criterion in the diagnosis. If there is indeed an important pathophysiologic role for a longer lasting inflammatory response, it should not be possible to

define PPS before postoperative day 5. Findings from the PEPPSY study, in which differences between early and late effusions will be investigated might help us in further refining the definition. We propose the following, refined definition for PPS:

Diagnosis PPS if two or more criteria are present from the fifth postoperative day:
1. Fever ≥ 38.0˚ Celsius without alternative cause
2. Pericardial/pleural rub or pericarditis characteristics on the ECG
3. Typical pericardial or pleuritic chest pain
4. Significant pericardial effusion (>10 mm)
5. Significant pleural effusion (above the highest level of the diaphragm)

Similar to the prior definition, a sign of pericardial or pleural inflammation must be accompanied by a supportive sign of pericardial/pleural inflammation or systemic inflammation. We have added a time criterion (from the 5th postoperative day), pericarditis characteristics on the ECG and a minimal amount of effusion to the definition. By adding a minimal amount of effusion we aim to exclude small effusions which are not uncommon after cardiac surgery. We did not include laboratory markers of inflammation (such as CRP) to the definition, because results of **chapter 7** show that CRP is likely to be elevated on the 5th day after cardiac surgery. With this new proposed definition, it is more likely that only patients with inflammation fall within the diagnosis PPS. Studies investigating anti-inflammatory treatment and prevention strategies might therefore be more successful when this definition is used.

DEXAMETHASONE PROPHYLAXIS

The pathogenesis of the inflammatory response following cardiac surgery is very complex and involves multiple triggers and pathways. The surgical trauma, contact of blood with artificial material of the cardiopulmonary bypass (CPB), endotoxemia and ischemia-reperfusion injury are triggers that lead to activation of the immune system. This occurs via complement activation and synthesis of pro-inflammatory cytokines (12). Dexamethasone is an effective inhibitor of the inflammatory response. It binds to glucocorticoid receptors, which regulate the transcription of genes (via nuclear factor κB) that are important in the inflammatory process. It inhibits the gene transcription of pro-inflammatory cytokines and adhesion molecules and stimulates the transcription of anti-inflammatory cytokines (12-14). Multiple prior studies have shown that dexamethasone effectively reduces systemic inflammation after cardiac surgery (15). This is further supported by the results in chapter 7 of this thesis, in which postoperative peak CRP was significantly lower in the dexamethasone treated group. However, dexamethasone prophylaxis was not able to reduce clinically relevant cardiac complications that are related to this inflammatory response after cardiac surgery.
In **chapter 5** of this thesis, we report that dexamethasone prophylaxis was not able to prevent from postoperative (new-onset) atrial fibrillation (AF). Inflammation in cardiac tissue plays an important role in the development of (postoperative) AF. Atrial biopsies of patients with AF show infiltration of immune cells in cardiac tissue, while such infiltration is not present in

patients without AF. Furthermore inflammatory markers (CRP, white blood cell count, interleukin-6, interleukin-8 and tumor necrosis factor α) are higher in patients with AF versus patients without AF (16). Also, a higher baseline CRP predicts the risk of developing AF, suggesting that patients with persistent (low-grade) inflammation have an increased vulnerability for AF (16, 17). However, the question remains whether or not inflammation directly causes postoperative AF or that it is an epiphenomenon of another process. Pressure overload, volume overload and ischemia of atrial tissue lead to atrial injury and result in local inflammation. In atrial tissue, infiltration of macrophages, oxidative stress, edema, apoptosis and fibrosis lead to structural and electrical remodeling. This remodeling could be a focus for new re-entry arrhythmias and lead to a change in conduction properties (12, 16, 18). Intraoperative dexamethasone treatment inhibits many inflammatory processes in the heart and therefore could be effective in the prevention of postoperative AF. However, it is imaginable that decreasing inflammation in an already injured heart (for example a heart with dilated atria and atrial fibrosis) will be less effective. A diseased heart showing electrical and structural remodelling already has a substrate for arrhythmias. This hypothesis is further supported by the findings of the subgroup analysis in **chapter 5**, in which dexamethasone treatment seems to be effective in preventing postoperative AF in patients with a normal left ventricular ejection fraction. Furthermore, in the ARMYDA-3 trial, treatment with atorvastatin was able to significantly reduce the incidence of postoperative AF after cardiac surgery. Prior studies have shown that statins have anti-inflammatory effects, however CRP levels did not significantly differ between patients treated with atorvastatin and placebo (19). This implies that statins might have an, other than inflammatory effect on cardiac tissue, such as antioxidant effects and cell membrane ion channel stabilization (19).

In **chapter 6** of this thesis, significantly more patients remained free of transfusion of blood products in the dexamethasone group as compared to the placebo group. However, the number of transfused blood products was not different between the two groups. Postoperative bleeding disorders are common after cardiac surgery and the underlying mechanism is believed to be multifactorial. Inflammation is proposed as one of the factors affecting the complex balance between coagulation and fibrinolysis during the postoperative period, however the exact effects of inflammation remain unclear. Acute systemic inflammation with increased levels of tumor necrosis factor α (TNF-α) induces tissue plasminogen activator (t-PA) release from endothelial cells. This process enhances fibrinolysis and might lead to increased bleeding tendency (20, 21). On the other hand, inflammation is associated with an increased risk of thrombosis, by increasing tissue factor expression and thrombin generation via NF-κB (22). Dexamethasone treatment interacts with all the aforementioned processes and may therefore have an effect on postoperative coagulation status. In preclinical studies, dexamethasone treatment inhibited thrombosis by impairing platelet aggregation. At higher doses, dexamethasone caused a decrease in fibrinolytic activity (23). On the contrary, dexamethasone treatment in humans increased circulating P-selectin and von Willebrand factor (vWF), possibly leading to enhanced hemostasis (24). The underlying mechanism of a decreased bleeding risk in dexamethasone treated patients is difficult to explain due to these conflicting results. Hypothermia, anticoagulant therapy (heparin, antiplatelet therapy) and use of CPB are some other important factors that

affect postoperative coagulation and might be more important in disturbing the balance between coagulation and bleeding in the postoperative phase (22).

In cardiac surgery the duration of ischemia is known to be related to the extent of myocardial injury. An important part of myocardial injury is however caused during reperfusion. Inflammation plays an important role in the pathogenesis of ischemia-reperfusion injury after cardiac surgery. Myocardial and endothelial injury lead to local inflammation and increase vascular permeability. Expression of adhesion molecules by the injured tissue promote invasion of inflammatory cells (mainly neutrophils). These cells are toxic to the myocardium by generating reactive oxygen species, proteases and occluding the capillaries and therefore further enhance myocardial injury (25). Multiple prior studies investigated the use of anti-inflammatory agents to reduce the extent of myocardial injury in acute myocardial infarction and in cardiac surgery, with variable results (26-28). In chapter 7, systemic inflammation (measured in CRP) was not associated with the extent of myocardial injury. This suggests that other factors, such as ion accumulation (causing calcium overload and acidosis), reactive oxygen species, endothelial dysfunction and micro-embolization (25), are more important in the pathogenesis of ischemia-reperfusion injury. The finding that systemic inflammation is not associated with the extent of myocardial injury was further supported by the fact that dexamethasone treatment was not able to reduce myocardial injury after cardiac surgery.

FUTURE PERSPECTIVES

Given the aforementioned, systemic and local inflammation after cardiac surgery are associated with postoperative cardiac complications. However, the causal relationship between these two is unclear. Postoperative AF, coagulation disorders and myocardial injury are affected by many other processes and therefore have a multifactorial etiology. It is possible that inflammation is an expression of other processes that are more important in the pathogenesis of these complications. This might be an explanation why dexamethasone prophylaxis was not able to prevent these complications from occurring. Another explanation might be the use of co-medication. Many patients who undergo cardiac surgery use aspirin and/or statins on a daily basis. The anti-inflammatory effect of aspirin and statins works via inhibition of the NF-κB pathway, which is the same pathway on which dexamethasone works (14, 29). There are however some indications from existing literature, as well as from this thesis that anti-inflammatory therapy could still play a role in the prevention of inflammation related cardiac complications after heart surgery. Two main issue are important herein.

First, the inflammatory response after cardiac surgery is an ongoing process. This is supported by the fact that PPS can develop until 3 months postoperatively (30). Furthermore long-term, daily postoperative anti-inflammatory treatment has been shown to be effective for the prevention of PPS and AF. Daily colchicine treatment (until postoperative day 30) successfully reduced the incidence of PPS and AF (31-33). Daily statin therapy was successful in reducing postoperative AF (19). It might be interesting to investigate whether daily, low-dose corticosteroid

treatment after cardiac surgery can be of added value for the prevention of PPS and postoperative AF. However, given the unfavourable side effects of corticosteroid treatment, there should be convincing evidence in favour of corticosteroids as compared to statin and colchicine treatment. Second, selection of patients in which inflammation plays an important role in the development of inflammatory complications is important. It is still unclear why the severity of the inflammatory response varies so much between individuals. The DECS trial found subgroups that might benefit from dexamethasone prophylaxis as well as subgroups in which dexamethasone treatment might be harmful (7). The challenge for further research is to identify patients who are at risk of developing a major inflammatory response, because this group is more likely to benefit from anti-inflammatory therapy.

CONCLUDING REMARKS

Inflammation in and around the heart after cardiac surgery is associated with several cardiac complications, however it remains unclear whether inflammation directly causes these complications or is an expression of other processes that take place in the heart. The pathogenesis of these complications is multifactorial. Inflammation is likely to play an important role, but only in a part of the patients. Future research should therefore focus on identifying patients in whom inflammation is indeed the main cause of these complications. This thesis provides some indications which patient groups might benefit from targeted anti-inflammatory treatment and prevention strategies.

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Appendix

MEMBERS OF THE DECS STUDY GROUP

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NEDERLANDSE SAMENVATTING

In Nederland ondergaan jaarlijks ongeveer 16.000 volwassenen een open hart operatie. Bij een open hart operatie wordt vaak gebruik gemaakt van de hart-longmachine. Deze machine zorgt ervoor dat het bloed tijdens de operatie van zuurstof wordt voorzien en wordt rondgepompt, terwijl het hart van de patiënt stilstaat. Het gebruik van de hart-longmachine (waarbij het bloed van de patiënt in contact komt met lichaamsvreemd materiaal), het chirurgische trauma en ischemie-reperfusie schade zijn enkele factoren die bijdragen aan activatie van het immuunsysteem en het ontstaan van zowel een lokale als systemische ontstekingsreactie. Deze ontstekingsreactie kan leiden tot een systemisch inflammatoir respons syndroom (SIRS); een syndroom dat geassocieerd wordt met meerdere postoperatieve complicaties in verschillende organen, waaronder het hart. Het huidige proefschrift focust zich op enkele complicaties in het hart die het gevolg zijn van deze hevige ontstekingsreactie. Het eerste deel van het proefschrift richt zich specifiek op het Post Pericardiotomie Syndroom (PPS). Het tweede deel focust zich op het gebruik van dexamethason (een ontstekingsremmend medicijn) om ontstekingsgerelateerde complicaties in het hart te voorkomen.

Post Pericardiotomie Syndroom (PPS)

PPS wordt gekarakteriseerd door hinderlijke, postoperatieve pericard- en pleura-effusies (vocht in het hartzakje en in de longen). De precieze oorzaak van dit syndroom is nog niet geheel opgehelderd, waardoor het onduidelijk blijft hoe men dit syndroom het best kan voorkomen en behandelen. Daarnaast is er weinig onderzoek verricht naar de lange termijn effecten van PPS. In het eerste deel van dit proefschrift wordt dan ook getracht deze vragen te beantwoorden.
Om meer inzicht te verkrijgen in het ontstaan van PPS werd allereerst, middels een systematische review, alle beschikbare literatuur omtrent determinanten van PPS op een rij gezet. De resultaten van deze review worden weergegeven in **hoofdstuk 2**. De meest opvallende bevinding van deze review is het feit dat er in de afgelopen 60 jaar 14 verschillende definities van PPS zijn gebruikt. Door deze inconsistentie zijn de studies naar PPS onderling niet te vergelijken. Het belang van het gebruik van een uniforme definitie wordt dan ook onderstreept, alsmede de belangrijkste tekortkomingen van de huidige definitie zoals deze sinds 2013 wordt gebruikt. Verder zijn er aanwijzingen dat perioperatief bloedverlies en inflammatie een rol spelen bij het ontstaan van PPS, echter doordat de studies onderling niet goed te vergelijken zijn, is deze bevinding slechts van beperkte waarde.
In **hoofdstuk 3** werden risicofactoren voor het optreden van PPS onderzocht, evenals de één-jaars prognose van patiënten met dit syndroom. Als belangrijkste bevinding werd een acht keer hoger risico op een reoperatie vanwege een tamponade bij patiënten met PPS (20.9%) gevonden in vergelijking met patiënten zonder PPS (2.5%). Verder lagen patiënten met PPS langer in het ziekenhuis (13 dagen) dan patiënten zonder PPS (11 dagen). Deze bevindingen onderstrepen dat PPS een belangrijke complicatie is die leidt tot meer reoperaties en een langere opnameduur, echter dit leidt niet tot een hogere mortaliteit na één jaar.

In **hoofdstuk 9** worden, onder andere op basis van de bevindingen uit bovenstaande studies en de beschikbare literatuur, de belangrijkste tekortkomingen van de huidige definitie van PPS

besproken en wordt een voorstel gedaan voor een nieuwe definitie van PPS. Verder wordt besproken hoe het onderzoek naar PPS in de toekomst beter kan en waar men zich op zou moeten richten. Daarnaast wordt de studie opzet van de "PEricardial tissue and the Post Pericardiotomy Syndrome" (PEPPSY) studie besproken, een studie met als doel meer inzicht te verkrijgen in het ontstaan van PPS. Meer inzicht in de ontstaanswijze van PPS zal helpen om PPS in de toekomst beter te kunnen behandelen en voorkomen.

Preventie van complicaties met dexamethason

Dexamethason is een ontstekingsremmend medicijn (een corticosteroïd) dat zeer effectief ontstekingsreacties in het lichaam kan afremmen. Vanuit de literatuur zijn er aanwijzingen dat het preventief toedienen van dit middel voorafgaand aan een hartoperatie mogelijk leidt tot minder complicaties nadien. Eerder werd er in Nederland al een grote studie verricht naar het preventieve gebruik van dexamethason: de "DExamethasone for Cardiac Surgery" (DECS) trial. Het belangrijkste resultaat van deze studie was dat het routinematig toedienen van dexamethason voorafgaand aan een hartoperatie niet leidt tot een vermindering van het aantal ernstige complicaties. De DECS studie onderzocht met name het optreden van zeer ernstige cardiovasculaire complicaties en overlijden, echter meer specifieke ontstekingsgerelateerde complicaties die optreden in het hart werden niet primair onderzocht. Om deze reden werd in het tweede deel van dit proefschrift onderzocht of het preventief toedienen van dexamethason een effectieve manier is om PPS, postoperatief atriumfibrilleren, reoperaties en myocardschade te voorkomen. Dit werd post hoc onderzocht in de patiëntenpopulatie van de DECS studie.
Uit deze studies bleek dat het preventief toedienen van dexamethason geen effect heeft op het optreden van PPS (**hoofdstuk 4**), postoperatief atriumfibrilleren (**hoofdstuk 5**) en de mate van perioperatieve myocardschade (**hoofdstuk 7**).
Een opvallende bevinding was het feit dat patiënten die met dexamethason werden behandeld een groter risico hadden om een reoperatie te ondergaan (**hoofdstuk 6**). Voor patiënten die met dexamethason waren behandeld was dit risico 9.7% tegenover 7.3% van de patiënten die waren behandeld met placebo. Dit verschil werd met name veroorzaakt door meer 'late' tamponades (>24 uur na de operatie) in de dexamethason behandelde groep. Een mogelijke verklaring hiervoor is dat achtergebleven bloed in het hartzakje leidt tot lokale ontsteking. Deze ontstekingsreactie zorgt ervoor dat bloed uit het hartzakje wordt opgeruimd. Teveel onderdrukking van deze ontstekingsreactie door toediening van dexamethason zou dit proces kunnen verstoren en kunnen leiden tot meer achtergebleven bloed in het hartzakje en daardoor meer tamponades.
In **hoofdstuk 9** wordt bediscussieerd waarom het preventief toedienen van dexamethason niet effectief was ter voorkoming van bovengenoemde complicaties. Een van de redenen hiervoor is dat het om complicaties gaat die niet enkel door ontsteking veroorzaakt worden, maar waarbij vele andere factoren een rol spelen. Het is van belang om in toekomstig onderzoek de vraag te beantwoorden bij welk type patiënten ontsteking de grootste rol speelt bij het ontstaan van deze complicaties, aangezien ontstekingsremmende medicatie mogelijk enkel bij die groep patiënten effectief is. Verder lijkt onderhoudsbehandeling met ontstekingsremmende medicatie mogelijk effectiever dan een eenmalige dosis aangezien het bij de genoemde complicaties gaat om een langdurig postoperatief ontstekingsproces.

DANKWOORD

Het begon in 2012 met een wetenschapsstage van zes weken bij de afdeling Cardiologie van het UMC Utrecht. Op dat moment had ik nooit gedacht dat dit project dusdanig uit de hand zou lopen dat het uiteindelijk zou resulteren in dit proefschrift. Dit proefschrift was nooit tot stand gekomen zonder de hulp en steun van een heleboel mensen en daarvan wil ik er een aantal in het bijzonder bedanken.

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LIST OF PUBLICATIONS

van Osch D, Nathoe HM, Peelen LM, Hack CE, Nierich AP, van Dijk D, Doevendans PA, Dieleman JM, DExamethasone for Cardiac Surgery (DECS) study group. The association between inflammation and myocardial injury following cardiac surgery. *Submitted*

van Osch D, Nathoe HM, Jacob KA, Doevendans PA, van Dijk D, Suyker WJ, Dieleman JM. Determinants of the Post Pericardiotomy Syndrome: a systematic review. *Submitted*

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van Osch D, Dieleman JM, Nathoe HM, Boasson MP, Kluin J, Bunge JJ, Nierich AP, Rosseel PM, van der Maaten JM, Hofland J, Diephuis JC, de Lange F, Boer C, van Dijk D, DExamethasone for Cardiac Surgery (DECS) study group. Intraoperative High-Dose Dexamethasone in Cardiac Surgery and the Risk of Rethoracotomy. *Ann Thorac Surg*. 2015 Dec;100(6):2237-42.

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CURRICULUM VITAE

Dirk van Osch was born on 15 April 1988 in Naarden, The Netherlands. After graduating from high school (Minkema Collega, Woerden) in 2006, he studied Medicine at Utrecht University. During his study, he became interested in Cardiology and started a research project at the Cardiology department of the University Medical Center Utrecht (UMCU) in 2012. He got involved in the DExamethasone for Cardiac Surgery (DECS) trial and performed several substudies within this trial, supervised by prof. dr. P.A.F.M. Doevendans, prof. dr. D. van Dijk, dr. H.M. Nathoe and dr. J.M. Dieleman. These efforts during his study eventually led to three publications in scientific journals.

After obtaining his medical degree in December 2013, he started working as a clinician (ANIOS) at the Cardiology department of the UMCU. In July 2015, he started working as a PhD student to complete the unfinished research projects that he started during his study and his work as a clinician. The main focus of his research was on inflammatory cardiac complications of heart surgery, specifically the post pericardiotomy syndrome (PPS) and dexamethasone prophylaxis of several inflammatory cardiac complications. These projects eventually resulted in this thesis. During his period as a PhD student, he also wrote a study protocol of a study investigating pericardial tissue and pericardial fluid samples in PPS. He executed this study in the UMCU since it started recruiting patients in June 2016. After finishing the research projects in September 2016, he started working as a resident Cardiology under supervision of dr. J.H. Kirkels on the first of October 2016.