International Journal of Cardiology 228 (2017) 971–976

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

White blood cell count and new-onset atrial fibrillation after cardiac surgery☆

Kirolos A. Jacob [a,b,*], Marc P. Buijsrogge [a], Jos F. Frencken [b], Maarten J. ten Berg [c], Willem J.L. Suyker [a], Diederik van Dijk [a], Jan M. Dieleman [a]

[a] Department of Cardio-thoracic Surgery, University Medical Centre, Utrecht, The Netherlands
[b] Department of Anesthesiology and Intensive Care Medicine, University Medical Centre, Utrecht, The Netherlands
[c] Department of Clinical Chemistry and Hematology, University Medical Centre, Utrecht, The Netherlands

ARTICLE INFO

Article history:
Received 13 May 2016
Received in revised form 20 August 2016
Accepted 5 November 2016
Available online 17 November 2016

Keywords:
Atrial fibrillation
Inflammatory response
Inflammatory cells
Perioperative care
Cardiac surgery

ABSTRACT

Background: Postoperative new-onset atrial fibrillation (PNAF) is the most common complication following cardiac surgery. The inflammatory response, as a potential underlying mechanism, has been extensively studied. In small studies, the white blood cell count (WBC) has been shown to be the only consistent inflammatory marker associated with PNAF. This study aimed to determine the association between perioperative WBC response and PNAF in a larger study cohort.

Methods: Patients ≥18 years, undergoing elective cardiac surgery with a preoperative sinus rhythm were included. WBC was routinely measured preoperatively, and daily during the first four postoperative days. Main outcomes were the difference between peak postoperative WBC and neutrophil/lymphocyte ratio (N/L ratio) and preoperative WBC and N/L ratio (ΔWBC and ΔN/L ratio respectively). Development of PNAF was evaluated in all patients with continuous 12-lead ECG monitoring.

Results: 657 patients were included and 277 (42%) developed PNAF. Univariable analyses showed a statistically significant relationship between ΔWBC ($P = 0.030$) and ΔN/L ratio ($P = 0.002$), and PNAF. In multivariable analysis no significant relationship was found between ΔWBC (OR: 1.14 per 1×10^9/L increase; 95% CI: 0.65–2.03; $P = 0.645$), ΔN/L ratio (OR: 1.65 per 1×10^9/L increase; 95% CI: 0.94–2.90; $P = 0.089$), and PNAF. Increasing age (OR: 1.08 per year; 95% CI: 1.01–1.16; $P = 0.022$) and (additional) valve surgery (versus CABG) (OR: 4.96; 95% CI: 2.07–6.91; $P \leq 0.001$) were associated with PNAF.

Conclusions: The perioperative WBC response and its components were not associated with the development of PNAF.

1. Introduction

Postoperative new-onset atrial fibrillation (PNAF) is a frequent complication after cardiac surgery. The reported incidence of PNAF in the literature varies from 25% to 40% after coronary artery bypass grafting (CABG) and from 33% to 67% after complex valve surgery [1–3]. PNAF is self-limiting in the majority of cardiac surgical patients. However, it nearly always necessitates adjuvant medical management, and leads to a prolonged length of hospital stay [1]. Associations between PNAF and adverse outcomes, such as postoperative myocardial infarction, early and late mortality, and decreased quality of life have been demonstrated in several studies [1,4–9].

Despite the large number of studies that have investigated risk factors associated with PNAF after cardiac surgery, the etiology is still not completely understood. Several studies have suggested that there is a relationship between the perioperative inflammatory response to cardiac surgery and PNAF [2,8,9]. Both the systemic inflammatory response after cardiac surgery and the onset of PNAF peak 48–72 h after surgery [9,10]. Nevertheless, the actual association between serum markers of inflammation, such as C-reactive protein and several interleukins, and PNAF is contradictory [9–11]. The only inflammatory biomarker that has consistently been associated with PNAF in previous studies, is the white blood cell count (WBC). A total of five previous studies have investigated the relationship between WBC and PNAF [12–16]. These studies have included relatively small sample sizes (60–275 patients) [12–16], while restricting inclusion criteria to patients aged above 60 (13), excluding any (additional) valve surgery [12–14,16] or patients with moderate to significant left ventricular dysfunction [15], or are

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

* Corresponding author at: University Medical Centre Utrecht, Department of Cardio-thoracic Surgery, Mail Stop E03.511 - PO Box 85500, Heidelberglaan 100, 3508 GA Utrecht, The Netherlands.
E-mail address: k.a.jacob@umcutrecht.nl (K.A. Jacob).

http://dx.doi.org/10.1016/j.ijcard.2016.11.038

limited by administration of high-dose *anti*-arrhythmic drugs [15]. Also, some of these studies have used only one measurement in time of the WBC [14] and none has corrected for hemodilution [12–16]. All the above are risk factors that potentially influence and limit any observed associations of PNAF and WBC. Therefore, the direct relationship between PNAF and the inflammatory response remains debatable.

The aim of this study was to investigate in detail the association between the perioperative WBC response and PNAF in a large cohort of patients undergoing cardiac surgery.

2. Methods

2.1. Study design and population

This was a prospective observational study conducted in participants of the multicenter Dexamethasone for Cardiac Surgery (DECS) study, which has been reported previously [17]. This trial compared dexamethasone with placebo in patients undergoing elective cardiac surgery with cardiopulmonary bypass. For the current post-hoc analysis of the aforementioned prospective study, we only used data from the patients who were randomized to placebo in the University Medical Center Utrecht (UMCU). Patients who were not in sinus rhythm preoperatively were excluded from the current analysis. The research ethics committee approved the research protocol of the current study, and waived the requirement for additional informed consent.

2.2. Operation technique

A midline sternotomy was performed to achieve access to the heart. Balanced anesthesia with a combination of intravenous opioids, muscle relaxants and volatile anesthetics was used in all patients. Techniques for cardioplegia, myocardial protection and cardiopulmonary bypass (CPB) were standardized [17].

2.3. Data collection and outcome

Data on baseline patient demographics, cardiovascular risk factors, surgical characteristics, medication use, need for transfusion, intra- and postoperative fluid intake and the incidence of PNAF, were all prospectively collected as part of the Case Record Form for the DECS study [17]. Also, as postoperative infection could be an important confounding factor in the relationship between white blood cell count and PNAF, data on the most common infections postoperatively, i.e. pulmonary, catheter-related, urinary and wound infections were collected and assessed in the multivariable model.

2.4. White blood cell count analysis

Blood samples were routinely taken at five different time points. The first time point comprised preoperative laboratory tests prior to surgery. The WBC parameters measured closest to the time of surgery were used for analysis. Postoperative blood samples were collected in EDTA tubes at 24, 48, 72 and 96 h postoperatively. Routine blood cell count analyses were performed using the Cell-Dynl Sapphire hematology analyzer (Abbott Diagnostics, Santa Clara, CA, USA) [18]. For each blood sample, all measured hematology parameters were stored in the Utrecht Patient Oriented Database, including absolute cell counts data. This database has been described in detail elsewhere, and is a relational database platform which comprises all electronic clinical data from patients treated within the UMC Utrecht [18]. From these measurements, pre- and postoperative total WBC, the N/L ratio and the differential counts were derived.

For the analysis of the association between the perioperative WBC response as a main indicator of inflammation, and PNAF, the changes during the first four postoperative days and the preoperative period in each of the parameters were used. A maximum postoperative increase in WBC (ΔWBC) was defined as the peak postoperative WBC (maximum peak level during the first four postoperative days) minus the preoperative WBC. This was chosen above isolated preoperative or postoperative values of WBC as a ΔWBC would illustrate the initiation of an inflammatory response postoperatively in a more detailed manner. In addition, components of the WBC response were subsequently calculated in the same manner, i.e. ΔN/L ratio, ΔNeutrophils, ΔLymphocytes, ΔMonocytes, ΔEosinophils and ΔBasophils.

2.5. Outcomes

The occurrence of PNAF was evaluated in all patients using continuous 12-lead ECG monitoring data, routinely collected during the first 5 days postoperatively. Additional postoperative heart rhythm information was obtained by manually screening the medical records, intensive care unit and ward discharge letters, as well as any additional postoperative ECGs. Data collection was performed by an independent cardiology resident who was blinded to other study data. To confirm the diagnosis of PNAF, at least one of the following criteria had to be met: 1) absence of P-waves in combination with irregular ventricular beats for ≥10 s on a 12-lead ECG; 2) any type of PNAF (paroxysmal, persistent or permanent); and 3) any therapeutic intervention performed for PNAF (i.e. medication or cardioversion).

2.6. Statistical analysis

Univariable comparisons were made between patients who developed PNAF and patients who did not develop PNAF. Normality of continuous variables was checked using the Kolmogorov–Smirnov test. Normally distributed variables are presented as means with standard deviations (SD) and comparisons made using an independent Student *t*-test. Data that were not normally distributed are presented as medians with interquartile range (IQR), and compared using a Mann–Whitney *U* test. Dichotomous characteristic variables are presented as absolute numbers with percentages, and compared using the χ^2-test. Correlations between the main determinant ΔWBC and the variables age, EuroSCORE, aortic cross clamp time, type of surgery, intra- and postoperative fluid intake were assessed using the Spearman's rank test.

Multivariable logistic regression analysis was used to correct for the effect of potential confounding factors. All baseline clinical and surgical variables (Table 1) were considered potential confounders based on previous literature and hence were included in the multivariable logistic regression model, along with the main aforementioned WBC parameters preoperatively, i.e. total WBC, N/L ratio, neutrophils and lymphocytes. These baseline variables included demographics (age, gender and body mass index), clinical variables (hypertension, diabetes mellitus, left ventricular function, EuroSCORE, preoperative medication), intraoperative variables (surgery type, intraoperative bypass and aortic cross clamp time), hemodilution parameters (need for transfusion, intra- and postoperative fluid intake), postoperative infection, and the aforementioned preoperative WBC components. To make sure that the assumptions of linearity of the logit and homoscedasticity were valid in the model, a natural logarithm transformation was used for variables which were not normally distributed. Subsequently the following variables were transformed: EuroSCORE, CPB time, intra- and postoperative fluid intake, pre- and postoperative neutrophils and N/L ratio and ΔN/L ratio. All variables were then forced entered in the multivariable logistic regression model. Interactions between two variables that were hypothesized to interact and thus influence the relationship between each of the interacting variables and PNAF, were also added in the multivariable model. The subsequent model was analyzed and the odds ratios (OR) along with 95% confidence intervals were calculated for the remaining variables [19].

In a subset of patients, data on postoperative fluid intake on the intensive care unit (ICU) were known to be randomly missing beforehand (time period 2006–2008; 114 [17.5%] cases), since the DECS study

Table 1
Clinical, surgical and preoperative serum characteristics for the overall population as well as specifically for patients with and without PNAF. Data are shown as N (%) unless otherwise specified.

Characteristics	Study population $N = 657$	PNAF $N = 277$	No PNAF $N = 380$	P-value
Demographics				
Age, mean (±SD), years	65.0 (11.4)	68.0 (10.4)	62.9 (11.7)	<0.001
Male sex	461 (70.2)	191 (69.0)	270 (71.1)	0.561
BMI, mean (±SD), kg/m^2	26.7 (4.1)	26.8 (4.3)	26.6 (4.0)	0.481
Coexistent medical conditions				
Hypertension	367 (55.9)	156 (56.3)	211 (55.5)	0.84
Diabetes mellitus	120 (18.3)	54 (19.5)	66 (17.4)	0.486
Left ventricular function,[a]				
Good	499 (76.0)	231 (76.9)	286 (75.3)	0.888
Poor	30(4.6)	12 (4.3)	18 (4.7)	0.806
EuroSCORE, median (IQR),[b]	4 (2–6)	5 (3–7)	4 (2–5)	<0.001
Preoperative medication				
Corticosteroid	33 (5.0)	10 (3.6)	23 (6.1)	0.157
Perioperative *anti*-arrhythmic drugs,[c]	343 (65.3)	155 (66.8)	188 (64.2)	0.527
Statins	184 (28.0)	81 (29.2)	103 (27.1)	0.612
Cardiac surgery type				
Isolated CABG	311 (47.3)	94 (33.9)	217 (57.1)	<0.001
Combined CABG and valve surgery,[d]	94 (14.3)	57 (20.6)	37 (9.7)	<0.001
Valve surgery,[d]	346 (52.7)	183 (66.1)	163 (42.9)	<0.001
Intraoperative parameters				
CPB time, median (IQR), minute	92 (74–134)	104 (77–153)	86 (70–120)	<0.001
AOX time, median (IQR), minute	70 (53–100)	81 (57–118)	65 (50–90)	<0.001
Hemodilution parameters				
Need for transfusion,[e]	212 (37.6)	96 (38.9)	116 (36.6)	0.58
Intraoperative fluid intake, median (IQR), mL	3000 (2100–4000)	3000 (2100–4000)	3000 (2005–3900)	0.26
Postoperative fluid intake up to 24 h after surgery, median (IQR), mL	3146 (2189–4442)	3211 (2313–4739)	3088 (2158–4314)	0.315
Preoperative WBC and components serum levels ($\times 10^9$)				
Total WBC, mean (±SD)	7.8 (2.2)	7.8 (2.6)	7.7 (1.9)	0.762
Preoperative N/L ratio, median (IQR)	2.49 (1.84–3.48)	2.64 (2.02–3.60)	2.39 (1.77–3.39)	0.164
Neutrophils, mean (±SD)	4.9 (1.6)	4.9 (1.6)	4.9 (1.6)	0.757
Lymphocytes, mean (±SD)	2.0 (1.2)	2.0 (1.8)	2.0 (0.7)	0.976
Monocytes, mean (±SD)	0.6 (0.2)	0.6 (0.2)	0.6 (0.2)	0.385
Eosinophils, mean (±SD)	0.2 (0.2)	0.2 (0.2)	0.2 (0.2)	0.967
Basophils, mean (±SD)	0 (0)	0 (0)	0 (0)	0.374

Abbreviations: AOX: aortic cross clamp; BMI: body mass index; CABG: coronary artery bypass grafting; CPB: cardiopulmonary bypass; CI: confidence interval; EuroSCORE: European System for Cardiac Operative Risk Evaluation [25]; IQR, interquartile range; N: number; N/L ratio: neutrophil/lymphocyte ratio; OR: odds ratio; PNAF: postoperative new-onset atrial fibrillation; SD: standard deviation; WBC: white blood cell count.

[a] Definition of left ventricular function classes [25]: good, ejection fraction of >50%, moderate, ejection fraction of 30%–50%; and poor, ejection fraction of <30%. Good left ventricular function was analyzed versus moderate/poor function. Poor left ventricular function was analyzed versus good/moderate function.

[b] Higher EuroSCORE presents increased risk of perioperative mortality [25].

[c] Anti-arrhythmic drugs included B-blockers, amiodarone, digoxin and flecainide.

[d] Valve surgery included aortic and/or mitral valve surgery. CABG analyzed versus valve surgery; combined CABG/valve surgery analyzed versus CABG or valve surgery alone; valve surgery analyzed versus CABG.

[e] Transfusion included red blood cells, thrombocytes and/or fresh frozen plasma during the operation and the total length of intensive care stay.

started before implementation of electronic medical records in the intensive care unit. Consequently, we expected that the data on postoperative fluid intake to be missing at random, since these data were missing only due to the period of inclusion. Conducting analyses on complete cases only is however known to be prone to biased effect estimates. We therefore analyzed differences in baseline variables in cases with complete data and in cases with missing values. If major differences were observed, concluding that bias was potentially present, we attempted to reduce that risk of bias by imputing those missing data for the variable "postoperative fluid intake", along with other few missing values of other baseline variables (13 [1.8%] cases; totaling 127 (19.3%) cases with missing values), using multiple imputation [20,21]. We used 20 imputation sets; results of these separate imputation sets were pooled using Rubin's rule to obtain correct estimates and standard errors [20,21]. To investigate the effects of imputation on regression analysis, a sensitivity analysis in cases with complete data were performed.

Throughout the analyses a two-sided P-value <0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 21.0 (IBM SPSS Statistics, Armonk, NY: IBM Corp).

3. Results

3.1. Patient data

A total of 1565 patients were included in the DECS trial at the UMCU, of which 781 were randomized to the placebo group. Of those, 657 patients were ultimately included in the primary analyses; 124 patients had previous atrial fibrillation (Fig. 1). Baseline characteristics of those included are displayed in Table 1. Forty-two percent ($N = 277$) of patients developed PNAF. Characteristics of patients with any missing data versus complete-case analysis are found in Supplementary Table 1. Data were incomplete in a total of 127 (19.3%) patients and were imputed.

No significant differences were found in preoperative comorbidities and medication, need for transfusions, perioperative fluid intake, preoperative total WBC, N/L ratio and differential counts between the two groups. Patients who developed PNAF were older and underwent more often (additional) valve surgery. Subsequently, the EuroSCORE was higher, and cardiopulmonary bypass and aortic cross-clamping

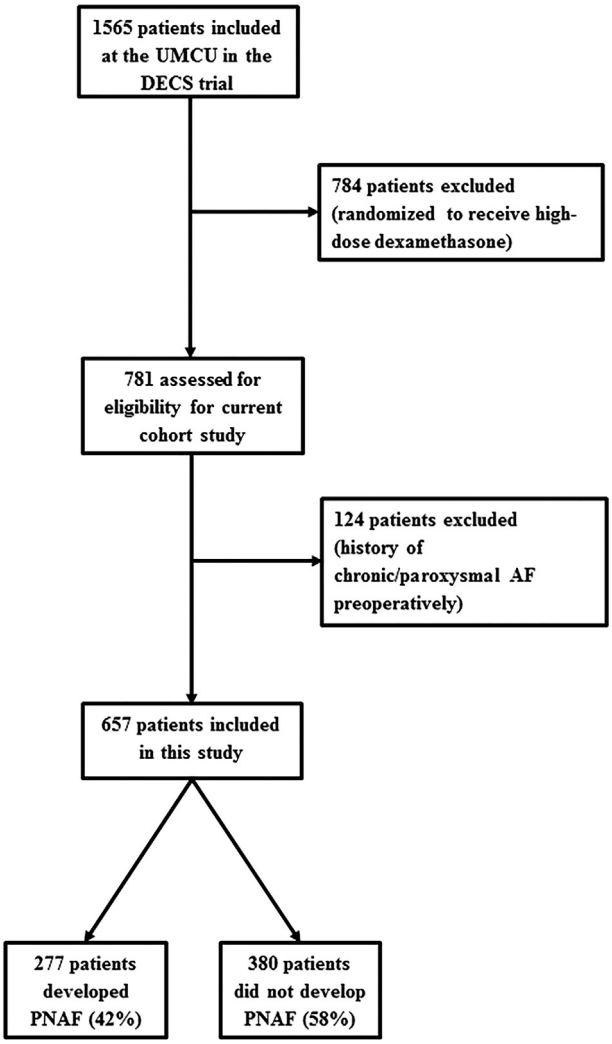

Fig. 1. Enrolment Flowchart. DECS: Dexamethasone for Cardiac Surgery; PNAF: postoperative new-onset atrial fibrillation; UMCU: University Medical Centre Utrecht.

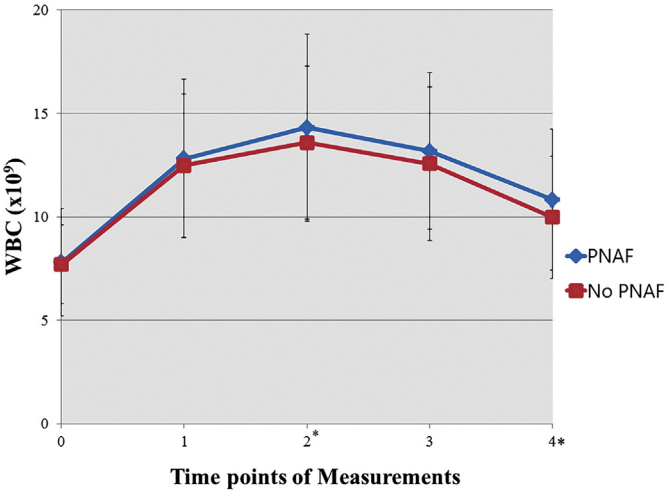

Fig. 2. Course of postoperative peak of WBC (mean and standard error of the mean) at baseline (0) and during the four consecutive postoperative days [1–4], in patients with and without PNAF. *: *P*-value <0.05; PNAF: postoperative new-onset atrial fibrillation; WBC: white blood cell count.

Table 2
Differences (Δ) between maximum peak postoperative (highest serum value in first 4 postoperative days) and preoperative WBC and leukocyte differentials for patients with and without PNAF. Data are shown as mean number $\times 10^9$/L (±SD) unless otherwise specified.

Inflammatory marker	PNAF $N = 277$	No PNAF $N = 380$	*P*-value
ΔWBC	7.1 (3.7)	6.5 (3.5)	0.030
ΔN/L ratio, median (IQR)	9.97 (6.33–18.67)	8.73 (5.37–13.23)	0.002
ΔNeutrophils	7.3 (3.4)	6.7 (3.2)	0.050
ΔLymphocytes	−0.1 (0.7)	−0.2 (0.5)	0.078
ΔMonocytes	0.7 (0.4)	0.6 (0.4)	0.285
ΔEosinophils	0 (0.2)	0 (0.2)	0.639
ΔBasophils	0 (0.1)	0 (0)	0.272

Abbreviations: IQR: interquartile range; N: number; N/L ratio: neutrophil/lymphocyte ratio; PNAF: postoperative new-onset atrial fibrillation; SD: standard deviation; WBC: white blood cell count.

times were longer in patients who developed PNAF (Table 1). Forty patients (6.1%) developed a postoperative infection episode.

3.2. White blood cell count and PNAF

The detailed course of the postoperative WBC is shown in Fig. 2.

The absolute numbers of ΔWBC, ΔN/L ratio along with the differences of the several differential counts and their association with PNAF are presented in Table 2. In univariable logistic regression analyses, solely a larger ΔWBC (OR: 1.03 per 1×10^9/L increase; 95% CI: 1.00–1.08; $P = 0.030$) and larger ΔN/L ratio (OR: 1.5 per 1×10^9/L increase; 95% CI: 1.12–2.01; $P = 0.002$) were associated with PNAF. Furthermore, detailed data on the maximum postoperative peak of

Table 3
Multivariable regression analysis for the risk of PNAF after cardiac surgery ($N = 657$).

Characteristic/variable	Odds Ratio	95% CI	*P*-value
Age, per year	1.08	1.01–1.16	0.022
Male sex	1.09	0.57–2.08	0.806
BMI, per kg/m^2	1.06	0.99–1.13	0.128
Hypertension	0.95	0.52–1.71	0.852
Diabetes Mellitus	1.51	0.71–3.22	0.29
Left ventricular function, poor[e]	0.69	0.23–1.37	0.615
EuroSCORE	0.61	0.32–1.18	0.143
Preoperative use of corticosteroids	0.48	0.16–1.42	0.184
Perioperative *anti*-arrhythmic drugs,[a]	0.73	0.38–1.41	0.347
Preoperative statins	1.19	0.58–2.43	0.643
Valve Surgery,[b]	4.96	2.07–6.91	<0.001
CPB time, per minute,[c]	1.31	0.70–2.69	0.297
Need for transfusion,[d]	0.99	0.47–2.03	0.979
Intraoperative fluid intake, per mL	1.06	0.55–2.06	0.859
Postoperative fluid intake (≤24 h after surgery), per mL	1.17	0.68–2.03	0.575
Postoperative infection	0.81	0.24–2.69	0.73
Preoperative WBC	1.37	0.73–2.59	0.297
Preoperative N/L ratio	1.48	0.78–2.81	0.232
Preoperative neutrophils	0.79	0.48–1.97	0.438
Preoperative lymphocytes	0.65	0.28–1.52	0.45
ΔWBC	1.14	0.65–2.03	0.645
ΔN/L ratio	1.65	0.94–2.90	0.089
ΔNeutrophils	0.97	0.79–1.20	0.803
ΔLymphocytes	1.32	0.76–3.08	0.138

The odds ratios for all the inflammatory markers are per 1×10^9/L increase. Abbreviations: AOX: aortic cross clamp; CI: confidence interval; CPB: cardiopulmonary bypass; EuroSCORE: European System for Cardiac Operative Risk Evaluation [25]; N/L ratio: neutrophil/lymphocyte ratio; PNAF: postoperative new-onset atrial fibrillation; WBC: white blood cell count.

[a] Anti-arrhythmic drugs included B-blockers, amiodarone, digoxin and flecainide.

[b] Valve surgery included aortic and/or mitral valve surgery. Valve surgery was analyzed versus the control group, i.e. coronary artery bypass grafting (CABG).

[c] Only CPB time was added to the model and not AOX due to significant multicollinearity between both variables. CPB was chosen as it also comprises AOX.

[d] Transfusion included red blood cells, thrombocytes and/or fresh frozen plasma during the operation and the total length of intensive care stay.

[e] Poor left ventricular function was analyzed versus good/moderate function.

WBC and the differential counts during the first four postoperative days, as well as specifically on day 2, the highest incidence of PNAF, is illustrated in Supplementary Tables 3–5.

No correlations were found between ΔWBC, and age ($\rho = -0.041$, $P = 0.307$), EuroSCORE ($\rho = 0.06$, $P = 0.138$), aortic cross clamp time ($\rho = 0.09$, $P = 0.297$), type of surgery ($\rho = -0.042$, $P = 0.30$), intraoperative fluid intake ($\rho = 0.03$, $P = 0.457$) and postoperative fluid intake ($\rho = 0.03$, $P = 0.482$). Interaction between variables which could be correlated to each other and PNAF simultaneously, were also added to the model. No significant association was found between these interactions (ΔWBC and Age, ΔWBC and ΔNeutrophils, ΔWBC and ΔLymphocytes) and the presence of PNAF.

In the multivariable logistic regression analysis, no statistically significant relationship between a larger ΔWBC (OR: 1.14 per 1×10^9/L increase; 95% CI: 0.65–2.03; $P = 0.645$), ΔN/L ratio (OR: 1.65 per 1×10^9/L increase; 95% CI: 0.94–2.90; $P = 0.089$), or the other differential counts and PNAF remained present. Only older age (OR: 1.08 per year; 95% CI: 1.01–1.16; $P = 0.022$) and (additional) valve surgery (versus CABG) (OR: 4.96; 95% CI: 2.07–6.91; $P \leq 0.001$) remained associated with PNAF (Table 3). The model did not violate the assumptions of linearity of the logit and homoscedasticity. Interactions between variables, were also added to the model. No significant association was found between these interactions (ΔWBC and Age, ΔWBC and ΔNeutrophils, ΔWBC and ΔLymphocytes) and the presence of PNAF.

To examine whether the results of the multivariable regression analysis were different if no imputation was performed, the 127 patients with incomplete data on postoperative fluid intake and other baseline values were excluded from analysis and a sensitivity analysis was performed in the 530 patients in which all data was complete. Analyzing results on complete cases only did not change our findings with respect to the association between perioperative WBC response and PNAF (Supplementary Table 2).

4. Discussion

The present study has been the largest study to date to investigate the association between perioperative WBC response and the development of PNAF following cardiac surgery. This study shows that the perioperative WBC response and its components are not associated with an increased risk of PNAF.

Among the multitude of potential acute perioperative factors, the postoperative inflammatory response has been postulated to play a significant role in the pathophysiology of PNAF. To this date, only the WBC, and more specifically the N/L ratio, has consistently been shown to be correlated with PNAF [9]. Nevertheless, the studies that have investigated WBC as a risk factor for PNAF have only included small sample sizes, have been limited to a single perioperative measurement of inflammatory parameters or had restrictive inclusion criteria for patients; all of which potentially influence and limit any observed associations of PNAF and WBC [12–16].

In contrast to the aforestated studies, our study did not find a relationship between PNAF and the perioperative WBC response and its components. As this is by far the largest study to date, we believe that it is reasonable to assume that the absence of an association is a true negative finding. Thus, our results suggest that WBC should be regarded as no more than a general biological marker of inflammation postoperatively and hence not causally associated with PNAF. Our findings are also in line with the negative results of several studies that have looked at the effects of systemic anti-inflammatory drugs for the prevention of PNAF [2,9,22]. The two largest trials, the Steroids In caRdiac Surgery (SIRS) trial and the previously stated DECS trial, investigating the role of methylprednisolone and dexamethasone respectively, found no protective value of glucocorticoids against PNAF after cardiac surgery [17,23,24]. Henceforth, other non-inflammatory medication targeting PNAF are recommended.

A strength of our study is that it included a large and broad group of cardiac surgical patients to focus on the association between PNAF and the perioperative WBC response and its components, enhancing generalizability of the results. Also, the use of measurements of WBC at multiple time points makes the results more robust. Furthermore, the risk for selection bias in this study tends to be low. Patients were prospectively included in the DECS trial and allocation to the placebo group was random and well-concealed. Risk of selection bias due to selectively missing data was further diminished by the use of multiple imputation. Our study is also the first to collect prospective data on multiple variables that could have affected perioperative WBC, including need for blood transfusion and total perioperative fluid intake which are potential factors. Finally, another strength is the detection of PNAF, as it was detected on continuous postoperative 12-lead Holter monitoring for 5 days and the medical records of all patients included were thoroughly examined, which further increases the detection of any occurrence of PNAF.

4.1. Study limitations

Despite the above strengths, we acknowledge the following limitations. As in all observational studies possible unmeasured confounding could have played a role in this cohort study. This is a post-hoc analysis, and PNAF was a pre-specified secondary outcome and the WBC components not pre-specified determinants at the time the original DECS study was designed. However, all data were prospectively collected, blood samples were taken at multiple time points and the incidence of PNAF has been comprehensively investigated as is stated before. Secondly, postoperative fluid intake data were only collected up to 24 h after surgery, during intensive care unit stay. On the ward no data were collected on fluid intake. While this might have limited analyzing hemodilution effects with regard to the concentrations of the WBC and its components, one might argue that in cardiac surgical patients most fluid infusions take place during the first 16 h after surgery with little to no extra infusions on the ward afterwards.

5. Conclusions

In this large study on the relationship between the inflammatory response after cardiac surgery and the development of PNAF, no association was found between the postoperative WBC response and the incidence of PNAF.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

Acknowledgments

This work was supported by the Netherlands Organization for Health Research and Development (ZonMw) [grant number 80-82310-98-08607] and the Dutch Heart Foundation [grant number 2007B125]. The DECS trial is registered with ClinicalTrials.gov, NCT00293592.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ijcard.2016.11.038.

References

[1] L.L. Creswell, R.B. Schuessler, M. Rosenbloom, J.L. Cox, Hazards of postoperative atrial arrhythmias, Ann. Thorac. Surg. 56 (3) (1993) 539–549.
[2] N. Echahidi, P. Pibarot, G. O'Hara, P. Mathieu, Mechanisms, prevention, and treatment of atrial fibrillation after cardiac surgery, J. Am. Coll. Cardiol. 51 (8) (2008) 793–801.

[3] C. Hurt, A. Coisne, T. Modine, et al., Contrasting effects of diabetes and metabolic syndrome on post-operativeatrial fibrillation and in-hospital outcome after cardiac surgery, Int. J. Cardiol. 167 (5) (Sep 1 2013) 2347–2350.
[4] S. Bramer, F.J. ter Woorst, M.W. van Geldorp, et al., Does new-onset postoperative atrial fibrillation after coronary artery bypass grafting affect postoperative quality of life? J. Thorac. Cardiovasc. Surg. 146 (1) (2013) 114–118.
[5] G.H. Almassi, T.H. Wagner, B. Carr, et al., Postoperative atrial fibrillation impacts on costs and one-year clinical outcomes: the veterans affairs randomized on/off bypass trial, Ann. Thorac. Surg. 99 (1) (2015) 109–114.
[6] H. Tulla, M. Hippeläinen, A. Turpeinen, O. Pitkänen, J. Hartikainen, New-onset atrial fibrillation at discharge in patients after coronary artery bypass surgery: short- and long-term morbidity and mortality, Eur. J. Cardiothorac. Surg. 48 (5) (2015) 747–752.
[7] K. Phan, H.S. Ha, S. Phan, C. Medi, S.P. Thomas, T.D. Yan, New-onset atrial fibrillation following coronary bypass surgery predicts long-term mortality: a systematic review and meta-analysis, Eur. J. Cardiothorac. Surg. 48 (6) (2015) 817–824.
[8] A. Paschalis, D. Tousoulis, M. Demosthenous, et al., Pre-operative inflammation and post-operative atrial fibrillation in coronary artery bypass surgery, Int. J. Cardiol. 173 (2) (May 1 2014) 327–328.
[9] K.A. Jacob, H.M. Nathoe, J.M. Dieleman, D. van Osch, J. Kluin, D. van Dijk, Inflammation in new-onset atrial fibrillation after cardiac surgery: a systematic review, Eur. J. Clin. Investig. 44 (4) (2014) 402–428.
[10] P. Bruins, H. te Velthuis, A.P. Yazdanbakhsh, et al., Activation of the complement system during and after cardiopulmonary bypass surgery: postsurgery activation involves C-reactive protein and is associated with postoperative arrhythmia, Circulation 96 (10) (1997) 3542–3548.
[11] A.J. Ahlsson, L. Bodin, O.H. Lundblad, A.G. Englund, Postoperative atrial fibrillation is not correlated to C-reactive protein, Ann. Thorac. Surg. 83 (4) (2007) 1332–1337.
[12] R.H. Abdelhadi, H.S. Gurm, D.R. Van Wagoner, M.K. Chung, Relation of an exaggerated rise in white blood cells after coronary bypass or cardiac valve surgery to development of atrial fibrillation postoperatively, Am. J. Cardiol. 93 (9) (2004) 1176–1178.
[13] M.L. Fontes, D. Amar, A. Kulak, et al., Increased preoperative white blood cell count predicts postoperative atrial fibrillation after coronary artery bypass surgery, J. Cardiothorac. Vasc. Anesth. 23 (4) (2009) 484–487.
[14] P.H. Gibson, B.H. Cuthbertson, B.L. Croal, et al., Usefulness of neutrophil/lymphocyte ratio as predictor of new-onset atrial fibrillation after coronary artery bypass grafting, Am. J. Cardiol. 105 (2) (2010) 186–191.
[15] G. Lamm, J. Auer, T. Weber, R. Berent, C. Ng, B. Eber, Postoperative white blood cell count predicts atrial fibrillation after cardiac surgery, J. Cardiothorac. Vasc. Anesth. 20 (1) (2006) 51–56.
[16] S.J. Mirhosseini, S. Ali-Hassan-Sayegh, S.K. Forouzannia, What is the exact predictive role of preoperative white blood cell count for new-onset atrial fibrillation following open heart surgery? Saudi J. Anaesth. 7 (1) (2013) 40–42.
[17] J.M. Dieleman, A.P. Nierich, P.M. Rosseel, et al., Intraoperative high-dose dexamethasone for cardiac surgery: a randomized controlled trial, JAMA 308 (17) (2012) 1761–1767.
[18] M.J. ten Berg, A. Huisman, P.M. van den Bemt, A.F. Schobben, A.C. Egberts, W.W. van Solinge, Linking laboratory and medication data: new opportunities for pharmacoepidemiological research, Clin. Chem. Lab. Med. 45 (1) (2007) 13–19.
[19] D.W. Hosmer Jr., Model-building strategies and methods for logistic regression, in: D.W. Hosmer Jr., S. Lemeshow, R.X. Sturdivant (Eds.), Applied Logistic Regression, third ed.John Wiley & Sons, Inc., New York 2013, pp. 91–142.
[20] M.G. Kenward, J. Carpenter, Multiple imputation: current perspectives, Stat. Methods Med. Res. 16 (3) (2007) 199–218.
[21] J.L. Schafer, Multiple imputation: a primer, Stat. Methods Med. Res. 8 (1) (1999) 3–15.
[22] A. Anselmi, G. Possati, M. Gaudino, Postoperative inflammatory reaction and atrial fibrillation: simple correlation or causation? Ann. Thorac. Surg. 88 (1) (2009) 326–333.
[23] R.P. Whitlock, P.J. Devereaux, K.H. Teoh, et al., Methylprednisolone in patients undergoing cardiopulmonary bypass (SIRS): a randomised, double-blind, placebo-controlled trial, Lancet 386 (10000) (2015) 1243–1253.
[24] D. van Osch, J.M. Dieleman, D. van Dijk, et al., Dexamethasone for the prevention of postoperative atrial fibrillation, Int. J. Cardiol. 182 (2015) 431–437.
[25] S.A. Nashef, F. Roques, P. Michel, E. Gauducheau, S. Lemeshow, R. Salamon, European system for cardiac operative risk evaluation (EuroSCORE), Eur. J. Cardiothorac. Surg. 16 (1) (1999) 9–13.