Perioperative inflammation and hypotension

Thijs Clemens David Rettig

ISBN: 978-94-6169-941-1

Cover: de 'beeldbank', St. Antonius Ziekenhuis Nieuwegein

Perioperative inflammation and hypotension

Perioperatieve inflammatie en hypotensie

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van de rector magnificus, prof.dr. G.J. van der Zwaan, ingevolge het besluit van het college voor promoties in het openbaar te verdedigen op dinsdag 6 december 2016 des middags te 2.30 uur

door

Thijs Clemens David Rettig
geboren op 3 februari 1983 te Roermond

Promotor:	Prof. dr. W.A. van Klei
Copromotoren:	Dr. P.G. Noordzij
	Dr. E.M.W. van de Garde

Dit proefschrift werd mede mogelijk gemaakt door financiële steun van de Nederlandse Hartstichting en de Research & Development van de afdeling Anesthesiologie van het Sint Antonius Ziekenhuis, Nieuwegein.

TABLE OF CONTENTS

Chapter 1

Preface

CLINICAL SCENARIO:

A 76-year old patient with bowel cancer was seen at the outpatient anesthesia clinic two weeks before bowel surgery. Medical history revealed high blood pressure, diabetes and a heart attack three years earlier. Besides occasional shortness of breath, his cardiac condition was stable and the diabetes well-regulated. Medications used included aspirin and drugs for lowering blood pressure, glucose and cholesterol (statin therapy). On physical examination blood pressure was 142/91 mmHg (mean arterial pressure 108 mmHg), heart rate 65 beats per minute, length 1.74 meters and weight 98 kilograms (body mass index 33 kg/m^2).

After the start of general anesthesia the mean arterial pressure dropped to 50 mmHg for five minutes and increased to 73 mmHg as surgery began. During the procedure several other three to five minute periods of a mean arterial pressure of 45 mmHg occurred. After the procedure the patient was woken up from anesthesia and transferred to the Intensive Care Unit for postoperative care. The attending anesthesiologist-intensivist continued the aspirin therapy, but the statin therapy was withheld until the 3^{rd} postoperative day. Eight hours after surgery the Intensive Care Unit nurse drew attention to the following patients' vital signs: temperature was 38.5°C, heart rate 102 beats per minute and respiratory rate 26 breaths per minute. Physical examination did not reveal additional abnormalities. Blood cultures were drawn, which later turned out to be negative. The following day laboratory tests showed increased inflammatory markers and a decline in kidney function: a leucocyte count of 13 10^9/L, a C-reactive protein of 115 mg/L and an elevated serum creatinine of 109 µmol. The patient was transferred to the surgical ward. On the fourth postoperative day he complained of upper abdominal pain and shortness of breath. His temperature was 38.3°C, heart rate 110 beats per minute, respiratory rate 31 breaths per minute and oxygen saturation of 89% with oxygen delivered by a nasal cannula at a rate of 4 L/min. Physical examination revealed right upper abdominal pain and crackles were heard in the lower lungs. Laboratory tests showed a worsening of results: a leucocyte count of 22 10^9/L, a C-reactive protein of 280 mg/L and a serum creatinine of 173 µmol. The anesthesiologist-intensivist was asked for re-admission to the Intensive Care Unit. On suspicion of bowel leakage, a computed tomographic (CT) scan was performed. This revealed no clear signs of bowel leakage but abnormalities in the right lower lung consistent with pneumonia. The patient was re-admitted to the Intensive Care Unit, treated with antibiotics and high flow oxygen therapy. His clinical condition improved over the following days and the kidney function recovered. On the seventh postoperative day he was dismissed from the Intensive Care Unit and fourteen days after surgery he was discharged home.

Each year over 1.4 million surgical procedures are performed in the Netherlands.[1] In general, surgery is considered safe by doctors and their patients, which is confirmed by an average mortality risk less than one percent for many surgical procedures.[2] However, postoperative outcome can vary greatly between different types of surgery. In patients undergoing minor, day-care procedures complications as reoperation and readmission occur both in 0.004% and 30-day mortality is 0.0004%.[3] These results are in contrast to the adverse event rates in patients undergoing major surgical procedures, such as abdominal or cardiac procedures. For example, for colorectal surgery the incidence of reoperation and infection is 4.7% and 14.2%, respectively and 30-day mortality is 2.9%.[4] The disability free-survival, a patient-centered outcome parameter considered increasingly important, is approximately 76% at six months after surgery.[5] For cardiac surgery myocardial infarction and infection are reported in 4.1% and 8.8% of patients, respectively and 30-day mortality is 3.1%.[6, 7] In addition, the disability free-survival at six months is approximately 85%.[5]

Anesthesiologists play an important role in the care for surgical patients. For example, the patient described earlier was first evaluated for risk assessment and optimisation at the outpatient anesthesia clinic before surgery. The anesthetic plan tailored to the patient was provided during surgery, including pain management and hemodynamic and respiratory support. After the procedure, the deteriorating physical status of the patient required assessment of an ICU physician (which is often an anesthesiologist) for treatment at a higher level of care. Sometimes, anesthesiologists take part on ward rounds in high risk surgical patients. The expanded role of anesthesiologists described here is particularly present in Western Europe. Currently this model of perioperative care is adopted in the United States where it is referred to as 'the Perioperative Surgical Home'.[8]

Thus, anesthesiologists are frequently involved in the prevention and treatment of postoperative complications. To further improve perioperative care, it is fundamental to identify determinants of adverse outcome after surgery and to early recognize patients at (increased) risk for postoperative complications. Our patient suffered from low blood pressure during surgery (i.e. intraoperative hypotension), had symptoms of systemic inflammation after surgery and had his statin therapy discontinued at the Intensive Care Unit. It can be questioned whether inflammation after surgery contributed to his outcome, in how far intraoperative hypotension played a role in the development of acute kidney injury and whether the continuation of statin therapy would have been of any benefit.

INFLAMMATION IN SURGICAL PATIENTS

After incision, macrophages, monocytes and neutrophils are attracted to the surgical site and trigger the production of cytokines.[9] These cytokines include the pro-inflammatory cytokines tumor necrosis factor-α, interleukin-6 and interleukin-8, who in their turn stimulate the liver to produce acute phase proteins (e.g. C-reactive protein). Inflammation in response to surgery is essential. It provides host defence by amplifying immune cell activation, proliferation and differentiation, increasing the production of antimicrobial products and by supporting homeostasis and wound healing. However, an overwhelming release of pro-inflammatory mediators can, among other things, lead to endothelium dysfunction. The subsequent overproduction of nitric oxide interacts with mitochondrial function by adenosine triphosphate depletion and causes mitochondrial anergy and cell apoptosis. Thus, when the inflammatory response is inadequate (i.e. uncontrolled), a local useful inflammatory reaction can change to a clinical syndrome of systemic inflammation and possibly organ dysfunction.[9] The clinical syndrome of systemic inflammation is called the systemic inflammatory response syndrome. The systemic inflammatory response syndrome is present if two or more of the following variables are abnormal; heart rate, temperature, leukocyte count and respiratory rate.[10] Individual systemic inflammatory response syndrome criteria, such as heart rate and respiratory rate, may be affected by non-inflammatory states. For example, a patient suffering from pain after surgery with tachypnea and tachycardia meets the criteria of the systemic inflammatory response syndrome but without any real systemic inflammation. The systemic inflammatory response syndrome is therefore less specific for systemic inflammation than inflammatory biomarkers, as cytokines.

Surgery may trigger systemic inflammation in several ways. Most commonly, inflammation occurs as a result of tissue trauma. Besides surgical trauma other causes for increased inflammation may be involved. For example, the use of cardiopulmonary bypass to temporarily replace the function of heart and lungs during cardiac procedures affects the inflammatory response. Exposure of blood to the non-physiological circuit of cardiopulmonary bypass triggers an immune response by inducing the complement and contact system.[11] Another cause of systemic inflammation after surgery is ischemia/reperfusion injury. Reperfusion after a period of tissue ischemia activates inflammatory and prothrombogenic cascades and cytokine release.[12] Ischemia/reperfusion injury can occur in any type of surgery as a result of a low cardiac output state, intraoperative hypotension or (un)intentional interrupted blood flow (e.g. aortic cross clamping).

Studies in patients undergoing cardiac surgery showed that increased systemic inflammation after surgery affects outcome negatively.[13, 14] However, cardiac surgery is characterized by a unique combination of large tissue injury, use of cardiopulmonary bypass and ischemia/reperfusion injury. All these factors greatly contribute to systemic

inflammation. It is not completely clear whether and why systemic inflammation is also present after other types of surgery. And, if present, whether the severity of systemic inflammation results in adverse outcome. For example, aortic valve replacement with transcatheter aortic valve implantation does not require the use of cardiopulmonary bypass. In addition, the surgical induced tissue injury is far more limited than with conventional aortic valve replacement. Transcatheter aortic valve implantation may result in less systemic inflammation compared to conventional aortic valve replacement and improved outcome.[15]

Finally, several small studies suggested that postoperative systemic inflammation may affect outcome after major abdominal surgery.[16, 17] Interestingly, a recent retrospective study showed that intraoperative administration of steroids was associated with improved outcome after surgery for pancreatic carcinoma.[18] This seems to indicate that systemic inflammation is present and important after major abdominal procedures.

Postoperative infectious complications are commonly seen after surgery. Examples are surgical wound infection, pneumonia and urinary tract infection. After cardiac surgery, the incidence of infections is five to twenty percent despite the use of antibiotic prophylaxis.[19, 20] Postoperative infections are associated with increased morbidity and mortality, emphasizing the need for therapies that reduce these numbers.[21]

Statins are widely prescribed for the primary and secondary prevention of cardiovascular diseases and known for their pleiotropic effects.[22] This includes immunomodulatory and anti-inflammatory properties, which may decrease infectious complications after surgery. Previous studies investigating the effect of preoperative statin therapy on postoperative infections have shown conflicting results. For example, Mohammed et al. studied patients after cardiac surgery and found that the incidence of infections was similar in patients with and without statin use (8.1% vs. 8.4%).[23] However, pneumonia was not scored and this may have influenced the results. In contrast, in another retrospective cohort study in patients undergoing cardiac surgery, statin therapy was associated 33% reduced risk of infections.[24]

INTRAOPERATIVE HYPOTENSION

Intraoperative hypotension is common during surgery and often a side effect of anesthesia.[25] General anesthetics cause intraoperative hypotension by a dose dependent decrease in cardiac output and systemic vascular resistance. In addition, neuraxial techniques such as epidural anesthesia block thoracic and lumbar sympathetic outflow resulting in vasodilatation, relative hypovolemia and intraoperative hypotension. Other non-anesthetic causes include blood loss, myocardial stunning (e.g. after cardiopulmonary bypass), and hypovolemia (due to fasting, vomiting or diarrhea). Frequently used

definitions of intraoperative hypotension include a systolic blood pressure of less than 80 mmHg, a mean arterial pressure of less than 55 mmHg and a decrease in systolic blood pressure of 20% from baseline. As a result of these different definitions, the reported incidence ranges from 5% to 99%.[25]

Intraoperative hypotension may contribute to the development of adverse outcome. For example, a reduced renal blood flow due to intraoperative hypotension could lead to postoperative acute kidney injury. Normally, renal blood flow is guaranteed by renal autoregulation; within certain levels of blood pressure renal blood flow is constant.[26] Outside these levels blood flow is pressure dependent and renal blood flow decreases when hypotension is present. If this period is long enough renal ischemia and cell death occurs. Recently, two large retrospective studies showed that intraoperative hypotension defined as a mean arterial pressure less than 55 mmHg was associated with an increased risk of acute kidney injury after non-cardiac surgery.[27, 28] However, due to the study design of both investigations and methodological issues such as information bias, these results can be questioned.

The role of intraoperative hypotension in the development of acute kidney injury after cardiac surgery may differ from non-cardiac surgery for several reasons. Most importantly, the strong inflammatory response associated with cardiac surgery contributes to the risk of acute kidney injury.[29] Also, perioperative anemia caused by hemodilution during cardiopulmonary bypass may induce renal ischemia and acute kidney injury. Interestingly, systemic inflammation and anemia may contribute to intraoperative hypotension as well.

At the same time, the use of cardiopulmonary bypass enables the preservation of a desired cardiac index and organ blood flow which can be adjusted if deemed appropriate. Thus, renal blood flow may be ensured despite the occurrence of intraoperative hypotension. Whether intraoperative hypotension during on-pump cardiac surgery is associated with postoperative acute kidney injury is not clear yet.[30, 31]

AIM OF THIS THESIS

In this thesis the focus is on two important issues in the perioperative care of patients undergoing major surgery. The first part of this thesis concentrates on perioperative inflammation. This part describes the relation between increased systemic inflammation after transcatheter aortic valve implantation and adverse outcome (**chapter 2**), and the inflammatory (biomarker) response after transcatheter aortic valve implantation (**chapter 3**). In **chapter 4** the association between statin therapy and infectious complications after cardiac surgery was studied. The predictive value of inflammatory biomarkers in patients undergoing major abdominal surgery is presented in **chapter 5**.

The second part of this thesis addresses the relation between intraoperative hypotension and renal function among patients who underwent major abdominal surgery (**chapter 6**) and among coronary artery bypass grafting patients (**chapter 7**).

REFERENCES

1. http://statline.cbs.nl/Statweb/publication/?DM=SLNL&PA=80386ned&D1=a&D2=0&D3=0&D4=a&D5=l&VW=T.
2. Noordzij PG, Poldermans D, Schouten O, Bax JJ, Schreiner FA, Boersma E: Postoperative mortality in The Netherlands: a population-based analysis of surgery-specific risk in adults. Anesthesiology 2010; 112: 1105-1
3. Ahmad J, Ho OA, Carman WW, Thoma A, Lalonde DH, Lista F: Assessing patient safety in Canadian ambulatory surgery facilities: A national survey. Plast Surg (Oakv) 2014; 22: 34-8
4. Kannan U, Reddy VS, Mukerji AN, Parithivel VS, Shah AK, Gilchrist BF, Farkas DT: Laparoscopic vs open partial colectomy in elderly patients: Insights from the American College of Surgeons - National Surgical Quality Improvement Program database. World J Gastroenterol 2015; 21: 12843-50
5. Shulman MA, Myles PS, Chan MT, McIlroy DR, Wallace S, Ponsford J: Measurement of disability-free survival after surgery. Anesthesiology 2015; 122: 524-36
6. Zheng Z, Jayaram R, Jiang L, Emberson J, Zhao Y, Li Q, Du J, Guarguagli S, Hill M, Chen Z, Collins R, Casadei B: Perioperative Rosuvastatin in Cardiac Surgery. N Engl J Med 2016; 374: 1744-53
7. Papachristofi O, Sharples LD, Mackay JH, Nashef SA, Fletcher SN, Klein AA, Association of Cardiothoracic Anaesthetists (ACTA): The contribution of the anaesthetist to risk-adjusted mortality after cardiac surgery. Anaesthesia 2016; 71: 138-46
8. Prielipp RC, Morell RC, Coursin DB, Brull SJ, Barker SJ, Rice MJ, Vender JS, Cohen NH: The Future of Anesthesiology: Should the Perioperative Surgical Home Redefine Us? Anesth Analg 2015; 120: 1142-8
9. Castellheim A, Brekke OL, Espevik T, Harboe M, Mollnes TE: Innate immune responses to danger signals in systemic inflammatory response syndrome and sepsis. Scand J Immunol 2009; 69: 479-91
10. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, Schein RM, Sibbald WJ, ACCP/SCCM Consensus Conference Committee: Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. 1992. Chest 2009; 136: e28
11. Paparella D, Yau TM, Young E: Cardiopulmonary bypass induced inflammation: pathophysiology and treatment. An update. Eur J Cardiothorac Surg 2002; 21: 232-44
12. Kalogeris T, Baines CP, Krenz M, Korthuis RJ: Cell biology of ischemia/reperfusion injury. Int Rev Cell Mol Biol 2012; 298: 229-317
13. Moat NE, Shore DF, Evans TW: Organ dysfunction and cardiopulmonary bypass: the role of complement and complement regulatory proteins. Eur J Cardiothorac Surg 1993; 7: 563-73
14. Trop S, Marshall JC, Mazer CD, Gupta M, Dumont DJ, Bourdeau A, Verma S: Perioperative cardiovascular system failure in South Asians undergoing cardiopulmonary bypass is associated with prolonged inflammation and increased Toll-like receptor signaling in inflammatory monocytes. J Surg Res 2014; 187: 43-52
15. Lindman BR, Goldstein JS, Nassif ME, Zajarias A, Novak E, Tibrewala A, Vatterott AM, Lawler C, Damiano RJ, Moon MR, Lawton JS, Lasala JM, Maniar HS: Systemic inflammatory response syndrome after transcatheter or surgical aortic valve replacement. Heart 2015; 101: 537-45
16. Dimopoulou I, Armaganidis A, Douka E, Mavrou I, Augustatou C, Kopterides P, Lyberopoulos P, Tzanela M, Orfanos SE, Pelekanou E, Kostopanagiotou G, Macheras A, Giamarellos-Bourboulis EJ: Tumour necrosis factor-alpha (TNFalpha) and interleukin-10 are crucial mediators in post-

operative systemic inflammatory response and determine the occurrence of complications after major abdominal surgery. Cytokine 2007; 37: 55-61
17. Mokart D, Merlin M, Sannini A, Brun JP, Delpero JR, Houvenaeghel G, Moutardier V, Blache JL: Procalcitonin, interleukin 6 and systemic inflammatory response syndrome (SIRS): early markers of postoperative sepsis after major surgery. Br J Anaesth 2005; 94: 767-73
18. Call TR, Pace NL, Thorup DB, Maxfield D, Chortkoff B, Christensen J, Mulvihill SJ: Factors associated with improved survival after resection of pancreatic adenocarcinoma: a multivariable model. Anesthesiology 2015; 122: 317-24
19. De Santo LS, Bancone C, Santarpino G, Romano G, De Feo M, Scardone M, Galdieri N, Cotrufo M: Microbiologically documented nosocomial infections after cardiac surgery: an 18-month prospective tertiary care centre report. Eur J Cardiothorac Surg 2008; 33: 666-72
20. Michalopoulos A, Geroulanos S, Rosmarakis ES, Falagas ME: Frequency, characteristics, and predictors of microbiologically documented nosocomial infections after cardiac surgery. Eur J Cardiothorac Surg 2006; 29: 456-60
21. Fowler VG,Jr, O'Brien SM, Muhlbaier LH, Corey GR, Ferguson TB, Peterson ED: Clinical predictors of major infections after cardiac surgery. Circulation 2005; 112: I358-65
22. Terblanche M, Almog Y, Rosenson RS, Smith TS, Hackam DG: Statins and sepsis: multiple modifications at multiple levels. Lancet Infect Dis 2007; 7: 358-68
23. Mohamed R, McAlister FA, Pretorius V, Kapoor AS, Majumdar SR, Ross DB, Norris CM, Alberta Provincial Program for Outcome Assessment in Coronary Heart Disease Investigators: Preoperative statin use and infection after cardiac surgery: a cohort study. Clin Infect Dis 2009; 48: e66-72
24. Coleman CI, Lucek DM, Hammond J, White CM: Preoperative statins and infectious complications following cardiac surgery. Curr Med Res Opin 2007; 23: 1783-90
25. Bijker JB, van Klei WA, Kappen TH, van Wolfswinkel L, Moons KG, Kalkman CJ: Incidence of intraoperative hypotension as a function of the chosen definition: literature definitions applied to a retrospective cohort using automated data collection. Anesthesiology 2007; 107: 213-20
26. Hill JV, Findon G, Appelhoff RJ, Endre ZH: Renal autoregulation and passive pressure-flow relationships in diabetes and hypertension. Am J Physiol Renal Physiol 2010; 299: F837-44
27. Walsh M, Devereaux PJ, Garg AX, Kurz A, Turan A, Rodseth RN, Cywinski J, Thabane L, Sessler DI: Relationship between intraoperative mean arterial pressure and clinical outcomes after noncardiac surgery: toward an empirical definition of hypotension. Anesthesiology 2013; 119: 507-15
28. Sun LY, Wijeysundera DN, Tait GA, Beattie WS: Association of intraoperative hypotension with acute kidney injury after elective noncardiac surgery. Anesthesiology 2015; 123: 515-23
29. Rosner MH, Okusa MD: Acute kidney injury associated with cardiac surgery. Clin J Am Soc Nephrol 2006; 1: 19-32
30. Gold JP, Charlson ME, Williams-Russo P, Szatrowski TP, Peterson JC, Pirraglia PA, Hartman GS, Yao FS, Hollenberg JP, Barbut D: Improvement of outcomes after coronary artery bypass. A randomized trial comparing intraoperative high versus low mean arterial pressure. J Thorac Cardiovasc Surg 1995; 110: 1302,11; discussion 1311-4
31. Azau A, Markowicz P, Corbeau JJ, Cottineau C, Moreau X, Baufreton C, Beydon L: Increasing mean arterial pressure during cardiac surgery does not reduce the rate of postoperative acute kidney injury. Perfusion 2014; 29: 496-504

Part one.

Perioperative inflammation

Chapter 2

The systemic inflammatory response syndrome predicts short-term outcome after transapical transcatheter aortic valve implantation

Thijs C.D. Rettig
Sander Rigter
Vincent J. Nijenhuis
Jan-Peter van Kuijk
Jurriën M. ten Berg
Robin H. Heijmen
Ewoudt M.W. van de Garde
Peter G. Noordzij

J Cardiothorac Vasc Anesth. 2015 Apr;29(2):283-7

ABSTRACT

Objective: Despite the minimally invasive nature of transcatheter aortic valve implantation (TAVI), the incidence of acute kidney injury (AKI) and mortality is of major concern. Several studies showed that outcome was influenced by the systemic inflammatory response syndrome (SIRS) in patients undergoing percutaneous TAVI. The purpose of this study was to investigate whether SIRS after transapical TAVI was associated with short-term outcome.

Design: Retrospective analysis of prospectively collected data.

Setting: Intensive care unit in a tertiary-care hospital.

Participants and measurements: In 121 patients undergoing transapical TAVI for severe aortic stenosis between March 2010 and October 2013 the incidence of SIRS during the first 48 hours was studied. We investigated the relation between the occurrence of SIRS and any adverse event during hospital stay. Any adverse event was defined as the composite of mortality, AKI, infection, stroke, myocardial infarction and bleeding.

Results: Sixty-five (53.7%) patients developed SIRS during 48 hours following transapical TAVI. The occurrence of SIRS was independently associated with an increased risk of any adverse event (Adjusted odds ratio 4.0, 95% CI: 1.6 - 9.6; $P = 0.002$), which was mainly an increased risk of death (Odds ratio 5.5, 95% CI: 1.1 - 25.9; $P = 0.031$). Patients with SIRS had a longer median duration of Intensive Care Unit stay compared to patients without SIRS (2 vs. 1 day; $P < 0.001$).

Conclusions: SIRS predicts short-term outcome in patients undergoing transapical TAVI.

INTRODUCTION

Since the introduction in 2007, every year approximately 9000 patients in Europe undergo transcatheter aortic valve implantation (TAVI) for symptomatic severe aortic stenosis.[1] This treatment modality is reserved for high-risk cardiac patients not suitable for conventional open-heart surgery. An important difference between surgical and transcatheter aortic valve replacement is that in the latter cardiopulmonary bypass, known for inducing an inflammatory response and subsequent organ failure, is not used.[2] Despite the less invasive nature of TAVI, postprocedural mortality and morbidity rates are high.[3,4] A pilot study in 40 patients showed that patients undergoing transapical TAVI had a higher level of high-sensitive C-reactive protein and a higher leucocyte count compared to patients undergoing transfemoral TAVI.[5] Few studies examined the relation between postprocedural systemic inflammatory response syndrome (SIRS) and outcome in patients undergoing percutaneous TAVI.[6, 7] The impact of SIRS on short-term outcome after transapical TAVI has yet to be determined. Our objective was to determine the incidence of SIRS after transapical TAVI and its effect on short-term outcome.

METHODS

Patients and procedure

The local Medical Ethics Committee (Research and Development Department, St. Antonius Hospital) approved the study and waived the need for informed consent.

From March 2010 until October 2013 a total of 127 consecutive patients with severe symptomatic aortic stenosis underwent elective transapical TAVI under general anesthesia. Operative risk was considered high for all patients and a transfemoral approach was not feasible due inaccessible femoral arteries. Detailed information about the transapical TAVI procedure has been described before.[8,9] In short, a small anterolateral mini-thoracotomy was used in the fifth intercostal space, followed by puncture of the left ventricular apex after obtaining adequate ACT (≥ 250 seconds) with heparin. Then, under fluoroscopic guidance, balloon valvuloplasty of the native aortic valve was performed using a short run of rapid ventricular pacing (180 beats per minute), followed by positioning of the prosthesis using a second rapid pacing run when indicated. Several types of valves were used; Edwards SAPIEN (Edwards Lifesciences, Irvine, California), JenaValve (JenaValve Technology GmbH, Munich) or Medtronic Engager (Medtronic, Minneapolis, Minnesota). Afterwards all patients were admitted to the Intensive Care Unit (ICU). Patients were extubated at the ICU immediately after arrival or, if necessary, after rewarming until core temperature exceeded 36.5°C. If a temporary cardiac pacemaker was necessary, the pacing rate did not exceed 90 beats per minute. None of the

patients received beta-blockers during the procedure or during the first 48 hours after TAVI. Patients in whom the inflammatory response after transapical TAVI was affected by confounding variables (reoperation within 48 hours and use of cardiopulmonary bypass during TAVI) or when the inflammatory response could not be studied (death within 48 hours of surgery) were excluded. All patients were followed up until hospital discharge. Periprocedural data were routinely prospectively gathered in a computerized medical system and subsequently analyzed. Since the operative procedure time could not be retrieved in all patients, we used fluoroscopy time as a surrogate for operative procedure time.

Clinical course

The systemic inflammatory response syndrome was defined according to existed guidelines as fulfilling at least two of the following criteria for 1 hour or more: temperature <36.0 or >38.0°C, heart rate >90 beats/minute, respiratory rate >20 breaths/minute or PaCO2 <32 mmHg, leucocyte count <4 or >12 (10^9/L).[10]

The outcome parameters were acute kidney injury (AKI), stroke, postprocedural infectious complication, bleeding complication, myocardial infarction and in-hospital mortality and were scored after the inclusion period of SIRS. A postprocedural infectious complication was defined as clinical evidence of infection (e.g. new infiltrate on chest x-ray, fever, productive cough) that required antibiotic treatment. The other parameters were defined as stated by the updated Valve Academic Research Consortium (VARC) consensus report.[11] We determined the effect of SIRS on any adverse event, a composite of all outcome parameters previously mentioned. Other study parameters were length of ICU stay, length of hospital stay, in-hospital mortality and the highest sequential organ failure assessment (SOFA) score (total and for each organ system separately) during the first 72 hours of ICU admission. The total SOFA score consists of the score of 6 organ systems (respiratory, central nervous, cardiovascular, liver, renal and coagulation) and assesses the degree of organ failure.[12] This score was calculated daily during ICU stay. T.R. collected all preprocedural data and outcome parameters. P.G. or S.R. determined in each patient if SIRS occurred.

Laboratory methods

Serum creatinine level, leucocyte count and C-reactive protein (CRP) were measured the day prior to the procedure and on postprocedural day 1, 2 and 3. Acute kidney injury was defined as an increase in serum creatinine to 150% or more (1.5 fold compared to baseline) or an increase of >26 µmol/L within 72 hours after TAVI.[11] Chronic renal failure was defined as an estimated glomerular filtration rate (eGFR) calculated by the simplified Modification of Diet in Renal Disease formula < 60 ml/min/1.73m2.[13]

Statistical analysis

Continuous data are presented as the mean ± standard deviation (sd) or median and interquartile range (IQR) as appropriate. The Kolmogorov-Smirnov test was used to test for normal distribution. To compare variables between groups, the chi square-test was used for dichotomous variables and Student's t-test or Mann-Whitney U test was used for continuous variables, where appropriate. Univariate analyses were performed to examine the crude associations of periprocedural characteristics and SIRS and outcome parameters. Multivariate analysis was performed to examine the adjusted association of SIRS and any adverse event. To do so, a multivariable logistic regression model was constructed considering all variables that were imbalanced between the arms ($P \leq 0.10$) as depicted in Table 1, 2 and 3. A variable was retained in the model as a confounder if it changed the odds ratio (OR) of SIRS and any adverse event by more than 10%. *P*-values of < 0.05 were considered significant in all analyses. Data were analyzed using IBM SPSS Statistics 22.0 software.

We performed a power analysis to determine optimal sample size. Based on prior literature reports we estimated the incidence of SIRS and any adverse event at least 30% and 7% respectively.[7] Based on the assumption that patients with SIRS have a three-fold risk of any adverse event compared to patients without SIRS the number of study patients needed was 88 (power = 80%, $\alpha = 0.05$). The sample size is not adequate to detect risks less than three-fold with adequate power. Individual outcome parameters were not powered to detect risk increases.

RESULTS

Of the 127 studied patients 6 were excluded (4 patients underwent sternotomy or rethoracotomy within 48 hours after the procedure, 1 patient died within 24 hour of admission due to periprocedural dissection of the left main coronary artery and 1 patient was on cardiopulmonary bypass during TAVI). The final study population consisted of 121 patients.

During the first 48 hours following TAVI, SIRS occurred in 65 (53.7%) patients. The use of preprocedural β-blocker therapy, steroids or statins did not influence the incidence of SIRS (Table 1). Potential risk factors for the development of SIRS such as red blood cell transfusion (23.1% vs. 19.6%; $P = 0.647$), number of rapid ventricular pacing runs (3 vs. 3; $P = 0.670$), valve-in-valve implantation (4.6% vs. 3.6%; $P = 1.000$), post-dilatation of the valve prosthesis (26.2% vs. 30.9%; $P = 0.565$) and fluoroscopy time (30 vs. 24 minutes; $P = 0.145$) were comparable in patients with and without SIRS. The valve type used was not associated with the occurrence of SIRS. Fourty-eight (39.7%) patients suffered from any adverse event. Baseline and periprocedural characteristics of patients with and without any adverse event are presented in Table 2 and 3.

Table 1: Baseline characteristics according to the occurrence of SIRS

Variable	SIRS (n=48)	No SIRS (n=73)	*p*-value
Male gender [n (%)]	30 (46.2)	28 (50.0)	0.673
Age (years)	80.1±6.7	79.5±6.5	0.651
BMI [kg/m^2 (%)]	26.2±5.0	26.8±4.5	0.454
Comorbidity			
Diabetes [n (%)]	17 (26.2)	16 (28.6)	0.766
COPD [n (%)]	28 (43.1)	19 (33.9)	0.303
Hypertension [n (%)]	63 (96.9)	52 (92.9)	0.414
Coronary artery disease [n (%)]	55 (84.6)	47 (83.9)	0.918
Congestive heart failure [n (%)]			
- NYHA ≤2	28 (43.1)	19 (33.9)	0.303
- NYHA >2	37 (56.9)	37 (66.1)	
Atrial fibrillation [n (%)]	22 (33.8)	17 (30.4)	0.682
Previous myocardial infarction [n %)]	18 (27.7)	18 (32.1)	0.593
Previous PCI [n (%)]	24 (36.9)	22 (39.3)	0.790
Previous cardiac surgery [n (%)]	21 (32.3)	28 (50.0)	0.048
Previous stroke [n (%)]	14 (21.5)	13 (23.2)	0.825
Peripheral artery disease [n (%)]	27 (41.5)	19 (33.9)	0.390
Chronic renal failure [n (%)]	27 (41.5)	24 (42.9)	0.884
Pulmonary hypertension [n (%)]	22 (33.8)	17 (30.4)	0.682
Additive EuroSCORE	10 (9-11)	10 (8-11)	0.842
Normal LVEF	24 (36.9)	22 (39.3)	0.790
Preoperative medication use			
β-blocker	17 (26.2)	20 (35.7)	0.255
Statin [n (%)]	47 (72.3)	35 (62.5)	0.250
Steroids [n (%)]	4 (6.2)	6 (10.7)	0.511

BMI indicates body mass index; COPD, chronic obstructive pulmonary disease; NYHA, New York Heart Association class; PCI, percutaneous coronary intervention; EuroSCORE, European System for Cardiac Operative Risk Evaluation score; LVEF, left ventricular ejection fraction.

Table 2: Baseline characteristics according to the occurrence of any adverse event

Variable	Adverse event (n=48)	No event (n=73)	*p*-value
Male gender [n (%)]	26 (54.2)	32 (43.8)	0.266
Age (years)	79.4±6.4	80.1±6.7	0.592
BMI [kg/m^2 (%)]	25.9±4.4	27.2±5.1	0.154
Comorbidity			
Diabetes [n (%)]	23 (47.9)	10 (13.7)	<0.001
COPD [n (%)]	18 (37.5)	29 (39.7)	0.806
Hypertension [n (%)]	48 (100)	67 (91.8)	0.080
Coronary artery disease [n (%)]	40 (83.3)	62 (84.9)	0.813
Congestive heart failure [n (%)]			
- NYHA ≤2	14 (29.2)	33 (45.2)	0.077
- NYHA >2	34 (70.8)	40 (54.8)	

Table 2: Baseline characteristics according to the occurrence of any adverse event (continued)

Variable	Adverse event (n=48)	No event (n=73)	*p*-value
Atrial fibrillation [n (%)]	17 (35.4)	22 (30.1)	0.543
Previous myocardial infarction [n %)]	19 (39.6)	17 (23.3)	0.055
Previous PCI [n (%)]	17 (35.4)	29 (39.7)	0.633
Previous cardiac surgery [n (%)]	20 (41.7)	29 (39.7)	0.832
Previous stroke [n (%)]	11 (22.9)	16 (21.9)	0.897
Peripheral artery disease [n (%)]	19 (39.6)	27 (37.0)	0.773
Chronic renal failure [n (%)]	26 (54.2)	25 (34.2)	0.030
Pulmonary hypertension [n (%)]	19 (39.6)	20 (27.4)	0.161
Additive EuroSCORE	10 (9-11)	10 (8-11)	0.496
Normal LVEF	25 (52.1)	50 (68.5)	0.069
Preoperative medication use			
β-blocker	18 (37.5)	19 (26)	0.180
Statin [n (%)]	33 (68.8)	49 (67.1)	0.851
Steroids [n (%)]	5 (10.4)	5 (6.8)	0.515

BMI indicates body mass index; COPD, chronic obstructive pulmonary disease; NYHA, New York Heart Association class; PCI, percutaneous coronary intervention; EuroSCORE, European System for Cardiac Operative Risk Evaluation score; LVEF, left ventricular ejection fraction.

Table 3: Periprocedural characteristics

Variable	Adverse event (n=48)	No event (n=73)	*p*-value
Procedural characteristics			
Rapid pacing runs [n]	3 (3-3)	3 (3-3)	0.281
Valve-in-valve [n (%)]	4 (8.3)	1 (1.4)	0.080
Post-dilatation [n (%)]	13 (27.7)	21 (28.8)	0.895
Fluoroscopy time (min)	30±23	24±10	0.145
Red blood cell transfusion [n (%)]	11 (22.9)	15 (20.5)	0.756
Valve type			
- Edwards SAPIEN	40 (83.3)	54 (74.0)	0.470
- JenaValve	6 (12.5)	15 (20.5)	
- Medtronic Engager	2 (4.2)	4 (5.5)	
Prosthetic valve performance			
Aortic insufficiency [n (%)]	26 (54.2)	40 (54.8)	0.946
- Grade 1	13 (27.1)	25 (34.2)	0.773
- Grade 2	11 (22.9)	12 (16.4)	
- Grade 3	2 (4.2)	3 (4.1)	
Postoperative medication use			
Statin [n (%)]	20 (41.7)	19 (26.0)	0.072
Steroids [n (%)]	4 (8.3)	7 (9.6)	1.000

The development of SIRS was associated with a greater degree of postprocedural organ failure as assessed by total SOFA score (4, IQR 3-6 vs. 3, IQR 2-4.75, Figure 1). Patients with SIRS had an almost 3-fold increased risk of any adverse event compared to patients without SIRS (OR 2.8, 95% CI: 1.3 - 6.1; $P = 0.007$, Table 4). Patients with SIRS were more likely to experience postprocedural bleeding (OR 3.6, 95% CI: 1.0 - 13.6) or death (OR 5.5, 95% CI: 1.1 - 25.9). The rate of postprocedural infections was 18.5% in patients with SIRS and 10.7% in patients without SIRS ($P = 0.232$). In multivariate regression analyses the occurrence of SIRS was independently associated with an increased risk of any adverse event (Adjusted odds ratio (AOR) 4.0, 95% CI: 1.6 - 9.6; $P = 0.002$, Table 5). Total median length of hospital stay was similar in both groups (7 days in patients with SIRS vs. 6 days in patients without SIRS, $P = 0.518$), while SIRS did affect the median length of ICU stay (2 vs. 1 day; $P < 0.001$, Figure 2).

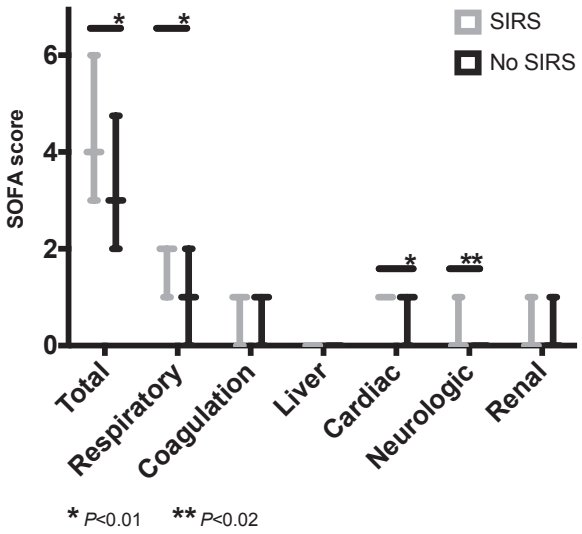

Figure 1. Highest SOFA scores during the first 72 hours of ICU admission after transapical TAVI dependent on the occurrence of SIRS

Table 4: Clinical outcomes for the occurrence of SIRS

	SIRS (n=65)	No SIRS (n=56)	*p*-value
Mortality [n (%)]	11 (16.9)	2 (3.6)	0.018
AKI [n (%)]	16 (24.6)	10 (17.9)	0.367
Stroke [n (%)]	1 (1.5)	0 (0.0)	1.000
Infection [n (%)]	12 (18.5)	6 (10.7)	0.232
Bleeding [n (%)]	11 (16.9)	3 (5.4)	0.047
Myocardial infarction [n (%)]	4 (6.2)	0 (0.0)	0.123
Any adverse event [n (%)]	33 (50.8)	15 (26.8)	0.007

All *p*-values are nominal

Individual outcomes, except for any adverse event, were not powered to show differences

SIRS, systemic inflammatory response syndrome; AKI, acute kidney injury

Table 5: Multivariate logistic regression analysis for predictors of any adverse event

Univariate analysis				Multivariate analysis			
	OR	(95% CI)	*p*-value		OR	(95% CI)	*p*-value
SIRS	2.8	(1.3 – 6.1)	0.008	SIRS	4.0	(1.6 – 9.6)	0.002
Diabetes	5.8	(2.4 – 13.9)	<0.001	Diabetes	6.9	(2.6 – 18.1)	<0.001
Previous MI	2.2	(0.9 – 4.7)	0.057	Previous MI	2.2	(0.9 – 5.5)	0.089
Decreased LVEF	2.0	(0.9 – 4.2)	0.220				
eGFR < 60 ml/min	2.6	(1.4 – 5.0)	0.003				
Valve-in-valve	6.6	(0.7 – 60.5)	0.098				

MI, myocardial infarction; eGFR, estimated glomerular filtration rate; other abbreviations as in Table 1

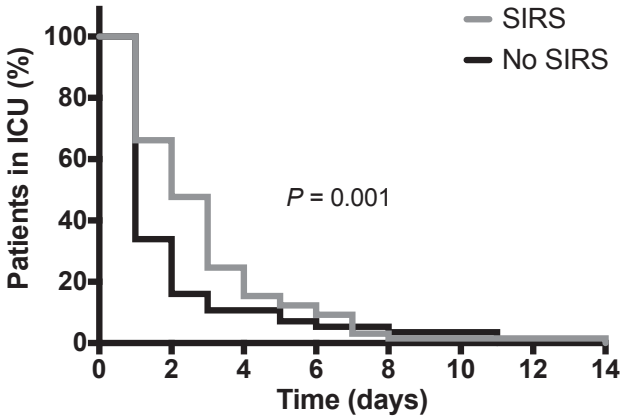

Figure 2. Median length of ICU stay after transapical TAVI dependent on the occurrence of SIRS

DISCUSSION

Our results demonstrate that SIRS after transapical TAVI is common and that SIRS is independently associated with worse short-term outcome, including an increased risk of in-hospital mortality. Sinning et al. performed a prospective study investigating the relation between SIRS and outcome in 152 patients undergoing percutaneous TAVI.[7] In that study, postprocedural SIRS occurred in 40.1% of all patients and this was independently associated with an increased 1-year mortality risk (HR 4.0; 95% CI: 1.8 - 9.2; $P = 0.001$). In another paper the same author studied the influence of periprocedural renal function on outcome after percutaneous TAVI.[6] Systemic inflammatory response syndrome after TAVI was present in 60% of all patients and closely related to AKI (60% in patients with SIRS vs. 21% in patients without SIRS, $P = 0.002$). Furthermore, patients with SIRS were at increased risk for 1-year mortality (OR 2.5; 95% CI: 1.0 - 6.2; $P = 0.04$). Although preprocedural impaired renal function and AKI were associated with mortality in our study cohort, we did not observe different numbers of AKI in patients with or without SIRS (24.6% and

17.9%, $P = 0.367$, respectively). Our results confirm that SIRS is independently associated with outcome after TAVI and that this association is also present in patients undergoing a transapical approach. In contrast to the previously mentioned studies reporting an independent association of SIRS and 1-year mortality, we observed that SIRS was associated with short-term outcome. This difference might resemble the fact that, in general, patients undergoing transapical TAVI are less healthy and potentially more susceptible to postoperative insults, e.g. SIRS, than patients undergoing transfemoral TAVI.

It is not clear whether SIRS is actually related to specific procedure related factors, except for surgery on itself. In our study, no risk factors for the occurrence of SIRS were identified. The question is whether SIRS occurs by chance or whether we simply did not identify all possible risk factors. Sinning et al. showed that an increased number of rapid ventricular pacing runs, a surrogate for low cardiac output, predicted the development of SIRS after percutaneous TAVI (OR 1.8; 95% CI: 1.1 - 2.8; $P = 0.025$).[7] These periods of low cardiac output are likely to induce ischemic injury to organs and initiate a systemic inflammatory response.[14,15] Balloon valvuloplasty of the native aortic valve, dilatation of the prosthesis and arrhytmias may also contribute to a low cardiac output state. In addition, the impact of low cardiac output may be aggravated by pre-existing vascular insufficiency, which is often present in patients undergoing TAVI (38% of our patients suffered from peripheral artery disease). Consequently, SIRS related mortality might be a result of multiple organ injury due to procedure related tissue hypoperfusion. The numbers of rapid ventricular pacing runs in patients with and without SIRS were similar in our study, but it is possible that patient with SIRS suffered from worse hypotension induced by rapid ventricular pacing runs than patients without SIRS. Unfortunately we could not obtain data regarding perioperative blood pressure in all patients.

Numerous studies showed that excessive inflammation after cardiac and non-cardiac surgery was associated with an increased risk of mortality and morbidity.[16-21] Why inflammation may lead to worse outcome after surgery is not straightforward. The exact mechanism is beyond the scope of this article, but involves tissue damage triggering the innate immune system.[22] In short, the innate immune system initiates the production of pro-inflammatory mediators and biomarkers. Inflammatory mediators (chemokines, cytokines, plasma cascades and nitrogen and reactive oxygen species) reduce the production of nitric oxide, which may lead to mitochondrial dysfunction, the development of multi organ failure (MOF) and ultimately death.[10] In this light, it is interesting that prophylactic corticosteroids led to a reduced incidence of respiratory failure and pneumonia and a reduced length of ICU and hospital stay in a recent randomized controlled trial in patients undergoing cardiac surgery.[23]

The systemic inflammatory response syndrome may emerge after a wide variety of non-infectious insults. Pancreatitis, trauma, tissue injury, surgery, ischemia, haemorrhagic shock and burns may lead to SIRS. The definition of SIRS relies on vital signs and

laboratory values that may be, but are not exclusively related to a generalized inflammatory response. For example, heart rate and respiratory rate are also influenced by non-inflammatory factors, e.g. pain or stress. We acknowledge that the individual SIRS criteria are non-specific. The addition of inflammatory biomarkers such as interleukin-6 (IL-6) or tumour necrosis factor- α (TNF-α) would have advanced the argument that postprocedural systemic inflammation was indeed present. Nonetheless, prior studies showed that patients with SIRS have higher levels of IL-6, IL-8, procalcitonin and TNF-α compared to patients without SIRS, confirming that SIRS is an expression of systemic inflammation.[7,24-27]

A second limitation is that patient data was routinely prospectively gathered in a computerized database. Although this database contains specific periprocedural data, we faced some of its limitations. For example, we could not obtain detailed information about the length and duration of periprocedural hypotension in all patients, which is a possible confounder for the development of SIRS and mortality. Third, we used a composite endpoint and all established limitations apply. However, postoperative inflammation has it influence on many different outcome parameters that have no individual relationship and therefore it would be incorrect not to study outcome in general.[23] Also, individual outcomes are rare and statistical power may not be sufficient for each individual outcome parameter. And fourth, we studied the incidence of SIRS after transapical TAVI, but we did not clarify the pathophysiological mechanism.

SIRS following transapical TAVI is common and associated with short-term outcome. Future work studying outcome in TAVI patients should focus on the cause of SIRS.

REFERENCES

1. Mylotte D, Osnabrugge RL, Windecker S, Lefevre T, de Jaegere P, Jeger R, Wenaweser P, Maisano F, Moat N, Sondergaard L, Bosmans J, Teles RC, Martucci G, Manoharan G, Garcia E, Van Mieghem NM, Kappetein AP, Serruys PW, Lange R, Piazza N: Transcatheter aortic valve replacement in Europe: adoption trends and factors influencing device utilization. J Am Coll Cardiol 2013; 62: 210-9
2. Kirklin JK, Westaby S, Blackstone EH, Kirklin JW, Chenoweth DE, Pacifico AD: Complement and the damaging effects of cardiopulmonary bypass. J Thorac Cardiovasc Surg 1983; 86: 845-57
3. Van Linden A, Kempfert J, Rastan AJ, Holzhey D, Blumenstein J, Schuler G, Mohr FW, Walther T: Risk of acute kidney injury after minimally invasive transapical aortic valve implantation in 270 patients. Eur J Cardiothorac Surg 2011; 39: 835-42
4. Thomas M, Schymik G, Walther T, Himbert D, Lefevre T, Treede H, Eggebrecht H, Rubino P, Colombo A, Lange R, Schwarz RR, Wendler O: One-year outcomes of cohort 1 in the Edwards SAPIEN Aortic Bioprosthesis European Outcome (SOURCE) registry: the European registry of transcatheter aortic valve implantation using the Edwards SAPIEN valve. Circulation 2011; 124: 425-33
5. Stahli BE, Grunenfelder J, Jacobs S, Falk V, Landmesser U, Wischnewsky MB, Luscher TF, Corti R, Maier W, Altwegg LA: Assessment of inflammatory response to transfemoral transcatheter aortic valve implantation compared to transapical and surgical procedures: a pilot study. J Invasive Cardiol 2012; 24: 407-11
6. Sinning JM, Ghanem A, Steinhauser H, Adenauer V, Hammerstingl C, Nickenig G, Werner N: Renal function as predictor of mortality in patients after percutaneous transcatheter aortic valve implantation. JACC Cardiovasc Interv 2010; 3: 1141-9
7. Sinning JM, Scheer AC, Adenauer V, Ghanem A, Hammerstingl C, Schueler R, Muller C, Vasa-Nicotera M, Grube E, Nickenig G, Werner N: Systemic inflammatory response syndrome predicts increased mortality in patients after transcatheter aortic valve implantation. Eur Heart J 2012; 33: 1459-68
8. Walther T, Falk V, Borger MA, Dewey T, Wimmer-Greinecker G, Schuler G, Mack M, Mohr FW: Minimally invasive transapical beating heart aortic valve implantation--proof of concept. Eur J Cardiothorac Surg 2007; 31: 9-15
9. Rodes-Cabau J, Dumont E, De LaRochelliere R, Doyle D, Lemieux J, Bergeron S, Clavel MA, Villeneuve J, Raby K, Bertrand OF, Pibarot P: Feasibility and initial results of percutaneous aortic valve implantation including selection of the transfemoral or transapical approach in patients with severe aortic stenosis. Am J Cardiol 2008; 102: 1240-6
10. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, Schein RM, Sibbald WJ, ACCP/SCCM Consensus Conference Committee: Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. 1992. Chest 2009; 136: e28
11. Kappetein AP, Head SJ, Genereux P, Piazza N, van Mieghem NM, Blackstone EH, Brott TG, Cohen DJ, Cutlip DE, van Es GA, Hahn RT, Kirtane AJ, Krucoff MW, Kodali S, Mack MJ, Mehran R, Rodes-Cabau J, Vranckx P, Webb JG, Windecker S, Serruys PW, Leon MB, Valve Academic Research Consortium-2: Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. J Thorac Cardiovasc Surg 2013; 145: 6-23
12. Ferreira FL, Bota DP, Bross A, Melot C, Vincent JL: Serial evaluation of the SOFA score to predict outcome in critically ill patients. JAMA 2001; 286: 1754-8

13. Levey AS, Eckardt KU, Tsukamoto Y, Levin A, Coresh J, Rossert J, De Zeeuw D, Hostetter TH, Lameire N, Eknoyan G: Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int 2005; 67: 2089-100
14. Asimakopoulos G: Mechanisms of the systemic inflammatory response. Perfusion 1999; 14: 269-77
15. Brunkhorst FM, Clark AL, Forycki ZF, Anker SD: Pyrexia, procalcitonin, immune activation and survival in cardiogenic shock: the potential importance of bacterial translocation. Int J Cardiol 1999; 72: 3-10
16. Moat NE, Shore DF, Evans TW: Organ dysfunction and cardiopulmonary bypass: the role of complement and complement regulatory proteins. Eur J Cardiothorac Surg 1993; 7: 563-73
17. Rosner MH, Okusa MD: Acute kidney injury associated with cardiac surgery. Clin J Am Soc Nephrol 2006; 1: 19-32
18. Mokart D, Merlin M, Sannini A, Brun JP, Delpero JR, Houvenaeghel G, Moutardier V, Blache JL: Procalcitonin, interleukin 6 and systemic inflammatory response syndrome (SIRS): early markers of postoperative sepsis after major surgery. Br J Anaesth 2005; 94: 767-73
19. Amar D, Zhang H, Park B, Heerdt PM, Fleisher M, Thaler HT: Inflammation and outcome after general thoracic surgery. Eur J Cardiothorac Surg 2007; 32: 431-4
20. Oka Y, Murata A, Nishijima J, Yasuda T, Hiraoka N, Ohmachi Y, Kitagawa K, Yasuda T, Toda H, Tanaka N: Circulating interleukin 6 as a useful marker for predicting postoperative complications. Cytokine 1992; 4: 298-304
21. Szczepanik AM, Scislo L, Scully T, Walewska E, Siedlar M, Kolodziejczyk P, Lenart M, Rutkowska M, Galas A, Czupryna A, Kulig J: IL-6 serum levels predict postoperative morbidity in gastric cancer patients. Gastric Cancer 2011; 14: 266-73
22. Castellheim A, Brekke OL, Espevik T, Harboe M, Mollnes TE: Innate immune responses to danger signals in systemic inflammatory response syndrome and sepsis. Scand J Immunol 2009; 69: 479-91
23. Dieleman JM, Nierich AP, Rosseel PM, van der Maaten JM, Hofland J, Diephuis JC, Schepp RM, Boer C, Moons KG, van Herwerden LA, Tijssen JG, Numan SC, Kalkman CJ, van Dijk D, Dexamethasone for Cardiac Surgery (DECS) Study Group: Intraoperative high-dose dexamethasone for cardiac surgery: a randomized controlled trial. JAMA 2012; 308: 1761-7
24. Takenaka K, Ogawa E, Wada H, Hirata T: Systemic inflammatory response syndrome and surgical stress in thoracic surgery. J Crit Care 2006; 21: 48-53
25. Ueda S, Nishio K, Minamino N, Kubo A, Akai Y, Kangawa K, Matsuo H, Fujimura Y, Yoshioka A, Masui K, Doi N, Murao Y, Miyamoto S: Increased plasma levels of adrenomedullin in patients with systemic inflammatory response syndrome. Am J Respir Crit Care Med 1999; 160: 132-6
26. Dimopoulou I, Armaganidis A, Douka E, Mavrou I, Augustatou C, Kopterides P, Lyberopoulos P, Tzanela M, Orfanos SE, Pelekanou E, Kostopanagiotou G, Macheras A, Giamarellos-Bourboulis EJ: Tumour necrosis factor-alpha (TNFalpha) and interleukin-10 are crucial mediators in post-operative systemic inflammatory response and determine the occurrence of complications after major abdominal surgery. Cytokine 2007; 37: 55-61
27. Sarbinowski R, Arvidsson S, Tylman M, Oresland T, Bengtsson A: Plasma concentration of procalcitonin and systemic inflammatory response syndrome after colorectal surgery. Acta Anaesthesiol Scand 2005; 49: 191-6

Chapter 3

Systemic inflammation and ischemia/reperfusion injury after transcatheter aortic valve implantation: a prospective exploratory study

Thijs C.D. Rettig
Vincent J. Nijenhuis*
Bob Meek*
Sander Rigter
Jurrien M. ten Berg
Bart Vlaminckx
Wilton A. van Klei
Ewoudt M.W. van de Garde
Linda M. Peelen
Peter G. Noordzij

*These authors contributed equally to this study

Submitted

ABSTRACT

Aims: To investigate the relation between ischemia/reperfusion injury and systemic inflammatory response syndrome (SIRS) after transcatheter aortic valve implantation (TAVI).

Methods and Results: Levels of interleukin (IL)-6, IL-8, tumor necrosis factor-α, intestinal fatty acid bind protein (IFABP), C-reactive protein (CRP) and leukocyte count were prospectively investigated in patients undergoing TAVI. Rapid ventricular pacing (RVP) runs, mean arterial pressure and cerebral oxygenation during RVP and levels of IFABP were used as markers for tissue hypoperfusion. SIRS occurred in 18 (46%) of the 39 patients included and was characterized by increased leucocyte count and levels of CRP and IL-6. The total duration of RVP was 16 seconds (IQR 13-23) versus 13 seconds (IQR 10-14, $P = 0.81$) in patients with and without SIRS, respectively. Overall, levels of IFABP peaked at three hours after TAVI (1169 [IQR 906-1483] pg/mL) and decreased 44% below baseline two days after TAVI (410 (IQR 284-538) pg/mL on day two vs. 728 (IQR 520-927) pg/mL at baseline, $P < 0.01$). The correlation between absolute increase in IFABP and IL-6 levels was 0.331 ($P = 0.04$).

Conclusions: A rise and fall of IFABP levels shortly after TAVI may suggest that intestinal I/R injury contributes to systemic inflammation.

INTRODUCTION

Until recently the cornerstone of severe aortic stenosis treatment in symptomatic patients was surgical aortic valve replacement.[1] Nowadays, high risk surgical patients are candidates for the less invasive transcatheter aortic valve implantation (TAVI) procedure. These patients are typically frail, elderly and suffering from multiple comorbidities. As a result, mortality is still approximately 9% and 24% at 30 days and one year after TAVI, respectively.[2, 3]

One of the factors influencing outcome after TAVI is the occurrence of the systemic inflammatory response syndrome (SIRS). Several studies showed that increased systemic inflammation after TAVI is associated with a higher risk of morbidity and mortality.[4-6] The pathogenesis of SIRS after TAVI is not clear yet. In one study patients with SIRS had more rapid ventricular pacing (RVP) runs and higher postoperative lactate levels compared to patients without SIRS.[4] RVP and other characteristics of the TAVI procedure, such as balloon-valvuloplasty and post-dilatation of the native aortic valve, interfere with normal cardiac function. The subsequent low cardiac output state may lead to tissue hypoperfusion, ischemia/reperfusion (I/R) injury and systemic inflammation. Moreover, SIRS in non-surgical patients with cardiogenic shock has been linked to I/R injury and bacterial translocation due to intestinal injury.[7]

The aim of this exploratory study was to investigate the inflammatory response after TAVI and to assess the potential relation with procedure related I/R injury.

METHODS

Study population and design

The patients included in this prospective observational study took part in the randomized controlled Antiplatelet Therapy for Patients Undergoing Transcatheter Aortic Valve Implantation (POPular-TAVI) trial (ClinicalTrials.gov Identifier NCT02247128). Patients undergoing TAVI in the POPular-TAVI trial were randomized to three months of additional postprocedural clopidogrel versus monotherapy with aspirin (cohort A) or oral anticoagulation therapy (cohort B). Patients were eligible for inclusion if they required aortic valve replacement but were inoperable or considered at high-risk for complications according to the heart team. Exclusion criteria were the need for long-term anticoagulation (cohort A), implantation of a drug eluting stent within three months of TAVI, implantation of a bare-metal stent within one month of TAVI and allergy or intolerance to aspirin (cohort A) or clopidogrel. A more detailed description of the POPular-TAVI study has been previously described.[8]

In the current study we investigated the inflammatory response after TAVI and the relation with procedure related tissue hypoperfusion. Additional exclusion criteria were (suspected) infection prior to TAVI and reoperation within 48 hours. The study was ap-

proved by the local Medical Research Ethics Committee (trial number NL45668.100.13, R13.030) and has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Informed consent was obtained for this specific study in all patients.

TAVI procedure and anesthetic management

Before the TAVI procedure, each patient was discussed for TAVI, valve type and access site in a dedicated heart team composed by a cardiologist and cardiac surgeon. The TAVI procedure and the different approaches have been described in detail in prior reports.[9, 10] RVP was performed depending on patient characteristics, and the type of valve used. The pacing rate was 180 beats per minute. V.N. recorded the number and duration of RVP runs. Various types of valves were used during the study period: Medtronic Engager (Medtronic, Minneapolis, Minnesota), Medtronic Corevalve (Medtronic, Minneapolis, Minnesota), Edwards SAPIEN (Edwards Lifesciences, Irvine, California), Direct Flow Medical (Direct Flow Medical GmbH, Gießen), JenaValve (JenaValve Technology GmbH, Munich) and Lotus (Boston Scientific, Marlborough, Massachusetts).

All TAVI procedures were performed under general anesthesia. Patients were treated according to a standardized anesthesia protocol, which included placement of an arterial line, a central venous line and a transvenous cardiac pacing wire in the right ventricle. Near-infrared spectroscopy (NIRS) electrodes were applied to the forehead (NIRO-200, Hamamatsu, Japan) to measure cerebral oxygen saturation. Cerebral oxygen saturation and the mean arterial pressure (MAP) were noted at the start of RVP and every minute for five minutes thereafter. After the procedure, patients who underwent transapical TAVI were admitted to the Intensive Care Unit for at least 24 hours. Patients who underwent transfemoral TAVI were admitted to the Intensive Care Unit for at least six hours and afterwards the Coronary Care Unit. None of the patients received beta-blocker therapy and non-steroidal anti-inflammatory drugs for at least 48 hours after TAVI. The use of steroids was left to the discretion of the treating physicians. Medication administered in context of the POPular-TAVI trial was not considered to affect the inflammatory response after TAVI.

Inflammatory response

The occurrence of SIRS was defined as the development of two or more of the following symptoms during the first 48 hours after TAVI and that lasted for one hour or more: leukocyte count >12 or <4 (10^9/L), respiratory rate >20 breaths/minute or PaCO2 <32 mmHg, temperature <36.0 or >38.0°C, heart rate >90 beats/minute.[11]

To further characterize the inflammatory response after TAVI blood samples were drawn on the day of TAVI immediately after induction of anesthesia and after one, three, six, 24 and 48 hours to measure levels of interleukin (IL)-6, IL-8, tumor necrosis factor (TNF)-α and intestinal fatty acid bind protein (IFABP). C-reactive protein and leukocyte count were determined on the day of TAVI after induction of anesthesia and after six, 24, 48 and 72 hours.

Supernatantia were divided in 1-mL aliquots and stored at -80°C until assay. Blood was collected in EDTA tubes, centrifuged, and aliquoted plasma samples were stored at -80°C until assay. IL-6, IL-8 and TNF-α concentrations were determined using multiplex assays and executed according to instructions from each manufacturer (Milliplex Human Sensitivity Cytokine kit, Merck Millipore, Darmstadt, Germany and ProcartaPlex, Bio-Techne, Abingdon, United Kingdom) and acquired on a BioPlex100 apparatus (BioRad, Hercules, United States). IFABP concentrations were determined by ELISA and executed according to instructions provided by manufacturer (Hycult Biotech, Uden, The Netherlands).

Markers of tissue hypoperfusion

Together with levels of IFABP, the MAP and cerebral oxygenation during RVP and the number and total duration of RVP runs were used as markers for tissue hypoperfusion. Several studies showed that IFABP is a reliable early marker for diagnosing intestinal ischemia.[12, 13] Cerebral blood flow changes can be monitored by measuring cerebral oxygen saturation with NIRS.[14]

Statistical analysis

Baseline and periprocedural characteristics were compared for patients with and without SIRS. Continuous data are described as the mean and standard deviation (SD) or median and interquartile range (IQR) for normally and non-normally distributed data, respectively. Categorical data are presented by numbers and percentages. The chi-square test or Fisher's exact test were used to compare dichotomous variables between patients with and without SIRS. The Student's t-test and the Mann-Whitney U test were used to compare independent continuous normally and non-normally distributed data between patients with and without SIRS and patients with and without RVP. The paired samples t-test was used for dependent continuous normally distributed data and the Wilcoxon Signed Rank test for non-normally distributed data for each separate time interval. We used the mean cerebral oxygen saturation of the left and right hemisphere combined to compare cerebral oxygenation in patients with and without SIRS groups in whom rapid pacing was performed. Correlation between the absolute increase in IFABP and IL-6 levels was tested using the Spearman's ranks correlation coefficient. A *P*-value of < 0.05 was considered significant. For statistical analysis IBM SPSS version 22 was used.

RESULTS

During the study period 40 patients were eligible for analysis. One patient required sternotomy due to excessive bleeding within 24 hours of TAVI and was excluded. The final study population consisted of 39 patients. The mean age was 81±6 years and 64% were males. The median length of hospital stay was six days (IQR 5-9) and 30-day mortality was 10%.

SIRS and inflammatory biomarkers

Eighteen patients (46%) developed SIRS; fourteen patients within 24 hours and four patients in the following 24 hours. SIRS was mostly characterized by a temperature of <36.0 or >38.0°C (Figure 1). The baseline and periprocedural variables in relation to whether or not SIRS occurred are presented in Table 1 and 2.

Before TAVI, leukocyte count and levels of IL-6, IL-8, TNF-α, and CRP were similar in patients with and without SIRS. The courses of the inflammatory biomarkers after TAVI are shown in Figure 2.

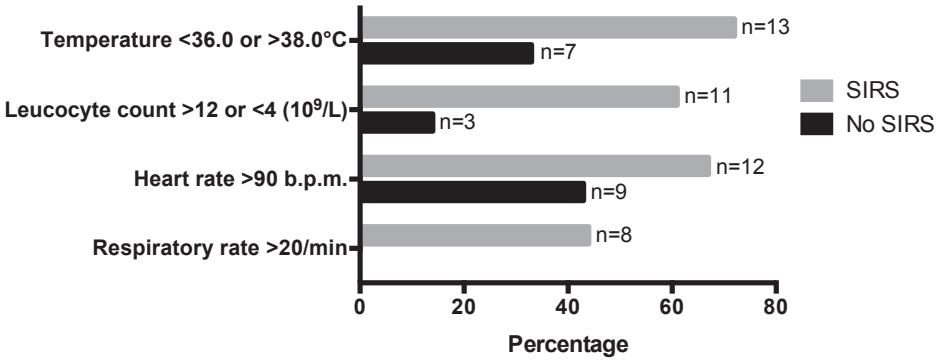

Figure 1. Individual SIRS criteria according to the occurrence of SIRS

Table 1: Baseline characteristics

Variable	All (n=39)	SIRS (n=18)	No SIRS (n=21)	*p*-value
Male [n (%)]	25 (64.1)	13 (72.2)	12 (57.1)	0.33
Age (years)	81±6	79±7	83±5	0.07
BMI [kg/m^2 (%)]	25.7±3.9	26.7±3.9	24.8±3.7	0.13
Comorbidity				
Diabetes [n (%)]	14 (35.9)	7 (38.9)	7 (33.3)	0.72
COPD [n (%)]	8 (20.5)	4 (22.2)	4 (19.0)	1.00
Hypertension [n (%)]	23 (59.0)	8 (44.4)	15 (71.4)	0.09
Coronary artery disease [n (%)]	20 (51.3)	9 (50.0)	11 (52.4)	0.88
Atrial fibrillation [n (%)]	21 (53.8)	11 (61.1)	10 (47.6)	0.40
Previous myocardial infarction [n %)]	8 (20.5)	6 (33.3)	2 (9.5)	0.11
Previous cardiac surgery [n (%)]	19 (48.7)	8 (44.4)	11 (52.4)	0.62
Previous stroke [n (%)]	6 (15.4)	4 (22.2)	2 (9.5)	0.39
Peripheral artery disease [n (%)]	5 (12.8)	2 (11.1)	3 (14.3)	1.00
Chronic renal failure [n (%)]	13 (33.3)	5 (27.8)	8 (38.1)	0.50
Pulmonary hypertension [n (%)]	13 (33.3)	6 (33.3)	7 (33.3)	1.00
EuroSCORE	18 (11-32)	18 (11-32)	18 (13-32)	0.84
STS score	5.6 (3.7-8.6)	4.6 (3.2-9.9)	5.9 (4.6-8.6)	0.55
Normal LVEF [n (%)]	17 (43.6)	5 (27.8)	12 (57.1)	0.07
Hemoglobin (mmol/L)	8.0±1.0	8.0±1.1	8.0±0.9	0.95
Creatinine (μmol/L)	102 (80-128)	104 (83-120)	97 (77-131)	0.81

Table 1: Baseline characteristics (continued)

Variable	All (n=39)	SIRS (n=18)	No SIRS (n=21)	*p*-value
Medication use				
Preoperative				
- Statin [n (%)]	20 (51.3)	8 (44.4)	12 (57.1)	0.43
- Steroids [n (%)]	11 (28.2)	8 (44.4)	3 (14.3)	0.04
- B-blocker [n (%)]	24 (61.5)	11 (61.1)	13 (61.9)	0.96
- Aspirin [n (%)]	16 (41.0)	8 (44.4)	8 (38.1)	0.69
Postoperative				
- Statin [n (%)]	19 (48.7)	7 (38.9)	12 (57.1)	0.26
- Steroids [n (%)]	10 (25.6)	7 (38.9)	3 (14.3)	0.14
- Aspirin [n (%)]	13 (33.3)	5 (27.8)	8 (38.1)	0.50

BMI indicates body mass index; COPD, chronic obstructive pulmonary disease; STS, Society of Thoracic Surgeons; LVEF, left ventricular ejection fraction

Table 2: Periprocedural characteristics

Variable	All (n=39)	SIRS (n=18)	No SIRS (n=21)	*p*-value
Approach				
- Transfemoral [n (%)]	29 (74.4)	11 (61.1)	18 (62.1)	0.14
- Apical [n (%)]	10 (25.6)	7 (38.9)	3 (14.3)	
Procedural characteristics				
Rapid pacing used [n (%)]	25 (64.1)	11 (61.1)	14 (66.7)	0.72
Rapid pacing runs [n]	1 (0-2)	1 (0-2)	1 (0-3)	0.79
Total pacing duration (sec)	13 (0-37)	18 (0-40)	13 (0-34)	0.81
Pre-dilatation [n (%)]	20 (51.3)	8 (44.4)	12 (57.1)	0.43
Post-dilatation [n (%)]	9 (23.1)	6 (33.3)	3 (14.3)	0.26
Intervention time (min)	106±50	97±24	114±64	0.31
PRBC transfusion [n (%)]	3 (7.7)	2 (11.1)	1 (4.8)	0.59
Number of PRBC [n]	0 (0-0)	0 (0-0)	0 (0-0)	0.73
Contrast (ml)	79 (60-126)	80 (57-120)	70 (60-138)	0.84
Vasopressor use [n (%)]	10 (25.6)	6 (33.3)	4 (19.0)	0.47
Inotropic use [n (%)]	10 (25.6)	3 (16.7)	7 (33.3)	0.29
Postprocedural hemoglobin	6.9±1.1	6.9±1.1	6.9±1.1	0.92
Prosthetic valve type				
- Self expandable [n (%)]	21 (53.8)	12 (66.7)	9 (42.9)	0.20
- Non-self expandable [n (%)]	18 (46.2)	6 (33.3)	12 (57.1)	
Outcome				
AKI [n (%)]	5 (12.8)	4 (22.2)	1 (4.8)	0.16
Length of hospital stay (days)	6 (5-9)	8 (6-12)	6 (5-9)	0.20
30-day mortality [n (%)]	4 (10.3)	4 (22.2)	0	0.04

PRBC indicates packed red blood cell (during the first 48 hours after TAVI)

Acute kidney injury (AKI) was defined as an increase of >26 µmol or an increase in serum creatinine of 50% or more within 72 hours after TAVI

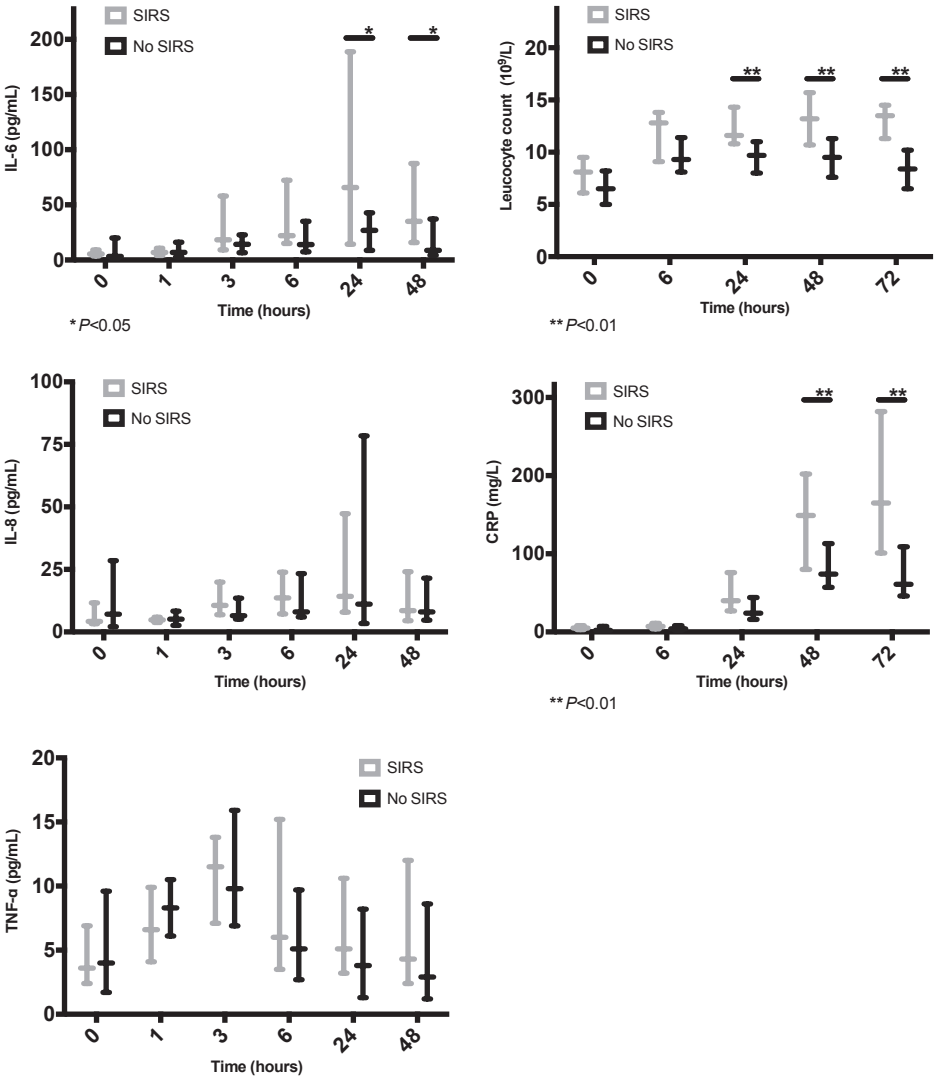

Figure 2. Inflammatory biomarkers according to the occurrence of SIRS (values are median and IQR)

I/R injury and systemic inflammation

RVP was used in 25 (64%) patients. Leukocyte count and levels of IL-6, IL-8 and CRP in patients with and without RVP are shown in Figure 3. The number and the total duration of RVP runs were 1 (IQR 0-2) versus 1 (IQR 0-3, $P = 0.79$) and 16 seconds (IQR 13-23) versus 13 seconds (IQR 10-14, $P = 0.81$) in patients with and without SIRS, respectively.

In general, the mean MAP and the mean cerebral oxygen saturation at the start of RVP were 57±14 mmHg and 61±11%, respectively. During the five minutes after the start of RVP the MAP was 56±12, 59±11, 62±12, 62±13 and 62±15 mmHg and the mean cerebral

oxygen saturation 62±10, 62±10, 61±10, 61±10 and 63±11%. The MAP and cerebral oxygenation at the start and during the five minutes after the start of RVP in patients with and without SIRS are presented in Figure 4.

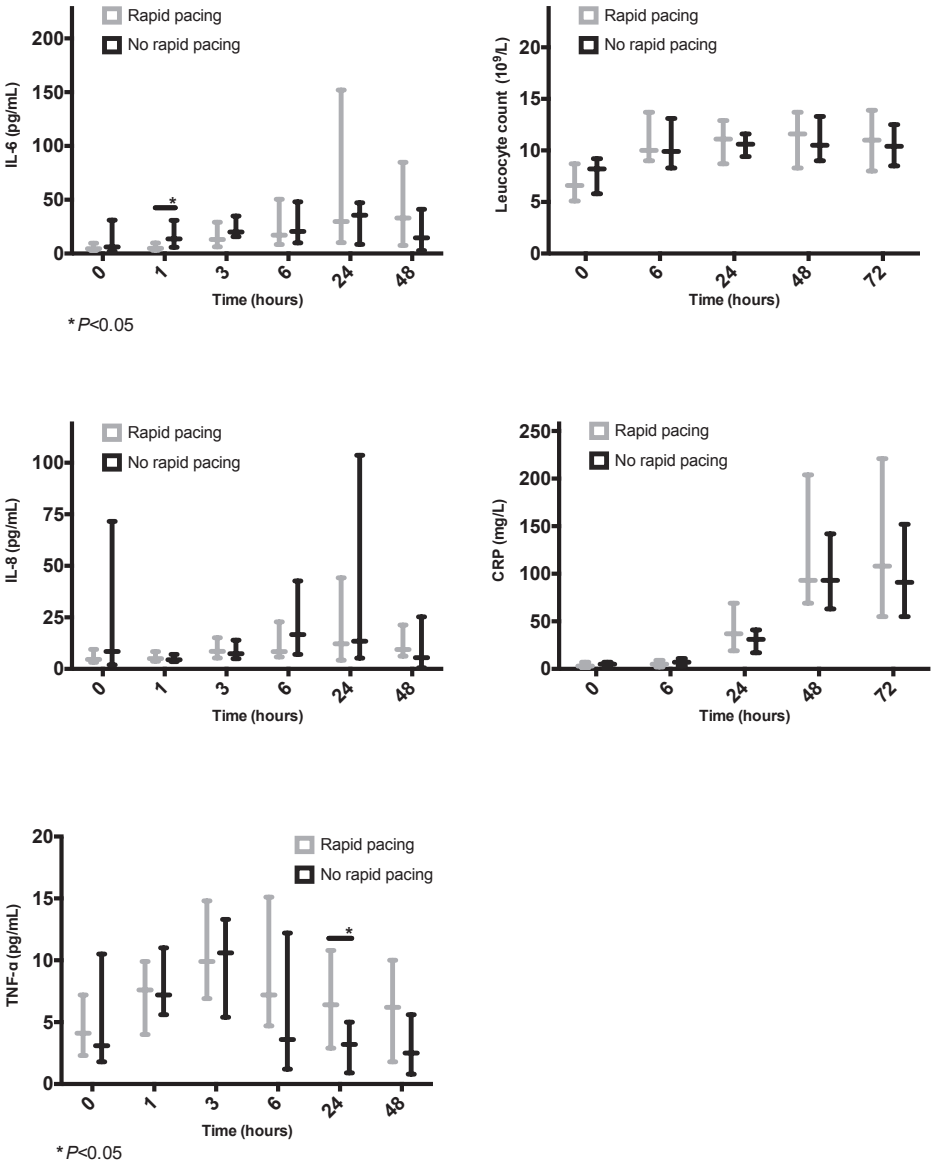

Figure 3. Inflammatory biomarkers according to RVP (values are median and IQR)

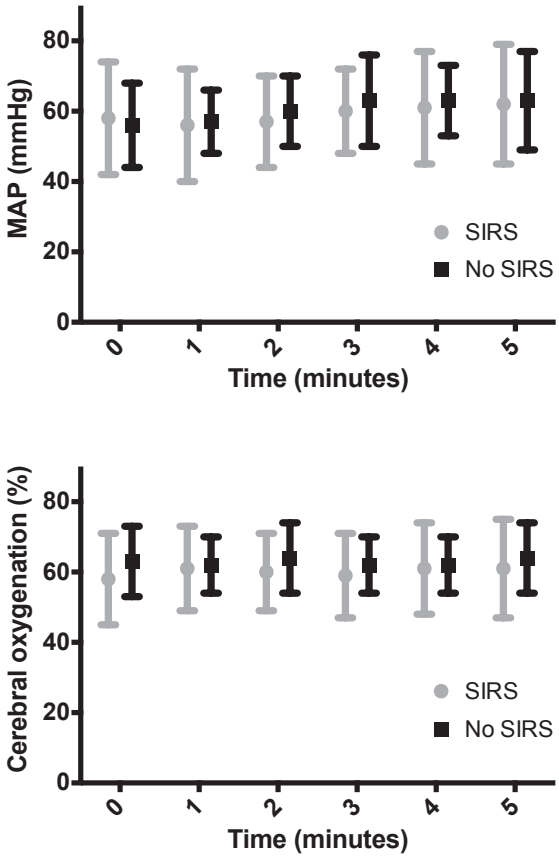

Figure 4. MAP and cerebral oxygenation according to the occurrence of SIRS. Values (mean±SD) are shown at the start of RVP and for the five minutes thereafter

In the overall group, IFABP level was 728 (IQR 520-927) pg/mL at baseline and peaked at three hours after TAVI (1169 [IQR 906-1483] pg/mL, $P < 0.01$ compared to baseline). Levels of IFABP declined below baseline on day two (410 [IQR 284-538] pg/mL, $P < 0.01$ compared to baseline) with a median decrease of 44%. Levels of IFABP peaked before levels of IL-6 (Figure 5A) and the correlation between the absolute increase in IFABP and IL-6 levels was 0.331 ($P = 0.04$). IFABP levels in patients with and without SIRS are shown in Figure 5B.

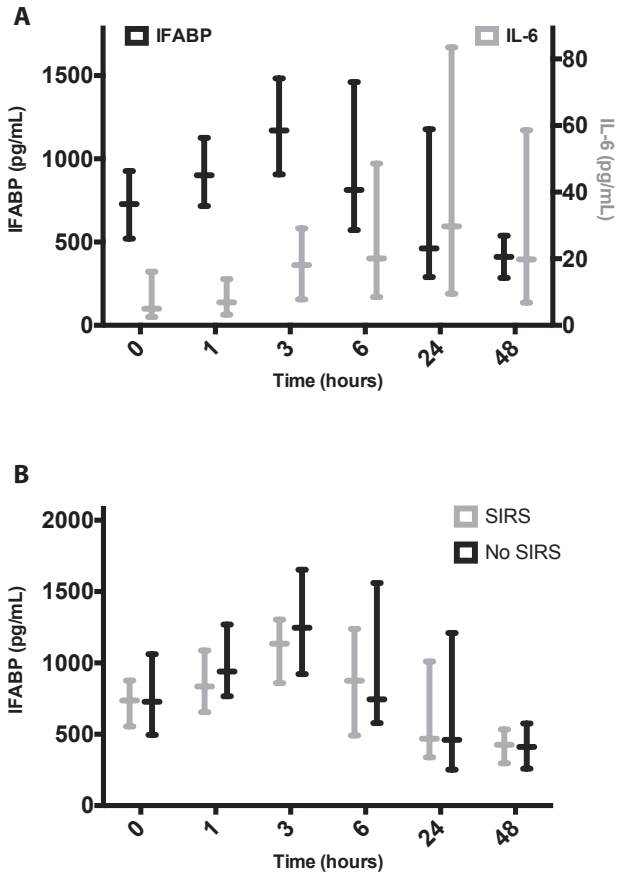

Figure 5A and 5B. Levels of IFABP and IL-6 after TAVI (5A) and levels of IFABP according to the occurrence of SIRS (5B) (values are median and IQR)

DISCUSSION

This exploratory observational study confirms that the incidence of SIRS after TAVI is high and that SIRS is characterized by increased inflammatory biomarkers. We did not observe an association between procedure related tissue hypoperfusion markers and SIRS after TAVI. The typical pattern of a rise and fall of IFABP levels shortly after TAVI may suggest that intestinal I/R injury contributes to systemic inflammation after TAVI.

In recent years, several studies showed that SIRS after TAVI is common and associated with adverse outcome.[4, 5, 15] It is unclear whether there is a specific cause for SIRS after TAVI. In one study repeated RVP was independently associated with SIRS (adjusted odds ratio 1.8, 95% confidence interval: 1.1 - 2.8, $P = 0.025$).[4] Given the deleterious impact of RVP on cardiac output this may suggest that tissue hypoperfusion and subsequent I/R injury is the catalyst for systemic inflammation and organ dysfunction after TAVI. It seems evident that RVP causes tissue hypoperfusion. This was confirmed in a study of 42 patients undergoing TAVI with assessment of sublingual microvascular tissue perfusion during RVP using Sidestream-Darkfield imaging.[16] The mean duration of RVP was 14 seconds (range 6-29) and this was associated with a time-dependent decrease of tissue perfusion in small and large vessels. Twelve seconds after the end of RVP tissue perfusion was largely recovered and the MAP returned to baseline.

The question remains whether the compromised microcirculation during RVP is sufficiently important to cause I/R injury, systemic inflammation and subsequent adverse outcome. In general, the duration of RVP is short with an average length of 10 to 20 seconds. In agreement with the findings of Selle et al, we observed that 1 minute after the start of RVP, the MAP was comparable to the baseline MAP.[16] In our study population, we did not observe a relation between RVP and the development of SIRS or increased inflammatory biomarkers. Also, other markers for tissue hypoperfusion, such as cerebral oxygenation, MAP and IFABP levels, were similar in patients with and without SIRS.

Levels of IFABP were high at baseline and decreased more than 40% after TAVI. This may indicate that patients scheduled for TAVI suffer from asymptomatic intestinal injury. Patients with severe aortic stenosis are unable to increase cardiac output when needed and, in addition, often have hypertension and concomitant peripheral artery disease, potentially leading to intestinal oxygen supply-demand mismatch. Previous studies showed that the chronic venous congestion associated with chronic heart failure causes increased endotoxin levels.[17] TAVI restores the aortic valve area, leading to improved hemodynamics within 48 hours of TAVI.[17, 18] This could result in enhanced intestinal perfusion and lower IFABP levels. Therefore levels of IFABP could be interpreted as a surrogate for TAVI success.

At the same time restoration of intestinal perfusion could cause harm. Intestinal I/R injury induces inflammation, either by leakage of damage-associated molecular patterns

(DAMPs) from intestinal cells or by bacterial translocation. A study in a human intestinal I/R model showed that levels of IFABP increased during the initiation of intestinal ischemia and decreased to baseline during reperfusion, while levels of inflammatory biomarkers, such as IL-6, increased during the reperfusion period.[19] In our study cohort the absolute increase in IFABP and IL-6 levels were correlated. Although speculative, this may suggest that the inflammatory response after TAVI is at least partly explained by intestinal I/R injury.

Other causes of SIRS after TAVI remain to be elucidated. It is possible that systemic inflammation after TAVI is not a consequence of procedure related characteristics but explained by genetic variability. For example, the observation that polymorphisms in genes encoding for proinflammatory biomarkers are involved in the biological response to bacteria may also apply to the immune response after surgical trauma.[20]

This study has several limitations. First, the results of this study are clearly exploratory due to its small sample size. For example, we found that levels of IFABP decreased after TAVI. To our knowledge, this is not reported before. Although this finding may be the logical result of restored cardiac output, this could also be attributed to bias. Small studies are less precise and more likely to report false positive results. And second, we used cerebral oxygen saturation and levels of IFABP as surrogates for tissue hypoperfusion. Assessment of tissue perfusion (for example, using transcranial Doppler ultrasonography or Sidestream-Darkfield imaging) could have strengthened our conclusions.

In summary, SIRS after TAVI is characterized by increased inflammatory biomarkers. We did not observe a relation between tissue hypoperfusion biomarkers and SIRS after TAVI. The decrease in IFABP levels may suggest that intestinal I/R injury plays a role in the inflammatory response after TAVI and deserves further study.

REFERENCES

1. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP,3rd, Guyton RA, O'Gara PT, Ruiz CE, Skubas NJ, Sorajja P, Sundt TM,3rd, Thomas JD, ACC/AHA Task Force Members: 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014; 129: e521-643
2. Biancari F, Rosato S, D'Errigo P, Ranucci M, Onorati F, Barbanti M, Santini F, Tamburino C, Santoro G, Grossi C, Covello RD, Ventura M, Fusco D, Seccareccia F, OBSERVANT Research Group: Immediate and Intermediate Outcome After Transapical Versus Transfemoral Transcatheter Aortic Valve Replacement. Am J Cardiol 2016; 117: 245-51
3. Thomas M, Schymik G, Walther T, Himbert D, Lefevre T, Treede H, Eggebrecht H, Rubino P, Colombo A, Lange R, Schwarz RR, Wendler O: One-year outcomes of cohort 1 in the Edwards SAPIEN Aortic Bioprosthesis European Outcome (SOURCE) registry: the European registry of transcatheter aortic valve implantation using the Edwards SAPIEN valve. Circulation 2011; 124: 425-33
4. Sinning JM, Scheer AC, Adenauer V, Ghanem A, Hammerstingl C, Schueler R, Muller C, Vasa-Nicotera M, Grube E, Nickenig G, Werner N: Systemic inflammatory response syndrome predicts increased mortality in patients after transcatheter aortic valve implantation. Eur Heart J 2012; 33: 1459-68
5. Rettig TC, Rigter S, Nijenhuis VJ, van Kuijk JP, Ten Berg JM, Heijmen RH, van de Garde EM, Noordzij PG: The systemic inflammatory response syndrome predicts short-term outcome after transapical transcatheter aortic valve implantation. J Cardiothorac Vasc Anesth 2015; 29: 283-7
6. Lindman BR, Goldstein JS, Nassif ME, Zajarias A, Novak E, Tibrewala A, Vatterott AM, Lawler C, Damiano RJ, Moon MR, Lawton JS, Lasala JM, Maniar HS: Systemic inflammatory response syndrome after transcatheter or surgical aortic valve replacement. Heart 2015; 101: 537-45
7. Brunkhorst FM, Clark AL, Forycki ZF, Anker SD: Pyrexia, procalcitonin, immune activation and survival in cardiogenic shock: the potential importance of bacterial translocation. Int J Cardiol 1999; 72: 3-10
8. Nijenhuis VJ, Bennaghmouch N, Hassell M, Baan J,Jr, van Kuijk JP, Agostoni P, van 't Hof A, Kievit PC, Veenstra L, van der Harst P, van den Heuvel AF, den Heijer P, Kelder JC, Deneer VH, van der Kley F, Onorati F, Collet JP, Maisano F, Latib A, Huber K, Stella PR, Ten Berg JM: Rationale and design of POPular-TAVI: antiPlatelet therapy fOr Patients undergoing Transcatheter Aortic Valve Implantation. Am Heart J 2016; 173: 77-85
9. Rodes-Cabau J, Dumont E, De LaRochelliere R, Doyle D, Lemieux J, Bergeron S, Clavel MA, Villeneuve J, Raby K, Bertrand OF, Pibarot P: Feasibility and initial results of percutaneous aortic valve implantation including selection of the transfemoral or transapical approach in patients with severe aortic stenosis. Am J Cardiol 2008; 102: 1240-6
10. Walther T, Falk V, Borger MA, Dewey T, Wimmer-Greinecker G, Schuler G, Mack M, Mohr FW: Minimally invasive transapical beating heart aortic valve implantation--proof of concept. Eur J Cardiothorac Surg 2007; 31: 9-15
11. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, Schein RM, Sibbald WJ, ACCP/SCCM Consensus Conference Committee: Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. 1992. Chest 2009; 136: e28

12. Matsumoto S, Sekine K, Funaoka H, Yamazaki M, Shimizu M, Hayashida K, Kitano M: Diagnostic performance of plasma biomarkers in patients with acute intestinal ischaemia. Br J Surg 2014; 101: 232-8
13. Vermeulen Windsant IC, Hellenthal FA, Derikx JP, Prins MH, Buurman WA, Jacobs MJ, Schurink GW: Circulating intestinal fatty acid-binding protein as an early marker of intestinal necrosis after aortic surgery: a prospective observational cohort study. Ann Surg 2012; 255: 796-803
14. Brady K, Joshi B, Zweifel C, Smielewski P, Czosnyka M, Easley RB, Hogue CW,Jr: Real-time continuous monitoring of cerebral blood flow autoregulation using near-infrared spectroscopy in patients undergoing cardiopulmonary bypass. Stroke 2010; 41: 1951-6
15. Schwietz T, Behjati S, Gafoor S, Seeger F, Doss M, Sievert H, Zeiher AM, Fichtlscherer S, Lehmann R: Occurrence and prognostic impact of systemic inflammatory response syndrome in transfemoral and transapical aortic valve implantation with balloon- and self-expandable valves. EuroIntervention 2015; 10: 1468-73
16. Selle A, Figulla HR, Ferrari M, Rademacher W, Goebel B, Hamadanchi A, Franz M, Schlueter A, Lehmann T, Lauten A: Impact of rapid ventricular pacing during TAVI on microvascular tissue perfusion. Clin Res Cardiol 2014; 103: 902-11
17. Gotzmann M, Lindstaedt M, Bojara W, Mugge A, Germing A: Hemodynamic results and changes in myocardial function after transcatheter aortic valve implantation. Am Heart J 2010; 159: 926-32
18. Fraccaro C, Al-Lamee R, Tarantini G, Maisano F, Napodano M, Montorfano M, Frigo AC, Iliceto S, Gerosa G, Isabella G, Colombo A: Transcatheter aortic valve implantation in patients with severe left ventricular dysfunction: immediate and mid-term results, a multicenter study. Circ Cardiovasc Interv 2012; 5: 253-60
19. Grootjans J, Lenaerts K, Derikx JP, Matthijsen RA, de Bruine AP, van Bijnen AA, van Dam RM, Dejong CH, Buurman WA: Human intestinal ischemia-reperfusion-induced inflammation characterized: experiences from a new translational model. Am J Pathol 2010; 176: 2283-91
20. Schwartz DA: The genetics of innate immunity. Chest 2002; 121: 62S-8S

Chapter 4

Postoperative interleukin-6 level and early detection of complications after elective major abdominal surgery

Thijs C.D. Rettig
Lisa Verwijmeren
Ineke M. Dijkstra
Djamila Boerma
Ewoudt M.W. van de Garde
Peter G. Noordzij

Ann Surg. 2016 Jun;263(6):1207-12

ABSTRACT

Objective: To assess the association of systemic inflammation and outcome after major abdominal surgery.

Background: Major abdominal surgery carries a high postoperative morbidity and mortality rate. Studies suggest that inflammation is associated with unfavorable outcome.

Methods: Levels of C-reactive protein (CRP), interleukin-6 (IL-6), tumour necrosis factor-α and the systemic inflammatory response syndrome (SIRS) were assessed in 137 patients undergoing major abdominal surgery. Blood samples were drawn on day 0, 1, 3 and 7 and SIRS was scored during 48 hours after surgery. Primary outcome was a composite of mortality, pneumonia, sepsis, anastomotic dehiscence, wound infection, non-cardiac respiratory failure, atrial fibrillation, congestive heart failure, myocardial infarction and reoperation within 30 days of surgery.

Results: An IL-6 level >432 pg/ml on day 1 was associated with an increased risk of complications (adjusted odds ratio 3.3, 95% CI: 1.3 - 8.5) and a longer median length of hospital stay (7 vs. 12 days, $P < 0.001$). As a single test, an IL-6 cut-off level of 432 pg/ml on day 1 yielded a specificity of 70% and a sensitivity of 64% for the prediction of complications (area under the curve (AUC): 0.67, 95% CI: 0.56 - 0.77). Levels of CRP started to discriminate from day 3 onwards with a specificity of 87% and a sensitivity of 58% for a cut-off level of 203 mg/l (AUC: 0.73, 95% CI: 0.63 - 0.83).

Conclusion: A high IL-6 level on day 1 is associated with postoperative complications. Levels of IL-6 distinguish between patients at low and high risk for complications prior to levels of CRP.

INTRODUCTION

Abdominal surgery is one of the most commonly performed non-day case procedures.[1] Up to 28% of patients undergoing major abdominal surgery suffer from postoperative complications, including wound infection, sepsis, anastomotic dehiscence, pneumonia, cardiovascular or respiratory events and mortality.[2-4] Early identification of patients at high risk for developing such complications may aid clinical decision-making and possibly improve outcome.

Several studies suggest that systemic inflammation after surgery has a negative impact on outcome.[5-7] The magnitude of this inflammatory response varies widely between individuals and depends on, for example, the type, duration and extent of surgery, type of anesthesia and perioperative blood transfusion.[8-11] Interestingly, polymorphisms in genes encoding for interleukin-6 (IL-6) and tumour necrosis factor-α (TNF-α) are associated with the development of postoperative complications after lung resection.[12, 13] Also, perioperative use of dexamethasone is associated with improved outcome in patients undergoing cancer resection, suggesting that systemic inflammation is related to adverse outcome.[14] However, most of these studies were performed in patients undergoing cardiothoracic surgery, included few patients, defined outcome parameters vaguely or had data collected retrospectively which may have influenced data quality. Whether systemic inflammation after major abdominal surgery is associated with unfavorable outcome remains to be elucidated.[15-17]

The aim of this study was to investigate the inflammatory response after major abdominal surgery and its association with outcome.

METHODS

Study population and design

This prospective single centre cohort study is a substudy of the Myocardial Injury and Complications after major abdominal surgery (MICOLON) study (ClinicalTrials.gov Identifier NCT02150486). In short, the MICOLON study investigated the association between high-sensitive cardiac troponin T levels and non-cardiac complications after major abdominal surgery in patients at risk for coronary artery disease. Inclusion criteria were elective major (defined as an expected 30-day mortality rate >3%[1] abdominal surgery, age >45 and presence of 1 or more major cardiovascular (CV) risk factors: congestive heart failure, peripheral artery disease (intermittent claudication or history of vascular surgery), diabetes mellitus, coronary artery disease (history of myocardial infarction, angina pectoris, history of ischemia or coronary artery disease on cardiac tests), cerebrovascular accident, renal insufficiency (serum creatinine >150 umol/l), aortic valve

stenosis (valve area <1 cm^2), atrial fibrillation, decreased left ventricular function (<55%) or 2 or more minor CV risk factors: age >70, hypertension, hypercholesterolemia, low functional capacity (4 metabolic equivalents or less), transient ischemic attack, chronic obstructive pulmonary disease) A more elaborate description of study methodology has been previously described.[18] The study was approved by the local Medical Ethics Committee (Research and Development Department, St. Antonius Hospital) and informed consent was obtained in all patients. In this substudy we investigated the systemic inflammatory response and its association with outcome in the first 137 patients included in the MICOLON study. To do so, we determined the occurrence of the systemic inflammatory response syndrome (SIRS) within 48 hours of surgery and evaluated perioperative leucocyte count and levels of IL-6, TNF-α and C-reactive protein (CRP). Blood samples were collected at the day of surgery after induction of general anesthesia (baseline) and on the 1st, 3rd and 7th postoperative day during the routine blood drawing round in the morning. Systemic inflammatory response syndrome was considered present if at least two of the following clinical findings were present: temperature <36.0 or >38.0°C, heart rate >90 beats/minute, respiratory rate >20 breaths/minute or PaCO2 <32 mmHg, leucocyte count <4 or >12 (10^9/L).[19] Patients on antibiotic therapy prior to surgery were excluded. Perioperative antimicrobial prophylaxis was routinely administered in all patients. Patients were operated under general anesthesia or general anesthesia combined with epidural anesthesia. Perioperative anesthetic management was at the discretion of the attending anesthesiologist.

Primary study parameter was a composite of 30-day mortality (death of any cause), pneumonia (purulent sputum, positive sputum or blood culture and clinical symptoms, e.g. cough, fever or consolidation on chest radiograph), sepsis (SIRS with suspected or proven infection), anastomotic dehiscence (luminal contents through drain or wound site or leak detected on imaging studies), wound infection (purulent drainage from superficial incision or deliberate opening of superficial incision by surgeon and pain, tenderness, swelling or redness), reoperation, respiratory insufficiency (hypoxia or hypercapnia leading to ICU (re) admission), atrial fibrillation (new-onset atrial fibrillation), congestive heart failure (pleural effusion or pulmonary edema requiring diuretic therapy) and myocardial infarction (elevated cardiac biomarkers in combination with clinical symptoms or electrocardiography changes). Length of hospital stay was recorded. Each individual study parameter was assessed after careful review of medical charts and during patient visits performed by research personnel blinded to laboratory results. At thirty days after surgery a follow-up telephone interview was performed if patients were discharged from the hospital at that time. Patients were asked if a medical complication had occurred since their discharge from the hospital. If so, medical details were retrieved from their treating physicians. Information from routine postoperative clinic visits was used if patients could not be reached by telephone. An event committee consisting of

two independent medical doctors judged every individual study parameter and, if no consensus was reached, a third specialist was consulted.

Biochemical analyses

After blood samples were drawn and centrifuged, samples were stored in frozen aliquots at -80° C. After inclusion of all patients samples were shipped to laboratory HaemoScan (Groningen, the Netherlands) for batch analyses. Tumour necrosis factor-α and IL-6 were determined by means of a solid-phase ELISA, with capture and peroxidase labelled tracer antibody (Biolegend, San Diego, CA, USA). The oxidase converts phenyldiamine-dihydrochloride to a yellow colour, which is proportional to the concentration of TNF-α or IL-6. A microtiter plate reader measured the colour at 490 nm. Leucocyte count and levels of CRP were part of routine perioperative laboratory tests and were retrieved from computerized medical charts.

Clinical characteristics

Each patient visited the outpatient preoperative anesthesia clinic. During this visit medical history and preoperative medicine use (e.g. steroids, statins, aspirin) were recorded. Information regarding duration of surgery, operative blood loss, packed red blood cell transfusion (during the first 48 hours after surgery), type of anesthesia and postoperative temperature, heart and respiratory rate were collected from computerized medical records.

Statistical analysis

For statistical analysis IBM SPSS version 22 was used. A two-tailed *P*-value of < 0.05 was considered statistically significant in all tests. Continuous data are presented as mean and standard deviation (SD) if normally distributed and as median and interquartile range (IQR) if not normally distributed. The Kolmogorov-Smirnov test was used to test for normality. To compare independent continuous variables between groups a Student t-test or Mann-Whitney-U test was performed where appropriate. Categorical variables are given as frequencies and percentages. To compare dichotomous variables between groups a χ^2-test or Fishers exact test was used. A receiver operator characteristics (ROC) curve was created to determine the optimal cut off point for continuous variables. The goodness of fit for the multivariable predictive model was quantified by the c-statistic. The length of hospital stay in patients with and without postoperative complications was presented using a Kaplan-Meier curve together with the logrank test. For multivariable analysis we used binary logistic regression. All variables that were imbalanced between the two groups ($P \leq 0.10$) as depicted in Table 1 were considered potential confounders of the association between inflammatory state and the occurrence of postoperative complications. In addition, variables known for their immunomodulatory effects, such as

anti-inflammatory drug use, packed red blood cell transfusion, malignancy and diabetes mellitus were also considered. A variable was retained in the final model as a confounder if it changed the odds ratio (OR) of the inflammatory marker of interest and the outcome by more than 10%.

RESULTS

Patient characteristics and outcome

One hundred and thirty-seven patients were included. Two patients had a more than 4000-fold increased baseline IL-6 level compared to the average baseline IL-6 level and were excluded from analysis. The final study population consisted of 135 patients. Mean age was 68 years and 59% of all patients were male. Forty patients (30%) had an ASA physical status of 3 or more. Most commonly performed abdominal procedures were colorectal surgery, gastric-esophageal surgery and pancreatic surgery in 50%, 22% and 10% of patients respectively. Two-thirds of the procedures (67%) were performed to treat malignant tumours. Medications that suppress inflammation, such as statins, aspirin and steroids, were used by 49%, 34% and 5% of all patients, respectively. Other baseline characteristics are shown in Table 1.

Thirty-nine patients (29%) suffered from at least 1 postoperative complication (Table 2). The median time between surgery and a complication was 5 days (IQR 3-8). Intra-operative characteristics such as an increased duration of surgery and blood loss were associated with adverse outcome. Preoperative statin ($P = 0.723$), aspirin ($P = 0.488$) or steroid use ($P = 1.000$) was not related to the occurrence of a complication.

Inflammatory markers in patients with and without complications

Before surgery levels of IL-6, TNF-α, CRP and leucocyte count were similar in patients with and without a postoperative complication (Figure 1). After surgery the inflammatory marker levels between patients with and without complications were most pronounced for IL-6: 596 [219-989] pg/ml vs. 303 [127-501] pg/ml ($P < 0.01$) on day 1, 128 [61-342] pg/ml vs. 69 [30-115] pg/ml, ($P < 0.01$) on day 3, and 76 [20-175] pg/ml vs. 27 [11-48] pg/ml ($P = 0.02$) on day 7 (Figure 1a). C-reactive protein level was similar in both groups on day 1 (90 [62-119] mg/l vs. 78 [53-109] mg/l, $P = 0.131$), but diverged on day 3 (223 [145-316] vs. 131 [87-189], $P < 0.001$) to day 7 (131 [65-178] mg/l vs. 63 [33-84] mg/l, $P < 0.001$) (Figure 1b). Tumour necrosis factor-α level was different only on day 7 between patients with and without a postoperative complication (0.5 [0-1.8] pg/ml vs. 0 [0-0.4] pg/ml, $P < 0.01$) (Figure 1c). Postoperative leucocyte count was similar in both groups on all sample days (Figure 1d).

Table 1: Baseline characteristics according to the occurrence of a postoperative complication

Variable	Complication (n=39)	No complication (n=96)	*p*-value
Male gender [n (%)]	27 (69.2)	53 (55.2)	0.133
Age (years)	69±10	67±11	0.425
BMI [kg/m^2]	27.1±5.2	28.9±8.3	0.218
Comorbidity			
Diabetes [n (%)]	13 (33.3)	31 (32.3)	0.907
Current smoking [n (%)]	4 (10.3)	19 (19.8)	0.182
COPD [n (%)]	8 (20.5)	29 (30.2)	0.252
Hypertension [n (%)]	32 (82.1)	74 (77.1)	0.524
Coronary artery disease [n (%)]	9 (23.1)	20 (20.8)	0.774
Atrial fibrillation [n (%)]	10 (25.6)	5 (5.2)	0.001
Previous stroke [n (%)]	12 (30.8)	13 (13.5)	0.020
Surgery for malignancy [n (%)]	28 (71.8)	62 (64.6)	0.420
ASA physical status ≥III [n (%)]	12 (30.8)	28 (29.2)	0.853
POSSUM	6.0 (1.9-13.0)	4.5 (1.9-10.6)	0.189
Medication use			
Aspirin [n (%)]	11 (28.2)	33 (34.4)	0.488
Statin [n (%)]	20 (51.3)	46 (47.9)	0.723
RAAS inhibitors [n (%)]	24 (61.5)	31 (32.3)	0.002
Other antihypertensive drugs [n (%)]	30 (76.9)	69 (61.5)	0.086
Steroids [n (%)]	2 (5.1)	5 (5.2)	1.000
Type of surgery			
Colorectal [n (%)]	19 (48.7)	48 (50.0)	0.893
Gastric-esophageal [n (%)]	14 (35.9)	15 (15.6)	0.009
Pancreatic [n (%)]	5 (12.8)	9 (9.4)	0.545
Gastric bypass [n (%)]	1 (2.6)	13 (13.5)	0.067
Hepatic [n (%)]	1 (2.6)	8 (8.3)	0.446
Other [n (%)]	2 (5.1)	4 (4.2)	1.000
Type of anesthesia			
TIVA [n (%)]	29 (74.4)	53 (55.2)	0.039
Epidural anesthesia [n (%)]	30 (76.9)	58 (60.4)	0.068
Duration of surgery (min)	154 (120-240)	120 (75-180)	0.028
Blood loss (ml)	200 (58-400)	100 (20-300)	0.037
RBC transfusion [n (%)]	12 (30.8)	11 (11.5)	0.007

Data are presented as mean (SD), median with interquartile range or absolute numbers.

BMI: body mass index, COPD: chronic obstructive pulmonary disease, ASA: American Association of Anesthesiologists physical status classification system, POSSUM: Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity, RAAS: renin-angiotensin-aldosterone system inhibitors, TIVA: total intravenous anesthesia, RBC: red blood cell transfusion.

Stroke is the composite of patients with a history of transient ischemic attack or cerebrovascular accident

Table 2: Clinical outcomes according to IL-6 levels on day 1

	High[§] IL-6 (n=52)	Low[#] IL-6 (n=80)	*p*-value
Sepsis [n (%)]	11 (21.2)	4 (5.0)	0.004
Reoperation [n (%)]	9 (17.3)	4 (5.0)	0.020
Anastomotic dehiscence [n (%)]	9 (17.3)	2 (2.5)	0.007
Atrial fibrillation [n (%)]	7 (13.5)	5 (6.3)	0.216
Respiratory insufficiency [n (%)]	7 (13.5)	1 (1.3)	0.006
Pneumonia [n (%)]	5 (9.6)	3 (3.8)	0.263
Wound infection [n (%)]	6 (11.5)	3 (3.8)	0.154
Congestive heart failure [n (%)]	4 (7.7)	3 (3.8)	0.433
Myocardial infarction [n (%)]	0	0	
Mortality [n (%)]	3 (5.8)	0 (0.0)	0.059
Any event [n (%)]	23 (44.2)	13 (16.3)	0.000

In 3 patients levels of IL-6 on day 1 was not available.
Patients could suffer from more than one complication.
[§] High IL-6 > 432pg/ml
[#] Low IL-6: ≤ 432pg/ml

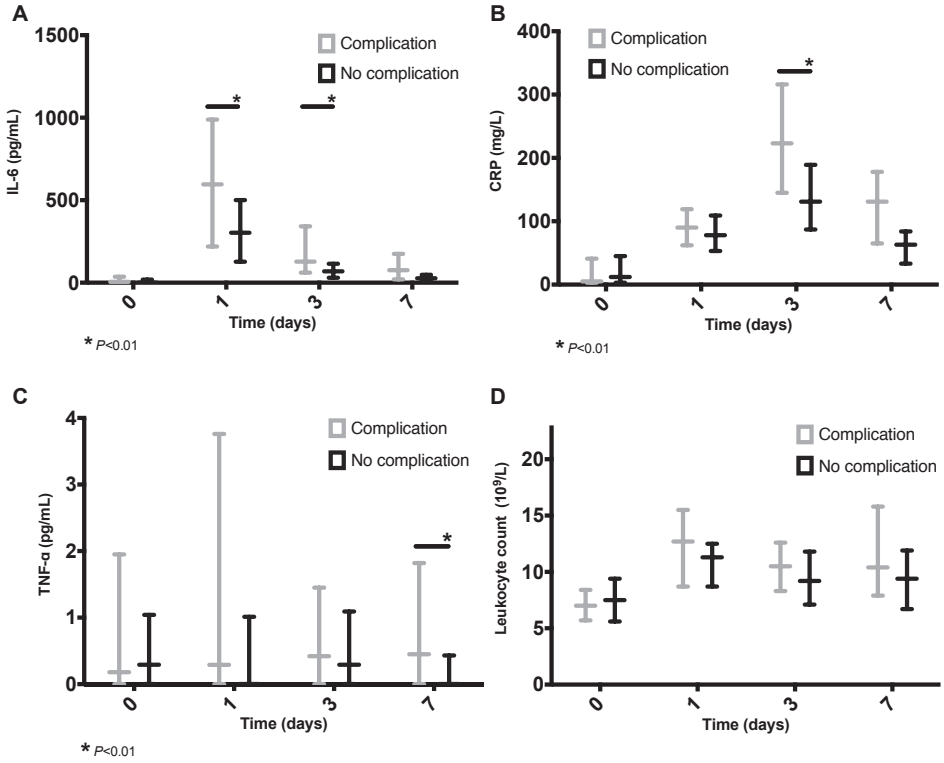

Figure 1. Inflammatory markers before surgery and on day 1, 3 and 7 depending on the occurrence of a postoperative complication.

Predictive value of inflammatory markers

Using a ROC curve the ideal cut-off point for IL-6 on day 1 for the prediction of a postoperative complication was set at 432 pg/ml. This yielded a specificity of 70%, a sensitivity of 64%, a positive predictive value of 44%, a negative predictive value 84% and area under the curve of 67% (95% CI: 56% - 77%). Patients with an IL-6 level of >432 pg/ml ('high' group) on day 1 had an increased length of hospital stay compared to patients with an IL-6 level of ≤432 pg/ml ('low' group) (12 days (IQR 7-22) vs. 7 days (IQR 4-9), $P < 0.001$) (Figure 2). In multivariable regression analysis a high IL-6 level on day 1 was independently associated with a postoperative complication (AOR 3.3, 95% CI: 1.3 - 8.5; $P < 0.02$) (Table 3). The c-statistic of the model including a high IL-6 level on day 1, atrial fibrillation, gastric esophageal-surgery and the preoperative use of renin-angiotensin-aldosterone-system (RAAS) inhibitors was 0.83 (95% CI: 75% - 91%; $P < 0.001$) (Figure 3).

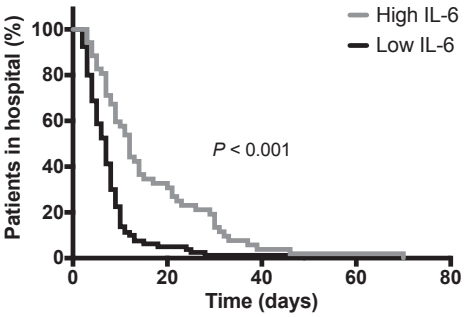

Figure 2. Median length of hospital stay dependent on high (>432 pg/ml) or low (≤432 pg/ml) IL-6 level.

Table 3. Uni- and multivariate logistic regression analysis for predictors of a postoperative complication

Univariate analysis				Multivariate analysis			
	OR	(95% CI)	*p*-value		OR	(95% CI)	*p*-value
'High' IL-6 level[§] on day 1	4.1	(1.8 - 9.2)	0.001	'High' IL-6 level on day 1	3.3	(1.3 – 8.5)	0.016
Atrial fibrillation	6.3	(2.0 - 19.9)	0.002	Atrial fibrillation	10.6	(2.4 - 47.7)	0.002
RAAS inhibitor	3.4	(1.6 - 7.3)	0.002	RAAS inhibitor	9.0	(3.0 - 27.2)	0.000
Gastric-esophageal surgery	3.0	(1.3 – 7.1)	0.011	Gastric-esophageal surgery	4.9	(1.6 - 14.9)	0.005
SIRS	3.3	(1.4 – 7.5)	0.005				
Previous stroke	2.8	(1.2 – 7.0)	0.023				
RBC transfusion	3.4	(1.4 – 8.7)	0.009				
TIVA	2.4	(1.0 – 5.4)	0.042				
Duration of surgery (min)	1.0	(1.0 – 1.0)	0.099				
Blood loss (ml)	1.0	(1.0 – 1.0)	0.182				

SIRS: systemic inflammatory response syndrome, other abbreviations as in Table 1

[§] High IL-6 > 432pg/ml

Using a ROC curve the ideal cut-off point for CRP on day 3 for the prediction of a complication was set at 203 mg/l. This yielded a specificity of 87%, a sensitivity of 58%, a positive predictive value of 65%, a negative predictive value 82% and area under the curve of 73% (95% CI: 63% - 83%). Patients with a CRP level of >203mg/l on day 3 were at increased risk of a postoperative complication (OR 8.8, 95% CI: 3.6 - 21.5; $P < 0.001$). When levels of CRP on day 3 were added to the multivariable model including a high IL-6 level on day 1, atrial fibrillation, gastric-esophageal surgery and the preoperative use of RAAS inhibitors, the c-statistic increased to 0.87 (95% CI: 0.80 - 0.93; $P < 0.001$) (Figure 3). The combination of IL-6 level on day 1 and CRP level on day 3 yielded a specificity of 93%, a sensitivity of 39%, a positive predictive value of 67% and a negative predictive value of 80%.

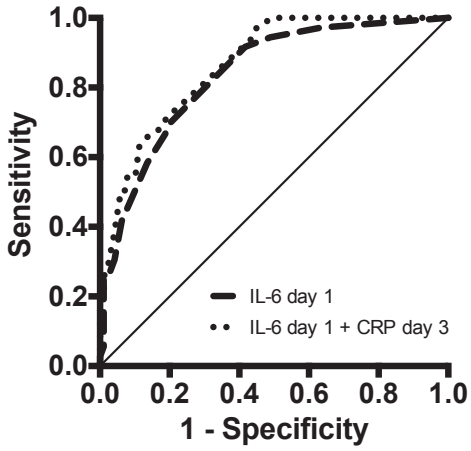

Figure 3. Receiver operating characteristic (ROC) curve to determine the goodness of fit for the multivariable predictive model. Interleukin-6 day 1 represents the model that includes a high (>432 pg/ml) IL-6 level on day 1, atrial fibrillation, gastric-esophageal surgery and the preoperative use of RAAS inhibitors. Interleukin-6 day 1 and CRP day 3 represents the same model with the addition of a high (>203mg/l) CRP level on day 3.

Seventy-four patients (55%) developed SIRS during the first 48 hours after surgery. Patients with SIRS had higher levels of IL-6 (418 [219-775] pg/ml vs. 260 [83-456] pg/ml, $P < 0.01$) and CRP (90 [61-120] mg/l vs. 72 [51-101] mg/l, $P < 0.02$) on day 1 and day 3 (95 [52-214] pg/ml vs. 53 [17-117] pg/ml, $P < 0.01$, and 182 [115-226] mg/l vs. 123 [78-176] mg/l, $P < 0.01$ respectively) compared to patients without SIRS. The development of SIRS was associated with an increased risk of a postoperative complication (OR 3.3, 95% CI: 1.4 - 7.5; $P < 0.01$), but this relation was lost in multivariable analysis. The specificity, sensitivity, positive predictive value and negative predictive value of SIRS for the prediction of postoperative complications were 53%, 74%, 39% and 84% respectively. The addition of SIRS criteria to levels of IL-6 did not improve the prediction of postoperative complications.

DISCUSSION

Our results show that patients with a high IL-6 level on the first postoperative day had a 3-fold increased risk of a postoperative complication and an increased length of hospital stay. Levels of IL-6 distinguished between patients at low and high risk for postoperative complications in an earlier stage than levels of CRP. As a single test, both high IL-6 levels on day 1 and high CRP levels on day 3 showed low diagnostic accuracy for predicting complications. The diagnostic value of IL-6 levels on day 1 in predicting postoperative complications improved when combined with CRP levels on day 3.

Few studies investigated the diagnostic value of IL-6 in predicting complications after major abdominal surgery. Szczepanik et al. prospectively studied 99 patients undergoing subtotal or total gastrectomy for malignancy.[4] Twenty-eight (28%) patients developed a postoperative complication within 30 days of surgery. Patients were divided into 2 groups: high (>279 ng/l) vs. low (≤279 pg/l) IL-6 level on the first postoperative day. A high IL-6 level was independently associated with an increased risk of a postoperative complication (Hazard ratio 3.6, 95% CI: 1.2 - 11.0), which is similar with our results (AOR 3.3, 95% CI: 1.3 - 8.5). In another study 50 patients undergoing major gastrointestinal and gynaecological tumour resection were studied.[17] Levels of IL-6, CRP and procalcitonin were evaluated on the first postoperative day as early markers for postoperative sepsis. Patients who developed sepsis within 5 days of surgery had higher levels of IL-6 on the first postoperative day compared to patients without sepsis (741 pg/ml vs. 276 pg/ml, $P < 0.01$). The accuracy of IL-6 in predicting postoperative sepsis was highest with the cut-off point set at 310 pg/ml. A multivariable analysis of levels of IL-6 and sepsis was not reported.

There is no specific IL-6 cut-off level known in literature to distinguish patients at increased risk for postoperative complications. Sczepanik et al. used the 90th percentile (279 pg/l), while the optimal cut-off level in the study of Mokart et al. was 310 pg/ml as assessed using a ROC curve.[4, 17] In our patient group the accuracy of IL-6 on day 1 was highest with a cut-off level of 432 pg/l, suggesting that the optimal cut-off level for the prediction of complications in major abdominal surgery is somewhere between 300 to 400 pg/l.

Major abdominal surgery is a commonly performed procedure and associated with a high complication rate. It is plausible that early recognition of postoperative complications optimizes the chance of better outcome. One way to enhance early detection of complications is using inflammatory markers as predictors of outcome.[20] Usually levels of CRP are used to monitor the condition of a patient over time after surgery. For example, high levels may support the decision to perform a reoperation when anastomotic dehiscence is suspected. However, inflammatory biomarkers, such as a CRP, are only useful as predictors for such complications when their diagnostic accuracy is sufficient enough to

identify patients at increased risk of complications well in advance of clinical symptoms. In a recent meta-analysis levels of CRP for the prediction of postoperative complications were assessed.[21] In this study 1832 patients undergoing colorectal surgery were included and levels of CRP were evaluated during the first 5 postoperative days. The diagnostic performance of CRP to predict postoperative infectious complications was worst on day 1 (area under the curve 0.64) and highest on day 4 (area under the curve 0.81). The time between surgery and complications was not provided. In our study population, levels of CRP on day 1 were similar in patients with and without a complication and the median time from surgery to a complication was 5 days (IQR 3-8). That means that a substantial part of the patients is diagnosed with a postoperative complication before CRP is even able to identify patients at increased risk of complications. Our results show that levels of IL-6 on the first postoperative day could be helpful to distinguish between patients with and without complications. We recognize that high levels of IL-6 showed poor accuracy for predicting postoperative complications. Interestingly, the accuracy of IL-6 was in accordance with the accuracy of CRP, an inflammatory marker that is commonly used for the detection of postoperative complications. The diagnostic value of IL-6 level on day 1 in our study population was also similar to the accuracy of CRP level in the meta-analysis previously mentioned.[21] Furthermore, the accuracy of CT scanning for anastomotic dehiscence after colorectal surgery matched the accuracy of IL-6 level on day 1 in the present study.[22]

Patients who developed SIRS had higher levels of IL-6 and CRP on day 1 and 3, confirming that the combination of relatively unspecific clinical symptoms such as tachycardia, high respiratory rate and fever are an expression of inflammation.[5, 23] However, in multivariable analysis the association of SIRS and outcome was lost, indicating that IL-6 is a more specific marker for inflammation. Also, SIRS did not contribute to the prediction of postoperative complications in contrast to results previously mentioned.[17] This might be explained by the difference in endpoints studied.

Why outcome is influenced by postoperative systemic inflammation is not straightforward. In short, tissue damage induces the proliferation of immune competent cells, such as monocytes, macrophages, dendritic cells, lymphocytes and neutrophils.[24] This in turn triggers the production of cytokines and chemokines. As a result, the endothelium produces nitric oxide (NO) to maintain normal homeostasis. However, altered concentrations of NO inhibit the function of mitochondria, which may lead to adenosine triphosphate (ATP) depletion. Excessive depletion of ATP results in cell necrosis and ultimately induces organ failure.[25]

Our study has several limitations. First, we used a composite endpoint including infectious and non-infectious complications. At the start of the study we considered to study individual outcomes (e.g. anastomotic dehiscence), but since these outcomes are rare, statistical power is often insufficient. Moreover, the effect of postoperative inflamma-

tion is not confined to infectious complications alone, but to many different types of complications.[26] Second, we only investigated inflammatory biomarkers prior to surgery, on day 1, 3 and 7. Levels of CRP peak after 48 hours, and a CRP level on day 2 could have resulted in a higher accuracy of predicting complications, although this is not seen in previous studies.[21] Also, it may be that levels of IL-6 on day 2 have better discriminative power than IL-6 levels on day 1 for the prediction of postoperative complications. Third, time between surgery and the collection of blood samples on day 1 was somewhat variable between patients due to variations in surgical starting times. Considering the vivid dynamics of levels of IL-6 during the early phase of inflammation, this may have introduced variation in IL-6 levels outside the development of postoperative complications. On the other hand, measuring IL-6 levels in the morning on the first postoperative day is more suitable in clinical practice than individualising the exact sampling moment for every patient. Besides this, other studies that investigated inflammatory markers after surgery had a similar study approach, what allowed us to compare our results with previous work. And fourth, this is a single-centre observational study in a relative small cohort of patients.

In conclusion, a high IL-6 level on the first postoperative day after major abdominal surgery is independently associated with the occurrence of postoperative complications. The diagnostic accuracy of IL-6 on day 1 for predicting postoperative complications is similar to the accuracy of CRP on day 3. Interleukin-6 levels can have added value in early clinical decision-making.

REFERENCES

1. Noordzij PG, Poldermans D, Schouten O, Bax JJ, Schreiner FA, Boersma E: Postoperative mortality in The Netherlands: a population-based analysis of surgery-specific risk in adults. Anesthesiology 2010; 112: 1105-15
2. Cloyd JM, Ma Y, Morton JM, Kurella Tamura M, Poultsides GA, Visser BC: Does chronic kidney disease affect outcomes after major abdominal surgery? Results from the National Surgical Quality Improvement Program. J Gastrointest Surg 2014; 18: 605-12
3. Arozullah AM, Khuri SF, Henderson WG, Daley J, Participants in the National Veterans Affairs Surgical Quality Improvement Program: Development and validation of a multifactorial risk index for predicting postoperative pneumonia after major noncardiac surgery. Ann Intern Med 2001; 135: 847-57
4. Szczepanik AM, Scislo L, Scully T, Walewska E, Siedlar M, Kolodziejczyk P, Lenart M, Rutkowska M, Galas A, Czupryna A, Kulig J: IL-6 serum levels predict postoperative morbidity in gastric cancer patients. Gastric Cancer 2011; 14: 266-73
5. Sinning JM, Scheer AC, Adenauer V, Ghanem A, Hammerstingl C, Schueler R, Muller C, Vasa-Nicotera M, Grube E, Nickenig G, Werner N: Systemic inflammatory response syndrome predicts increased mortality in patients after transcatheter aortic valve implantation. Eur Heart J 2012; 33: 1459-68
6. Amar D, Zhang H, Park B, Heerdt PM, Fleisher M, Thaler HT: Inflammation and outcome after general thoracic surgery. Eur J Cardiothorac Surg 2007; 32: 431-4
7. Wen XH, Kong HY, Zhu SM, Xu JH, Huang SQ, Chen QL: Plasma levels of tumor necrotic factor-alpha and interleukin-6, -8 during orthotopic liver transplantation and their relations to postoperative pulmonary complications. Hepatobiliary Pancreat Dis Int 2004; 3: 38-41
8. Chimienti G, Aquilino F, Rotelli MT, Russo F, Lupo L, Pepe G: Lipoprotein(a), lipids and proinflammatory cytokines in patients undergoing major abdominal surgery. Br J Surg 2006; 93: 347-53
9. Veenhof AA, Sietses C, von Blomberg BM, van Hoogstraten IM, vd Pas MH, Meijerink WJ, vd Peet DL, vd Tol MP, Bonjer HJ, Cuesta MA: The surgical stress response and postoperative immune function after laparoscopic or conventional total mesorectal excision in rectal cancer: a randomized trial. Int J Colorectal Dis 2011; 26: 53-9
10. Gilliland HE, Armstrong MA, Carabine U, McMurray TJ: The choice of anesthetic maintenance technique influences the antiinflammatory cytokine response to abdominal surgery. Anesth Analg 1997; 85: 1394-8
11. Blajchman MA: Immunomodulation and blood transfusion. Am J Ther 2002; 9: 389-95
12. Schwartz DA: The genetics of innate immunity. Chest 2002; 121: 62S-8S
13. Shaw AD, Vaporciyan AA, Wu X, King TM, Spitz MR, Putnam JB, Dickey BF: Inflammatory gene polymorphisms influence risk of postoperative morbidity after lung resection. Ann Thorac Surg 2005; 79: 1704-10
14. Call TR, Pace NL, Thorup DB, Maxfield D, Chortkoff B, Christensen J, Mulvihill SJ: Factors associated with improved survival after resection of pancreatic adenocarcinoma: a multivariable model. Anesthesiology 2015; 122: 317-24
15. Abdelmalak BB, Bonilla A, Mascha EJ, Maheshwari A, Tang WH, You J, Ramachandran M, Kirkova Y, Clair D, Walsh RM, Kurz A, Sessler DI: Dexamethasone, light anaesthesia, and tight glucose control (DeLiT) randomized controlled trial. Br J Anaesth 2013; 111: 209-21
16. Dimopoulou I, Armaganidis A, Douka E, Mavrou I, Augustatou C, Kopterides P, Lyberopoulos P, Tzanela M, Orfanos SE, Pelekanou E, Kostopanagiotou G, Macheras A, Giamarellos-Bourboulis

EJ: Tumour necrosis factor-alpha (TNFalpha) and interleukin-10 are crucial mediators in post-operative systemic inflammatory response and determine the occurrence of complications after major abdominal surgery. Cytokine 2007; 37: 55-61

17. Mokart D, Merlin M, Sannini A, Brun JP, Delpero JR, Houvenaeghel G, Moutardier V, Blache JL: Procalcitonin, interleukin 6 and systemic inflammatory response syndrome (SIRS): early markers of postoperative sepsis after major surgery. Br J Anaesth 2005; 94: 767-73
18. Noordzij PG, van Geffen O, Dijkstra IM, Boerma D, Meinders AJ, Rettig TC, Eefting FD, van Loon D, van de Garde EM, van Dongen EP: High-sensitive cardiac troponin T measurements in prediction of non-cardiac complications after major abdominal surgery. Br J Anaesth 2015; 114: 909-18
19. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Crit Care Med 1992; 20: 864-74
20. Tsujimoto H, Ono S, Takahata R, Hiraki S, Yaguchi Y, Kumano I, Matsumoto Y, Yoshida K, Aiko S, Ichikura T, Yamamoto J, Hase K: Systemic inflammatory response syndrome as a predictor of anastomotic leakage after esophagectomy. Surg Today 2012; 42: 141-6
21. Warschkow R, Beutner U, Steffen T, Muller SA, Schmied BM, Guller U, Tarantino I: Safe and early discharge after colorectal surgery due to C-reactive protein: a diagnostic meta-analysis of 1832 patients. Ann Surg 2012; 256: 245-50
22. Kornmann VN, Treskes N, Hoonhout LH, Bollen TL, van Ramshorst B, Boerma D: Systematic review on the value of CT scanning in the diagnosis of anastomotic leakage after colorectal surgery. Int J Colorectal Dis 2013; 28: 437-45
23. Rettig TC, Rigter S, Nijenhuis VJ, van Kuijk JP, Ten Berg JM, Heijmen RH, van de Garde EM, Noordzij PG: The systemic inflammatory response syndrome predicts short-term outcome after transapical transcatheter aortic valve implantation. J Cardiothorac Vasc Anesth 2015; 29: 283-7
24. Castellheim A, Brekke OL, Espevik T, Harboe M, Mollnes TE: Innate immune responses to danger signals in systemic inflammatory response syndrome and sepsis. Scand J Immunol 2009; 69: 479-91
25. Brealey D, Brand M, Hargreaves I, Heales S, Land J, Smolenski R, Davies NA, Cooper CE, Singer M: Association between mitochondrial dysfunction and severity and outcome of septic shock. Lancet 2002; 360: 219-23
26. Dieleman JM, Nierich AP, Rosseel PM, van der Maaten JM, Hofland J, Diephuis JC, Schepp RM, Boer C, Moons KG, van Herwerden LA, Tijssen JG, Numan SC, Kalkman CJ, van Dijk D, Dexamethasone for Cardiac Surgery (DECS) Study Group: Intraoperative high-dose dexamethasone for cardiac surgery: a randomized controlled trial. JAMA 2012; 308: 1761-7

Chapter 5

Preoperative statin therapy and infectious complications in cardiac surgery

Nelleke L. Hartholt*
Thijs C.D. Rettig*
Maarten Schijffelen
Wim J. Morshuis
Ewoudt M.W. van de Garde
Peter G. Noordzij

* These authors contributed equally to this study

Neth Heart J. 2014 Nov;22(11):503-9

ABSTRACT

Aim: To assess whether preoperative statin therapy is associated with the risk of postoperative infection in patients undergoing cardiac surgery.

Methods: 520 patients undergoing cardiac surgery in 2010 were retrospectively examined. Data regarding statin and antibiotic use prior to and after surgery were available from the hospital pharmacy information system. Cultures and clinical data of patients on postoperative antibiotics other than standard prophylactic therapy were studied to identify postoperative infections up to 30 days from day of surgery.

Results: 370 (71.2%) patients were on preoperative statin therapy. Overall, 82 patients (15.8%) suffered from postoperative infection of which 11 were surgical site infections. In multivariable regression analysis, statin therapy was associated with a reduced risk of postoperative infection (adjusted odds ratio 0.33, 95%: CI 0.19 - 0.57; $P < 0.001$).

Conclusions: Preoperative statin use was associated with a considerable reduced risk of postoperative infections following cardiac surgery. Randomised controlled trials are required to clarify the role of statin therapy in the prevention of postoperative infections.

INTRODUCTION

Annually, approximately 16,000 patients are scheduled for cardiothoracic surgery in the Netherlands.[1] Postoperative infections are important causes of increased length of hospital stay and mortality. Despite prophylactic antibiotic therapy, the incidence of postoperative infectious complications is 5 to 21%.[2-4]

In a search for additional ways to decrease the postoperative infection rate, statin therapy is gaining increasing attention. In addition to cholesterol-lowering characteristics, statins have anti-inflammatory, immunomodulatory, antioxidant and antiapoptotic effects that could alter the response to infections.[5] Whether statins have a beneficial effect on postoperative infectious complications in patients undergoing cardiac surgery is unknown, as prior studies have shown conflicting results.[6-8]

This study aims to assess whether preoperative statin therapy is associated with the risk of postoperative infection in patients undergoing cardiac surgery.

METHODS

Study population

The total population of 1868 adult patients who had undergone cardiac surgery in the St. Antonius Hospital, Nieuwegein, the Netherlands in 2010 was the target population for this study. From this population we selected all patients with data on preoperative drug use in the hospital pharmacy information system. This means that only patients who were hospitalised more than 24 hours before the day of surgery could be studied (n=593), as these are the patients with reviewed preoperative medication profiles available in the hospital pharmacy information system. Additionally, 73 patients were excluded as they were on antimicrobial therapy prior to their surgical procedure outside the routine antimicrobial prophylaxis (cefazolin 2 gram intravenously before skin incision followed by additional cefazolin every four hours for the duration of the procedure and continued up to 48 hours for patients with valve or aortic surgery with exogenous materials). Finally, all patients with a statin in the preoperative medication profile were considered exposed at the time of surgery and all other patients were classified as controls. The local Medical Ethics Committee (Research and Development Department, St. Antonius Hospital) approved the study.

Outcome assessment

The primary outcome was postoperative infection within 30 days of surgery. We used the following approach to determine if a postoperative infection was present: first, all patients on postoperative antibiotic therapy, aside from perioperative antibiotic

prophylaxis, were identified. Secondly, N.H. and T.R. independently examined the medical records of these patients to determine if clinical data (e.g. fever, white cell count) supported the diagnosis of infection. When N.H. and T.R. agreed that a postoperative infection was present, it was classified as a surgical site or non-surgical site infection. Subsequently, M.S. and T.R. used microbiological data to identify the microbial aetiology. When N.H., T.R. and M.S. could not reach an agreement on whether an infection was present or on the site of infection, P.N. was consulted. For all patients, in-hospital mortality was noted.

Potential confounders

To be able to control for potential confounding, medical information was obtained on risk factors for infection that could potentially confound the association between statin treatment and outcome. For each patient we evaluated the presence of the following comorbidities as potential confounders: diabetes, chronic obstructive pulmonary disease (COPD, graded according to the GOLD classification where all smokers were considered class I unless otherwise stated)[9], peripheral artery disease, three-vessel coronary artery disease, renal insufficiency (defined as serum creatinine >120 µmol/l), heart failure (according to New York Heart Association functional classification), prior myocardial infarction, and history of cardiac surgery. In addition, the following surgery-related parameters were assessed: type of surgery (coronary artery bypass graft (CABG), valve surgery, aortic surgery or other), urgent procedure (patients not electively admitted for operation who require surgery before hospital discharge), perfusion time, aortic clamp time and whether rethoracotomy has taken place. Aspirin, antidiabetic agents, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, proton pump inhibitors (PPIs) and prednisone were examined as possible confounding drugs. A patient was considered exposed to a drug if it was listed in the preoperative medication profile. Furthermore, we calculated the body mass index and European System for Cardiac Operative Risk Evaluation (EURO) score as proxy for overall health status and complication risk. During the study period, glucose values were standardly targeted at 4.5-8 mmol/l during surgery and ICU admission, and 4.5-10 mmol/l on the surgical ward in all patients.

Statistical analysis

Data were analysed using International Business Machines Statistical Package for the Social Science (IBM SPSS) Statistics 19.0 software. Univariate analysis by χ^2 tests and Student's t tests was used to test for significant differences in characteristics between statin users and non-users and patients with and without postoperative infections. Multivariable logistic regression analysis was used to estimate the strength of the association between statin treatment and the risk of postoperative infection and expressed as odds ratios (OR) with 95% confidence intervals (CI). First, we included all potential

confounders and age and gender in a multivariable model if a variable was imbalanced ($P < 0.10$) related to either statin use or occurrence of infection. Second, a final model was obtained after stepwise backward elimination of potential confounders if they did not alter the OR by more than 10%. Stratified analyses were conducted to detect possible differences in effects related to timing of statin exposure (continued use, commenced use or discontinued use). For all tests, a *P*-value of 0.05 was considered significant.

RESULTS

A total of 370 (71.2%) patients received statin treatment until the day of surgery, while 150 (28.8%) patients did not. Patients receiving statin treatment were more likely to be male, and suffering from COPD, diabetes, peripheral artery disease, and three-vessel coronary artery disease. Furthermore, they experienced more myocardial infarction and isolated CABG surgery and received more frequent other cardiovascular drug therapies, such as aspirin, beta-blockers and ACE-inhibitors. Compared with non-users, patients on statin therapy had shorter perfusion times and aortic clamp times. Baseline characteristics are shown in Table 1.

Overall, 82 (15.8%) patients suffered from postoperative infection. Of the patients with an infectious complication, 87% had a non-surgical site infection. The occurrence of a surgical site infection was less common and was present in 13% of patients with postoperative infection. Pneumonia was the most common infection and accounted for 59% of all infectious complications. In 59 (72%) patients with a postoperative infection, one or more microorganisms were detected. Characteristics of patients with and without postoperative infection are shown in Table 2.

Patients on preoperative statin therapy suffered less frequently from postoperative infection compared with non-users (12.2% versus 24.7%, respectively; adjusted odds ratio (AOR) 0.33, 95% CI: 0.19 - 0.57; $P < 0.001$; Table 3). Statin users had fewer non-surgical site infections compared with non-users (AOR 0.25, 95% CI: 0.14 - 0.45; $P < 0.001$). This was mainly caused by a reduction in postoperative pneumonia and urinary tract infection (Table 4). A surgical site infection occurred in 11 (3%) patients on statin therapy, whereas non-users did not develop any. Overall, in-hospital mortality was 4.4%; 3.2% in patients on preoperative statin therapy and 7.3% in non-users ($P = 0.041$).

After surgery, statin therapy was initiated in 37 (7.1%) patients who did not use statins prior to surgery. Postoperative initiation of statin therapy was not associated with a reduced risk of infection (AOR 0.68, 95% CI: 0.26 - 1.75; $P = 0.422$).

Table 1: Patient characteristics according to the use of statins

Variable	Statin group (n=370)	Control group (n=150)	*p*-value
Patient characteristics			
Sex (male)	260 (70.3)	87 (58.0)	0.007
Age (yr)	68.3±10.0	69.5±13.7	0.277
BMI (kg/m^2)	27.7±4.5	26.7±4.9	0.037
COPD	206 (55.7)	70 (46.7)	0.062
Diabetes	112 (30.3)	27 (18.0)	0.004
Congestive heart failure	140 (37.8)	75 (50.0)	0.011
Renal failure	56 (15.1)	28 (18.7)	0.322
Peripheral artery disease	79 (21.4)	19 (12.7)	0.018
Three-vessel coronary artery disease	209 (56.5)	30 (20.0)	<0.001
EURO-score	5.2±3.7	5.7±3.3	0.106
Previous myocardial infarction	180 (48.6)	24 (16.0)	<0.001
Previous cardiac surgery	39 (10.5)	23 (15.3)	0.127
Preoperative medication			
Beta-blocker	293 (79.2)	91 (60.7)	<0.001
ACE-inhibitor	163 (44.1)	47 (31.3)	0.007
Prednisone	43 (11.6)	16 (10.7)	0.756
Proton pump inhibitor	161 (43.5)	60 (40.0)	0.463
Aspirin	150 (40.5)	23 (15.3)	<0.001
Postoperative medication			
Statin	349 (94.3)	37 (24.7)	<0.001
Beta-blocker	301 (81.4)	110 (73.3)	0.056
ACE-inhibitor	168 (45.4)	68 (45.3)	0.968
Prednisone	35 (9.5)	21 (14.0)	0.126
Proton pump inhibitor	272 (73.5)	103 (68.7)	0.291
Type of surgery			
CABG	219 (59.2)	25 (16.7)	<0.001
Major procedure (other or in addition to CABG)	152 (41.1)	124 (82.7)	<0.001
Valve surgery	110 (29.7)	90 (60.0)	<0.001
Aortic surgery	22 (5.9)	28 (18.7)	<0.001
Other cardiac surgery	9 (2.4)	19 (12.7)	<0.001
Perioperative characteristics			
Perfusion time (min)	88.6±55.6	126.8±415.5	0.084
Aortic clamp time (min)	60.0±37.9	59.2±55.4	0.836
Off pump	12 (3.2)	3 (2.0)	0.443
Urgent surgery	33 (8.9)	9 (6.0)	0.268
Rethoracotomy	29 (7.8)	20 (13.3)	0.053

Dichotomous variables are shown as number (%) and continuous variables are presented as mean ± sd.

Table 2: Patient characteristics according to the occurrence of postoperative infection

Variable	Infection group (n=82)	Control group (n=438)	*p*-value
Patient characteristics			
Sex (male)	56 (68.3)	291 (66.4)	0.744
Age (yr)	70.2±12.0	68.4±11.0	0.189
BMI (kg/m^2)	27.8±4.9	27.3±4.6	0.393
COPD	57 (69.5)	219 (50.0)	0.001
Diabetes	21 (25.6)	118 (26.9)	0.803
Congestive heart failure	41 (50.0)	174 (39.7)	0.083
Renal failure	20 (24.4)	64 (14.6)	0.027
Peripheral artery disease	18 (22.0)	80 (18.3)	0.389
Three-vessel coronary artery disease	40 (48.8)	199 (45.4)	0.494
EURO-score	6.0±3.5	5.2±3.6	0.074
Previous myocardial infarction	27 (32.9)	177 (40.4)	0.197
Previous cardiac surgery	9 (11.0)	53 (12.1)	0.773
Preoperative medication			
Statin	45 (54.9)	325 (74.2)	0.000
Beta-blocker	58 (70.7)	326 (74.4)	0.484
ACE-inhibitor	31 (37.8)	179 (40.9)	0.604
Prednisone	15 (18.3)	44 (10.0)	0.031
Proton pump inhibitor	34 (41.5)	187 (42.7)	0.836
Aspirin	26 (31.7)	147 (33.6)	0.744
Postoperative medication			
Statin	45 (54.9)	341 (77.9)	0.000
Beta-blocker	60 (73.2)	351 (80.1)	0.143
ACE-inhibitor	36 (43.9)	200 (45.8)	0.756
Prednisone	13 (15.9)	43 (9.8)	0.109
Proton pump inhibitor	53 (64.6)	322 (73.9)	0.087
Type of surgery			
CABG	34 (41.5)	210 (47.9)	0.280
Major procedure (other or in addition to CABG)	47 (57.3)	229 (52.3)	0.402
Valve surgery	32 (39.0)	168 (38.4)	0.909
Aortic surgery	9 (11.0)	41 (9.4)	0.649
Other cardiac surgery	4 (4.9)	24 (5.5)	0.825
Perioperative characteristics			
Perfusion time (min)	106.1±72.8	98.4±246.9	0.781
Aortic clamp time (min)	65.6±50.8	58.7±42.1	0.185
Off pump	0 (0.0)	15 (3.4)	0.089
Urgent surgery	8 (9.8)	34 (7.8)	0.543
Rethoracotomy	11 (13.4)	38 (8.7)	0.180

Dichotomous variables are shown as number (%) and continuous variables are presented as mean ± sd.

Table 3: Results of multivariate analysis for the effect of statin therapy on postoperative infection rate

	OR (95% CI)	*p*-value
Unadjusted	0.42 (0.26-0.69)	0.001
Adjusted for sex	0.41 (0.25-0.67)	<0.001
Adjusted for sex and age	0.42 (0.26-0.68)	<0.001
Adjusted for sex, age and three-vessel coronary artery disease	0.35 (0.20-0.60)	<0.001
Adjusted for sex, age, three-vessel coronary artery disease and COPD	0.32 (0,18-0.55)	<0.001
Adjusted for sex, age, three-vessel coronary artery disease, COPD and aortic clamp time more than 90 minutes	0.33 (0.19-0.58)	<0.001

COPD indicates chronic obstructive pulmonary disease

Table 4. Incidence of study endpoints in statin and control group

	Statin group No. (%)	Control group No. (%)	*p*-value
All	370 (100)	150 (100)	
Postoperative infection	45 (12.2)	37 (24.7)	0.001
Surgical site infection	11 (3.0)	0 (0.0)	n.a.*
Mediastinitis	6 (1.6)	0 (0.0)	
Wound infection	5 (1.4)	0 (0.0)	
Non-surgical site infection	34 (9.2)	37 (24.7)	<0.001
Pneumonia	28 (7.6)	20 (13.3)	
Urinary tract infection	2 (0.5)	11 (7.3)	
Sepsis	3 (0.8)	5 (3.3)	
Other	1 (0.3)[§]	1 (0.3)[¶]	
In-hospital mortality	12 (3.2)	11 (7.3)	0.041

*n.a.: not available
[§]prostatitis
[¶]unknown

DISCUSSION

In this cohort of 520 patients undergoing cardiac surgery, preoperative statin therapy was associated with a 67% reduced risk of a postoperative infectious complication. The reduction in postoperative infection by preoperative statin use was mainly caused by a reduction in non-surgical site infections, in particular less pneumonia and urinary tract infections.

Recently two meta-analyses studied the relationship between statins and outcome in patients undergoing high-risk cardiac procedures (e.g. CABG, valve replacement,

percutaneous coronary intervention). Guay et al. included 29 randomised controlled trials in which statin therapy was compared with placebo.[10] Statin therapy reduced the risk of myocardial infarction (risk ratio (RR) 0.48; 95% CI 0.38 - 0.61; $P < 0.001$) and there was a trend towards lower mortality (RR 0.26; 95% CI 0.06 - 1.02; $P = 0.053$). Another meta-analysis showed that preoperative statin therapy was associated with improved outcome after CABG, but not after aortic valve replacement.[11] However, postoperative infections were not studied in either studies. Papers investigating the effect of statins on postoperative infection in cardiac surgery patients have shown variable results. In a retrospective cohort study of 1934 patients undergoing CABG and/or valve surgery, 151 (7.8%) patients developed an infection.[6] Preoperative statin use was associated with a risk reduction of 33% ($P = 0.04$) for postoperative infection. The odds ratios for a non-surgical site infection such as pneumonia (OR 0.67; 95% CI: 0.43 - 1.04), urinary tract infection (OR 0.65; 95% CI: 0.31 - 1.39) or bacteraemia (OR 0.71; 95% CI: 0.32 - 1.58) tended to be less in patients on statins but did not reach statistical significance. Another retrospective cohort study from Kayani et al. in 6253 patients who underwent CABG showed statin use as being associated with a 26% reduction in the postoperative infection rate (OR 0.74; 95% CI: 0.60 - 0.90).[12] In contrast, Mohamed et al. studied 7733 patients undergoing cardiac surgery and in that study statin users had similar infection rates to nonusers: 8.1% versus 8.4%, respectively (AOR 1.08; 95% CI: 0.89 - 1.31).[8] The incidence of any specific infection was similar in both groups, except for deep sternal/organ space infection (16 (0.6%) statin users versus 54 (1.1%) nonusers; $P = 0.04$). Importantly, postoperative pneumonia was not scored; considering the fact that pneumonia was diagnosed in 62% of all infections in the study by Coleman et al. and 59% in our study, excluding pneumonia could have influenced the results in the study by Mohamed et al.

We noticed a significant difference in infection type between statin users and nonusers. Patients on statin therapy had fewer non-surgical site infections, mainly caused by a reduced incidence of postoperative pneumonia and urinary tract infection. This finding is consistent with the results of previous studies. Using the United Kingdom (UK) General Practice Research Database, Schlienger et al. performed a retrospective case-control study in non-surgical patients and showed that statin therapy was associated with fewer cases of pneumonia, in particular, fatal pneumonia (OR 0.47, 95% CI: 0.25 - 0.88).[13] Van de Garde et al. showed that in patients with a history of diabetes only, statin users had a significantly reduced risk of pneumonia (OR 0.49, 95% CI: 0.35 - 0.69).[14] In contrast, in our study, surgical site infections occurred more often in patients on statin therapy than nonusers. This finding has not been described before. Known risk factors for surgical site infections, e.g. diabetes, obesity, prolonged operation time, did not appear to be more common in patients on statins in our study. Unfortunately, due to the small numbers we were not able to further investigate these effects with multivariable analysis. The same

applies for potential effects of statins on mortality. Crude significant reduced in-hospital mortality could be observed in our study.

If statin therapy is associated with less postoperative non-surgical site infections, is there a reasonable explanation? It is known that statins suppress the expression of various cytokines, chemokines and adhesion molecules and modulate coagulation toward a less prothrombotic state, but is there a direct effect on bacterial growth?[5] In an experimental study, mice pretreated with low-dose simvastatin and challenged with *Staphylococcus aureus* intratracheally or intravenously had lower lung bacterial burden compared with mice that were pretreated with placebo.[15] Bacterial killing was enhanced in simvastatin-pretreated mice, while mortality was decreased. Catron et al. studied mice pretreated with lovastatin and intraperitoneally infected with *Samonella enterica*.[16] Intracellular proliferation of *Salmonella enterica* was inhibited 6- to 10-fold by lovastatin. In summary, *in animals*, statins seem to be bactericidal and decrease bacterial proliferation. However, well-conducted human studies remain lacking.

During hospitalisation, a patient's drug treatment is modified frequently. For example, statin therapy can be initiated after surgery or discontinued for the remainder of the postoperative period. In a recent randomised controlled trial in patients admitted with severe sepsis, patients were randomised to atorvastatin treatment or placebo.[17] Patients in whom statin treatment was continued showed improved survival, while new-onset statin treatment did not result in improved outcome. Our study revealed that statin therapy was initiated in 37 (7%) patients following surgery. Newly initiated statin therapy, however, was not associated with a reduced chance of developing an infection. These results may imply that the possible protective effect of statin therapy on postoperative infection is not immediately reached after the start of therapy, but that it may take weeks before a beneficial effect is apparent.

Compared with other reports, postoperative infection and mortality rates appeared to be relatively high in our study population. The most plausible explanation for this could be the fact that we applied a broad definition for postoperative infection and that we studied patients who were hospitalised more than one day before surgery. One could hypothesise that these patients represent unstable cases and that these patient have a prolonged risk of nosocomial infections. Unfortunately, we were not able to test this hypothesis in depth because of lacking information on outcomes and antibiotic exposure for the excluded patients. Nevertheless, the final population in the present study represents the population that could benefit from interventions such as initiating statins in hospital before surgery if proven beneficial.

Our study has several limitations. First, the results of our study are limited because the data were derived in a retrospective manner. Second, compared with similar studies, our study population is relatively small. And third, we did not have specific information

on the length of statin therapy prior to surgery, which prevented additional analysis on timing of statin exposure.

In conclusion, this study describes a protective association between preoperative statin therapy and postoperative infectious complications in a high-risk cardiac surgical cohort. Randomised controlled trials are required to further clarify the role of statin therapy in preventing postoperative infections in cardiac surgery.

REFERENCES

1. http://www.hartstichting.nl/9800/13333/13374/hvz_in_nederland_2011.
2. De Santo LS, Bancone C, Santarpino G, Romano G, De Feo M, Scardone M, Galdieri N, Cotrufo M: Microbiologically documented nosocomial infections after cardiac surgery: an 18-month prospective tertiary care centre report. Eur J Cardiothorac Surg 2008; 33: 666-72
3. Michalopoulos A, Geroulanos S, Rosmarakis ES, Falagas ME: Frequency, characteristics, and predictors of microbiologically documented nosocomial infections after cardiac surgery. Eur J Cardiothorac Surg 2006; 29: 456-60
4. Kollef MH, Sharpless L, Vlasnik J, Pasque C, Murphy D, Fraser VJ: The impact of nosocomial infections on patient outcomes following cardiac surgery. Chest 1997; 112: 666-75
5. Terblanche M, Almog Y, Rosenson RS, Smith TS, Hackam DG: Statins and sepsis: multiple modifications at multiple levels. Lancet Infect Dis 2007; 7: 358-68
6. Coleman CI, Lucek DM, Hammond J, White CM: Preoperative statins and infectious complications following cardiac surgery. Curr Med Res Opin 2007; 23: 1783-90
7. Daneman N, Thiruchelvam D, Redelmeier DA: Statin use and the risk of surgical site infections in elderly patients undergoing elective surgery. Arch Surg 2009; 144: 938-45
8. Mohamed R, McAlister FA, Pretorius V, Kapoor AS, Majumdar SR, Ross DB, Norris CM, Alberta Provincial Program for Outcome Assessment in Coronary Heart Disease Investigators: Preoperative statin use and infection after cardiac surgery: a cohort study. Clin Infect Dis 2009; 48: e66-72
9. Rabe KF, Hurd S, Anzueto A, Barnes PJ, Buist SA, Calverley P, Fukuchi Y, Jenkins C, Rodriguez-Roisin R, van Weel C, Zielinski J, Global Initiative for Chronic Obstructive Lung Disease: Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med 2007; 176: 532-55
10. Guay J, Ochroch EA: Effects of adding statins before surgery on mortality and major morbidity: a meta-analysis. J Cardiothorac Vasc Anesth 2014; 28: 255-66
11. Kuhn EW, Liakopoulos OJ, Stange S, Deppe AC, Slottosch I, Scherner M, Choi YH, Wahlers T: Meta-analysis of patients taking statins before revascularization and aortic valve surgery. Ann Thorac Surg 2013; 96: 1508-16
12. Kayani WT, Bandeali SJ, Lee VV, Elayda M, Khan A, Nambi V, Jneid H, Alam M, Wilson JM, Huang HD, Birnbaum Y, Ballantyne CM, Virani SS: Association between statins and infections after coronary artery bypass grafting. Int J Cardiol 2013; 168: 117-20
13. Schlienger RG, Fedson DS, Jick SS, Jick H, Meier CR: Statins and the risk of pneumonia: a population-based, nested case-control study. Pharmacotherapy 2007; 27: 325-32
14. van de Garde EM, Hak E, Souverein PC, Hoes AW, van den Bosch JM, Leufkens HG: Statin treatment and reduced risk of pneumonia in patients with diabetes. Thorax 2006; 61: 957-61
15. McDowell SA, Ma Y, Kusano R, Akinbi HT: Simvastatin is protective during Staphylococcus aureus pneumonia. Curr Pharm Biotechnol 2011; 12: 1455-62
16. Catron DM, Lange Y, Borensztajn J, Sylvester MD, Jones BD, Haldar K: Salmonella enterica serovar Typhimurium requires nonsterol precursors of the cholesterol biosynthetic pathway for intracellular proliferation. Infect Immun 2004; 72: 1036-42
17. Kruger P, Bailey M, Bellomo R, Cooper DJ, Harward M, Higgins A, Howe B, Jones D, Joyce C, Kostner K, McNeil J, Nichol A, Roberts MS, Syres G, Venkatesh B, ANZ-STATInS Investigators-ANZICS Clinical Trials Group: A multicenter randomized trial of atorvastatin therapy in intensive care patients with severe sepsis. Am J Respir Crit Care Med 2013; 187: 743-50

Part two.

Perioperative hypotension

Chapter 6

Intraoperative hypotension and change in estimated glomerular filtration rate after major abdominal surgery: a prospective observational study

Thijs C.D. Rettig
Erik Vermeulen
Ineke M. Dijkstra
Wilton A. van Klei
Ewoudt M.W. van de Garde
Linda M. Peelen
Peter G. Noordzij

Accepted as a letter to the editor in European Journal of Anaesthesiology

ABSTRACT

Background: Approximately 7% of patients who undergo non-cardiac surgery suffer from acute kidney injury. The exact role of intraoperative hypotension (IOH) in postoperative decreased renal function is not clear.

Objective: To determine whether IOH is associated with a postoperative change in estimated glomerular filtration rate (eGFR) in patients undergoing major abdominal surgery.

Design: A secondary analysis of a prospective observational study.

Setting: Tertiary care hospital.

Patients: Two hundred two patients undergoing elective major abdominal surgery

Intervention: None.

Main outcome measures: IOH was defined according to several absolute and relative mean arterial pressure (MAP) threshold values and expressed as the area under the curve for several MAP thresholds. The eGFR was determined immediately before surgery and on the 1st, 3rd and 7th postoperative day using the Modification of Diet in Renal Disease 4 equation. The primary outcome variable was a change in eGFR expressed as a percentage of baseline eGFR. The association was investigated using linear regression analysis, both before and after adjustment for potential confounders.

Results: One hundred thirty patients (64%) in the study had a postoperative decline in eGFR (mean change -8±20%). In univariable analysis, IOH defined as a MAP below 75 mmHg and a decrease in MAP of 20% and 25% from baseline were all related to a similar change in eGFR of -0.05% (99% CI: -0.09% to -0.01%) per minute below the IOH threshold. After adjustment for confounders none of the investigated IOH threshold values were associated with a change in eGFR.

Conclusion: We did not observe an association between IOH and change in eGFR after major abdominal surgery. The different results between previous analyses and our study merits further investigation.

INTRODUCTION

Every year, 200 million patients worldwide undergo major non-cardiac surgery, 7% of which are complicated by acute kidney injury (AKI).[1-3] Although AKI does not involve clinical signs or symptoms in the majority of patients, even full recovery from a small change in serum creatinine is associated with the development of chronic kidney disease and short and long-term mortality.[3, 4]

One of the many possible factors that may contribute to postoperative AKI is a reduced renal blood flow due to intraoperative hypotension (IOH). In healthy patients renal autoregulation ensures that renal blood flow remains constant within certain levels of blood pressure.[5] Outside these levels, renal blood flow is pressure dependent and blood flow changes proportional to changes in blood pressure. Thus, when blood pressure decreases below the lower limit of autoregulation, renal blood flow decreases and renal ischemia and AKI may occur.[6]

Recently, two large retrospective cohort studies investigated the relation between IOH and AKI after non-cardiac surgery.[2, 7] Both studies showed that IOH, defined as a mean arterial pressure (MAP) below 55 mmHg, was associated with an increased risk of AKI. Pre- and postoperative serum creatinine values were not routinely measured in these studies, however, and this may have introduced bias. It is not unlikely that the number of postoperative serum creatinine measurements was unevenly distributed among patients with and without IOH, possibly obscuring the relation between IOH and AKI. Also, although serum creatinine is widely used as a marker of renal function, it may not reflect the actual degree of renal function. The estimated glomerular filtration (eGFR) rate is an alternative measure to estimate renal function and provides a more accurate assessment of the glomerular filtration rate than serum creatinine.[8]

We therefore conducted a prospective observational study in which serum creatinine was routinely measured. The aim was to determine whether IOH is associated with a postoperative change in eGFR in patients undergoing major abdominal surgery.

METHODS

Study population and design

Approval for this study was provided by the local Medical Research Ethics Committee (Research and Development Department, St. Antonius Hospital, Nieuwegein, trial number W15.032, Chairperson Prof D.H. Biesma) on 29 June 2015.

This study is a secondary analysis of the prospective observational Myocardial Injury and Complications after major abdominal surgery (MICOLON) study (ClinicalTrials.gov Identifier NCT02150486). In the MICOLON study the association between high-sensitive

cardiac troponin T levels and non-cardiac complications after major abdominal surgery was investigated in patients at risk for coronary artery disease. Eligible patients had elective major abdominal surgery (defined as an expected 30-day mortality rate >3%[9] were aged 45 years or older and had one or more major cardiovascular (CV) risk factors: diabetes, coronary artery disease (history of myocardial infarction, angina pectoris, history of ischemia or coronary artery disease on cardiac tests), congestive heart failure, peripheral artery disease (intermittent claudication or history of vascular surgery), atrial fibrillation, cerebrovascular accident, renal insufficiency (serum creatinine >150 μmol/l), decreased left ventricular function (<55%), aortic valve stenosis (valve area <1 cm^2) or 2 or more minor CV risk factors: age >70, hypertension, hypercholesterolemia, transient ischemic attack, low functional capacity (4 metabolic equivalents or less), chronic obstructive pulmonary disease. A more detailed description of the study has been previously described.[10]

The current analysis investigated the association of IOH with a postoperative change in eGFR. All patients that were included in the MICOLON study were eligible for inclusion in this study, except for patients on dialysis prior to surgery, patients without an available preoperative serum creatinine, and patients without at least one available postoperative serum creatinine.

Renal function and outcome variable

In the MICOLON study serum creatinine was routinely measured at the day of surgery immediately after induction of anaesthesia but before surgical incision, and on the 1st, 3rd and 7th postoperative day. Creatinine batch analysis was performed every three weeks with the use of an enzymatic method on an automated platform (Roche Diagnostics, Germany). In our analyses we only used creatinine values collected for this study; hence, if creatinine was not available in study-context, we did not use any creatinine values obtained from routine postoperative blood-drawings. Physicians treating study patients were blinded for creatinine values that were determined in study-context. Estimated glomerular filtration fraction was calculated using the Modification of Diet in Renal Disease 4 (MDRD-4) equation.[8]

The primary outcome was the change in eGFR, which was defined as the difference between the baseline eGFR and the lowest postoperative eGFR expressed as a percentage of the baseline eGFR value. We chose this way to define renal injury for several reasons. First, a continuous outcome variable results in less loss of information when compared with dichotomization of a continuous variable. Second, it allowed us to detect a graded toxicity (i.e. a progressive decrease in eGFR as a function of IOH). Third, eGFR represents renal function better than serum creatinine.[8] And fourth, the use of percentage change incorporates both change and baseline eGFR.

In a sensitivity analysis we used change in creatinine, defined as the difference between baseline creatinine and the highest postoperative creatinine expressed as a percentage of baseline creatinine, as outcome variable.

Blood pressure and intraoperative hypotension

At the outpatient preanaesthesia evaluation clinic blood pressure was measured using the Omron M6 device (Omron HEM-737 Intellisense, Omron Healthcare Inc., Illinois, US). The resulting MAP served as the baseline MAP in our analyses.

Intraoperative blood pressure was routinely collected in the electronic medical record system (MetaVision Suite, *iMDsoft*, Massachusetts US). In the case of invasive blood pressure monitoring MAP was recorded every minute and in the case of non-invasive blood pressure monitoring MAP was recorded every 1 to 3 minutes. In each patient the electronic medical record was manually checked for artefacts in MAP registration (by E.V. and T.R.). A MAP that was unlikely low (e.g. 25 mmHg), high (e.g. 180 mmHg) or deviant (e.g. twice as high compared to the previous and the next MAP) was considered as an artefact. In the case of an artefact or when MAP was not measured (between two non-invasive blood pressure measurements), the prior MAP was carried forward to the next (nonartifact) MAP measurement.

IOH was defined as several absolute and relative MAP threshold values and the area under the curve for several MAP threshold values. In each patient we calculated the total number of minutes spent below absolute (<45, <50, <55, <60, <65, <70 and <75 mmHg) and relative thresholds (>20%, >25%, >30%, >35%, >40%, >45% and >50% decrease from baseline). To combine depth and duration of hypotension the area under the curve (AUC) for absolute MAP threshold values (<40, <45, <50, <55, <60 and <65 mmHg) was calculated in addition (Figure 1). This variable was defined as (MAP threshold value - MAP measured) multiplied by time (minutes) spent under the MAP threshold value.

Perioperative anaesthetic management, in particular specific MAP or haematocrit goals and the use of vasopressors, was left to discretion of the attending anaesthesiologist.

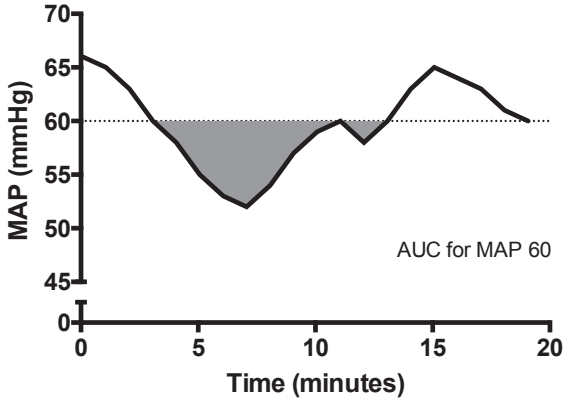

Figure 1. Area under the curve

Potential confounding variables

Potential confounders for the association of IOH and a change in eGFR were selected based on previous literature and biological plausibility and included: age, sex, use of drugs that inhibit the renin-angiotensin-aldosterone system, congestive heart failure, ASA classification, type of surgery, duration of surgery and blood loss (defined as the estimated intraoperative blood loss).[2, 3]

Statistical analysis

Continuous data are presented as mean and standard deviation (SD) or median and interquartile range (IQR) for normally and non-normally distributed data. Categorical data are described by numbers and percentages. In the univariable analysis, for categorical variables differences in change in eGFR were tested using Student's *t*-test (categorical variables with two categories) or Kruskal-Wallis test (for variables with more than two categories). For continuous variables the association with change in eGFR was tested using the Spearman's ranks correlation coefficient or Pearson correlation coefficient for non-normally and normally distributed data. Linear regression analysis was used to assess the relation of IOH with change in eGFR. These analyses were repeated for all aforementioned IOH thresholds, both as crude estimates and after adjustment for the potential confounders. We verified whether the assumptions underlying the linear regression model were met. To assess potential non-linearity of the association between IOH and change in eGFR we investigated models where the duration of IOH was included as a continuous variable directly, after square root and log transformation, and using restricted cubic splines. As log likelihood of the models did not improve significantly using the transformations, IOH was included in all subsequent modelling as a continuous variable. Effect estimates are expressed as unstandardized coefficients (betas) with their accompanying 99% confidence interval.

As use of vasopressors is possibly part of the causal pathway from IOH to postoperative change in eGFR, strictly speaking it cannot be a confounder. In addition, one would rather expect vasopressors to reduce the association of IOH on change in eGFR, if anything. However, as there is considerable discussion in the literature, we conducted a sensitivity analysis in which we additionally included vasopressor use as a potential confounder.[6, 11]

To adjust for multiple testing, we used a more stringent level of significance of $P < 0.01$ and hence present effect estimates with 99% confidence intervals. For statistical analysis IBM SPSS version 22 was used.

RESULTS

Two hundred ten patients were eligible for inclusion. Eight patients were excluded from the analysis: in three patients surgery was cancelled or aborted prematurely, in four patients blood samples were not collected due to logistic reasons and one patient had a more than fourfold increased duration of surgery compared to the average duration of surgery. The final study population consisted of 202 patients.

Mean age was 68 years and 63% of patients were male (Table 1). The majority of patients underwent colorectal or gastric-oesophageal surgery (Table 2). Sixty-one patients (30%) required intraoperative vasopressor support and 32 patients (16%) had one or more packed red blood cells transfused during the first 48 hours after surgery. Median length of postoperative hospital stay was 8 days (IQR 5-13 days) and in-hospital mortality was 4% (8/202).

Estimated glomerular filtration rate

Serum creatinine was available in all 202 patients at baseline, and in 99% (201/202), 96% (181/188), and 88% (106/121) of hospitalized patients on the 1st, 3rd and 7th postoperative day, respectively. Before surgery, the average creatinine was 76±29 μmol/L and the average eGFR was 94±29 ml/min (Table 3). After surgery, the mean creatinine increase was 14±32% and the decrease in mean eGFR 8±20%. One hundred thirty (64%) patients had a reduced postoperative eGFR and in this group of patients eGFR decreased on average with 19±15%. One patient required renal replacement therapy due to kidney failure.

Mean arterial pressure

Mean baseline MAP was 99±14 mmHg. During surgery, invasive blood pressure monitoring was performed in 120 patients (59%). In total 29.532 intraoperative MAP measurements were available for analysis. The duration of time spent under absolute and relative IOH threshold values are presented in Table 4. Intraoperative hypotension defined as a MAP below 55 mmHg was present in 93% of the patients with a median duration of 20 minutes (IQR 8-35). All but one patient experienced IOH defined as a decrease in MAP of 20% from baseline.

Relationship between MAP and change in eGFR

The association of IOH with change in eGFR is presented in Figure 2. After accounting for multiple testing, IOH defined as a MAP below 75 mmHg was associated with a change in eGFR (eGFR decreased with 0.05% for each minute spent below a MAP of 75 mmHg, 99% CI: -0.09 – -0.00, $P = 0.009$) in univariable analysis (Figure 2A). A similar association was observed for IOH defined as a decrease in MAP of 20% (-0.05%, 99% CI: -0.10 – -0.01, $P = 0.004$) and 25% from baseline (-0.05%, 99% CI: -0.09 – -0.01, $P = 0.004$, Figure 2B).

The AUC for IOH thresholds was not associated with a change in eGFR (Figure 2C). After accounting for potential confounders none of the investigated IOH definitions were associated with change in eGFR (Figure 2D-F).

Table 1. Baseline characteristics and association with change in eGFR

Variable	All (n=202)	Change in eGFR		
		For categorical variables: Mean ± SD		For continuous variables: correlation
		Variable present	Variable not present	
Age (years)	68±11			-0.034
BMI [kg/m^2 (%)]	28.4±7.3			-0.052
Baseline MAP (mmHg)	99±14			-0.012
Male gender [n (%)]	127 (62.9)	-7.8±20.3	-8.3±19.9	
Comorbidity				
Diabetes [n (%)]	59 (29.2)	-9.8±19.8	-7.3±20.2	
COPD [n (%)]	66 (32.7)	-7.6±18.6	-8.2±20.9	
Hypertension [n (%)]	147 (72.8)	-8.2±20.0	-7.5±20.5	
Hypercholesterolemia [n (%)]	94 (46.5)	-6.7±18.7	-9.0±21.3	
Congestive heart failure [n (%)]	15 (7.4)	-11.5±19.6	-7.7±20.2	
Coronary artery disease [n (%)]	48 (23.8)	-7.5±23.0	-8.1±19.2	
Peripheral artery disease [n (%)]	14 (6.9)	-3.2±17.4	-8.3±20.3	
Stroke [n (%)]	28 (13.9)	-12.2±18.6	-7.3±20.3	
Atrial fibrillation [n (%)]	28 (13.9)	-6.4±26.4	-8.2±19.0	
Malignancy [n (%)]	136 (67.3)	-7.0±18.8	-10.0±22.5	
Medication use				
Platelet inhibitor [n (%)]	60 (29.7)	-7.4±20.3	-8.2±20.1	
Statin [n (%)]	93 (46.0)	-8.8±20.4	-7.3±19.9	
β-blocker [n (%)]	80 (29.7)	-6.8±19.4	-8.7±20.6	
Calcium antagonist [n (%)]	31 (15.3)	-7.5±18.8	-8.1±20.4	
RAAS inhibitor [n (%)]	86 (42.6)	-9.0±20.8	-7.3±19.7	
Risk scores				
ASA ≥3 (%)	56 (27.7)	-9.2±19.0	-7.5±20.6	
RCRI ≥3 (%)	29 (14.4)	-12.0±25.2	-7.5±19.3	
POSSUM†	5 (2–11)			-0.075

eGFR, estimated glomerular filtration rate; BMI, body mass index; MAP, mean arterial pressure; COPD, chronic obstructive pulmonary disease; RAAS, renin-angiontensin-aldosterone system; ASA, American Association of Anesthesiologists physical status classification system; RCRI, Revised Cardiac Risk Index; POSSUM, Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity. Coronary artery disease is the composite of patients with angina pectoris or a history of myocardial infarction, coronary artery bypass grafting or percutaneous coronary angioplasty.

† estimated operative mortality according to POSSUM.

Table 2. Perioperative characteristics and association with change in eGFR

Variable	All (=202)	Change in eGFR		
		For categorical variables: Mean ± SD		For continuous variables: correlation
		Variable present	Variable not present	
Type of surgery [n (%)]				
Colorectal	103 (51.0)	-6.0±19.4	-10.1±20.7	
Gastric-oesophageal	43 (21.3)	-7.6±19.3	-8.1±20.4	
Pancreatic	21 (10.4)	-20.1±22.9	-6.6±19.3	
Gastric bypass	19 (9.4)	-7.8±22.5	-8.0±19.9	
Hepatic	9 (4.5)	-9.4±18.4	-7.9±20.2	
Other	7 (10.4)	-11.3±9.5	-7.9±20.3	
Epidural anaesthesia [n (%)]	138 (68.3)	-9.7±18.4	-4.4±23.0	
Vasopressor support during surgery [n (%)]	61 (30.2)	-11.9±28.8	-6.3±18.1	
PRBC transfusion [n (%)]	32 (15.8)	-9.1±22.7	-7.8±19.6	
Blood loss (L)	0.10 (0.03–0.26)			-0.186
Fluid balance after surgery (L)	1.9 (1.3–2.9)			-0.139
Duration of surgery (min)	135 (90–180)			-0.157
Preoperative hemoglobin (mmol/L)	7.9±1.2			-0.096

n.a. not applicable; PRBC, packed red blood cell; other abbreviations as in Table 1

Table 3. Perioperative kidney function data

Variable	Value
Preoperative creatinine (μmol/L)	76±29
Peak postoperative creatinine (μmol/L)	86±40
Δ creatinine (μmol/L)	10±25
% Δ creatinine (%)	14±32
Preoperative eGFR (ml/min)	94±29
Nadir eGFR (ml/min)	86±30
Δ eGFR (ml/min)	-9±18
% Δ eGFR (%)	-8±20
Postoperative dialysis	1 (0.5)

Δ creatinine, defined as the difference between peak postoperative and preoperative creatinine; % Δ creatinine, defined as peak postoperative creatinine fractional change; eGFR, estimated glomerular filtration rate calculated using the Modification of Diet in Renal Disease 4 (MDRD-4) equation; Δ eGFR, defined as the difference between nadir postoperative and preoperative eGFR; % Δ eGFR defined as nadir postoperative eGFR fractional change; abbreviations as in Tables 1 and 2.

Table 4. Time (minutes) spent under absolute and relative MAP thresholds

Threshold	Median	IQR	Patients without time spent under threshold (%)
Absolute (mmHg)			
<75	120	74-173	1 (0.5)
<70	98	58-142	1 (0.5)
<65	65	39-103	3 (1.5)
<60	37	20-68	9 (4.5)
<55	20	8-35	14 (6.9)
<50	8	3-18	30 (14.9)
<45	2	0-6	72 (35.6)
Relative (%)			
<20	121	71-174	1 (0.5)
<25	98	58-158	1 (0.5)
<30	74	36-135	3 (1.5)
<35	51	23-108	8 (4.0)
<40	28	9-75	21 (10.4)
<45	15	3-43	34 (16.8)
<50	6	0-21	60 (29.7)

MAP, mean arterial pressure; IQR, interquartile range

We performed two sensitivity analyses. In the first analysis, the addition of vasopressor use to the multivariable model decreased the effect of all absolute and relative IOH definitions on change in eGFR with increased levels of significance (Figure 3). The effect of IOH defined as AUC for MAP thresholds was also decreased with similar increased levels of significance, except AUC for MAP 65, 60 and 55 mmHg. In the other sensitivity analysis with change in creatinine instead of change in eGFR as outcome variable, univariable analysis showed that several IOH definitions were associated with change in creatinine but this was not observed in multivariable analysis (Figure 4).

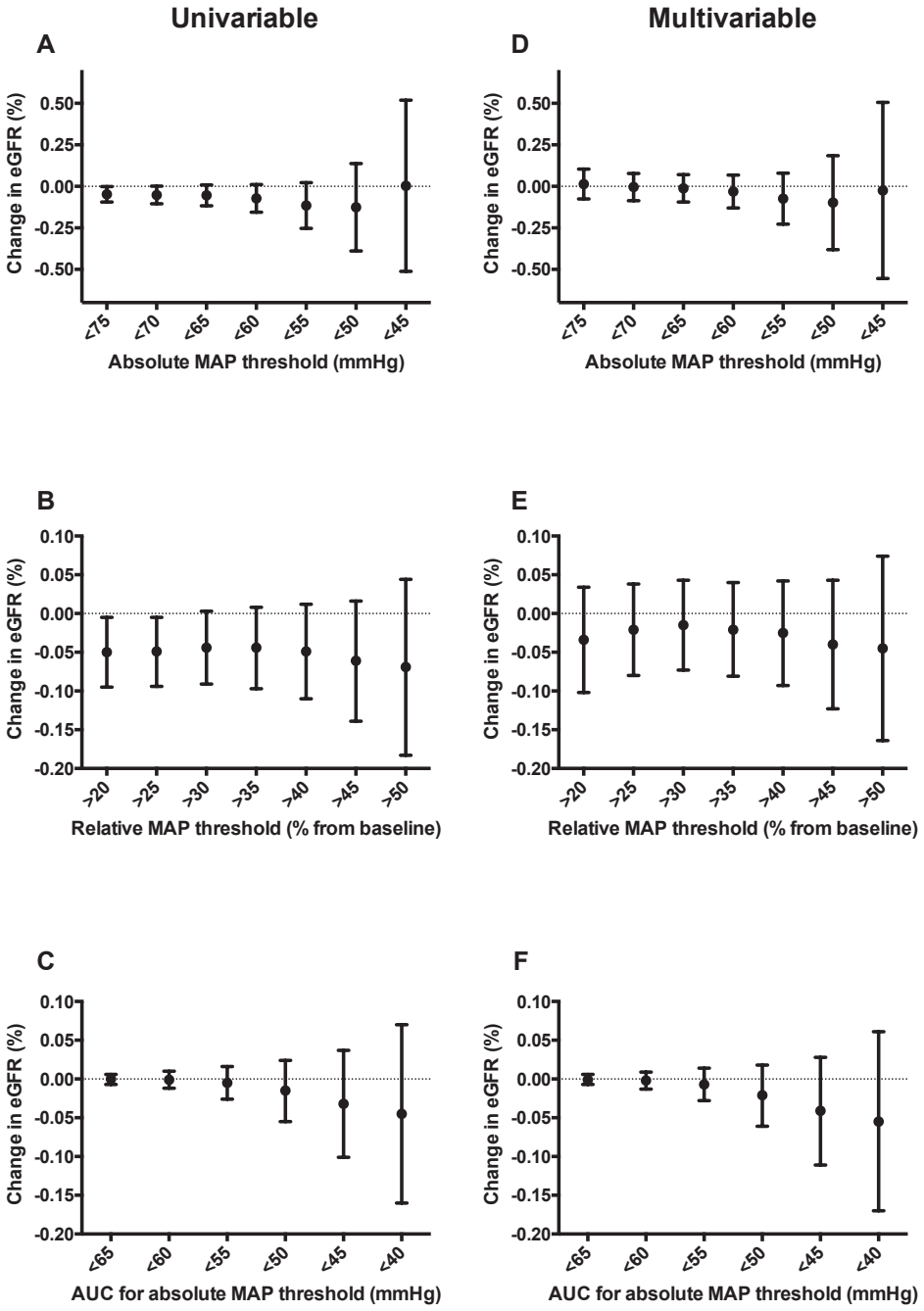

Figure 2. Uni- (A-C) and multivariable (D-F) analysis of absolute and relative MAP threshold values and AUC for MAP thresholds and change in eGFR

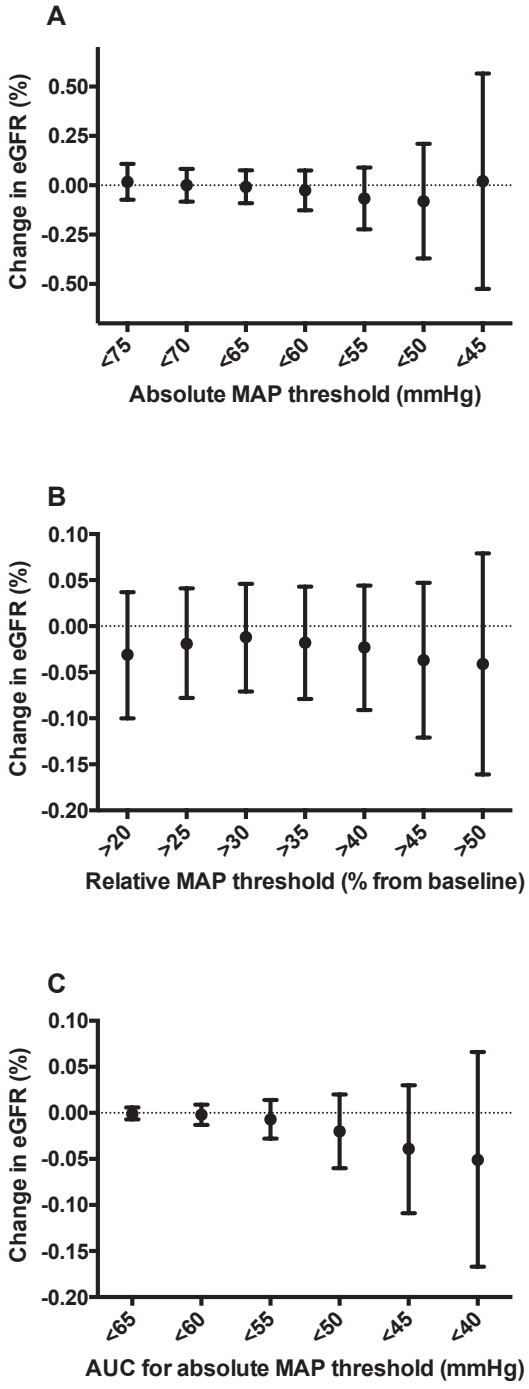

Figure 3. Multivariable analysis of absolute and relative MAP threshold values and AUC for MAP thresholds and change in eGFR with the addition of vasopressor use as a potential confounder

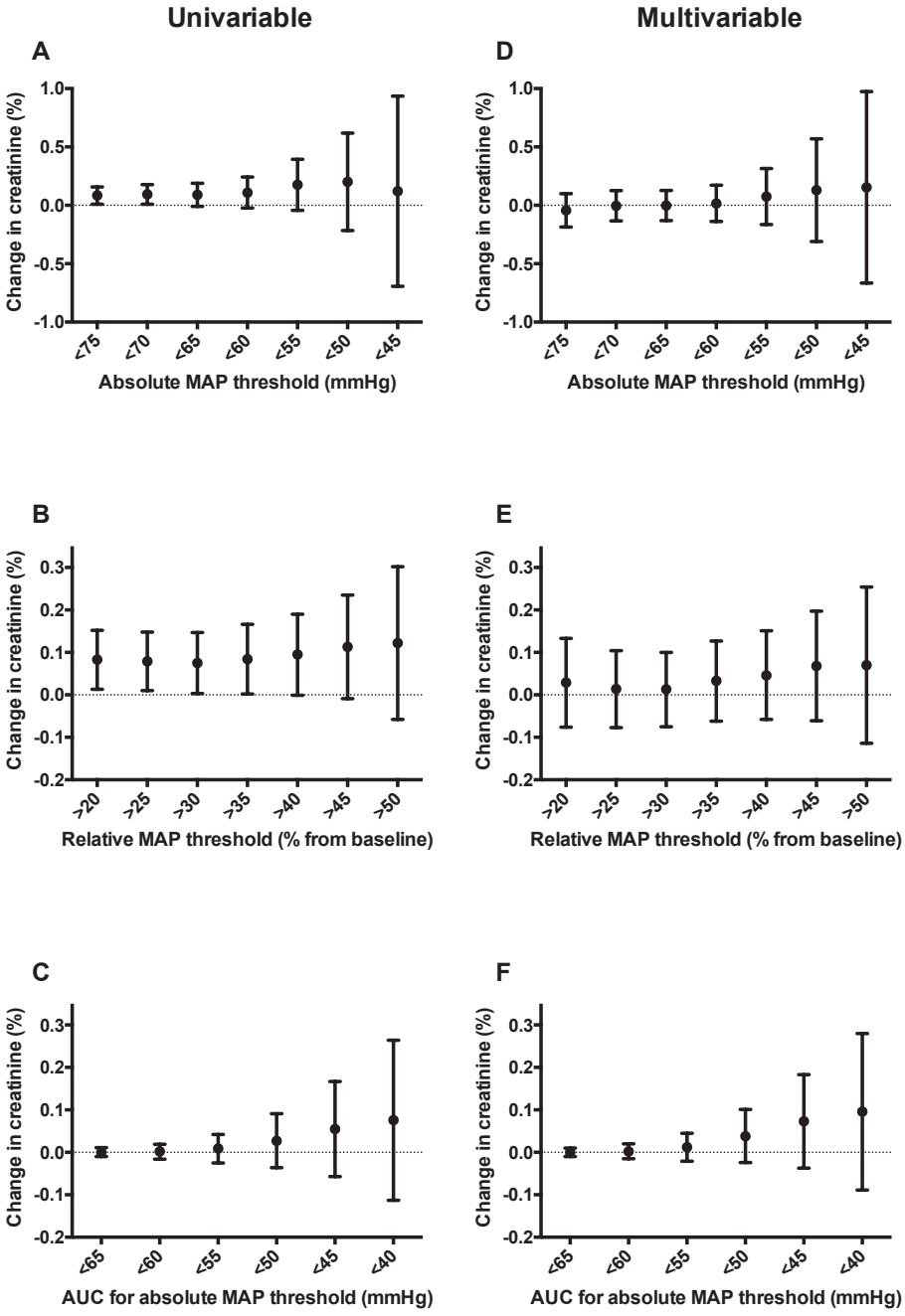

Figure 4. Uni- (A-C) and multivariable (D-F) analysis of absolute and relative MAP threshold values and AUC for MAP thresholds and change in creatinine

DISCUSSION

The eGFR decreased in approximately two-thirds of patients undergoing major abdominal surgery with on average 8%. In this analysis, IOH was not associated with a statistically significant change in eGFR after surgery.

The potential influence of intraoperative arterial perfusion pressure on organ function preservation is an ongoing debate, but IOH during surgery may be one of the possible causes of postoperative AKI. Recently, Walsh et al. and Sun et al. investigated the association between IOH and AKI in patients undergoing non-cardiac surgery.[2, 7] Both retrospective cohort studies found that in multivariable analysis IOH, defined as a MAP below 55 mmHg, was associated with an increased risk of AKI. This risk escalated with an increasing duration of time spent under this threshold. The results of these studies were reinforced by their large sample size. Our study differs in several ways from these analyses. As we were able to prospectively investigate the relation of IOH with a change in eGFR after surgery, we had highly detailed information on perioperative renal function available for all study patients. Instead of using creatinine values that were determined by treating physicians depending on medical indication (resulting in an increased risk of confounding by indication), we systematically performed creatinine measurements immediately prior to surgery and on the 1st, 3rd and 7th postoperative day. In contrast to prior studies, creatinine measurements were available in the vast majority of the patients on all days. We used eGFR as a primary outcome variable because it represents renal function better than creatinine, which is generally used.[8] Traditionally, a postoperative decline in renal function is dichotomized at a creatinine level of 1.5 - 1.9 times baseline or an increase $\geq$ 0.3 mg/dl ($\geq$ 26.5 µmol/l).[12] Although categorisation of continuous variables is often done to simplify statistical analysis, in reality the change renal function is not a binary variable. Dichotomizing a continuous variable increases the chance of a type 1 error ('false positive') and may result in finding an association that is actually not there.[13, 14] The use of a continuous variable as outcome measure allowed us to detect a graded toxicity of IOH on change in eGFR. Another difference with the previous analysis is that we used a stricter level of significance to adjust for testing multiple IOH thresholds.

Vasopressors were administered in approximately 30% of patients during surgery. When we included vasopressor use in our multivariable model, the effect of IOH on change in eGFR decreased. In statistical terms, after the addition of vasopressor use, change in eGFR for all investigated IOH thresholds in the primary analysis (eGFR decreased but without statistical significance) was distributed among the 'individual' variables IOH and vasopressor use. Although we are cautious in drawing conclusions from this observation, this may support the idea that the use of vasopressors may contribute to a decrease in eGFR. In a study of Kheterpal et al. predictors of renal failure after non-

cardiac surgery were identified and vasopressor use during surgery was an independent predictor of postoperative AKI.[15] However, since well-designed trials on this topic are lacking, it is unclear if this relationship implies correlation or causality.

Several limitations of this study need to be discussed. First, we did not observe an association between IOH and change in eGFR, but this does not necessarily exclude the presence of a relation between these two. A closer investigation of the effect estimates may suggest a general trend toward renal injury as blood pressure declines. Although we used a continuous outcome variable that typically increases power, a larger sample size would have resulted in a more precise effect estimate and possibly statistically significant association between IOH and change in eGFR. However, the effect estimates of change in eGFR per minute IOH had not been studied before and could lead to a more reasonable understanding of the strength of the association between IOH and change in eGFR. Our results could serve as a basis for power analyses and sample size calculations in future studies. A second limitation of this study lies in the fact that the eGFR is not validated for patients with unstable creatinine values as in the perioperative setting.[16] Nevertheless, the perioperative use of eGFR is recommended by others and our results did not change when we used change in creatinine instead of change in eGFR as primary outcome variable.[17] Third, the mean change in creatinine and eGFR were relatively small and in most cases well below the AKI threshold according to the RIFLE and AKIN criteria.[12] Previous prognostic studies however, showed the clinical importance of creatinine changes less than these criteria. Any increase in creatinine after surgery is associated with an increased risk of mortality compared to patients with stable of decreased postoperative creatine values.[18, 19] And fourth, we cannot comment on the association of change in eGFR and IOH threshold values lower than the ones we studied.

In the current analysis, a decrease in eGFR occurred in the majority of patients undergoing major abdominal surgery. We did not observe an association between IOH and change in eGFR, although we cannot exclude that our study was underpowered to detect a statistically significant relation. The different results between previous literature and our study merits further investigation.

REFERENCES

1. Weiser TG, Regenbogen SE, Thompson KD, Haynes AB, Lipsitz SR, Berry WR, Gawande AA: An estimation of the global volume of surgery: a modelling strategy based on available data. Lancet 2008; 372: 139-44
2. Walsh M, Devereaux PJ, Garg AX, Kurz A, Turan A, Rodseth RN, Cywinski J, Thabane L, Sessler DI: Relationship between intraoperative mean arterial pressure and clinical outcomes after noncardiac surgery: toward an empirical definition of hypotension. Anesthesiology 2013; 119: 507-15
3. Abelha FJ, Botelho M, Fernandes V, Barros H: Determinants of postoperative acute kidney injury. Crit Care 2009; 13: R79
4. Heung M, Chawla LS: Acute kidney injury: gateway to chronic kidney disease. Nephron Clin Pract 2014; 127: 30-4
5. Hill JV, Findon G, Appelhoff RJ, Endre ZH: Renal autoregulation and passive pressure-flow relationships in diabetes and hypertension. Am J Physiol Renal Physiol 2010; 299: F837-44
6. Bellomo R, Wan L, May C: Vasoactive drugs and acute kidney injury. Crit Care Med 2008; 36: S179-86
7. Sun LY, Wijeysundera DN, Tait GA, Beattie WS: Association of intraoperative hypotension with acute kidney injury after elective noncardiac surgery. Anesthesiology 2015; 123: 515-23
8. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D: A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 1999; 130: 461-70
9. Noordzij PG, Poldermans D, Schouten O, Bax JJ, Schreiner FA, Boersma E: Postoperative mortality in The Netherlands: a population-based analysis of surgery-specific risk in adults. Anesthesiology 2010; 112: 1105-15
10. Noordzij PG, van Geffen O, Dijkstra IM, Boerma D, Meinders AJ, Rettig TC, Eefting FD, van Loon D, van de Garde EM, van Dongen EP: High-sensitive cardiac troponin T measurements in prediction of non-cardiac complications after major abdominal surgerydagger. Br J Anaesth 2015; 114: 909-18
11. Sear JW: Kidney dysfunction in the postoperative period. Br J Anaesth 2005; 95: 20-32
12. Kidney Disease: Improving Global Outcomes (KDIGO) Lipid Work Group. KDIGO Clinical Practice Guideline for Lipid Management in Chronic Kidney Disease. *Kidney inter*., Suppl. 2013; 3: 259–305.
13. Royston P, Altman DG, Sauerbrei W: Dichotomizing continuous predictors in multiple regression: a bad idea. Stat Med 2006; 25: 127-41
14. Austin PC, Brunner LJ: Inflation of the type I error rate when a continuous confounding variable is categorized in logistic regression analyses. Stat Med 2004; 23: 1159-78
15. Kheterpal S, Tremper KK, Englesbe MJ, O'Reilly M, Shanks AM, Fetterman DM, Rosenberg AL, Swartz RD: Predictors of postoperative acute renal failure after noncardiac surgery in patients with previously normal renal function. Anesthesiology 2007; 107: 892-902
16. Nguyen MT, Maynard SE, Kimmel PL: Misapplications of commonly used kidney equations: renal physiology in practice. Clin J Am Soc Nephrol 2009; 4: 528-34
17. Wijeysundera DN, Karkouti K, Beattie WS, Rao V, Ivanov J: Improving the identification of patients at risk of postoperative renal failure after cardiac surgery. Anesthesiology 2006; 104: 65-72
18. Kork F, Balzer F, Spies CD, Wernecke KD, Ginde AA, Jankowski J, Eltzschig HK: Minor Postoperative Increases of Creatinine Are Associated with Higher Mortality and Longer Hospital Length of Stay in Surgical Patients. Anesthesiology 2015; 123: 1301-11

19. Lassnigg A, Schmidlin D, Mouhieddine M, Bachmann LM, Druml W, Bauer P, Hiesmayr M: Minimal changes of serum creatinine predict prognosis in patients after cardiothoracic surgery: a prospective cohort study. J Am Soc Nephrol 2004; 15: 1597-605

Chapter 7

Impact of intraoperative hypotension during cardiopulmonary bypass on acute kidney injury after coronary artery bypass grafting

Thijs C.D. Rettig
Linda M. Peelen
Guillaume S.C. Geuzebroek
Wilton A. van Klei
Christa Boer
Jan Willem van der Veer
Jan Hofland
Ewoudt M.W. van de Garde
Peter G. Noordzij

Accepted in Journal of Cardiothoracic and Vascular Anesthesia

ABSTRACT

Objective: The aim of this study was to investigate whether AKI after coronary artery bypass grafting (CABG) can be attributed to intraoperative hypotension during cardiopulmonary bypass (IOH-CPB).

Design: Retrospective analysis.

Setting: Tertiary-care hospital.

Participants: Patients undergoing on-pump coronary artery bypass grafting (CABG) from June 2011 until January 2014.

Interventions: None.

Measurements and Main Results: IOH-CPB was defined as blood pressure below several absolute and relative mean arterial pressure (MAP) thresholds and as the area under the curve (AUC) for absolute MAP thresholds. AKI was defined as an absolute increase in serum creatinine of ≥ 26 μmol/L within 48 hours or an increase to 150% or more within 7 days of surgery. Poisson regression with robust standard errors both before and after adjustment for confounders was used.

Of the 1891 included patients, 386 (20%) developed AKI. In univariable analysis all IOH-CPB thresholds defined as a MAP of 50 mmHg or less and as a decrease in MAP of 60% from baseline were associated with a 1.07 to 1.11 times increased risk of AKI per 10 minutes of IOH-CPB ($P < 0.01$). After adjustment for potential confounders, IOH-CPB, irrespective of the definition chosen, was not associated with an increased risk of AKI.

Conclusions: In our study population, univariable analysis showed an association of IOH-CPB with AKI in patients undergoing isolated CABG, but this relationship disappeared after correction for well-known risk factors for AKI.

INTRODUCTION

Each year over one million coronary artery bypass graft (CABG) procedures are performed in Europe and the United States alone.[1] A major determinant of outcome after CABG is the development of postoperative acute kidney injury (AKI), which occurs in up to 30% of the patients.[2, 3] A recently published report showed that the occurrence of AKI after cardiac surgery increased in the past decade.[4] Although this effect is at least partially explained by better coding practices, these data also indicate that the pathophysiological mechanisms of AKI after cardiac surgery are still not fully understood, which hampers development and use of preventive or treatment strategies.

The use of cardiopulmonary bypass (CPB) is a well-recognized cause of AKI after cardiac surgery.[5] Exposure of blood to the CPB circuit and the surgical trauma itself induces a systemic inflammatory response and may lead to a reduced glomerular filtration rate through, for example, glomerular fibrin deposition.[6] Also, oxygen delivery to the renal medulla may be compromised by severe hemodilution during CPB.[7] The role of intraoperative hypotension during CPB (IOH-CPB) in the development of postoperative AKI is unclear.

A randomized controlled trial in 300 patients undergoing cardiac surgery compared a mean arterial pressure (MAP) of 75-85 mmHg with 50-60 mmHg during CBP and reported similar AKI rates in both groups.[8] In a comparable study performed in the early nineties, 248 patients randomized to a MAP of 80-100 mmHg during CPB seemed to have fewer cardiac and neurologic complications compared to patients randomized to a MAP of 50-60 mmHg, but the incidence of AKI was not assessed.[9] From these few studies, with a limited number of patients, it cannot be concluded whether IOH-CPB is involved in the pathophysiology of AKI after cardiac surgery.[10] In addition, the MAP targeted in these studies is higher than in daily practice and other than absolute IOH thresholds, such as a decrease in MAP from baseline or the area under the curve (AUC) below IOH thresholds were not investigated. The aim of this study was to determine whether IOH-CPB was associated with the development of AKI using various definitions of IOH-CPB in a large cohort of patients undergoing CABG.

METHODS

Study population and design

All patients who underwent a CABG procedure from June 2011 until January 2014 in the St. Antonius Hospital, Nieuwegein, The Netherlands, with an available serum creatinine within seven days prior to surgery and at least one available serum creatinine within seven days after surgery were eligible for inclusion in this observational retrospective

study. Exclusion criteria were renal replacement therapy prior to surgery, unavailable perioperative blood pressure values, off-pump or concomitant open chamber surgery and postoperative extracorporeal membrane oxygenation.

The local Medical Research Ethics Committee approved the study and waived the need for informed consent (Research and Development Department, St. Antonius Hospital, trial number W15.024).

Anesthetic and surgical management

Routine perioperative care included induction of anesthesia with propofol, midazolam, fentanyl and pancuronium and maintenance of anesthesia with propofol and fentanyl or remifentanil. All patients received antimicrobial prophylaxis (cefazolin) at induction of anesthesia followed by additional cefazolin every four hours for the duration of surgery. After sternotomy heparin was intravenously administered and at the end of surgery neutralized by protamine. For CPB nonpulsatile perfusion was used with a flow of 2.0 to 2.4 L/min/m^2. After aortic cross-clamping, cardiac arrest was initiated using a cold crystalloid (Bleese) or blood (in case of minimal extracorporeal circulation) cardioplegic solution. Patients were cooled to a nasopharyngeal temperature of 32°C to 35°C. Before separation from CPB patients were rewarmed to a nasopharyngeal temperature of at least 35.5°C.

Intraoperative management targeted a hematocrit of 22% and a SvO2 of 65%. The MAP during CPB was left to discretion of the attending anesthesiologist and was dependent on the medical history (e.g. hypertension, stroke). In general, a MAP of 45 to 50 mmHg was targeted during CPB. Red blood cell transfusion trigger was a hematocrit of 20% during CPB and a hematocrit of 25% after separation from CPB. After the surgical procedure all patients were admitted at the Intensive Care Unit for at least 24 hours.

Acute kidney injury

Serum creatinine was routinely measured as part of standard postoperative laboratory tests on postoperative day one, two and five. In some patients, additional creatinine measurements were available if ordered by the treating physician, and these were also included in our analyses. Creatinine analysis was performed with the use of an enzymatic method on an automated platform (Roche Diagnostics, Germany).

The primary outcome was development of postoperative AKI. Acute kidney injury was defined according to the 2011 Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Acute Kidney Injury: an absolute increase in serum creatinine of ≥ 26 µmol/L within 48 hours or an increase in serum creatinine to 150% or more within 7 days.[11]

Blood pressure and IOH-CPB

Preoperatively, blood pressure was measured using the Omron M6 (Omron HEM-737 Intellisense, Omron Healthcare Inc., Illinois, US) at the outpatient preanesthesia evaluation clinic. Blood pressure was measured in the sitting position with the cuff on the upper arm. The MAP resulting from this measurement served as the baseline MAP used in clinical practice and in our analyses. During surgery, the MAP was invasively monitored and recorded every minute in the electronic medical record system (MetaVision Suite, *i*MD*soft*, Massachusetts US). IOH-CPB was defined according to several absolute and relative MAP threshold values. We calculated the time spent below absolute (<40, <45, <50, <55, <60 and <65 mmHg) and relative MAP thresholds (>35%, >40%, >45%, >50%, >55% and >60% decrease from baseline) in each patient. In addition, we calculated the area under the curve (AUC) for absolute MAP threshold values (<40, <45, <50, <55, <60 and <65 mmHg). The area under the curve was defined as the sum of each blood pressure (MAP threshold value - MAP measured) multiplied by time (minutes) spent under the MAP threshold value.

Data collection and confounder selection

Medical history and preoperative drug therapy were registered at the outpatient preanesthesia evaluation clinic. Intra- and postoperative data were routinely collected in the electronic medical record system. Potential confounders for the association of IOH-CPB and postoperative AKI were selected based on previous literature and biological plausibility and included: age, sex, diabetes (+type), hypertension, left ventricular ejection fraction (LVEF), preoperative hemoglobin, preoperative creatinine, EuroSCORE, critical preoperative state (defined as ventricular tachycardia or fibrillation or aborted sudden death, preoperative cardiac massage, preoperative ventilation before arrival in the operating room, preoperative inotropic support or intra-aortic balloon counter pulsation), allogeneic red blood cell (RBC) transfusion during surgery, autologous RBC transfusion during surgery and duration of CPB.[12, 13]

Missing data

Omitting patients with missing data from the analyses (so-called complete case analysis) can result in biased effect estimates, as missing data typically does not occur completely at random, but are associated with patient characteristics. To overcome this problem, we conducted multiple imputation analysis, a well-accepted statistical technique to model the values that are missing and incorporate these into the analyses in the appropriate way. We used ten imputation sets; analyses were conducted in each of the imputation sets, and resulting estimates from each of these sets were pooled and adjusted standard errors were calculated using Rubin's rule.[14-16]

Statistical analysis

Baseline and perioperative characteristics were compared for patients with and without AKI. Continuous data are presented as mean and standard deviation (SD) or median and interquartile range (IQR) for normally and non-normally distributed data. Categorical data are described as numbers and percentages. The Student's t-test and the Mann-Whitney U test were used to compare independent continuous variables between patient with and without AKI for normally and non-normally distributed variables respectively. The Fisher's exact test and the Pearson chi-squared test were used to compare categorical variables between patients with and without AKI when appropriate.

Subsequently we assessed the association between IOH-CPB and AKI using regression analysis. We conducted Poisson regression analysis with robust standard errors and present resulting effect estimates as risk ratios (RR) with accompanying confidence intervals.[17] These analyses were conducted using only IOH-CB within the models (crude estimate) and after adjustment for the aforementioned potential confounders. We included IOH-CPB in the analyses as a continuous variable. To assess potential non-linearity of the association between IOH-CPB and AKI we investigated models where duration of IOH-CPB was included as a continuous variable, and after square root or log transformation, and compared their model fit based on log likelihood of the model. All analyses were repeated for all aforementioned IOH-CPB thresholds. To adjust for multiple testing, we used a more stringent level of significance of $P < 0.01$ and hence present effect estimates with 99% confidence intervals. For statistical analysis IBM SPSS version 22 was used.

RESULTS

During the study period 1983 patients were eligible for analysis. After the exclusion of patients requiring renal replacement therapy prior to surgery (n=10), patients who underwent off-pump or concomitant open chamber surgery (n=47), patients without an available preoperative or without at least one available postoperative creatinine (n=24) and patients without perioperative blood pressure values available (n=13) the final study population consisted of 1891 patients (95%).

The mean age was 67 years and 79% of the patients were male (Table 1). The most common comorbidities were hypertension (60%), diabetes (25%) and prior myocardial infarction (25%). Almost a quarter of the patients had a reduced LVEF. The average baseline MAP was 98±13 mmHg and the mean baseline creatinine was 88±24 μmol/L. During CPB the average MAP was 55±9 mmHg. The median EuroSCORE was three (IQR 2-5) and 151 patients (8%) underwent an emergency procedure (Table 2). The mean duration of CPB and aortic cross-clamping was 89±39 and 57±27 minutes, respectively. Two hundred thirty three patients (12%) received intraoperative allogeneic RBC transfusion.

Baseline and perioperative characteristics according to complete and incomplete cases are shown in Supplementary Table 1 and 2.

Table 1. Baseline characteristics

Variable	All (n=1891)	AKI (n=386)	No AKI (n=1505)	*p*-value	Incomplete
Male gender [n (%)]	1488 (78.7)	296 (76.7)	1192 (79.2)	0.281	0
Age (years)	67±10	70±9	66±10	<0.001	0
BMI [kg/m^2 (%)]	27.6±4.4	28.4±4.8	27.3±4.3	<0.001	0
Comorbidity					
COPD [n (%)]	134 (7.1)	40 (10.4)	94 (6.2)	0.005	0
Diabetes [n (%)]					0
- Insulin dependent	153 (8.1)	51 (13.2)	102 (6.8)	<0.001	
- Non-insulin dependent	317 (16.8)	86 (22.3)	231 (15.3)		
Hypertension [n (%)]	1136 (60.1)	265 (68.7)	871 (57.9)	<0.001	0
Congestive heart failure [n (%)]	29 (1.5)	14 (3.6)	15 (1.0)	<0.001	0
Myocardial infarction [n (%)]	466 (24.6)	107 (27.7)	359 (23.9)	0.116	0
Peripheral artery disease [n (%)]	184 (10.0)	64 (16.9)	120 (8.2)	<0.001	42 (2.2)
Previous stroke [n (%)]	72 (3.8)	24 (6.2)	48 (3.2)	0.006	0
Previous cardiac surgery [n (%)]	54 (2.9)	18 (4.8)	36 (2.4)	0.017	42 (2.2)
Pulmonary hypertension [n (%)]	3 (0.2)	2 (0.5)	1 (0.1)	0.108	42 (2.2)
LVEF [n (%)]					2 (0.1)
- > 50%	1462 (77.4)	263 (68.3)	1199 (79.7)	<0.001	
- > 30% and ≤50%	368 (19.5)	95 (24.7)	273 (18.2)		
- ≤ 30%	59 (3.1)	27 (7.0)	32 (2.1)		
Baseline MAP (mmHg)	98±13	98±14	98±13	0.977	412 (21.8)
Laboratory values					
Preoperative creatinine (μmol/L)	88±24	103±34	84±19	<0.001	0
Preoperative hemoglobin (mmol/L)	8.5±0.9	8.1±1.0	8.6±0.8	<0.001	130 (6.9)

Values are mean (standard deviation) or absolute number (percentage). The Student's T-test was used to test for the association of continuous variables and AKI. The Fisher's exact test and the Pearson chi-squared test were used to test for the association of categorical variables and AKI when appropriate.
BMI indicates body mass index; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; MAP, mean arterial pressure

The times spent below the investigated IOH-CPB thresholds studied are presented in Table 3. All but 37 patients (2%) experienced IOH-CPB defined as a MAP below 50 mmHg with a median duration of 28 minutes (IQR 13-47). The median duration of IOH-CPB defined as a decrease in MAP of 60% from baseline was six minutes (IQR 1-16).

After surgery, 386 patients (20%) suffered from AKI and eight patients (0.4%) required renal replacement therapy due to kidney failure. The median length of hospital stay was seven (IQR 5-10) and five (IQR 3-6) days in patients with and without AKI, respectively ($P < 0.001$). In-hospital mortality was 3.1% in patients with AKI and 0.4% in patients without AKI ($P < 0.001$).

Table 2. Perioperative characteristics

Variable	All (n=1891)	AKI (n=386)	No AKI (n=1505)	*p*-value	Incomplete
Operative					
Emergency procedure [n (%)]	151 (8.2)	46 (12.2)	105 (7.1)	0.001	42 (2.2)
Critical preoperative state [n (%)]	49 (2.7)	24 (6.3)	25 (1.7)	<0.001	42 (2.2)
EuroSCORE	3 (2-5)	5 (3-7)	3 (1-5)	<0.001	42 (2.2)
Duration of CPB (min)	89±39	95±64	87±29	0.028	0
Duration of aortic cross-clamping (min)	57±27	58±23	57±28	0.838	215 (11.4)
Average MAP during CPB (mmHg)	55±9	55±11	56±9	0.046	0
Intraoperative RBC transfusion [n (%)]	233 (12.3)	95 (24.6)	138 (9.2)	<0.001	0
Outcome					
Resternotomy [n (%)]	71 (3.8)	33 (8.5)	38 (2.5)	<0.001	0
Length of stay (days)	5 (4-7)	7 (5-10)	5 (3-6)	<0.001	14 (0.7)
In-hospital mortality [n (%)]	18 (1.0)	12 (3.1)	6 (0.4)	<0.001	10 (0.5)

Values are mean (standard deviation), median (interquartile range) or absolute number (percentage). The Student's T-test and the Mann-Whitney U test were used to test for the association of normally and non-normally distributed continuous variables and AKI. The Fisher's exact test and the Pearson chi-squared test were used to test for the association of categorical variables and AKI when appropriate.
CPB indicates cardiopulmonary bypass; MAP, mean arterial pressure; RBC transfusion, red blood cell transfusion; AKI, acute kidney injury

Table 3. Time (minutes) spent under absolute and relative MAP thresholds according to the occurrence of AKI.

Threshold	No AKI	AKI	*P* value
Absolute (mmHg)			
<65	63 (42-83)	68 (47-88)	0.009
<60	53 (31-74)	60 (37-80)	<0.001
<55	40 (21-61)	47 (26-70)	<0.001
<50	26 (13-46)	34 (16-54)	<0.001
<45	15 (6-29)	19 (8-35)	<0.001
<40	7 (2-14)	8 (3-17)	0.004
Decrease from baseline (%)			
<35	58 (36-81)	65 (43-86)	0.005
<40	48 (26-73)	54 (32-77)	0.010
<45	35 (17-60)	41 (23-66)	0.005
<50	23 (9-45)	26 (11-53)	0.016
<55	12 (4-29)	15 (6-34	0.055
<60	5 (1-15)	6 (2-17)	0.043

Values are median and interquartile range
MAP indicates mean arterial pressure

The association between IOH-CPB and AKI is presented in Figure 1. As transformation of duration of IOH-CPB did not improve model fit, we included duration of IOH-CPB expressed in minutes in all subsequent models. In univariable analysis the risk of AKI

increased when the duration of IOH-CPB increased for absolute and relative IOH-CPB thresholds (Figure 1A and 1B) or when the AUC for IOH-CPB thresholds increased (Figure 1C) and this was more pronounced for the lowest IOH-CPB thresholds. For example, for IOH-CPB defined as a MAP of 65 mmHg the risk of AKI increased by 1.004 (99% confidence interval (CI): 1.000 - 1.007) per minute below this threshold and the risk increased

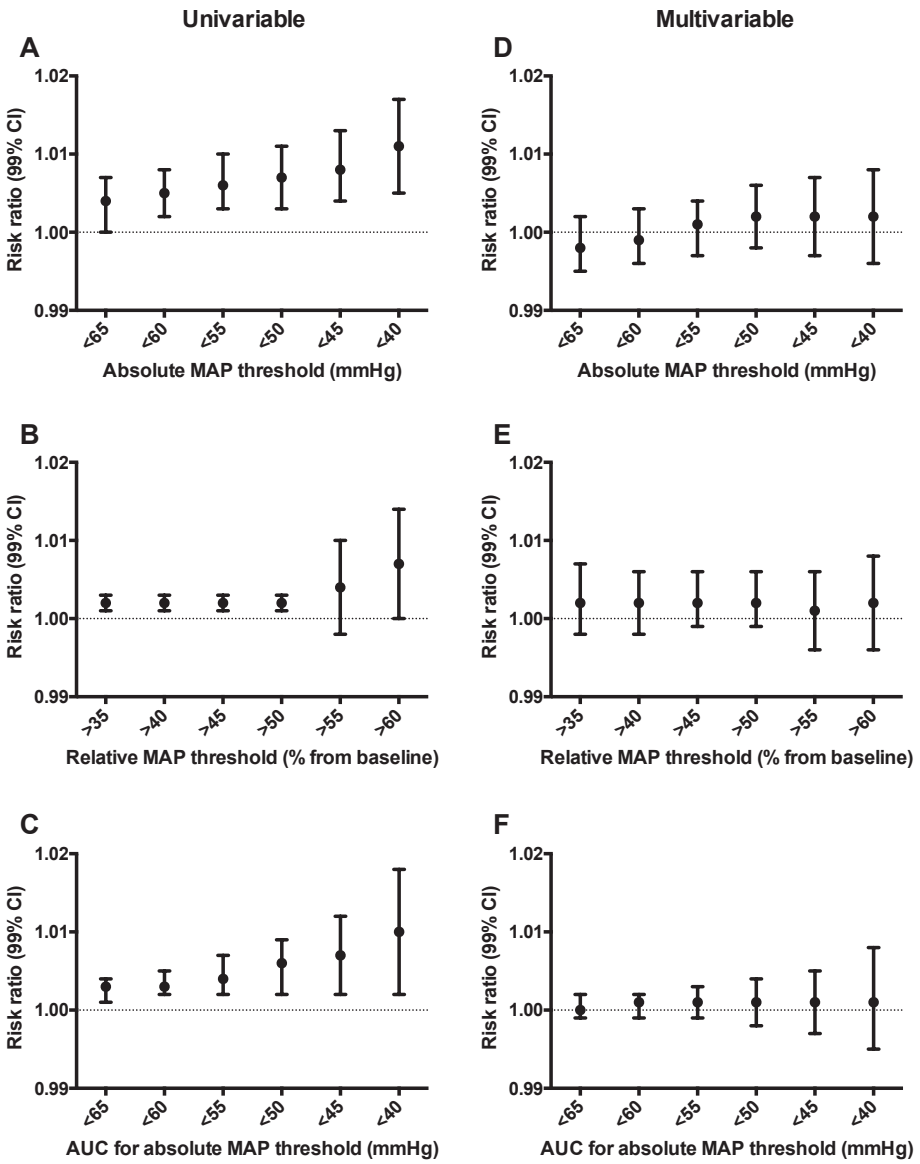

Figure 1. Uni- and multivariable analysis of absolute and relative MAP threshold values and AUC for MAP thresholds and AKI

to 1.011 (99% CI: 1.005 - 1.017) per minute for IOH-CPB defined as a MAP of 40 mmHg. This means that a patient who has a MAP below 40 mmHg for 10 minutes has a 1.011^{10} = 1.12 times higher risk to develop AKI postoperatively when compared to a patient whose MAP stays above 40 mmHg. After accounting for potential confounders none of the IOH-CPB thresholds were associated with AKI (Figure 1D-F).

DISCUSSION

In this study including 1891 patients undergoing on-pump CABG, the incidence of postoperative AKI was 20% and 0.4% of patients required renal replacement therapy. IOH-CPB was not associated with an increased risk of postoperative AKI.

Previous studies have shown that AKI or even a slight increase of serum creatinine that does not even meet the AKI criteria is associated with morbidity and mortality after surgery.[18] Whether postoperative AKI results from IOH-CPB is a matter of debate. Recently, several large retrospective analyses have addressed this topic in non-cardiac surgery and most of the studies carried out point to an association between IOH and AKI. For example, Walsh et al. showed that a short duration of IOH defined as a MAP of 55 mmHg increased the risk of AKI after non-cardiac, non-urological surgery and Sun et al. reported similar findings in a smaller but more detailed investigation.[19, 20] The question is to what extent we can extrapolate these results from non-cardiac surgery to cardiac surgery. We performed a large retrospective analysis in patients undergoing on-pump CABG in which pre-and postoperative serum creatinine was routinely measured. Our results did not show an association between IOH-CPB and AKI. This is in accordance with the results of Azau et al.[8] They randomized 300 patients undergoing elective cardiac surgery to a MAP during CPB of 50-60 mmHg vs. 75-85 mmHg, and did not find an association with postoperative AKI, despite investigating different definitions for AKI. Haase et al. retrospectively investigated 920 patients undergoing on-pump cardiac surgery.[21] Twenty percent of the patients developed AKI and this was not dependent on IOH-CPB. The combination of severe hypotension (>75th percentile of the AUC for MAP 50 mmHg) and severe anemia (<25th percentile of the lowest hemoglobin) did yield an increased risk of AKI (adjusted odds ratio 3.4, 95% CI: 1.3 - 8.4, P = 0.010). Interestingly, in another retrospective study that included patients undergoing CABG and valve surgery, the incidence of AKI was 36% and this was not dependent on IOH-CPB or the combination of IOH-CPB and anemia.[22]

Rather than studying IOH-CPB defined as an absolute MAP threshold as in the previous studies, Kanji et al. investigated a relative decrease in MAP in 157 patients undergoing on-pump cardiac surgery at high risk for developing AKI.[23] Forty one percent of the patients developed AKI and the occurrence of IOH-CPB defined as an arbitrarily chosen

decrease in MAP of 26% from baseline was independently associated with AKI (odds ratio 2.8, 95% CI: 1.3 - 6.1, $P = 0.009$). The smallest relative decrease in MAP that we studied was 35% and yielded a risk ratio of 1.001 (99% CI: 0.997 - 1.006, $P = 0.455$) per minute below this threshold for the development of AKI. Also, IOH-CPB defined as greater relative decreases than 35% were not associated with AKI. It is possible that patients at high risk for postoperative AKI as in the study of Kanji et al. are more susceptible to IOH-CPB than patients at normal risk as in our population.

If IOH is indeed associated with AKI after non-cardiac surgery, why is this relation not observed in on-pump cardiac surgery? A possible explanation may be that IOH during non-cardiac surgery is often the result of a low cardiac output state caused by general anesthesia and a potential sign of reduced organ oxygen delivery, while in on-pump cardiac surgery cardiac output and organ oxygen delivery is maintained by CPB. In an experimental study in pigs increasing the pump flow rate increased visceral organ perfusion, while increasing the MAP with phenylephrine did not, suggesting that for preserving renal oxygen delivery the focus should be on cardiac output and to a lesser extent IOH-CPB.[24] Another animal study showed that the mixed venous oxygen saturation, a sensitive marker for organ hypoperfusion, did not decline during normothermic CPB until pump flow rate was reduced to less than 2 L/min/m^2 despite a decrease in MAP from 71 mmHg to 56 mmHg.[25]

In our study patients the average MAP during CPB was 55 mmHg and 95.2% experienced IOH-CPB defined as a MAP below 45 mmHg with a median duration of 16 minutes. Compared to the MAP during CPB in other studies this is rather low.[8, 22] For example, in the study of Azau the average MAP during CPB was 60 mmHg in the group randomized to a MAP of 50-60 and 79 mmHg in the group randomized to a MAP of 75-85 and in the study of Haase et al. the median MAP during CPB was 68 (IQR 64-73). Interestingly, despite this difference the incidence of AKI was comparable between the studies (17% in the study of Azau et al., 20% in the study of Haase et al. and 20% in our study).

Among the strengths of our study is the large sample size of 1891 patients undergoing on-pump CABG, and the use of multiple imputation to deal with missing values. As a result, the number of patients developing AKI was large, which enabled us to adjust for many confounders in the multivariable analysis. Also, we investigated multiple IOH-CPB thresholds values (absolute, relative and the AUC) ranging in severity from mild to severe. And finally, we corrected for multiple testing using a level of significance of $P < 0.01$, minimizing the risk of a false positive finding (type 1 error).

Several limitations have to be addressed. First, this was a retrospective observational study and the limitations of this design must be considered. For example, serum creatinine was not measured on each postoperative day and information regarding postoperative urine output was unavailable. As a result, the incidence of AKI may have been underestimated. It is also possible that additional serum creatinine measurements

outside the standard postoperative laboratory tests were mainly ordered in patients at high risk of AKI. If the targeted MAP during CPB in these patients was increased in an attempt to prevent AKI, a possible effect of IOH-CPB on AKI may have been dampened (so-called confounding by contra-indication). Another limitation of the design of our study concerns the fact that there are many factors influencing the risk of AKI after on-pump CABG. Although we adjusted for a large number of potential confounders, we cannot exclude the possibility of residual confounding. In that regard, the study design we used may be less suitable for studying IOH-CPB as a single phenomenon in the development of AKI after CABG. Also, as occurs in non-randomized studies, treatment of IOH may have influenced the association between IOH-CPB and AKI. For example, the risk of AKI in a patient with a MAP of 50 mmHg while on vasopressor therapy may be different from a patient with a MAP of 50 mmHg without treatment, while in our analyses both situations are considered similar. Second, IOH-CPB occurred in the vast majority of patients making it hard to distinguish patients with and without IOH-CPB for some thresholds. Third, we can only comment on the association between IOH-CPB and AKI for the IOH-CPB thresholds analyzed. Fourth, we studied the relation between AKI and the MAP during CPB and not the MAP before or after the institution of CPB. Patients with IOH-CPB may have experienced IOH before and after the use CPB (e.g. due to a low hematocrit) and for patients without IOH-CPB the opposite may have been true. In theory this may have overestimated the effect of IOH-CPB on AKI. And fifth, our results can only be interpreted in the context of AKI. We are not able to draw inferences on the association between IOH-CPB and other complications such as stroke.

Altogether, in this large cohort of patients undergoing CABG, we did not observe an association between IOH-CPB and AKI when we corrected this association for well-known confounders. Given the observational design of our study we cannot draw firm conclusions on the potential causal association between IOH-CPB and AKI. To this end, future studies randomizing patients to various IOH-CPB thresholds for CABG are warranted.

REFERENCES

1. Nichols M, Townsend N, Luengo-Fernandez R, Leal J, Gray A, Scarborough P, Rayner M (2012). European Cardiovascular Disease Statistics 2012. European Heart Network, Brussels, European Society of Cardiology, Sophia Antipolis.
2. Schopka S, Diez C, Camboni D, Floerchinger B, Schmid C, Hilker M: Impact of cardiopulmonary bypass on acute kidney injury following coronary artery bypass grafting: a matched pair analysis. J Cardiothorac Surg 2014; 9: 20,8090-9-20
3. Rosner MH, Okusa MD: Acute kidney injury associated with cardiac surgery. Clin J Am Soc Nephrol 2006; 1: 19-32
4. Lenihan CR, Montez-Rath ME, Mora Mangano CT, Chertow GM, Winkelmayer WC: Trends in acute kidney injury, associated use of dialysis, and mortality after cardiac surgery, 1999 to 2008. Ann Thorac Surg 2013; 95: 20-8
5. Lamy A, Devereaux PJ, Prabhakaran D, Taggart DP, Hu S, Paolasso E, Straka Z, Piegas LS, Akar AR, Jain AR, Noiseux N, Padmanabhan C, Bahamondes JC, Novick RJ, Vaijyanath P, Reddy S, Tao L, Olavegogeascoechea PA, Airan B, Sulling TA, Whitlock RP, Ou Y, Ng J, Chrolavicius S, Yusuf S, CORONARY Investigators: Off-pump or on-pump coronary-artery bypass grafting at 30 days. N Engl J Med 2012; 366: 1489-97
6. Paparella D, Yau TM, Young E: Cardiopulmonary bypass induced inflammation: pathophysiology and treatment. An update. Eur J Cardiothorac Surg 2002; 21: 232-44
7. Ranucci M, Aloisio T, Carboni G, Ballotta A, Pistuddi V, Menicanti L, Frigiola A, Surgical and Clinical Outcome REsearch (SCORE) Group: Acute Kidney Injury and Hemodilution During Cardiopulmonary Bypass: A Changing Scenario. Ann Thorac Surg 2015; 100: 95-100
8. Azau A, Markowicz P, Corbeau JJ, Cottineau C, Moreau X, Baufreton C, Beydon L: Increasing mean arterial pressure during cardiac surgery does not reduce the rate of postoperative acute kidney injury. Perfusion 2014; 29: 496-504
9. Gold JP, Charlson ME, Williams-Russo P, Szatrowski TP, Peterson JC, Pirraglia PA, Hartman GS, Yao FS, Hollenberg JP, Barbut D: Improvement of outcomes after coronary artery bypass. A randomized trial comparing intraoperative high versus low mean arterial pressure. J Thorac Cardiovasc Surg 1995; 110: 1302,11
10. Murphy GS, Hessel EA,2nd, Groom RC: Optimal perfusion during cardiopulmonary bypass: an evidence-based approach. Anesth Analg 2009; 108: 1394-417
11. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney Int Suppl 2012; 2:1-138
12. Palomba H, de Castro I, Neto AL, Lage S, Yu L: Acute kidney injury prediction following elective cardiac surgery: AKICS Score. Kidney Int 2007; 72: 624-31
13. Berg KS, Stenseth R, Wahba A, Pleym H, Videm V: How can we best predict acute kidney injury following cardiac surgery?: a prospective observational study. Eur J Anaesthesiol 2013; 30: 704-12
14. Li P, Stuart EA, Allison DB: Multiple Imputation: A Flexible Tool for Handling Missing Data. JAMA 2015; 314: 1966-7
15. Rubin DB (1987) Multiple imputation for non response in surveys. Wiley, New York.
16. Donders AR, van der Heijden GJ, Stijnen T, Moons KG: Review: a gentle introduction to imputation of missing values. J Clin Epidemiol 2006; 59: 1087-91
17. Knol MJ, Le Cessie S, Algra A, Vandenbroucke JP, Groenwold RH: Overestimation of risk ratios by odds ratios in trials and cohort studies: alternatives to logistic regression. CMAJ 2012; 184: 895-9

18. Karkouti K, Wijeysundera DN, Yau TM, Callum JL, Cheng DC, Crowther M, Dupuis JY, Fremes SE, Kent B, Laflamme C, Lamy A, Legare JF, Mazer CD, McCluskey SA, Rubens FD, Sawchuk C, Beattie WS: Acute kidney injury after cardiac surgery: focus on modifiable risk factors. Circulation 2009; 119: 495-502
19. Walsh M, Devereaux PJ, Garg AX, Kurz A, Turan A, Rodseth RN, Cywinski J, Thabane L, Sessler DI: Relationship between intraoperative mean arterial pressure and clinical outcomes after noncardiac surgery: toward an empirical definition of hypotension. Anesthesiology 2013; 119: 507-15
20. Sun LY, Wijeysundera DN, Tait GA, Beattie WS: Association of intraoperative hypotension with acute kidney injury after elective noncardiac surgery. Anesthesiology 2015; 123: 515-23
21. Haase M, Bellomo R, Story D, Letis A, Klemz K, Matalanis G, Seevanayagam S, Dragun D, Seeliger E, Mertens PR, Haase-Fielitz A: Effect of mean arterial pressure, haemoglobin and blood transfusion during cardiopulmonary bypass on post-operative acute kidney injury. Nephrol Dial Transplant 2012; 27: 153-60
22. Sickeler R, Phillips-Bute B, Kertai MD, Schroder J, Mathew JP, Swaminathan M, Stafford-Smith M: The risk of acute kidney injury with co-occurrence of anemia and hypotension during cardiopulmonary bypass relative to anemia alone. Ann Thorac Surg 2014; 97: 865-71
23. Kanji HD, Schulze CJ, Hervas-Malo M, Wang P, Ross DB, Zibdawi M, Bagshaw SM: Difference between pre-operative and cardiopulmonary bypass mean arterial pressure is independently associated with early cardiac surgery-associated acute kidney injury. J Cardiothorac Surg 2010; 5: 71,8090-5-71
24. O'Dwyer C, Woodson LC, Conroy BP, Lin CY, Deyo DJ, Uchida T, Johnston WE: Regional perfusion abnormalities with phenylephrine during normothermic bypass. Ann Thorac Surg 1997; 63: 728-35
25. Boston US, Slater JM, Orszulak TA, Cook DJ: Hierarchy of regional oxygen delivery during cardiopulmonary bypass. Ann Thorac Surg 2001; 71: 260-4

Supplementary table 1. Baseline characteristics according to incomplete (one or more missing variables) and complete (no missing variables) cases

Variable	All (n=1891)	Incomplete cases (n=540)	Complete cases (n=1351)	*p*-value
Male gender [n (%)]	1488 (78.7)	420 (77.8)	1068 (79.1)	0.541
Age (years)	67±10	67±10	67±10	0.820
BMI [kg/m^2 (%)]	27.6±4.4	27.7±4.3	27.5±4.5	0.534
Comorbidity				
COPD [n (%)]	134 (7.1)	35 (6.5)	99 (7.3)	0.517
Diabetes [n (%)]				
- Insulin dependent	153 (8.1)	42 (7.8)	111 (8.2)	0.293
- Non-insulin dependent	317 (16.8)	102 (18.9)	215 (15.9)	
Hypertension [n (%)]	1136 (60.1)	318 (58.9)	818 (60.5)	0.506
Congestive heart failure [n (%)]	29 (1.5)	10 (1.9)	19 (1.4)	0.476
Myocardial infarction [n (%)]	466 (24.6)	73 (13.5)	393 (29.1)	<0.001
Peripheral artery disease [n (%)]	184 (10.0)	33 (6.6)	151 (11.2)	0.004
Previous stroke [n (%)]	72 (3.8)	23 (4.3)	49 (3.6)	0.516
Previous cardiac surgery [n (%)]	54 (2.9)	6 (1.2)	48 (3.6)	0.008
Pulmonary hypertension [n (%)]	3 (0.2)	1 (0.2)	2 (0.1)	1.000
LVEF [n (%)]				
- > 50%	1462 (77.4)	406 (75.5)	1056 (78.2)	<0.001
- > 30% and ≤50%	368 (19.5)	111 (20.6)	257 (19.0)	
- ≤ 30%	59 (3.1)	21 (3.9)	38 (2.8)	
Baseline MAP (mmHg)	98±13	101±13	98±13	0.018
Laboratory values				
Preoperative creatinine	88±24	88±24	88±24	0.768
Preoperative hemoglobin (mmol/L)	8.5±0.9	8.4±1.0	8.6±0.9	<0.001

Values are mean (standard deviation) or absolute number (percentage). The Student's T-test was used to test for the association of continuous variables and AKI. The Fisher's exact test and the Pearson chi-squared test were used to test for the association of categorical variables and AKI when appropriate.
BMI indicates body mass index; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; MAP, mean arterial pressure

Supplementary table 2. Perioperative characteristics according to incomplete (one or more missing variables) and complete (no missing variables) cases

Variable	All (n=1891)	Incomplete cases (n=540)	Complete cases (n=1351)	*p*-value
Operative				
Emergency procedure [n (%)]	151 (8.2)	135 (27.1)	16 (1.2)	<0.001
Critical preoperative state [n (%)]	49 (2.7)	40 (8.0)	9 (0.7)	<0.001
EuroSCORE	3 (2-5)	4 (2-6)	3 (2-5)	<0.001
Duration of CPB (min)	89±39	88±31	89±42	0.505
Duration of aortic cross-clamping (min)	57±27	57±22	58±29	0.485
Average MAP during CPB (mmHg)	55±9	55±10	56±9	0.255
Intraoperative RBC transfusion [n (%)]	233 (12.3)	88 (16.3)	145 (10.7)	0.001

Values are mean (standard deviation), median (interquartile range) or absolute number (percentage). The Student's T-test and the Mann-Whitney U test were used to test for the association of normally and non-normally distributed continuous variables and AKI. The Fisher's exact test and the Pearson chi-squared test were used to test for the association of categorical variables and AKI when appropriate.
CPB indicates cardiopulmonary bypass; MAP, mean arterial pressure; RBC transfusion, red blood cell transfusion; AKI, acute kidney injury

Chapter 8

Discussion

Postoperative complications are a major determinant of long-term survival after surgery. Complications after major surgery may be even more important than preoperative risk factors and type of surgery in determining survival up to five years.[1] Efforts should be made to prevent these complications to improve long-term surgical outcome. Unfortunately, little is known about the exact reasons why patients develop postoperative complications and which patients are at increased risk.

This thesis analyzed two possible determinants of adverse outcome after major abdominal and cardiac surgery. A discussion of the results and potential implications for future research are described here. In the first part of this thesis inflammation after major surgery was discussed, the second part dealt with the relation between intraoperative hypotension (IOH) and postoperative renal function.

PERIOPERATIVE INFLAMMATION

Systemic inflammation after major surgery is a well-known phenomenon. Clinicians involved in the perioperative care of surgical patients are often confronted with signs of systemic inflammation, such as fever and leucocytosis. For example, 90% of the patients undergoing aortic valve replacement develop the systemic inflammatory response syndrome (SIRS).[2, 3] The combination of sternotomy, the use of cardiopulmonary bypass (CPB) and ischemia/reperfusion injury (I/R) injury can be held responsible for the high incidence of SIRS after aortic valve replacement.[4]

In 2007 the less invasive transcatheter aortic valve implantation (TAVI) was introduced. This technique allows treatment of severe aortic stenosis in patients considered to be inoperable due to comorbidities and advanced age.[5] An advantage of TAVI is that CPB is not required and that the extent of the surgical trauma is limited, potentially leading to a less severe inflammatory response.

Chapter 2 and **3** describe the inflammatory response after transapical and percutaneous TAVI. SIRS within 48 hours of TAVI occurred in 53% and 46%, respectively, which is considerably less than reported after aortic valve replacement. Nevertheless, despite the minimally invasive character of TAVI the incidence of SIRS is comparable to the incidence observed after major abdominal surgery as shown in previous studies and **chapter 4**.[6, 7] In that chapter, 137 patients undergoing procedures such as colorectal, pancreatic and gastric-esophageal surgery were studied and 55% of all patients developed SIRS. The occurrence of SIRS was associated with increased levels of interleuking-6 (IL-6) and C-reactive protein (CRP) on day one and three.

The question is whether this is an innocent physiological response or negatively impacts outcome after major surgery. For example, systemic inflammation after cardiac

surgical procedures is associated with adverse outcome. Patients developing SIRS following cardiac surgery are at increased risk of multiple-organ failure and mortality.[3] In a recent investigation the occurrence of SIRS after percutaneous TAVI was associated with one-year mortality.[8] Although the study did not give information on the mechanism why SIRS affects long-term mortality, the compensatory anti-inflammatory response syndrome (CARS) may play a role. Immunoparalysis after, or during SIRS may contribute to the development of infections and late mortality. In **chapter 2** the relation between SIRS after TAVI and worse outcome was confirmed. Patients with SIRS had an almost threefold increased risk of any adverse event (odds ratio 2.8, 95% confidence interval 1.3 - 6.1; $P = 0.007$). The difference between the previously mentioned analysis and **chapter 2** was that SIRS, apart from its association with mortality, was related to the development of complications such as acute kidney injury (AKI) and infection. In addition, SIRS after TAVI was associated with short-term outcome.

Whether systemic inflammation after non-cardiac surgery is associated with adverse outcome was not clear yet. For this reason, the inflammatory response after major abdominal surgery was investigated in **chapter 4**. Primary outcome was a composite of postoperative complications such as sepsis, pneumonia and 30-day mortality. The results showed that increased inflammation, as measured by a high IL-6 on day one, was independently associated with an increased risk of a postoperative complication (adjusted odds ratio 3.3, 95% confidence interval 1.3 - 8.5; $P < 0.02$). In addition to the inflammatory biomarkers used in clinical practice (e.g. CRP, leukocyte count), levels of cytokines, such as IL-6 and tumor necrosis factor-α (TNF-α) were determined. The diagnostic value of the individual inflammatory biomarkers for predicting postoperative complications was moderate. For example, the area under the curve (AUC) for CRP, a biomarker that is frequently used to monitor the condition of patients after surgery, was 0.73 on the third postoperative day. Interestingly, this was approximately the same as the diagnostic value of IL-6 on the first postoperative day (AUC 0.67). This implies that, if these findings are validated by others, introducing routine IL-6 measurements after major abdominal surgery may improve outcome by earlier detection of patients at risk for adverse outcome. For example, a high IL-6 after major surgery may support the decision to perform a reoperation instead of a 'wait and see' approach in a patient with suspected anastomotic leak. It should be noted that the introduction of IL-6 measurements is associated with substantially increased costs. However, this may be recouped by the reduction of health care expenditures by decreasing the costs of postoperative complications.

The most important cause of postoperative inflammation is the extent of surgery. Transapical TAVI may result in increased inflammation compared to percutaneous TAVI because it requires a mini-thoracotomy, while the percutaneous approach uses a small

incision in the groin or the subclavian region. However, the incidence of SIRS in patients undergoing transapical TAVI (**chapter 2**) was comparable to the incidence after percutaneous TAVI in prior studies.[8, 9] This may suggest that procedure specific characteristics cause similar systemic inflammation after TAVI. Sinning et al. identified rapid ventricular pacing as an independent risk factor for the development of SIRS after TAVI.[8] Rapid ventricular pacing, used in both transfemoral and transapical TAVI approach, causes an intentional temporary low cardiac output state. This low output state facilitates balloon valvuloplasty, deployment of the aortic valve prosthesis and post-dilation. As a result of the compromised hemodynamics induced by rapid ventricular pacing, I/R injury and subsequently SIRS may occur.[10] Also, bacterial translocation due to intestinal ischemia may induce SIRS after periods of low cardiac output.[11] In **chapter 3** the potential relation between procedure related I/R injury and SIRS was addressed in patients undergoing TAVI. Procedure related tissue hypoperfusion appeared not associated with systemic inflammation. For example, the number and total duration of rapid ventricular pacing runs was similar in patients with and without SIRS.

An interesting and hypothesis generating finding of this study was a high intestinal fatty acid-binding protein (IFABP) level, a marker for intestinal ischemia, at baseline which peaked three hours after TAVI and subsequently decreased 44% below the median baseline level on day two. This may suggest that patients undergoing TAVI suffer from asymptomatic intestinal ischemia caused by an oxygen delivery-utilization mismatch. In general, patients undergoing TAVI are aged above 80 with multiple comorbidities. The inability to increase cardiac output when needed, often combined with left ventricular dysfunction and peripheral artery disease puts these patients at risk for intestinal ischemia. To test this hypothesis future studies might repeat measurements of baseline levels of IFABP in patients undergoing TAVI. When increased baseline IFABP levels are confirmed, baseline levels of bacterial endotoxins should be measured as a surrogate of intestinal hypoperfusion.

From the observations in **chapter 3** a second hypothesis could be generated. The rise and fall of IFABP levels after TAVI may be indicative of intestinal I/R injury. An experimental study showed that reperfusion after intestinal ischemia leads to loss of intestinal barrier integrity due to enterocyte damage with increased levels of IFABP.[12] This was accompanied by translocation of bacterial endotoxins into the circulation and increased cytokines levels that peaked at the end of reperfusion. Restauration of the aortic valve area increases blood pressure and decreases left ventricular end-diastolic pressure.[13] The enhanced circulation improves intestinal blood flow and may induce I/R injury.[14]

Chapter 2 and **chapter 4** showed that systemic inflammation was associated with adverse outcome after TAVI and major abdominal surgery, respectively. If SIRS is harmful, suppression of inflammation may result in better outcome. Recently, two large multi-

centre randomized controlled trials studied the effect of steroids on inflammation and outcome after on-pump cardiac surgery. In the DECS trial patients were randomized to a single intraoperative dose of dexamethasone or placebo and in the SIRS trial patients were randomized to two intraoperative doses of methylprednisolone or placebo.[15, 16] While inflammation was successfully suppressed in the DECS trial, as measured by levels of CRP (these data were not given in the SIRS trial), both trials failed to show an overall effect of steroids on mortality or major morbidity. At the present time no other drugs are known for their anti-inflammatory effect and, at the same time, beneficial effect on outcome in patients with increased inflammation after surgical procedures. As a result, the attention of clinicians should focus on the prevention of increased inflammation after surgery. For example, if future studies confirm that patients with aortic stenosis scheduled for TAVI suffer from asymptomatic intestinal ischemia and show that increased bacterial endotoxins are related to worse outcome, periprocedural selective digestive tract decontamination (SDD) might be initiated in order to decrease the release of bacterial endotoxins in the circulation. SDD, with or without systemic antibiotics, clears the gastrointestinal tract from pathogenic bacteria. Studies showed that the application of SDD improved outcome in patients with severe sepsis and patients undergoing gastrointestinal surgery.[17, 18] Another possible way to prevent systemic inflammation might be introducing perioperative ischemic preconditioning. Aksoyek et al. showed that I/R injury and bacterial translocation after intestinal ischemia can be reduced by intestinal ischemic preconditioning in a rat model.[19] It would be interesting to investigate whether remote ischemic preconditioning (consisting of several cycles of inflation and deflation of a blood pressure cuff to one upper arm) protects the intestine against I/R injury in patients undergoing TAVI.

Statin therapy may decrease systemic inflammation after major surgery by lowering the number of infections. Prior studies in cardiac surgery showed that statins may decrease postoperative infection rate.[20, 21] To test this hypothesis, the relation between preoperative statin therapy and postoperative infections in patients undergoing cardiac surgery was studied in **chapter 5**. Statin use was associated with a 67% decreased risk of infectious complications. In a meta-analysis of Tleyjeh et al. statin therapy was associated with an odds ratio of 0.81 (confidence interval: 0.64 - 1.01, $P = 0.06$) for the occurrence of a postoperative infection.[22] The conclusion of this study was that further investigation was warranted given the potential benefit of statin therapy. The findings of **chapter 5** support this conclusion. Currently two studies that investigate the relation between statin therapy and postoperative infections are registered in the ClinicaTrials.gov registry. One is an observational study (STAR-VaS 2 study) in vascular surgery which is completed in 2011 but not yet published and the other study is a randomized controlled trial (StaRT-CABG) in patients undergoing CABG with wound infections as a secondary outcome measure, that is currently recruiting.[23, 24] It is doubtful whether randomized

controlled trials aimed purely on the effect of statin therapy on infections after cardiac surgery will be conducted in the future. The majority of patients undergoing cardiac surgery should be on statins, apart from its potential benefit on postoperative infectious complications. It would be more rational to investigate the relation between statin use and postoperative infections in patient groups that are more likely statin naïve' and are likely to develop postoperative infections. Major abdominal surgery for example, with an infection rate of up to 20%, possibly fulfils these criteria.[25]

In **chapter 2,3** and **5** SIRS was used as a study parameter. SIRS is thought to reflect biochemical inflammation. However, because the individual SIRS criteria are rather non-specific, this is not always the case. Consequently, the SIRS criteria may have limited validity as a tool to predict outcome. For example, the predictive validity of SIRS for in-hospital mortality was lower compared to the logistic organ dysfunction system (LODS) score and the sequential organ failure assessment (SOFA) score in a recent retrospective cohort study.[26] Despite its relatively non-specific nature, SIRS may remain a useful concept in patients with suspected inflammation for several reasons. First, patients with SIRS had increased inflammatory biomarkers (such as IL-6) compared to patients without SIRS. This confirms that, on average, inflammation is indeed present in SIRS patients (**chapter 2** and **4**). A second reason is that the individual SIRS criteria are easy to obtain in clinical practice. Heart rate, temperature and respiratory rate are quickly and easily measured. The only laboratory test required is leukocyte count, which is an inexpensive test and commonly performed in hospitalized patients. Third, more specific markers for inflammation, such as IL-6, are expensive. In addition, the routine measurement of IL-6 is not possible in most hospitals due to logistic reasons. And fourth, **chapter 2** and **4** showed that the development of SIRS after TAVI and major abdominal surgery is associated with outcome. This could make SIRS a possible target for interventions aimed at improving postoperative outcome.

INTRAOPERATIVE HYPOTENSION

Although IOH is common during surgical procedures as a result of anesthesia, there is no clear conclusion on which IOH threshold is harmful and which IOH threshold is safe with respect to renal function. Randomized controlled trials comparing different IOH thresholds and their effect on renal function after non-cardiac surgery do not exist. As a result, targeting specific MAP values during surgery differs between anesthesiologists. Instead of targeting an intraoperative MAP derived from clinical trials, most commonly medical history and the MAP measured at the preoperative outpatient clinic are used to determine which MAP is appropriate with respect to organ perfusion, such as the kidney. For example, most anesthesiologists will target a higher intraoperative MAP in

an 80-year-old patient with a history of hypertension or stroke, than in a healthy 50-year-old patient with a normal preoperative blood pressure. This is based on the fact that in hypertensive patients the autoregulatory range is shifted to the right, i.e. the MAP range in which blood flow remains preserved is higher.[27]

Recently, two large retrospective analyses showed that IOH defined as a MAP of less than 55 mmHg was associated with AKI in non-cardiac surgery.[28, 29] The strength of the relation between various IOH definitions and renal function after major abdominal surgery as measured by change in estimated glomerular filtration fraction (eGFR) was assessed in **chapter 6**. This study is the first to quantify the effect of IOH on postoperative change in eGFR. The results showed that IOH was common during major abdominal surgery. For example, IOH defined as a MAP of less than 55 mmHg was present in 93% of patients with a median duration of 20 minutes (IQR 8-35). A decrease in MAP of 50% from baseline for at least one minute was present in 70% of all patients. Despite the fact that the intraoperative MAP's observed in our study group were often well below IOH thresholds that were previously associated with AKI (MAP less than 55 mmHg), the postoperative change in eGFR was modest with an average decrease of 8%. More importantly, none of the investigated IOH thresholds were significantly related to a deterioration of postoperative renal function. Unfortunately, the number of patients included was relatively small, in contrast to the previously mentioned retrospective analyses. A larger study group may have resulted in a statistically significant association. If it is assumed that a larger sample size would have resulted in a significant association for IOH defined as a MAP below 55 mmHg, ten minutes below a MAP of 55 mmHg decreases the eGFR with approximately 2% after surgery. This means that, if the observations in **chapter 6** are confirmed in a larger trial, the clinically relevance of IOH in the development of AKI may be limited.

Randomized controlled trials are warranted to clarify the relationship between IOH and postoperative renal function. The results of **chapter 6** may help with sample size calculations for such studies. For example, the change in eGFR observed for IOH defined as a MAP of less than 55mmHg would have required inclusion of 876 patients to reach statistical significance.

Chapter 7 describes the relation between IOH during on-pump CABG and AKI. Generally, a MAP of 45-50 mmHg was targeted during CPB in the patients studied. The main reason for this relatively low MAP is the believe that 'flow (i.e. cardiac output) is more important than pressure'. Despite the low MAP targeted and a wide definition of AKI studied, the incidence of AKI was comparable or even slightly below the average incidence of AKI for on-pump CABG reported in other studies.[30, 31] Most importantly, an association between IOH during CPB and AKI was not observed. These results may indicate two things. First, as long as flow is maintained the impact of lower MAPs during CPB may be limited. The use of CPB ensures a minimum flow (e.g. cardiac output) that

can be adjusted when deemed necessary according to variables as the central venous oxygen saturation. And second, the fact that on-pump IOH was not associated with AKI may also be the result of non-randomized anesthetic management as occurs in an observational study like ours. In other words, IOH causes AKI but anesthesiologists are able to determine which patient can tolerate IOH and which not. Patients susceptible for organ dysfunction due to IOH may have had a higher MAP targeted during CPB. Subsequently, the results of **chapter 6** and **7** may indicate that future trials should not focus on a 'one size fits all' strategy and not apply a similar MAP target during surgery to all patients. Intraoperative MAP targets should rather be tailored to the patient. The autoregulation may be identified in each patient to determine which IOH threshold is safe with respect to organ ischemia for every individual patient. Indeed, Hogue at al. showed in several observational studies that only the duration and degree to which the MAP was below the lower limit of autoregulation (determined with near-infrared spectroscopy) was associated with the development of AKI.[32]

Altogether, future improvements in perioperative medicine should focus on prevention and early detection of complications after major surgery. Given the fact that increased postoperative systemic inflammation is associated with adverse outcome, prevention or suppression of inflammation may decrease the occurrence of postoperative complications. Also, pro-inflammatory biomarkers, such as IL-6, might enable clinicians to recognize patients prone to complications at an earlier stage.

Whether the prevention and management of IOH improves patient outcome remains to be elucidated. The extent to which IOH influences postoperative renal function loss after non-cardiac surgery seems limited. And IOH during on-pump cardiac surgery was also not associated with the development of AKI. Future studies investigating IOH should probably focus on individually targeted MAP during surgery.

REFERENCES

1. Khuri SF, Henderson WG, DePalma RG, Mosca C, Healey NA, Kumbhani DJ, Participants in the VA National Surgical Quality Improvement Program: Determinants of long-term survival after major surgery and the adverse effect of postoperative complications. Ann Surg 2005; 242: 326,41
2. Lindman BR, Goldstein JS, Nassif ME, Zajarias A, Novak E, Tibrewala A, Vatterott AM, Lawler C, Damiano RJ, Moon MR, Lawton JS, Lasala JM, Maniar HS: Systemic inflammatory response syndrome after transcatheter or surgical aortic valve replacement. Heart 2015; 101: 537-45
3. MacCallum NS, Finney SJ, Gordon SE, Quinlan GJ, Evans TW: Modified criteria for the systemic inflammatory response syndrome improves their utility following cardiac surgery. Chest 2014; 145: 1197-203
4. Paparella D, Yau TM, Young E: Cardiopulmonary bypass induced inflammation: pathophysiology and treatment. An update. Eur J Cardiothorac Surg 2002; 21: 232-44
5. Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Williams M, Dewey T, Kapadia S, Babaliaros V, Thourani VH, Corso P, Pichard AD, Bavaria JE, Herrmann HC, Akin JJ, Anderson WN, Wang D, Pocock SJ, PARTNER Trial Investigators: Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med 2011; 364: 2187-98
6. Sarbinowski R, Arvidsson S, Tylman M, Oresland T, Bengtsson A: Plasma concentration of procalcitonin and systemic inflammatory response syndrome after colorectal surgery. Acta Anaesthesiol Scand 2005; 49: 191-6
7. Mokart D, Leone M, Sannini A, Brun JP, Tison A, Delpero JR, Houvenaeghel G, Blache JL, Martin C: Predictive perioperative factors for developing severe sepsis after major surgery. Br J Anaesth 2005; 95: 776-81
8. Sinning JM, Scheer AC, Adenauer V, Ghanem A, Hammerstingl C, Schueler R, Muller C, Vasa-Nicotera M, Grube E, Nickenig G, Werner N: Systemic inflammatory response syndrome predicts increased mortality in patients after transcatheter aortic valve implantation. Eur Heart J 2012; 33: 1459-68
9. Sinning JM, Ghanem A, Steinhauser H, Adenauer V, Hammerstingl C, Nickenig G, Werner N: Renal function as predictor of mortality in patients after percutaneous transcatheter aortic valve implantation. JACC Cardiovasc Interv 2010; 3: 1141-9
10. Selle A, Figulla HR, Ferrari M, Rademacher W, Goebel B, Hamadanchi A, Franz M, Schlueter A, Lehmann T, Lauten A: Impact of rapid ventricular pacing during TAVI on microvascular tissue perfusion. Clin Res Cardiol 2014; 103: 902-11
11. Brunkhorst FM, Clark AL, Forycki ZF, Anker SD: Pyrexia, procalcitonin, immune activation and survival in cardiogenic shock: the potential importance of bacterial translocation. Int J Cardiol 1999; 72: 3-10
12. Grootjans J, Lenaerts K, Derikx JP, Matthijsen RA, de Bruine AP, van Bijnen AA, van Dam RM, Dejong CH, Buurman WA: Human intestinal ischemia-reperfusion-induced inflammation characterized: experiences from a new translational model. Am J Pathol 2010; 176: 2283-91
13. Gotzmann M, Lindstaedt M, Bojara W, Mugge A, Germing A: Hemodynamic results and changes in myocardial function after transcatheter aortic valve implantation. Am Heart J 2010; 159: 926-32
14. Fraccaro C, Al-Lamee R, Tarantini G, Maisano F, Napodano M, Montorfano M, Frigo AC, Iliceto S, Gerosa G, Isabella G, Colombo A: Transcatheter aortic valve implantation in patients with severe left ventricular dysfunction: immediate and mid-term results, a multicenter study. Circ Cardiovasc Interv 2012; 5: 253-60

15. Dieleman JM, Nierich AP, Rosseel PM, van der Maaten JM, Hofland J, Diephuis JC, Schepp RM, Boer C, Moons KG, van Herwerden LA, Tijssen JG, Numan SC, Kalkman CJ, van Dijk D, Dexamethasone for Cardiac Surgery (DECS) Study Group: Intraoperative high-dose dexamethasone for cardiac surgery: a randomized controlled trial. JAMA 2012; 308: 1761-7
16. Whitlock RP, Devereaux PJ, Teoh KH, Lamy A, Vincent J, Pogue J, Paparella D, Sessler DI, Karthikeyan G, Villar JC, Zuo Y, Avezum A, Quantz M, Tagarakis GI, Shah PJ, Abbasi SH, Zheng H, Pettit S, Chrolavicius S, Yusuf S, SIRS Investigators: Methylprednisolone in patients undergoing cardiopulmonary bypass (SIRS): a randomised, double-blind, placebo-controlled trial. Lancet 2015; 386: 1243-53
17. de Smet AM, Kluytmans JA, Cooper BS, Mascini EM, Benus RF, van der Werf TS, van der Hoeven JG, Pickkers P, Bogaers-Hofman D, van der Meer NJ, Bernards AT, Kuijper EJ, Joore JC, Leverstein-van Hall MA, Bindels AJ, Jansz AR, Wesselink RM, de Jongh BM, Dennesen PJ, van Asselt GJ, te Velde LF, Frenay IH, Kaasjager K, Bosch FH, van Iterson M, Thijsen SF, Kluge GH, Pauw W, de Vries JW, Kaan JA, Arends JP, Aarts LP, Sturm PD, Harinck HI, Voss A, Uijtendaal EV, Blok HE, Thieme Groen ES, Pouw ME, Kalkman CJ, Bonten MJ: Decontamination of the digestive tract and oropharynx in ICU patients. N Engl J Med 2009; 360: 20-31
18. Roos D, Dijksman LM, Tijssen JG, Gouma DJ, Gerhards MF, Oudemans-van Straaten HM: Systematic review of perioperative selective decontamination of the digestive tract in elective gastrointestinal surgery. Br J Surg 2013; 100: 1579-88
19. Aksoyek S, Cinel I, Avlan D, Cinel L, Ozturk C, Gurbuz P, Nayci A, Oral U: Intestinal ischemic preconditioning protects the intestine and reduces bacterial translocation. Shock 2002; 18: 476-80
20. Coleman CI, Lucek DM, Hammond J, White CM: Preoperative statins and infectious complications following cardiac surgery. Curr Med Res Opin 2007; 23: 1783-90
21. Kayani WT, Bandeali SJ, Lee VV, Elayda M, Khan A, Nambi V, Jneid H, Alam M, Wilson JM, Huang HD, Birnbaum Y, Ballantyne CM, Virani SS: Association between statins and infections after coronary artery bypass grafting. Int J Cardiol 2012
22. Tleyjeh IM, Alasmari FA, Bin Abdulhak AA, Riaz M, Garbati MA, Erwin PJ, Kashour T, Al-Mallah MH, Baddour LM: Association between preoperative statin therapy and postoperative infectious complications in patients undergoing cardiac surgery: a systematic review and meta-analysis. Infect Control Hosp Epidemiol 2012; 33: 1143-51
23. https://clinicaltrials.gov/ct2/show/NCT00967252?term=statin+infection+surgery&rank=1.
24. https://clinicaltrials.gov/ct2/show/NCT01715714?term=start-cabg&rank=1.
25. Paun BC, Cassie S, MacLean AR, Dixon E, Buie WD: Postoperative complications following surgery for rectal cancer. Ann Surg 2010; 251: 807-18
26. Seymour CW, Liu VX, Iwashyna TJ, Brunkhorst FM, Rea TD, Scherag A, Rubenfeld G, Kahn JM, Shankar-Hari M, Singer M, Deutschman CS, Escobar GJ, Angus DC: Assessment of Clinical Criteria for Sepsis: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016; 315: 762-74
27. Carlstrom M, Wilcox CS, Arendshorst WJ: Renal autoregulation in health and disease. Physiol Rev 2015; 95: 405-511
28. Walsh M, Devereaux PJ, Garg AX, Kurz A, Turan A, Rodseth RN, Cywinski J, Thabane L, Sessler DI: Relationship between intraoperative mean arterial pressure and clinical outcomes after noncardiac surgery: toward an empirical definition of hypotension. Anesthesiology 2013; 119: 507-15
29. Sun LY, Wijeysundera DN, Tait GA, Beattie WS: Association of intraoperative hypotension with acute kidney injury after elective noncardiac surgery. Anesthesiology 2015; 123: 515-23

30. Azau A, Markowicz P, Corbeau JJ, Cottineau C, Moreau X, Baufreton C, Beydon L: Increasing mean arterial pressure during cardiac surgery does not reduce the rate of postoperative acute kidney injury. Perfusion 2014; 29: 496-504
31. Haase M, Bellomo R, Story D, Letis A, Klemz K, Matalanis G, Seevanayagam S, Dragun D, Seeliger E, Mertens PR, Haase-Fielitz A: Effect of mean arterial pressure, haemoglobin and blood transfusion during cardiopulmonary bypass on post-operative acute kidney injury. Nephrol Dial Transplant 2012; 27: 153-60
32. Ono M, Brady K, Easley RB, Brown C, Kraut M, Gottesman RF, Hogue CW,Jr: Duration and magnitude of blood pressure below cerebral autoregulation threshold during cardiopulmonary bypass is associated with major morbidity and operative mortality. J Thorac Cardiovasc Surg 2014; 147: 483-9

Summary

Despite advances in surgical and anesthetic techniques in the past decades, complications are common after major surgery. The negative impact of postoperative complications on outcome is of significant concern to patients and their clinicians. The pathophysiological mechanisms of complications after surgery, however, are largely unknown. This thesis described the relation between two possible determinants of adverse events after major surgery: perioperative inflammation and hypotension.

PERIOPERATIVE INFLAMMATION

Increased inflammation, as reflected by the occurrence of the systemic inflammatory response syndrome (SIRS), is frequently observed after major surgery. In **chapter 2** the relation between SIRS and any adverse event (defined as the composite of acute kidney injury (AKI), infection, stroke, bleeding and mortality) after transapical transcatheter aortic valve implantation (TAVI) was investigated. SIRS was present in 53.7% of patients within 48 hours after the TAVI procedure. The development of SIRS was associated with an independently increased risk of any adverse event (adjusted odds ratio (AOR) 4.0, 95% confidence interval (CI); 1.6 - 9.6). In addition, patients with SIRS had a longer median duration of Intensive Care Unit stay (2 days versus 1 day in patients with and without SIRS, respectively, $P < 0.001$).

The exact pathogenesis of SIRS after TAVI is not clear yet. Therefore, the potential role of ischemia/reperfusion (I/R) injury in the development of SIRS after TAVI was assessed in an exploratory analysis in **chapter 3**. Levels of intestinal fatty acid-binding protein (IFABP, a marker of intestinal ischemia), the mean arterial pressure (MAP) and cerebral oxygenation during rapid ventricular pacing (RVP) and the number and total duration of RVP runs were used as markers for tissue hypoperfusion in 39 patients undergoing TAVI. An association between these markers and SIRS was not observed. In general, the median total pacing duration was short with 13 seconds (interquartile range (IQR) 0-37) and probably such short decrease in cardiac output does not result in significant tissue hypoperfusion and I/R injury. Interestingly, levels of IFABP were high at baseline, peaked at three hours and decreased more than 40% two days after TAVI. This finding may suggest that intestinal I/R injury, independent from RVP, plays a role in the inflammatory response after TAVI.

In **chapter 4** the relation between systemic inflammation and complications was investigated in 135 patients undergoing major abdominal surgery. Systemic inflammation was assessed by levels of inflammatory biomarkers (i.e. levels of interleukin-6 (IL-6), C-reactive protein (CRP) and tumour necrosis factor-α) and the occurrence of SIRS. Thirty-nine patients (29%) suffered from at least one postoperative complication. An IL-6 level of >432 pg/ml was an independent predictor of postoperative complications

(AOR 3.3, 95% CI; 1.3 - 8.5). The diagnostic accuracy of IL-6 levels on postoperative day one for predicting complications, as measured by a receiver operating characteristic (ROC) curve, was 0.67, compared to 0.73 for CRP on day three. The findings of **chapter 4** suggest that using levels of IL-6 after major abdominal surgery may help in early clinical decision-making and improve the detection of postoperative complications.

Statin therapy may mitigate postoperative inflammation by decreasing the postoperative infection rate. In **chapter 5** the possible protective effect of statins against infectious complications after cardiac surgery was investigated in 520 patients. 71.2% of all patients were on preoperative statin therapy and 15.8% developed a postoperative infection. Statin therapy prior to surgery was associated with a 67% reduced risk of infectious complications (AOR 0.3, 95% CI; 0.2 - 0.6). This result is in line with several other observational studies in patients undergoing cardiac surgery. Whether initiation of statin therapy before surgery prevents postoperative infections needs to be evaluated in future trials.

INTRAOPERATIVE HYPOTENSION

Depending on the definition used intraoperative hypotension (IOH) occurs in up to 99% of patients undergoing surgery. Whether IOH influences postoperative renal function was analysed in **chapter 6** and **7**.

In **chapter 6** the association of IOH and postoperative renal function was studied in 202 patients undergoing major abdominal surgery. Creatinine measurements were routinely performed on the day of surgery and on 1st, 3rd and 7th postoperative day. Instead of using a binary outcome parameter (i.e. AKI or no AKI) primary outcome was the change in the estimated glomerular filtration rate (eGFR) allowing to quantify the strength of the effect of IOH on postoperative renal function. On average the eGFR decreased with 8±20%. None of the investigated IOH definitions (i.e. several absolute and relative MAP thresholds and the AUC below several absolute MAP thresholds) were associated with a change in the eGFR. These results were in contrast with previous analysis and can be caused by insufficient statistical power to detect a relationship. Nevertheless, based on the results of **chapter 6** the impact of IOH on change in eGFR in patients undergoing major abdominal surgery may be limited.

In **chapter 7** the relation between IOH during cardiopulmonary bypass (CPB) and AKI after coronary artery bypass grafting (CABG) was investigated. The study population consisted of 1891 patients and 20% developed AKI according to the Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Acute Kidney Injury criteria. IOH was defined according to several absolute and relative MAP threshold values and to the area under the curve (AUC) for several absolute MAP threshold values. IOH defined

as a MAP below 50 mmHg was present in 98% of patients with a median duration of 28 minutes (IQR 13-47). In multivariable analysis, none of the IOH definitions investigated were associated with AKI. These results indicate that IOH during CPB, according to the definitions used in **chapter 7**, is not harmful with respect to the development of AKI in patients undergoing CABG. The use of CPB may ensure sufficient oxygen delivery to the kidneys by maintaining organ flow despite IOH.

Samenvatting

Ondanks de vooruitgang van chirurgische en anesthesiologische technieken in de afgelopen decennia komen complicaties na grote chirurgie frequent voor. De negatieve invloed van postoperatieve complicaties op uitkomst is een grote zorg voor patiënten en hun artsen.

De pathofysiologische van complicaties na chirurgie zijn grotendeels onbekend. Dit proefschrift beschrijft de relatie tussen twee mogelijke determinanten van ongunstige uitkomst na grote chirurgie: perioperatieve inflammatie en hypotensie.

PERIOPERATIEVE INFLAMMATIE

Toegenomen inflammatie, tot uitdrukking komend in het 'systemic inflammatory response syndrome' (SIRS), komt vaak voor na grote chirurgie. In **hoofdstuk 2** is de relatie tussen SIRS en elke ongewenste gebeurtenis (gedefinieerd als de combinatie van 'acute kidney injury' (AKI), infectie, cerebrovasculair accident, bloeding en mortaliteit) na 'transapical transcatheter aortic valve implantation' (TAVI) onderzocht. SIRS binnen 48 uur na de operatie kwam voor in 53.7% van de patiënten. De ontwikkeling van SIRS was geassocieerd met een onafhankelijk verhoogd risico op elke ongewenste gebeurtenis (adjusted odds ratio (AOR) 4.0, 95% confidence interval (CI); 1.6 - 9.6). Bovendien hadden patiënten met SIRS een langere Intensive Care opnameduur (2 dagen versus 1 dag in patiënten met en zonder SIRS, respectievelijk, $P < 0.001$).

The precieze pathogenese van SIRS na TAVI is nog onduidelijk. Daarom is de potentiële rol van ischemie/reperfusie (I/R) schade in het ontstaan van SIRS na TAVI onderzocht in een verkennende analyse in **hoofdstuk 3**. De concentratie van 'intestinal fatty acid-binding protein' (IFABP, een marker voor darmischemie), de 'mean arterial pressure' (MAP) en de cerebrale oxygenatie tijdens 'rapid ventriculair pacing' (RVP) runs en het aantal en de totale duur van de RVP runs werden gebruikt als surrogaat markers voor weefselhypoperfusie in 39 patiënten die een TAVI procedure ondergingen. Er werd geen relatie gezien tussen deze markers en SIRS. In het algemeen was de totale RVP duur kort met een mediane duur van 13 seconden (interquartile range (IQR) 0-37) en waarschijnlijk onvoldoende lang om relevante weefselhypoperfusie en I/R schade te veroorzaken. Een interessante bevinding was dat de waardes van IFABP hoog waren bij aanvang van TAVI, na drie uur piekte en twee dagen na TAVI met meer dan 40% daalde. Dit kan betekenen dat intestinale I/R schade, onafhankelijk van RVP, een rol speelt in het ontstaan in de inflammatoire respons na TAVI.

In **hoofdstuk 4** is de relatie tussen systemische inflammatie en complicaties onderzocht in 135 patiënten die grote abdominale chirurgie ondergingen. Systemische inflammatie werd geëvalueerd door het meten van inflammatoire biomarkers (IL-6 (IL-6), C-reactive protein (CRP), en tumor necrose factor-α) en het vòòrkomen van SIRS.

Negenendertig patiënten (29%) kregen een of meerdere complicaties. Een IL-6 waarde van >432 pg/ml was een onafhankelijke voorspeller voor een postoperatieve complicatie (AOR 3.3, 95% CI; 1.3 - 8.5). De diagnostische nauwkeurigheid van IL-6 voor het voorspellen van complicaties op de eerste postoperatieve dag, gemeten met een 'receiver operating characteristic' (ROC) curve, was 0.67, vergeleken met 0.73 voor CRP op dag drie. De bevindingen van **hoofdstuk 4** suggereren dat het bepalen van IL-6 waardes na grote abdominale chirurgie kan helpen in het maken van vroege klinische beslissingen en de detectie van postoperatieve complicaties kan verbeteren.

Statines kunnen postoperatieve inflammatie beperken door het aantal postoperatieve infecties te verlagen. In **hoofdstuk 5** is de mogelijke protectieve werking van statines op het ontstaan van infectieuze complicaties na cardiale chirurgie bekeken in 520 patiënten. 71.2% van alle patiënten gebruikte een statine voor de operatie en 15.8% ontwikkelde een postoperatieve infectie. Statine gebruik voor chirurgie was geassocieerd met een 67% gereduceerd risico op het ontstaan van een infectieuze complicatie (AOR 0.3, 95% CI; 0.2 - 0.6). Deze bevinding komt overeen met de resultaten van verschillende andere observationele studies in patiënten die cardiale chirurgie ondergingen. Of het preoperatief starten van een statine infecties voorkomt moet uitgezocht worden in toekomstige studies.

INTRAOPERATIEVE HYPOTENSIE

Afhankelijk van de gebruikte definitie komt 'intraoperative hypotension' (IOH) voor in tot 99% van de patiënten die chirurgie ondergaan. Of IOH invloed heeft op de postoperatieve nierfunctie is onderzocht in **hoofdstuk 6** en **7**.

In **hoofdstuk 6** is de relatie tussen IOH en de postoperatieve nierfunctie bestudeerd in 202 patiënten die grote abdominale chirurgie ondergingen. Het creatinine werd routinematig bepaald op de dag van chirurgie en op de eerste, derde en zevende postoperatieve dag. In plaats van een binaire uitkomst variabele te gebruiken (wel of geen AKI) was de primaire uitkomstmaat de verandering in de 'estimated glomerular filtration rate' (eGFR) wat het mogelijk maakt om de sterkte van de relatie tussen IOH en postoperatieve nierfunctie te kwantificeren. Gemiddeld daalde de eGFR met 8±20%. Geen van de geanalyseerde IOH definities (verschillende absolute en relatieve MAP grenzen en de 'area under the curve' (AUC) onder verschillende absolute MAP grenzen) waren geassocieerd met een verandering van de postoperatieve eGFR. Deze bevinding is in tegenstelling tot de resultaten in eerdere studies en kan komen doordat de studie onvoldoende statistische power had om een relatie aan te tonen. Niettemin lijkt op basis van de resultaten in **hoofdstuk 6** de impact van IOH op de verandering van de eGFR in patiënten die grote abdominale chirurgie ondergaan gering.

In **hoofdstuk 7** is de associatie tussen IOH tijdens het gebruik van de hart-longmachine en AKI na 'coronary artery bypass grafting' (CABG) onderzocht. De studie populatie bestond uit 1891 patiënten en 20% hiervan ontwikkelde AKI volgens Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Acute Kidney Injury criteria. IOH werd gedefinieerd volgens verschillende absolute en relatieve MAP grenzen en volgens de AUC onder verschillende absolute MAP grenzen. IOH gedefinieerd als een MAP onder de 50 mmHg kwam voor in 98% van de patiënten met een mediane duur van 28 minuten (IQR 13-47). In multivariabele analyse was geen van de onderzochte IOH definities gerelateerd aan AKI. Deze resultaten wijzen erop dat IOH (overeenkomstig met de definities die onderzocht zijn) tijdens het gebruik van de hart-longmachine niet schadelijk is met betrekking tot het ontwikkelen van AKI in patiënten die een CABG ondergaan. Het gebruik van de hart-longmachine kan ervoor zorgen dat er voldoende zuurstofaanbod is aan de nieren door het preserveren van de bloeddoorstroming ondanks IOH.

Publications

PAPERS RELATED TO THIS THESIS

Hartholt NL, Rettig TC, Schijffelen M, Morshuis WJ, van de Garde EM, Noordzij PG: Preoperative statin therapy and infectious complications in cardiac surgery. Neth Heart J 2014; 22: 503-9

Rettig TC, Rigter S, Nijenhuis VJ, van Kuijk JP, ten Berg JM, Heijmen RH, van de Garde EM, Noordzij PG: The systemic inflammatory response syndrome predicts short-term outcome after transapical transcatheter aortic valve implantation. J Cardiothorac Vasc Anesth 2015; 29: 283-7

Rettig TC, Verwijmeren L, Dijkstra IM, Boerma D, van de Garde EM, Noordzij PG: Postoperative Interleukin-6 Level and Early Detection of Complications After Elective Major Abdominal Surgery. Ann Surg 2016; 263: 1207-12

Rettig TC, Peelen LM, Geuzebroek GS, van Klei WA, Boer C, Hofland J, van de Garde EM, Noordzij PG: Impact of intraoperative hypotension during cardiopulmonary bypass on acute kidney injury after coronary artery bypass grafting. J Cardiothorac Vasc Anesth. In press

Rettig TC, Vermeulen E, Dijkstra IM, van Klei WA, van de Garde EM, Peelen LM, Noordzij PG: Intraoperative hypotension and change in estimated glomerular filtration rate after major abdominal surgery: results of a prospective observational study. European Journal of Anaesthesiology. In press

Rettig TC, Verwijmeren L, Van de Garde EM, Boerma D, Noordzij PG: Biomarkers Capable to Early Predict Postoperative Complications: The Grail. Ann Surg 2016 Jun 22

Rettig TC, Verwijmeren L, Van de Garde EM, Boerma D, Noordzij PG: No Cytokine is an Island: IL-6 alone is not enough to predict the morbidity after major abdominal surgery. Ann Surg. In press

Rettig TC, Nijenhuis VJ, Meek B, Rigter S, ten Berg JM, van Klei WA, van de Garde EM, Peelen LM, Noordzij PG: Systemic inflammation and ischemia/reperfusion injury after transcatheter aortic valve implantation: a prospective exploratory study. Submitted

PAPERS NOT RELATED TO THIS THESIS

Rettig TC, Bouma BJ, van den Brink RB: Influence of transoesophageal echocardiography on therapy and prognosis in young patients with TIA or ischaemic stroke. Neth Heart J 2009; 17: 373-7

Rettig TC, de Jongh BM, van Hannen EJ, Rigter S: Rapid diagnosis of *Coxiella burnetii* bacteremia in an ICU patient with community-acquired pneumonia. Neth J Crit Care 2012; 16: 57-59

Arts MP, Rettig TC, de Vries J, Wolfs JF, in't Veld BA: Maintaining endotracheal tube cuff pressure at 20 mm Hg to prevent dysphagia after anterior cervical spine surgery; protocol of a double-blind randomised controlled trial. BMC Musculoskelet Disord 2013; 14: 280,2474-14-280

Noordzij PG, van Geffen O, Dijkstra IM, Boerma D, Meinders AJ, Rettig TC, Eefting FD, van Loon D, van de Garde EM, van Dongen EP: High-sensitive cardiac troponin T measurements in prediction of non-cardiac complications after major abdominal surgery. Br J Anaesth 2015; 114: 909-18

Noordzij PG, Rettig TC, van de Garde EM, van Dongen EP: Letter in response to 'Testing the limits: high-sensitivity cardiac troponin in the prediction of non-cardiac complications after major abdominal surgery'. Br J Anaesth 2016; 116: 305-6

Dankwoord

Ik wil graag iedereen bedanken die op enigerlei wijze aan dit proefschrift heeft bijgedragen en in het bijzonder:

Dr. Peter Noordzij, ik ben blij dat jij mij begeleid hebt. De voortgang van de onderzoeken bespreken op de gang van de OK, de altijd snelle reactie op e-mails en je ongezouten commentaar op de eerste (vaak zeer matige) versies van de verschillende manuscripten paste mij wel. Het heeft even geduurd voordat het eerste artikel gepubliceerd werd (je hebt mij dan ook regelmatig bemoedigend toe moeten spreken met de woorden 'het komt goed') maar daarna kwamen we goed op stoom! Wanneer gaan we weer fietsen?

Dr. Ewoudt van de Garde, aan jou heb ik mijn enthousiasme voor statistiek en epidemiologie te danken. Bedankt voor de hulp bij de verschillende analyses en je inhoudelijke ideeën. Het is er nog niet van gekomen, maar ik ben nog steeds van plan een master epidemiologie te volgen.

Prof. Wilton van Klei, ik kan mij voorstellen dat het lastig kan zijn om halverwege een promotietraject in te stappen. Toch is dit zeer voorspoedig verlopen. Dank voor je inhoudelijke input en feedback bij de laatste drie manuscripten.

Dr. Linda Peelen, Poisson regressie analyse, odds ratio's die het relatieve risico overschatten bij een hoge incidentie van de outcome parameter, multiple imputation: er is een wereld voor mij open gegaan! Bedankt voor je uitleg en begeleiding.

De maatschap anesthesiologie in het Sint Antonius Ziekenhuis, bedankt voor de ondersteuning en faciliteiten om alle onderzoeken te verrichten. In het bijzonder Sander Rigter, voor het bedenken van de eerste TAVI studie.

De researchmedewerksters, Ingeborg Lange en Renske Elferink, bedankt voor jullie hulp bij de verschillende studies.

Lisa Verwijmeren en Erik Vermeulen. Lisa, soms pak ik jouw PDF-file er nog bij met aanwijzingen wanneer je welke *P*-waarde moet gebruiken bij de Student's t-Test. Bedankt voor je hulp bij de 'MICOLON-inflammatie' studie. Erik, gelukkig kon jij beter overweg met Excel dan ik! Dank voor je inspanningen voor het 'MICOLON-hypotensie' manuscript.

Guillaume, je gaat steeds verder weg wonen. Toch bedankt!

Mijn familie, ouders en zusje. Pap, jouw promotie heeft mij gestimuleerd (om het in een iets eerder stadium te doen). To, met je bijna 90 jaar ontstijg je mij nog steeds verbaal. Deze promotie is ook een beetje voor Rolf.

En ten slotte mijn vrouw Roene, mijn steun en toeverlaat. Lieve PERDIE, na 6 december heb ik overal tijd voor...(behalve als ik moet sporten natuurlijk :P)

Curriculum vitae

Thijs Clemens David Rettig was born in Roermond on February 3th, 1983. After graduating from the Erasmiaans Gymnasium in Rotterdam in 2001, he enrolled in the Faculty of Medicine of the University of Amsterdam. After finishing his Medicine study in 2007, Thijs worked as an Intensive Care resident at the Slotervaartziekenhuis (Amsterdam) in 2008 and as a Cardiology resident at the Sint Lucas Andreas Ziekenhuis (Amsterdam) in 2009. From September 2009 to October 2014 he was trained in Anesthesiology at the Sint Antonius Hospital (Nieuwegein). During his residency in Anesthesiology he initiated the investigations that are part of this thesis under the guidance of dr. Peter Noordzij. In November 2014 he worked as an Anesthesiologist in the Horacio E. Oduber Hospital (Aruba). From December 2015 to February 2016 Thijs followed a fellowship Intensive Care at the VU Medical Centre (Amsterdam). Currently, he is working as an Anesthesiologist-Intensivist at the Amphia Ziekenhuis (Breda).