Myocardial injury after non-cardiac surgery

- clinical course and value of imaging -

Myocardschade na niet-cardiale chirurgie, kliniek en rol van beeldvorming

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PART I

AN INTRODUCTION TO POSTOPERATIVE MYOCARDIAL INJURY

CHAPTER 1

GENERAL INTRODUCTION AND THESIS OUTLINE

Annually, over 200 million people undergo major noncardiac surgery worldwide. Such surgical procedures are associated with a high risk of death (up to 8% in high-risk populations) which can be attributed to adverse cardiovascular events such as myocardial infarction in up to half of the cases.[1] Recognition of these events, however, can be difficult because typical angina is often masked by strong analgesics or by wound pain, and electrocardiographic abnormalities can be subtle and transient.[2]

Predictive value of cardiac troponin

Cardiac troponin is a structural component of the myocardial contractile apparatus and is released into the bloodstream in case of myocardial necrosis (i.e. mostly in the setting of suspected ischemia).[3] Because of its high specificity to the myocardium, troponin became the cornerstone in the diagnosis of myocardial infarction.[3] Interestingly, troponin also showed to convey important predictive value for adverse events in the short and long-term after non-cardiac surgery.[4,5] Van Waes and colleagues, for instance, reported that patients with a serum Troponin-I concentration ≥60 nanograms per liter (ng/L) had a significantly higher risk of death when compared to patients with troponin levels below that level (relative risk of 2.4, 95%CI 1.3–4.2).[4] This association proved to be concentration-dependent, i.e. the relative risk increased to 4.2 (95%CI 2.1 – 8.6) for troponin levels ≥600 ng/L. It was therefore suggested that troponin could be useful for early detection of postoperative myocardial infarction (POMI), thereby creating a window for a timely cardiac intervention.

The initial enthusiasm regarding troponin's predictive potential was somewhat tempered because of uncertainty regarding the underlying pathology and optimal treatment. Indeed, elevated troponin levels proved to be especially common in patients with a poor clinical condition (e.g. congestive heart failure, sepsis, cerebrovascular pathology, large amounts of perioperative blood loss, or those undergoing emergency surgery) in whom the benefit of cardiac intervention was deemed limited or even contra-indicated (i.e. anticoagulation and antiplatelet may be associated with an unacceptable risk of bleeding).[6–8]

Etiology of troponin elevations after non-cardiac surgery

Postoperative troponin elevations are generally considered to be caused by an oxygen supply / demand mismatch in the presence of stable coronary artery disease (i.e. type II ischemia) or by a rupture of a coronary atherosclerotic plaque (i.e. type I ischemia).[1,3] In high-risk symptomatic POMI, the share of type I ischemia has been reported to range between 45% and 55%. Data for patients without symptoms (i.e. the vast majority of patients with PMI), however, is sparse.[8] Notably, a small number of postoperative troponin elevations may be attributable to extracardiac factors such as cerebral pathology (e.g. stroke and intracranial

hemorrhage), pulmonary embolism, sepsis and renal failure. [9,10] These mechanisms are further explicated in chapter 2, 3 and 5.

Perioperative cardiac interventions

Multiple interventions have been investigated in order to improve patient outcomes after non-cardiac surgery. The efficacy of such interventions, however, has mostly been limited. For instance, beta-blockers lowered the number of nonfatal POMI but were associated with a higher rate of 30-day mortality and stroke.[11],[12] A similar trend was observed for aspirin and clonidine; both did not improve the incidence of major adverse cardiac events yet a higher rate of major bleeding was observed in case of aspirin, and more clinically relevant hypotension and nonfatal cardiac arrest in case of clonidine.[13],[14] Furthermore, routine preoperative coronary revascularization did not improve mortality.[15] Such failure of cardiac interventions may imply that the prognosis of patients with postoperative myocardial injury is not easily modified. On the other hand, it may also indicate that a one-size-fits-all interventional model does not suit the heterogeneous non-cardiac surgery population. Indeed, as the substrate and trigger of postoperative myocardial injury vary greatly between patients, one might consider to improve the selection of patients that would benefit from a cardiac intervention by using additional imaging such as echocardiography and cardiac CT (i.e. diagnostic interventions). Especially the latter has high potential, since it is minimally invasive, well-tolerated, and it adequately depicts both coronaries and adjacent structures such as the pulmonary artery. Furthermore, in contrast to coronary angiography, it does not require use of additional heparin, which is generally considered undesirable in postoperative patients. Importantly, patients can adequately be directed towards medical optimization or coronary revascularization in case of coronary artery disease whilst treatment of silent non-coronary pathology (e.g. pulmonary embolism) can be considered in an early stage.

Thesis outline

This thesis is divided into three parts. Part I provides a general introduction of myocardial injury after non-cardiac surgery in which its different pathologies are further explicated (**chapter 2**). In part II, the clinical relevance of postoperative myocardial injury is described. **Chapter 3** concerns a study that examines the association of troponin with one-year mortality. In this, the causes of death are included, as they could provide valuable insight into the potential value of cardiac interventions. **Chapter 4** describes an assessment of the value of routine troponin measurements after carotid endarterectomy, which was a reaction to trial reports that the efficacy of carotid endarterectomy regarding stroke prevention was hampered by higher numbers of (silent) POMI. Part III explicates the value of cardiac imaging of patients with postoperative myocardial injury. **Chapter 5** provides an assessment of the

incidence of coronary artery disease in patients with and without troponin elevation using cardiac CT. As pulmonary embolism is one of the potential causes of myocardial injury after non-cardiac surgery, the diagnostic and prognostic value of troponin for pulmonary embolism was examined in patients who were clinically suspected of PE (**chapter 6**). Furthermore, we sought to assess the incidence of silent PE after endovascular aortic repair (EVAR); this population was chosen because of the extensive antithrombotic prophylaxis and the requirement of an aortic CT angiography before and after surgery (**chapter 7**). Finally, a general discussion is provided in **chapter 8**.

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CHAPTER 2

BACKGROUND AND STUDY DESIGN, ADAPTED FROM: THE AETIOLOGY OF MYOCARDIAL INJURY AFTER NON-CARDIAC SURGERY

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ABSTRACT

Recognition of myocardial injury after non-cardiac surgery is difficult, since strong analgesics (e.g. opioids) can mask angina, and ECG abnormalities are subtle or transient. Thorough knowledge of the pathophysiological mechanisms is therefore essential. These mechanisms can be subdivided into four groups: type I myocardial infarction (MI), type II MI, non-ischaemic cardiac pathology, and non-cardiac pathology. The incidence of type I MI in patients with a clinical suspicion of perioperative acute coronary syndrome (ACS) is 45–57 %. This percentage is higher in patients with a high likelihood of MI such as patients with ST-elevation ACS. Of note, the generalisability of this statement is limited due to significant study limitations. Non-ischaemic cardiac pathology and non-cardiac pathology should not be overlooked as a cause of perioperative myocardial injury (PMI). Especially pulmonary embolism and dysrhythmias are a common phenomenon, and may convey important prognostic value. Implementation of routine postoperative troponin assessment and accessible use of minimally invasive imaging should be considered to provide adequate individualised therapy. Also, addition of preoperative imaging may improve the stratification of high-risk patients who may benefit from preoperative or perioperative interventions.

INTRODUCTION

Annually, over 200 million people undergo major non-cardiac surgery worldwide.[1] Despite technical improvements and increased patient monitoring, these procedures currently remain associated with high mortality and morbidity. Overall 30-day mortality exceeds 2 %, and reaches 6 % in high-risk populations (e.g. certain vascular populations).[2-6] Over half of these deaths are attributable to adverse cardiovascular events.[3, 7]

Recognition of an adverse cardiovascular event in the perioperative phase is difficult. Typical angina is often masked due of the use of strong analgesics (e.g. opioids), and changes on the electrocardiogram are predominantly subtle or transient.[3, 6, 8] Moreover, the diagnostic value of cardiac biomarkers such as cardiac troponin and creatine kinase muscle and brain isotype (CK-MB) remains controversial in the perioperative period, since factors such as skeletal muscle damage, inflammation and renal insufficiency interfere with serum levels.[9] An adequate and timely diagnosis is therefore frequently delayed, and subsequent therapy may not be initiated at all.

In order to improve early recognition of perioperative myocardial injury (PMI), thorough knowledge of its pathophysiological mechanisms is required. In this article we will elaborate these mechanisms, and review the available evidence concerning perioperative myocardial infarction (MI).

AETIOLOGY OF PMI

PMI may originate from four distinct pathophysiological mechanisms:

1. MI type I is caused by fissuring or rupturing of an unstable coronary artery atherosclerotic plaque. Consecutive platelet activation and aggregation causes thrombus formation that occludes the vessel, and induces myocardial ischaemia.[10] Surgical patients are especially vulnerable to such adverse events due to a hypercoagulable state in a setting of tachycardia, anaemia, intraoperative hypotension, and postoperative hypertension.[8]
2. MI type II is caused by either a haemodynamic equilibrium disturbance combined with the presence of significant coronary artery disease (CAD), a severe coronary vasospasm, or endothelial dysfunction.[8] These mechanisms induce a myocardial oxygen supply–demand mismatch that leads to a more generalised type of myocardial ischaemia than type I.[11] Common perioperative factors that increase myocardial oxygen demand include hypertension, tachycardia and elevated levels of catecholamines.[8] Decreased myocardial oxygen supply is attributable to blood loss, intraoperative hypotension, anaemia, and/or coronary vasospasm.[8] Furthermore, an oxygen supply deficit may develop if the coronary collateral blood supply falls short.[12]

3. Non-ischaemic cardiac pathology.[8, 10] This group can be subdivided into cardiac dysrhythmias, congestive heart failure (due excessive perioperative fluid administration), acute non-ischaemic cardiomyopathies (e.g. cerebrally or stress-induced), and inflammatory and/or infectious processes. Presence of postoperative electrolyte disturbances, inflammation, hypertension and myocardial ischaemia catalyse the commencement of a dysrhythmia.[13, 14] Non-ischaemic causes other than dysrhythmias are rare, yet can be provoked by certain factors commonly associated with major surgery or trauma (e.g. high stress levels in case of a Takotsubo / stress-induced cardiomyopathy, or a bacteraemia in case of endocarditis).[15, 16]
4. Non-cardiac causes such as pulmonary embolism (PE) and sepsis. The perioperative phase is associated with prolonged periods of immobilisation in a period of haemodynamic changes. Therefore, ideal circumstances are present for the formation of venous thromboembolisms.[17] In case of pulmonary embolism, postoperative troponin elevation may be caused by both a right ventricular pressure overload, and more generalized hypoxemia. Of note, the mechanism of sepsis is also thought to be multifactorial: circulating cytokines, endothelial dysfunction and regional myocardial ischemia due to impaired coronary flow may all be influential. [18]

A combination of two or more pathophysiological mechanisms is also possible. For instance, a myocardial oxygen supply–demand mismatch (i.e. type II MI) may lead to increased shear stress of an atherosclerotic plaque that consecutively causes the plaque to fissure or rupture (i.e. type I MI induction).[8, 10]

LITERATURE

Angiographic, histological or alternative imaging studies that provide an overview of the prevalence of all four aetiological mechanisms of PMI are currently not available. Therefore, we have to extrapolate data from studies that have focussed on subgroups. Myocardial infarction type I and II will be emphasised, as myocardial ischaemia has been suggested to be the main cause of postoperative morbidity and mortality.[3, 8]

Type I versus type II myocardial infarction

The incidence of ST-segment elevation myocardial infarction (STEMI) after non-cardiac surgery ranges from 0.06 % to 1.5 %, and is therefore very low.[11, 19, 20] In contrast, transient periods of ST depression are relatively common, as incidences range from 0.6 % to 50 % (i.e. numbers vary based on study population and the use of continuous or interval ECG monitoring).[11, 20, 21] The ST depressions have historically been associated with type II MI, yet – especially in the perioperative phase - merely provide a suggestion of the underlying

pathophysiological mechanism.[11] Routine postoperative measurement of cardiac biomarkers, which are highly sensitive for myocardial damage and provide a broader diagnostic window than a non-continuous ECG, essentially suffers from the same inability to provide evidence concerning the pathophysiological mechanism.[19, 22]

Four studies were conducted to assess the incidence of the two types of myocardial infarction after surgery: two necropsy studies and two angiographic studies (Table 1). Appraisal of study relevance and validity is shown in Table 2, and results are shown in Table 3.

- Dawood et al. [23] performed a histopathological analysis of coronary arteries and myocardium of autopsy heart specimens of patients who suffered either a fatal perioperative MI (n = 42), or a non-perioperative MI (n = 25). Patients in the former group were eligible for inclusion if they had suffered an intraoperative MI, or a MI <30 days of elective or emergency surgery. The latter group was characterised by evidence of MI in a non-surgical phase (i.e. no surgery for at least 3 months prior to their infarction). Diagnostic criteria for MI were based on laboratory biomarkers, clinical parameters (e.g. chest pain and/or pulmonary oedema), and an electrocardiogram (ECG). Histological evidence of plaque rupture and haemorrhage into the plaque cavity or into the lumen was considered direct evidence of disruption of an unstable plaque (type I MI). This was found in 55% (95%CI 40 - 70%) of patients with a fatal perioperative MI, and in 40 % of patients with a fatal non-perioperative MI. Hence, no significant differences between the two groups were reported regarding type I MI. Intracoronary thrombus was found in 28 %.
- Cohen et al. [24] performed a necropsy study that assessed the underlying pathophysiological mechanism of a fatal postoperative MI <72 h of elective surgery (n = 26). The presence of plaque cap fissuring (i.e., disruption of a fibrous cap), plaque haemorrhage, or luminal thrombus containing plaque elements (e.g., cholesterol crystals and lipid-laden macrophages) was considered evidence of plaque rupture (i.e. type I MI). This was present in 46% (95%CI 27 - 67 %) of patients. Thrombus was found in 35%.
- Gualandro et al. [25] performed a prospective angiographic study to assess the cardiac pathophysiological mechanism in 120 patients with a clinical suspicion of acute coronary syndrome (ACS)) within 30 days after non-cardiac surgery. Results were compared with angiographic data from 120 non-surgical patients with spontaneous ACS, and 240 patients with stable CAD. Ambrose type II eccentric lesions (Table 4) and complex morphological features (Table 5) were considered evidence of type I MI.[26, 27] In the postoperative group, these incidences were 45 % (95 % CI 36–54 %) and 57 % (95 % CI 48-66 %), respectively. These numbers were significantly higher in the non-perioperative ACS group (57 % and 79 %, respectively), and significantly lower in the stable CAD group (16 % and 32 %, respectively). Thrombus was reported in 7.5 %, 32.5 %, and 8.8 % for perioperative ACS, spontaneous ACS, and stable CAD, respectively.

- Berger et al. [28] performed a retrospective therapeutic study to assess the best immediate intervention in 48 patients referred for coronary angiography because of a suspicion of acute coronary syndrome within 7 days after non-cardiac surgery. All patients had ischaemic chest pain ≥30 min or haemodynamic instability combined with typical ECG changes. Evidence of type I MI was present in 90 % (95 % CI 81 %–98 %) of patients, and intracoronary thrombus was found in 63 %.

Non-ischaemic cardiac and extra-cardiac pathophysiological mechanisms of PMI

PMI is not exclusively caused by myocardial infarction. It can also be a result of non-ischaemic cardiac pathology (e.g. dysrhythmias, congestive heart failure due to excessive fluid administration, acute non-ischaemic cardiomyopathies, inflammatory or infectious processes) and/or extracardiac pathology (i.e. predominantly pulmonary embolism).

Non-ischaemic cardiac pathology

The pathophysiology of the non-ischaemic causes of PMI can be subdivided into cardiac dysrhythmias, acute non-ischaemic cardiomyopathies (e.g. cerebrally or stress-induced), and inflammatory and/or infectious processes.

A cardiac dysrhythmia after non-cardiac surgery is a common phenomenon.[14, 29] Yet, available evidence is predominantly based on retrospective studies using non-continuous ECG monitoring. These studies have designated atrial fibrillation (AF) as the most frequent arrhythmia, affecting an average of 3–4 % of patients undergoing non-cardiac surgery.[14, 29] An additional 3–4 % develop a supraventricular tachycardia (SVT) other than AF. All dysrhythmias are associated with a worse outcome; a large multicentre trial reported an increased risk of mortality (adjusted odds ratio 1.72; 95 % CI, 1.59–1.86), longer hospital stays (adjusted relative difference, +24.0 %; 95 % CI 21.5–26.5 %), and increased hospitalisation costs (adjusted difference, +$4177; 95 % CI $3764–4590). Perioperative mortality directly resulting from a dysrhythmia is seldom reported after non-cardiac surgery, and its incidence is pragmatically believed to be lower than 0.6%.[30] Factors associated with an increased risk of developing a perioperative dysrhythmia include age, significant valvular disease, congestive heart failure, prior dysrhythmias, myocardial ischaemia, and electrolyte disturbances.[14] Also, a (pro-dysrhythmogenic) myocardial contusion should be considered in patients who have experienced blunt thoracic trauma prior to hospitalisation.[31]

A perioperative cerebrally or stress-induced cardiomyopathy can be provoked by an acute cerebrovascular event (stroke or subarachnoid haemorrhage) and/or high preoperative stress levels.[15, 32] Especially stress-induced cardiomyopathies may clinically present as an acute coronary syndrome, as characteristic ECG signs of a myocardial infarction may be present,

and cardiac biomarkers may be elevated.[33] The incidence of such cardiomyopathies is low, and current evidence mainly consists of case reports.[15, 32, 34]

Postoperative infections and systemic inflammatory response syndromes (SIRS) are a frequent complication of surgery in general.[16] Yet, inflammation or infection of cardiac structures (i.e. myocarditis, pericarditis or endocarditis) after non-cardiac procedures is rare, and generally restricted to patients with prosthetic heart valves.[35] In those patients, pathogens such as Staphylococcus aureus are capable of causing acute valvular failure, which is associated with a very poor prognosis.[36]

Extracardiac pathology

The perioperative phase is associated with prolonged periods of immobilisation and a hypercoagulable state. Therefore, ideal conditions are present for the formation of a venous thromboembolism and a pulmonary embolism (PE). Studies regarding postoperative PE have mainly focussed on orthopaedic and oncological populations, in which the incidence of symptomatic and fatal PE is approximately 1 % and 0.1 %, respectively.[17, 18, 37] Asymptomatic PE is observed in 2 - 4%, and is therefore at least twice as common as its symptomatic counterpart.[38,39] Of note, these numbers are based on studies using a ventilation/perfusion (V/Q) scan. Using computed tomography pulmonary angiography (CTPA), which has better spatial resolution and diagnostic accuracy than a ventilation-perfusion (V/Q) scan, small (asymptomatic) perfusion defects can be detected more accurately.[40,41] If these perfusion defects are taken into account, the incidence of asymptomatic PE after non-cardiac surgery is expected to exceed 4%. [37, 42, 43] However, the clinical relevance of small—mostly asymptomatic - perfusion defects has not yet been fully determined.[44]

Another acute extracardiac cause of PMI is sepsis, which is a common complication of non-cardiac surgery. [45] The mechanism of PMI due to sepsis is thought to be multifactorial, and may include circulating cytokines, endothelial dysfunction and regional myocardial ischemia due to impaired coronary flow.[16]

DISCUSSION

The incidence of type I MI in patients who suffer a fatal perioperative MI ranges from 45 - 55% (Table 3) which is slightly lower than non-surgical patients with fatal MI or sudden cardiac death, in whom type I MI represents 50 - 80%.[23, 46, 47] In contrast, type I MI is observed in 45 - 57% of patients with a clinical suspicion of acute coronary syndrome after non-cardiac surgery (Table 3).[28] It should be noted, however, that the validity and generalisability of these results are limited for the noncardiac surgery population due a number of limitations.

First, the study populations and designs of the aforementioned studies are not interchangeable (Table 1). Dawood studied 42 patients with MI <30 days of elective or emergency surgery using a case–control design, whilst Cohen studied 26 patients with MI <72 h after elective surgery using a cohort design. Of note, the study populations and designs of the angiographic studies were even less interchangeable: Gualandro performed a prospective aetiological study that assessed the incidence of type I MI in patients suspected of ACS, whilst Berger performed a retrospective therapeutic study to assess the best immediate invasive strategy in patients with an (almost certain) perioperative MI (Table 1).

Second, the methods to define MI (Table 1) are different; Dawood and Cohen used a histopathological analysis (i.e. the gold standard), whilst the in-vivo studies used conventional coronary angiography (CAG). A CAG has high diagnostic accuracy for MI, yet a number of limitations have to be recognised.[48, 49] For instance, its interpretation is primarily based on the assessment of significant coronary lesions. Yet, a significant stenosis is not a necessity for a type I MI, since normal angiographic findings have been reported in 4–31% of non-surgical patients with acute MI. [48, 49] In those cases, outward remodelling of an unstable atherosclerotic plaque may have only caused a slight, or even a non-existent coronary lumen reduction.[50] The share of type I MI may thus be underestimated.

Third, the incidence of clinical signs and symptoms suggestive of MI varies between studies (Table 3); Cohen and Gualandro reported incidences of 42.5% and 41%, respectively. Berger reported angina in 100 %, and Dawood did not provide any numbers. The high incidence reported by Berger reflects its methodological shortcomings to answer our clinical question. Moreover, it underlines the fact that its population does not fully correspond to the average POMI patient. The incidences reported by Gualandro appear to be consistent with a large prospective study that reported an incidence of ischaemic symptoms in patients with perioperative non-fatal MI of 38.1%.[4] However, Gualandro did not perform routine assessments of cardiac biomarkers and/or continuous ECG monitoring. PMI could therefore have been missed in patients using strong analgesics. As a result, a clinically moderate group was studied, and the incidence of type I may have been overestimated. This suggestion is supported by high numbers of multi- or three-vessel disease (Table 3). Of note, the overestimation may have been somewhat tempered by missing data from critically ill patients who died before the angiography was performed.[25]

Fourth, the incidence of coronary thrombus differs between the angiographic studies; Gualandro reported 7% compared to 63% reported by Berger (Table 3). The low incidence found by Gualandro may have been related to the long interval between the MI and the angiography (average delay of 5.5 days versus 0.5 days in Gualandro versus Berger, respectively), the use of statins, antiplatelet and anticoagulant agents, and a lower likelihood of a type I MI than Berger. All of these factors may have contributed to (spontaneous) thrombolysis. The diagnostic delay can be explained by the undesirability of coronary

angiography in the (very) early postoperative period, which is a result of its invasive nature, and the necessity of administration of antiplatelet agents and heparin.

Furthermore, the share of non-ischaemic and extracardiac pathology may not be overlooked as a cause of PMI. Especially cardiac dysrhythmias and pulmonary embolisms are common after noncardiac surgery, yet—as with perioperative MI—frequently remain asymptomatic. Current studies tend to be biased toward symptomatic cases that represent a population with a worse prognosis. In case of pulmonary embolisms, this is underlined by a high incidence of impaired right ventricular function, which correlates with a higher risk of death within 3 months (hazard ratio 2.2, 95%CI 1.4–3.4).[17] Increased accessibility of computed tomography angiography (CTA) will lead to an increased recognition of (asymptomatic) PE.[51] Yet, the clinical relevance of small asymptomatic perfusion defects detected by CTA is currently unknown and should be evaluated in the near future.[44]

Clinical signs and ECGs cannot guarantee early recognition of PMI, and the implementation of standard continuous ECG monitoring is difficult. Additional screening therefore appears to be indispensable. This creates a window of opportunity for routine postoperative assessment of biomarkers such as cardiac troponin, which has recently shown to be a strong and independent predictor of short- and intermediate-term mortality. [3, 19, 22] Its diagnostic interpretation, however, can be troublesome due to the interference of renal dysfunction, cerebral pathology and inflammation.[9] Troponin can therefore not be used as hard evidence of myocardial injury. Yet, it can be used to stratify patients who could benefit from additional anticoagulant therapy or a percutaneous coronary intervention (PE/MI or MI, respectively). Non and minimally invasive modalities (i.e. CTA, MRA and echocardiography) should be accessibly used in the early postoperative phase to avoid initiation of superfluous anticoagulant and antiplatelet agents that are a necessity for CAG. The most valuable diagnostic modality should be individually determined based on the patient's type of surgery, medical history, clinical presentation and comorbidities (Table 6).

Conclusion

Recognition of myocardial injury after non-cardiac surgery is difficult due to the masking of angina, and the subtlety and transiency of ECG abnormalities. Thorough knowledge of the pathophysiologic mechanisms is therefore essential. These mechanisms can be subdivided into four groups: type I MI, type II MI, non-ischaemic cardiac pathology, and non-cardiac pathology. In symptomatic patients who are clinically suspected of a perioperative acute coronary syndrome, the incidence of type I MI is 45 - 57% which is even higher patients with presenting with ST-elevation ACS. Of note, the generalisability of this statement is limited due to multiple study limitations. Furthermore, non-ischaemic cardiac pathology and non-cardiac pathology should not be overlooked as a cause of PMI. Especially pulmonary embolisms and dysrhythmias are a common phenomenon, and may convey important prognostic value.

Implementation of routine postoperative troponin assessment and accessible use of minimally invasive imaging should be considered to provide adequate individualised therapy. Also, the addition of preoperative imaging may also improve stratification of high-risk patients that will benefit from pre- or perioperative interventions.

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None declared.

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TABLE 1. Study design

	Design 1	Design 2	Design 3	Design 4	Method to define MI
Dawood	Necropsy[a]	Retrospective	Aetiological	Case control	HP[e]
Cohen	Necropsy[b]	Retrospective	Aetiological	Cohort	HP[e]
Gualandro	In-vivo[c]	Prospective	Aetiological	Case control	CAG[f,g]
Berger	In-vivo [d]	Retrospective	Therapeutic	Cohort	CAG[h]

Legend:
Abbreviations: MI = Myocardial infarction, CAG = Coronary Angiography, HP = Histopathology
[a] Fatal intraoperative MI, or a MI <30 days after non-cardiac surgery versus fatal non-perioperative MI
[b] Fatal postoperative MI ≤72 h after non-cardiac surgery
[c] Suspicion of ACS <30 days after non-cardiac surgery versus non-perioperative ACS versus stable CAD
[d] Referred for CAG because of a suspicion of acute coronary syndrome <7 days after non-cardiac surgery
[e] Histopathological evidence of unstable plaque with disruption
[f] Complex atherosclerotic plaque morphology based on Goldstein's criteria
[g] Ambrose type II eccentric lesions
[h] Intracoronary evidence of thrombus

TABLE 2. Appraisal

	Generalisability				Validity				
	Study design	Domain	Determinant	Outcome	Blinding	Baseline	Standard	Routine screening	Missing data
Dawood	+/−	+	+	+	−	−	+	−	?
Cohen	+/−	+	+	+	+	−	+	−	?
Gualandro	+	−	+	+	+	+	+	−	+
Berger	−	+	−	−	−	+/−	?	−	?

Legend:

Study design — Prospective aetiological study (+); retrospective aetiological study (+/−); other (−)

Domain — Patients with a perioperative ACS: <7 days (+); >7 days (−)

Determinant — Methods to define type I MI well described: yes (+); no (−)

Outcome — Angiographic or histopathological data well described: yes (+); no (−)

Blinding — Blinding of assessor for clinical characteristics: present (+); absent (−); incomplete documentation (?)

Baseline — Adequate description of angina, relevant comorbidities and prior cardiac adverse events, ECG characteristics, relevant drug use: 4/4 determinants (+); 3 determinants (+/−), <3 determinants (−)

Standard — Use of angiographic or histopathological data in accordance to objectified principals: yes (+); no (−); insufficient description (?)

Routine screening — Use of routine diagnostic screening (routine ECG assessment, continuous ECG monitoring or routine biomarker assessment): yes (+); no (−)

Missing data — < 10 % (+); >10 % (−); not mentioned (?)

TABLE 3. Results

		Clinical signs				Angiographic / histopathological data				
	Sample size (n)	Clinical signs of MI	Angina	STE-ACS	NSTE-ACS	Time to CAG	Multi-vessel disease	No CAD	MI type I	Presence of thrombus
Dawood	42	100 %	–	–	–	–	95.3 %	4.7 %	55%[a]	28 %
Cohen	26	42.3 %	–	–	–	–	88 %	11.5 %	46%[a]	35 %
Gualandro	120	100 %	40.7 %	5.8 %	65.1 %	5.5 days	–	5.8 %	45%[b] 57% [c]	7 %
Berger	48	100 %	100 %	68.8 %	31.3 %	0.5 days	87.5 %	0 %	90%[d]	63 %

Legend:

Abbreviations: n = Number of included patients with perioperative MI, MI = Myocardial infarction, STE-ACS = ST-segment-elevation acute coronary syndrome, NSTE-ACS = Non ST-segment-elevation acute coronary syndrome, CAG = Coronary angiography, CAD= Coronary artery disease

- Data not available

a Histopathological evidence of unstable plaque with disruption

b Ambrose type II eccentric lesions

c Complex atherosclerotic plaque morphology based on Goldstein's criteria

d Unknown

TABLE 4. Ambrose criteria [26]

Type	Characteristics
Concentric	Symmetric and smooth narrowing
Type I eccentric	Asymmetric stenosis with smooth borders and a broad neck
Type II eccentric	Asymmetric stenosis in the form of a convex intraluminal obstruction with a narrow neck due to one or more overhanging edges or irregular or scalloped borders, or both
Multiple irregularities	Three or more serial, closely spaced narrowing or severe diffuse irregularities within a vessel

TABLE 5. Criteria for complex lesions, adapted from Goldstein et al. [27]

- An intraluminal filling defect consistent with thrombus, defined as abrupt vessel cutoff with persistence of contrast, or an intraluminal filling defect in a vessel within or adjacent to a stenotic region with surrounding homogeneous contrast opacification
- Plaque ulceration, defined by the presence of contrast and hazy contour beyond the vessel lumen;
- Plaque irregularity (haziness), defined by irregular margins or overhanging edges
- Impaired flow (TIMI flow < 3, except lesions characteristic of chronic total occlusion, identified as tapering lesions with multiple fine collaterals)

Legend:
TIMI "Thrombolysis in Myocardial Infarction" Grade flow

TABLE 6. Useful diagnostic modalities to determine the pathophysiology of PMI

Type		Characteristics
CAG	Pro	Best diagnostic accuracy for in-vivo assessment of myocardial infarction. Gold standard. Option of immediate assessment of clinical significance of coronary stenoses with FFR. Also, immediate PCI is possible
	Con	Invasive, risk of iatrogenic coronary dissection. Not attractive in the early postoperative phase. Use of contrast fluid. Radiation exposure. Expensive
IVUS	Pro	Assessment of both coronary lumen, and plaque morphology (e.g. atheroma). Assessment of unstable/vulnerable plaques; plaque rupture, erosion, and intracoronary thrombus. Especially useful in situations in which angiographic imaging is considered unreliable, such overlapping vessels that cannot be adequately assessed with CAG, and in case of outward plaque remodeling
	Con	Expensive, invasive, time-consuming. Only performed by specialised angiographers. Use of contrast fluid. Radiation exposure. Measurement difficulties in case of bifurcations
OCT	Pro	Approximately 10 times higher resolution than IVUS. Well suited for plaque morphologies within 500 µm. Furthermore, similar to IVUS
	Con	Vessel occlusion by means of gentle balloon inflation, and vessel flushing with saline during imaging acquisition is required. Therefore, assessment of the left main coronary artery might not be desirable. Shallow penetration depth in comparison to IVUS. Not appropriate for evaluation of arterial remodelling. Furthermore, similar to IVUS
Echocardiogram	Pro	Assessment of myocardial segmental wall kinetics, right ventricular kinetics, and valvular apparatus. No radiation exposure
	Con	Coronary and pulmonary arteries no visualised, variable image quality
CCTA	Pro	Number and degree of coronary artery stenoses, coronary calcifications, aspect of coronary plaque. Possibility of obtaining coronary artery calcium score
	Con	Artefacts due to calcifications. Pulmonary arteries not or only partially visualised. Overestimation of stenosis degree in calcified plaques (blooming). Use of contrast fluid. Radiation exposure
CTPA	Pro	Assessment of pulmonary arteries. Highly sensitive for PE
	Con	Diagnosis of small perfusion defects with unknown prognostic value. Coronaries and heart are not accurately visualised. Use of contrast fluid. Radiation exposure
Cardiac MRI	Pro	Highly sensitive for MI. Assessment of myocardial contraction, and segmental wall kinetics. No radiation exposure
	Con	Coronaries and pulmonary arteries not or only partially visualised. Expensive, time-consuming. Use of gadolinium
Cardiac adenosine stress MRI	Pro	Highly sensitive for MI. Assessment of clinical significance of coronary stenoses by generating chemically-induced myocardial ischaemia.
	Con	Coronaries and pulmonary arteries not or only partially visualised. Expensive, time-consuming. Use of gadolinium. Use of adenosine. Limited availability

Legend:
PMI Perioperative Myocardial Injury, CAG Coronary Angiography, PCI Percutaneous Coronary Intervention, FFR Fractional Flow Reserve, IVUS Intravascular ultrasound, OCT Optical Coherence Tomography, CCTA Coronary Computed Tomography Angiography, PE Pulmonary Embolism, CTPA Computed Tomography Pulmonary Angiography, MRI Magnetic Resonance Imaging

PART II

PREDICTIVE VALUE OF POSTOPERATIVE MYOCARDIAL INJURY

CHAPTER 3

ONE-YEAR MORTALITY, CAUSES OF DEATH, AND CARDIAC INTERVENTIONS IN PATIENTS WITH POSTOPERATIVE MYOCARDIAL INJURY

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ABSTRACT

Background To evaluate the role of routine troponin surveillance in patients undergoing major noncardiac surgery, unblinded screening with cardiac consultation per protocol was implemented at a tertiary care center. This study evaluated one-year mortality, causes of death, and consequences of cardiac consultation of this protocol.

Methods This observational cohort included 3,224 patients ≥60 years of age undergoing major noncardiac surgery. Troponin I was measured routinely on the first three postoperative days. Myocardial injury was defined as troponin I >0.06 mcg/L. Regression analysis was used to determine the association between myocardial injury and one-year mortality. The causes of death, the diagnoses of the cardiologists and interventions were determined for different levels of troponin elevation.

Results Postoperative myocardial injury was detected in 715 patients (22%) and was associated with one-year all-cause mortality (RR 1.4, p=0.004; RR 1.6, p<0.001; and RR 2.2, p<0.001 for minor, moderate and major troponin elevation respectively). Cardiac death within one year occurred in 3%, 5% and 11% of patients respectively, as compared to 3% of the patients without myocardial injury (p=0.059). A cardiac consultation was obtained in 290 of the 715 patients (41%). In 119 (41%) of these patients, the myocardial injury was considered to be due to a predisposing cardiac condition, and in 111 (38%) an intervention was initiated.

Conclusions Postoperative myocardial injury was associated with an increased risk of one-year all-cause, but not cardiac mortality. A cardiac consultation with intervention was performed in less than half of these patients. The low number of interventions may be explained by a low suspicion of a cardiac etiology in most patients and lack of consensus for standardized treatment in these patients.

INTRODUCTION

Postoperative adverse cardiovascular events are a leading cause of morbidity and mortality after noncardiac surgery.[1] The reported incidence of postoperative myocardial infarction (POMI) among patients undergoing noncardiac surgery is between 3 and 6%.[2–4] Prevention of POMI by perioperative suppression of the compensatory sympathetic effects of surgery or the inhibition of platelet function have showed no beneficial effect in several major clinical trials.[2,3,5] Failure of such preventive strategies has led to strategies aimed at early recognition and subsequent treatment of POMI after surgery.[1,6,7] Therefore, routine monitoring of cardiac biomarkers has been advocated to identify patients at risk of postoperative cardiovascular events early after surgery.[8]

Routine troponin I (TnI) measurements on the first three days after surgery, followed by a cardiac consultation in patients with troponin elevation were implemented in our hospital. This clinical protocol was part of our standard postoperative care in patients aged 60 years or older undergoing all types of intermediate to high risk noncardiac surgery. In a previous study, we showed that postoperative myocardial injury as measured by troponin elevation above the clinical cut-off level of 0.06 mcg/L with or without clinical symptoms occurred in 19% of these patients. Myocardial injury was strongly associated with short-term mortality, and troponin elevation improved risk stratification of patients at risk for death.[7] Consequently, we hypothesized that this clinical protocol would facilitate cardiovascular optimization to prevent further myocardial injury, POMI and long-term cardiovascular mortality.
The primary aim of this study was therefore to determine the association between myocardial injury and long-term death, and to assess the causes of death in patients with myocardial injury. Furthermore, we aimed to evaluate the effects of implementing routine postoperative troponin measurements by studying their impact on cardiologists consultation recommendations and whether specific interventions were implemented in such patients.

METHODS

Patients
This observational cohort study included consecutive patients undergoing noncardiac surgery between January 1st 2011 and December 31st 2012 at the University Medical Center Utrecht, The Netherlands, a 1,000 bed tertiary referral hospital. Some of this cohort was used in a previous study.[7] Patients were eligible if they were aged 60 years or older, were undergoing intermediate to high risk noncardiac surgery under general or spinal anesthesia and had an expected postoperative length of hospital stay of at least 24 hours. For patients who underwent surgery more than once, the first surgery was included in the analyses. A reoperation was included as a novel case if this surgery took place at least one year after the

first surgery. Patients were excluded if they were lost to follow-up within one year after surgery.
The local medical ethics committee approved the study protocol. The need for informed consent was waived, as only routinely collected patient data were used and data were anonymized before analysis (UMC Utrecht Medical Research Ethics Committee 11-120/C).

Routine Postoperative Troponin Measurements
Routine troponin measurements were implemented as part of the standard postoperative care protocol on January 1st, 2011. According to this protocol, troponin was measured daily on the first three days after surgery. In the first phase of the protocol implementation, troponin measurements were ordered by the attending anesthesiologist. In case of a troponin elevation above the clinical cut-off level of 0.06 mcg/L, the ward physician was notified. As the optimal treatment of patients with postoperative troponin elevation was not protocolized, it was left at the discretion of the treating physician (surgical specialist) whether further diagnostic procedures including an ECG or cardiology consult was indicated. Thus, troponin elevation was simply considered as a marker for myocardial injury, warranting additional attention.

The logistics of the protocol were changed on May 2012 as troponin was not consistently measured in all eligible patients previously, and cardiology consultations were not performed in all patients with troponin elevation. Thus, troponin measurements were subsequently ordered by dedicated anesthesiology nurses, who also requested a postoperative ECG and a cardiology consultation in positive patients. Further diagnostic procedures such as cardiac or pulmonary CT-angiography, and coronary angiography (CAG) were only performed if indicated according to the consultant cardiologist. Cardiac interventions including prescription of medication were carried out in concurrence with the treating physician.

Myocardial injury
Troponin was analyzed using the third-generation enhanced AccuTnI assay (Beckman Coulter, Brea, California). Myocardial injury was defined as a TnI above the clinical cut-off level of 0.06 mcg/L, which was the lowest value measurable with a 10% coefficient of variation above the 99th percentile of 0.04 mcg/L.[7] For each patient, the highest value of all routine troponin measurements was used in the analysis.

Data collection
All preoperative and postoperative data were obtained from electronic medical and administrative records. Data collected in all patients included patient characteristics, preoperative physical status, comorbidities including factors from the Revised Cardiac Risk Index,[9] postoperative troponin measurements and death within one year. Additionally, data on postoperative symptoms, ECG changes, the occurrence of in-hospital POMI and other diagnoses, and the treatment initiated by the consultant cardiologist were collected in those

patients who had a postoperative cardiac consult. The unique hospital patient identifier was used to merge databases. The municipal personal records database was consulted for one-year mortality data. Causes of death were obtained from general practitioners.

Outcomes

The primary outcome was defined as all-cause mortality within one year after surgery. Secondary outcomes included cardiac death within one year and the incidence of in-hospital POMI. Cardiac death was defined as death resulting from a cardiac arrest or heart failure. Myocardial infarction was defined according to the third universal definition of myocardial infarction.[8]

Cardiac consultations

In patients with a cardiology consultation, we determined the suspected etiology of the troponin elevation as proposed by the consultant cardiologist. These were divided into predisposing cardiac conditions and perioperative triggers.[1,10] Predisposing cardiac conditions included tachyarrhythmias (supraventricular or ventricular tachycardia), pre-existent coronary artery disease, cardiomyopathy, left ventricular hypertrophy and cardiac contusion. Perioperative triggers included tachycardia, anemia, hypertension, sympathetic storm in the presence of intracranial pathology, hypotension, inflammation and sepsis, pulmonary embolism, renal failure, fluid overload and hypoxia. Furthermore, we recorded the interventions recommended by the cardiologist.

Statistical analysis

Baseline characteristics were compared between patients with and without postoperative myocardial injury using the Chi-square test or two-sample t-test, as appropriate. The incidence of one-year mortality was compared using the Chi-square test, and a relative risk with 95% confidence interval was calculated. The median time to death was compared using the Mann-Whitney-U test.

Multivariable log-binomial regression analysis was used to adjust the association between myocardial injury and one-year mortality for patient and surgery characteristics and comorbidities. For this purpose, univariable regression analysis was used to identify variables that were associated with one-year mortality. Variables with a p-value of 0.10 or less were included in the multivariable model. In this model, patients were classified according to their highest postoperative troponin value. Therefore, we defined more or less equally sized groups for the patients with troponin elevation, based on one, two and ten times the TnI cut-off level: TnI ≤0.06 mcg/L, TnI 0.07-0.12 mcg/L (minor elevation), TnI 0.13-0.60 mcg/L (moderate elevation) and TnI >0.60 mcg/L (major elevation). High risk surgery was defined as intra-abdominal, intrathoracic, or suprainguinal vascular surgery[9], and emergency surgery was defined as surgery required within 72 hours after the indication for surgery was set. Ischemic heart disease was defined as previous myocardial infarction and/or coronary

revascularization, heart failure was defined as a left ventricular ejection fraction <40%, and preoperative renal failure was defined as a glomerular filtration rate <45 mL/min/1.73m^2. Next, we checked for interaction of troponin with any of the significant variables in the multivariable model by including interaction terms. We used log binomial regression analysis to facilitate presenting effect measures as risks ratios.[11]

A Kaplan-Meier survival analysis was used to determine the survival of patients in each category of troponin elevation. Survival was compared using the log rank test. Furthermore, causes of death were compared between these groups. Finally, we recorded the number of cardiology consultations and the diagnoses and interventions by the cardiologist.

All hypothesis testing was conducted two-sided and throughout the analyses we used a level of significance of 0.05. The analysis was performed using SPSS (release 21.0.0 for Windows).

RESULTS

During the study period 4,099 patients were eligible for inclusion, of which 49 patients (1%) were excluded from the analyses (Figure 1). Of the remaining 4,050 patients, 826 patients (20%) were excluded because troponin was not measured during the first three postoperative days. Thus, 3,224 patients were included in this study (Table 1). Myocardial injury occurred in 715 patients (22%): 344 (11%) had minor troponin elevations (TnI 0.07-0.12 mcg/L), 255 (8%) had moderate troponin elevations (TnI 0.13-0.60 mcg/L), and 116 (4%) had major troponin elevations (TnI >0.60 mcg/L).

One-year all-cause mortality

Of the 715 patients with myocardial injury, 182 patients (26%) died within one year after surgery, as compared to 318 (13%) of the 2,509 patients without myocardial injury (RR 2.0, 95% CI 1.7-2.4, p<0.001). The median time to death was 55 days (IQR 11-173) in patients with myocardial injury as compared to 135 days (IQR 47-236) in patients without myocardial injury (p<0.001). The one-year survival in patients with minor, moderate and major troponin elevations was 21%, 25% and 40%, respectively (p<0.001) (Figure 2). After adjustment for variables that are known to predict death, the RR of one-year mortality was 1.4 (95% CI 1.1 – 1.8, p=0.004) in patients with minor troponin elevations, 1.6 (95% 1.3-2.1, p<0.001) in patients with moderate troponin elevations, and 2.2 (95% CI 1.7-2.8, p<0.001) in patients with major troponin elevations, as compared to patients without myocardial injury (Table 2). Other independent predictors of death were age, preoperative renal failure, preoperative insulin use and emergency surgery. Interaction terms for each of these predictors with troponin in the multivariable model were not statistically significant.

Causes of death

Data on the cause of death were available for 358 of the 500 patients (72%) who died within one year (Table 3). Cardiac death occurred in 2 (3%), 3 (5%) and 5 patients (11%) with minor, moderate and major troponin elevations respectively, as compared to 9 patients (3%) without myocardial injury (p=0.059). Predominant causes of death in patients with major troponin elevations were sepsis (20%), cerebrovascular (15%), and cardiac causes (11%), whereas most of the patients without myocardial injury died of cancer (43%).

ECG results

A postoperative ECG was performed in 424 of the 715 patients (59%) with myocardial injury. ECG changes suggestive of new ischemia were found in 96 of the 424 patients (23%), and were more frequent in patients with major troponin elevations (43 of 112 patients, 38%), as compared to patients with moderate troponin elevations (32 of 187 patients, 17%) or minor troponin elevations (21 of 135 patients, 16%). Three (0.7%) of these ECGs showed ST elevation ≥1mm, 52 (12%) ECGs showed ST depression ≥1mm, and 41 (10%) ECGs showed ST depression <1mm or T-wave inversion, respectively. Twenty-five of the 715 patients (3%) with myocardial injury had typical chest pain.

Cardiology consultations

A cardiology consultation followed in 290 of the 715 patients (41%) with myocardial injury (i.e. 9% of the total study population). The proportion of patients with a cardiac consultation was 18%, 54% and 79% in patients with a minor, moderate and major troponin elevation, respectively.

For the 290 patients who had cardiology consultation, the suspected etiologies of myocardial injury as determined by the consultant cardiologist, are given in Figure 3. In 119 of the 290 patients (41%) with a cardiac consultation, the myocardial injury was considered to be due to predisposing cardiac conditions, including tachyarrhythmia and pre-existent coronary artery disease, and in 81 patients (28%) the myocardial injury was considered to be due to perioperative triggers. In 126 patients (43%) the etiology of myocardial injury was not specified. Of note, the number of patients within the different groups of suspected etiologies exceeds the total number of patients, as 36 patients (12%) were assigned to more than one group (e.g. a patient with myocardial injury due to anemia in the presence of left ventricular hypertrophy).

POMI

POMI defined according to the third universal definition occurred in 97 of the 715 patients (14%) with myocardial injury: STEMI in 3 patients and NSTEMI in 94 patients, i.e. 3% of the total study population. However, only 18 of them who were in the group that received cardiologist consultation, were diagnosed by the cardiologist in real time as having POMI, including the 3 patients with STEMI. In addition, 5 patients who in retrospect did not fulfill the criteria of the third universal definition of myocardial infarction were diagnosed in real time

as having POMI, because of high TnI values with a rise-and-fall pattern in four patients and high TnI values with ventricular tachycardia in one patient. In total 23 patients were diagnosed by the cardiologist with POMI. In all of these 23 patients POMI was considered to be due to a predisposing cardiac condition, and in 9 of these 23 patients a perioperative trigger was suspected as well.

Interventions

A cardiac intervention was initiated in 111 of the 290 patients (38%) with a cardiology consultation. In the remaining 179 patients (62%) only follow-up of troponin was carried out, and the clinical course was further awaited without any intervention. Interventions were more often done in patients with a major troponin elevation (48 of 92 patients, 52%), as compared to patients with a moderate troponin elevation (45 of 138 patients, 33%) or a minor troponin elevation (18 of 60 patients, 30%). In patients in whom the myocardial injury was considered to be due to predisposing cardiac conditions or perioperative triggers, a cardiac intervention was initiated in 72 of 119 patients (61%) and 45 of 81 patients (56%) respectively, whereas when the etiology of myocardial injury was not specified, a cardiac intervention was done in 20 of 126 patients (16%) (Figure 3).

The cardiac interventions consisted of the following: in 104 of the 290 patients (36%), new medication or a dose increase was prescribed. This included beta-blockers in 52 patients (18%), other antihypertensive agents including renin angiotensin inhibitors, diuretics and calcium channel blockers in 21 patients (7%), aspirin in 34 patients (12%), other antiplatelet agents in 15 patients (5%), (low molecular weight) heparin in 28 patients (10%), statins in 22 patients (8%) and other medication in 25 patients (9%). In 14 patients (5%), red cell transfusion was advised by the cardiologist. Seventeen patients (6%) were transferred to the coronary care unit or medium care for cardiac monitoring. Coronary angiography (CAG) was performed in 15 patients (5%). The median time to CAG was 10 days (IQR 4-62). Significant coronary artery stenoses were found in 12 patients (4%). Nine patients (3%) underwent percutaneous coronary intervention (PCI), and one patient (0.3%) underwent coronary artery bypass graft surgery. Finally, in two patients (0.7%) coronary revascularization was not performed because the risk of intervention was considered too high, or because it was considered to be not beneficial because of the patients' poor condition.

Of the three patients with STEMI, only one underwent CAG and PCI. In this patient, CAG and PCI were not performed in the acute phase because of an initial diagnostic delay (>6 hours), but 14 and 33 days after STEMI was diagnosed, respectively. This patient survived the follow-up time of one year. In one STEMI patient who underwent neurosurgery, CAG (and PCI) was not performed because the risk of intracranial bleeding with antiplatelet and anticoagulant therapy was considered too high. This patient died 15 days later of cerebral empyema. In another STEMI patient a diagnostic delay occurred because of difficulties in interpreting the ECG (pre-existent ST elevation in the anterior leads due to a prior anterior wall myocardial infarction). By the time STEMI was diagnosed, the ECG was normalized and CAG was not considered beneficial anymore. The patient was admitted to the medium care for cardiac

monitoring and treated with antiplatelet therapy, and survived the follow-up time of one year.

DISCUSSION

This study determined the association between postoperative myocardial injury and one-year mortality in a large cohort of patients, and assessed causes of death in patients with myocardial injury. In addition, we studied the diagnoses and cardiac interventions in these patients. Postoperative myocardial injury, as detected by troponin elevation, was found in 22% of the patients, and was associated with a 1.5 to 3-fold increased risk of one-year mortality. The protocol led to a cardiac intervention in only 111 (16%) of the 715 patients with myocardial injury.

Our hospital is one of the first that implemented routine troponin measurements after noncardiac surgery, in order to improve early identification of patients with myocardial injury who are at risk of (silent) POMI and death. Because data from clinical care obtained in the implementation period of a new protocol were used in this study, the results represent daily care, instead of a controlled research setting.

Limitations

Several limitations must be addressed. First, because troponin was only measured on the first three days after surgery, myocardial injury that may have occurred after the third postoperative day was missed. However, previous research has shown that myocardial injury occurs primarily within the first three postoperative days.[12–14] Second, as troponin was not measured in 20% of patients, selection bias may be present. However, we showed in a previous report including a part of this cohort that there were no large differences between patients with and without troponin measurements, and that imputation of the missing troponin values did not alter the association between myocardial injury and death.[7] Third, exclusion of patients who were lost to follow-up (1%) may have introduced potential bias. Fourth, troponin was not measured prior to surgery; hence the results could not be adjusted for possible preexisting troponin elevations. [15–17] Fifth, in evaluating postoperative troponin measurements, the occurrence of complications of resulting interventions (e.g. bleeding caused by anticoagulants) [3,18,19] would have been valuable to report, but these data were not available for all patients. Finally, data on the cause of death were not available for all patients. As the cause of death may have been reported as ‘unknown’ in some patients with sudden death, the incidence of sudden cardiac death may be underestimated.

Literature

The association between postoperative myocardial injury and long-term mortality has previously been assessed in several smaller cohort studies that included patients undergoing

major surgery. Myocardial injury as measured by troponin elevation was reported to be associated with a two- to 41-fold increased risk of death within one year after surgery, which is consistent with the result of our study.[20–33] In the VISION trial, even troponin levels below the upper limit of normal were found to be related to mortality.[4] Cardiac death occurred in 19 of the 3,224 patients (0.6%) in our study, which is in accordance with the incidence of cardiovascular death in the POISE-2 trial (0.7%).[3] Furthermore, Chong and colleagues reported that cardiovascular death occurred more frequent in patients who suffered from postoperative myocardial injury after orthopedic surgery, like in our study.[20]

The incidence of POMI according to the third universal definition of myocardial infarction (3%) is comparable to previous reports (3-6%).[2–4] It should be noted that only 0.7% of patients were diagnosed with POMI in real time by the cardiologist. This implies that - in clinical practice - myocardial injury in the postoperative phase is evaluated differently than outside the perioperative setting, e.g. in patients who are suspected of myocardial infarction in the emergency department. Also, POMI appears to be less often diagnosed in a daily clinical care setting than in a controlled research setting, even if routine postoperative monitoring of troponin is used.

Because many of the patients with postoperative myocardial injury do not fulfill the criteria of myocardial infarction, a new diagnosis of MINS (Myocardial Injury after Noncardiac Surgery), defined as prognostically relevant myocardial injury due to ischemia that occurs during or within 30 days after noncardiac surgery, was proposed to guide timely diagnosis and intervention.[34] Current guidelines concur that early postoperative troponin measurements could have therapeutic consequences and therefore that it may be considered in high risk patients,[35] but it is emphasized that its usefulness is uncertain in the absence of established risks and benefits of a defined management strategy,[36] which is confirmed by our study.

Although many causes of postoperative myocardial injury have been put forward, including noncardiac causes,[1,10] it is not known in how many patients and to what extent perioperative factors contribute to the development of myocardial injury. Furthermore, if POMI is diagnosed, there is uncertainty whether this is mainly caused by plaque rupture with thrombosis (type 1 myocardial infarction) or an imbalance between myocardial oxygen supply and demand (type 2 myocardial infarction),[37–40] which hampers the initiation of proper treatment options. Moreover, even in patients with type 2 myocardial infarction outside the perioperative setting no established treatment guidelines exist.[41]

Few studies evaluated cardiac treatment initiated after surgery in patients with postoperative myocardial injury. Foucrier and colleagues studied the effect of cardiovascular medical optimization in 667 patients undergoing elective major vascular surgery. They reported that patients with treatment optimization, consisting of prescription or a dose increase of antiplatelet drugs, beta blockers, angiotensin converting enzyme inhibitors and statins, had a lower risk of adverse cardiac events than patients without treatment optimization.[42] Treatment interventions were much more frequent (65%) than in our study (16%), which may be explained by the type of patients included, i.e. those at higher risk of cardiovascular

complications who may have had more benefit from cardiovascular optimization. Chong and colleagues randomized 70 patients with troponin elevation after orthopedic surgery to cardiology care, consisting of assessment by a cardiologist and admission to a coronary care unit, versus standard treatment. Prescription of new medication, mainly beta blockers and aspirin, was more frequent (83% of the patients), as compared to our study (36% of the patients with cardiology consultation). However, cardiology care had no effect on in-hospital cardiac complications and one-year mortality.[43]

Clinical implications

Several strategies to prevent the occurrence of POMI, including suppression of the sympathetic nervous system and antiplatelet therapy, have failed to show an effect or the beneficial effect was outweighed by severe side effects.[3,5] As an alternative strategy, in those patients in whom postoperative myocardial injury has occurred, further myocardial injury and infarction may be prevented by adequate treatment early after surgery and consequently prognosis in terms of survival may be improved.[6,7] Indeed, we found that among patients with postoperative myocardial injury, the most common causes of death were cardiac, cerebrovascular and sepsis (Table 3), whereas among the patients without myocardial injury most patients died of cancer. Although we showed that it is feasible to identify these patients at risk early after surgery by routine troponin measurements, this resulted in treatment interventions in less than half (38%) of the patients who had a cardiac consultation. In patients in whom the myocardial injury was considered to be due to predisposing cardiac conditions, a cardiac intervention was carried out in 60% of patients. However, in many patients (43%) the etiology of the myocardial injury was not clear, hence it was likely not known what treatment should be initiated to prevent further injury and death. Furthermore, in about half of the patients with perioperative triggers for troponin elevation, no treatment was initiated. In a part of these patients who were at high risk of death, the myocardial injury may have been inherent to the underlying disease, e.g. in patients with myocardial injury due to sympathetic storm in the presence of intracranial pathology, or in patients with severe sepsis. Hence, it is conceivable that cardiac interventions were not carried out in these patients because this may not have been beneficial.

The findings from the current study support that attempts to improve prognosis in patients with myocardial injury are limited by insufficient knowledge of the underlying pathophysiology and adequate treatment options in individual cases, and by insufficient capability to select those patients in whom cardiac treatment may be beneficial. It is likely that one single intervention is not simply beneficial in all patients. Given the high mortality rate in patients who suffer from postoperative myocardial injury, future research efforts should first and foremost focus on unraveling the pathophysiology of postoperative myocardial injury in order to guide treatment options, and on identifying the patients who may benefit from (different) treatments. As long as these questions are not answered, we would recommend carefully weigh the benefits and risks of measuring troponin routinely in all patients after noncardiac surgery.

Conclusion

Postoperative myocardial injury as detected by routine troponin measurements is associated with one-year mortality. However, implementation of a clinical protocol including a cardiology consultation in patients with postoperative myocardial injury in order to improve prognosis in these patients, resulted in a cardiac consultation and intervention in less than half of the patients with myocardial injury. The low number of interventions may be explained by the suspicion of a cardiac condition in only a minority of the patients, and the lack of a standardized treatment protocol in our study, which in turn is attributable to a lack of knowledge of the underlying pathophysiology and treatment options in patients with postoperative myocardial injury.

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TABLE 1. Baseline characteristics in patients with and without postoperative myocardial injury.

	No myocardial		Myocardial injury		p-value
Male	1282	(51)	424	(59)	<0.001
Mean age (SD)	70	(7)	73	(8)	<0.001
Smoking[a]	446	(19)	122	(20)	0.452
Hypertension	1243	(50)	434	(61)	<0.001
Diabetes	404	(16)	150	(21)	0.002
COPD	233	(9)	76	(11)	0.282
History of myocardial infarction	193	(8)	106	(15)	<0.001
History of coronary	251	(10)	130	(18)	<0.001
History of heart failure	56	(2)	38	(5)	<0.001
(Paroxysmal) atrial fibrillation	262	(10)	107	(15)	0.001
Pacemaker/Implantable	50	(20)	36	(5)	<0.001
History of cerebrovascular disease	361	(14)	135	(19)	0.003
Renal failure	223	(9)	151	(21)	<0.001
Peripheral vascular disease	245	(10)	111	(16)	<0.001
Medication use					
Beta blockers	722	(29)	268	(38)	<0.001
Calcium antagonists	414	(17)	134	(19)	0.159
RAS[b] inhibitors	845	(34)	294	(41)	<0.001
Diuretics	630	(25)	219	(31)	0.003
Aspirin	688	(27)	264	(37)	<0.001
Warfarins	264	(11)	100	(14)	0.010
Statins	863	(34)	300	(42)	<0.001
Insulin	130	(5)	55	(8)	0.011
Oral anti-diabetics	309	(12)	99	(14)	0.278
ASA class[c]					<0.001
1	355	(14)	58	(8)	
2	1641	(65)	401	(56)	
3	497	(20)	237	(33)	
4	16	(1)	19	(3)	
General anesthesia	2333	(93)	693	(97)	<0.001
High risk surgery	725	(29)	311	(44)	<0.001
Emergency surgery	437	(17)	256	(36)	<0.001
Re-operation within one year	408	(16)	172	(24)	<0.001
Surgical specialty					<0.001
General surgery	517	(21)	240	(34)	
Neurosurgery	630	(25)	147	(21)	
Vascular surgery	365	(15)	145	(20)	
ENT and dental surgery	339	(14)	65	(9)	
Orthopedic surgery	267	(11)	78	(11)	
Gynaecology / Urology	391	(16)	40	(6)	

Legend:

Figures are numbers of patients (%), unless indicated otherwise. [a] N=2354 and N=601

respectively, due to missing data on smoking. [b] Renin angiotensin system inhibitors; [c] Classification system by the American Society of Anesthesiologists.

TABLE 2. The association between postoperative myocardial injury for different categories of troponin elevation, and one-year mortality, adjusted for age, comorbidities and surgery characteristics.

	Unadjusted analysis			*Adjusted analysis*		
	RR[a]	***95% CI***[b]	***p-value***	***RR***[a]	***95% CI***[b]	***p-value***
TnI[c] (mcg/L)						
≤0.06	*Ref*			*Ref*		
0.07-0. 12	1.7	1.3 – 2.1	<0.001	1.4	1.1 – 1.8	0.004
0.13-0.60	2.0	1.6 – 2.5	<0.001	1.6	1.3 – 2.1	<0.001
>0.60	3.1	2.4 – 4.0	<0.001	2.2	1.7 – 2.8	<0.001
Age (per 10 years increase)	1.4	1.2 – 1.5	<0.001	1.2	1.1 – 1.3	<0.001
Female sex	0.9	0.8 – 1.1	0.920			
Ischemic heart disease	1.0	0.8 – 1.2	0.877			
Hypertension	0.9	0.8 – 1.1	0.203			
(Paroxysmal) atrial fibrillation	1.3	1.0 – 1.6	0.022	1.1	0.9 – 1.4	0.383
Heart failure	1.3	0.9 – 2.0	0.190			
Pacemaker and/or ICD[d]	1.2	0.8 – 1.9	0.414			
Cerebrovascular disease	1.1	0.9 – 1.4	0.217			
Preoperative renal failure	1.8	1.5 – 2.2	<0.001	1.3	1.1 – 1.6	0.014
Preoperative insulin use	1.7	1.3 – 2.3	<0.001	1.4	1.1 – 1.7	0.012
COPD	1.0	0.8 – 1.4	0.730			
Peripheral vascular disease	1.0	0.8 – 1.3	0.851			
High risk surgery	1.0	0.9 – 1.2	0.728			
Emergency surgery	1.9	1.6 – 2.2	<0.001	1.5	1.3 – 1.8	<0.001
Reoperation within one year	1.3	1.1 – 1.6	0.002	1.2	1.0 – 1.4	0.111

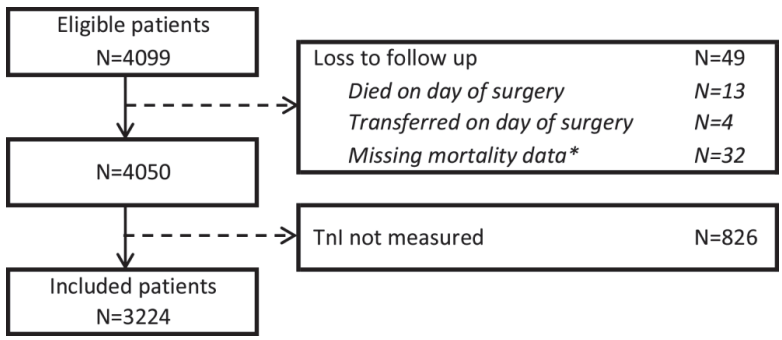
Figures are numbers (%) of patients. [a] Relative Risk; [b] Confidence Interval; [c] Troponin I; [d] Implantable Cardioverter Defibrillator

TABLE 3. Causes of death within one year after surgery for each category of troponin elevation (total N=500).

	TnI[a] (mcg/L)								p-value
	<0.06 N=318		0.07-0.12 N=72		0.13-0.60 N=64		>0.60 N=46		
Cardiac	9	(3)	2	(3)	3	(5)	5	(11)	0.059
Cardiac arrest	6	(2)	2	(3)	3	(5)	2	(4)	
Heart failure	3	(1)	0	(0)	0	(0)	3	(7)	
Pulmonary embolism	3	(1)	0	(0)	2	(3)	0	(0)	0.249
Other pulmonary	10	(3)	8	(11)	5	(8)	4	(9)	0.024
Cerebrovascular/brain injury	19	(6)	10	(14)	13	(20)	7	(15)	0.001
Malignancy	135	(43)	22	(31)	10	(16)	1	(2)	<0.001
Infection/sepsis	23	(7)	6	(8)	10	(16)	9	(20)	0.018
Other	18	(6)	5	(7)	8	(13)	11	(24)	<0.001
Unknown	101	(32)	19	(26)	13	(20)	9	(20)	0.125

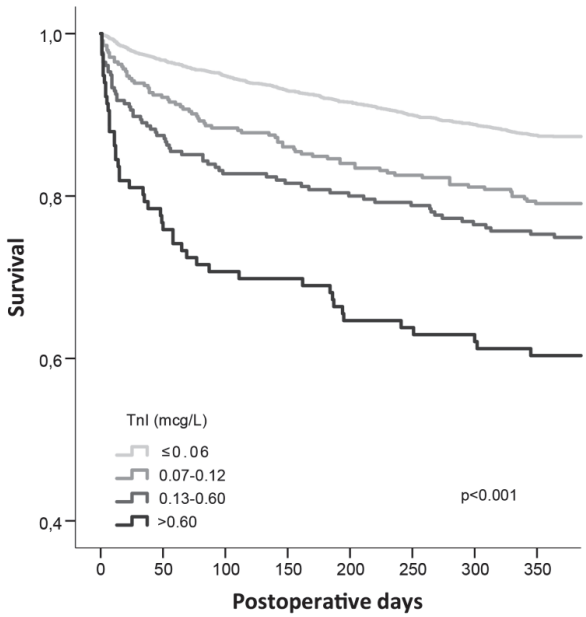
Figures are numbers (%) of patients. [a] Troponin I

FIGURE 1. Flow chart of patient inclusion.



* These patients were not known by the municipal personal records database.

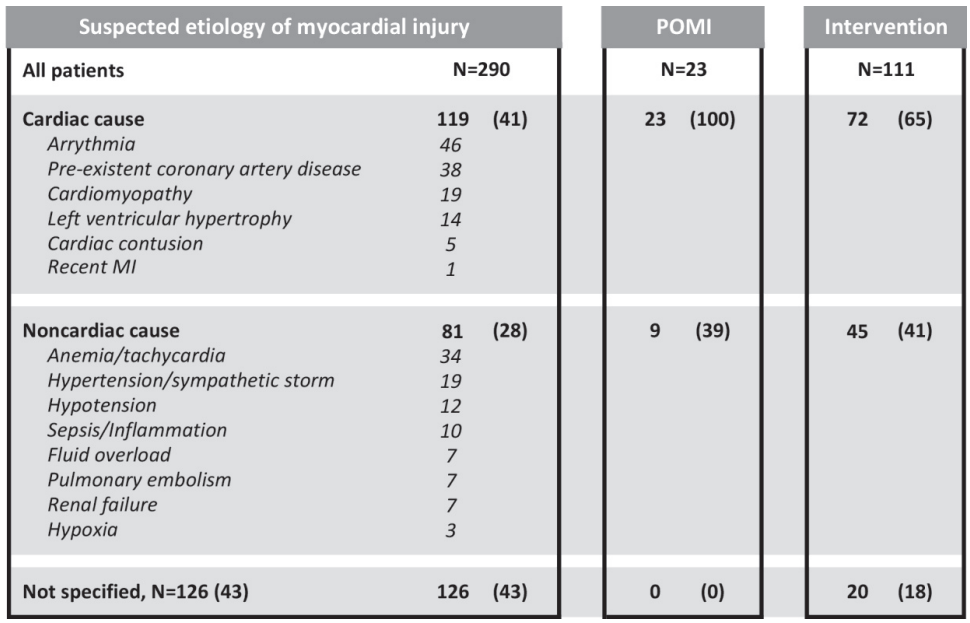
FIGURE 2. Kaplan Meier plot of patients with different levels of troponin elevation.



Legend:

TnI = Troponin-I

FIGURE 3.



Suspected etiology of myocardial injury			POMI		Intervention	
All patients	**N=290**		**N=23**		**N=111**	
Cardiac cause	**119**	**(41)**	**23**	**(100)**	**72**	**(65)**
Arrythmia	*46*					
Pre-existent coronary artery disease	*38*					
Cardiomyopathy	*19*					
Left ventricular hypertrophy	*14*					
Cardiac contusion	*5*					
Recent MI	*1*					
Noncardiac cause	**81**	**(28)**	**9**	**(39)**	**45**	**(41)**
Anemia/tachycardia	*34*					
Hypertension/sympathetic storm	*19*					
Hypotension	*12*					
Sepsis/Inflammation	*10*					
Fluid overload	*7*					
Pulmonary embolism	*7*					
Renal failure	*7*					
Hypoxia	*3*					
Not specified, N=126 (43)	**126**	**(43)**	**0**	**(0)**	**20**	**(18)**

Suspected etiologies of myocardial injury, postoperative myocardial infarction and interventions in the 290 patients with a cardiac consultation. The suspected etiologies as determined by the consultant cardiologist were classified as predisposing cardiac conditions and perioperative triggers. The number of patients with postoperative myocardial infarction and the number of patients with a cardiac intervention are given for each of these groups. Of note, the number of patients in each column exceeds the total number of patients, because in 36 patients the myocardial injury was suspected to be due to both a predisposing cardiac condition and perioperative triggers. Figures are numbers (%) of patients.
*Postoperative myocardial infarction.

CHAPTER 4

CLINICAL RELEVANCE OF CARDIAC TROPONIN ASSESSMENT IN PATIENTS UNDERGOING CAROTID ENDARTERECTOMY.

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ABSTRACT

Objectives. Myocardial infarction (MI) is a frequent complication of carotid endarterectomy (CEA) yet most events are silent. Routine postoperative monitoring of cardiac troponin was implemented in our center to facilitate timely recognition of MI and stratify high-risk patients. We aimed to evaluate the incidence of troponin elevation after CEA and its association with adverse cardiovascular events.

Design and materials. This analysis included patients ≥ 60 years old who underwent CEA, whose Troponin-I levels were routinely monitored postoperatively and were included in a cohort study that assessed clinical outcomes. A clinical troponin cutoff of 60 nanograms per liter was used. The primary endpoint was the composite of MI, stroke and cardiovascular death. Secondary endpoints were MI, stroke, coronary intervention, cardiovascular death and all-cause death.

Results. 225 consecutive patients were included in the analysis. Troponin elevation occurred in 34 patients (15%) and a postoperative MI was diagnosed in 8 patients. After a median follow-up of 1.8 years (IQR 1.0-2.6), the primary endpoint occurred in 29% of patients with troponin elevation versus 6.3% without (HR 5.6, 95%CI 2.4 – 13), MI in 24% versus 1.6% (HR 18.0, 95%CI 4.7 – 68), stroke in 5.9% versus 4.2% (HR 1.4, 95%CI 0.3 – 6.7), coronary intervention in 5.9% versus 2.6% (HR 2.7, 95%CI 0.5 – 14), cardiovascular death in 5.9% versus 0.5% (HR 11.8, 95%CI 1.1 – 131) and all-cause death in 15% versus 5.8% (HR 3.0, 95%CI 1.0 – 8.7), respectively. Incidences of the primary endpoint and all-cause mortality in patients with a postoperative MI versus 'troponin only' were 25% versus 7.7% and 25% versus 12%, respectively.

Conclusion. Troponin elevation after CEA occurred in 15% of patients. The incidence of adverse cardiovascular events was significantly higher in patients with troponin elevation, which was mainly attributable to silent non-ST segment elevation MIs that occurred in the early postoperative phase.

INTRODUCTION

Carotid endarterectomy (CEA) is the treatment of choice for symptomatic and selected asymptomatic patients with severe ipsilateral carotid artery stenosis.[1] Although CEA was challenged by endovascular treatment in the nineties, randomized controlled trials indicated that endovascular treatment was associated with a significantly higher 30-day rate of ipsilateral stroke and death.[2, 3] CEAs superiority regarding stroke prevention, however, was hampered by a higher risk of silent periprocedural myocardial infarction (MI).[2-5]

Routine postoperative assessment of cardiac troponin has been suggested to facilitate MI diagnostics and improve efficacy of cardiac risk stratification models.[6] Troponin is a highly sensitive and specific marker for myocardial injury and a postoperative serum elevation is associated with adverse cardiovascular events in a wide range of surgical populations.[7] Yet, serum troponin levels may be influenced by perioperative factors such as high postoperative blood pressure, anemia, cerebral pathology such as stroke or increased intracranial pressure, and renal failure.[8, 9]

To obtain more insight into the clinical relevance of routine postoperative troponin assessment after CEA, we first aimed to estimate the incidence of post-procedural troponin elevations and analyzed the influence of relevant baseline- and procedure related factors on postoperative troponin elevation. Second, the clinical relevance of troponin elevation and perioperative MI on long-term adverse cardiovascular events was assessed.

METHODS

Study design & population

Patients included in this study were ≥ 60 years old, underwent CEA between January 1st 2011 and December 31th 2013 and underwent routine postoperative troponin measurements as part of the standard postoperative protocol in our tertiary referral center. Patients were excluded if troponin was not measured after surgery or if CEA was combined with cardiac surgery. If patients underwent more than one CEA within the study period only the first CEA was used in the analyses. Indications for CEA were based on current recommendations and discussed in a weekly multidisciplinary meeting.[10] All patients were assessed by a vascular surgeon and an anesthesiologist prior to surgery; referral to a cardiologist occurred in case of angina or ischemia/conduction abnormalities on ECG. All CEAs were performed under general anesthesia using a standardized technique. Cerebral monitoring was performed with electro encephalography (EEG) in all patients and Trans Cranial Doppler (TCD) in patients with a

suitable temporal bone window. Shunting was performed on indication based on EEG and TCD. Closure of the longitudinal arteriotomy was done by patch or primary closure, depending on the surgeon's preference. Dual antiplatelet therapy - acetylsalicylic acid 100 mg once daily and dipyridamol 200mg twice daily - was prescribed before and after surgery in accordance to standard-of-care in our hospital.

Data was obtained from electronic medical records and from the Athero-Express study database, which is a longitudinal observational cohort of patients undergoing endarterectomy.[11] Patients completed a questionnaire regarding medical history and medication use. Clinical adverse events were assessed 30 days after surgery and during follow-up (after 12 months and annually after that time). Follow-up consisted of a questionnaire filled out by the patient in addition to a review of the electronic hospital database; ultimate follow-up was October 2014. The general practitioner and/or treating medical specialist were contacted if an adverse event was apparent. All outcomes were validated by two independent observers who were blinded for postoperative troponin outcomes (i.e. troponin elevations were only considered relevant in the diagnosis of the early postoperative myocardial infarctions). Loss to follow-up was defined as missing data on all follow-up moments. The need for informed consent for this analysis was waived by the local medical ethics committee (UMC Utrecht 15-142/C).

Perioperative determinants of postoperative troponin elevation

Postoperative hypertension and anemia were identified as possibly relevant perioperative determinants of postoperative troponin elevation. Blood pressure was routinely measured three times per day from the moment of hospital admission (one day prior to CEA) until discharge. Postoperative hypertension was defined as a systolic blood pressure of > 160 mmHg or a relative increase in systolic blood pressure of > 20% in comparison to preoperative systolic blood pressure. The highest postoperative blood pressure before the first troponin elevation was used in patients with troponin elevation, and the highest blood pressure on the first three postoperative days in patients without troponin elevation. The lowest hemoglobin level (g/dL) within the first two postoperative days was used to assess troponin's association with anemia. The threshold for red blood cell transfusion was 8 g/dL. For patients with signs of cardiac ischemia (i.e. troponin elevation, STT deviations on ECG, and/or angina) the threshold was 10 g/dL.

Postoperative cardiac Troponin-I assessment and cardiac consultation

Troponin-I was routinely assessed in all patients in citrate plasma on postoperative days 1, 2 and 3. The highest troponin concentration was used in the analysis. A 3rd generation AccuTnI assay (Beckman Coulter, Brea, California) with a clinical upper reference limit (URL) of 60 ng/L was used.[6] In case of troponin elevation, an ECG was performed and troponin measurement was repeated to assess biomarker dynamics. Additional cardiologic tests and outpatient follow-up were performed based on the cardiologist's discretion.

Clinical outcomes

The primary study outcome was major adverse cardiovascular events, which was defined as the composite of MI, stroke and cardiovascular death. Secondary endpoints were MI, stroke, all-cause death, cardiovascular death and coronary revascularization. All endpoints were assessed during hospital admission and follow-up. All MIs were defined according to the third universal definition.[6] A postoperative MI was defined as an MI within 30 days of surgery, and patients were classified as 'troponin only' in case of troponin elevation without angina or ischemic changes on the ECG (based on the most recent definition of MI). All ECGs and MI diagnoses were confirmed by an accredited cardiologist. Stroke was defined as relevant neurological features over more than 24 hours causing an increase in disability and was assessed by an independent neurologist. Cardiovascular death was defined as fatal MI, fatal stroke, fatal abdominal aortic aneurysm rupture, fatal heart failure, or sudden death that was not otherwise specified. Coronary revascularization was defined as a percutaneous coronary intervention and/or coronary artery bypass grafting.

Statistical Analysis

Patients with troponin elevation were compared to patients without troponin elevation with respect to patient- and procedure characteristics, cardiovascular risk factors, and clinical outcomes using the chi-square or Fisher's Exact test for categorical variables; and *t* test or Mann-Whitney U test for normally distributed or non-normally distributed continuous variables, respectively. Clinical outcomes were also assessed using Hazard Ratios (HR) with 95% confidence intervals (95% CI). Kaplan-Meier and lifetable analyses were used to analyze survival. In addition, in order to assess the differences between patients with 'postoperative MI', 'troponin only', and 'without troponin elevation', three groups were created accordingly. Baseline characteristics were compared using the chi-square test for categorical variables and ANOVA for continuous variables. SPSS version 21.0 and Rstudio version 0.98.932 were used for the statistical analysis.

RESULTS

Patient selection

During the study period, 309 patients fulfilled the inclusion criteria of whom 48 were excluded because troponin was not measured, and two because CEA was combined with cardiac surgery. Staged bilateral CEA was performed in 8 patients within the study period and 11 patients were not included in the Athero-Express. Fifteen patients were lost to follow-up after hospital discharge. Therefore, 225 patients (73% of total) were included in the analysis (figure 1). Baseline characteristics are depicted in table 1. Indications for CEA in these patients were transient ischemic attack (39%), stroke (32%), ocular symptoms (19%) and asymptomatic

high-degree stenosis (10%); median time to event for the former three was 14.0 days (IQR 22.0), 14.0 days (IQR 14.0) and 18.0 (IQR 19.0) days, respectively. Preoperative cardiac assessment was performed in 19 patients; in 6 patients because of angina and in 13 patients because of ischemia/conduction abnormalities on the ECG. In addition to routine assessment, a coronary angiogram was made in one patient, transthoracic echocardiography in seven patients and a combination of an exercise test and an echocardiogram in two patients.

Patient characteristics and cardiac Troponin-I

Postoperative troponin elevation occurred in 34 patients (15%). Peak troponin concentrations were most frequently observed on the first two days after surgery, i.e. 13 (39%) on day one and 13 (39%) on day two. Troponin elevation was significantly associated with age, renal failure (glomerular filtration rate <45 ml/min), clinical presentation and type of closure (table 1). None of the patients with angina prior to surgery had troponin elevation. An ECG was made in 83% of patients with troponin elevation, and a cardiologist was consulted in 77%. A non-ST segment elevation MI (NSTEMI) was diagnosed in eight patients (24%), of whom four were admitted to the Coronary Care Unit and three to the Medium Care of the surgical ward. One NSTEMI was attributed to a myocardial supply/demand mismatch secondary to a bilateral pneumonia; rhythm control was not deemed necessary in that patient. Optimization of cardiac medication was performed in all patients with a postoperative MI except for the patient with pneumonia. In contrast, optimization of cardiac therapy in patients with 'troponin only' was performed in 6 patients (23%). Nitrates, beta-blockers, diuretics, and antiarrhythmic drugs were administered in four (50%), six (75%), zero and zero patients with postoperative MI and zero, two (8%), two (8%) and one (4%) patient(s) with 'troponin only', respectively. No additional antiplatelet agents were administered because all patients were already on a dual antiplatelet regimen. One coronary angiogram was performed during hospital admission in a patient with a postoperative MI.

Perioperative determinants of postoperative troponin elevation

Routine pre- and postoperative blood pressure measurements were performed in 222 patients (98%); postoperative hypertension occurred in 9 patients (28%) with troponin elevation versus 92 (48%) without (p = 0.05). Postoperative hemoglobin was assessed in 181 patients (80%); in 32 (94%) with troponin elevation and in 149 (78%) without. Median postoperative hemoglobin concentrations in patients with troponin elevation were 10.9 (IQR 2.8) g/dL versus 12.2 (IQR 2.2) g/dL in patients without; p=0.002.

Clinical outcomes

During a median follow-up time of 1.8 years (IQR 1.0-2.6), major adverse cardiovascular events occurred in 29% of patients with troponin elevation versus 6% without (HR 5.6, 95%CI 2.4 – 13), and MI occurred in 24% versus 2% (HR 18.0, 95%CI 4.7 – 68), respectively (table 2). All MIs in patients with troponin elevation occurred within 30 days of surgery, six (75%) were

silent and all concerned a NSTEMI. In contrast, none of the patients without troponin elevation suffered a MI within 30 postoperative days and only one of three MIs was non-ST segment elevated. Stroke occurred in 6% versus 4% of patients (HR 1.4, 95%CI 0.3 – 6.7), coronary intervention in 6% versus 3% of patients (HR 2.7, 95%CI 0.5 – 14), cardiovascular death in 6% versus 0.5% of patients (HR 11.8, 95%CI 1.1 – 131), and all-cause death in 15% versus 6% of patients (HR 3.0, 95%CI 1.0 – 8.7). Seven patients that suffered a stroke had a symptomatic carotid stenosis at the time of CEA, and three strokes occurred in asymptomatic patients. Hospital admission was more likely to be prolonged in case of troponin elevation (median time until discharge 6.0 days (IQR 4.5) versus 3.0 days (IQR 2.0), respectively ($P < 0.001$).

Clinical outcome data specified for 'postoperative MI' and 'troponin only' is shown in table 3 and baseline characteristics for these groups are shown in addendum 1. During follow-up, MACE occurred in two patients (25%) with postoperative MI versus two patients (8%) with 'troponin only'. Myocardial infarction and stroke occurred in one (13%) versus zero and one (13%) versus one (4%) patient with postoperative MI versus 'troponin only', respectively. Coronary revascularization was performed in two patients (25%) with postoperative MI versus none in the 'troponin only' group. A total of two patients (25%) died in the 'postoperative MI' group versus three (12%) in the 'troponin only' group of which one death was due to cardiovascular disease in each group. The cardiovascular death in the postoperative MI group concerned a postoperative stroke that was complicated by a MI on the Intensive Care Unit. Mean peak troponin levels in patients with troponin elevation – specified for perioperative MI and 'troponin only' – are shown in table 4.

DISCUSSION

In this study, troponin elevation occurred in 15% and was associated with multiple patient and procedure-specific factors such as age, renal failure, stroke as clinical indication of CEA, and postoperative anemia. During a median follow-up time of 1.8 years, the incidence of major adverse cardiovascular events was significantly higher in patients with troponin elevation, which was attributable to a higher incidence of MI in patients with troponin elevation. All MIs in patients with troponin elevation occurred within 30 days after surgery and concerned NSTEMIs whilst all MIs in patients without troponin elevation occurred outside the perioperative phase and only 1 of 3 MIs concerned a NSTEMI.

The overall incidence of early postoperative MIs (i.e. within 30 days of surgery) in our population was 3.6% (table 3), which is considerably higher than the pooled incidence of 2.3% that was reported by a recent meta-analysis.[12] This difference can be explained by heterogeneity regarding study populations, MI definitions, and incorporation of routine

postoperative biomarker assessment. For instance, the CREST trial - which reported a MI incidence of 2.3% - assessed cardiac biomarkers 6-8 hours after surgery and used a definition of postoperative MI that allowed for use of creatinine kinase MB fraction (CK-MB).[2] The ICSS and EVA-3S trials, in contrast, did not perform routine cardiac marker assessment, and the SAPPHIRE trial used an MI definition that was solely based on a creatine kinase level > 2 x the upper limit of normal with a positive MB fraction.[3, 5, 13] The high incidence reported by Galyfos et al can be explained by the description of myocardial damage rather than MI.[14]

The clinical relevance of a postoperative MI according to its latest definition has been assessed by few trials that convey sufficient power. CREST reported a 30-day mortality rate of 2.4% in patients with postoperative MI, 5.0% in patients with 'troponin only' and 0.4% in patients without myocardial injury.[2] In our analysis, however, we found 12.5% versus 0% versus 0.5%, respectively. These discrepancies are probably attributable to smaller numbers in our study and CREST's slightly different definition of MI that allowed for use of CK / CK-MB.[2] Moreover, the 12-month mortality in the CREST population was assessed in a post hoc analysis that demonstrated an incidence of 14.3% in 'postoperative MI' patients, 5.0% in 'biomarkers only' and 2.2% in patients without biomarker elevation.[4] Our data shows a similar trend: 25% versus 11.5% versus 5.8%, which was also observed for cardiovascular mortality (table 3). Other studies with sufficient power are generally characterized by heterogeneity in the definition of MI and do not differentiate between perioperative MI and troponin only. Nonetheless, long-term outcomes analyses uniformly demonstrate an increased mortality risk in patients with troponin elevation.[12]

The overall incidence of stroke is relatively high in our population, which may be explained by a high-risk population of elderly patients of whom 90% were symptomatic, 15% had renal failure, 14% had a contralateral occlusion and all patients underwent general anesthesia. The reason for the additional risk of stroke in patients with troponin elevation is unknown yet may be explained by more extensive vascular disease, more advanced age and a higher number of patients who underwent CEA because of stroke.[15]

Troponin's association with MACE and hard endpoints such as all-cause – and cardiovascular death suggests that there is room for further cardiovascular optimization in patients with troponin elevation. However, studies that assessed the efficacy of coronary revascularization before vascular surgery have been contradictory. For instance, a randomized trial in 510 patients undergoing elective vascular surgery reported no improvement on long-term outcome, and even suggested a higher mortality rate prior to surgery due to complications of the cardiac procedure.[16] A more recent trial that focused on CEA only, in contrast, observed significantly fewer postoperative MIs and deaths in patients with on-indication coronary revascularization (0% and 0%) in comparison to patients without preoperative coronary angiography (4.3% and 0.9%), which was sustained during long-term follow-up.[17, 18] The effect, however, may have been overestimated because the control group did not receive

optimal cardiac medical therapy. Moreover, the complete lack of early postoperative MIs in the intervention group suggests that minor demand ischemia is likely causative in most MI cases, which in concurrence with the relatively minor cardiac biomarker elevations and transient ECG dynamics of the postoperative MIs in our study (table 4).

The suggestion of minor ischemia combined with the influence of patient- and procedure specific factors demands clinical scrutiny when interpreting patients with troponin elevation and underlines the risk of excessive MI diagnoses in the early postoperative phase. On the other hand, troponin's prognostic value on hard endpoints such as (cardiovascular) death cannot be discarded. To overcome these issues, one should consider accessible use of cardiac imaging to ensure adequate cardiac optimization. The optimal timing of such optimization, however, is currently unknown. In any case, the potential benefit of aggressive preoperative cardiac optimization should be weighed against the potential disadvantage of delaying CEA. Furthermore, due to the possibility of excessive MI diagnoses, one should be reticent in using a composite endpoint that contains both stroke and MI in studies assessing the procedural safety and efficacy of CEA.

Some study limitations have to be recognized. First, multivariable analysis to adjust for risk factors was not feasible due to a limited number of outcomes. It has to be kept in mind that the association between troponin elevations and clinical outcomes may be confounded by risk factors such as renal function and age. Still, this study provides valuable insights into the prevalence of troponin elevations after CEA, the factors associated with it, and the clinical picture of the early postoperative MIs. Second, troponin assessment was not routinely performed in all eligible patients (15% was missed because of logistic difficulties), and selection bias cannot be excluded entirely. Moreover, an ECG was not made in 17% of patients with troponin elevation, which may have led to missing of MIs in those patients. Yet, this number is expected to be negligible since all of these patients were asymptomatic and troponin levels were low (mean peak troponin level was 150 ±70 ng/L). Third, validity of the three strata may be limited due to small numbers. Finally, some clinical outcomes may have been missed due to a varying follow-up time.

Conclusion

In this study, troponin elevation after CEA occurred in one of every six patients and was associated with several patient- and procedure-specific factors. The long-term incidence of major adverse cardiovascular events was higher in patients with troponin elevation, which was mainly attributable to silent non-ST elevation myocardial infarctions that occurred in the early postoperative phase.

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TABLE 1. Baseline characteristics

	Troponin elevation N = 34 (15%)	**No troponin elevation** N = 191 (85%)	**P-value**
Age (mean, SD)	76.0 (6.4)	72.5 (7.6)	0.01
Male sex	28 (82.4)	136 (71.2)	0.26
Comorbidities			
History of myocardial infarction	11 (32.4)	44 (23.0)	0.34
History of coronary intervention	13 (38.2)	49 (25.9)	0.21
Congestive heart failure (LVEF < 35%)	3 (8.8)	9 (4.7)	0.58
History of peripheral vascular intervention	9 (26.5)	39 (20.4)	0.57
Renal failure (GFR <45 ml/min)	11 (32.4)	22 (11.6)	0.004
Cardiovascular risk factors			
Current smoking	9 (26.5)	58 (30.4)	0.80
Diabetes mellitus	11 (32.4)	46 (24.1)	0.42
History of hypertension	30 (88.2)	158 (82.7)	0.58
Hypercholesterolemia	21 (80.8)	121 (73.3)	0.57
Body Mass Index (mean, SD))	25.2 (3.8)	26.2 (3.8)	0.14
Medication			
Beta-blocker	13 (38.2)	74 (38.7)	1.00
ACE inhibitor	16 (47.1)	57 (29.8)	0.08
Calcium channel blocker	11 (32.4)	47 (24.6)	0.46
Other antihypertensive drugs	10 (29.4)	90 (47.1)	0.08
Oral anticoagulation	2 (5.9)	21 (11.0)	0.55
Antiplatelet	27 (79.4)	169 (88.5)	0.24
Statin	27 (79.4)	155 (81.2)	1.00
Contralateral carotid stenosis (50-99%)	10 (35.7)	40 (26.3)	0.43
Contralateral occlusion	7 (25.0)	19 (12.5)	0.15
Clinical presentation			0.01
Stroke	19 (55.9)	53 (27.7)	
TIA	9 (26.5)	78 (40.8)	
Ocular	4 (11.8)	39 (20.4)	
Asymptomatic	2 (5.9)	21 (11.0)	
Type of closure			0.02
Primary	3 (8.8)	2 (1.1)	
Venous patch	4 (11.8)	33 (18.2)	
Bovine patch	27 (79.4)	135 (74.6)	
Dacron/PTFE patch	0	11 (6.1)	
Event to operation time, days (median, IQR)	14.0 (9.0)	15.0 (17.0)	0.25
Preoperative hemoglobin (median, IQR)*	13.8 (2.4)	14.2 (2.1)	0.07

Legend:

Categorical variables are shown as percentages, continuous variables as mean (standard deviation) or median (interquartile range). LVEF: left ventricular ejection fraction, GFR: glomerular filtration rate; PTFE: polyfluoroethylene; IQR: interquartile range.

* Time between last cerebrovascular event and operation, in case of symptomatic disease.

TABLE 2. Clinical outcomes during follow-up

	Troponin elevation N = 34 (15%)	**No troponin elevation** N = 191 (85%)	**Hazard Ratio (95% CI)**	
30 days				
MACE	9 (26.5)	5 (2.6)	11.1 (3.7 – 33)	P<0.001
MI	8 (23.5)	0	-	P<0.001
Stroke	2 (5.9)	5 (2.6)	2.3 (0.4 – 12)	P=0.33
Cardiovascular death	1 (2.9)	0	-	P=0.15
All-cause death	1 (2.9)	1 (0.5)	5.7 (0.4 – 91)	P=0.22
Coronary revascularization	1 (2.9)	0	-	P=0.15
Follow-up				
MACE	10 (29.4)	12 (6.3)	5.6 (2.4 – 13)	P<0.001
MI	8 (23.5)	3 (1.6)	18.0 (4.7 – 68)	P<0.001
Stroke	2 (5.9)	8 (4.2)	1.4 (0.3 – 6.7)	P=0.66
Cardiovascular death	2 (5.9)	1 (0.5)	11.8 (1.1 – 131)	P=0.04
All-cause death	5 (14.7)	11 (5.8)	3.0 (1.0 – 8.7)	P=0.04
Coronary revascularization	2 (5.9)	5 (2.6)	2.7 (0.5 – 14)	P=0.25

Legend:

CI: confidence interval; MACE: major adverse cardiovascular events (defined as the composite of MI, stroke and cardiovascular death); MI: myocardial infarction

TABLE 3. Clinical outcomes during follow-up for troponin subgroups

	Postoperative MI N = 8 (4%)	**Troponin only** N = 26 (11%)	**No troponin elevation** N = 191 (85%)
30 days			
MACE	*0*	*1 (3.8)*	5 (2.6)
MI	*0*	*0*	0
Stroke	*1 (12.5)*	*1 (3.8)*	5 (2.6)
Cardiovascular death	*1 (12.5)*	*0*	0
All-cause death	*1 (12.5)*	*0*	1 (0.5)
Coronary revascularization	*1 (12.5)*	*0*	0
Follow-up			
MACE	2 (25.0)*	2 (7.7)	12 (6.3)
MI	1 (12.5)*	0	3 (1.6)
Stroke	1 (12.5)	1 (3.8)	8 (4.2)
Cardiovascular death	1 (12.5)	1 (3.8)	1 (0.5)
All-cause death	2 (25.0)	3 (11.5)	11 (5.8)
Coronary revascularization	2 (25.0)	0	5 (2.6)

Legend:
MACE: major adverse cardiovascular events (defined as the composite of MI, stroke and cardiovascular death); MI: myocardial infarction
* The early postoperative MIs are not incorporated in this number

TABLE 4. Infarct size based on troponin concentration

	N	Peak troponin (ng / L) Median (IQR)
Overall / troponin elevation	34	156 (89 - 320)
Troponin only	26	140 (80 - 181)
Postoperative MI	8	2345 (534 - 6865)
Symptomatic	2	779 (290 - 1270)*
Asymptomatic	6	4390 (1666 - 8140)

Legend:
ng/L: nanograms per liter; IQR: Interquartile range; MI: myocardial infarction
* range

FIGURE 1. Flowchart

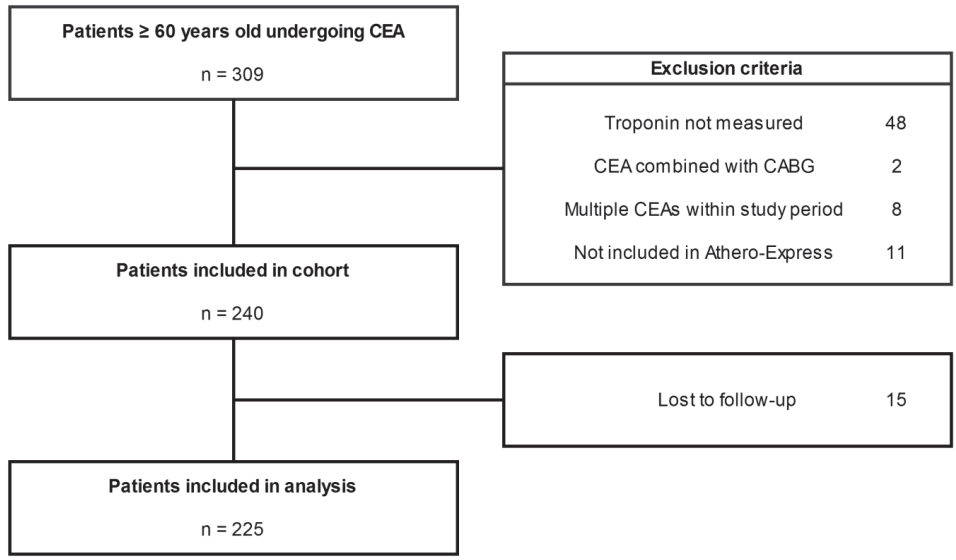
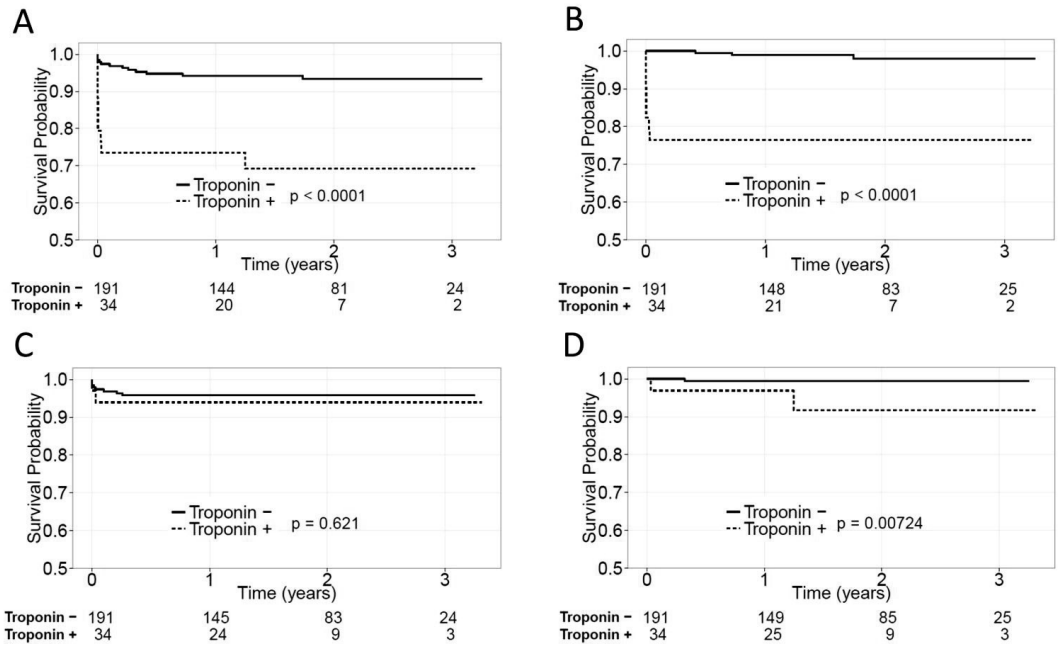


FIGURE 2. Survival plots



Legend

Kaplan-Meier survival plots for different clinical events after carotid endarterectomy, for groups with (dashed line) and without (continuous line) postoperative cardiac troponin elevation. A: major adverse cardiovascular events; B: MI; C: stroke; D: cardiovascular death. P-values are derived from log-rank analyses.

SUPPLEMENTAL FILE. Baseline characteristics for troponin subgroups

	MI N=8 (4%)	**Troponin only** N=26 (14%)	**No troponin elevation** N=191 (85%)	**p-value**
Age (mean, SD)	76.1 (6.4)	76.0 (6.6)	72.5 (7.6)	0.045
Male sex	5 (62.5)	23 (88.5)	136 (71.2)	0.14
Comorbidities				
History of myocardial infarction	2 (25.0)	9 (34.6)	44 (23.0)	0.44
History of coronary intervention	3 (37.5)	10 (38.5)	49 (25.9)	0.34
Congestive heart failure (LVEF < 35%)	1 (12.5)	2 (7.7)	9 (4.7)	0.54
History of peripheral vascular intervention	3 (37.5)	6 (23.1)	39 (20.4)	0.50
Renal failure (GFR <45 ml/min)	5 (62.5)	7 (23.1)	22 (11.6)	< 0.001
Cardiovascular risk factors				
Current smoking	2 (25.0)	7 (26.9)	58 (30.4)	0.90
Diabetes mellitus	3 (37.5)	8 (30.8)	46 (24.1)	0.55
History of hypertension	8 (100)	22 (84.6)	158 (82.7)	0.43
Hypercholesterolemia	3 (60.0)	18 (85.7)	121 (73.3)	0.36
Body Mass Index (mean, SD)	26.4 (4.8)	24.8 (3.4)	26.2 (3.8)	0.20
Medication				
Beta-blocker	4 (50.0)	9 (34.6)	74 (38.7)	0.74
ACE inhibitor	3 (37.5)	13 (50.0)	57 (29.8)	0.11
Calcium channel blocker	3 (37.5)	8 (30.8)	47 (24.6)	0.59
Other antihypertensive drugs	4 (50.0)	6 (23.1)	90 (47.1)	0.065
Oral anticoagulation	0	2 (11.0)	21 (11.0)	0.54
Antiplatelet	8 (100)	19 (73.1)	169 (88.5)	0.048
Statin	5 (62.5)	22 (81.2)	155 (81.2)	0.37
Contralateral carotid stenosis (50-99%)	1 (12.5)	9 (45.0)	40 (26.3)	0.13
Contralateral occlusion	3 (37.5)	4 (20.0)	19 (12.5)	0.13
Clinical presentation				0.087
Stroke	5 (62.5)	14 (53.8)	53 (27.7)	
TIA	2 (25.0)	7 (26.9)	78 (40.8)	
Ocular	1 (12.5)	3 (11.5)	39 (20.4)	
Asymptomatic	0	2 (7.7)	21 (11.0)	
Type of closure				0.019
Primary	0	3 (11.5)	2 (1.1)	
Venous patch	0	4 (15.4)	33 (18.2)	
Bovine patch	8 (100)	19 (73.1)	135 (74.6)	
Dacron/PTFE patch	0	0	11 (6.1)	
Event to operation time, days (median, IQR) *,**	14.0 (7.0)	14.0 (10.0)	17.0 (21.0)	0.45
Preoperative hemoglobin (median, IQR) **	14.2 (2.1)	13.3 (2.4)	14.0 (2.2)	0.12

Legend:
Categorical variables are shown as percentages and continuous variables as mean (standard deviation) or median (IQR). LVEF: left ventricular ejection fraction, GFR: glomerular filtration rate; PTFE: polyfluoroethylene; IQR: interquartile range.
* Time between last cerebrovascular event and operation, and in case of symptomatic disease.
** Statisctical significance tested using Kruskal-Wallis test

PART III

THE ETIOLOGY OF

POSTOPERATIVE MYOCARDIAL INJURY

CHAPTER 5

UNEXPECTED CARDIAC CT FINDINGS IN PATIENTS WITH POSTOPERATIVE MYOCARDIAL INJURY

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SUBMITTED

ABSTRACT

Background. Postoperative myocardial injury (PMI) is a strong predictor of mortality after noncardiac surgery. PMI is believed to be attributable to coronary artery disease (CAD) yet its etiology is largely unclear. We aimed to quantify the prevalence of significant CAD in patients with and without PMI using coronary computed tomography angiography (CCTA).

Materials: Prospective cohort study in patients ≥60 years old with and without PMI after intermediate to high-risk noncardiac surgery. PMI was defined as any serum Troponin-I level ≥60 ng/L on the first three postoperative days. Main exclusion criteria were known cardiac disease and post-operative ischemic symptoms or ECG abnormalities. Non-invasive imaging consisted of a postoperative CCTA. Outcomes were CAD defined as >50% coronary stenosis on CCTA, and 30-day mortality.

Results: The analysis included 66 patients. Median troponin levels in the PMI (n= 46) and control group (n = 20) were 150 (IQR 120 – 298) versus 15 (IQR 10 – 31) ng/L (p<0.01). CAD was found in 23 patients with PMI (50%) versus 3 without PMI (15%) (RR 3.3, 95%CI 1.1 – 9.8). Remarkably, pulmonary embolism was present in 15 patients with PMI (33%) versus 4 without PMI (20%) (RR 1.6, 95%CI 0.6 – 4.3). 30-day mortality was 0% in both groups.

Conclusions: Myocardial injury after noncardiac surgery is associated with CAD. In addition, a clinically silent pulmonary embolism was found in a third of patients with PMI.

INTRODUCTION

Annually, over 200 million people undergo major noncardiac surgery worldwide.[1] These procedures are associated with a high risk of mortality and morbidity, which can be attributed to major adverse cardiovascular events (MACE) in up to 50% in high-risk populations.[2-4] Recognition of such events, however, is difficult in the early postoperative phase because of the use of strong analgesics and transiency of ischemic signs on electrocardiography.[5] These difficulties may delay adequate treatment and consecutively influence prognosis.

A promising method to improve early recognition of MACE after surgery is routine postoperative assessment of cardiac troponin, which is a sensitive biomarker with high specificity for the myocardium.[6] Indeed, serum troponin elevations are a strong and independent predictor of 30-day and 12-month mortality.[2, 3] Such postoperative myocardial injury (PMI) is believed to be primarily attributable to an oxygen supply / demand mismatch in the presence of pre-existent coronary artery disease (type II ischemia) or thrombosis on a ruptured atherosclerotic carotid plaque (type I ischemia).[5-8] However, recent trials have shown that platelet aggregation inhibition and suppression of the sympathetic nervous system does not result in a decrease in postoperative MIs and may even be harmful.[9, 10]

In order to improve prognosis, it is imperative to understand the etiology of PMI and in particular the role of CAD. The aim of this study was to quantify the prevalence of CAD in patients with and without asymptomatic PMI using non-invasive cardiac imaging.

METHODS

This prospective single-center cohort study included patients of 60 years or older who underwent elective intermediate to high-risk noncardiac surgery requiring ≥ 24 hours of hospital admittance in the University Medical Center Utrecht between October 1st 2012 and March 31th, 2015 and whose Troponin-I levels were routinely monitored on the first three postoperative days.[11] Exclusion criteria were prior CAD or myocardial infarction, ST-elevation myocardial infarction, typical angina, non-coronary heart disease (i.e. heart valve disease, cardiomyopathy and/or diastolic heart failure) and contra-indications for cardiac CT angiography (CCTA). The local medical ethics committee approved the study protocol and all study subjects provided informed consent (local Medical Research Ethics Committee number 12-017).

All study subjects underwent standardized preoperative anesthesia evaluation including an ECG. Postoperative troponin assessment was performed using a 3rd generation AccuTnI assay (Beckman Coulter, Brea, California).[6] Patients were classified as having PMI if at least one of the troponin measurements exceeded the clinically used threshold of 60 ng/L, which is the lowest value measurable with a 10% coefficient of variation above the 99th percentile of 40

ng/L.[6] Patients without PMI were characterized by a peak troponin below that level. We aimed to include 50 patients with PMI and 20 patients without PMI.

Study procedures consisted of an ECG within 3 days after surgery and a Cardiac CT Angiography (CCTA) during hospital admission. The CCTA was made on a 256-slice CT scanner (Brilliance iCT, Philips Healthcare, Best, The Netherlands) using a prospectively ECG-triggered step-and-shoot mode. Beta-blockade was used – if necessary - to achieve a heart rate of approximately 60 beats per minute. Furthermore, 0.4 mg nitroglycerin spray was administered 3-5 minutes prior to the scan. A non-enhanced scan was performed to calculate the calcium score using the Agatston method.[12] Intravenous contrast fluid (Ultravist 300®) followed by 50 ml of saline flush was subsequently injected into the antecubital vein. Scans were initiated 10 seconds after mean region of interest contrast reached a pre-set threshold of 100 Hounsfield Units. All images were prospectively triggered at 75% of the R–R interval. Scanning parameters included 0.45 mm slice increment, 250 mm field-of-view that included the pulmonary artery, 512x512 matrix, 270 ms gantry rotation-time, tube-voltage and reference tube current were adjusted for patient body-mass index. The degree of stenosis was classified as none (0% stenosis), mild (0 – 25% stenosis), moderate (25 – 50% stenosis) or significant (>50% stenosis) by a radiologist. Also, presence of a total occlusion was assessed. CCTA images were assessed by an experienced cardiovascular radiologist who was blinded for the troponin values (TL). Follow-up was performed at the cardiology outpatient clinic after 30 days and included an ECG and assessment of adverse cardiovascular events.

The primary study endpoint was CAD, defined as > 50% stenosis in one or more major epicardial vessels on CCTA. The secondary endpoint was 30-day mortality. Incidental findings included pulmonary embolism, which was defined as a sharply delineated pulmonary artery filling defect in at least two consecutive image sections of the CCTA, either located centrally within the vessel or with acute angles at its interface with the vessel wall.[13]

Statistical analysis

The PMI group was compared to the group without PMI using a two-tailed chi-square or Fisher's Exact test for categorical variables, and the *t* test and Mann-Whitney U test for normally distributed and non-normally distributed continuous variables, respectively. Associations between PMI and study endpoints were expressed as unadjusted Relative Risk (RRs) with 95% confidence intervals (95%CI). Loss-to-follow-up was defined as withdrawal of consent between the CCTA and the outpatient clinic visit. SPSS 21.0 and GraphPad Prism 6 were used for the statistical analysis. A value of 0.05 was used as level of significance.

RESULTS

Of the 1205 patients who were screened for study participation (943 with PMI and 262 without PMI), 685 were eligible (Figure 1). Within those patients, 322 were unable to provide consent, 106 refused participation and 187 were not included for logistic reasons (e.g. CCTA not available). Four patients were excluded from the analysis because of insufficient imaging quality. Therefore, 66 patients were included in the analysis; 46 with PMI and 20 without. Patients with PMI were significantly older, were more often diabetics and more often used beta-blockers (Table 1). None of the patients underwent additional cardiac tests prior to surgery. The median peak troponin level in the PMI group compared to the group without PMI was 150 (IQR 120 – 298) versus 15 (IQR 10 – 31) ng/L (p<0.01). The postoperative ECGs showed new ST depression or T wave inversion in nine patients with PMI (20%) versus four patients without PMI (31%) (p=0.46) and a supraventricular arrhythmia was observed in two (4%) patients versus zero, respectively (p>0.99). Median postoperative hemoglobin levels (g/dL) were 10.9 (IQR 9.7 – 11.9) in patients with PMI versus 10.7 (IQR 9.4 – 12.0) in patients without (p=0.52) and median duration of hospital admittance was 9 days (IQR 7 – 12) versus 9 days (IQR 5 – 11) (p=0.32), respectively.

CCTA outcomes

CAD was diagnosed in 23 patients with PMI (50%) versus in three patients without PMI (15%, RR 3.3, 95%CI 1.1 – 9.8) (Table 2). This concerned an occlusion in two patients (4%) versus one patient (5%), respectively. None of the patients had a left main stenosis. CAD in the proximal LAD was observed in six patients with PMI (13%) versus one patient without PMI (5%). The median coronary artery calcium score was 283 (IQR 40–707) in the PMI group versus 68 (IQR 7–289) in the group without PMI (p=0.031). Incidentally, pulmonary embolism was diagnosed in 15 patients with PMI (33%) versus four patients without PMI (20%) (RR 1.6, 95%CI 0.6 – 4.3). In patients with PMI, the emboli were central, segmental, and subsegmental in four (27%), eight (53%) and three patients (20%), respectively. For patients without PMI, these numbers were zero, two (50%) and two (50%), respectively. Furthermore, pulmonary embolism occurred after orthopedic (8/15), neurosurgical (4/9), head and neck (2/6) and abdominal surgery (1/10) in the PMI group, in comparison to orthopedic (2/5) and abdominal (2/5) in the control group. Median time from surgery to CCTA was 5 days (IQR 4-7) in patients with PMI versus 6 days (IQR 4-7). Median troponin levels for subgroups are shown in Figure 2.

Patient management

In 22 of 26 patients with CAD on CCTA (85%), a cardiac MRI was performed. This MRI showed late gadolinium enhancement in two patients and a perfusion defect in five. Furthermore, in the four patients that did not have a MRI, a coronary angiogram was performed in two, both of which confirmed CAD. 18 patients with PMI (39%) were treated with aspirin, beta-blocker, statin and/or antihypertensive drugs, whereas in the group without PMI, 4 patients (20%)

were treated as such. Oral anticoagulation was started in 14 (30%) versus 3 patients (15%), respectively. Furthermore, coronary revascularization was performed in the four patients (i.e. two patients with confirmed CAD on coronary angiography and two patients with a perfusion defect on MRI). The 30-day mortality was 0% in both patients with PMI and without PMI.

DISCUSSION

The prognostic relevance of PMI on short and intermediate-term mortality has been established in a variety of surgical populations.[11, 14] Such PMI is believed to be attributable to an oxygen supply and demand mismatch or a coronary plaque rupture which is provoked by postoperative anemia and tachycardia.[15] Our study indeed demonstrated an association of PMI with obstructive CAD. To the best of our knowledge, this is the first study using CCTA in patients with PMI in the post-operative setting.

Studies that assessed the underlying pathophysiologic mechanism of PMI have predominantly focused on symptomatic patients with evident ST segment deviations in whom the prevalence of coronary plaque rupture is relatively high (45%).[8] These patients, however, do not represent the typical patient with PMI, who is generally characterized by absence of clinical symptoms and subtle and/or transient ECG abnormalities.[11] In our study in patients without known CAD or prior MI, silent CAD was present in half of the patients with PMI versus fifteen percent in the control group. Based on the combination of relatively minor ECG abnormalities, low troponin levels and a general absence of late enhancement on MRI, it would appear that the vast majority of PMI was caused by demand ischemia rather than an occlusive coronary thrombus. Of note, the association with CAD and PMI in our study is in line with studies that reported an association between moderate to severe perfusion defects on stress-echocardiography and thallium imaging, and perioperative MI.[16] Furthermore, they concur with Sheth and colleagues, who performed CCTA prior to noncardiac surgery (i.e. mostly orthopedic and vascular procedures) in 995 patients. In that study, extensive obstructive CAD - defined as ≥50% stenosis in two vessels including the proximal left anterior descending artery, three vessels, or left main - was associated with perioperative MI and cardiac death within 30 days (Hazard Ratio 3.76 (1.12 – 12.62).[17] Interestingly, CAD was absent in 28% of patients who experienced this endpoint, which may indicate that noncardiac pathology may play a larger role in the occurrence of postoperative MI than initially anticipated. Of note, this is in line with Noordzij and colleagues, who reported an association of PMI with respiratory insufficiency, sepsis, anastomotic dehiscence, wound infection and bleeding after elective major abdominal surgery.[18]

An important finding of our study is the presence of silent pulmonary embolism in one third of the patients with PMI, of which the majority (80%) was central or segmental. Within these patients, minor dyspnea, transient hypotension and atypical thoracic complaints did occur, yet none of them were clinically suspected due to the prevalence of such symptoms. It is

therefore likely that these embolisms would have been missed. Of note, the high incidence of pulmonary embolism in our study is discrepant with registries that reported numbers up to 1%, which can be explained by the predominance of symptomatic pulmonary embolism and lack of modern CT pulmonary angiography use in those studies.[19, 20] Indeed, more recent CTA studies in asymptomatic orthopedic and vascular patients have suggested postoperative embolism rates of 7% and 26%, respectively.[21, 22] A possible explanation for the higher incidence of pulmonary embolism in the PMI group is that the PMI could be a result of increased right ventricular pressures or hypoxemia due to a perfusion/ventilation mismatch.[23, 24] Of note, the suggestion of pulmonary embolism as a cause of PMI may potentially explain part of the absence of obstructive CAD in over a quarter of patients that suffered a postoperative MI.[17] It should also be noted that elevated cardiac markers due to pulmonary embolism are independent predictors of adverse events in the nonsurgical population.[25, 26] One could hypothesize that such an association is also present in the surgical population, which – in part – could explain the association of PMI with mortality.[11]

Multiple observational and intervention studies have been performed in order to improve cardiovascular outcomes after noncardiac surgery yet progress has been slow. For instance, the predictive accuracy of clinical risk stratifying models is generally limited, and adding preoperative imaging either led to underestimation (i.e., in case of perfusion imaging) or overestimation of the cardiac risk (i.e., in case of cardiac CT).[16, 17, 27] Furthermore, preoperative coronary interventions did not improve postoperative mortality, nor did perioperative administration of beta-blockers, aspirin or clonidine.[28-31] Our study results, in contrast, suggest that postoperative CCTA may be useful for identification and differentiation of silent cardiovascular pathology, which – in turn - could improve patient management. Notably, other non-invasive cardiac imaging modalities such as echocardiography and MRI may suffer from poor imaging quality (as a result of suboptimal patient positioning) and inability to lay flat for a considerable amount of time. CCTA, however, is able to differentiate most underlying PMI pathologies and is only impractical in patients with arrhythmia or with renal failure.[32, 33] CCTA could therefore be considered to guide treatment in high-risk patients with PMI, in whom a more aggressive treatment strategy may be beneficial. Of note, such a timely intervention may even have partly explain the low incidence of 30-day mortality. However, it is more likely that absence of 30-day mortality is attributable to selection of a relatively healthy group of patients (i.e., patients without known CAD or prior MI). Future studies should focus on the association of pulmonary embolism with both PMI and (cardiovascular) mortality, and the potential of troponin to identify high-risk patients who require more aggressive therapy.[25, 34, 35]

Some study limitations should be recognized. First, our study was performed in patients without known CAD or prior MI. Selection of such a population implies that our results pertain to relatively “vascular-clean” patients, which may limit the generalizability for the entire non-cardiac surgery population. Second, the inclusion rate was low, which was primarily a result

of selection of patients without prior CAD, patients who were unable to give informed consent (e.g. due to stroke, sepsis or delirium) and difficult logistics (e.g. transfer to other hospital or unavailability of research-CCTA slots on short notice). Yet, since patients were recruited consecutively, and exclusion percentages and baseline characteristics were similar for both groups, it is unlikely that selection bias will have influenced our results. Third, some (sub)segmental pulmonary embolisms may have been missed due to the CCTA's limited field of view. This comprised 250 mm and included the pulmonary trunk yet typically did not include the subsegmental branches of especially the superior lobes, which may have led to an underestimation of the incidence of pulmonary embolism. Finally, no power calculation was performed because no data were available regarding the prevalence of CAD in asymptomatic PMI at the time of study initiation.

CONCLUSION

Myocardial injury after noncardiac surgery is associated with CAD. In addition, a clinically silent pulmonary embolism was found in a third of patients with PMI.

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TABLE 1. Baseline characteristics

	PMI n=46 (70%)	No PMI n=20 (30%)	P-value
Age *	68 (65-75)	65 (63-69)	0.029
Male sex	25 (54)	13 (65)	0.59
History of myocardial infarction	0 (0)	0 (0)	-
History of coronary intervention	1 (2)	0 (0)	>0.99
History of stroke	3 (7)	1 (5)	>0.99
Current atrial fibrillation	2 (4)	0 (0)	>0.99
COPD	6 (13)	0 (0)	0.17
Renal failure (GFR <30 ml/min/1.73mm^2)	0 (0)	0 (0)	-
Cardiovascular risk factors			
Current smoking	9 (20)	2 (10)	0.48
Diabetes mellitus	9 (20)	0 (0)	0.048
Hypertension	27 (59)	8 (40)	0.26
Hypercholesterolemia	14 (31)	4 (20)	0.53
Body Mass Index †	26 (4)	26 (4)	0.74
Medication			
Beta-blocker	13 (28)	1 (5)	0.048
Ca-antagonist	6 (13)	3 (15)	>0.99
ACE-inhibitor	6 (13)	4 (20)	0.48
Other antihypertensive drugs	12 (26)	2 (10)	0.20
Aspirin	8 (17)	3 (15)	>0.99
Clopidogrel	3 (7)	0 (0)	0.55
Oral anticoagulation	3 (7)	0 (0)	0.55
Statin	9 (20)	5 (25)	0.75
Insulin	2 (4)	0 (0)	>0.99
ASA class			0.42
1 or 2	39 (85)	19 (95)	
3 or 4	7 (15)	1 (5)	
Type of surgery			0.33
Orthopedic	15 (33)	5 (25)	
Vascular	5 (11)	0	
Neurosurgical	9 (20)	3 (15)	
Abdominal	10 (22)	5 (25)	
Head and neck	6 (13)	5 (25)	
Gynecologic and urologic	1 (2)	2 (10)	

Legend:

PMI: postoperative myocardial injury; COPD = chronic obstructive pulmonary disease; GFR = glomerular filtration rate; ASA = American Society of Anesthesiologists

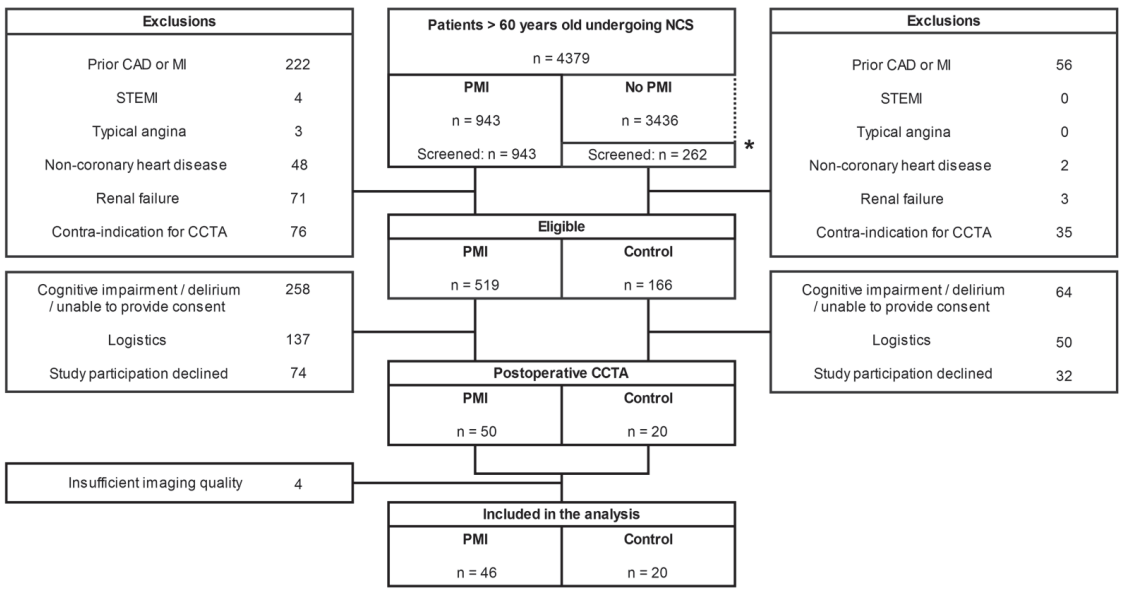
* Median (interquartile range); † Mean (standard deviation)

TABBLE 2. CCTA outcomes

	PMI N = 46 (%)	No PMI N = 20 (%)	Relative Risk (95%CI)	p-value
Coronary artery disease	23 (50)	3 (15)	3.3 (1.1 – 9.8)	0.016
Total occlusion	2 (4)	1 (5)		
Coronary artery calcium score	283 (40–707)	68 (7–289)		0.031
Pulmonary embolism	15 (33)	4 (20)	1.6 (0.6 – 4.3)	0.46

Legend:
CI: confidence interval, PMI: postoperative myocardial injury

FIGURE 1. Flowchart

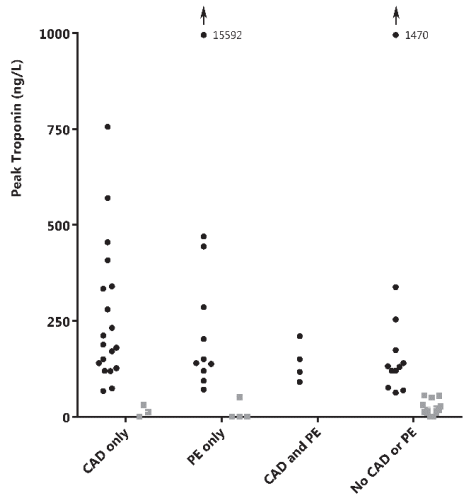


Legend:

* 262 consecutive patients were screened for the group without PMI

PMI: postoperative myocardial injury; NCS: noncardiac surgery; CAD: coronary artery disease; MI; myocardial infarction; STEMI: ST-elevation MI; CCTA: coronary computed tomography angiography.

FIGURE 2. Median peak troponin concentration for CAD and PE



	PMI group		Control group	
	n =	median (IQR)	n =	median (IQR)
CAD only	19	188 (127 - 340)	3	12 (0 - 31)
PE only	11	150 (120 - 444)	4	10 (0 - 28)
CAD and PE	4	134 (98 - 195)	0	
No CAD or PE	12	131 (87 - 234)	13	18 (10 - 41)

Legend:

CAD: coronary artery disease; PE: pulmonary embolism.

CHAPTER 6

ROUTINE POSTOPERATIVE TROPONIN-I ASSESSMENT IN PATIENTS SUSPECTED OF PULMONARY EMBOLISM AFTER NON-CARDIAC SURGERY

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SUBMITTED

ABSTRACT

Introduction: Pulmonary embolism (PE) after non-cardiac surgery is hard to recognize because clinical symptoms are difficult to interpret and risk stratifying tools are less valuable after surgery. Troponin elevation is common in patients with PE and may have additional value in patients suspected of postoperative PE.

Methods: This retrospective, single-center study included patients ≥60 years-old who underwent CT pulmonary angiography (CTPA) or a ventilation/perfusion scan after non-cardiac surgery. Troponin was routinely assessed on the first three postoperative days. The primary outcome was presence of PE and the secondary outcome was one-year mortality.

Results: PE was diagnosed in 57 of 207 included patients (28%). Troponin elevation was observed in 32 patients with PE (56%) versus 61 patients without PE (41%) (p=0.046). Sensitivity, specificity, positive and negative predictive value were 55% (95%CI 42–68), 59% (95%CI 51–67), 33% (95%CI 24–44) and 78% (95%CI 69–85), respectively. Addition of troponin to the Wells score led to a significant improvement of the area under the ROC curve from 0.58 (95%CI 0.49–0.67) to 0.64 (95%CI 0.55-0.72) (p=0.02). In patients with PE, 30-day and one-year mortality were 16% and 35% in the troponin elevation group versus 8% and 25% in the group without troponin elevation (Hazard Ratio 1.9, 95%CI 0.4–9.9 and 1.6, 95%CI 0.5–4.6).

Conclusion: PE after non-cardiac surgery was diagnosed in 28% of patients with a clinical suspicion of PE. Addition of troponin elevation significantly improved the diagnostic value of the Wells score but its overall predictive accuracy remained poor.

INTRODUCTION

Recognition of pulmonary embolism (PE) is difficult after non-cardiac surgery because clinical signs and symptoms of PE (e.g. dyspnea, thoracic complaints, tachycardia and decreased oxygen saturation) are often masked by perioperative factors such as wound pain, anemia and respiratory complications.[1] Risk stratification tools that are based on clinical signs and symptoms - such as the Wells score - may therefore be less valuable in the postoperative period.

Cardiac troponin is an independent predictor of mortality and adverse cardiovascular events after non-cardiac surgery.[2] Because of its sensitivity and specificity for coronary insufficiency, troponin elevation is believed to be primarily caused by coronary artery disease.[3, 4] However, troponin elevation can also occur in the presence of non-cardiac pathology such as PE.[5] In fact, up to 50% of patients with non-perioperative PE have troponin levels that exceed the clinical cut-off, which is thought to result from acute pressure overload of the right ventricle, impaired coronary artery flow and/or a hypoxic state.[6-8] Such troponin elevations after PE are associated with a poor outcome.[6]

In this study, we assessed the diagnostic value of troponin elevation in patients clinically suspected for PE after non-cardiac surgery. In addition, the prognostic value of troponin elevation on one-year mortality was examined.

METHODS

This retrospective, single center study included patients ≥60 years-old with a clinically suspected PE within one week after major non-cardiac surgery that was performed between January 1st 2011 and December 31st 2015 in a tertiary referral center in The Netherlands. A patient was considered to be clinically suspected of PE if a CT pulmonary angiography (CTPA) or ventilation perfusion scan was made to exclude/confirm PE, with annotation on the radiology request form as such. Major surgery was defined as surgery that required ≥24 hours of hospital admittance. Patients were excluded if the CTPA was inconclusive and if the clinical troponin monitoring protocol was not adhered to. In case of a re-operation within one year of surgery, only the first surgery was included; surgical procedures ≥1 year after the initial surgery were considered a novel case. Baseline and perioperative data were obtained from hospital databases. One-year mortality was obtained by linking our database to the municipal registry followed-up by a telephone call to the general practitioner if the cause of death was unclear. The local Institutional Reviewing Board waived the need for informed consent, as only routine clinical care data were used for this study (document number 15-606).

Troponin-I was assessed on the first three postoperative days as a part of a routine postoperative care protocol. A 3rd generation AccuTnI assay (Beckman Coulter, Brea, California) was used with a clinical cut-off value of 60 ng/L.[9] In case of troponin elevation, an ECG was made and the cardiology department was consulted; therapy and additional imaging was initiated based on the cardiologist's discretion. For each patient, the highest troponin value was used in the analysis.

Conventional diagnostic factors for PE were clinical signs, Wells criteria and postoperative ECG findings. The clinical signs included dyspnea, thoracic pain and oxygen saturation <90%. The Wells criteria included (1) clinical signs and symptoms of deep venous thrombosis (DVT); (2) tachycardia; (3) immobilization; (4) previous objectively diagnosed deep venous thrombosis or pulmonary embolism; (5) hemoptysis; (6) malignancy; and (7) PE as likely as or more likely than an alternative diagnosis.[10] The criteria "Clinical signs of DVT" and "PE as likely as or more likely than an alternative diagnosis" were assessed based on findings of the consultant pulmonologist or ward physician. "Immobilization" was scored positive in all patients because all patients included in our study were within one week after surgery. As some of the other Wells criteria were expected to occur in many study patients, we used both the Wells score and its individual components in our analyses. The ECG criteria were sinus tachycardia, new-onset atrial fibrillation, a S1Q3T3 pattern, a right/extreme axis, new right bundle branch block and T-wave inversion in leads V1-V3.[11] A composite was also created that contained right axis, S1QT3 pattern, new right bundle branch block and T-wave inversion in V1-V3. ECGs were retrospectively assessed by two investigators (RG+KZ) who were blinded for troponin and PE.

The CTPAs were performed on a 256-slice CT (Brilliance iCT, Philips Healthcare, Best, The Netherlands). PE was defined as a sharply delineated pulmonary arterial filling defect on at least two consecutive CTPA image sections, either located centrally within the vessel or with acute angles at its interface with the vessel wall.[12] The degree of PE was scored as central, segmental and subsegmental. All CTPAs were assessed by staff radiologists in a setting of routine clinical care. The radiologists had access to all clinical patient characteristics that were stored in the electronic hospital databases at the moment of CTPA, which also included troponin values. Ventilation studies were performed with 15-30mCi of 133Xe using a posterior,100,000-count single-breath image followed by two 2-mm posterior equilibrium images. Perfusion studies were performed with 4 mCi of ^{99}Tc-LYOMAA. A standard eight-view study was obtained with 750,000 counts collected per view for all views except the lateral views. The lateral view with best perfusion was imaged with 500,000 counts while the other lateral view was obtained using the same acquisition time. Both ventilation and perfusion images were obtained using parallel-hole, low-energy all-purpose collimation on gamma cameras with a 38-cm field of view. Ventilation / perfusion scans were assessed by staff nuclear radiologists.

The primary study endpoint was diagnosis of PE within one week after surgery. Secondary outcomes were 30-day and one-year mortality.

Statistical analysis

Continuous variables are presented as mean ±SD or median plus interquartile range and categorical variables as numbers and percentages. Levene's test for equality of variances was used to test variables for normality. Baseline characteristics were compared between patients with and without PE; continuous variables were compared using the unpaired Student's t-test or the Mann-Whitney U test in case of a non-normal distribution. Categorical variables were compared using Pearson χ^2-test or Fisher's Exact test, where applicable. Subsequently, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) with corresponding 95% Confidence Intervals (95%CI) were calculated for clinical symptoms, postoperative ECG characteristics, components of the Wells score and postoperative troponin elevation. Receiver Operating Characteristic (ROC) curves were created in which the Wells score and troponin elevation were assessed both individually and combined using binary logistic regression analysis (7). Added value of troponin elevation on top of the Wells score was assessed by comparing the areas under the ROC curves using the method by Delong et al.[13] Furthermore, the association between troponin and 30-day and one-year mortality in patients diagnosed with PE was compared between patients with and without troponin elevation and expressed in terms of a Hazard Ratio with corresponding 95%CI. All tests were two-tailed and $P<0.05$ was considered statistically significant. SPSS 21.0 was used for the statistical analysis.

RESULTS

During the study period, 223 (1.8%) of a total number of 12261 patients undergoing non-cardiac surgery had a clinical suspicion of PE within one week after surgery. Within this group, one patient underwent a V/Q scan because of renal failure. Thirteen patients (6%) were excluded because troponin was not routinely measured and three patients (1%) because of an inconclusive CTPA (two because of insufficient contrast fluid in the pulmonary artery and one because of movement artefacts). As a consequence, 207 of the 223 patients (93%) were included in the analysis of whom 93 had a postoperative troponin elevation (45%). The median age of patients with troponin elevation was 71 (IQR 64-74) versus 68 (IQR 67-76) in patients without such elevation (p=0.006). Patients with troponin elevation more often had congestive heart failure (Table 1).

PE was diagnosed in 57 (28%) of the 223 suspected cases. Nine (16%) of these PEs were central, 32 (56%) were segmental and 16 (28%) were subsegmental. In patients with a postoperative troponin elevation, PE was detected in 35% versus 22% in patients without troponin elevation (p=0.046). In patients with troponin elevation, the PE was central in four

patients (13%), segmental in 18 (56%) and subsegmental in ten (31%) whereas these numbers were five (20%), fourteen (56%) and six (24%) in patients without troponin elevation.

In total, 135 patients (65%) were classified as high-risk according to the Wells score and 72 (35%) as low-risk. Forty-four patients in the high-risk group (33%) were diagnosed with PE, compared to 13 (18%) in the low-risk group. Table 2 describes patients diagnosed with and without PE on their clinical signs and symptoms, the components of the Wells score, ECG characteristics, and postoperative troponin values. Patients eventually diagnosed with PE were more often classified as high-risk by the Wells score (77% versus 61%, p=0.03) and more often PE was the most likely diagnosis at the time of request of the CTPA or V/Q scan (75% versus 58%, p=0.02).

Diagnostic value

Table 3 shows the diagnostic value for the clinical symptoms, the components of the Wells score, ECG findings and troponin. Sensitivity, specificity, PPV and NPV of troponin were 55% (95%CI 42–68), 59% (95%CI 51–69), 33% (95%CI 24–44) and 78% (95%CI 69–85), respectively. The area under the ROC curve for the Wells score with a cut-off of 4 points was 0.58 (95%CI 0.50–0.67); which was the same for troponin elevation 0.58 (95%CI 0.49–0.67). Addition of troponin elevation to the dichotomized Wells score (cut-off 4) led to a significant improvement of the area under the ROC curve to 0.64 (95%CI 0.55–0.72) (p=0.02).

Treatment and prognosis

Of the 57 patients with PE, 33 were treated with oral anticoagulation (58%), 22 with therapeutic low-molecular-weight heparin (38%), one patient with a vena cava filter (2%) and one patient with an EkoSonic Endovascular System (2%). Postoperative thrombosis prophylaxis in patients who developed PE consisted of prophylactic low-molecular-weight heparin (LMWH) in 44 patients (77%) and therapeutic LMWH in six patients (11%); seven patients (12%) did not receive prophylaxis because of a contra-indication for anticoagulation (e.g. patients with subarachnoid bleeding).

In patients with PE, 30-day and one-year mortality occurred in five (16%) and ten patients (35%) in the troponin elevation group versus two (8%) and five (24%) in the group without troponin (Hazard Ratio 1.9, 95%CI 0.4–9.9 and 1.6 95%CI 0.5–4.6). The causes of death in PE-patients with troponin elevation were PE-related in two patients, malignancy in one, sepsis in four, cerebral in one and unknown in two patients. In the group without troponin elevation, these numbers were one, two, one and one, respectively.

DISCUSSION

PE is difficult to diagnose in the early postoperative period because clinical signs and symptoms are often misinterpreted in the perioperative period. Risk stratification tools such as the Wells score – which rely partly on clinical factors - may therefore be less reliable for use in the postoperative period. Based on our data, the Wells score indeed had a low diagnostic value for PE in patients with clinically suspected PE. Adding troponin elevation to the Wells score led to a significant improvement in the area under the ROC curve yet the discriminatory power remained limited.

The relatively low predictive accuracy of the Wells score in the postoperative period can be explained by presence of Wells criteria in the perioperative phase. For instance, malignancy (valued at 1 point) is often the reason for major surgery, tachycardia (valued at 1.5 points) occurs due to stress, inflammation and anemia, and hemoptysis (valued at 1 point) is frequently observed in patients with gastro-esophageal and oropharyngeal surgery. If these points are combined with the 1.5 points that are granted for immobilization after major surgery, one could appreciate that the cut-off of 4 points is easily reached. From this perspective it is surprising that the occurrence of 'being classified as high risk' was significant between patients with and without PE. Of note, the association seemed to be attributable to the criterion "PE is number one diagnosis or equally likely" (Table 3), which likely reflects the fact that a physician is able to provide a more individualized assessment that incorporates medical history, risk factors, clinical signs, symptoms and ECG findings. Notably, the low diagnostic yield of the Wells score in this study is in concurrence with Young and colleagues, who suggested absence of an association with PE for both the traditional and the alternative Wells score in orthopedic trauma patients who underwent CTPA for clinical suspicion of PE.[14]

PE is the most common non-cardiac cause of troponin elevation in patients at the emergency department.[5] In such patients, the troponin elevation is thought to result from an acute right ventricular pressure overload, increased myocardial wall tension, reduced coronary perfusion, hypoxemia and hypotension.[7, 8] Troponin could therefore be useful to guide the diagnostic work-up for patients suspected of PE. In our non-cardiac surgery population, the incidence of PE was significantly higher in patients with troponin elevation (34%) than in those without (22%). The diagnostic yield, however, was limited (Table 3) which is probably attributable to underlying triggers of troponin elevation like postoperative stress, anemia, hypertension and coronary insufficiency. Interference of these factors may also explain the high number of patients with troponin elevation in the overall population (45%). Furthermore, one should acknowledge the possibility that a number of (clinically silent) PEs were missed ; this may have led to an underestimation of troponin's association with PE. Nonetheless, our results are in concurrence with Kilinc et al and Dieter et al, who reported that troponin elevation occurred significantly more often in patients with PE in the emergency department yet sensitivity and NPV were poor.[15, 16]

Troponin elevation is associated with an increased risk of death in non-surgical setting.[6] In comparison, the risk of 30-day postoperative mortality in our study was approximately twice as high in patients with troponin elevation (i.e. 16% versus 8%), which could warrant more aggressive therapy. The absence of a statistically significant association may be attributable to the fact that our study was not powered to address this issue. Also, it may have been caused by the interference of factors other than PE that are associated with a higher risk of death in patients after surgery (e.g. coronary artery disease or sepsis).

Limitations

First, the Wells score was assessed retrospectively in the majority of cases. This may have led to underreporting of components such as 'signs of DVT', which – in turn – may have resulted in underestimation of the Wells score in some cases. Second, some patients with a clinical suspicion of PE may have been missed in case of contra-indications for angiography (e.g. renal failure or contrast allergy), patients that were already on a therapeutic anticoagulation regimen or patients in whom no CTPA was made because of a (very) low Wells score. These missing patients imply that there is a small chance of selection bias yet the risk thereof is likely negligible because they constitute for a very small portion of the population. Third, assessment of PE by the radiologists may have been more thorough in patients with troponin elevation yet the chance of detection bias is very low because the CTPA applications did not include information regarding troponin. Finally, troponin was only assessed on the first three postoperative days and PE could have occurred between the fourth and seventh postoperative day.

Conclusion

PE was diagnosed in 28% of the patients with a clinical suspicion of PE after non-cardiac surgery. Addition of troponin elevation significantly improved the diagnostic value of the Wells score but the overall predictive accuracy remained poor.

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Disclosures: None for all authors

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TABLE 1. Baseline characteristics

	Troponin elevation N = 93	No troponin elevation N = 114	P-value
Age *	71 (67 – 76)	68 (64 – 74)	0.006
Male sex	51 (55)	61 (54)	0.85
BMI	26 (23 – 29)	27 (24 – 32)	0.10
History of myocardial infarction	15 (16)	10 (9)	0.11
History of coronary revascularization	12 (13)	11 (10)	0.46
Congestive heart failure	7 (8)	1 (1)	0.024
Current atrial fibrillation	16 (17)	14 (12)	0.32
History of stroke	8 (9)	8 (7)	0.67
COPD	13 (14)	11 (10)	0.33
Renal insufficiency (GFR <45 ml/min)	9 (10)	9 (8)	0.65
History of malignancy	54 (58)	62 (54)	0.60
History of PE or DVT	8 (9)	12 (11)	0.64
Cardiovascular risk factors			
Current smoking	12 (14)	15 (14)	0.98
Diabetes mellitus	24 (26)	24 (21)	0.42
Hypertension	46 (50)	65 (57)	0.28
Medication			
Beta-blocker	26 (28)	42 (37)	0.18
Calcium antagonist	20 (22)	28 (25)	0.60
ACE-inhibitor(/AT2-blockers)	31 (33)	37 (33)	0.89
Diuretics	20 (22)	33 (29)	0.22
Aspirin	28 (30)	31 (27)	0.64
Oral anticoagulation	15 (16)	13 (11)	0.32
Statin	34 (37)	40 (35)	0.83
Insulin	7 (8)	8 (7)	0.89
ASA class			0.17
1 or 2	55 (59)	78 (68)	
≥ 3	38 (41)	36 (32)	
Type of Surgery			0.30
Orthopedic	13 (14)	22 (19)	
Neurosurgical	23 (25)	23 (20)	
Vascular	6 (6)	1 (1)	
Abdominal/Gastro intestinal	33 (35)	43 (38)	
Gynecologic	8 (9)	8 (7)	
Head and neck	8 (9)	12 (11)	
Other	2 (2)	5 (4)	
Wells score			0.63
Low risk (≤ 4 points)	34 (37)	38 (33)	
High risk (> 4 points)	59 (63)	76 (67)	

Legend:

Abbreviations: BMI: Body Mass Index, CVA: Cerebral Vascular Accident, COPD: Chronic Obstructive Pulmonary Disease, GFR = glomerular filtration rate AP: Angina Pectoris, DVT: *Deep vein Thrombosis, ASA class: American Society of Anesthesiologists Class*

*Mean (standard deviation)

TABLE 2. Results

	PE N = 57	No PE N = 150	P-value
Clinical symptoms			
Dyspnea	31 (54)	88 (59)	0.58
Thoracic pain	12 (21)	43 (29)	0.27
Oxygen saturation < 90%	35 (61)	81 (54)	0.34
Wells score			
High risk (> 4 points)	44 (77)	91 (61)	0.026
Clinical signs of DVT *	2 (4)	6 (4)	1.00
PE #1 diagnosis **	43 (75)	87 (58)	0.020
Tachycardia	26 (46)	63 (42)	0.64
Immobilization †	57 (100)	150 (100)	-
Previous PE or DVT	8 (14)	12 (8)	0.19
Hemoptysis	5 (9)	8 (5)	0.36
Active malignancy ‡	27 (47)	69 (46)	0.86
Postoperative ECG findings (n=171)			
Sinus tachycardia	16 (33)	33 (27)	0.46
New onset atrial fibrillation	9 (18)	20 (16)	0.76
SVT other than atrial fibrillation	1 (2)	1 (1)	0.49
S1Q3T3	6 (12)	5 (4)	0.079
New RBBB	2 (4)	2 (2)	0.32
Right / extreme axis	3 (6)	3 (3)	0.36
T-wave inversion V1-V3	7 (14)	13 (11)	0.50
Composite for PE §	14 (29)	20 (16)	0.053
Postoperative troponin elevation (clinical cut-off of 60 ng/L)	32 (56)	61 (41)	0.046
Median troponin level (ng/L)	80 (33 – 296)	50 (30 - 130)	0.07

Legend:

PE: Pulmonary Embolism, DVT = Deep Venous Thrombosis, SVT supraventricular tachycardia, RBBB = right bundle branch block

* Objectively measured leg swelling and pain with palpation in the deep-vein region, ** Pulmonary embolism is the most likely diagnosis or equally likely, † bedrest except to access the bathroom for ≥ 3 consecutive days or surgery within the previous 4 weeks. As a result of the inclusion criteria of this study, every included patients was scored as positive and statistical analysis was considered redundant for this criterion, ‡ patients with cancer who were receiving treatment, those in whom treatment had been stopped within the past 6 months, or those who were receiving palliative care. § Composite of right axis, S1Q3T3 pattern, new right bundle branch block and T wave inversion in V1-V3.

TABLE 3. Diagnostic value

	Sensitivity	Specificity	PPV	NPV	AUC (95% CI)
Wells criteria					
Clinical signs of DVT	4 (1 – 13)	96 (91 – 98)	25 (4 – 64)	73 (66 – 79)	
PE #1 diagnosis	75 (62 – 85)	42 (34 – 50)	33 (25 – 42)	82 (71 – 89)	
Tachycardia *	45 (32 – 58)	58 (49 – 66)	28 (19 – 39)	74 (65 – 81)	
Immobilization †	100 (97 – 100)	0 (0 – 8)	73 (66 – 79)	-	
Previous PE or DVT	14 (7 – 27)	92 (86 – 96)	40 (20 – 64)	74 (67 – 80)	
Hemoptysis	9 (3 – 20)	95 (89 – 98)	38 (15 – 68)	74 (67 – 80)	
Active malignancy ‡	46 (33 – 60)	54 (45 – 62)	27 (19 – 37)	73 (64 – 81)	
Clinical symptoms					
Dyspnea	54 (40 – 67)	41 (33 – 49)	25 (18 – 34)	70 (60 – 79)	
Angina	21 (12 – 35)	72 (64 – 78)	22 (12 – 35)	71 (63 – 80)	
Saturation dips	39 (27 – 53)	54 (46 – 62)	24 (16 – 34)	71 (61 – 79)	
ECG findings (n = 171)					
Sinus tachycardia	33 (21 – 49)	73 (64 – 81)	33 (20 – 48)	74 (65 – 81)	
New onset atrial fibrillation	29 (9 – 33)	84 (76 – 90)	31 (16 – 51)	73 (64 – 80)	
SVT other than atrial fibrillation §	21 (1 – 13)	99 (95 – 100)	50 (3 – 98)	72 (65 – 79)	
S1Q3T3	13 (5 – 26)	96 (90 – 98)	55 (25 – 82)	74 (66 – 80)	
New RBBB	42 (7 – 15)	98 (94 – 100)	50 (9 – 91)	73 (65 – 79)	
T-wave inversion V1-V3	15 (6 – 28)	89 (82 – 94)	35 (16 – 59)	73 (65 – 80)	
Composite for PE **	29 (17 – 43)	84 (77 – 90)	41 (25 – 59)	75 (67 – 82)	
Wells stratification					
Cut-off 4 points	77 (64 – 87)	39 (32 – 48)	33 (25 – 41)	82 (71 – 90)	0.58 (0.50 – 0.67)
Continuous					0.60 (0.51 – 0.68)
Troponin-I					
Cut-off 60 ng/L	55 (42 – 68)	59 (51 – 67)	33 (24 – 44)	78 (69 – 85)	0.58 (0.49 – 0.67)
Cut-off 120 ng/L	39 (27 – 53)	75 (67 – 81)	37 (25 – 50)	77 (69 – 83)	0.58 (0.49 – 0.67)
Wells + troponin					0.64 (0.55 – 0.72)
Wells (continuous) + troponin					0.64 (0.55 – 0.72)

Legend:

* Heart rate > 100 beats per minute, † Immobilization at least 3 days, or surgery in the previous 4 weeks, ‡ malignancy with treatment within 6 months, or palliative, § Supraventricular tachycardia other than atrial fibrillation, ** composite of right axis, S1QT3 pattern, new right bundle branch block and T wave inversion in V1-V3.
Abbreviations: PPV = positive predictive value, NPV = negative predictive value, AUC = Area Under the Receiving Operator Characteristics Curve, CI = Confidence Interval, PE = Pulmonary Embolism, DVT = Deep Venous Thrombosis, SVT = supraventricular tachycardia, RBBB = right bundle branch block

APPENDIX. Baseline characteristics for patients with and without Pulmonary Embolism

	PE N = 57 (28%)	No PE N = 150 (78%)	P-value
Age *	71 (65 – 76)	69 (65 – 74)	0.29
Male sex	30 (53)	82 (55)	0.79
BMI	28 (25 – 32)	26 (23 – 30)	0.04
History of myocardial infarction	6 (11)	19 (12)	0.67
History of coronary revascularization	5 (9)	18 (12)	0.51
Congestive heart failure	2 (4)	6 (4)	1.00
Current atrial fibrillation	8 (14)	22 (15)	0.91
History of stroke	2 (4)	14 (9)	0.16
COPD	8 (14)	16 (11)	0.50
Renal insufficiency (GFR <45 ml/min)	3 (5)	15 (10)	0.41
History of malignancy	32 (56)	84 (56)	0.99
History of PE or DVT	8 (14)	12 (8)	0.19
Cardiovascular risk factors			
Current smoking	8 (17)	19 (14)	0.60
Diabetes mellitus	13 (23)	35 (23)	0.94
Hypertension	31 (54)	80 (53)	0.89
Medication			
Beta-blocker	17 (30)	51 (34)	0.57
Calcium antagonist	12 (21)	36 (24)	0.65
ACE-inhibitor(/AT2-blockers)	24 (42)	44 (29)	0.08
Diuretics	14 (25)	39 (26)	0.97
Aspirin	11 (19)	48 (32)	0.07
Oral anticoagulation	12 (21)	16 (11)	0.051
Statin	17 (30)	57 (38)	0.27
Insulin	4 (7)	11 (7)	0.94
ASA class			0.90
1 or 2	37 (65)	96 (64)	
≥ 3	20 (35)	54 (36)	
Type of Surgery			0.55
Orthopedic	9 (16)	26 (17)	
Neurosurgical	18 (31)	28 (19)	
Vascular	2 (3)	5 (3)	
Abdominal/Gastro intestinal	17 (30)	59 (40)	
Gynecologic	5 (9)	11 (7)	
Head and neck	5 (9)	15 (10)	
Other	1 (2)	6 (4)	

Legend:

PE: Pulmonary Embolism, CVA: Cerebral Vascular Accident, COPD: Chronic Obstructive Pulmonary Disease, GFR = glomerular filtration rate AP: Angina Pectoris, DVT: Deep vein Thrombosis ASA class: American Society of Anesthesiologists Class

CHAPTER 7

PULMONARY EMBOLISM AFTER ENDOVASCULAR AORTIC REPAIR

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SUBMITTED

ABSTRACT

Objectives: Endovascular aortic repair (EVAR) is associated with an increased risk of pulmonary embolism, which is often clinically silent and therefore difficult to recognize. We aimed to investigate the incidence of pulmonary embolism after EVAR using routinely performed pre- and postoperative aortic Computed Tomography Angiography (CTA), and its association with mortality.

Methods: This single-center retrospective cohort study included adult patients who underwent EVAR in the University Medical Center Utrecht between January 2010 and July 2015 and had a total aortic, thoracic aortic or pulmonary CTA within one month postoperatively. Baseline and mortality data were obtained by reviewing hospital and general practitioner records. The primary outcome was pulmonary embolism within one month after surgery. Secondary outcomes were 30-day and six-month mortality.

Results: During the study period, 526 EVARs were performed, of which 74 were included in the analysis: 40 thoracic EVARs and 34 abdominal EVARs. In nine patients (12%, 95%CI 7–22) pulmonary embolism was observed of which one was central, two were segmental and six were subsegmental. Seven were clinically silent and two were present on the preoperative CTA. Mortality was significantly higher in patients with pulmonary embolism (Relative Risk 14.4, 95%CI 1.4– 143, p=0.037) though none of the deaths seemed directly attributable to pulmonary embolism.

Conclusions: Despite routine thromboembolism prophylaxis, the incidence of pulmonary embolism exceeded 10% in patients who underwent abdominal or thoracic EVAR. PE was associated with a higher risk of 30-day mortality yet it was not the primary cause of death in any of these patients.

INTRODUCTION

Endovascular aortic repair (EVAR) has surpassed open surgery for the treatment of aortic aneurysms as a result of a lower invasiveness and less postoperative morbidity and mortality.[1] Despite this, EVAR remains associated with an increased risk of (venous) thromboembolism. Indeed, all pillars of Virchow's triad are present; *hemodynamic changes* as a result of introducing and deployment of a stent graft in the aorta, *endothelial injury* as a result of maneuvering guidewires through the aorta and infusion of contrast media, and *hypercoagulability* as a result of the increased thrombin generation, thrombin activity and fibrin turnover that is associated with an aortic aneurysm and endovascular repair.[2,3]

The incidence of pulmonary embolism (PE) after EVAR has been reported to be approximately 0.4%.[4,5] This estimate is primarily derived from small studies that only assessed symptomatic PE. Most PEs in the postoperative period, however, are clinically silent due to masking of pathognomonic signs and symptoms. For instance, thoracic complaints may be misinterpreted in the presence of postoperative pain whilst dyspnea and low oxygen saturation may be attributed to postoperative anemia.[6] As some PEs may consequently have been missed, the incidence of PE after EVAR could be underestimated.

In our hospital, an aortic Computed Tomography Angiography (CTA) is routinely made after EVAR - preferably within one week – to assess graft position and endoleak (i.e. blood leakage between the prosthesis and the aneurysm wall). Because these CTAs include the chest, they are potentially suitable for assessment of PE. In addition, it is possible to distinguish a new PE from a pre-existing or chronic PE, since preoperative CTAs are also routinely made. The aim of this study was to investigate the incidence of PE and its association with mortality after EVAR.

METHODS

Study design and population

This retrospective, single-center study included patients ≥ 18 years old who underwent EVAR in the University Medical Center Utrecht – a tertiary referral center - between January 2010 and July 2015, and had a CTA of the thoracic aorta or a CT pulmonary artery within one month after the procedure. CTAs with insufficient contrast in the pulmonary artery were excluded. In case of a complicated EVAR requiring multiple procedures, only the first procedure was included. If multiple EVARs were performed in one patient for different aneurysms, patients could be included more than once. The institutional Reviewing Board waived the need for informed consent (reference number WAG/mb/16/001927).

EVARs were stratified into abdominal and thoracic EVAR and graded on complexity.

Abdominal EVAR was defined as an endovascular stent graft in the abdominal part of the aorta, i.e. under the level of the diaphragm, and a thoracic EVAR as an endovascular stent above the level of the diaphragm. If a stent covered both the abdominal and the thoracic part of the aorta, the procedure was defined as an abdominal EVAR. Non-complex EVARs were defined as bifurcated stent grafts with ipsilateral or contralateral leg extensions, or both. Complex EVARs were defined as all procedures in which fenestrated or branched stent-grafts were used or a chimney technique was applied.

Until July 2014, routine intraoperative anti-thrombosis therapy consisted of 5000IE intravenous heparin . After July 2014 this regimen was changed to 100IE heparin/kg. In complex EVAR procedures, Activated Clotting Time (ACT) was measured after 30 minutes and every hour thereafter; additional heparin was administered when ACT was below 250 seconds. Postoperatively, low-molecular-weight-heparin 2500 IE or 50000IE (dosage based on body weight) was administered daily until hospital discharge. Therapeutic dosages of low-molecular-weight-heparin were given if indicated (e.g. in case of a thromboembolism prior to surgery or a mechanical heart valve prosthesis). Platelet inhibition was continued peri-operatively. Patients who had a complex EVAR got dual antiplatelet therapy for 3 months and lifelong single antiplatelet therapy after that period.

Data collection

Patient demographic data, comorbidities and operative details were extracted from electronic patient records. Relevant perioperative characteristics were clinical signs and symptoms of PE (dyspnea, thoracic pain, signs of deep venous thrombosis (DVT), heart rate > 100 bpm and hemoptysis) and signs of myocardial injury. The clinical signs and symptoms were assessed by reviewing electronic medical records from the procedure day until the day of the CTA. Of note, in intubated or delirious patients, clinical signs were scored as absent if not clinically overt. Myocardial injury was assessed using routine postoperative Troponin-I measurements. Troponin-I was routinely measured on the first three postoperative days using a 3rd generation AccuTnI assay (Beckman Coulter, Brea, CA) with a clinical cut-off value of 60ng/L. The highest Troponin-I value was used in analysis. An electrocardiogram (ECG) was only made in case of a troponin elevation above the clinical cut-off or in case of a clinical indication (e.g. angina or suggestion of an arrhythmia). ECGs made within three postoperative days and within two days before or after the postoperative CTAs. An experienced investigator, who was blinded for the outcome, retrospectively assessed all ECGs. Recorded ECG findings were: new onset arrhythmia, new onset signs of ischemia, pathologic Q's, a S1Q3T3 pattern and new right bundle branch block.

Outcomes

The primary outcome was PE within one month after surgery, which was defined as a sharply marginated pulmonary artery filling defect on at least two consecutive CTPA images, located either centrally within the vessel or with acute angles at its interface with the vessel wall. All CTAs were performed on a 256-slice CT scanner (Brilliance iCT, Philips Healthcare Best, The Netherlands). To diagnose PE, an experienced reviewer assessed all total aortic, thoracic aortic or pulmonary CTAs that were made within one month after surgery without knowledge of clinical findings (i.e. baseline characteristics, clinical signs and symptoms, laboratory and ECG values). The degree of PE was scored as central, segmental and subsegmental. An experienced radiologist confirmed all PEs. To observe whether (chronic) PE was present prior to surgery, preoperative CTAs that were made up until a year earlier were assessed likewise. Secondary outcomes were 30-day and six-month mortality. Mortality data were obtained by linking our database to the municipal registry. Causes of death were obtained by consulting the electronic patient record of our center. In case of an out-of-hospital death, the patient's general practitioner was contacted.

Statistical analyses

Categorical data are presented as number count and percentage. Continuous data are presented as mean ± standard deviation, or median and interquartile range, as appropriate. The incidence of PE was expressed as number with percentage, accompanied by a 95% confidence interval. Subsequently, perioperative characteristics were compared for patients with and without PE. Levene's test for equality of variances was used to test continuous variables for normality and the Student's t-test or the Mann-Whitney was used in case of a parametric and non-parametric distribution, respectively. Categorical variables were compared using the Pearson χ^2-test or the Fisher's Exact test. Survival was compared between patients with and without postoperative PE using a Kaplan Meier survival curve and differences were tested using the log-rank test. Statistical significance was defined as $P \leq 0.05$. All statistical analyses were performed using SPSS 21.0.

RESULTS

During the study period, 526 EVARs were performed, i.e. 464 abdominal and 62 thoracic EVARs. Forty-five procedures were excluded because no postoperative CTA was available within one month, 391 because the pulmonary arteries were not fully visible on abdominal CTA, which was made after abdominal EVAR, and 14 because of insufficient contrast in the pulmonary artery on CTA. Furthermore, two cases were excluded because of a re-EVAR within the study period. Consequently, 74 procedures were included in analysis: 34 abdominal EVARs and 40 thoracic EVARs (Figure 1). Baseline characteristics and indications for surgery are

shown in Table 1 and in Appendix A, respectively, and procedure and hospitalization characteristics are depicted in Table 2.

PE was observed in nine patients (12%, 95%CI 7 – 22); six after abdominal EVAR (18%, 95%CI 8 – 34) and three after thoracic EVAR (8%, 95%CI 3 – 20). One PE was central, two were segmental and six were subsegmental (Appendix B). Two of these PEs were present on the preoperative CTA (one segmental and one subsegmental PE), showing similar size as the postoperative PE. One segmental and one central PE were clinically diagnosed on the first and second postoperative day, respectively, as a result of dyspnea, low oxygen saturation and tachycardia. The remaining segmental PE was clinically diagnosed on the 30th postoperative day in a patient with persistent chest pain and dyspnea after surgery (Appendix B, patient 3). In retrospect, the PE in that patient was already present on the CTA on the 5th postoperative day. All six subsegmental PEs were clinically silent.

Postoperative clinical signs and symptoms, and Troponin-I values are shown in Table 2. Dyspnea and thoracic pain were noted in two (22%) and zero patients with PE versus twelve (19%) and eight patients (12%) without PE, respectively. Furthermore, in patients with PE, clinical signs of DVT, tachycardia and hemoptysis occurred in one patient (11%), four patients (44%) and none. These numbers were twelve (19%), eight (21%) and four (6%) in the group without PE. The peak Troponin concentration was similar in both groups (Table 2). Patients with PE more often had Chronic Obstructive Pulmonary Disease (COPD), used inhalation steroids or bronchodilators and were more often admitted to the Intensive Care Unit. Furthermore, although not statistically significant, the duration of surgery was longer in patients with PE (Table 2). Postoperative thromboembolism prophylaxis was routinely administered in all except one patient with a subsegmental PE, in whom anticoagulant therapy was withheld because of a ruptured aorta (Appendix B).

30-day and six-month mortality occurred in two (22%) and two patients with PE (22%) versus one (2%) and four patients (6%) without PE, respectively. Both deaths in the PE group were patients with a subsegmental PE. The causes of death in these patients were sepsis / bowel ischemia and massive hemorrhage after aorta rupture, which was confirmed by autopsy in both patients (Appendix B, patient 6 and 7). In the group without PE, the causes of death were postoperative myocardial infarction, multi-organ failure, malignancy and sepsis. The Kaplan Meier survival curve is shown in Figure 2 (log rank test $p = 0.073$).

DISCUSSION

Despite the fact that all patients received routine thromboembolism prophylaxis after EVAR, PE occurred in over 10% of the patients. A third of these PE was central or segmental. Only two of these PE were symptomatic at the time of the aortic CTA. PE was associated with a higher risk of mortality yet it was not the primary cause of death in any of these patients. To our knowledge, this is the first study to assess PE after EVAR using routinely made aortic CTAs.

Prior studies have suggested that the incidence of PE after EVAR is approximately 0.4% which is considerably lower than the 12% that was found in this study.[4,5] This discrepancy can be explained by the fact that most of these studies focused on symptomatic PE. One should appreciate, however, that interpretation of signs and symptoms suggestive of PE can be challenging in the early postoperative period because pleuritic pain can be mimicked by 'normal' postoperative pain and dyspnea can easily be attributed to (postoperative) anemia. This notion is underlined by the diagnostic delay of almost four weeks that resulted from misinterpretation of minor dyspnea and thoracic complaints in a patient with a segmental PE in this study (patient 3, Appendix B). It should also be noted that two of the PEs (i.e. one segmental and one subsegmental) were present prior to surgery. In these patients, clinical signs may be influenced by vasoconstriction in the presence of perioperative stressors.[7]

The perioperative diagnostic difficulties warrant further identification of risk factors. In this study, COPD and inhalation steroids / bronchodilators were associated with PE and – although not statistically significant - Intensive Care Unit admission and duration of surgery were longer, and the ASA score was higher (Table 2). COPD is not considered a typical risk factor for PE though an association has been suggested. Indeed, a meta-analysis by Rizkallah and colleagues reported an incidence of PE of 24.7% (95%CI 17.9 – 31.4) in patients hospitalized for an acute COPD exacerbation.[8] A timely diagnosis in that particular population is especially difficult because of the similarity of PE and COPD symptoms. The trend towards an association with Intensive Care Unit admission and prolonged surgery could be attributable to prolonged immobilization, whilst a higher ASA score likely indicates relevant co-morbidities or a worse clinical condition.[9,10] It should be noted that prolonged immobilization occurs mainly in complex procedures (i.e. branched or fenestrated stent grafts) which – in turn – may account for the higher incidence of PE after abdominal EVAR in comparison to thoracic EVAR.

The incidence of subsegmental PE has strongly risen over the last decades as a result of an increase in spatial and temporal resolution of multi-detector CTA.[11] These subsegmental PEs often have a mild clinical presentation, a favorable biomarker profile, a low coincidence with DVT and relatively low right ventricular pressures on echocardiography in comparison to patients with segmental or central PE.[12] As a consequence of such favorable characteristics, it is unknown whether such PEs warrant aggressive anticoagulation. Indeed, a clear benefit of anticoagulation has not yet been established because of a significant risk of (major)

bleeding.[12,13] Donato and colleagues, for instance, performed a retrospective study in 93 patients with isolated subsegmental PE and reported an incidence of 3-month mortality, recurrent PE and bleeding in 3%, 1% and 11% (of which 7% major) in patients treated with anticoagulation or a vena cava filter. No mortality, recurrent PE or bleeding occurred in the group without treatment.[13] These ratios were somewhat contradicted by Eyer and colleagues, who studied 77 patients with a subsegmental PE, and reported 3-month mortality in 4% and 15% in patients treated with and without anticoagulation, respectively.[14] The difference in mortality between these studies is likely attributable to the small number of inclusions and the more benign profile of the patients that did not receive anticoagulation in Donato's study. Furthermore, all deaths in the latter two studies were non-PE related which is consistent with our study. It is therefore plausible that a subsegmental PE is a contributing factor of death or an expression of co-morbidities / prolonged immobilization rather than the primary cause of death. This assumption is underlined by autopsy studies in which the incidence of grossly recognizable emboli ranges from 1.5% - 30%.[15] Hence, in the absence of conclusive evidence regarding anticoagulant therapy, physicians should carefully weigh the benefits of anticoagulation against the risk of bleeding when confronted with a clinically silent subsegmental PE in especially hemodynamically stable postoperative patients.

The overall 30-day mortality in our study was 4% which is higher than the 0.5 % – 2.3% mortality that is generally reported after EVAR.[16] This discrepancy is likely explained by the fact that most studies were designed to compare simple EVAR to open surgery and therefore included patients who were physically eligible for open repair. Of note, the population in our tertiary center consisted predominantly of patients with complex pathology and comorbidities, some of whom were unfit for open surgery.

Clinical implications

PE occurs frequently after EVAR yet most events are clinically silent. Despite the lack of symptoms, their clinical relevance should not be underestimated as they may turn symptomatic, especially when located in a central or segmental artery. Vascular surgeons and radiologists should therefore be wary of PE.

Strengths and limitations

The main strength of this study is that the CTAs were routinely made as a part of a clinical care, which allowed for assessment of silent PE. However, a number of limitations have to be recognized. First, a substantial proportion of patients (i.e. mostly abdominal EVARs) were excluded from the analysis because the chest was not included in the field of view of the postoperative CTA. It is possible that patients who were more severely ill or had a more complicated abdominal EVAR procedure were more likely to undergo a CTA that included the chest. As a consequence, the incidence of PE in the abdominal EVAR may be slightly overestimated. It is therefore possible that the incidence of PE after thoracic EVAR (8%) provides a better representation of the true PE incidence than the abdominal EVAR group

(18%). Second, the CTAs were primarily intended to assess the aorta rather than the presence of pulmonary embolism, which resulted in insufficient contrast fluid in the pulmonary artery in 14 of 88 CTAs (16%) (Figure 1). Since this occurred at random, it is unlikely that it affected the validity of the results. Third, multivariate analysis was not possible due to due to a small sample size. Finally, a preoperative CTA was absent for one patient with a postoperative PE and the time between the preoperative CTAs and surgery was more than one month in a half of the cases.

Conclusion

Despite routine thromboembolism prophylaxis, the incidence of pulmonary embolism exceeded 10% in patients who underwent abdominal or thoracic EVAR. PE was associated with a higher risk of 30-day mortality yet it was not the primary cause of death in any of these patients.

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TABLE 1. Patient characteristics

	Overall n = 74	**PE** n = 9	**No PE** n = 65	**P-value** [a]
Age in years, mean (SD)	72 (8)	72 (6)	69 (12)	0.57
Male sex	55 (74)	6 (67)	49 (75)	0.69
BMI, mean (SD)	26 (4)	26 (3)	26 (4)	0.96
ASA class				
I or II	45 (61)	3 (33)	42 (65)	0.14
III or higher	29 (39)	6 (67)	23 (35)	
Emergency procedure	19 (26)	3 (33)	16 (25)	0.69
Medical History				
Current smoking	17 (23)	3 (33)	14 (26)	0.69
Hypertension	47 (64)	6 (67)	41 (63)	1.00
Diabetes	11 (15)	2 (22)	9 (14)	0.62
Current angina	5 (7)	0	5 (8)	1.00
Coronary revascularization	17 (23)	1 (11)	16 (25)	0.68
History of myocardial infarction	19 (26)	2 (22)	17 (26)	1.00
Peripheral artery disease	18 (24)	1 (11)	17 (26)	0.44
Congestive heart failure	5 (7)	1 (11)	4 (6)	0.49
Atrial fibrillation	10 (14)	0	10 (15)	0.35
Pacemaker	0	0	0	
Prior stroke	17 (23)	2 (22)	15 (23)	1.00
COPD	11 (15)	4 (44)	7 (11)	0.024
Renal insufficiency (eGFR <45 ml/min)	9 (12)	1 (11)	8 (12)	1.00
Preoperative medication				
Aspirin	47 (64)	4 (44)	43 (66)	0.24
Other platelet inhibitor	6 (8)	0	6 (9)	1.00
Oral anticoagulation	12 (16)	2 (22)	10 (15)	0.63
NSAID other than aspirin	3 (4)	0	3 (5)	1.00
Statin	41 (55)	3 (33)	38 (59)	0.18
Inhaled bronchodilators or Steroids	13 (17)	4 (44)	9 (14)	0.047

Legend:
Abbreviations: PE: Pulmonary embolism, SD: Standard deviation, BMI: Body Mass Index in kg/m^2, *ASA class: American Society of Anesthesiologists Class,* COPD: Chronic Obstructive Pulmonary Disease, eGFR : estimated Glomerular Filtration Rate, NSAID: Non-Steroidal Anti-Inflammatory Drugs.
[a] Patients with and without PE are compared.

TABLE 2. Procedure and hospitalization characteristics

	PE n = 9 (12%)	No PE n = 65 (88%)	P-value
PROCEDURE CHARACTERISTICS			
Abdominal EVAR	***6 (67)***	***28 (43)***	
Non-complex [a]	*3 (50)*	*16 (57)*	1.00
Complex [b]	3 (50)	12 (43)	
Thoracic EVAR	***3 (33)***	***37 (57)***	
Non-complex [a]	*2 (67)*	*35 (95)*	0.21
Complex [b]	1 (33)	2 (5)	
Emergency procedure	3 (33)	16 (25)	0.69
General anesthesia	8 (89)	64 (99)	0.23
Duration of surgery in minutes, median (IQR) [c]	231 (111-317)	126 (101–241)	0.23
HOSPITALIZATION CHARACTERISTICS			
Clinical symptoms			
Dyspnea	2 (22)	12 (19)	0.68
Thoracic pain	0	8 (12)	0.58
Clinical signs of DVT [d]	1 (11)	4 (6)	0.49
Tachycardia (> 100 bpm)	4 (44)	17 (26)	0.26
Hemoptysis	0	0	-
Postoperative myocardial infarction	0	8 (12)	0.27
Routine postoperative Troponin-I assessment	***n = 8 (89)***	***n = 49 (75)***	
Troponin elevation (> 60 ng/L)	3 (38)	19 (39)	1.00
Peak troponin, median (IQR)	36 (25–767)	40 (21–207)	0.66
Hospital stay in days, median (IQR)	12 (7-15)	7 (4-11)	0.14
ICU admission	7 (78)	24 (37)	0.03
Duration of ICU admission in days, median (IQR)	2 (1-5)	2 (2-3)	0.98

Legend:

Abbreviations: PE: Pulmonary embolism, SD: standard deviation, IQR: inter quartile range, EVAR: endovascular aortic repair, ICU: Intensive Care Unit, bpm: beats per minute, DVT:

Deep Venous Thrombosis, STEMI=ST-segment elevation myocardial infarction, non-STEMI: non-ST-segment elevation myocardial infarction.

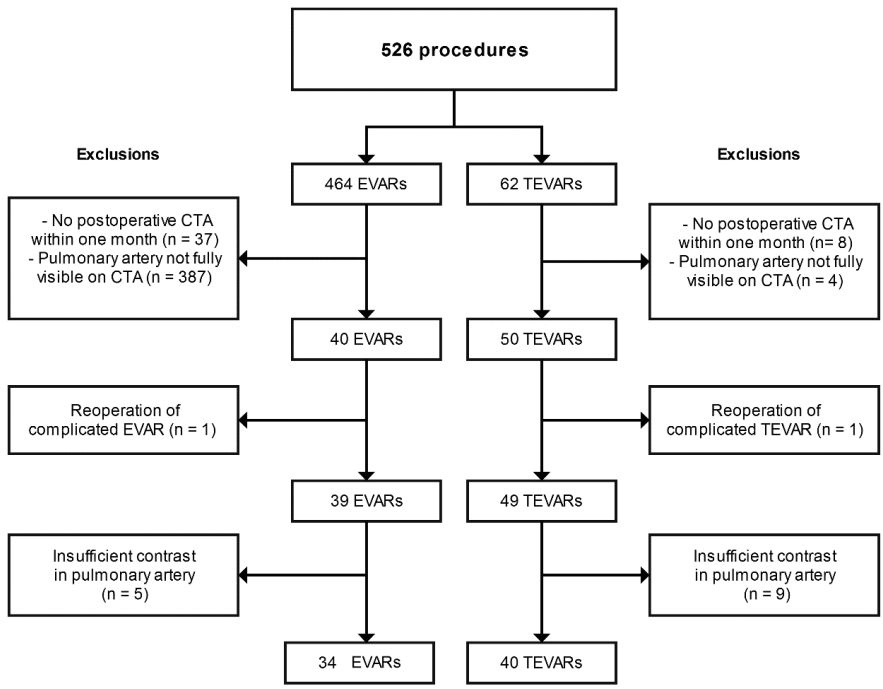
[a] Non-complex EVARs: bifurcated stent grafts with ipsilateral or contralateral leg extensions, or both.

[b] Complex EVARs: use of a chimney, fenestrated, branched or custom-made stent-graft.

[c] Time between first incision and closing suture.

[d] Objectively measured leg swelling and pain with palpation in the deep-vein region

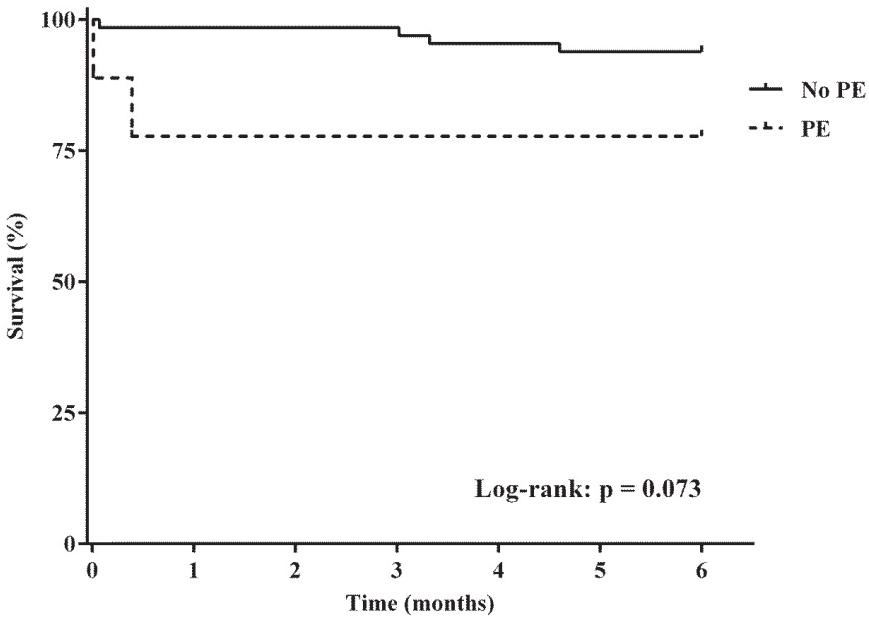
FIGURE 1. Flowchart of in- and exclusion criteria



Legend:

Abbreviations: EVAR: Abdominal endovascular aortic repair, TEVAR: thoracic endovascular aortic repair

FIGURE 2. 6-months survival



Legend:

Abbreviations: PE = Pulmonary Embolism

APPENDIX A. EVAR indications and characteristics

	Abdominal EVAR n = 34	**Thoracic EVAR** n = 40
Abdominal aortic aneurysm	18 (53)	-
Ruptured abdominal aortic aneurysm	6 (18)	-
Thoraco-abdominal aneurysm	3 (9)	-
Thoracic aortic aneurysm	-	27 (66)
Ruptured thoracic aortic aneurysm	-	3 (8)
Aortic dissection		
Type A	-	2 (5)
Type B	-	3 (8)
Traumatic	-	3 (8)
Other		
Type I endoleak	3 (9)	-
Aorto-enteric fistula	2 (6)	-
Seam failure	1 (3)	-
Aortic rupture after seam failure	1 (3)	-
Subclavian artery aneurysm	-	1 (3)
Trauma after esophagus resection	-	1 (3)
Characteristics		
Complex [a]	15	3
Non-complex [b]	19	37

Legend:

Abbreviations: EVAR: Endovascular aortic repair

[a] Complex EVARs: use of a chimney, fenestrated, branched or custom-made stent-graft.

[b] Non-complex EVARs: bifurcated stentgrafts with ipsilateral or contralateral leg extensions, or both.

APPENDIX B. Characteristics of the patients with postoperative pulmonary embolism

Patient	Postoperative prophylactic anticoagulation	Type of surgery	Indication for surgery	Pre-operative CTA			Postoperative CTA			Clinical symptoms leading to diagnosis	Treatment	Mortality cause (time from surgery)
				Type	Days to surgery	PE present yes/no, type	Type	Days after surgery	Type of PE			
1	Prophylactic LMWH	Emergency EVAR	Ruptured AAA	Aortic CTA	0	No	Pulmonary CTA	2	Central	Elevated troponin, right bundle branch block, right ventricular strain on echocardiography	Therapeutic LMWH	-
2	Therapeutic LMWH because of PE on first postoperative day	Elective chimney EVAR and fem-fem crossover	AAA	Aortic CTA	59	Yes, segmental	Pulmonary CTA	1	Segmental[1]	Abdominal pain (flanks), high blood pressure, low saturation	Therapeutic LMWH	-
3	Prophylactic LMWH	Elective chimney TEVAR	Thoracic aortic aneurysm	Aortic CTA	8	No	Aortic CTA	5	Segmental	Silent[2]		-
4	Prophylactic LMWH	Elective EVAR	Thoraco-abdominal AAA	Aortic CTA	102	Yes, subsegmental	Aortic CTA	4	Subsegmental[1]	Silent	-	-
5	Prophylactic LMWH	Emergency EVAR and fem-fem crossover	Ruptured AAA	Aortic CTA	0	No	Aortic CTA	31	Subsegmental	Silent	-	-
6	Prophylactic LMWH	Elective EVAR	AAA	Aortic CTA	35	No	Aortic CTA	10	Subsegmental	Silent	-	Sepsis and bowel ischemia (12 days)

7	None	Emergency TEVAR	Ruptured TAA	Aortic CTA	0	No	Aortic CTA	0	Subsegmental	Silent	-	Ruptured TAA (same day as surgery)
8	Therapeutic heparin because of recent thrombus in the SMA	Elective TEVAR	TAA	N/a [4]	N/a	N/a	Aortic CTA	2	Subsegmental	Silent	-	-
9	Prophylactic LMWH	Elective fenestrated EVAR	AAA	Aortic	200d	No	Aortic CTA	4	Subsegmental	Silent	-	-

Legend:

Abbreviations: F: female, M: masculine, CTA: Computed Tomography Angiography, PE: pulmonary embolism, EVAR: Endovascular Aortic Repair, TEVAR: Thoracic Endovascular Aortic Repair, Abdominal Aortic Aneurysm, TAA: Thoracic Aortic Aneurysm, fem-fem crossover: femorofemoral crossover bypass graft, LMWH: Low-Molecular-Weight-Heparin, COPD: Chronic Obstructive Pulmonary Disease, CABG: Coronary artery bypass grafting, SMA: superior mesenteric artery.

1: PE present on the same location as visualized on pre-operative CTA.

2: This patient returned to the emergency department 25 days after the first CTA with dyspnea, throbbing chest pain, headache and shivering. A pulmonary CTA was subsequently made and progression of the pre-existent PE was visible. He was treated with therapeutic LMWH.

3: Bentall procedure: replacement of the aortic valve, aortic root and ascending aorta.

4: This patient had a preoperative abdominal angiography instead of a CTA.

CHAPTER 8

GENERAL DISCUSSION

After half a decade of routine postoperative troponin measurements, a strong dose-dependent relation of troponin elevation with mortality has been demonstrated in many – if not all - non-cardiac surgery populations.[1–5] In our hospital, this implied that 26% of the patients with a troponin elevation died within one year after surgery, as compared to 13% without troponin elevation (relative risk 2.0, 95%CI 1.7-2.4, p<0.001). For minor (60 – 120 ng/L), moderate (120 – 600 ng/L) and major troponin elevations (>600 ng/L) these numbers were 21%, 25% and 40%, respectively (**chapter 3**). Similar numbers were reported by other studies that performed routine postoperative troponin assessment.[1]

It is essential to acknowledge that troponin's association with mortality does not directly imply a causal relation. Indeed, ST-elevation myocardial infarctions were rare, cardiac interventions were deemed necessary in just 16% of patients with troponin elevation, and – most importantly - cardiac death only accounted for a minor portion of patients with troponin elevation (**chapter 3**). This suggests that most troponin elevations are a byproduct of prior coronary artery disease or a poor clinical condition rather than a primary cardiac event. Here, patient-specific characteristics (e.g. pre-existent cardiac, renal or cerebral disease) and procedure-specific characteristics (e.g. more invasive procedures, anemia, tachycardia, tachy-arrhythmia, stroke or sepsis) can be considered as the substrate and the trigger for myocardial injury, respectively (**chapter 3** and **4**).[6,7] Of note, substrate and triggers vary significantly between different study populations. In vascular patients - who often have a delicate cardiac equilibrium - myocardial ischemia is easily induced by minor triggers such as tachycardia, intraoperative hypotension and perhaps even general anesthesia.[8,9] Yet, other major pathology should not be overlooked as the cause of troponin elevation. Indeed, perioperative stroke is also associated with troponin elevation, ECG abnormalities and even regional wall motion abnormalities, which is thought to result from excessive catecholamine release.[10] Finally, despite thrombosis prophylaxis, pulmonary embolisms (PE) may occur (**chapter 7**). In oncologic populations, the substrate is likely characterized by frailty and impaired systolic and diastolic cardiac function due to chemotherapy, whilst the most common trigger is infection and pulmonary embolism (PE).[6] The latter two are also frequently observed in orthopedic patients, combined with excessive blood loss (i.e. anemia).[4]

In an attempt to evade incorrect adjudication of postoperative myocardial infarctions (POMI), Devereaux and colleagues introduced the concept of "Myocardial Injury after Noncardiac Surgery" (MINS), which eliminates myocardial injury due to documented non-ischemic etiology (Table 1).[11] An important limitation of this concept, however, is that common diagnostic tools in patients with myocardial injury (i.e. clinical assessment and ECG) are not sufficient to assess the underlying pathology. Indeed, symptoms are sparse in patients with a POMI or PE (**chapter 3 - 5**) and the value of ECG may be limited due to the transiency of ischemia and the potential interference of electrolyte disturbances, stroke, intracranial hemorrhage, sepsis and PE.[10,12]

Table 1 – Statement regarding MINS [11]

"Emerging evidence suggests that many patients sustain myocardial injury in the perioperative period which will not satisfy the diagnostic criteria for myocardial infarction. Nevertheless, these events portend a poor prognosis that timely and appropriate intervention could potentially improve. This suggests that a new diagnosis of Myocardial Injury after Noncardiac Surgery (MINS) may be useful to patients and clinicians. Our proposed definition of MINS is as follows: myocardial injury caused by ischemia (that may or may not result in necrosis), has prognostic relevance and occurs during or within 30 days after noncardiac surgery. The definition of MINS is broader than the definition of myocardial infarction in that it includes not only myocardial infarction but also the other prognostically relevant perioperative myocardial injuries due to ischemia. MINS does not include perioperative myocardial injury which is due to a documented nonischemic etiology (e.g., pulmonary embolism, sepsis, cardioversion)."

An important finding of **chapter 5** that argues against immediate adaptation of the MINS concept, is the high incidence of PE in patients with troponin elevation (33%) of which 80% was central or segmental. In these patients, troponin elevation may be attributable to demand ischemia secondary to an hypoxic state, impaired coronary flow or a right ventricular pressure overload.[13–15] Of note, this occurs predominantly in the presence of a proximal arterial occlusion (central PE) or a generalized vasoconstriction of the pulmonary vascular bed in response to regional pulmonary hypoxia ((sub)segmental PE).[13,16] Such a potential association of troponin with PE could also partly explain the absence of obstructive coronary artery disease in approximately a third of patients with a postoperative MI, and it might even attribute to troponin's association with mortality.[16,17] Furthermore, it may have important diagnostic and therapeutic consequences, as clinicians could consider echocardiography and cardiac or pulmonary artery CT in patients with troponin elevation, and may alter or initiate anticoagulation treatment, respectively. Of course, chapter 5 is unable to provide conclusive evidence regarding this matter due to the small number of patients and selection of a relatively "healthy" group of patients. Results should consequently be considered as "hypothesis generating", warranting further investigation.

The foundation for troponin's potential association with PE was further strengthened by **chapter 6**, in which troponin elevation showed to convey additional value over the Wells score in patients who were clinically suspected of a postoperative PE. It is worth noting that the discriminatory power of both tests was poor; the limited diagnostic value of troponin could be explained by the variety of underlying triggers of troponin elevation on the one hand (i.e., many causes of acute respiratory distress can induce troponin elevation) and the possible requirement of elevated right ventricular pressures to induce troponin release on the other hand (i.e., only in the more severe PE cases troponin release is likely to occur).[13] Results should be validated in a prospective study in consecutive patients undergoing noncardiac

surgery. Yet, importantly, in this difficult population of patients with various underlying diseases, the association of troponin with PE was viable.

To further investigate the occurrence of silent PE, we looked into patients who underwent endovascular aortic repair (EVAR), a population in which hardly any PE were expected due to extensive antithrombotic prophylaxis **(chapter 7**). An additional advantage of this population is the routine requirement of an aortic CT angiography before and after surgery. Within the 74 included patients, PE was found in 12%; 95%CI 7-22%, which greatly exceeds the 0.4% that was reported in other vascular populations and the absence in the included vascular patients in chapter 5. It should be noted that only 8% of abdominal EVARs underwent an aortic CTA that included the chest, which may suggest that the thoracic EVAR group (in whom the chest was included in the CTA in 94%) provides a more accurate estimation of the incidence (i.e. 9%). Notably, an interesting aspect of chapter 7 regards PE's association with 30-day mortality (p=0.037), where none of the deaths were directly related to PE. This likely indicates that some subsegmental PEs are an expression of a poor clinical condition, more severe (pulmonary) pathology or prolonged immobilization / Intensive Care Unit admission rather than an adverse event with a causal relation with mortality.

Future perspectives

In order to clarify the relevance of postoperative troponin elevation and to improve patient outcomes, a number of issues have to be addressed.

First, due to use of different cardiac biomarkers and definitions of postoperative MI, a comparison of existing studies is difficult. This issue has become subject to much debate and although recent efforts to standardize study endpoints are a step in the right direction, the effect of standardization will not be observed in the next two to three years.[18] In the meantime, one should focus on studies that used hard endpoints and derived postoperative MI incidences from routine troponin measurements rather than creatine kinase since the latter is affected by skeletal muscle damage and is less sensitive and specific to myocardial necrosis.[19] Moreover, if one were to consider a composite endpoint that contains postoperative MI, it should be acknowledged that it may have a significant influence on study outcomes and sample size calculations. This is perhaps best illustrated by the carotid endarterectomy population, in which the benefit regarding stroke prevention was hampered by minor postoperative myocardial ischemia / infarctions.[20]

Second, as most postoperative MIs are likely attributable to demand ischemia with little evidence that supports a direct causal relation with mortality, we need to focus on treating the root of the problem (which may include arrhythmia, PE, congestive heart failure, infection, stroke or a combination of factors) rather than plainly initiating MI prophylaxis.[6,7]

This is, however, easier said than done, as a result of the difficulties in recognition and discrimination of the underlying cause (**chapter 2 and 3**). Clinicians should therefore consider non-invasive cardiac imaging such as echocardiography and cardiopulmonary CT in patients with troponin elevation. Such additional imaging and subsequent cardiac optimization - if indicated – is perhaps best initiated after multidisciplinary deliberation by anesthesiologists, cardiologists, surgeons and/or pulmonologists. Indeed, better deliberation could integrate perioperative data (e.g. intraoperative hypotension or ST-segment deviations) with postoperative data (e.g. chest pain, dyspnea, headache, painfully swollen extremities and ECG abnormalities compatible with CAD or PE), and may improve the discussion regarding the potential benefit of postoperative initiation of MI prophylaxis or anticoagulation versus the additional risk of bleeding. Perhaps the anesthesiologists are most qualified to guide this discussion, as they were in charge of perioperative surveillance. In this, one could consider extending the anesthesiologists surveillance to the surgical ward, in order to facilitate recognition and treatment of common triggers of myocardial ischemia (e.g. arrhythmias, anemia and congestive heart failure due to excessive fluid administration, and perhaps also PE).

Third, perioperative interventional strategies should be optimized. Of course, the best option would be to prevent mortality and major cardiac events by initiating pre- and perioperative MI prophylaxis. However, perioperative administration of beta-blockers, aspirin and clonidine is either ineffective or counterbalanced by other adverse events such as bleeding or clinically relevant hypotension.[21–23] In addition, preoperative coronary interventions suffered a similar faith, as they did not improve postoperative mortality.[24] The inefficacy of common MI prophylactics strongly concurs with the theorem that most troponin elevations concern type II ischemia without a strong causal relation with mortality. Also, it leads to believe that a one-size-fits-all interventional model may not be applicable to the heterogeneous non-cardiac surgery population. This – in turn - offers little perspective for ongoing trials assessing the efficacy of perioperative statin.[25] Another preoperative option would be to optimize risk stratification models, for instance by adding troponin, brain natriuretic peptide (BNP), or cardiac imaging. However, although all of these factors may be associated with postoperative MI and mortality, it is unlikely that widespread implementation is pertinent.[17,26] Indeed, preoperative cardiac marker elevations likely reflect high wall stress in the presence of (mostly known) prior cardiac or cerebral disease, and additional cardiac tests generally have either led to underestimation (i.e. in case of perfusion imaging) or overestimation of the cardiac risk (i.e. in case of cardiac CT).[17,27] Hence, in the absence of conclusive evidence supporting more aggressive preoperative interventions, it is most prudent to focus on improving early recognition and treatment of relevant pathology using troponin. During this period, it has been suggested that patients with postoperative troponin elevation could benefit from early cardiovascular optimization. Yet, due to methodological shortcomings in that study, the reduction could also pertain to earlier recognition of anemia, tachy-arrhythmia and congestion. In regard to initiation of antiplatelet or anticoagulation therapy, it may be

best to reserve such therapy for the late postoperative period or the outpatient setting, since bleeding complications may outweigh the benefits in the first postoperative days.[22] This suggestion, of course, does not apply to hemodynamically instable patients, patients with ST-segment elevation MI, or those with a central or segmental PE.

In essence, it is questionable whether the additional risk on mortality in case of troponin elevation can be significantly modified. Those opposing might opt that it is probably not, as the ideal timing for intervention has often passed and the majority of events are secondary to other events. Those in favor, in contrast, will argue that we are on the verge of unravelling the enigma of postoperative troponin elevation, and that more adequate treatment could both influence mortality and have a profound effect on morbidity.[28] After over three years of experience with patients with (asymptomatic) troponin elevation, I clearly reside with the latter group.

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APPENDIX

NEDERLANDSE SAMENVATTING

Een hartinfarct is een belangrijke oorzaak van sterfte na grote operaties buiten het hart (niet-cardiale operaties). (1) Om dergelijke postoperatieve hartinfarcten te kunnen te voorspellen, zijn de afgelopen decennia meerdere klinische modellen gemaakt. Deze modellen gaven doorgaans een grove indicatie van het cardiovasculaire risico, maar bleken helaas niet altijd in staat om alle hartinfarcten adequaat te voorspellen. (2) Er is daarom gesuggereerd om alle patiënten te behandelen met aspirine en bèta-blokkers, ofwel de hoeksteen van de behandeling van kransslagaderziekte. De positieve werking van deze middelen werd helaas teniet gedaan door respectievelijk een verhoogd risico op overlijden en bloedingen. (3; 4) Men focust daarom op het moment op vroege herkenning van postoperatieve hartinfarcten met behulp van cardiale biomarkers als troponine.

Troponine is een eiwit dat een deel uitmaakt van het samenknijpende (contractiele) deel van de hartspiercel. Wanneer de hartspier beschadigd raakt (meestal in het kader van een hartinfarct), komt troponine vrij in de bloedbaan. Om deze reden is het de hoeksteen van de diagnostiek naar een hartinfarct. (5) In het afgelopen decennium is tevens gebleken dat troponine een belangrijke voorspeller is van complicaties na niet-cardiale operaties. (6) Van Waes et al. hebben bijvoorbeeld aangetoond dat patiënten met een verhoogd troponine-I (>60 ng/L) een hoger risico hebben op overlijden dan patiënten zonder troponinestijging (relatief risico van 2.4 95% CI1.3-4.2) (7) Opvallend hierbij was dat de relatie met overlijden afhankelijk was van de hoogte van de troponine concentratie, aangezien het relatieve risico toenam tot 4.2 (95%CI 2.1-8.6) bij patiënten met een troponine van ≥600 nanogram per liter.

In hoofdstuk 2 wordt een gedetailleerd overzicht van de verschillende oorzaken van een postoperatieve troponinestijging beschreven. In het kort kunnen de volgende factoren van invloed zijn: het scheuren van een kwetsbare kransslagader plaque (type I hartinfarct), een zuurstof vraag / aanbod mismatch in aanwezigheid van stabiele kransslagaderziekte (type II hartinfarct) en extra-cardiale aandoeningen (bijvoorbeeld een longembolie, hersenaandoeningen, infecties of nierfalen). Er is slechts een aantal studies gedaan die het aandeel van deze verschillende groepen heeft onderzocht. Deze onderzoeken hebben voornamelijk gefocust op hoog-risicogroepen zoals patiënten met pijn op de borst en specifieke afwijkingen op het hartfilmpje. Het overgrote deel van de patiënten met een postoperatief hartinfarct heeft echter geen of subtiele klachten en slechts geringe afwijkingen op het hartfilmpje. Het is dus de vraag in hoeverre de uitkomsten van die studies opgaan voor deze groep.

In hoofdstuk 3 worden de problemen met betrekking tot het herkennen en behandelen van postoperatieve hartinfarcten behandeld. Er wordt een studie beschreven van 3224 patiënten die niet-cardiale operaties hebben ondergaan, waarin een troponinestijging voorkwam in 22% van de patiënten. In deze laatste groep stierf 26% binnen één jaar na de operatie, vergeleken met 13% van de patiënten zonder troponinestijging (relatief risico 2.0, 95% CI 1.7-2.4, p <0.001). Opvallend hierbij was dat sterfte door een cardiale oorzaak relatief weinig voorkwam: in 3%, 5% en 11% van de patiënten met respectievelijk een minimale (70 - 120 ng / L), matige (120 - 600 ng / L) en hoge troponinestijging (> 600 ng / L). Bij patiënten zonder troponinestijging was dit 3% (p = 0.059). Enerzijds suggereren deze getallen dat patiënten wel degelijk baat zullen hebben van optimalisering van cardiale behandeling, echter anderzijds wekken de percentages de suggestie dat het effect op sterfte mogelijk beperkt zal zijn. Een opvallende bevinding in hoofdstuk 3 is het feit dat er slechts een cardiale interventie is verricht in 16% van de patiënten met troponinestijging. Dit is deels te wijten aan een gebrek aan cardiologie consulten bij patiënten met minimale troponinestijgingen (≤100 ng / L) en deels aan de terughoudendheid van cardiologen om de diagnose “postoperatief hartinfarct” te stellen in verband met de klinische / therapeutische gevolgen.

Door de relevantie van postoperatieve hartinfarcten voor sterfte op de korte en lange termijn, zijn de postoperatieve troponine metingen (al dan niet gecombineerd met afwijkingen op het hartfilmpje) meegenomen in de eindpunten van studies. Dit heeft er echter toe geleid dat minimale postoperatieve hartschade grote effecten kan hebben op de effectiviteit van nieuwe behandelingen. Carotis endartiëctomie (CEA), waarbij een vernauwing in de halsslagader operatief wordt verwijderd, wordt bijvoorbeeld beïnvloed door een dergelijk verschijnsel, aangezien het positieve effect qua bescherming voor de behandeling van herseninfarcten teniet wordt gedaan door een hoger aantal postoperatieve hartinfarcten. In ons ziekenhuis bleken postoperatieve hartinfarcten in 3.6% van de patiënten na CEA voor te komen (hoofdstuk 4). Al deze hartinfarcten waren echter beperkt en kwamen alleen voor binnen drie dagen na de operatie, wat de suggestie wekt dat de overgrote meerderheid van de postoperatieve hartinfarcten waarschijnlijk “demand ischemie” betreft. Relevant hierbij is dat de rol van perioperatieve beroerte als een oorzaak van myocardschade niet moet worden onderschat, aangezien een beroerte kan leiden overmatige afgifte van catecholamine (stress hormoon) en zelfs regionale wandbewegingen kan veroorzaken. (8, 9)

Hoofdstuk 5 beschrijft een studie waarin met een CT scan wordt gekeken naar de aanwezigheid van kransslagaderziekte bij patiënten met en zonder postoperatieve troponinestijging. Hierbij werd kransslagaderziekte gevonden in 50% van de patiënten met troponinestijging in vergelijking met 15% in de controlegroep (RR 3.3, 95% CI 1.1-9.8 p = 0.02), wat overeen komt met eerdere studies die preoperatieve cardiale CT en thallium scans hebben gebruikt (10, 11). Opmerkelijk is dat een derde van de patiënten met

troponinestijging een longembolie had, wat een stuk hoger is dan wat bekend was uit eerdere studies waarin tot 1% wordt gevonden. Aangezien een longembolie een bekende reden is voor een troponinestijging (voornamelijk bij kortademige patiënten op de spoedeisende hulp), wordt op basis van onze resultaten de suggestie gewekt dat longembolieën mogelijk ook een rol kunnen spelen bij postoperatieve troponinestijgingen. In theorie zou dit zelfs een gedeeltelijke verklaring kunnen zijn voor de afwezigheid van kransslagaderlijden in een derde van de patiënten met een postoperatief hartinfarct in een studie van Sheth et al. (10)

Een groot probleem omtrent postoperatieve longembolieën is de moeilijke herkenning. Bevindingen passend bij een longembolie (zoals kortademigheid, pijn op de borst, snelle hartfrequentie en verminderde zuurstofverzadiging) komen namelijk ook veel voor in de "normale" postoperatieve fase, waarin wondpijn, bloedarmoede, stress en (long)ontstekingen frequent worden gezien.(11) Bij dergelijke patiënten kan een troponinestijging één van de weinige aanwijzingen zijn voor een longembolie. We hebben daarom de diagnostische waarde van troponine voor postoperatieve longembolieën bekeken (hoofdstuk 6). Troponine bleek inderdaad extra waarde te hebben boven de risico stratificatie tool die normaliter wordt gebruikt (Wells score). Echter, een belangrijke kanttekening hierbij was dat de diagnostische waarde van zowel troponine als de Wells score slecht was. Dit is waarschijnlijk een gevolg van de vele onderliggende triggers van een troponinestijging en mogelijk ook de voorwaarde van een verhoogde rechter kamer druk. Bovendien is het onderzoek gedaan in patiënten die klinisch verdacht waren van een longembolie, waarbij a priori de kans op een longembolie dus een stuk hoger is.

Om een idee te krijgen van het aantal asymptomatische postoperatieve longembolieën, zijn de CT scans van patiënten na endovasculaire aorta reparatie (EVAR) opnieuw beoordeeld op aanwezigheid van longembolieën. Deze populatie was erg geschikt voor dit onderzoek, omdat er voor en na de procedure standaard een CT scan wordt gemaakt (hoofdstuk 7). In de 74 studiepatiënten werd in 12% (95% CI 7-22) een longembolie gevonden. Dit getal is veel hoger dan de 0,4% die gemeld worden door andere EVAR studies, wat deels verklaard kan worden door de mogelijkheid van selectie bias in de abdominale EVAR groep (slechts 8% van de abdominale aorta EVARs onderging een thoracale CT). Vandaar dat de thoracale EVAR groep - waarbij 94% van de CT´s de volledige thorax bevatte - waarschijnlijk een betere afspiegeling is van de werkelijkheid. Hierbij werd in 8%, 95%CI 3 – 20 van de gevallen een longembolie gezien. Dit getal is een stuk lager dan het aantal longembolieën dat werd gevonden in hoofdstuk 5, wat waarschijnlijk toe te schrijven aan het feit dat EVAR patiënten veel bloedverdunners gebruiken (1), dat er in hoofdstuk 5 ook orthopedische operaties zijn opgenomen (2) en de mogelijke associatie troponine met longembolieën (3). Een ander interessant aspect van dit hoofdstuk betreft de associatie van longembolieën met 30-dagen mortaliteit (p = 0.037) en een trend naar 6-maanden mortaliteit (p = 0.073). Daarbij moet worden opgemerkt dat geen van deze sterfgevallen rechtstreeks verband hield met de

longembolie. Als gevolg daarvan kunnen we niet uitsluiten dat vooral de kleine longembolieën een uiting zijn van meer uitgebreide (pulmonale) co-morbiditeit of langdurige Intensive Care Unit opname.

Toekomstperspectieven

De huidige diagnostiek (ECG en laboratoriumonderzoek) bij patiënten met troponine verhoging is niet voldoende om de onderliggende pathologie te achterhalen. Men moet daarom laagdrempelig non-invasieve cardiale beeldvorming (zoals echocardiografie en cardiale CT) overwegen bij hoog-risico patiënten (zoals patiënten met troponinestijging) om verdere behandeling te begeleiden. Hierbij is het verstandig om de keuze voor agressieve of conservatieve behandeling te bepalen na multidisciplinair overleg. Agressieve antistolling / bloedplaatjesremming dient gereserveerd te blijven voor hemodynamisch instabiele patiënten of andere hoog-risico groepen, gezien het risico op bloedingen in het operatiegebied. Aangezien de meerderheid van troponinestijgingen een gevolg is van verschillende uitlokkende factoren, is het onwaarschijnlijk dat de sterfte aanzienlijk kan worden verminderd door een “one-size-fits-all” aanpak qua preventieve medicatie. Toekomstige studies moeten bepalen of vroege detectie van mogelijk relevante aandoeningen (bijvoorbeeld kransslagaderziekte en longembolieën) leidt tot een verbetering van mortaliteit en morbiditeit.

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CURRICULUM VITAE

Remco Grobben was born in Goirle on May 6th of 1986 to Hans Grobben and Marike Schaafsma. He grew up in Goirle with his younger sister Carlijn. During childhood and adolescence, Remco played tennis and national level field hockey. After graduating the Theresialyceum Tilburg in 2004, Remco started medical school at the University Medical Center Utrecht, and obtained his `propedeuse´ in 2005. During the last years of the study, he merged his passion for travelling by performing clinical rotations in Léon, Nicaragua. Remco obtained his M.D. degree in July 2012.

During his medical education, Remco was intrigued by the field of cardiology which led to the start of his PhD project in October 2012 under the supervision of Pieter A. Doevendans, Wilton A. van Klei, Hendrik M. Nathoe and Linda M. Peelen. His research focused primarily on the etiology of troponin elevations after non-cardiac surgery.

In August 2016, he started his residency in cardiology under the supervision of Johannes H. Kirkels and Steven A. Chamuleau.

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