Incidence and hospital mortality of vascular surgery patients with perioperative myocardial infarction (PMI) or myocardial injury after non-cardiac surgery (MINS)

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Background: Perioperative myocardial infarction (PMI) and prognostically relevant myocardial injury following non-cardiac surgery (MINS) increases perioperative mortality. Studies in vascular patients show an increased incidence and mortality from PMI. However, there remains limited data on the relative prognostic importance of PMI and MINS in South African vascular surgical patients. The primary objective was to evaluate the incidence and prognosis of PMI and MINS in vascular surgical patients admitted to intensive care. The secondary objective was to identify predictors of PMI and hospital mortality.
Methods: A retrospective electronic patient record review of all patients aged at least 45 years admitted to Inkosi Albert Luthuli Central Hospital (IALCH) intensive care unit (ICU) following vascular surgery between 1 January 2011 and 31 December 2013 was carried out.
Results: A total of 140 vascular patients were reviewed; 24.3% of the patients had a PMI and a further 25% had MINS. PMI was associated with significantly increased hospital mortality of 58.8% ($p < 0.01$) and MINS was not (20%, $p = 1.00$). Increasing age, the highest postoperative B-type natriuretic peptide (BNP) and a blood transfusion within the first three days postoperatively were independent predictors of PMI. PMI and a history of congestive cardiac failure were independent predictors of hospital mortality.
Conclusion: PMI and MINS are present in nearly 50% of vascular patients admitted to intensive care postoperatively. PMI but not MINS in these patients was significantly associated with hospital mortality. MINS requires strict diagnostic criteria in the intensive care where other non-ischaemic pathologies may be associated with myocardial injury.

Keywords: brain natriuretic peptide, critical illness, myocardial injury after non-cardiac surgery, perioperative myocardial infarction, vascular surgery

Introduction

Of the estimated 312 million adults globally that undergo surgery annually,[1] approximately 100 million have non-cardiac surgery, are at least 45 years old and at risk of PMI or myocardial injury.[2] Following non-cardiac surgery, approximately 3.3 million patients have a perioperative myocardial infarction (PMI) and 4.6 million have myocardial injury after non-cardiac surgery (MINS).[2] MINS by definition is myocardial injury (as reflected by postoperative troponin elevation), which is deemed to be secondary to myocardial ischaemia, and does not fulfil the Universal Definition of Myocardial Infarction.[3] The estimated 30-day mortality for MINS is 7.8% and up to 12.5% for PMI.[2]

The multinational Vascular events In noncardiac Surgery patIents cOhort evaluatioN (VISION) Study[4] showed that the peak troponin T (TnT) value within the first 3 days of surgery was the strongest independent predictor of 30-day mortality with a population-attributable risk of 41.8%. Monitoring TnT for the first 3 days following surgery substantially improved 30-day mortality risk stratification when compared with a predictive model limited to preoperative risk factors only, with a net reclassification improvement of 25.0% ($p < 0.001$). The Third Universal Definition of Myocardial Infarction[5] recommends that the term acute myocardial infarction (MI) should be used when there is evidence of 'myocardial necrosis in a clinical setting consistent with acute myocardial ischaemia'. It is essential to recognise that the

perioperative clinical setting often confounds or limits the clinician's ability to make a diagnosis based on these criteria, as patients are often asymptomatic due to systemic analgesics and postoperative intensive care patients may be sedated and ventilated. Fundamentally, the Universal Definition of MI may therefore be flawed in determining postoperative patients at risk of cardiovascular complications by explicitly excluding patients with prognostically relevant perioperative myocardial ischaemic insults where the troponin elevation is above the 99th percentile for the upper reference limit (URL), but the postoperative clinical scenario prevents a diagnosis of myocardial infarction. For this reason, Myocardial Injury after Noncardiac Surgery (MINS) was defined, and described as a 'prognostically relevant myocardial injury due to ischaemia that occurs during or within 30 days after noncardiac surgery'.[3] In the MINS[3] study, 58.2% of the patients who experienced MINS did not meet the Third Universal Definition criteria for an MI and nearly 85% of the patients were asymptomatic with no ischaemic symptoms. MINS was an independent predictor of 30-day mortality with the highest population attributable risk of all the perioperative complications for 30-day mortality (34.0%, 95% CI 26.6–41.5). The Vascular events In noncardiac Surgery patIents cOhort evaluatioN (VISION) Study[4] showed that the majority of MINS occurred during the first two days following surgery when most patients are receiving analgesics that may mask ischaemic pain.

A number of studies have emphasised the importance of postoperative troponin elevation in vascular surgical patients. A meta-analysis[6] showed that an isolated troponin leak was present in 10.2% of vascular surgical patients and 6.3% had a PMI, and both an isolated troponin leak and PMI were associated with an increased 30-day mortality. A peak postoperative troponin I (TnI) level above the URL has been significantly associated with increased mortality at 2.5 years following vascular surgery. Postoperative troponin levels more than three times the URL outperformed clinical risk prediction variables.[7] When the absolute change in highly sensitive cardiac troponin T (hsTnT) within the first 24 postoperative hours of vascular surgery was added to the Revised Cardiac Risk Index (RCRI), the predictive accuracy of the score was significantly improved.[8]

The incidence of PMI or MINS and its impact on hospital mortality in the postoperative vascular surgical patient requiring intensive care in a South African context has not been described. Non-cardiac patients in the intensive care unit (ICU) have been reported to have a high incidence of postoperative troponin elevation with 84% of patients with hsTnT above the 99th percentile.[9] Furthermore, the relationship between other biomarkers, postoperative predictors of cardiac complications and postoperative troponin elevation is poorly understood. Elevated brain natriuretic peptide (BNP) and N-terminal fragment BNP measured within 7 days following non-cardiac surgery were shown to be independent predictors of a composite of mortality and non-fatal myocardial infarction, mortality, cardiac mortality and cardiac failure at 30 and ≥ 180 days,[10] while a perioperative blood transfusion was an independent predictor of postoperative cardiac complications.[11] The diagnosis of MINS requires exclusion of other causes of troponin elevation, in order to attribute the troponin leak to myocardial ischaemia. Other factors such as early sepsis or postoperative inotropic requirements may, however, result in early troponin release, which may compromise the prognostic importance of MINS in intensive care patients.

The objectives of this study were therefore to determine the incidence of perioperative myocardial infarction (PMI) or MINS and the associated hospital mortality in vascular surgical patients requiring postoperative intensive care.

Methods

This is a retrospective observational cohort study of patients aged 45 years or older who were admitted to ICU 2 at Inkosi Albert Luthuli Central Hospital (IALCH) following vascular surgery between 1 January 2011 and 31 December 2013. Where patients were admitted more than once to the intensive care unit, we analysed only the first admission. This is a closed surgical intensive care unit in a quaternary level central hospital in Durban, KwaZulu-Natal. An a priori decision was taken to include only patients aged ≥ 45 years in the study, to ensure consistency with the published literature.[3,4] PMI was defined according to the 2012 Third Universal Definition of Myocardial Infarction by the ESC/ACCF/AHA/WHF Taskforce,[5] as the detection of a rise and/or fall of cardiac biomarker values with at least one value above the 99th percentile URL and with one of the following criteria: symptoms of ischaemia, new or presumed new ischaemic ECG changes, imaging evidence of new loss of viable myocardium or new regional wall motion abnormality or identification of an intracoronary thrombus by angiography or autopsy.

Troponin I (TnI) is the assay clinically available at IALCH and is measured routinely, as per unit policy, during the patient's ICU stay. The peak levels on days 0–3 postoperatively were extracted.

Postoperative ECGs were adjudicated for PMI, and if they were not available, the ECG changes recorded in the patient's medical chart were used in the adjudication for PMI. The echocardiogram reports were used in the analysis. Angiography or autopsy results were reviewed, if necessary. Patients who were intubated and on a ventilator were unable to report symptoms of ischaemia.

A TnI elevation in the first 3 days postoperatively that was above the assay-specific laboratory normal threshold of 40 ng/l (99th percentile of URL) but below the diagnostic threshold of 600 ng/l for myocardial infarction, and adjudicated to be due to an ischaemic cause, was categorised as MINS. All known non-ischaemic causes of troponin elevation were excluded from the MINS categorisation. The preoperative brain natriuretic peptide (BNP) and the highest value in the first three days following surgery were extracted. The patient's lowest haemoglobin, whether the patient was transfused red cell concentrate and the number of units transfused within the first three postoperative days were extracted. Mechanical ventilation and use of inotropes (adrenaline or dobutamine) within the first three days following surgery was also extracted.

The patient demographics and preoperative risk predictors of cardiovascular disease (age, gender, history of diabetes mellitus, hypertension, ischaemic heart disease, congestive cardiac failure, previous coronary revascularisation, previous cerebrovascular accident, smoking within six months) were recorded. Due to the retrospective nature of this study, patients were not routinely followed up after hospital discharge, and it was therefore impossible to evaluate the 30-day mortality for all patients. The primary outcome was therefore hospital mortality. Surgical factors are also presented.

Data sources/measurement

The Siemens ADVIA Centaur XP® Immunoassay System (Tarrytown, NY, USA) was used by the laboratory. The TnI-Ultra® and the Centaur XP® kits were used for troponin I analysis and the Centaur BNP® used for BNP analysis. According to the scorecard concept,[12] if a troponin assay meets two proposed criteria it is regarded as a 'high-sensitivity' assay. The total imprecision (coefficient of variation) at the 99th percentile value should be < 10% and, second, levels below the 99th percentile should be measurable in at least 50% of healthy individuals.[12,13] The troponin assays in the Siemens ADVIA Centaur XP® Immunoassay System are classified as contemporary sensitive.[12–14] The TnI assay used meets the criteria of < 10% imprecision at the 99th percentile URL and as recommended by the Third Universal Definition of MI, the manufacturer defined 99th percentiles URL were used.

Statistical methods

SPSS® package version 22 (IBM Corp, Armonk, NY, USA) was used for the analysis. The categorical data were analysed using the chi-squared distribution table while the unpaired Student's t-test was used for continuous data and the Mann–Whitney U test for non-parametric data. A *p*-value < 0.05 was considered statistically significant. An a priori decision was taken to include PMI, MINS and postoperative BNP in a multivariate logistic regression for hospital mortality. In order not to violate the rule of 10 events per variable,[15] only the preoperative characteristics with a univariate association with hospital mortality or PMI were also included in the multivariate logistic regression. Results are reported as odds ratios (OR) and 95% confidence intervals (CI).
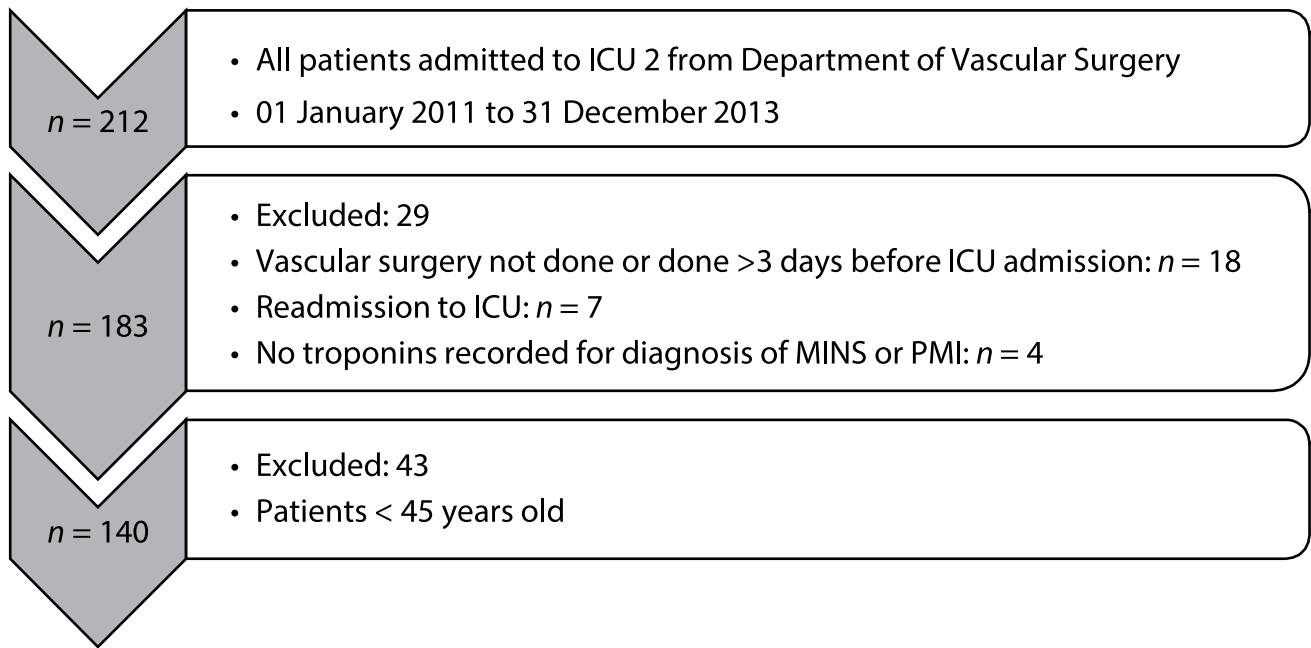
Figure 1: Patient flow chart.

Results

Figure 1 shows the patients included in this study. A total of 212 individual patient electronic records were reviewed for extraction of the relevant data. Patients with the following non-ischaemic causes of troponin elevation were excluded from the MINS cohort: pulmonary embolism ($n = 2$), post-CPR ($n = 2$), cardiac contusion $n = (2)$.

The patient characteristics are given in Table 1. The mean age was 61.7 years and 73.6% were male. Hypertension was the most prevalent cardiovascular risk factor, followed by smoking, diabetes mellitus, previous cerebrovascular accident, history of ischaemic heart disease and congestive cardiac failure. Survivors and non-survivors were similar with the exception that the patients who died had significantly more congestive cardiac failure. Emergency surgery was performed in 17.8% of the patients and this was associated with a significantly increased hospital mortality of 37.8%. The most common site of surgery was carotid (34.3%), followed by aorta (21.4%), aorta-iliac (20%) and infra-inguinal (23.6%). Infra-inguinal surgery was associated with significantly increased hospital mortality of 45% ($p = 0.01$). Patients that were mechanically ventilated or on inotropes in the first three days postoperatively had a significantly increased hospital mortality ($p < 0.01$). In patients with MINS, there was a significantly increased inotrope dependence within the first three days postoperatively ($p = 0.03$).

Within the study population, 25% were classified as having MINS and 24.3% a PMI. The overall hospital mortality for the study population was 28.6%. The hospital mortality in the MINS group was not significantly different from patients without an isolated troponin leak ($p = 1.00$). PMI was associated with significantly increased hospital mortality (58.8% vs. 18.3%, $p < 0.001$). The multivariate analyses of the predictors of hospital mortality and PMI are given in Tables 2 and 3 respectively. PMI and a history of congestive cardiac failure were independent predictors of hospital mortality. The median postoperative BNP in the total population was 210 ng/l (IQR = 72.5–462). The postoperative BNP was significantly higher in non-survivors ($p = 0.04$) but it was not an independent predictor of mortality. MINS was not associated with hospital mortality.

The median BNP of 920 ng/l (IQR = 217–1822) in patients with a PMI was significantly increased ($p < 0.001$) compared with the median BNP of 144 ng/l (IQR = 49–316) in those without a troponin elevation. The patient's age, postoperative BNP and the need for a postoperative blood transfusion were independent predictors of a PMI (see Table 3).

Discussion

The main findings of this study are that in vascular surgical patients requiring postoperative intensive care at IALCH, the incidence of postoperative troponin elevation approaches 50%, although only 24.3% fulfil the Third Universal Definition of MI. While those patients who fulfilled the Third Universal Definition of MI were at a significantly increased risk of mortality, patients with MINS were not.

The incidence of troponin elevation in our vascular patients requiring intensive care admission is similar to other vascular intensive care cohorts.[7] The reported incidence of PMI in vascular patients of between 5% and 26.5%[6,16] is comparable to the 24.3% found in our patients. The finding that PMI and a history of congestive cardiac failure were independent predictors of hospital mortality is consistent with the VISION[4] study. The significantly increased hospital mortality in those with a PMI is consistent with the hospital mortality of another study in vascular surgery patients.[16]

An important difference from the published literature[3] is that MINS in our patients was not independently associated with increased mortality. There are a number of possible reasons for this, and they have important implications for clinical management in the intensive care unit. In the MINS study by Botto *et al.*[3] fourth-generation troponin T levels above 0.03 ng/ml were determined as the diagnostic threshold for MINS. This was below the abnormal laboratory threshold at the time of the study. While an abnormal troponin elevation adjudicated to be

Table 1: Patient demographics and perioperative risk factors

Factor	Total	Survivors	Non-survivors	p-value
	n (%)	n (%)	n (%)	
	100 (71.4)	40 (28.6)		
Preoperative risk factors				
Age: mean (SD)*	61.7 (9)	60.9 (8.5)	63.8 (10.1)	0.085
Gender: male	103 (73.6)	74 (74.0)	29 (72.5)	0.84
Diabetic	53 (37.8)	37 (37)	16 (40)	0.85
Hypertensive	105 (75)	72 (72)	33 (82.5)	0.28
Ischaemic heart disease	44 (31.4)	29 (29)	15 (37.5)	0.42
Congestive cardiac failure	9 (6.4)	3 (3)	6 (15)	0.01
Previous coronary revascularisation	9 (6.4)	7 (7)	2 (5)	0.66
Previous cerebrovascular accident	49 (35)	38 (38)	11 (27.5)	0.33
Smoking (within last 6 months)	67 (47.8)	50 (50)	17 (42.5)	0.46
Surgical risk factors				
Emergency surgery	25 (17.8)	11 (11.5)	14 (37.8)	0.01
Postoperative risk factors				
Inotrope requiring within first 3 days	68 (48.6)	35 (35.4)	33 (82.5)	<0.01
Invasive ventilation within first 3 days	39 (27.8)	35 (35.7)	34 (87.2)	<0.01
Postoperative troponin surveillance:				
Below diagnostic threshold (0–40 ng/l)	71 (50.7)	58 (81.7)	13 (18.3)	Reference
MINS† (> 40 ng/l–600 ng/l)	35 (25)	28 (80.0)	7 (20.0)	1.00‡
PMI§ (≥ 600 ng/l)	34 (24.3)	14 (41.2)	20 (58.8)	<0.001‡
Median postoperative BNP‖ within first 3 days (IQR)**	137 (97.8)	172 ng/l (62–370)	365.5 ng/l (114–1092)	0.04
Transfusion in 3 days postoperatively	53 (37.85)	35 (35)	18 (45)	0.33

*Standard deviation.
†Myocardial injury following non-cardiac surgery.
‡Compared with reference group.
§Perioperative myocardial infarction.
‖Brain natriuretic peptide.
**Interquartile range.

due to ischaemia was classified as MINS in our study, there are no validated troponin I reference values for MINS. The use of the URL for troponin I may be inappropriate and this needs to be addressed urgently.

Table 2: Independent predictors of hospital mortality

Variable	OR* (95% CI)†	p-value
Congestive cardiac failure	5.51 (1.13–26.87)	0.03
MINS‡	1.06 (0.36–3.10)	0.91
PMI§	4.3 (1.43–12.94)	0.01
Postoperative BNP‖ within the first 3 days	1.0 (1.00–1.00)	0.17

*Odds ratio.
†Confidence interval.
‡Myocardial injury following non-cardiac surgery.
§Perioperative myocardial infarction.
‖Brain natriuretic peptide.

Table 3: Independent predictors of perioperative myocardial infarction (PMI)

Variable	OR* (95% CI)†	p-value
Age	1.07 (1.00–1.13)	0.04
Postoperative BNP‡ within the first 3 days	1.00 (1.00–1.01)	< 0.001
Postoperative transfusion within the first 3 days	3.96 (1.24–12.68)	0.02

*Odds ratio.
†Confidence interval.
‡Brain natriuretic peptide.

Furthermore, the diagnosis of MINS requires exclusion of non-ischaemic causes of troponin elevation, which may be clinically difficult in the early postoperative period in intensive care patients. There are also many non-ischaemic factors, e.g. myocarditis, pericarditis, cardiac failure, vasopressor use, pulmonary disease, intracranial events (e.g. haemorrhage) and sepsis, that may lead to troponin release in critical illness.[9] In a study of critically ill patients, BNP and TnI levels were significantly higher in those with sepsis or septic shock.[17] There were four patients (11.4%) in our MINS group that had coexisting sepsis during the first three days of ICU admission which may have led to troponin release. Another potential confounder for MINS in intensive care may be inotropes, which were used in 48.6% of our study patients.

BNP elevation may help in distinguishing between ischaemic-associated MINS and non-ischaemic aetiologies of troponin release in the early postoperative period in the intensive care unit. After 24 hours in the critically ill patient with sepsis, the BNP level has been shown to be significantly associated with ICU mortality[17] and at days 3 and 4 with left ventricular systolic dysfunction.[17] However, in our patients an early elevated BNP was associated only with PMI. In patients with suspected MINS in intensive care, evaluation of an early BNP may be necessary to identify patients at risk of PMI (as in our study) or ICU mortality and a later elevation may, rather, suggest a septic patient with myocardial dysfunction.[17]

While a blood transfusion predicted an increased risk of a PMI, it was not associated with increased hospital mortality. The evidence on the prognostic impact of postoperative blood transfusion is variable, depending on the patient population and the perioperative setting. The transfusion practices in the present study were clinician directed with no specified transfusion triggers or target, which may account for it not being a predictor of hospital mortality.

Limitations

Our study may be underpowered to determine the prognostic significance of MINS in vascular surgical intensive care patients, or the importance of postoperative BNP for hospital mortality.

The retrospective nature of the study did limit the information that was available for analysis. The reasons for admission to the ICU were not extracted but the higher level of organ support and monitoring could indicate a greater severity of illness compared with a vascular surgery patient who is cared for in a general ward. The site of surgery and surgical urgency were not included in the multivariate analyses, and these may have an impact on the prognosis of the patient.

Generalisability

The study group represents the typical South African vascular surgical population with their underlying risk of perioperative complications. It may not be applicable to the vascular surgical population as a whole, but rather those who require ICU admission for organ support or intensive monitoring.

Conclusion

PMI and MINS were present in nearly half of the vascular surgery patients requiring postoperative ICU admission. Patients with a PMI have a significantly increased hospital mortality. In patients with suspected MINS, an early postoperative BNP may help accurately identify patients at risk of PMI.

The correct identification of MINS in these vascular surgical intensive care patients is difficult, due to the use of inotropes, a high incidence of subclinical sepsis, and no clearly defined diagnostic troponin thresholds for MINS. Urgent research in this area is needed.

Conflict of interest – The authors have no conflict of interest.

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