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# Kinetics of troponin I in patients with myocardial injury after noncardiac surgery

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**Abstract**

**Background:** Myocardial injury after noncardiac surgery, as measured by troponin elevation, is strongly associated with mortality. However, it is unknown in which patients prognosis can be improved. The presence of kinetic changes of troponin may be associated with a worse prognosis and warrant more aggressive management. Therefore, we aimed to study the kinetics of troponin in patients with postoperative myocardial injury, and to determine the added predictive value of kinetic changes of troponin on mortality.
**Methods:** This cohort study included patients with myocardial injury after noncardiac surgery. Troponin I (TnI) was measured on the first three postoperative days. The primary outcome was all-cause 1-year mortality. We studied both absolute and relative TnI changes, and determined the delta TnI that was associated with mortality to distinguish a rise-and-fall TnI pattern from a stable TnI pattern. Next, we determined the added predictive value of a rise-and-fall TnI pattern for mortality.
**Results:** In total, 634 patients were included. The risk ratio (RR) for mortality increased significantly with an absolute delta TnI of ≥ 200 ng/L (RR 1.5, 99.4% CI 1.0–2.2, p = 0.003). Using this delta TnI to define a rise-and-fall pattern, 459 patients (72%) had a stable TnI pattern and 175 patients (28%) had a rise-and-fall pattern. When added to a model including the highest TnI value and variables from the revised cardiac risk index (RCRI), the TnI pattern did not increase the predictive value for mortality.
**Conclusions:** A postoperative TnI rise-and-fall pattern was associated with 1-year mortality, but had no added value in addition to the highest TnI level to predict 1-year mortality. Therefore, postoperative TnI kinetics are not useful for further mortality risk stratification in patients with myocardial injury after noncardiac surgery.

**Keywords:** kinetics; myocardial injury; perioperative; surgery; troponin.

## Introduction

Postoperative myocardial injury as measured by troponin elevation after noncardiac surgery is strongly associated with mortality [1–3]. Therefore, routine postoperative monitoring of cardiac biomarkers has been recommended to identify patients at risk [4–6].

Routine troponin I (TnI) measurements were implemented in our hospital as part of our postoperative care protocol, in order to facilitate early identification and subsequent cardiovascular optimization of patients at risk of death. However, a major problem in initiating or optimizing treatment in individual patients is the lack of knowledge of the underlying etiology of myocardial injury in the postoperative phase [7]. When the cause of the injury is often not clear, it is difficult to determine in which patients prognosis can be improved. Consequently, in more than half of the patients the clinical course is awaited without any intervention [8].

Since the introduction of high sensitivity troponin assays, the number of patients in which elevated troponin is attributable to other conditions than myocardial infarction has increased [9]. Therefore, the pattern of cardiac biomarkers over time has become an important criterion in the diagnosis of myocardial infarction. A pattern with

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a rise and/or fall of troponin above the 99th percentile of the upper reference limit in the presence of clinical signs and symptoms is considered as evidence of myocardial infarction [4]. In the non-surgical population, absolute troponin changes discriminate well between acute myocardial infarction and other causes of myocardial injury, and have high accuracy in identifying candidates for early coronary angiography [10]. Likewise, the presence of kinetic changes of troponin in the postoperative phase may reflect clinically relevant myocardial ischemia that is associated with a worse prognosis and that warrants more aggressive therapy as compared to troponin elevation without kinetic changes. This may help to identify patients who require follow up and treatment, but evidence for this hypothesis is lacking.

We therefore aimed to study the kinetics of troponin in patients with myocardial injury after noncardiac surgery, and to determine the added predictive value of kinetic changes of troponin on 1-year mortality.

# Materials and 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 1000 bed tertiary referral hospital. Patients were eligible if they were aged 60 years or older, were undergoing intermediate to high-risk noncardiac surgery under general or spinal anesthesia with an expected postoperative length of hospital stay of at least 24 h. In these patients, troponin was measured routinely on the first three postoperative days as part of our postoperative care protocol. Patients who had troponin elevation after surgery were included in this study. 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 1 year after the first surgery. Patients were excluded if troponin was not measured or measured only once after surgery, or if patients were lost to follow-up within 1 year after surgery.

The local medical Ethics Committee waived the need for informed consent, as only routinely collected patient data were used and data were anonymized before analysis (UMC Utrecht Medical Research Ethics Committee, protocol number 11/120-C).

## Data collection

All preoperative and postoperative data were obtained from electronic medical and administrative records. Data collected of all patients included patient characteristics, preoperative physical status, comorbidities including factors from the revised cardiac risk index (RCRI), [11] postoperative TnI measurements and 1-year mortality. Emergency surgery was defined as surgery required within 72 h. High-risk surgery was defined as intrathoracic, intra-abdominal or suprainguinal vascular surgery [11]. Ischemic heart disease was defined as a history of myocardial infarction or coronary revascularization. Preoperative renal insufficiency was defined as a preoperative glomerular filtration rate $< 45$ mL/min/1.73 m$^2$. Chronic heart failure was defined as a left ventricular ejection fraction $< 40\%$. The municipal personal records database was consulted for mortality data.

## Routine postoperative troponin measurements

According to the postoperative care protocol for older surgical patients in our hospital, the occurrence of postoperative myocardial injury was assessed routinely by TnI measurements. TnI was measured daily in the morning on the first three postoperative days. In case of a TnI elevation above the clinical cut-off level (TnI > 60 ng/L), the ward physician was notified and a cardiac consult was requested. It was left at the discretion of the ward physician and cardiologist whether follow-up of TnI and further diagnostic procedures were indicated. Myocardial infarction was diagnosed by the cardiologist according to the third universal definition by judging the height of the TnI level, the presence or absence of a rise and fall in TnI, clinical symptoms, electrocardiography and/or cardiac imaging. In this, a rise and fall in TnI was not defined beforehand [4].

In the current study, for each patient all postoperative TnI measurements within 10 days after surgery were used, including follow-up measurements in addition to the routine TnI measurements. Troponin elevation was defined as a TnI > 60 ng/L, which was the lowest value measurable with a 10% coefficient of variation above the 99th percentile of 40 ng/L of the assay used. TnI was analyzed using the third-generation enhanced AccuTnI assay (Beckman Coulter, Brea, CA, USA).

## Kinetics of troponin

For each patient we first expressed the kinetics of troponin in terms of the absolute and relative change in TnI. The absolute change in TnI was defined as the highest minus the lowest postoperative TnI value. The relative change in TnI was defined as the difference between the highest and the lowest postoperative TnI value, divided by the lowest TnI value.

Subsequently, we categorized patients according to their pattern of TnI changes into two categories (stable pattern and rise-and-fall pattern) as follows. First, we identified potential cut-off values of the highest TnI value and the absolute and relative change in TnI, by grouping patients in deciles, and rounding to the nearest tenths or hundredths. For the highest TnI value, this resulted in the following TnI categories: 70–79 ng/L, 80–89 ng/L, 90–99 ng/L, 100–129 ng/L, 130–169 ng/L, 170–259 ng/L, 260–499 ng/L, 500–1499 ng/L and ≥ 1500 ng/L. Next, the risk ratio for mortality was calculated for each of these cut-off values. Because nine different cut-off values were tested, Bonferroni correction was used to adjust for multiple comparisons, resulting in a 99.4% confidence interval (p value of $0.05/9 = 0.006$) as level of statistical significance. Based on these results, the change in TnI for which the risk of mortality was increased, was used as a cut-off value to distinguish a stable TnI

pattern from TnI patterns with a rise and fall. In assigning each of the patients to either one of the patterns (stable pattern, rise-and-fall) patients with only a rise in TnI or only a fall in TnI were taken together with patients with a rise-and-fall pattern; i.e. these patients were considered to actually have a rise-and-fall pattern where the initial rise or the fall was not measured.

### Outcomes

The primary outcome was all-cause mortality within 1 year after surgery. Postoperative myocardial infarction, defined according to the third universal definition, [4] was included as a secondary outcome.

### Statistical analysis

Baseline characteristics were compared between the two different patterns of TnI that we identified. Categorical variables were compared using the $\chi^2$ test and age was compared using the two-sample t-test. The number of TnI measurements was compared between these two groups using the Mann-Whitney U test.

The highest TnI value and the absolute and relative change in TnI were then compared between patients who were deceased and alive after 1 year, and between patients with and without postoperative myocardial infarction using the Mann-Whitney U test. We compared 1-year survival between patients with a stable TnI pattern and a rise-and-fall pattern using Kaplan-Meier analysis and the log-rank test.

Cox regression analysis was used to determine the hazard ratio (HZ) for mortality in patients with a rise-and-fall pattern, as compared to a stable TnI pattern. Multivariable cox regression analysis was used to determine the added predictive value of the TnI pattern on 1-year mortality on top of the highest TnI value and RCRI variables. Therefore, we compared the predictive value of a multivariable model including the highest TnI value, RCRI variables and the TnI pattern to a model only including the highest TnI value and RCRI variables using the area under the receiver operating curve (AUROC).

Next, we compared cardiac interventions between the patients with a stable TnI pattern and a rise-and-fall pattern. Furthermore, in the patients with myocardial infarction, we compared 1-year mortality between the patients with a stable TnI pattern and a rise-and-fall pattern using the $\chi^2$ test.

Finally, we considered that patients with evident non-cardiac causes of TnI elevation, i.e. patients with sepsis or severe intracranial pathology, may confound the results. Therefore we conducted a sensitivity analysis after exclusion of these patients.

The analysis was performed using SPSS (release 21.0 for Windows). Throughout the analysis a level of significance of 0.05 was used, apart from the aforementioned adaptation of the $\alpha$ to 0.006 in the definition of the TnI pattern.

## Results

During the study period 4105 patients were eligible for inclusion, of which 55 (1%) patients were excluded: four patients were transferred to another hospital on the day of surgery, 19 patients died on the day of surgery, hence TnI could not be measured in these patients, and 32 patients were lost to follow-up as mortality data could not be obtained from the municipal personal records database. Of the remaining 4050 patients, TnI was measured after surgery in 3224 (80%) patients. TnI was elevated in 715 (22%) of these 3224 patients. From these 715 patients, 66 were excluded because TnI was only measured once, hence the change in TnI could not be calculated. In addition, in 15 patients the first elevated TnI was measured on clinical indication at >72 h after the start of surgery, and was not part of the postoperative care protocol, and therefore they were excluded. In total, 634 patients were included in the analysis (Figure 1).

Figure 2 shows the risk ratios (RR) for 1-year mortality for several cut-off values. The risk of mortality increased significantly with peak TnI values ≥ 90 ng/L (RR 1.9, 99.4% CI 1.1–3.1, p = 0.001). Furthermore, the risk of mortality increased significantly with an absolute change in TnI of ≥ 200 ng/L (RR 1.5, 99.4% CI 1.0–2.2, p = 0.003), i.e. this was the lowest absolute change at which the risk of mortality was significantly increased. The risk of mortality was not increased for relative changes in TnI. Based on these results, an absolute change in TnI ≥ 200 ng/L was used as a cut-off level to distinguish a rise-and-fall pattern from a stable pattern.

Of the 634 patients, 459 patients (72%) had a stable TnI pattern, 110 patients (17%) had a rise-and-fall pattern, 26 patients (4%) had a rising pattern, and 39 patients (6%) had a falling pattern. In the further analysis, the patients with a rising pattern or a falling pattern were taken together with the patients with a rise-and-fall pattern. Baseline characteristics, stratified for the different TnI patterns, are given in Table 1. Patients with a rise-and-fall pattern more often had diabetes and renal insufficiency, used more cardiovascular medications, and more often underwent vascular surgery and re-operations as compared to patients

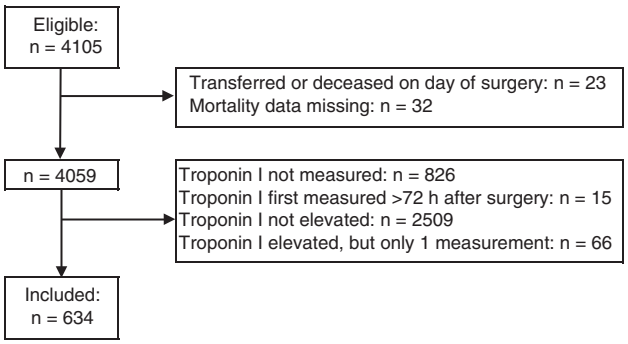


**Figure 1:** Flow chart of patient inclusion.

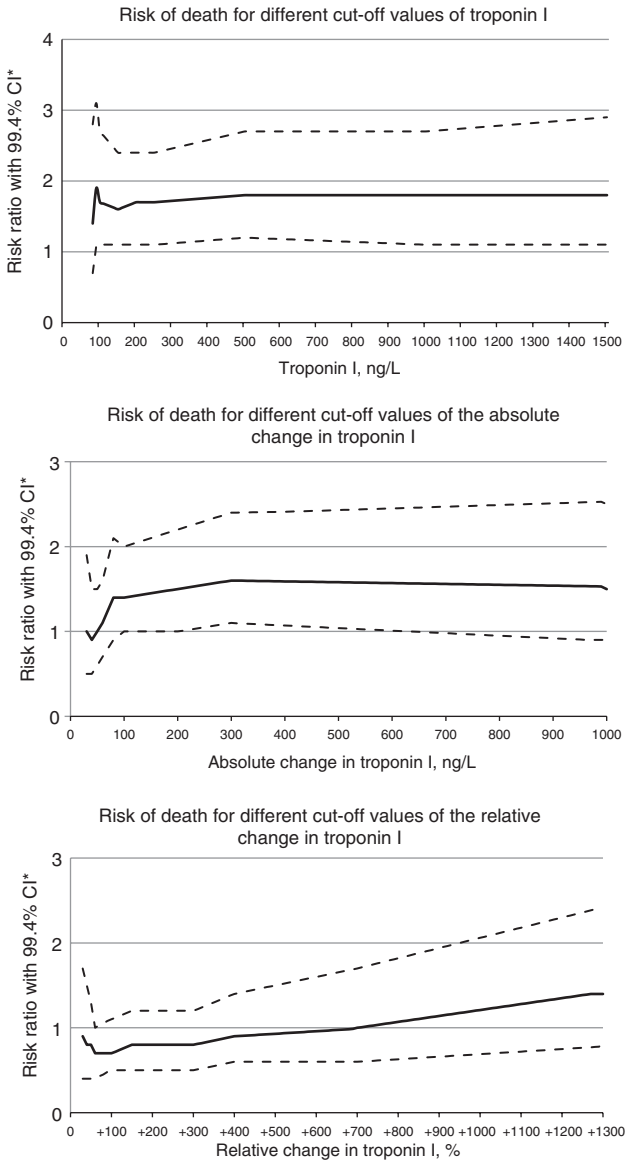


**Figure 2:** Risk of 1-year mortality for different cut-off values of the highest TnI value, the absolute change in TnI, and the relative change in TnI.
*Confidence interval.

with a stable TnI pattern. The median number of TnI measurements was four [Interquartile range (IQR) 3–5] in patients with a rise-and-fall pattern, as compared to three measurements (IQR 3–3) in patients with a stable pattern.

## Primary outcome

One-year mortality occurred in 155 (24%) patients. In patients who died, the median highest TnI value was 190 ng/L (IQR 100–660 ng/L), as compared to 120 ng/L in patients who were alive (IQR 80–280 ng/L, $p < 0.01$). The median absolute change in TnI was 110 ng/L (IQR 50–460 ng/L) in patients who died within 1 year, as compared to 71 ng/L (IQR 50–180 ng/L) in patients who survived ($p = 0.02$). The median relative change in TnI was +175% in patients who died (IQR +60% to +510%), as compared to +243% in alive patients (IQR +96% to +600%) ($p = 0.18$) (Figure 3). One-year survival was better in patients with a stable TnI pattern, as compared to patients with a rise-and-fall or falling TnI pattern (Figure 4).

Univariable regression analysis showed that the HZ for mortality was 1.7 (95% CI 1.2–2.3, $p < 0.01$) in patients with a rise-and-fall pattern as compared to patients with a stable TnI pattern. After adjustment for the highest TnI value and the variables from the RCRI, the TnI pattern was not associated with mortality (Table 2). Adding the TnI pattern to a model including the highest TnI value and the RCRI variables did not increase the predictive value on mortality: AUROC 0.67 (95% CI 0.62–0.72) vs. 0.66 (95% CI 0.61–0.71).

A sensitivity analysis excluding patients with evident non-cardiac causes of TnI elevation, i.e. intracerebral pathology ($n = 6$) or sepsis ($n = 6$) did not alter the results.

## Secondary outcome

Ninety patients (14%) fulfilled the criteria of myocardial infarction. In those patients, the median highest TnI value was 745 ng/L (IQR 160–6335 ng/L), as compared to 120 ng/L (IQR 80–260 ng/L) in patients without myocardial infarction ($p < 0.01$). The median absolute change in TnI was 525 ng/L (IQR 68–4955 ng/L) in patients with myocardial infarction, as compared to 70 ng/L (50–160 ng/L) in patients without ($p < 0.01$). The median relative change in TnI was +375% (IQR +67% to +3029%) in patients with myocardial infarction, as compared to +200% (IQR +80% to +450%) in patients without ($p < 0.01$).

Of the 90 patients with postoperative myocardial infarction, 34 patients (38%) had a stable TnI pattern, and 56 (62%) had a rise-and-fall pattern. In these patients with myocardial infarction, mortality within 1 year occurred in 26 of the 56 patients (46%) with a rise-and-fall pattern, as compared to nine of the 34 patients (26%) with a stable pattern ($p = 0.06$).

## Cardiac interventions in patients with different TnI patterns

A cardiac consultation was performed in 130 (74%) of the 175 patients with a rise-and-fall pattern, as compared

**Table 1:** Baseline characteristics, stratified by the pattern of postoperative TnI measurements.

| | Tn stable: ΔTn < 200 ng/L n = 459 | Tn rise-and-fall: ΔTn ≥ 200 ng/L n = 175 | p-Value |
|---|---|---|---|
| Male | 283 (62.0) | 98 (56.0) | 0.19 |
| Mean age, SD | 73.0 (8.2) | 73.1 (8.2) | 0.94 |
| Hypertension | 280 (61.0) | 114 (65.1) | 0.34 |
| Diabetes | 84 (18.3) | 46 (26.3) | 0.03 |
| History of myocardial infarction | 61 (13.3) | 33 (18.9) | 0.08 |
| History of coronary revascularization | 84 (18.3) | 35 (20.0) | 0.62 |
| Chronic heart failure | 24 (5.2) | 10 (5.7) | 0.81 |
| (Paroxysmal) atrial fibrillation | 72 (15.7) | 23 (13.1) | 0.42 |
| Pacemaker and/or ICD | 21 (4.6) | 10 (5.7) | 0.55 |
| History of cerebrovascular disease | 80 (17.4) | 39 (22.3) | 0.16 |
| Chronic obstructive pulmonary disease | 52 (11.3) | 18 (10.3) | 0.71 |
| Preoperative renal insufficiency | 85 (18.5) | 50 (28.6) | < 0.01 |
| Peripheral vascular disease | 66 (14.4) | 34 (19.4) | 0.12 |
| Chronic medication use | | | |
| Beta blockers | 177 (38.6) | 68 (38.9) | 0.95 |
| Angiotensin renin blockers | 179 (39.0) | 84 (48.0) | 0.04 |
| Calcium channel blockers | 89 (19.4) | 36 (20.6) | 0.74 |
| Diuretics | 148 (32.2) | 57 (32.6) | 0.94 |
| Statins | 187 (40.7) | 89 (50.9) | 0.02 |
| Aspirin | 159 (34.6) | 83 (47.4) | 0.03 |
| Warfarins | 70 (15.3) | 18 (10.3) | 0.11 |
| ASA class Δ | | | |
| 1 | 36 (7.8) | 9 (5.1) | 0.51 |
| 2 | 265 (57.7) | 98 (56.0) | |
| ≥ 3 | 158 (34.4) | 68 (38.9) | |
| General anesthesia | 442 (96.3) | 170 (97.1) | 0.60 |
| High-risk surgery | 200 (43.6) | 83 (47.4) | 0.38 |
| Emergency surgery | 148 (32.2) | 65 (37.1) | 0.24 |
| Re-operation within 1 year | 99 (21.6) | 55 (31.4) | 0.01 |
| Surgical specialty | | | |
| General | 162 (35.3) | 57 (32.6) | 0.16 |
| Neuro | 89 (19.4) | 28 (16.0) | |
| Vascular | 81 (17.6) | 49 (28.0) | |
| ENT and dental | 45 (9.8) | 13 (7.4) | |
| Orthopedic | 54 (12.0) | 20 (11.4) | |
| Gynecology/urologic | 28 (6.1) | 8 (4.6) | |

Figures are numbers of patients (%), unless indicated otherwise. SD, standard deviation; ICD, implantable cardiovertor defibrillator; Δ, Classification System by the American Society of Anesthesiologists; ENT, ear nose throat.

to 141 (31%) of the 459 patients with a stable pattern ($p < 0.01$). This was followed by an intervention in 61 patients (35%) as compared to 42 patients (9%) ($p < 0.01$). New medication or a dose increase, including beta-blockers, renin-angiotensin inhibitors, calcium channel blockers, diuretics, statins, aspirin, other antiplatelet drugs, and (low molecular weight) heparin, was prescribed in 60 patients with a rise-and-fall pattern (34%), as compared to 37 patients (8%) with a stable pattern ($p < 0.01$). Of the patients with a rise-and-fall pattern, more patients were transferred to the coronary care unit or medium care unit for cardiac monitoring, more patients underwent coronary angiography, and more patients underwent percutaneous coronary intervention (Table 3).

## Discussion

To help clinicians in interpreting postoperative troponin elevation, we described the kinetic changes of TnI in patients with myocardial injury after noncardiac surgery using troponin values that were routinely measured as part of a clinical protocol. In addition, the added predictive

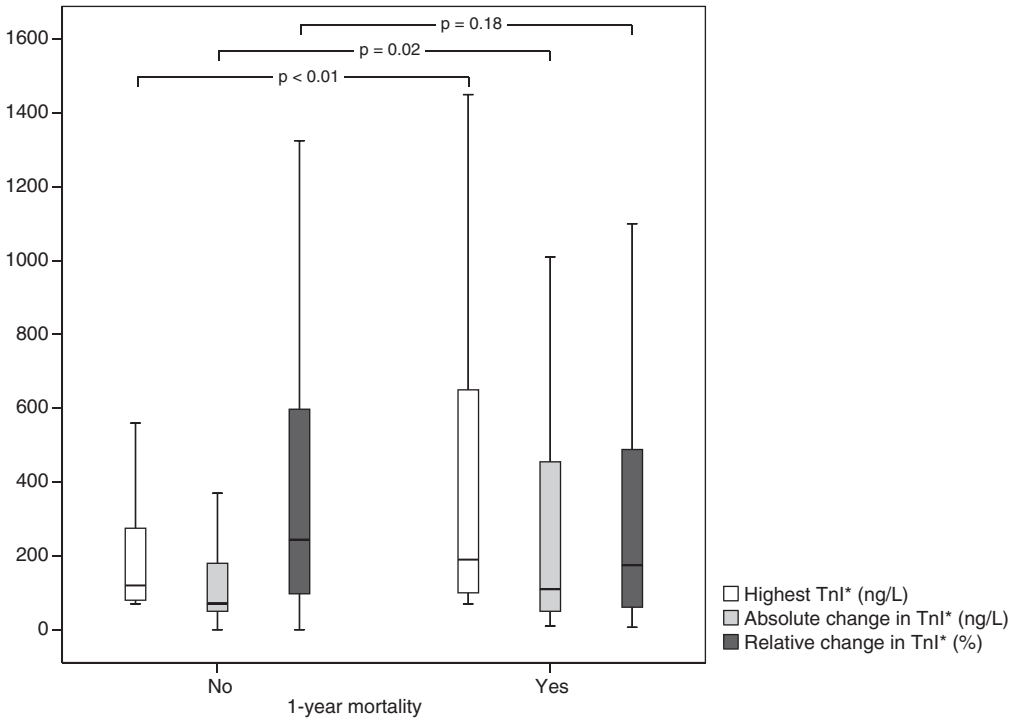


**Figure 3:** The median highest troponin I value, the median absolute change in troponin I, and the median relative change in troponin I in patients who died within 1 year and patients who survived.
*Troponin I.

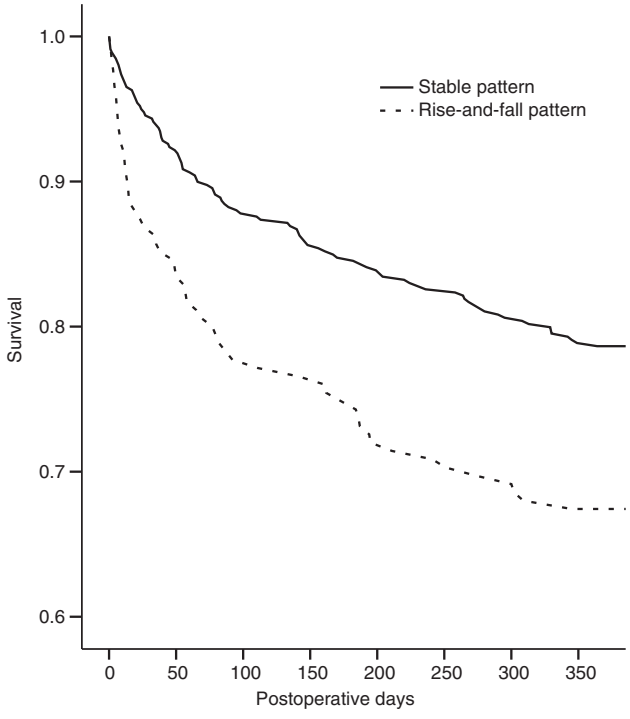


**Figure 4:** Survival curve of patients with different TnI patterns.
A stable troponin I pattern was defined as an absolute change in TnI < 200 ng/L, and a rise-and-fall pattern was defined as an absolute change in TnI ≥ 200 ng/L.

value of kinetic changes in TnI after noncardiac surgery to predict 1-year mortality was determined.

Among patients with myocardial injury after surgery, we found that an absolute change in TnI of at least 200 ng/L was associated with mortality. Such a change showing a rise-and-fall pattern was found in 28% of patients. Adding the absolute TnI change to a model including the highest TnI level, did not improve the ability to predict mortality. Relative changes in TnI did not predict mortality.

## Limitations

This study has some obvious limitations. First of all, since TnI was not measured before surgery, the results of this study cannot be used to interpret postoperative TnI values in relation to preoperative values. The patients with a stable TnI pattern after surgery may in fact have had a rise-and-fall pattern in relation to a preoperative value, i.e. in those patients the perioperative rise and fall may have been missed because TnI was not measured before surgery. However, this study determined the additional value of TnI kinetics in patients in whom troponin is only measured after surgery, like in our standard postoperative care. In the future, it would be of interest to study

**Table 2:** The hazard ratio of 1-year mortality in patients with a rise-and-fall pattern as compared to a stable TnI pattern, adjusted for the highest TnI value and variables from the RCRI.

| | Adjusted analysis | | |
|---|---|---|---|
| | HR | 95% CI | p-Value |
| TnI pattern | | | |
| Stable (absolute change in TnI < 200 ng/L) | Ref | | |
| Rise-and-fall (absolute change in TnI ≥ 200 ng/L) | 0.5 | 0.3–1.1 | 0.11 |
| Highest TnI value, ng/L | | | |
| 70–79 | Ref | | |
| 80–89 | 0.7 | 0.3–1.5 | 0.35 |
| 90–99 | 1.5 | 0.7–3.5 | 0.31 |
| 100–129 | 1.4 | 0.7–2.7 | 0.31 |
| 130–169 | 1.0 | 0.5–2.1 | 0.96 |
| 170–259 | 1.9 | 1.0–3.7 | 0.06 |
| 260–499 | 1.9 | 0.9–4.3 | 0.10 |
| 500–1499 | 4.1 | 1.5–10.7 | < 0.01 |
| ≥ 1500 | 4.3 | 1.7–11.0 | < 0.01 |
| RCRI | | | |
| High-risk surgery | 1.0 | 0.7–1.4 | 0.89 |
| Ischemic heart disease | 0.9 | 0.6–1.3 | 0.57 |
| Chronic heart failure | 1.1 | 0.6–2.2 | 0.70 |
| Cerebrovascular disease | 1.1 | 0.6–1.7 | 0.84 |
| Preoperative renal insufficiency | 2.1 | 1.5–3.0 | < 0.01 |
| Insulin use | 1.0 | 0.6–1.7 | 0.98 |

HR, hazard ratio; CI, confidence interval.

postoperative troponin changes in relation to preoperative values. Second, because follow-up of elevated TnI levels was not strictly protocolized, yet was performed at discretion of the attending cardiologist, TnI was not measured every 4–6 h in all patients. Therefore, a rise-and-fall pattern may have been missed in some patients. Finally, the analysis was not adjusted for treatment interventions that were undertaken in patients with myocardial injury and that may have influenced prognosis. This may have led to an underestimation of the predictive value of TnI kinetics.

## Literature

Kinetics of troponin have been well studied and implemented in the diagnosis of myocardial infarction in patients suspected of acute coronary syndrome in a non-perioperative setting. Although a relative change in troponin of > 20% is considered to be diagnostic for myocardial infarction in patients after percutaneous coronary intervention or reinfarction, [4] absolute troponin changes are superior to relative changes in discriminating myocardial infarction in patients presenting in the emergency department [10, 12–15]. Absolute TnI changes discriminate well between acute myocardial infarction and cardiac noncoronary artery disease, and are useful in selecting patients who require invasive treatment [10]. To predict outcome however, TnI changes do not improve risk prediction as compared to absolute troponin values and clinical risk factors [16].

Few studies have evaluated troponin kinetics in the perioperative period. Kavsak and colleagues studied relative changes of postoperative troponin T (TnT) in vascular surgery patients by using two cut-off levels that were

**Table 3:** Cardiology consultation and cardiac interventions, stratified by the pattern of postoperative TnI measurements.

| | Tn stable: ΔTn < 200 ng/L n = 459 | Tn rise-and-fall: ΔTn ≥ 200 ng/L n = 175 | p-Value |
|---|---|---|---|
| Cardiology consultation | 141 (30.7) | 130 (74.3) | < 0.01 |
| Any intervention | 42 (9.2) | 61 (34.9) | < 0.01 |
| New prescribed medication or dose increase | 37 (8.1) | 60 (34.3) | < 0.01 |
| Beta blockers | 12 (2.6) | 37 (21.1) | < 0.01 |
| Other antihypertensive drugs[a] | 7 (1.5) | 12 (6.9) | < 0.01 |
| Statins | 5 (1.1) | 16 (9.1) | < 0.01 |
| Aspirin | 10 (2.3) | 24 (13.7) | < 0.01 |
| Other antiplatelet drugs | 0 (0) | 14 (8.0) | < 0.01 |
| (Low molecular weight) heparin | 10 (2.3) | 15 (8.6) | < 0.01 |
| Other | 13 (2.8) | 10 (5.7) | 0.08 |
| Cardiac monitoring | 4 (0.9) | 11 (6.3) | < 0.01 |
| Coronary angiography | 2 (0.4) | 12 (6.9) | < 0.01 |
| Percutaneous coronary intervention | 1 (0.2) | 7 (4.0) | < 0.01 |
| Coronary artery bypass grafting | 0 (0) | 1 (0.6) | 0.11 |

Figures are numbers of patients (%). [a]Including renin angiotensin blockers, calcium channel blockers and diuretics.

based on previous studies in healthy volunteers and patients suspected of acute coronary syndrome [17]. They reported that half of the patients with postoperative troponin elevation had a relative change in TnT >85% as compared to the preoperative TnT level, and one in four patients had a relative TnT change >242%. Gillmann and colleagues studied both absolute and relative changes in patients undergoing vascular surgery, and found that an absolute change in TnT of as small as 6 ng/L, as compared to the preoperative TnT level, was independently associated with major adverse cardiac events, and that adding the TnT absolute change to clinical risk factors improved the predictive accuracy for major adverse cardiac events [18]. These results differ from our study, which may be explained by the fact that they calculated postoperative troponin changes in relation to preoperative troponin levels, while we only studied postoperative troponin values. Furthermore, Gillmann and colleagues reported that absolute TnT changes were superior to relative TnT changes for perioperative risk prediction, which is in concordance with our finding that relative changes were not related to mortality [18].

### Clinical implications

Several studies have shown that myocardial injury after noncardiac surgery as measured by troponin elevation, is an independent predictor of mortality. Yet, because troponin elevation may occur in a variety of conditions and the cause of myocardial injury is often unclear, it is not known in which patients prognosis can be improved. Therefore, improved risk stratification of patients with myocardial injury is warranted. Since kinetic changes of cardiac biomarkers, described as a typical rise and fall, are the cornerstone in the diagnosis of myocardial infarction in the non-perioperative setting, kinetic changes of troponin may be considered important in the further assessment of prognosis in patients with myocardial injury after surgery. Although we found that postoperative absolute TnI changes of more than 200 ng/L are associated with mortality, these absolute TnI changes had no added value to predict mortality in addition to the highest TnI level. Since absolute changes are larger in patients with high TnI levels, a large absolute change in TnI is inherent to high TnI values, which may explain why TnI changes alone do not have any added predictive value to absolute values. Furthermore, relative changes were not associated with mortality, which may be explained by the fact that relative changes cannot distinguish a patient with low TnI levels, and therefore a relatively good prognosis, from a patient with very high TnI levels and a poor prognosis, e.g. the relative change in TnI from 80 ng/L to 120 ng/L is similar to the relative change in TnI from 2000 ng/L to 3000 (both +50%).

Of note, 38% of the patients with a postoperative myocardial infarction did not show a rise-and-fall in TnI as determined in this study (absolute change >200 ng/L), although a rise-and-fall is required according to the third universal definition of myocardial infarction. This finding highlights an important problem in interpreting the universal definition: since the rise-and-fall that is required to diagnose myocardial infarction is not defined, in fact any change in troponin may be considered a rise-and-fall, hence even patients with very small changes may be diagnosed with myocardial infarction. This issue may be further complicated by the use of high sensitivity troponin assays: it has been shown that when high sensitivity troponin assays are used, the use of troponin changes on top of absolute troponin values improves specificity but reduces sensitivity in patients who are suspected of myocardial infarction in the emergency department [19]. In the perioperative setting, the use of troponin changes as detected by high sensitivity assays are subject to further investigation.

Although only 43% of all patients had cardiology consultation, and interventions were only performed in 24% of patients, this was done more often in patients with a rise-and-fall pattern (in 74% and 35% of patients, respectively). Apparently, cardiologists were more likely to adjudicate a TnI rise-and-fall pattern as a myocardial infarction.

## Conclusions

Among patients with myocardial injury after noncardiac surgery, as detected by routine postoperative TnI measurements, kinetics of postoperative TnI showed a rise-and-fall pattern in one third of patients. An absolute change in TnI of more than 200 ng/L was associated with 1-year mortality, but had no added predictive value in addition to the highest TnI level. Therefore, we consider TnI kinetics not useful for further stratification of mortality risk in patients with postoperative myocardial injury.

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