Role of N-terminal pro B-type natriuretic peptide in identifying patients at high risk for adverse outcome after emergent non-cardiac surgery

S. Farzi1*, T. Stojakovic2, Th. Marko1, C. Sankin1, P. Rehak3, R. Gumpert4, A. Baumann5, B. Höfler6, H. Metzler1 and E. Mahla1

1 Department of Anaesthesiology and Intensive Care Medicine, 2 Clinical Institute of Medical and Chemical Laboratory Diagnostics, 3 Department of Surgery, Unit of Medical Engineering and Computing, 4 Department of Trauma Surgery, 5 Department of Surgery, Division of Vascular Surgery, and 6 Department of Surgery, Division of General Surgery, Medical University of Graz, Graz, Austria

* Corresponding author. E-mail: sylvia.farzi@medunigraz.at

Editor’s key points

- Emergency surgical procedures are associated with a high risk of postoperative complications, but accurate risk assessment is difficult.
- A prospective single-centre observational study was designed to test N-terminal pro B-type natriuretic peptide (NT-proBNP) as a risk predictor in emergent non-cardiac surgery.
- Elevated preoperative NT-proBNP was associated with a significant risk for major postoperative complications and death.

Background. Patients undergoing emergency surgery continue to be at very high risk, but accurate risk identification for the individual patient remains difficult. This study tested the usefulness of perioperative N-terminal pro B-type natriuretic peptide (NT-proBNP) for in-hospital and long-term risk stratification.

Methods. We conducted a prospective single-centre observational cohort study in an Austrian university hospital. Two hundred and ninety-seven consecutive patients $>50$ yr of age undergoing a variety of emergency non-cardiac procedures were included. The primary endpoint was a composite of non-fatal myocardial infarction (MI), acute heart failure, or death between index surgery and 3 yr follow-up. The secondary endpoint was in-hospital major adverse cardiac events (MACE), defined as non-fatal MI, acute heart failure, or cardiac death.

Results. During a median follow-up of 34 months (inter-quartile range: 16–39), 31% of subjects reached the primary endpoint. A preoperative NT-proBNP $\geq 725$ pg ml$^{-1}$ was associated with a 4.8-fold univariate relative risk (95% confidence interval (CI): 3.1–7.6) and a postoperative NT-proBNP $\geq 1600$ pg ml$^{-1}$ was associated with a four-fold univariate relative risk (95% CI: 2.7–6.2) for reaching the primary endpoint. Moreover, preoperative NT-proBNP remained a significant and independent (hazards ratio 1.91, 95% CI 1.08–3.37, $P=0.027$) predictor in a multivariate Cox proportional hazards model. A preoperative NT-proBNP $\geq 1740$ pg ml$^{-1}$ was associated with a 6.9-fold univariate relative risk (95% CI: 3.5–13.4) for MACE during the index hospital stay, but did not remain significant in a multivariate logistic regression model.

Conclusions. Preoperative NT-proBNP can help identify patients at high risk for adverse long-term outcome after emergency surgery.

Keywords: B-type natriuretic peptide (BNP); emergency surgery; postoperative complications; risk stratification

Accepted for publication: 19 October 2012

Major emergency surgery, particularly in the elderly, carries up to 30% risk of in-hospital cardiac complications associated with 10–70% of in-hospital mortality.1–3 Moreover, postoperative complications have a huge impact on long-term survival.4 At the same time, emergency patients are least likely to undergo formal risk stratification.

The American College of Cardiology/American Heart Association’s perioperative guidelines strongly emphasize functional status as a tool for risk stratification. However, emergency surgery patients often have limited preoperative physical activity due to advanced age, frailty, and comorbidities such as peripheral vascular disease,2 which makes accurate assessment of cardiac risk difficult.

B-type natriuretic peptides (BNPs) perform better than traditional clinical risk scores and preoperative diagnostic tests, and are relatively cheap and non-invasive.5–9 BNP is released from cardiac myocytes in response to ischaemia10 and myocardial stretch.11 Plasma levels of these peptides

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correlate well with the extent of inducible ischaemia and reflect the severity of heart failure. The ability of preoperative BNs to predict early and long-term cardiovascular events and all-cause mortality after elective non-cardiac surgery has been established. Lately, their role in the perioperative setting was extended to septic patients. In patients undergoing elective vascular surgery, we demonstrated that a single postoperative determination of N-terminal proBNP (NT-proBNP) provides additional important short- and long-term prognostic information, presumably by reflecting the dynamic consequences of anaesthesia and surgery exerted by catecholamine surges and hypercoagulability with their potential to precipitate myocardial ischaemia and dysfunction.

Although currently no consensus exists regarding the reference range of pre- and postoperative BNP and NT-proBNP levels, the specifics of emergency surgery suggest an enhanced stress reaction and consequently elevated perioperative levels of BNs compared with levels in elective surgery, as demonstrated by previous studies in selected patients. We therefore aimed to test the usefulness of pre- and postoperative NT-proBNP for in-hospital and long-term risk stratification in patients undergoing a variety of emergency surgery procedures.

Methods

This study was planned as a follow-up study to an NT-proBNP study in vascular surgery patients our research group conducted. We adapted the original study protocol, which is described in greater detail elsewhere.

Patient selection

After institutional review board approval (EK number 19-077 ex 7/08, December 4, 2007, Medical University of Graz, Austria), all consecutive patients presenting for emergent non-cardiac surgery (defined as surgery that must be performed within 24 h after admission) between February 2008 and August 2009 were screened for eligibility for this prospective observational study. All patients gave written informed consent before participating. Patients at least 50 yr of age were eligible if they were undergoing acute abdominal aortic aneurysm surgery, infrainguinal or axillofemoral arterial reconstruction as limb salvage surgery for critical ischaemia, carotid endarterectomy for symptomatic carotid stenosis, intraperitoneal abdominal surgery for acute abdomen, surgery for peripheral or hip fractures that could not be postponed, or emergency spine surgery, under either general or spinal anaesthesia. Patients unable to provide informed consent, patients undergoing thoracic surgery, and multiply injured patients were excluded.

Determination of biochemical markers

Troponin T (TnT; electrochemiluminescence sandwich immunoassay; Elecsys Troponin T STAT, Roche Diagnostics, Mannheim, Germany; cut-off: 0.03 ng ml⁻¹) was determined before surgery, on postoperative day (POD) 1, once between POD 3 and 5, on the day of hospital discharge, and whenever clinically indicated by signs and symptoms of myocardial ischaemia.

NT-proBNP determinations (electrochemiluminescence sandwich immunoassay; Elecsys ProBNP, Roche Diagnostics) were performed before surgery, once between POD 3 and 5, and on the day of hospital discharge.

Perioperative management

Serial 12-lead ECG recordings were performed on admission, once between POD 3 and 5, and whenever clinically indicated. After operation, echocardiography was performed in the case of a TnT >0.03 ng ml⁻¹ and a non-diagnostic ECG and whenever clinically indicated to establish heart failure and to guide therapeutic interventions. Anaesthetic management, perioperative care, and intensive care unit referral were at the discretion of the attending physicians. Preoperative β-blockers and statins were resumed after operation either orally or via a nasogastric tube. Postoperative analgesia was performed using i.v. infusions of piritramide 0.1–0.2 mg kg⁻¹ four to six times daily, supplemented by i.v. non-steroidal anti-inflammatory drugs (diclofenac 75 mg, and orphenadrine citrate 30 mg; Neodolpasse, Freesius Kabi, Austria GmbH, Graz, Austria) twice daily, or, in the case of renal dysfunction or whenever non-steroidal anti-inflammatory drugs were contraindicated, i.v. metamizol 3–5 g per day. The analgesic regimen was adjusted to achieve a visual analogue scale. A standardized protocol for thromboprophylaxis was followed in all subjects. In the case of postoperative myocardial infarction (MI), subjects received acetylsalicylic acid (325 mg, i.v., followed by 100 mg per day orally), 1 mg kg⁻¹ enoxaparin twice daily or unfractionated heparin (titrated to an activated partial thromboplastin time of 1.5 normal), and clopidogrel (300 mg bolus, continued by 75 mg per day), unless contraindicated by an increased risk of bleeding.

The perioperative haematocrit was maintained between 30% and 33%. The attending physicians were aware of perioperative TnT levels, but were blinded to NT-proBNP levels.

Follow-up

Subjects were monitored for in-hospital and long-term cardiac events and all-cause mortality. The primary endpoint was a composite of non-fatal MI, acute heart failure, or death between index surgery and 3 yr follow-up. The secondary outcome variable was in-hospital major adverse cardiac events (MACE), defined as non-fatal MI, acute heart failure, or cardiac death. In hospital, subjects were actively monitored by a daily visit of an investigator blinded to NT-proBNP results and referred to a cardiologist in the case of a suspected event. Long-term follow-up was performed at 12 and 36 months after index surgery by telephone interview. In the case of hospital readmission or death since index surgery, hospital charts, death certificates, and autopsy reports were reviewed. A state-wide electronic documentation system allows access to all data for a patient who...
once was admitted to our clinic. As death certificate data do not reliably identify the cause of death, we chose to use all-cause mortality rather than cardiovascular mortality for the long-term outcome. By restricting in-hospital events to MACE, we aimed to minimize the confounding factors that arise from the acute surgical illness.

Non-fatal MI was defined according to the new Universal Definition of MI: typical increase/decrease of troponin together with evidence of myocardial ischaemia with at least one of the following: symptoms of ischaemia; ECG changes indicative of new ischaemia or new Q waves; or imaging evidence of new regional wall motion abnormality.25 Cardiac death was defined as death secondary to MI, arrhythmia, or heart failure. Acute heart failure was defined as clinical signs and symptoms of heart failure with echocardiographic evidence of cardiac dysfunction and clinical response to treatment directed towards heart failure.26

Statistics
Sample size calculation before recruitment was not feasible due to unknown means/medians and distribution of perioperative NT-proBNP levels in acute surgical patients with and without adverse events.

All data were tested for normal distribution by the Shapiro–Wilk test. Results are presented as mean (sd), median (inter-quartile range), or absolute and relative frequencies as appropriate. Perioperative NT-proBNP values were compared by the Mann–Whitney U-test. To identify the best discriminatory level of perioperative NT-proBNP associated with the primary and secondary endpoint, receiver operating characteristics (ROC) curves were analysed and the best cut-off defined as a value providing equal to the sensitivity and specificity. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated. To assess event-free survival, a Kaplan–Meier analysis was performed. The event–time curve was separated into two curves according to the discriminatory preoperative NT-proBNP, and these curves were compared by log-rank test. Univariate Cox regression analysis was performed to test for differences between subjects with and without events between index surgery and long-term follow-up. In order not to evaluate postoperative NT-proBNP elevation as a predictor of events that had already occurred at the time of the postoperative blood draw (between days 3 and 5) and were thus merely reflected on admission also had a creatinine value of range: 16–39), 91 (31%) subjects reached the composite primary endpoint of non-fatal MI, acute heart failure, and death of any cause. Thirty-four non-fatal MIs, 26 episodes of heart failure, and 24 cardiac deaths occurred between index surgery and 3 yr follow-up in 74 patients. The overall mortality was 28%. Forty cardiac events occurred during the index hospital stay in 34 subjects, 29 within the first three postoperative days. Twenty-eight subjects sustained in-hospital MIs and six had in-hospital episodes of acute heart failure. Thirteen subjects died during their index hospital stay. Importantly, 33 subjects (11%) already presented with elevated TnT on admission, and 20 (61%) of these sustained an in-hospital MACE. Four out of the 13 in-hospital deaths occurred in subjects with elevated preoperative TnT. There was no significant difference between the proportion of subjects with asymptotically raised troponin on admission in the vascular (15%), trauma (10%), or abdominal (13%) group. Only seven of the 33 subjects with raised troponin on admission also had a creatinine value of >2 mg dl⁻¹.

Association of preoperative and postoperative NT-proBNP and the primary endpoint
For preoperative NT-proBNP association with the composite primary endpoint of non-fatal MI, acute heart failure, and all-cause mortality between index surgery and 3 yr follow-up, excluding any events occurring during the first five postoperative days, the area under the curve (AUC) was 0.77 (95% confidence interval (CI): 0.71–0.82) (Fig. 1). The optimum discriminatory threshold derived was 725 pg ml⁻¹, yielding a sensitivity of 73%, a specificity of 71%, a PPV of 53%, and an NPV of 85%. This threshold of 725 pg ml⁻¹ was associated with a 4.8-fold univariate relative risk (95% CI: 3.1–7.6) for reaching the primary endpoint.

For postoperative NT-proBNP association with the primary endpoint, excluding any events occurring during the first five postoperative days, the AUC was 0.73 (95% CI: 0.66–0.78) (Fig. 2). The optimum discriminatory threshold derived was 1600 pg ml⁻¹, yielding a sensitivity of 61%, a specificity of 73%, a PPV of 51%, and an NPV of 80%. This threshold of
1600 pg ml\(^{-1}\) was associated with a four-fold univariate relative risk (95% CI: 2.7–6.2) for reaching the primary endpoint. Separating the initial event–time curve by a preoperative NT-proBNP level of 725 pg ml\(^{-1}\) demonstrates the association of preoperative NT-proBNP levels and cumulative event rate (Fig. 3).

Age, history of coronary artery disease, previous heart failure, anaemia, a preoperative creatinine >2 mg dl\(^{-1}\), before operation increased TnT, preoperative and postoperative NT-proBNP, and type of surgery were significantly associated with the primary endpoint (Table 1). In a multivariate Cox proportional hazards model, only age [hazards ratio (HR) 1.08, 95% CI 1.05–1.11, \(P<0.001\)] and a preoperative NT-proBNP level of at least 725 pg ml\(^{-1}\) (HR 1.91, 95% CI 1.08–3.37, \(P=0.027\)) remained significantly and independently associated with the primary endpoint.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Baseline subject characteristics (n=297) separated by the primary endpoint. Data are expressed as number (%), mean ((\sigma)), or median (inter-quartile range) as appropriate. P-value indicates differences between subjects with and without adverse events. Anaemia is defined as haemoglobin &lt;13 g dl(^{-1}) for males and &lt;12 g dl(^{-1}) for females. HF, heart failure; TIA, transient ischaemic attack; TnT, troponin T; NT-proBNP, N-terminal pro B-type natriuretic peptide; POD 3–5, postoperative day 3–5.</th>
<th>All subjects</th>
<th>Subjects who reached the primary endpoint</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr), mean (range)</td>
<td>74 (51–103)</td>
<td>81 (52–103)</td>
<td>71 (51–95)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex (men/women)</td>
<td>117/180</td>
<td>37/54</td>
<td>80/126</td>
<td>NS</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of coronary artery disease</td>
<td>100 (34)</td>
<td>47 (52)</td>
<td>53 (26)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Previous HF</td>
<td>26 (9)</td>
<td>16 (18)</td>
<td>10 (5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Previous stroke/TIA</td>
<td>36 (12)</td>
<td>12 (13)</td>
<td>24 (12)</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes mellitus, insulin-dependent</td>
<td>15 (5)</td>
<td>7 (8)</td>
<td>8 (4)</td>
<td>NS</td>
</tr>
<tr>
<td>Anaemia</td>
<td>186 (63)</td>
<td>70 (77)</td>
<td>116 (56)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Creatinine &gt;2 mg dl(^{-1}) preoperative</td>
<td>12 (4)</td>
<td>8 (9)</td>
<td>4 (2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TnT &gt;0.03 ng ml(^{-1}) preoperative</td>
<td>33 (11)</td>
<td>16 (18)</td>
<td>17 (8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NT-proBNP preoperative (pg ml(^{-1}), median (IQR))</td>
<td>491 (189–1670)</td>
<td>1527 (544–3650)</td>
<td>296 (119–873)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NT-proBNP POD 3–5 (pg ml(^{-1}), median (IQR))</td>
<td>973 (373–3390)</td>
<td>2450 (839–6390)</td>
<td>679 (272–1800)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Surgery (abdominal=reference)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trauma</td>
<td>186 (63)</td>
<td>52 (57)</td>
<td>134 (65)</td>
<td>0.004</td>
</tr>
<tr>
<td>Vascular</td>
<td>41 (14)</td>
<td>9 (10)</td>
<td>32 (16)</td>
<td>0.02</td>
</tr>
<tr>
<td>Duration of surgery (min), mean ((\sigma))</td>
<td>145 (66)</td>
<td>152 (67)</td>
<td>142 (66)</td>
<td>NS</td>
</tr>
<tr>
<td>Regional anaesthesia (spinal)</td>
<td>56 (19)</td>
<td>20 (22)</td>
<td>36 (17)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Fig 1 ROC curve of preoperative NT-proBNP to predict the composite endpoint of non-fatal MI, acute heart failure, and all-cause mortality between index surgery and 3 yr follow-up. The blue line represents the non-discrimination curve. The AUC is 0.77 (95% CI: 0.71–0.82).

Fig 2 ROC curve of postoperative NT-proBNP to predict the composite endpoint of non-fatal MI, acute heart failure, and all-cause mortality between index surgery and 3 yr follow-up. The blue line represents the non-discrimination curve. The AUC is 0.73 (95% CI: 0.66–0.78).
Association of preoperative NT-proBNP and in-hospital MACE

The association of preoperative NT-proBNP and in-hospital MACE was assessed with an ROC curve. The AUC was 0.83 (95% CI: 0.78–0.87). The optimum discriminatory threshold for preoperative NT-proBNP was 1740 pg ml\(^{-1}\), yielding a sensitivity of 71%, a specificity of 82%, a PPV of 34%, and an NPV of 96%. This threshold was univariately associated with a 6.9-fold relative risk (95% CI: 3.5–13.4) for in-hospital MACE. In univariate analysis, the occurrence of in-hospital MACE was further significantly associated with age (\(P<0.001\)), a history of coronary artery disease (\(P<0.001\)), a history of heart failure (\(P<0.001\)), preoperative anaemia (\(P=0.014\)), a preoperative creatinine \(>2\) mg dl\(^{-1}\) (\(P<0.001\)), type of surgery (\(P=0.004\)), and before operation increased TnT \(>0.03\) pg ml\(^{-1}\) (\(P<0.001\)). However, in a multivariate logistic regression model, only a history of coronary artery disease [odds ratio (OR) 3.94, 95% CI 1.38–11.28, \(P=0.01\)], trauma surgery (OR 0.32, 95% CI 0.11–0.88, \(P=0.03\)), and a before operation increased TnT \(>0.03\) pg ml\(^{-1}\) (OR 6.47, 95% CI 2.32–18.05, \(P<0.001\)) remained significantly and independently associated with the secondary endpoint.

Discussion

In this prospective observational study including 297 consecutive patients over the age of 50 undergoing a variety of emergency procedures, preoperative NT-proBNP was the best predictor of the composite endpoint of non-fatal MI, acute heart failure, and all-cause mortality between index surgery and 3 yr follow-up, and preoperative TnT elevation \(>0.03\) ng ml\(^{-1}\) was the best predictor of in-hospital MACE. Despite a rather low incidence of coronary artery disease (34%) in our cohort, we observed an 11% rate of elevated TnT on admission, an 11% incidence of perioperative MACE, and 4.4% perioperative mortality. Our results confirm that patients undergoing emergency surgery continue to be at very high risk for perioperative complications. This may be due to asymptomatic cardiac disease, suboptimal preoperative therapy, preoperative pain,\(^{7}\) the increased stress response associated with the complexity of emergency surgery,\(^{21}\) and postoperative infectious complications.\(^{1,28}\)

In our cohort, preoperative NT-proBNP was an independent predictor of the composite endpoint of non-fatal MI, acute heart failure, and all-cause mortality during 3 yr follow-up, thus extending the findings of Payne and colleagues\(^{1,28}\) to the emergency setting. Notably, we have shown that patients with a preoperative NT-proBNP level of \(\geq 725\) pg ml\(^{-1}\) had an almost five times greater univariate risk and a two times greater adjusted risk for non-fatal MI, acute heart failure, or death within 3 yr of emergency surgery. Specifically, 85% of the patients with NT-proBNP levels below 725 pg ml\(^{-1}\) remained event-free, whereas 48% of the patients with an NT-proBNP level equal to or above 725 pg ml\(^{-1}\) reached the primary endpoint. This cut-off is considerably lower than the threshold of 3980 pg ml\(^{-1}\) found by Oscarsson and colleagues\(^{10}\) to best predict perioperative myocardial damage in elderly high-risk (ASA III and IV) patients undergoing unscheduled hip fracture surgery. Additionally, in our cohort, postoperative NT-proBNP was an independent predictor of non-fatal MI, acute heart failure, or death within 3 yr of surgery in a Cox proportional hazards model, when preoperative NT-proBNP was not entered, but its independent predictive effect was cancelled out by preoperative NT-proBNP, when both parameters were entered into the model. Preoperative NT-proBNP with an optimal cut-off of 1740 pg ml\(^{-1}\) was significantly associated with in-hospital MACE in univariate analysis. This threshold is in keeping with the findings of Oscarsson and colleagues\(^{10}\) who evaluated myocardial injury as the endpoint in a mixed cohort of 211 high-risk patients undergoing urgent/emergent surgery. In a multivariate model controlling for preoperative TnT elevation, preoperative NT-proBNP did not remain significantly and independently associated with in-hospital MACE in our cohort, even though only 61% of those patients presenting with elevated TnT sustained an in-hospital event. It should be noted that the prognostic value of BNP has been shown to be independent of conventional risk factors, but its additive value to troponin has not been well studied so far.\(^{15}\)

Few studies have evaluated BNP in the emergency setting and most previous studies focused on high-risk patients and short-term outcome.\(^{7,22,23}\)

Chong and colleagues\(^{24}\) found that NT-proBNP was a predictor of in-hospital cardiac events (defined as acute MI, congestive cardiac failure, atrial fibrillation, or major arrhythmia) and long-term mortality in 89 patients undergoing emergency lower-limb orthopaedic surgery. They demonstrated the predictive capacity of pre- and postoperative NT-proBNP in two separate multivariate Cox hazard regression models and concluded that both preoperative NT-proBNP \(\geq 842\) pg ml\(^{-1}\) and postoperative NT-proBNP \(\geq 1400\) pg ml\(^{-1}\) were independent predictors of long-term all-cause mortality. To the best of our knowledge, ours is the first study examining the role of pre- and postoperative NT-proBNP for both short- and long-term outcome in exclusively emergency patients undergoing a variety of surgical procedures.
The results of this study should be interpreted in the light of several limitations. First, although currently, no consensus exists concerning the reference range of perioperative NT-proBNP values, we identified 725 pg ml\(^{-1}\) as the optimal cut-off associated with the occurrence of non-fatal MI, acute heart failure, and all-cause mortality from index surgery to 3 yr follow-up in non-cardiac emergency surgery patients over the age of 50. The considerable heterogeneity in patient co-morbidities and surgical problems owing to consecutive inclusion of patients might better reflect everyday clinical practice than a selected high-risk subgroup, but does not make the threshold we identified generalizable. Secondly, we measured NT-proBNP rather than BNP because of better in vitro stability, a longer half-life, and less susceptibility to rapid haemodynamic changes. Even though there are data showing that increased circulating NT-proBNP might mainly be related to increased cardiac secretion and not decreased renal clearance,\(^{31}\) severely impaired renal function does reduce the specificity of NT-proBNP.\(^{32}\) This could have influenced our results, as we did not exclude patients with renal dysfunction. Nevertheless, specificity levels in ROC curve analysis were over 70% for the association of both pre-operative and postoperative NT-proBNP with the primary and secondary endpoints. Finally, we have no data on perioperative fluid management. However, postoperative NT-proBNP determination was performed between days 3 and 5, when most patients no longer received i.v. infusion therapy, thus reducing the possible influence of increased filling pressures on NT-proBNP levels.\(^{33}\)

In conclusion, our results suggest that preoperative NT-proBNP measurement can help identify patients at high risk for adverse outcome after emergency surgery. These patients should be considered for less invasive procedures and must receive optimized perioperative care. Either a pre-operative or a postoperative NT-proBNP measurement can be useful in identifying patients who should be considered for targeted postoperative interventions to improve long-term outcome. Larger studies are needed to suggest a threshold value in the perioperative (emergency) setting and to examine the potential impact of early intervention.

**Acknowledgements**

We thank Roche Diagnostics GmbH, Mannheim, Germany, for the provision of the N-terminal pro-B-type natriuretic peptide assays. The technical assistance of the laboratory staff at the Medical University of Graz is gratefully acknowledged.

**Declaration of interest**

None declared.

**Funding**

Funding was provided solely from departmental sources except for N-terminal pro B-type natriuretic peptide assays, which were provided at no cost by Roche Diagnostics GmbH, Mannheim, Germany.

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*Handling editor: H. C. Hemmings*