



## Mid-regional pro-adrenomedulin as a marker of perioperative mortality in non-cardiac surgery

### Mid-regionalni pro-adrenomedulin kao marker perioperativnog mortaliteta u nekardijalnoj hirurgiji

To the Editor:

Recently published study revealed that out of a total number of patients undergoing a major non-cardiac surgery, 5% of them could have myocardial infarction<sup>1</sup>. After 30 days from the major non-cardiac surgery, over 11% of patients would probably die, most likely due to cardiovascular (CV) causes.

There are several widely used methods for estimating preoperative cardiac risk based on risk scores and risk stratification scales, e.g., the Revised Cardiac Risk Index (RCRI)<sup>2,3</sup>.

It is known that patients suffering from different diseases (not only cardiovascular ones) with increased mid-regional fragment of the pro-adrenomedullin molecule (MR-proADM) levels (different mechanisms of secretion involved) are at high risk of mortality<sup>4-6</sup>. In a large number of trials, the predictive role of MR-proADM as a biomarker for clinical outcome was investigated in non-surgical patients<sup>7,8</sup>. Results of the GISSI and LAMP studies, conducted in patients with chronic heart failure and myocardial infarction, demonstrated that MR-proADM concentrations higher than 0.75 nmol/L and 0.73 nmol/L, respectively, were predictors of poor outcome<sup>5,9</sup>.

Because of that, we performed a prospective observational study with an aim to evaluate MR-proADM as a risk marker for CV mortality in non-cardiac surgical patients older than 55 years who had at least one CV risk factor, which is usually the case in the real-life. MR-proADM was determined before surgery by using a sandwich immunoluminometric assay (MR-proADM, BRAHMS AG, Hennigsdorf/Berlin, Germany). Mean MR-proADM in 264 healthy individuals in previous investigations was  $0.33 \pm 0.07$  nmol/L (range 0.10–0.64 nmol/L) and the assay had a measuring range from 0 to 100 nmol/L<sup>4</sup>.

We enrolled 81 patients undergoing major abdominal ( $n = 56$ ), thoracic ( $n = 4$ ), orthopedic ( $n = 20$ ) and vascular ( $n = 1$ ) surgery under general anesthesia with at least one of the following CV risk factors: diabetes mellitus, hypertension, hyperlipidemia, active smoking, or a family history of cardiac disease. Exclusion criteria were emergent surgery and the inability to understand or sign the informed consent. We

routinely calculated the Revised Cardiac Risk Index (Lee score)<sup>3</sup>. The clinical endpoint of the study was mortality within 30 days after the surgery.

The study included 42 women (51.9%) and 39 men (48.1%), aged  $71.29 \pm 6.62$  years (range: 55–87 years). Within 30 days after the surgery 14 (17.3%) patients died, all due to cardiac causes and all being subjected to the abdominal surgery. This high and early postoperative mortality rate in our study could be explained by the fact that study included relatively small number of elderly patients with different co-morbidities who underwent an extensive surgery carrying a particularly high risk for poor outcome. Patients who died were older than 65 years ( $75.7 \pm 6.7$ ) and all of them underwent the abdominal resection (mostly radical) due to malignant abdominal tumors. Our results are in line with those obtained in other studies with elderly patients. Heriot et al.<sup>10</sup> reported that postoperative mortality in elderly patients with colorectal cancer was as high as 15.6%. A mortality rate of 16% was found in patients over 70 years of age undergoing major elective orthopedic surgery<sup>11</sup>.

The concentration of MR-proADM was statistically significantly higher in the deceased patients when comparing to survivors ( $p < 0.001$ ). On the other hand, the values of Lee were not significantly different with respect to fatal outcome ( $p = 0.283$ ).

The patients with MR-proADM in the upper quartile had statistically significant shorter survival, comparing to other patients ( $p = 0.007$ ). The survival time of patients with MR-proADM in the upper quartile was 15 (95% CI 6.46–23.54) days and in other patients it was 28 (95% CI 20.7–28.66) days. The group of deceased patients included 9 (45%) patients with MR-proADM above 0.86 (the upper quartile) and 5 (8.2%) with MR-proADM below 0.86. Our patients with higher NYHA class and Lee score above 6.60 had MR-proADM in the upper quartile. They also had the worst 30-day prognosis. In a number of studies on patients with heart failure, good correlation between NYHA class, natriuretic peptides and MR-proADM was shown<sup>12</sup>.

In our study, MR-proADM compared to the Lee score was a better predictor of postoperative mortality in the pa-

tients (with at least one CV risk factor) subjected to extensive non-cardiac surgery. Therefore, measuring MR-proADM concentrations might help in identifying a high-risk patients before performing non-cardiac surgery. These patients could have benefit from a risk reduction measurements.

We need more studies regarding the prognostic role of MR-proADM in perioperative risk stratification keeping in mind that our study had several limitations (small number of patients, elderly population with different comorbidities who underwent an extensive non-cardiac surgery). Nevertheless, we believe that MR-proADM is a promising prognostic biomarker for the preoperative risk assessment, either alone or together with other risk factors. This biomarker is involved in many (patho)physiological processes and might be not only a marker of CV risk, but general perioperative risk.

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### R E F E R E N C E S

1. *Devereaux PJ, Xavier D, Pogue J, Guyatt G, Sigamani A, Garutti I, et al.* POISE (PeriOperative ISchemic Evaluation) Investigators. Characteristics and short-term prognosis of perioperative myocardial infarction in patients undergoing noncardiac surgery: a cohort study. *Ann Intern Med* 2011; **154**(8): 523-8.
2. *Perelman G, Bax JJ, Boersma E, De Hert S, Eeckhout E, Fonkes G, et al.* Task Force for Preoperative Cardiac Risk Assessment and Perioperative Cardiac Management in Non-cardiac Surgery of European Society of Cardiology (ESC); European Society of Anaesthesiology (ESA). Guidelines for preoperative cardiac risk assessment and perioperative cardiac management in non-cardiac surgery: the Task Force for Preoperative Cardiac Risk Assessment and Perioperative Cardiac Management in Non-cardiac Surgery of the European Society of Cardiology (ESC) and endorsed by the European Society of Anaesthesiology (ESA). *Eur J Anaesthesiol* 2010; **27**(2): 92-137.
3. *Lee TH, Marcantonio ER, Mangione CM, Thomas EJ, Polanczyk CA, Cook EF et al.* Derivation and prospective validation of a simple index for prediction of cardiac risk of major non cardiac surgery. *Circulation* 1999; **100**(10): 1043-9.
4. *Morgenthaler NG, Struck J, Alonso C, Bergmann A.* Measurement of midregional proadrenomedullin in plasma with an immunoluminometric assay. *Clin Chem* 2005; **51**(10): 1823-9.
5. *Khan SQ, O'Brien RJ, Struck J, Quinn P, Morgenthaler N, Squire I, et al.* Prognostic value of midregional pro-adrenomedullin in patients with acute myocardial infarction: the LAMP (Leicester Acute Myocardial Infarction Peptide) study. *J Am Coll Cardiol* 2007; **49**(14): 1525-32.
6. *Gegenhuber A, Struck J, Dieplinger B, Poelz W, Pacher R, Morgenthaler NG, et al.* Comparative evaluation of B-type natriuretic peptide, mid-regional pro-A-type natriuretic peptide, mid-regional proadrenomedullin, and Copeptin to predict 1-year mortality in patients with acute destabilized heart failure. *J Card Fail* 2007; **13**(1): 42-9.
7. *Smith JG, Newton-Cheb C, Hedblad B, Struck J, Morgenthaler NG, Bergmann A, et al.* Distribution and correlates of midregional proadrenomedullin in the general population. *Clin Chem* 2009; **55**(8): 1593-5.
8. *Neumann JT, Tzifkas S, Funke-Kaiser A, Wilde S, Appelbaum S, Keller T, et al.* Association of MR-proadrenomedullin with cardiovascular risk factors and subclinical cardiovascular disease. *Atherosclerosis* 2013; **228**(2): 451-9.
9. *Masson S, Latini R, Carbonieri E, Moretti L, Rossi MG, Ciricugno S, et al.* The predictive value of stable precursor fragments of vasoactive peptides in patients with chronic heart failure: data from the GISSI-heart failure (GISSI-HF) trial. *Eur J Heart Fail* 2010; **12**(4): 338-47.
10. *Heriot AG, Tekkis PP, Smith JJ, Cohen CR, Montgomery A, Audisio RA et al.* Prediction of postoperative mortality in elderly patients with colorectal cancer. *Dis Colon Rectum* 2006; **49**(6): 816-24.
11. *Asonbidou I, Asteri T, Sountoulides P, Natsis K, Georgiadis G.* Early postoperative mortality in the elderly: a pilot study. *BMC Res Notes* 2009; **2**: 118.
12. *von Haebling S, Filippatos GS, Papassotiriou J, Cicciara M, Jankowska EA, Doebner W, et al.* Mid-regional pro-adrenomedullin as a novel predictor of mortality in patients with chronic heart failure. *Eur J Heart Fail* 2010; **12**(5): 484-91.

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