Perioperative endothelin-1 levels: Searching for the hidden fingerprint of nonocclusive mesenteric ischemia

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See related article on pages 1436-42.

We commend the Saarland University Medical Centre group for its consistent effort in trying to identify the biological basis and the eventual biomarkers of nonocclusive mesenteric ischemia (NOMI) in patients undergoing cardiac surgery.¹ In fact, the present publication is just the last addition to a very well-defined scientific *excursus* the authors have developed in the last years.^{2,3} It should be emphasized that despite the fact that NOMI carries a heavy burden of mortality, its existence stays poorly acknowledged, and, as an obvious consequence, NOMI often remains unrecognized and untreated.

First, in the present study,¹ the authors report a 9% rate of NOMI, based on angiographic and clinical evaluation. This finding underlines the fact that in environments “tuned up” for diagnosis and treatment, NOMI occurrence is significantly high when compared with other morbidities often encountered in the perioperative phases of cardiac surgery. It is even more striking that when left untreated, NOMI has a mortality rate of more than 20%. As a consequence, misdiagnosis and mistreatment of this occurrence may increase to 2% the overall mortality rate after cardiac surgery on cardiopulmonary bypass. Per se, this is an important message to the readers.

Second, we should reflect on the present tools available for NOMI diagnosis. Postoperative visceral angiography cannot be accepted, because of its invasiveness, as a standard for diagnosis. For this reason, in the near future, we should aim at “less-invasive” tools, including endothelin (ET)-1 sampling. In this context, we should review critically review the authors’ findings.¹ Their receiver operating characteristic (ROC) analyses of preoperative ET-1 serum levels and the occurrence of NOMI revealed an optimal cut-off value of 11.7 pg/mL with a sensitivity of 44% and a

specificity of 85%. ROC analyses of post-operative ET-1 serum levels showed an optimal cutoff value of 14.5 pg/mL with a sensitivity of 51% and a specificity of 94%. Such a test sensitivity implies that if we were to make our diagnosis just on the basis of ET-1 sampling, we would fail to correctly diagnose NOMI in at least 1 of 2 patients (false-negative). Of note, even in the authors’ practice,¹ “ET-1 is not presently used as a routine stratification tool due to the fact, that this is not a routine laboratory value and therefore cannot be provided in daily care.”

Third, although we understand that Groesdonk and colleagues¹ are scientifically trying to identify a specific and independent determinant for NOMI, some realistic caution should be advised. ET-1 could be just one of the many markers and mediators increasing after cardiopulmonary bypass and being involved in the ischemic–reperfusion cascade. In this context, the same group recently proposed that there is also an association between serum procalcitonin levels and NOMI.⁴ In the same observational cohort study of 865 patients undergoing elective cardiac surgery, ROC analyses showed that elevated serum procalcitonin levels accurately predicted the occurrence of NOMI (optimal cutoff value, 6.6 ng/mL; area under the curve, 0.94; sensitivity, 71%; specificity, 94%).⁴ On this basis, it is reasonable to believe that the statistical correlation of ET-1 levels with the risk of developing NOMI will not necessarily imply a direct and independent causative relationship.

Fourth, the importance of other correlated risk factors and their multiplicative effect should be discussed, and the multifactorial genesis of NOMI should be clearly stated. As reported by Groesdonk and colleagues,¹ the addition of 3 independent clinical risk factors (loss of sinus rhythm, need for norepinephrine >0.1 µg/kg/min, and intra-aortic balloon pump) will determine a 7 times increase in the probability of developing NOMI. These findings should suggest to the readers that NOMI is not an “exclusive property” of cardiac surgery, and, on the contrary, it may occur and stay undiagnosed in many other patients we treat, even without the use of cardiopulmonary bypass, for other critical cardiovascular conditions.

Finally, the importance of detecting a specific role of ET-1 in the genesis of NOMI has to be pictured in light of a possible future specific treatment. The fact that in animal studies ET-receptor antagonists had a protective effect in ischemia–reperfusion injury of the small bowel^{5,6} is

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encouraging and should stimulate further research in humans, particularly in light of the authors' present findings.¹ If these initial hypotheses are confirmed, we could envisage, in the near future, a preventive treatment for patients with a higher risk of developing perioperative NOMI, on the basis of preoperatively elevated ET-1 levels.

Awareness of NOMI should be raised and its perioperative diagnosis should be simplified, achieving adequate specificity and improved sensitivity. Although the identification and diagnostic use of a single "hidden fingerprint" of intestinal ischemia are appealing, sampling of ET-1 levels should always be interpreted together with other clinical findings to further support clinicians in their daily practice. Moreover, the safety and efficacy of ET-1 antagonists in the preventive and treatment phases should be investigated in the future, within the premises of adequately sampled prospective randomized trials.

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