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In Reply:—We thank Dr. Navarro-Martinez and colleagues for their letter concerning our review on perioperative fluid management. In general, we would like to point out that our article was targeted on perioperative fluid therapy in patients who primarily have a steady state concerning their fluid compartments.[1] In these patients an intact vascular barrier function ensures that, despite a positive pressure within the circulatory space, plasma constituents are not distributed evenly across the whole extracellular compartment.[2,3] Rather, under normal physiologic conditions, they are predominantly retained where they are needed to maintain a sufficient cardiac preload. A small residual flow towards the interstitial space is managed by an intact lymphatic system.[1] In this situation, requirement-adapted fluid handling might limit tissue edema by considering physiologic and pathologic shifting, provided that the vascular barrier is primarily fully functioning.[1]

The septic patient, undergoing surgery or not, does not present such a steady state.[4] The normally accompanying capillary leakage syndrome, as a result of an insufficient vascular barrier, leads to a barely calculable shift of fluid and macromolecules (such as proteins and colloids) towards the interstitial space, representing a primary problem during sepsis.[5] Recent evidence suggested a deterioration of the endothelial glycocalyx by inflammatory mediators to be an important part of the underlying pathomechanism.[6,7] Therefore, a careful differential indication between crystalloids and colloids as suggested for the perioperative steady state might not only be insufficient in this context, but in vain.[1] Until today, we only know that we have to give enough, irrespective of the kind of fluid, to improve outcome of patients suffering from severe sepsis and septic shock.[8]

We support most of the interesting considerations by Dr. Navarro-Martinez and colleagues. However, septic patients were not the focus of our rational approach.

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Nitric Oxide Metabolites, Platelet Activation, and Myocardial Ischemia Reperfusion Injury

To the Editor:—We read with great interest the research article by Nagasaka *et al.* demonstrating a role of nitric oxide and its metabolites in the systemic circulation.[1] As the authors impressively demonstrate, active nitric oxide metabolites are carried into the systemic circulation where they accumulate in the blood and in the heart, and as a result have significant impact on the extent of myocardial ischemia reperfusion injury.

Nitric oxide induces cyclic guanosine phosphatase activation and increases cyclic guanosine monophosphate levels in several tissues, including platelets. Several investigators have demonstrated that this is caused not only by endogenous nitric oxide with significant impact on platelet activity, but also by inhalative nitric oxide.[2,3] The crucial importance of platelets and the activity state of platelets on the extent of myocardial ischemia reperfusion injury was outlined by previous investigations.[3–5] A downstream target of cyclic guanosine phosphatase activation in platelets is vasodilator-stimulated phosphoprotein (VASP), a central cytoskeletal binding protein.[6] The intracellular increase in cyclic guanosine phosphatase results in a phosphorylation of VASP, which is a crucial step in the control of platelet activity. Clini-

The above letter was sent to the authors of the referenced report. The authors did not feel that a response was required. —James C. Eisenach, M.D., Editor-in-Chief.