Nitric Oxide and the Paradox of Ischemic Acute Renal Failure-Again

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Dear Sir,

Peer et al. [1], in their stimulating editorial, reviewed the crucial role of nitric oxide (NO) in the regulation of hemodynamics of many different microvascular beds. The authors underscored the intriguing difference between the beneficial effects of L-arginine or NO donors on myocardial reperfusion injury as well as mesenteric and small intestine ischemia [2, 3] in contrast to the disappointing results observed in different kidney models of ischemia reperfusion [4, 5]. Treatment with NO donors does not reduce renal damage and, moreover, may be detrimental as NO seems to be a mediator of tubular injury in the reperfusion as well as the recovery phase, when it acts as an antiproliferative agent antagonizing the effect of factors able to accelerate the regeneration process such as many growth factors [6]. This is not the case for other models of nephrotoxic acute renal failure, in which arginine, as a NO donor, is beneficial. Reasons for the effect of NO on renal ischemic/postischemic damage include the fact that NO is a substrate for the formation of peroxynitrite [7], a potent reactive oxygen species (ROS). The paradox of NO which worsens renal ischemic damage while it ameliorates the ischemic damage to many other body districts, recalls the paradox underscored some years ago by Brezis et al. [8]: why is it that during hypotension, shock or hypovolemia, acute renal failure is a much more frequent complication than brain, myocardial or liver failure, i.e. the ischemic damage is more severe in the kidney, the best oxygenated organ?

We attempted to provide an answer to this glaring paradox based on the hypothesis that a substantial amount of damage in the so-called ischemic renal damage actually depends on the abundant ROS production during the postischemic phase. Should this component be prominent, it would be understandable why ischemic injury occurs in the better perfused organ: 'owing to the fact that a good deal of the damage is caused during reperfusion due to the return of molecular oxygen to the tissues, it follows that the organ most at risk is the one receiving the most oxygen ..., the enormous flow of blood needed to maintain a flow-dependent purification process results in the arrival of an enormous quantity of oxygen. This, instead of providing protection against potential ischemic injury, seems to portend a particular form of damage in the postischemic stage, especially if, as has been suggested, an excessive supply of oxygen is capable of promoting an excessive release' [9].

The paradoxical effect of NO donors in ischemic renal damage in respect to that observed in ischemic damage of other tissues, confirms the peculiar behavior of the kidney during ischemia/reperfusion, and is consistent with the hypothesis that, in this context, ROS production plays an important role in renal tissue damage.

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