Plasma S-nitrosothiols and chronic renal failure

To the Editor: Great importance has been given recently to the role of S-nitrosothiols (RSNOs) in the circulation, where they are believed to act as a buffer and transport system for NO. Moreover, because authentic nitric oxide (NO) is not accessible to analytical measurements, due to its very short life and concentration, RSNOs have been regarded as a good indicator for the presence of NO itself. However, it is noteworthy that only a small percentage of produced NO can be transformed into RSNOs and that most of it is probably inactivated by reacting with scavenging molecules (e.g., hemoglobin). Most of the factors influencing RSNO production in health and disease are still unknown. It has been recently reported (2, 11) that RSNO levels are elevated in plasma of patients affected by chronic renal failure and, more importantly, that these increased concentrations predict cardiovascular outcomes in patients with end-stage renal disease (3). The authors found 0.5 mM (2, 3) or 10 μM (11) basal RSNO levels and increased levels in plasma of end-stage renal disease patients.

Until today, many divergent values for RSNOs, ranging from 1 nM to 10 μM, have been measured (in healthy controls) by the use of different analytical procedures (1). With regard to this problem there is wide debate (1, 4–10), but recent findings seem to unequivocally downstage RSNO levels in blood to values close to 1 nM (4, 5). Therefore, we think that these results on RSNOs and renal disease (2, 3, 11) should be reconsidered as measured values that are largely overestimated with respect to how much they are generally accepted. The existence of analytical problems has also been pointed out by the authors of these papers (3), but they suggested that, in the absence of a standard method, any direct comparison of S-nitrosothiol concentrations measured in biological fluids should be limited to the results obtained with the same methodological procedure. This statement should be considered correct in the presence of methods that give results with a slight bias from real concentration. However, considering that real basal RSNO levels seem to be close to 10–20 nM (or lower), this means that >98% of the molecules identified as RSNOs in these papers are due to an artifact. It is noteworthy in this context that a fundamental feature of any analytical procedure is its selectivity, in the absence of which accuracy, precision, and reproducibility are of scarce importance.

In conclusion, the importance of an assessment of levels of RSNOs in the bloodstream in renal disease (as well as in other pathologies) is still to be demonstrated. However, once some methodologically evident problems are solved, this will represent in the future a useful tool to better understand the involvement of NO (and RSNOs as well) in various pathogenic processes. The application of reliable and sufficiently validated analytical procedures appear in this sense of fundamental importance, but this point is, at the moment, (unfortunately) poorly considered by researchers, reviewers, and editors of scientific journals.

REFERENCES


Daniela Giustarini
Ranieri Rossi
Department of Neurosciences, Pharmacology Unit
University of Siena
Via A.Moro, 4 53100 Siena, Italy
E-mail: giustarini@unisi.it

REPLY

To The Editor: We read with interest the comments formulated by Giustarini and Rossi regarding plasma S-nitrosothiols and chronic renal failure, and we are happy to provide a reply to it.

Regarding the specificity of our method of S-nitrosothiol determination, we have discussed this issue and the additional careful work done by D. Borderie (our biochemist who performed the S-nitrosothiol measurements) to exclude the possible presence of the residual nitrite, as is described in our previous published correspondence in another journal (1). We all agree that a deeper understanding of nitric oxide biology will provide important insight into the mechanisms of vascular homeostasis and will offer novel therapeutic strategies for the treatment of vascular pathologies. This issue is the subject of an active ongoing discussion, as attested to by the recent editorial by Stamler (5). He expressed the opinion that the quantitative aspect of S-nitrosothiol results is not meaningful, which may be due to the selection of inappropriate protein standards for S-nitrosothiol assays. Of note, the issue of discrepancies between various laboratories regarding biochemical determination methods is not new in the nitric oxide field, because it has been raised for asymmetric dimethylarginine or nitrite determination as well.

We are aware of previous reviews (2, 3) and Letters to the Editor (4) in which Giustarini and Rossi have questioned the accuracy of methods used to determine plasma S-nitrosothiol concentration. Instead, we would prefer seeing new original clinical contributions in CKD patients by them allowing an optimization of S-nitrosothiol determination. We also believe that such discrepancies between laboratories should be over-
come by active collaborative work, and we invite them to do such collaboration.

REFERENCES


Ziad Massy
Tilman Drueke
INSERM U507
Necker Hospital
Paris, France
E-mail: massy@necker.fr

Didier Borderie
Laboratory of Biochemistry A
Cochin Hospital
Paris, France

Bernard Lacour
Laboratory of Biochemistry A
Necker Hospital
Paris, France