S-Nitrosoalbumin and Other S-Nitrosothiols in the Blood

Is Their Quantity of No Relevance?

To the Editor:

Similarity of results is the most appropriate criterion to assess agreement between methods and clinical measurements. Reference intervals of a biochemical parameter are of particular importance for the definition of pathological conditions and the judgment of therapy success by pharmacological, nutritional, or physical measures. In this context, mass spectrometry is generally accepted as the gold standard. Recent advances in the methods of analysis make it possible to suggest reference intervals for many members of the L-arginine/nitric oxide family, including asymmetric dimethylarginine and 3-nitrotyrosine. Circulating S-nitrosothiols have evaded the definition of reference intervals to date. Stamler et al first reported on the presence of S-nitrosothiols in plasma of healthy humans of the order of 7000 nmol/L, with S-nitrosoalbumin suggested as the most abundant circulating S-nitrosothiol. At present, reported basal levels of circulating S-nitrosothiols range between 10 and 10 000 nmol/L. The single reported mass spectrometric method revealed S-nitrosothiol mean basal plasma levels of 181 nmol/L.

The physiological roles and the levels of S-nitrosothiols in the blood are the subject of active discussion. In an editorial recently published in Circulation Research, Stamler commented on this issue and the recent studies by Ng et al and Massy et al, but he did not consider critical contributions by other groups. Stamler expressed the opinion that the quantitative aspect of the results is not very meaningful. I would agree with Stamler’s opinion, when the basal S-nitrosothiol levels are on the same order of magnitude. However, this is not the case. The range is exceptionally wide, as it covers more than three orders of magnitude. Chemical lability of S-nitrosothiols is a crucial and important factor. However, there are numerous other well-known analytical problems, especially the interference by nitrite, which has not been adequately addressed by many investigators. For example, ammonium sulfamate cannot eliminate nitrite at plasma pH, but it absolutely requires acidic conditions. It is, therefore, likely that Marzinzig et al. and Wlodek et al. and Massy et al. have measured nitrite plus S-nitrosothiols in plasma, with nitrite representing by far the major fraction.

The most urgent and important future prospect in this research area is, in my opinion, the establishment of reference intervals for circulating S-nitrosoproteins, namely S-nitrosoalbumin and S-nitrosohemoglobin—the most abundant and most stable S-nitrosothiols in the blood. Not considering circulating intervals will give free rein to consider any value to be valid. We should pay more attention to the methods of analysis of S-nitrosothiols, both from the analytical and the review point of view. Thus, newly developed and validated analytical methods should be published in peer reviewed journals prior to use in clinical studies, and, in addition, clinical journals should nominate one (bio)chemist analyst as a referee who would serve as an expert in the analysis of S-nitrosothiols.

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