Myeloperoxidase up-regulation during haemodialysis: is heparin the missing link?

Sir,

We read with interest the recent series of articles showing a striking increase in blood myeloperoxidase (MPO) levels during haemodialysis (HD) sessions [1–3]. In this setting, the enzyme is traditionally regarded as a marker of neutrophil degranulation and thus, of dialyser membrane biocompatibility, as well as generation of oxidative stress [1–5]. Some results of the above studies and their interpretations seem, however, not to be corroborated enough and indicate the existence of other unrecognized factors responsible for MPO up-regulation during HD [1,2]. For example, in the study by Wu et al. [1] the increase in plasma MPO was as much as 3-fold vs baseline with a biocompatible polysulfone membrane, occurring as early as 15 min from the start of HD and, surprisingly, was not accompanied by a fall in circulating neutrophil counts. In the study by Gritters et al. [2] serum MPO levels almost doubled after the first passage of blood through the high-flux polysulfone dialyser. Notably, the effect was only observed when either unfractionated heparin or low-molecular-weight heparin dalteparin was used for temporary HD anticoagulation, and then disappeared with regional trisodium citrate anticoagulation [2]. The authors ascribed the latter absence of MPO release to the calcium-free environment created within the dialyser, and suggested that it could be a valuable approach to avoid overdialytic neutrophil degranulation. They seem, however, to have overlooked the previous report indicating no MPO up-regulation during HD treatments anticoagulated with nafamostate mesylate instead of heparin [4]. In the most recent trial, Krieter et al. [3] showed a remarkable, 6-fold rise in blood MPO levels taking place 5 min after the start of HD. They also revealed a small (~9%) but significant difference between MPO levels in blood leaving vs entering the filter, which confirms the actual but negligible intradialyser neutrophil degranulation. On the basis of the early high MPO levels in the pre-dialyser blood, the authors attentively concluded that the contact of blood with the filter membrane could not be the only cause of MPO generation [3]. Unfortunately, both Wu et al. [1,5] and Krieter et al. [3] failed to specify the anticoagulation strategy used in their HD patients, ascribed the very early MPO upregulation to either ‘the dialysis per se and dialysate contaminants’ [5] or ‘shear forces through the blood pump’ [3] and prematurely ended with the statement that MPO is a useful and reliable marker of HD-induced oxidative stress.

In recent years, compelling evidence has accumulated to show that MPO is not only a neutrophil secretagogue but also an abundant constituent of vascular wall, from which it can be easily and extensively mobilized into circulating blood by exogenous heparin (for review, refer [6]). This mechanism very likely underlies the markedly increased MPO upregulation encountered during heparin-anticoagulated HD procedures [6]. In this clinical setting, heparin should be viewed as an agent protecting the atherosclerotic arteries from oxidative stress (because of endothelial MPO depletion) rather than being harmful to them, as prematurely judged on the basis of marked plasma MPO elevations. Unfortunately, this relatively novel link between MPO and heparin [6] seems to have been either overlooked [1,3] or understudied [2] in the recent trials in HD patients, while it could clarify their results, as well as improve or call into question their meanings.

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Reply

Sir,

We would like to thank the authors for their comments on our study. In their letter, they suggest that the haemodialysis (HD)-induced rise in myeloperoxidase (MPO) results from mobilization from the endothelium by exogenously-administered heparin. However, as described in our recent [1] and earlier studies [2,3], MPO reached its peak levels directly after first passage ($t_1$ min). Moreover, substantial blood cell degranulation was observed in a closed loop recirculation model [4]. This process could be blunt by the chelation of plasmatic calcium (Ca) by sodium citrate or EDTA, and did not correlate with C3a or C5a concentrations [5]. The latter finding is in agreement with clinical studies, showing that degranulation and complement activation depend to a large extent on the type of dialyser used and are, in fact, independent of each other [6]. Based on the above mentioned data from clinical and experimental studies, it seems justified to conclude that MPO release occurs with certainty within the ECC, whereas endothelial mobilization remains to be proven. With respect to the cause of HD-induced degranulation, the mode of anticoagulation appears to be crucial. Several studies have indicated that Ca plays a critical role in the interaction between platelets and...