Reply

Sir,

We received the letter of Penne and associates regarding our recent observational, prospective RISCA VID (Rischio Cardiovascolare nei pazienti afferenti all’Area Vasta In Dialisi) study [1].

As we stated in our paper, our foremost intention was to show the link between systemic inflammation and mortality in this population. We acknowledge the fact that the published protocol of the Dutch CONvective TRAnsport STudy (CONTRAST) controlled trial is directed at evaluating the impact of different convection therapies on CV disease such as left ventricular hypertrophy, and vessel wall parameters [2]. Regarding the $Kt/V$, however, our $Kt/V$ that were not dissimilar between the two different modalities are reminiscent to those recently published by Carracedo et al. [3], who performed a double cross-over randomized clinical study on high-flux HD versus online haemodiafiltration (HDF). This brings up an important point. Despite similar $Kt/V$ (which are already in their high range of $>1.4$), online HDF still features as a superior technique. Beta-2 microglobulin (b2-m) clearance or pre-dialysis b2-m levels were not shown, since we had not deliberately considered it of value. As explained in the paper, our study had the advantage of being performed on a prevalent population relatively homogeneous for race, geography, medical care and HD management. Therefore, enhanced clearance of middle molecules was inherent to the homogeneity of our study population and clinical monitoring of the available data. This would, however, be a requirement for a randomized clinical trial.

We have stressed the limitations of any observational study and the possible biases inherent to it. Nevertheless, the difference in mortality between high-flux and online HDF was striking and well in agreement with previous data from the DOPPS study [4] and the EUCLID database [5]. We have also well clarified that in respect to the DOPPS, the RISCA VID population differed from other existing studies for the high incidence of mixed convective-diffusive techniques (HDF 44% of the entire population). This equalled to 333 patients being followed for thirty months in respect to the 89 over 443 Italian patients of the DOPPS study (35). Of interest in our study, the difference in cumulative survival started after fifteen months of observation after adjustment for age, dialysis vintage and co-morbidities. At variance with the paper with Canaud [4], we were not able to establish a relationship between mortality and volume exchange. Despite this limitation, HDF using sterile bags is customarily prescribed using 10–15 L/session of reinfusion fluid while on-line HDF is performed with at least 22–25 L/session.

We hope we have helped to clarify the issues raised by the letter of Penne et al. whom we thank for their appreciation and criticisms.

Conflict of interest statement. Ciro Tetta is fully employed by Fresenius Medical Care.

1 Internal Medicine Department, Vincenzo Panichi1, Nephrology Section, via roma 67, Pisa, 56100, Italy
2 Fresenius Medical Care Deutschland GmbH, Daimelerstrasse 15, D-61352 Bad Homburg, 61352, Germany
E-mail: vincenzo.panichi@med.unipi.it

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EPO induces rise in serum ADMA but does not prevent the increase in NO release: the likely involvement of HO-1

Sir,

We read with great interest Desai and co-workers’ report in the May issue of Nephrology Dialysis Transplantation that in spite of elevating serum asymmetric dimethyl-larginine (ADMA), erythropoietin (EPO) in animals did not compromise NO production as shown by the increased urinary NO metabolites [1]. These authors found a chronic upregulation of kidney NOS1 and NOS2 upon EPO treatment and concluded that a compensatory increase in NO release overcame the increased ADMA level induced by EPO.

We would like to suggest that results from our study of EPO effects in chronic haemodialysis (CH) patients [2] provide additional support for Desai and co-workers’ conclusions and add a mechanism for the effect of EPO on NO availability. CH patients are widely recognized as having...
increased oxidative stress and reduced NO availability [3]. When this CH cohort underwent EPO treatment (epoetin α at the dose of 50–100 UI/kg, three times/week aiming towards a target haemoglobin of 11 g/dl and then adjusted to maintain it), EPO increased mononuclear cell HO-1 gene expression via a possible direct effect of EPO [2]. HO-1 is a phase II enzyme induced by oxidative stress that possesses potent antioxidant, antiapoptotic and anti-inflammatory activities [4,5]. HO-1 expression in response to oxidative stress is transcriptionally regulated by the phosphatidylinositol 3-kinase (PI3K)/Akt pathway [6]. EPO-mediated attenuation of cell death in response to oxidative stress has been shown to be dependent on JAK2 signalling and PI3K-mediated phosphorylation of Akt which, once triggered, activates multiple antiapoptotic effects [7]. Given that both EPO and HO-1 antiapoptotic effects occur via the PI3K/Akt pathway, HO-1 probably plays an important role in the antiapoptotic effect of EPO. Moreover, there is a close relationship between HO-1 and NO production as the decreased eNOS expression and endothelial dysfunction seen after exposure to proinflammatory factors such as oxidated LDL and TNF-α were restored by HO-1 overexpression [8]. Further, increased HO-1 expression in diabetic rats boosted eNOS and normalized vascular relaxation while it differentially decreased iNOS protein levels [9].

In conclusion, our study showing increased HO-1 in CH patients treated with EPO supports Desai and co-workers’ conclusions that a compensatory increase of NO production capacity occurs upon EPO treatment and this then overcomes the increased ADMA level induced by EPO.

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1Department of Clinical and Experimental Medicine
Lorenzo A. Calò
Clinica Medica 4
University of Padova, Padova Italy

2Department of Nutrition
Paul A. Davis
University of California, Davis, CA USA

E-mail: renzcalo@unipd.it


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Reply

Sir,
The letter by Calò and Davis highlights some very interesting issues regarding the complex effects that exogenous erythropoietin (EPO) therapy may have on various cell types, tissues and organs and emphasizes the urgent need to define the effects of chronic EPO administration to patients with chronic kidney disease who are in a state of nitric oxide deficiency and heightened oxidative stress [1,2]. Based on their observations in mononuclear cells of hemodialysis patients, Calò and Davis suggest that EPO induces heme oxygenase-1 (HO-1) expression which may in turn upregulate expression of eNOS, thus producing the compensatory increase in NO observed in EPO-treated Balb/c mice in our study. At this time, we do not have any data in support of the proposed mechanism but intend to fully explore the potential link between HO-1 and EPO in future experiments. Moreover, our current results do not allow us to unequivocally conclude that EPO-mediated upregulation of renal NOS is responsible for the elevated urinary nitrite concentrations. It is also unclear whether the EPO-mediated rise in ADMA concentrations has any effect on NOS inhibition and, to our knowledge, no published study to date has addressed the effect of EPO on HO-1 activity in mice. The interaction between HO-1 and NOS in the rat has been investigated by several laboratories [3–5] and in vitro and in vivo studies support the idea that EPO induces the expression of HO-1 [6,7]. Hence, in summary, the hypothesis proposed by Calò and Davis is very reasonable and its validity needs to be investigated in our mouse model. We thank Calò and Davis for their comments.

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1Department of Internal Medicine
Anjali Desai

2Department of Pathology
Jeffrey S. Warren

University of Michigan Medical School, Ann Arbor, MI, USA

E-mail: desai@med.umich.edu
