Effect of intravenous heparin on serum levels of endostatin, VEGF and HGF

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We read with interest the article by Seko and colleagues [1], who document that serum levels of endostatin and VEGF (vascular endothelial growth factor) are increased markedly in patients with acute myocardial infarction, but subsequently decrease significantly by early reperfusion. We would like to point out important limitations in their findings not addressed in the study. This relates entirely to the administration of intravenous heparin during the reperfusion process. Firstly, we disagree that the significant decrease seen in serum VEGF levels 3–6 h after reperfusion relates to a down-regulation of VEGF production, but, in fact, is entirely due to intravenous heparin administration, which is known to modulate the interaction of VEGF with its receptor [2]. Kawamoto et al. [3] found that the serum concentration of VEGF in patients with acute myocardial infarction was reduced by up to 93 % 1 h after administration of intravenous heparin.

Secondly, endostatin is also a heparin-binding protein [4], and the measurement of serum levels after heparin administration is also likely to show a significant decrease. This may explain why Seko and colleagues [1] found a similar pattern of change in serum levels of VEGF and endostatin before and after reperfusion.

Thirdly, serum HGF (hepatocyte growth factor) levels are known to increase dramatically within 30 min after intravenous administration of heparin [5], which also explains the significant increase in HGF levels after reperfusion seen in their study [1], although the authors do address this point to a limited extent in their discussion.

In summary, the administration of heparin has substantial effects on the measured levels of serum VEGF, endostatin and HGF. As such, it would be unfair to make direct comparisons between these levels before (without heparin) and after reperfusion. Therefore we feel that the conclusions drawn from this study should be interpreted with a degree of caution.

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We thank Dr Bhatia, Dr Clesham and Dr Turner for their interest in our paper [1], and we agree with them that the studies on the serum levels of endostatin, VEGF and HGF under administration of heparin should be interpreted very carefully, and there is an important limitation in our study. However, we disagree with them on some points as follows. We think that the significant decrease in serum VEGF levels after reperfusion may be due to down-regulation of VEGF production (although we did not state in our paper) as well as internalization of VEGF after binding to its receptor (which may be facilitated by heparin [2]). VEGF was shown to be internalized in HUVECs (human umbilical vein endothelial cells) [3]. In fact, we found that VEGF concentrations in culture supernatants of cardiac myocytes increased rapidly and then decreased in response to acute hypoxia in vitro without addition of any drugs including heparin (Y. Seko, unpublished work). This is also the case for endostatin. Recently, it has been reported that AIDS-related Kaposi’s sarcoma cells rapidly internalize endostatin [4]. We also found that concentrations of endostatin in culture supernatants of cardiac myocytes subjected to hypoxia in vitro increased a little later than those of VEGF, suggesting that VEGF and endostatin are similarly released into culture supernatants in response to hypoxia (Y. Seko, unpublished work).

Kawamoto et al. [5] reported that the serum concentration of VEGF in patients with acute myocardial infarction was reduced by up to 93% 1 h after administration of intravenous heparin. However, it is strange that the authors [5] did not report the serum VEGF levels at the time of admission before the start of heparin administration, and that heparin administration markedly decreased the serum VEGF level, but had no effects on the serum bFGF (basic fibroblast growth factor) level, although both growth factors are heparin-binding proteins. Moreover, we analysed the same serum samples with an ELISA kit from R&D Systems and that from Immuno-Biological Laboratories (as used by Kawamoto et al. [5]), but the data were quite different between the two kits. As we stated in our paper [1], marked elevation of serum levels of HGF after reperfusion was thought to be at least in part (but not entirely) due to heparin administration. However, we could not exclude a possibility that HGF may be released into the circulation in response to reperfusion and play a protective role against the reperfusion-induced oxidative stress [6].

In conclusion, to know the precise effects of myocardial ischaemia/reperfusion on the serum levels of endostatin, VEGF and HGF, further studies using animal models without administration of any drugs, including heparin, are needed.

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