LETTER TO THE EDITORS

Reply to "*Ex situ* normothermic machine perfusion of donor livers using a haemoglobin-based oxygen carrier: a viable alternative to red blood cells"

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We highly appreciate the interest expressed in the letter by de Vries *et al.* [1,2] concerning our recent systematic review, and congratulate for the successful transplantation using hemoglobin-based oxygen carriers (HBOC) during normothermic perfusion. We agree, that *ex situ* normothermic and also subnormothermic liver perfusion using HBOC is *per se* an interesting option to spare red blood cells as oxygen carrier. This is however different from the use of HBOC *in vivo*, which is shown to increase the risk of death and myocardial infarction [3]. The mentioned clinical application in USA was only granted through an expanded access programme and additional institutional review board approval was required for such a use [4]. Of note, HBOC (Hemopure) is available under investigational status in USA, and is not FDA approved [5].

In addition, *ex vivo* application of HBOC during machine perfusion of organs has also limitations. First, measurement of perfusate parameters is known to be rather unreliable in haemolytic samples [6]. As HBOC behave similarly to free haemoglobin, it largely affects all colorimetric analysis [6,7]. Detection of liver transaminases, danger signalling proteins, and also synthetic parameters of liver function appear therefore difficult in perfusates containing HBOC, which limits the assessment of viability during machine perfusion.

Second, HBOC has proven vasoconstrictor effects because of NO scavenging [4,8,9], which may also be present during *ex vivo* liver perfusion. Third, HBOC can potentially activate Kupffer cells [10], which would explain the short half-life time of HBOC of 20 h *in vivo*, pointing to another limitation for its long-term machine perfusion use. Fourth, HBOC is expensive and the cost of one unit is much higher than one unit of red blood cells [8]. Increased cost was also the reason to use HBOC only in clinical situations where blood was unavailable or not an option [11]. Therefore, cost benefit analyses should include the use of artificial oxygen carriers in machine liver perfusion.

Finally, we would like to state, that the optimal composition of machine liver perfusates is still unclear, regardless of the technique used. It is however clear, that oxygen carriers play no role in hypothermic machine liver perfusion, as dissolved perfusate oxygen under cold conditions (<15 °C) was sufficient to achieve full mitochondrial energy upload within short perfusion time [12].

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Conflict of interest

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