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INVITED COMMENTARY

New trends in transient hyperthermia and liver preservation

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The investigations carried out by Charlotte von Horn and Thomas Minor [1] deal with the potential benefits of controlled hyperthermia for improving liver graft preservation against reperfusion insult. The authors, based on well-known heat shock preconditioning strategies as an effective method to protect the liver from subsequent IRI [2,3], suggest that a transient hyperthermia step graft reconditioning from 35 to 42°C for 10 min contributes to liver graft protection against reperfusion injury.

According to the contribution of Minor's team, livers preserved in HTK solution after 18-h cold storage and subjected to transient hyperthermia during oxygenated rewarming showed a better liver graft function, a significant diminution of liver mitochondrial damage [4] and LDH activity upon reperfusion when transient hyperthermia during oxygenated rewarming (THOR) was compared to controlled oxygenated rewarming (COR).

Certainly, an important indicator of liver graft conservation after THOR is the mitochondrial graft protection and the prevention of energy breakdown reflected by the increased (but not significant) ATP levels upon reperfusion conditions. Both facts confirm the relevance of using the perfusate temperature as a useful tool for "graft preconditioning." This induced graft protection is associated with the overexpression of heat shock protein (HSP), suggesting the involvement of heat shock preconditioning oxygenated rewarming, which is responsible for liver protection and mitochondrial machinery.

Data reported by Von Horn and Minor permit to speculate on the use of transient hyperthermia oxygenated conditions to be combined with other well-known protective dynamic preservation strategies, such as HOPE strategies [5,6]. The increase in temperature during HOPE graft oxygenation could contribute to increase graft protection. The only limitations would depend on the characteristics of the hyperthermic insult (duration and temperature) and how to apply the transient temperature gradient to obtain the most suitable graft protection (4/6°C up to hyperthermic conditions). The benefits of the transient hyperthermia evidenced by the authors in this experimental model could be combined with other *ex vivo* strategies such as HOPE [5,6] in subnormothermic conditions [7,8]. In any case, the induction of "hyperthermia strategies" during organ perfusion in hypothermic and subnormothermic conditions should be consistent with the subsequent increases in HSP expression (which usually needs longer time

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after heat exposure), and it would need to be evaluated. In addition, it is important to remark that there are some limitations of HOPE strategies associated with perfusion solutions containing glutathione, such as KPS [9], given that it is easily oxidized [10]. These limitations could be even more exacerbated when subnormothermic conditions (20°C) are used.

With this in mind, we could speculate that a "transient" hyperthermia strategy combined with HOPE would contribute to better protect the fatty liver by preventing damage-associated molecular patterns (DAMPs) generation, such as HMGB1 and others [11,12]. The regulation of these "alarm signals" may have a special interest in the preservation of marginal grafts, such as steatotic livers, which are highly vulnerable against ischemia-reperfusion injury [12].

In conclusion, using a "transient hyperthermic insult" during oxygenated perfusion in hypothermic and subnormothermic machine perfusion conditions may be useful to increase the graft protection against reperfusion injury. Further investigations are needed.

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Conflicts of interest

The author has declared no conflicts of interest.

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