



Commentary

HOPE (hypothermic oxygenated perfusion) strategies in the era of dynamic liver graft preservation

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Machine devices have been around since the early days of organ preservation. Recently, James Southard [1] explained the efforts and troubles that Folkert Belzer had in shipping a kidney recovered in San Francisco (USA), to Leiden (NL), which was thus the first successful "intercontinental" kidney transplant. Currently, we have machine devices for different organs as well as promising dynamic preservation strategies for graft preservation, such as hypothermic oxygenated perfusion (HOPE), allowing us to avoid the graft troubles of Folkert Belzer.

We read with great interest the latest article by Andrea Schlegel et al. [2] in *EBioMedicine*. In it, the authors use HOPE to establish beneficial biochemical mechanisms, by restoring mitochondrial function through succinate metabolism and prevention of energy breakdown. Notably, the presence of succinate alone already plays a decisive role when comparing HOPE to static hypothermic preservation and other dynamic normothermic / sub-normothermic ones.

During cold ischemia, oxygen deprivation and metabolic reduction leads to reduced mitochondrial respiratory chain function, increased levels of electron donors (e.g. NADH), succinate accumulation, and breakdown of ATP/ADP to purine metabolites. In contrast, during HOPE treatment, the mitochondrial respiratory function is sustained at basal levels, thereby preventing accumulation of electron overload at mitochondrial complexes I and II and facilitating the concomitant ATP/ADP reloading which assures a normal functioning of the liver mitochondrial machinery. In comparison, normothermic machine perfusion (NMP) leads to the rapid oxidation of succinate, provoking the retrograde electron flow, production of reactive oxygen species (ROS) at complex I, and an inflammatory cytokine cascade (3). Another relevant data reported by Andrea Schelegel et al. [2] is that measurement of mitochondrial flavin mononucleotide (FMN) and NAD levels can serve as new predictors of human liver graft function when HOPE is used.

The fact that benefits of HOPE come through mitochondrial regulation leads us to think that any additional strategies that improve

the mitochondrial integrity would enhance these positive effects. Indeed, in our previous investigations on PEG35 in hypothermic static preservation using IGL-1 solution [4], and on using PEG35 rinse solution for washing-out UW preserved livers [5], we have demonstrated the protective role of PEG35 in preserving mitochondria. In a recent contribution [4], we discuss and extend some of these results of the use of PEG35 in a new perfusate (IGL-2) for HOPE. Taking this into consideration, we think that PEG35 in a HOPE perfusate could lead to an additive better protection of the integrity of mitochondrial machinery and its basal activity function. This could be extended to NMP treatments.

We note that other mitochondrial bioregulators, such as aldehyde dehydrogenase 2 (ALDH2), have also been recently implicated in static hypothermic fatty liver graft preservation when UW, HTK, or IGL-1 solutions were used. The observed increases in ALDH2 protein expression and activity were associated with better mitochondrial damage and ATP breakdown prevention in IGL-1 cold storage vs the other solutions [6]. These facts reveal the importance of preserving against mitochondrial injury during hypothermic static preservation, in which the role of oncotic agent (PEG35 in IGL-1) is crucial for maintaining mitochondrial function and adequate levels of mitochondrial biosensors (such as ALDH2) during cold fatty graft storage.

Given the proved mitochondrial protection mediated by HOPE [2,3] and PEG35 protection in static preservation [4,5], we hypothesized that they could have additive effects on the mitochondria, and PEG would enhance HOPE protection. Previously, we reported some preliminary data on the effectiveness of PEG35 in a perfusate solution (IGL-2) during HOPE [4]. In this sense, IGL-2 could be a suitable tool in HOPE strategies, being especially promising for rescuing vulnerable liver grafts (DCD and steatotic grafts) for transplantation [7], for the following reasons:

- (a) PEG35 promotes the activation of cytoprotective and preconditioning agents, such as e-NOS and AMPK activation [5]. Notably, eNOS activation generates nitric oxide (NO), a well-known vasodilator. NO would contribute to reducing the exacerbated microcirculatory events associated with the presence of steatosis in liver grafts revascularization. AMPK activation is a "self-answer" of the grafts against oxygen deprivation conditions to restore energy breakdown in hypothermic static preservation. As it may also be involved in HOPE conditions [8], AMPK could also be an additional cytoprotective indicator to be considered.
- (b) PEG35 in HOPE perfusates (IGL-2 solution) would also contribute to favoring mechano-transduction processes inherent to fluid dynamics

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in HOPE, thereby also favoring a better protection of luminal glycocalyx [9]. HOPE fluid dynamics underlie glycocalyx destruction, which depends on viscosity properties of perfusate; in turn, these properties depend upon the oncotic agent, especially at lower temperatures [4,10]. Notably, addition of PEG35 lowers the viscosity in the currently Belzer-MPS used in HOPE by half [4].

In sum, this important contribution of Schlegel et al. [2] provides the basis of the protective mechanisms in HOPE for exploring new perspectives in dynamic preservation that will allow us to increase liver graft quality for clinical transplantation.

Contributors

Dr. Panisello-Rosello A. participated in the design draft, revision, and approval of the work. Dr. Rosello Catafau J. participated in the revision and approval of the work.

Declaration of Interests

The authors declare no conflicts of interest.

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