

# **The first clinical trial of hypothermic machine perfusion of human liver grafts prior to transplantation: A critical comment**

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Hepatic grafts can be preserved in University of Wisconsin solution by the static preservation for less than 12 hours for good outcome of liver transplantation surgery (1). For prolongation hepatic graft preservation, implementation of ex vivo extracorporeal graft perfusion into clinical practice was suggested (2).

The first clinical trial of hypothermic machine perfusion (HMP) (4°C - 6°C) (3) was carried out in Department of Surgery, Center for Liver Disease and Transplantation, Columbia New York (3). Authors showed improvement of a number of parameters over simple cold storage (4, 5). However, actual graft and patient survival, which are the most important parameters, were the same in both groups (3). In their abstract, authors proposed to carry out a multicenter clinical trial, using their procedure. However, literature on preservation-reperfusion injury of the liver clearly indicates that no multicenter clinical trial is warranted as suggested in ref. (3). If on progress, it should be stopped immediately, for the following reasons:

Firstly, perfusion of rat livers for 12 hours at broad range of temperatures (from 5°C to 30°C), exhibited tissue swelling in livers perfused at 5°C (in accordance with human grafts (3)) lower tissue ATP levels, and deterioration of liver function and structure after reperfusion (6). On the other hand, data showed that livers perfused for 12 hours at 10°C - 20°C (subnormothermia) and then reperfused were comparable to the control (6). These findings are in accord with the fact that Na<sup>+</sup>/K<sup>+</sup> ATP-ase, which consumes a major portion of energy, is inactivated at 20°C (7).

Secondly, the supply of oxygen to hypothermically perfused livers is needed (8). Authors provided no supply of oxygen (3).

Thirdly, the outcome of liver transplantation is strongly dependent on tissue ATP levels (9) (see for reviews 10, 11) and low oxygen pressure in Belzer solution cannot restore them.

Finally, it is clear that the best way of extracorporeal liver perfusion is the subnormothermic oxygenated perfusion (SNOP) (10-20 degrees of C<sup>0</sup>) (6) > followed by hypothermic oxygenated perfusion (HOPE) (12, 13) > over HMP (at 4° - 6°C). Both SNOP and HOPE are able to maintain liver integrity and function upon reperfusion (6, 12, 13). Thus, instead of HMP, SNOP, HOPE, or energy recharging of the graft with short-term oxygenated normothermic perfusion prior to implantation (14, 15) should be used for future clinical trial.

A question now arises: “Why authors in reference (3) used for a clinical trial the worst way for machine preservation-perfusion of human hepatic grafts?” First, they ignored a large body of the scientific knowledge (see refs. 10, 11). Second, authors do not realized that **cold ischemia-reperfusion injury of the liver is** not liver pathophysiology (unlike to in vivo warm ischemia-reperfusion injury, which occurs during liver surgery, shock or trauma), but **liver pathophysics**. Thus the extrapolation of results from ex vivo perfused rat liver to ex vivo perfused human liver is possible, since results are dependent on physical parameters and not on a size of perfused organ.

Concluding, a multicenter clinical trial as suggested in reference No. (3) for preservation-perfusion of human hepatic grafts will be a waste of money of American taxpayers.

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