The effect of a hydrogen sulfide releasing molecule on the cold storage of livers from dead donor rats

The liver is the largest organ inside our body and, as long as it keeps healthy, it will be in charge of a wide range of mechanisms that are essential for life. Liver will filter the blood coming from the digestive tract, helping us to metabolize and store nutrients and it is also responsible for detoxifying xenobiotics, a chemical compound foreign to a given biological system, that have entered our body. While doing so, liver secretes bile that will facilitate digestion in the intestines and produces proteins important for blood clotting and other functions. Furthermore, as we learnt from Prometheus, the liver has the amazing capacity to regenerate itself! No wonder the Greeks viewed the liver as being the organ in closest contact with divinity… Yet, there are a number of pathologies that might affect our liver and even push it to chronic or acute hepatic failure.

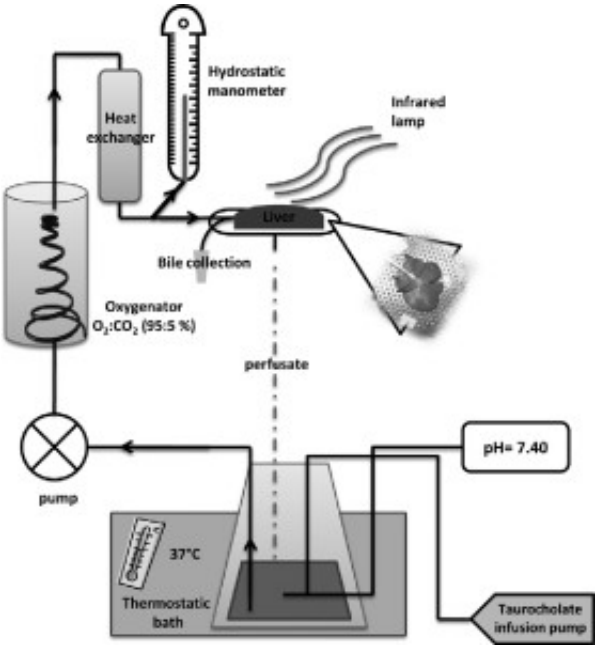

Fig. 1. Schematic representation of an ex vivo liver system designed for the experiments.

When damage is done and the liver can no longer perform its vital job, transplantation surgery becomes the only way to survive since there are no extracorporeal therapies to support hepatic function so far. Over the last five decades liver transplantation has become a well-recognized treatment option for people with organ failure, leading to a rapid increase in patient waiting lists that generates the need to expand potential donor pools. To address the donor shortage problem, liver grafts outside standard criteria such as those coming from deceased donors, are being reconsidered by the specialists in the field of transplantation. Procured grafts are inevitably

stressed by blood flow interruption prior to implantation and this is exacerbated in organs from non-heart beating donors. Hence, organ preservation techniques play a key role in expanding the limits of marginal graft inclusion.

In CAIC-UNR institute (Binational Argentinian-Italian Center for Clinical and Applied Investigations in Cryobiology – National University of Rosario, Argentine) Dr. Gilbert's team is focus in studying conventional liver storage solution modifications that could potentially enhance marginal grafts procurement outcomes. In their latest work published in Cryobiology, a specialized Journal of Low Temperature Biology and Medicine, they reported that molecules that release Hydrogen sulfide gas (H_2S) in solution might confer extra cytoprotective properties to the standard storage solution HTK (Histidine-Tryptophan-Ketoglutarate). Although previously known as a noxious environmental gas, hydrogen sulfide is endogenously produced by enzymatic activity in mammals in physiological conditions. Furthermore, H_2S is now recognized to be a member of the gaseous transmitters family along with carbon monoxide (CO) and nitric oxide (NO) involved in cytoprotective signaling in diverse stress models.

The authors presented a model of liver procurement after cardiac death in the rat, establishing 45 minutes of warm ischemia prior to cold storage in modified HTK solution. In order to judge graft "quality" after cold storage, experiments were performed in an ex vivo system (see figure) of reperfusion that re-circulates an oxygenated buffer through livers main veins while enabling multiple parameter recording and assessment of the isolated graft without the need of a complicated surgery on another animal. Researchers found that livers from deceased animals that were stored in the presence of a H_2S source showed several signs of ischemic injury reversion when contrasted with deceased donor livers that had been stored in conventional HTK solution. Signs of improvement were related to microcirculatory parameters, sustained bile production and oxygen consumption, cell membrane integrity and morphology of hepatic tissue.

These promising findings are the groundwork for new alternatives in the organ preservation field, making use of therapeutic properties of gaseous transmitters molecules to expand the pool of transplantable organs. Further studies regarding delivery systems, dose–response and molecular mechanisms are crucial in order to translate this concept into the clinical practice.

Publication

The effect of a hydrogen sulfide releasing molecule (Na2S) on the cold storage of livers from cardiac dead donor rats. A study in an ex vivo model.
Balaban CL, Rodríguez JV, Tiribelli C, Guibert EE.
Cryobiology. 2015 Aug