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DEVELOPMENT OF A COMPACT MACHINE PERFUSION SYSTEM FOR HUMAN LIVER GRAFTS IN THE RESEARCH PROJECT DELIVER (WORK IN PROGRESS)

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Abstract- During the last few decades,there has been a shortage of donor organs,while the need for optimal organs has been and still is remaining on a high level. To fill this gap,the TH Köln is developing,along with other research partners, an innovative machine perfusion system that realizes the transport and transplantation of marginal liver grafts. The research project DeLiver aims to develop a compact transport system for human liver grafts that has an integrated temperature regulation and an advanced monitoring of threshold values in machine perfusion of liver grafts.During transport, the livers will be oxygenated and supplied with nutrients by perfusion.The successful development of the DeLiver system can lead to sustainable improvements in the allocation and distribution of donor organs.
Keywords – Liver Transplantation, Machine Perfusion, Biomedical Engineering, Oxygenation

1. INTRODUCTION

A retrospective reviewof the required and performed liver transplantations in Germany indicatedthat a gap of donor livers has existed for several years (see figure 1). The consequences of this difference are made evident by 288 deceased in Germany in 2018[1].This problem cannot only be identified in Germany. The Annual Report of Eurotransplant, an organization that is responsible for allocation and cross-border exchange of donor organs, shows comparableresults[2].

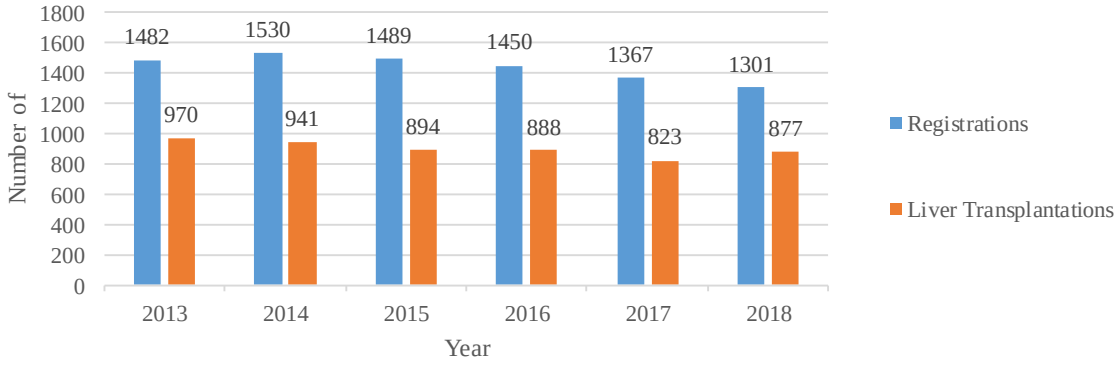

Figure 1: Comparison between liver transplantationsand registered patients on waiting lists in Germany between 2013 and 2018 (Data from the German Organ Transplantation Foundation (DSO) [1])

Static cold storage (SCS) is the state ofthe art in the transport of organs. The organs are transported in a cooled solution in polystyrene boxes. This can result in a graft injury as well as a reperfusion injury [3], which limits the available organs, as only optimal organs can be used for transplantation. With new systems for the transport of liver transplants, the shortage in donor livers should be decreased.Over the last ten years, systems have been increasingly developed to perfuse organs with blood or blood-like solutions. With this machine perfusion (MP), different temperature ranges can be adjusted as well as the perfusate oxygenated. [4, 5]Similar systems are also being developed for other organs such as lungs, hearts and kidneys[6].
The process of MP offers various advantages for liver grafts. Several studies have shown that the use of MP, especially a normothermic MP, can expand the donor pool. Marginal donor livers that could not previously be used for transplantations are partially recovered after this perfusion.[7–10]
Some of the existing MP systems have been designed for intraclinical use only and therefore do not improve the distribution of donor grafts. This innovation is the aim of the research project DeLiver. A compact and transportable MP system for liver transplants will be developed during the research project to counteract the above mentioned shortage of available donor organs.

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2.THE PROJECT DELIVER

2.1 Aims of the Project–

The DeLiver project aims to develop a compact transport system for liver transplants within three years. A temperature regulation and a monitoring of oxygen consumption of the organs will be integrated in the system. The livers will be oxygenated and supplied with nutrients by perfusion during transport. In the DeLiver project, the innovation is aimed at designing and manufacturing a concept device that fulfils the framework objectives of a compact, transportable, user-oriented and safe MP system. As a result of the project, the system is to be implemented in existing organ allocation procedures/guidelines, which offers the possibility to reevaluate and adapt them. This should result in the wanted increase in the availability of donor livers.

2.2 Current Stand of the Project –

A medical concept is being prepared for the development of the transport system, which takes the results of other research groups into account and records all medical parameters related to the transport and transplantation of livers. For this purpose, the required components for the monitoring of decisive parameters will be developed in order to transfer them into a much more compact system. These results will be used for the thermo- and fluid-dynamic conception, the design of the oxygenation system, the development of an organ monitoring concept as well as the development of user interfaces and ergonomic requirements.

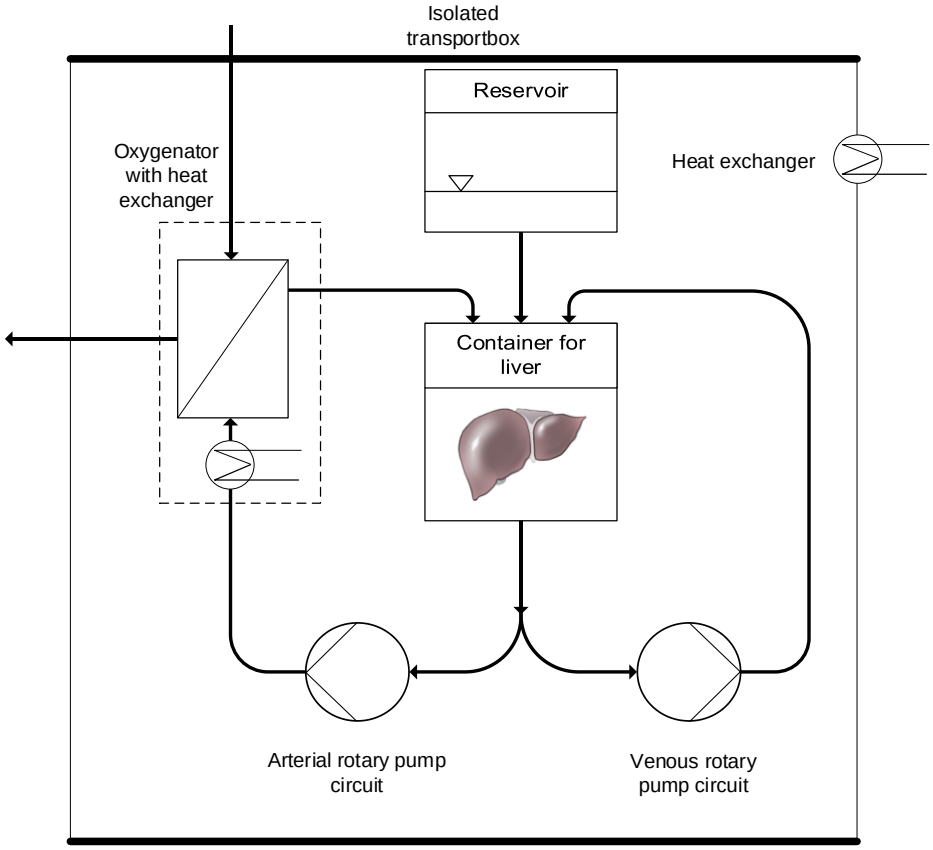

Figure 2: Schematic Structure of theDeLiverSystem

Initialinvestigations have resulted in the schematic structure shown in figure 2. The system is enclosed in a thermally insulated transport box. A heat exchanger is included in this box, which compensates heat losses to the environment and affects the temperature of the organ as well as the perfusate. The aim is to achieve temperatures in the hypothermic to normothermic range. In the system, a portal vein flow and a hepatica artery flow are circulated with a pump in order to satisfy the anatomical conditions of the liver. The circuits are connected to the vessels of the organ. The blood outflow from the liver circulates freely in the container for the liver. The blood enters the circulation via an outflow in this container. An oxygenator with a heat exchanger is integrated in the arterial circuit to satisfy the oxygen demand of the liver. A reservoir filled with blood is integrated to avoid air inclusions in the circuits. Elements not yet shown here are part of oxygen and energy management, which will be developed in the project.In coordination with the medical conception, a test set up will be developed and set up at the TH Köln´s laboratory for biomedical engineering. In this laboratory, results will be evaluated and possible improvementswill be pointed out. The transportability will not be tested in this test facility. However, statements about possible duration of MP and further threshold values of the DeLiver system will be researched.

Figure 3: Test Set Up of the DeLiver System

At present, a suitable casing has been designed and constructed for the test set up (see figure 3), an automatic temperature regulation system has been designed and a suitable pump has been integrated. The next step is to research an oxygenation concept that satisfies the oxygen demand of the liver. The findings from the research project MemO2 can be used for this purpose [11]. The DeLiver system has special requirements for oxygenators that will be used. It cannot exceed a certain size nor lead to damage of blood components due to narrow lumen. However, since the system works with lower pressures and volume flows than conventional oxygenators, the possible options need to be determined and assessed. Furthermore, a suitable container for the liver must be designed and manufactured.

3. OUTLOOK

3.1 Further Approach in the Project –

The results of the medical conception as well as the findings from the development of the test facility will form the basis for the concept device for the transport of liver grafts. The cooling and heating system as well as the energy management will be designed from these first steps. The system will be developed and manufactured by other partners in the further process. The experiments conducted at the test set up will have a major influence here, as critical points in handling can also be identified.
At the same time, a technical risk analysis and the documentation for certification will be prepared. However, it will not be possible to complete this to the full extent during the project as, for example, studies with human liver grafts will take several years.
Training programmes for the DeLiver system will need to be created to improve the usability of the system. This is intended to ensure safe handling of the system by all parties involved and thus further increase the safety of organs and patients.

3.2 Further Approach Beyond the Project –

In addition to the research project, the DeLiver system has to be evaluated with further studies. However, this requires a CE / FDA certification, to allow the system to be approved and be placed on the market. With the successful establishment of this system, the allocation and distribution of donor livers must be reassessed. In addition to increased transport times and distances, marginal organs can also be used to counteract the shortage of available donor livers.
Further investigations in the field of hepatology and machine perfusion will be carried out with the test set up. From this, further problems, such as the necessary medications and nutrients as well as their quantities, have to be researched. With the determination of essential threshold values of the liver, possibilities are also to be shown to further increase the duration of the machine perfusion and thus to further improve the distribution and allocation of the organs.
Another possible step is to examine whether the DeLiver system can be used for other organs, since it is conceivable that the DeLiver system with adjusted parameters and settings can also be used for other organs.

4. ACKNOWLEDGMENTS

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