Transplantation of extended criteria donor livers
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Chapter 8

Development of an Organ Preservation and Resuscitation Unit in a Multi-organ Transplant Center

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Submitted for publication
ABSTRACT
Due to worldwide shortage of donor organs, transplant surgeons have increasingly used donor organs with a risk of post-transplant complications. Such organs particularly benefit from the application of machine perfusion (MP). Therefore, in the past decades MP is increasingly used for organ preservation, organ viability assessment, and organ resuscitation. MP was first introduced in 2005 in clinical renal transplantation at the University Medical Center Groningen. Thereafter, MP has been applied in clinical lung and liver transplantation and has now come to play a central role in organ transplantation. To facilitate the use of MP we developed an organ preservation and resuscitation (OPR) unit. This manuscript describes the technical development and construction of the OPR unit which was specifically designed for simultaneous perfusion of lungs, livers, and kidneys, in addition to back table procedures for ex situ inspection of the organs. The use of the OPR unit has greatly improved the logistic and practical circumstances for MP. In addition, transplantation experts from various backgrounds are brought together in the same place, allowing development of organ preservation strategies that transcend single organ systems.
INTRODUCTION

Machine perfusion (MP) is a dynamic preservation strategy to assess, preserve, and improve organ viability in real-time. The technique is beneficial especially to organs with increased ischaemic damage, such as those derived from donation after circulatory death (DCD) and extended criteria donors (ECD) after brain death. Such organs demonstrate increased ischemia-reperfusion injury after revascularization and are associated with an increased risk of primary non-function, delayed function, or graft failure. MP decreases the effects of ischemia-reperfusion injury as well as post-transplant complications.

With the increased use of marginal organs for transplantation, MP is becoming more and more used in clinical settings. In many centers, MP is the standard preservation method for renal transplantation. In liver, lung, and heart transplantation, MP is also used more and more. In comparison to kidney MP, MP of liver, lung, and heart is more challenging and is mainly performed in the transplant hospital and not during transportation of the organ. Therefore, MP of non-renal organs was only recently introduced in the clinical setting. For example, at present all Dutch DCD livers are included in a randomized controlled trial of hypothermic oxygenated MP (Clinicaltrials.gov; NCT02584283), and recently normothermic MP has been initiated for ECD livers (www.trialregister.nl; NTR5972). Similar developments have been seen in heart and lung transplantation, as evidenced by clinical trials regarding MP of lungs with neurogenic edema, and DCD hearts. In the experimental setting, various modalities of MP are still being investigated, employing different temperatures, timing, and types of preservation solution.

The increased use of MP in clinical settings calls for professional facilities dedicated to MP and standardization of safety regulations. In this article, we describe the development of a unit for ‘Organ Preservation and Resuscitation’ (OPR).

DESIGN

Aim

We aimed to enable simultaneous extracorporeal MP of various organs. To this end we developed a specialized OPR unit, equipped to perform MP with maximum efficiency.

Design team

Numerous challenges had to be overcome while designing a multi-organ preservation unit, including regulations, logistics, and a budget. The design facilitated the various intended users, including lung, heart, kidney, and gastrointestinal transplant professionals. As the requirements were complex and new challenges arose during development, constant interaction between the engineers and the intended users was vital. The design team consisted of transplant surgeons, a dedicated organ perfusion team, scrub nurses, project and hospital construction managers, and an air ventilation expert. The clinical experience and knowledge of these health care professionals was vital in the development of the OPR unit.
Chapter 8

Technical requirements

The next step was to create a safe working environment with minimal risk of contamination and appropriate measures to minimize electrical, chemical or fire hazards. Many national and international laws and regulations govern the construction of operating rooms. For the OPR unit we adhered to the same requirements, with several exceptions (Table 1).

Table 1. Technical requirements with regard to safety

<table>
<thead>
<tr>
<th>Item</th>
<th>Laws and regulations</th>
<th>Operating room</th>
<th>OPR unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Air cleanliness</td>
<td></td>
<td>Operating table: ISO 5 Adjacent to operating table: ISO 7</td>
<td>Operating table: ISO 5 Adjacent to operating table: ISO 7</td>
</tr>
<tr>
<td>Classification operating room</td>
<td></td>
<td>Classification 1</td>
<td>Classification 2 (class 1 except for ventilation rate)*</td>
</tr>
<tr>
<td>Air inflow filter</td>
<td></td>
<td>HEPA H14</td>
<td>HEPA H14</td>
</tr>
<tr>
<td>Ventilation</td>
<td></td>
<td>Turnover of 20x per min</td>
<td>Turnover of 6x per min</td>
</tr>
<tr>
<td>Zones</td>
<td></td>
<td>3 zones</td>
<td>3 zones</td>
</tr>
<tr>
<td>Positive pressure</td>
<td></td>
<td>3 stages</td>
<td>3 stages</td>
</tr>
<tr>
<td>Electrotechnical safety</td>
<td></td>
<td>Classification 0</td>
<td>Classification 1*</td>
</tr>
<tr>
<td>Power supply</td>
<td></td>
<td>UPS</td>
<td>UPS</td>
</tr>
<tr>
<td>Sound limit</td>
<td></td>
<td>&lt;50 dB</td>
<td>&lt;50 dB</td>
</tr>
<tr>
<td>Temperature^</td>
<td></td>
<td>20-23°C ±2°C</td>
<td>20-23°C ±2°C</td>
</tr>
<tr>
<td>Relative humidity^</td>
<td></td>
<td>30-60%</td>
<td>±55%</td>
</tr>
</tbody>
</table>

*In the operating room, the use of anesthetic gasses requires an air ventilation turnover rate of 20 times per minute. As anesthesia was not used in the OPR unit, ventilation turnover was not regulated.

Classification of electrotechnical safety in medical rooms was determined lower in the OPR unit than in operation rooms because patients do not enter the OPR unit. Hence, there was no risk of cardiac arrhythmia of a patient in the OPR unit.

^The temperature and relative humidity were selected to reduce bacterial growth and suppress static electricity. Abbreviations: EC, European Community; GMP Annex 1, Good Manufacturing Practice; HEPA, high efficiency particle air; OPR, organ preservation and resuscitation; NEN1010, Netherlands Norm 1010; NEN-EN-ISO, Netherlands Norm, European Norm, and International Organization for Standardization; UPS, uninterruptible power source; WIP, Workgroup Infection Prevention (Dutch: Werkgroep Infectiepreventie richtlijn)

The next step was to design the area for MP. A ventilation system for this area was required to minimize microbial contamination. In the regular operating room, the ceiling over the operating table contains air filters which remove particles that might carry microorganisms. Laminar air flow is blown towards the operation table and creates a clean area – or “plenum” - underneath the filter. In the OPR, the area for MP needed to be protected by such laminar air flow. As the necessary airflow was not available within the existing ventilation system in our center, separate “plenum zones” were created for MP (Figure 1). As such, three zones of ±1.5 m² were designed to enable ventilated lung MP, liver MP, and back table procedures. To minimize obstruction of the laminar airflow, we chose cross-room flow to enable adequate lighting and ventilation.
Materials

The necessary equipment is listed in Table 2. This includes the perfusion machines, solutions, medical gasses, instruments, and disposables. As the gas mixture required for lung perfusion was not readily available in our center, a custom made gas outlet and channel was designed for the OPR unit. Other essential requirements for MP included a blood gas analyzer for real-time analysis of the perfusion solution to determine oxygenation status and organ function (Figure 1). Furthermore, as a room adjacent to the OPR unit was required for a three stage positive pressure system (Table 1), an ancillary room was planned for this function, containing supportive facilities such as a double sink, countertops, a refrigerator for preservation fluids, and a freezer for sterile ice.

Table 2. Equipment

<table>
<thead>
<tr>
<th></th>
<th>Lung</th>
<th>Liver</th>
<th>Kidney</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sterile environment</td>
<td>✓</td>
<td>✓</td>
<td>-</td>
</tr>
<tr>
<td>Gas requirement</td>
<td>Air, vacuum, gas mixture (6%O₂, 8% CO₂, 86% N₂)</td>
<td>Oxygen, carbon dioxide</td>
<td>Oxygen</td>
</tr>
<tr>
<td>Refrigerator</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Freezer</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Sink</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Blood gas analyzer</td>
<td>✓</td>
<td>✓</td>
<td>-</td>
</tr>
<tr>
<td>Computer</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Scales</td>
<td>✓</td>
<td>✓</td>
<td>-</td>
</tr>
<tr>
<td>Other</td>
<td>Pressure sensor</td>
<td>Ventilator</td>
<td>Operation tables</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Operation chairs</td>
<td></td>
</tr>
</tbody>
</table>

Figure 1. Blue print of the Organ Preservation and Resuscitation (OPR) unit. The surface area is a total of 44 m² which is divided over two distinct rooms: the preservation room and the ancillary room. In the ancillary room are located a refrigerator, freezer, washing facility, blood gas analyzer, and cupboards for storage. The preservation room contains three areas for organ benchwork and preservation, a computer, and cupboards for storage. There is a pressure gradient system between the preservation room, the ancillary room, and the hall way.
First use

The blueprints for the OPR unit were conceptualized in July 2014 (Figure 1). Construction was started in November 2014 and lasted until January 2015. The unit was then finalized for actual use by installing MP devices, instruments, and disposable materials (Figure 2). A simulated organ MP procedure was performed (Figure 3 and 4). Additionally, instructions for use and protocols were written to facilitate working with the OPR unit. Individual introduction sessions were held.

Figure 2. Wide angle photograph of the preservation room. In the walls are the three cross flow filters and a laminator distributing the air flow evenly over the entire surface. On the floor in front of the cross flow units are blue rectangles indicating the area in which the organ can be handled in a clean environment. Power sockets and gas outlets are available on each side of the cross flow units. The cupboards are located on the right side of the photograph.

Figure 3. Close up of the middle cross flow unit prepared for back table inspection and preparation of a kidney. Behind the operating table is the cross flow filter which is protected against damage by the vertical steel rods. The operation light is located above the cross flow and supplies 50.000 lux. If necessary, the operation light of the adjacent cross flow units can be added to provide additional light.
Development of an Organ Preservation and Resuscitation Unit in a Multi-organ Transplant Center

to familiarize the cleaning service, logistics staff, scub nurses, students, transplant technicians, researchers, and transplant surgeons with the new unit. The OPR unit was taken into use in February 2015. Per-case as well as periodic quality control evaluations were performed routinely. Maintenance of appliances and supply of materials such as solutions and disposables were incorporated into routine logistical procedures at the operating theater complex.

**Figure 4. Organ preservation and resuscitation (OPR) unit in use.** This photograph is taken from the ancillary room next to the preservation room. The wall separating both rooms has a window and an automatically sliding door with a sensor. There is also an intercom to minimize door movements. In the preservation room the device for liver perfusion can be seen on the left. Behind that is the area for organ inspection with two tables in front of the cross flow filter. To the right is the device for lung perfusion next to the table in front of the right cross flow filter. To the right and front of the right cross flow filter is the kidney machine which is placed on a counter.

**Figure 5. The ancillary room.** As in Figure 4, the window between the preservation room and the ancillary room can be observed. In the ancillary room, the blood gas analyzer is located on the counter. Underneath the counter are the refrigerator and the freezer. In the preservation room, the cross flow filter can be seen through the window.
DISCUSSION
This article describes the development of a facility for clinical-grade MP of three type of organs in a room named the Organ Preservation and Resuscitation unit. To enable replication in other centers, the design and implementation of the facility are described in this article.

With the creation of an OPR unit, optimal conditions were created to suit the increasing use of MP in our center, as well as to treat several different organs at once, derived from the same or different patients. The process was facilitated by periodic meetings of the design team which consisted of knowledgeable professionals with power of decision. As a result, the OPR unit now facilitates three types of organ perfusion, bringing together the professionals working with the different organs. This collaboration, which was formed during the design of the OPR unit, continues after its implementation, leading to a synergistic exchange of knowledge between the users of the OPR unit, creating new research ideas and scientific partnerships. The collaboration was also essential for acquisition of hospital budgetary means for the construction of the unit.

Although this facility provides a location for MP, financial support for additional personnel, materials, perfusion machines, and disposables will be compulsory to enable the use of MP in clinical care. In the Netherlands, dedicated personnel are trained to operate the OPR, creating a new job designation termed “organ perfusionist.” Certification of organ perfusionists, similar to cardiac bypass perfusionists, will be relevant as MP increasingly becomes the standard of care.

The OPR unit adheres to regulations for a safe working environment with minimal risk of contamination and other measures to minimize hazards to health. Its implementation has been received well by involved health care professionals and has continued to evolve in efficiency, quality, and accessibility.
References
