

# Prospects for the ex situ liver machine perfusion in Brazil

## *Perspectivas para a máquina de perfusão hepática ex situ no Brasil*

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### ABSTRACT

Brazil, like most countries in the world, experiences the expansion of extended criteria donors, mainly due to the aging of the population and the obesity epidemic. Concerns regarding the quality of these organs along with the vast territorial areas of the country compromise the utilization rate of livers from donors and aggravate the discrepancy between the number of liver transplants performed and the needed. Ex situ liver machine perfusion offers superior preservation for livers from extended criteria donors, limiting cold ischaemia time and offering the possibility of evaluation of their function before transplantation as well as the reconditioning of marginal organs. Objections such as the financial cost, difficulty in transporting the device between hospitals, and demand of trained professionals in the handling of the device must be pondered with the possibility of increasing the number of transplants and the utilisation rate of donor organs. The optimal use of this resource, through the careful selection of donors and the appropriate technical and scientific knowledge, can ensure an effective and successful implementation of this technology.

**Keywords:** Liver Transplant. Ex situ Liver Machine Perfusion. Extended Criteria Donors. Organ Preservation. Organ Donation.

### INTRODUCTION

In Brazil, the demand for livers for transplantation far exceeds supply<sup>1</sup>. Given the figures presented in the report of the Brazilian Association of Organ Transplantation (ABTO) in 2019, 5,212 liver transplants would be required, but only 2,245 were performed<sup>1</sup>. Moreover, the same report reveals that the mortality on the waiting list for a liver transplant was approximately 20%, considering the number of people who joined the list<sup>1</sup>. Therefore, there is a need to increase the number of transplants and assist more patients on the waiting list. Despite this need and the continued effort to increase organ donation, the ABTO 2018 report already pointed to an increase in the non-utilisation rate of organs

from deceased donors<sup>2</sup>. In 2019 in Brazil, only 52% of eligible donors had their organs transplanted<sup>1</sup>. A recent national retrospective study evaluating 1,772 potential organ donors described a 26% discard rate for livers<sup>3</sup>. These organs, which were functioning properly in the donor, were considered unsuitable for transplantation and discarded based on the subjective evaluation of the transplant surgeon on duty. This assessment, justifiably cautious, aims to protect possible future recipients, given that patients at the top of the waiting list have advanced stages of liver disease and low reserve to tolerate borderline-function organs. Thus, the reasons for the current rate of organ utilization in Brazil fall, briefly, into two categories: (1) concerns about the quality of the organ due to the morphological characteristics and/

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or data on the donor's history (age > 65, moderate or severe macrovesicular steatosis [ $> 30\%$ ], changes in liver enzymes, serum sodium  $> 160$  mEq/L, intensive care unit stay  $> 5$  days, use of vasopressors, and prolonged periods of static cold storage) that make it non-ideal — extended criteria donors; and (2) long distances between the retrieval and transplant centres, which often render the procedure unfeasible due to the high risk of postoperative complications following prolonged periods of static cold storage.

## Dynamic organ preservation – The ex situ liver machine perfusion

The dynamic preservation is carried out by medical devices known as machine perfusion and has received increasing attention from the transplant community worldwide. Although already used for some years in kidney transplant, the ex situ liver machine perfusion is currently being implemented in the clinical practice of several European transplant centres through research projects, for example in the University Hospitals Birmingham, in the United Kingdom, Groningen Medical Center, in the Netherlands, and University Hospital Zürich, in Switzerland<sup>4,5</sup>. In contrast to static cold storage, in which organs with reduced metabolic activity due to low temperature suffer ischaemic damage during preservation, in dynamic perfusion the organs receive a continuous flow of an oxygenated solution through the vasculature<sup>6</sup>. This continuous circulation improves the preservation of the liver microcirculation, provides nutrients and oxygen for cellular metabolism, and removes toxic metabolic waste products<sup>7</sup>. Therefore, the dynamic preservation limits ischaemic damage to donor organs (shortening cold ischaemia time) and, potentially, reconditions them before transplantation, which benefits mainly organs of marginal quality<sup>8</sup>.

The advancement in the use of the liver machine perfusion is justified by the need to improve the preservation of organs from extended criteria donors, which are more sensitive to ischaemic damage and the inherent injury during reperfusion in the recipient, aiming to increase their use to meet the growing number of patients on the waiting list for a liver transplant<sup>7</sup>.

For donors after brain death, this technology is

most commonly used after arriving at the transplant centre (ex situ), followed by a period of static cold storage for the transport of the organ (end-ischaemic)<sup>9</sup>. After preparing the organ and inserting the vascular and biliary cannulas, it will be subjected to dynamic preservation with an oxygenated perfusion solution. The perfusion solution is commonly maintained at  $37^{\circ}$  C in the normothermic liver perfusion, and approximately  $10^{\circ}$  C in the hypothermic liver perfusion<sup>7</sup>. Other modalities of perfusion, such as the subnormothermic and the combinations of perfusion techniques had their early preclinical and clinical studies recently published<sup>10-12</sup>.

The ex situ normothermic machine perfusion (NMP) simulates a physiological environment at  $37^{\circ}$  C, offering oxygen and nutrients to the organ<sup>13</sup>. Consequently, NMP limits ischaemic damage to donor organs during preservation, a fundamental factor for extended criteria donor organs<sup>7,13</sup>. In addition, NMP reestablishes the complete metabolism of the organ, allowing the safe, real time ex vivo function evaluation, although definitive criteria are not yet defined<sup>14,15</sup>. Despite variations in criteria, this assessment is usually based on hepatic lactate and glucose metabolism, maintenance of the perfusate pH at physiological levels, adequate vascular flows, and bile production<sup>14,15</sup>. Studies show that NMP improves the haemodynamic stability of the recipient and decreases graft dysfunction rates in the immediate postoperative period<sup>16</sup>. This suggests that NMP is able to recondition these organs before transplantation. However, NMP requires an oxygen carrier in the perfusate (i.e., packed red blood cells or haemoglobin-based acellular oxygen carriers) to supply the metabolic rate of fully functioning organs, which potentially increases the risk of disease transmission<sup>7</sup>. Furthermore, NMP has other points of attention, such as the risk of organ infection at  $37^{\circ}$  C and severe warm ischaemia if vascular cannulation complications arise during the perfusion, demanding trained staff to performing the procedure<sup>15,16</sup>.

The ex situ hypothermic machine perfusion (HMP), on its turn, is usually performed at  $10^{\circ}$  C. At this temperature, due to the organ's reduced metabolic rate, the necessary supply of oxygen is effectively served by diffusion in the perfusate, without the need for an oxygen carrier. In addition, the active oxygenation of the perfusion solution is still debatable<sup>7,17,18</sup>. Supporters of this

technique argue that the oxygen supply at this temperature is able to restore the mitochondrial electron transport chain (respiratory chain)<sup>17</sup>. The enhanced mitochondrial oxidative phosphorylation replenishes cells' energy stores (adenosine triphosphate) during hypothermic perfusion and prevents production of free oxygen radicals during reperfusion in the recipient. Consequently, it mitigates the oxidative injury, the activation of innate immune inflammatory response, and the release of inflammatory mediators (cytokines, chemokines, and adhesion molecules), with less tissue damage<sup>7,17</sup>. Despite these characteristics, it is worth noting that tests for evaluating the function of the organs during HMP are not yet available, but the dosage of mitochondrial flavin (flavin mononucleotide – FMN) released in the perfusate was recently associated with the graft function and loss in the postoperative period<sup>7,13,19,20</sup>. Furthermore, studies which have demonstrated the benefits of HMP in human livers focus mainly on donors after circulatory death—not in donors after brain death—with short cold ischaemia time and limited perfusion duration on the device (usually 2 hours)<sup>21,22</sup>.

## Applicability of the ex situ liver perfusion machine in Brazil

In Brazil, as presented above and in accordance with the global trend, there is a need to expand the use of extended criteria donors organs to meet the great number of patients on the waiting list. However, this need contrasts with the organ allocation policy of the sickest patients first established by the MELD (Model for End-Stage Liver Disease)-based liver allocation system<sup>22-24</sup>. Under this system, the organs are allocated to the sickest recipients on the waiting list and, if the organ displays any criterion indicating an increased risk of dysfunction in the postoperative period, they will be discarded by the transplant surgeon — based on the high probability of a poor postoperative result of the combination donor-recipient.

The 2018 and 2019 ABTO reports demonstrate that factors such as the global obesity epidemic and population aging are already affecting organ donors. For example, 47% of donors are over 50 years of age, and cerebrovascular diseases are already the leading

cause of death in this population (55%) — not traumatic causes anymore<sup>1</sup>. In addition, in 2019 there was a 62.5% increase in the rate of donors over the age of 65 years<sup>1</sup>. As a consequence, currently, there is a trend towards growth of the extended criteria donors' population, without a clear perspective of an intervention which could reverse this situation. Thus, interventions to better preserve marginal organs, limiting ischaemic injury and promoting the reconditioning of these high-risk organs, are crucial to improve its utilisation rate and to benefit the largest number of patients on the waiting list<sup>7,8</sup>.

Given this scenario, the ex situ liver machine perfusion has several advantages, described along with its limitations in Table 1. In Brazil, considering the absence of donors after circulatory death and the two aforementioned main reasons for the low utilisation rate of donor's organs, NMP could entail a major positive impact in this utilisation. Importantly, NMP permits objective and safe organ utilisation because it evaluates objectively its ex vivo function, mitigating concerns regarding its quality<sup>8,13,14</sup>.

The main limitation for the application of the ex situ liver machine perfusion is the financial cost related to the use of the device. Negotiation for the use of the device on loan would limit the fixed financial cost per perfusion to the disposable for organ perfusion and it may facilitate the introduction of this technology in the country. However, this matter is highly dependent on individual negotiations between suppliers and health institutions. Alternatively, the purchase or rental of the device may generate a potentially prohibitive additional cost that will hinder its introduction. The purchase of perfusate's supplements (for example, antibiotics and packed red blood cells) adds to this account, but they are commonly available in hospitals which perform transplants and usually do not have a significant economic impact on the cost of the procedure.

Another potential limitation is the difficulty in transporting the device between the retrieval and the transplant centre. It is noteworthy, however, that the use of machine perfusion — NMP or HMP — after arrival at the transplant centre, following a period of static cold storage for organ transportation (end-ischaemic), facilitates logistics and eliminates this obstacle. Therefore, this modality already has become the most usual NMP

technique for donation after brain death and has proved as effective as continuous preservation in the device during transport<sup>9</sup>. In addition, it should be highlighted the need for trained professionals to handle the device, which can be achieved through the development of educational programs on the subject.

It should be noted, though, that these restraints must be considered in view of the possibility of

increasing the number of transplants and a higher rate of utilisation of extended criteria donors' organs. However, to ensure proper implementation of this technology, it is necessary to optimize the use of this resource by careful donor selection, appropriate technical-scientific knowledge about this technology with implementation of the perfusion modality which allows improved and safe utilisation of organs from extended criteria donors.

**Table 1** - Advantages and limitations of the two main ex situ liver perfusion techniques.

Advantages of the ex situ machine perfusion of the liver	
Normothermic machine perfusion	
Advantage	Considerations
Objective ex situ assessment of donor liver function	<ul style="list-style-type: none"> <li>Increased safety regarding function and quality of the donor organ before use</li> </ul>
Safely prolongs donor livers' preservation time	<ul style="list-style-type: none"> <li>Especially beneficial in situations of long territorial extensions, with the possibility of transporting the organ with the device by road or plane</li> <li>Optimizes logistics in high-volume transplant centres</li> <li>Favors transplants in complex recipients who inevitably require longer surgical time</li> </ul>
Hypothermic machine perfusion	
Advantage	Considerations
Acellular perfusion solution (without the requirement of an oxygen carrier)	<ul style="list-style-type: none"> <li>Easier-to-perform technique</li> <li>Low risk of procedure-related complications</li> </ul>
Low temperature perfusions	<ul style="list-style-type: none"> <li>Improves cellular energy stores of donor organs before transplantation. Associated with lower incidence of biliary complications in donation after circulatory death transplantation</li> </ul>
Limitations of the ex situ machine perfusion of the liver	
Limitation	Considerations
Financial cost	<ul style="list-style-type: none"> <li>Fixed cost per perfusion related to the disposable kit and components of the perfusion fluid. Purchase, lease or use of the lended device depends on negotiations with the distributor</li> </ul>
Difficulty in transporting the device between the retrieval hospital and the transplant centre	<ul style="list-style-type: none"> <li>The use of the device only in the transplant centre, after a period of static cold storage for transport, facilitates logistics and makes it possible to overcome this possible limitation</li> </ul>
Team trained to handle the device	<ul style="list-style-type: none"> <li>Need for technical training and qualification of transplant teams</li> </ul>

## **CONCLUSION**

The ex situ machine perfusion represents a

promising advance for liver transplantation, giving hope to patients on the waiting list. Safely increasing the utilisation rate of donors' livers, it has the potential to reduce the

discrepancy between the number of transplants performed and the number of patients waiting for an organ.

If implemented with technical and scientific rigour, this technology can benefit Brazilian patients. Considering the characteristics of our donors, advantages

such as the ex vivo objective assessment of organ function before transplantation — mitigating concerns regarding the quality of organs — and the possibility of safely prolonging its preservation time, make the machine perfusion a promising tool.

## R E S U M O

*O Brasil, como a grande parte dos países no mundo, convive com a expansão de doadores de órgãos de critério estendido, principalmente devido ao envelhecimento da população e à epidemia de obesidade. Dúvidas em relação à qualidade desses órgãos juntamente com as longas extensões territoriais do país comprometem a taxa de utilização de fígados de doadores e agravam a discrepância entre o número de transplantes hepáticos realizados e o necessário. A máquina de perfusão hepática oxigenada ex situ oferece preservação superior para fígados de doadores de critério estendido, limitando o tempo de isquemia fria e oferecendo a possibilidade de avaliação da função antes do transplante bem como o condicionamento de órgãos de qualidade limítrofe. Objeções como o custo financeiro, dificuldade de transporte do dispositivo entre hospitais e a demanda de profissionais treinados para o manuseio devem ser apreciadas diante da possibilidade do aumento do número de transplantes e a maior taxa de utilização de órgãos de doadores. A otimização na utilização desse recurso, por meio da seleção cuidadosa de doadores, e o conhecimento técnico-científico adequado podem garantir a implementação eficaz e bem sucedida dessa tecnologia.*

**Palavras chave:** *Transplante de Fígado. Máquina de Perfusão Hepática ex situ. Doadores de Critério Estendido. Preservação de Órgãos. Doação de Órgãos.*

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