

Potential approaches to improve the outcomes of donation after cardiac death liver grafts

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Author contributions: Mahboub P wrote the manuscript; Bozorgzadeh A and Martins PN contributed to writing the manuscript.

Supported by University of Massachusetts (FDSP grant to Paulo N Martins).

Conflict-of-interest statement: The authors declare no conflicts of interest.

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Received: July 18, 2015
Peer-review started: July 19, 2015
First decision: September 17, 2015
Revised: December 24, 2015
Accepted: March 24, 2016
Article in press: March 25, 2016
Published online: June 24, 2016

Abstract

There is a growing discrepancy between the supply

and demand of livers for transplantation resulting in high mortality rates on the waiting list. One of the options to decrease the mortality on the waiting list is to optimize organs with inferior quality that otherwise would be discarded. Livers from donation after cardiac death (DCD) donors are frequently discarded because they are exposed to additional warm ischemia time, and this might lead to primary-non-function, delayed graft function, or severe biliary complications. In order to maximize the usage of DCD livers several new preservation approaches have been proposed. Here, we will review 3 innovative organ preservation methods: (1) different *ex vivo* perfusion techniques; (2) persufflation with oxygen; and (3) addition of thrombolytic therapy. Improvement of the quality of DCD liver grafts could increase the pool of liver grafts for transplantation, improve the outcomes, and decrease the mortality on the waiting list.

Key words: Biliary complications; Donation after cardiac death; Organ preservation methods

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Core tip: As the demand for more organs increases, the transplant community searches for new approaches to expand the pool of organs. Recently developed methods to improve the condition of donation after cardiac death (DCD) livers look promising. During the past decade, *ex vivo* machine perfusion method has demonstrated positive results and it is considered as a new potential preservation method for DCD organs. This paper provides an overview of the attempts to ameliorate the quality of DCD liver grafts and transplant outcomes by improving preservation techniques.

Mahboub P, Bozorgzadeh A, Martins PN. Potential approaches to improve the outcomes of donation after cardiac death liver grafts. *World J Transplant* 2016; 6(2): 314-320 Available from: URL: <http://www.wjgnet.com/2220-3230/full/v6/i2/314.htm> DOI:

<http://dx.doi.org/10.5500/wjt.v6.i2.314>

INTRODUCTION

Liver transplant is considered as the only available treatment for patients with end stage liver disease. Liver transplantation has been performed with success since 1963 and the outcomes continue to improve achieving 1-year graft survival superior to 90%^[1,2]. At the same time the demand for liver transplant has increased and many patients die on the waiting list. The organ shortage has led to an increase in the use of grafts with inferior quality such as from donation after cardiac death (DCD) donors, also called non-heart-beating donors. DCD livers undergo additional warm ischemia time (WIT) which is associated with inferior liver function and poor outcome after transplant. Therefore, searching for potential approaches to ameliorate the quality of organs from DCD donors and minimizing injury is of special importance for the transplantation field.

In this paper we discuss about the attempts to ameliorate the quality of DCD liver grafts by improving preservation techniques.

CHARACTERISTICS OF DCD DONORS

DCD donors are characterized by the termination of ventilation and blood circulation before cold flushing of organs^[3]. The idea to use DCD liver grafts was reintroduced in the 1990s after achieving success in kidney transplantation^[3]. The use of grafts from DCD donors in the United States has exponentially increased from 0.95% in 2000 to 5% in 2010 (1 UNOS).

In general DCD donors are divided into uncontrolled and controlled donation groups. In the uncontrolled group, the organ suffers from prolonged WIT, as the potential donor is dead on arrival or has been undergoing unsuccessful resuscitation. In this group, the organ suffers from long WIT which is a detrimental factor in organ quality. In the controlled group, cardiac arrest is planned and it happens following withdrawal of ventilator in the operating room or intensive unit care^[3,4]. It is generally accepted that DCD grafts have less energy stores and undergo more damage during the storage time^[5].

Biliary complications are much more common in patients that received grafts from DCD donors (20%-40% compared to 5% in grafts from brain-dead donors)^[6]. Post transplant biliary complications could lead to a number of serious complications such as graft loss, high morbidity which requires re-transplant or could result in patient's death^[7]. The most critical type of biliary complications are the so-called ischemic-type biliary lesions (ITBL), also called ischemic cholangiopathy, with an incidence varying between 5% and 15%^[8,9]. The risk of ischemic cholangiopathy with grafts from DCD donors is 10 times higher than for brain dead donors because

of severe warm ischemia suffered by these grafts^[6]. The reason why they develop more biliary complications is that bile ducts (cholangiocytes) are more sensitive to ischemia-reperfusion injury than hepatocytes^[10]. Many of DCD liver grafts are not used because longer warm or cold ischemia times have been associated with poor outcomes^[6,11,12]. Most of the transplant centers accept livers from DCD donors that have a maximum WIT, the period between extubation and cold flushing, of less than 30 min and short cold ischemia time (in general less than 6 h)^[11].

OXYGENATED COLD STORAGE (PERSUFFLATION)

Simple cold storage (SCS) is the currently widely used organ preservation method in the clinical setting because of the low cost and simplicity. The idea of CS is to decrease the metabolism level to provide protection from ischemia. However, even at 4 °C there is approximately 5% active metabolism in the organ which eventually leads to ATP depletion and accumulation of waste product^[13,14]. In order to improve organ preservation method, persufflation (PSF) had been introduced as an alternative method with the capacity of delivering oxygen during cold preservation. PSF has been used in rat livers for the first time between 1980 and 1990 by the Fischer group. They first established the model on rodent liver and continued with large animals (pig) and were able to demonstrate the benefits of PSF by improving the quality of liver grafts^[15]. They also showed the feasibility of this method by publishing the outcome of five patients transplanted with persufflated livers^[16]. The livers underwent WIT between 20-60 min and they were rejected by all the other transplant centers for transplant. They were flushed with University of Wisconsin (UW) or histidin-tryptophan-ketoglutarate and after arriving to the transplant center were subjected to retrograde PSF (R-PSF) at 18 mmHg for 70-200 min before the implantation. The results were promising and during the two years follow-up period, all the recipients showed good graft function. Later, in a study done by Minor *et al.*^[17], it was shown that PSF of Wistar rat liver grafts with 18 mmHg of oxygen for 48 h at 4 °C could lower the activity of Kupfer cells compared to simple SCS.

Following these preliminary results, the studies were extended to study the effect of PSF in DCD livers. Minor *et al.*^[18] introduced venous systemic oxygen PSF in DCD rat livers following 30 min of WIT. In a following study, the same group transplanted livers after 24 h PSF preservation, which showed that it improved mitochondrial function, and normalized ATP level^[19].

Following the increasing concern on potential reactive oxygen species (ROS) production during PSF, Minor *et al.*^[20] preserved DCD rat livers for 24 h with R-PSF and compared with the result of the livers that were preserved in UW solution. The ATP level, bile production

and perfusion flow was improved in R-PSF livers. The outcome of this study demonstrated the beneficial role of R-PSF in eliminating ROS and lipid peroxidation production. In another study by Minor *et al.*^[21] it was also demonstrated that treatment with anti-oxidants such as superoxide dismutase or allopurinol during normothermic R-PSF could eliminate lipid peroxidation and restore the energy level in liver grafts after 60 min of WIT and 60 min of SCS in Euro-Collins solution. They also reported that PSF alone could induce some oxidative damage^[21]. Recently in a study done by Lüer *et al.*^[22], it is shown that pulsatile PSF of DCD rat livers is beneficial in early graft recovery after reperfusion. In this study livers that were procured from male Wistar rats were subjected to 30 min WIT and then 18 h of cold ischemia. Later the grafts ($n = 5$ each group) were preserved with either nonpulsatile or pulsatile gaseous oxygen PSF. Pulsatile PSF demonstrated better parenchymal preservation, higher nitric oxide levels in perfusate, and decreased portal vein resistance^[22].

In the next step, PSF was tested on pig livers, and subsequently to human DCD livers. In 2001 Saad *et al.*^[23] showed that R-PSF with antioxidant treatment in a transplant model is a promising method in improving the quality of the porcine DCD livers. DCD livers underwent 60 min WIT followed by 4 h SCS in UW solution or R-PSF with antioxidant treatment. In R-PSF group all animals survived, while animals in SCS group died 3 h after transplantation^[23]. After successful animal experiments, the first clinical study was started in 2004 in Germany using R-PSF in 5 DCD livers. Liver grafts underwent R-PSF at 18 mmHg at least one hour before transplantation. Evaluation of the histological biopsies taken before and after R-PSF showed that ATP level was enhanced by 2-5 times after R-PSF treatment, and all the patients survived during the two years of observation period with good graft function panel^[16].

HYPOTHERMIC MACHINE PERFUSION

Hypothermic machine perfusion (HMP) is considered as one of the alternative preservation methods to SCS which have recently been increased in use for DCD grafts preservation. HMP is a continuous or pulsatile circulation of the cold preservation solution in an organ at 4 °C-8 °C, and it has already been shown that HMP can resuscitate DCD liver graft's in different rat models^[24-26]. Schlegel *et al.*^[27] demonstrated that hypothermic oxygenated perfusion (HOPE) in a rat model could impact down regulation of the immune system after transplantation, in addition to protecting against ischemia injury. In this study, using an acute rejection model, livers from the Lewis Rats were used to be transplanted into the Brown Norway Rats. Rat livers underwent one hour HOPE before implantation with or without low dose (0.03 mg/kg) tacrolimus treatment in the recipients during the four weeks of observation. The combination of tacrolimus with HOPE resulted in 100% survival in the recipients without any sign of rejection. As it was mentioned prior,

one of the important issues in using DCD liver is to overcome biliary complications, in particular ischemic cholangiopathy related to strictures. In 2013, in a study done by Schlegel *et al.*^[25], it was demonstrated that HOPE is a sufficient method to protect DCD livers from biliary complications. The rat livers underwent to 30 min warm ischemia and it was followed by 4 h SCS. In the HOPE group, livers underwent one hour HOPE prior to implantation. Subsequently, livers were implanted and the recipients were observed for four weeks. Kupffer cell and endothelial cell activation was reduced. Moreover, cholestasis parameters were also improved in the HOPE group. In another study, Op den Dries *et al.*^[28] in a DCD pig model indicated the efficacy of oxygenated hypothermic machine perfusion in decreasing and limiting arteriolonecrosis injury of the peribiliary vascular plexus of the bile ducts. After 30 min of warm ischemia, the livers were preserved by SCS or oxygenated hypothermic machine perfusion using dual perfusion machine for 4 h. Next step was liver reperfusion for two hours at 37 °C with oxygenated autologous blood to simulate transplantation. Studying the bile duct histology disclosed reduced arteriolonecrosis of the peribiliary vascular plexus in the livers that were subjected to HMP perfusion vs SCS.

The feasibility of HMP study on human livers of brain dead donors was performed by Guarrera *et al.*^[29] at Columbia University. They used dual perfusion to perfuse 20 livers and successfully transplant them. They reported reduced early graft dysfunction, peak transaminases and improved renal function^[29]. The first use of HMP for DCD livers was reported in 2014 by Dutkowski *et al.*^[30]. Eight DCD livers with median of 38 min WIT were included. Liver grafts underwent 1-2 h HOPE with perfusion pressure at 10 °C, 3 mmHg. After transplantation the grafts revealed good hepatic function and no evidence of ITBL. Using HMP in other organs such as kidney is more common. There have been several clinical trials done on kidney HMP and it has become routine to use this method to preserve the human kidney in some part of Europe and some states in United States. Cold static storage is still the most common method of preservation in liver since cannulation and perfusion is more complicated in liver, and currently there is no Food and Drug Administration approved liver perfusion machine for clinical use.

SUBNORMOTHERMIC MACHINE PERFUSION

Another new potential method to replace SCS is subnormothermic (SNP) machine perfusion. Olschewski *et al.*^[31] presented that SNP perfusion is more beneficial in DCD rat liver which were subjected to one hour warm ischemia and reperfused at body temperature. Berendsen *et al.*^[32] established a rat liver transplant model. In this study the livers underwent 3 h of SNP perfusion at 21 °C with Williams Medium E solution

after one hour of WIT^[32]. The survival rate was 83.3% in a one month observation period. In another study performed by the same group, they perfused 7 human discarded DCD livers at 21 °C for 3 h with oxygenated Williams Medium E^[33]. This study found that oxygen uptake and ATP content was improved with an increase in bile production, and better bile quality. They suggested that SNP perfusion is effective in improving DCD livers quality and hepatobiliary cellular parameters.

NORMOTHERMIC MACHINE PERFUSION

Normothermic machine perfusion (NMP) is one of the innovative organ preservation techniques. NMP consists of a pulsatile flow of oxygenated perfusion solution in the organ which supports cellular metabolism at body temperature, restores the energy content of the organ and washes out waste products prior to the reperfusion in the recipient body. Another advantage of this method is to provide the opportunity of assessing the organ viability prior to implantation. In 2001, Friend *et al.*^[34] published a paper in which they described maintaining viability of DCD livers for a minimum of 24 h by applying NMP. After 60 min of WIT the liver grafts were stored for 24 h in UW solution or were immediately subjected to NMP. To mimic the anastomosis time, the livers were not perfused for 45 min after flushing with cold preservation solution. After 45 min, livers were reperfused for another 24 h. The continuous bile production, lower resistance in portal flow, reduced alanine transaminase level in the NMP group suggested that the quality of preservation can be enhanced by NMP perfusion.

op den Dries *et al.*^[35] was the first group to report the feasibility of this method in human DCD livers. They perfused 4 DCD discarded livers for 6 h using a dual perfusion system. The perfusion fluid consisted of packed blood cells with fresh frozen plasma to provide a sufficient support for high metabolism activity at 37 °C. Reduced lactate level to the normal value, bile production, and well preserved hepatocytes and biliary sinusoids suggested that NMP is beneficial in improving the quality of DCD livers. One year later the same group published a study on criteria of assessing the graft viability during *ex vivo* NMP perfusion^[36]. They investigated whether bile production and the quality of the produced bile during NMP would be a reliable biomarker for viability assessment. Twelve discarded DCD livers with median cold storage of 6.5 h were included and subjected to 6 h NMP at 37 °C with plasma and red blood cells. Liver grafts were divided into two groups; high bile production (more than 30 g in 6 h, and low bile production (less than 20 g). Higher bilirubin and bicarbonate concentration in the bile samples and lower hepatic necrosis in the high bile production group suggested that bile production might be a potential biomarker to assess the organ viability during warm perfusion. In a recent case report, Watson *et al.*^[37] from Addenbrooke's Hospital revealed the effect of Normothermic perfusion on a DCD liver graft

before implantation. The liver graft was retrieved from a 57-year-old donor. Circulatory arrest occur 150 min after stopping of life-supporting treatment and the graft underwent 5 h cold storage. Later the graft was perfused at 37 °C for 132 min with a plasma free solution. During the first 74 min of perfusion, the lactate was decreased from 7.2 to 0.3 mmol/L. after implantation the liver biochemistry was normal and during 6 mo posttransplant observation, there was no evidence of cholangiopathy^[37].

GRADUAL REWARMING MACHINE PERFUSION

Minor *et al.*^[38] for the first time introduced the concept of thermally controlled oxygenated rewarming (COR) of the liver grafts prior to reperfusion. In this study, Porcine livers were subjected to 18 h SCS and then were perfused 90 min by COR perfusion, HMP and SNP. In the COR group, during the first part of the perfusion temperature was stabilized at 8 °C and then was gradually enhanced to 12 °C, 16 °C, and 20 °C after 30 min, 45 min and 60 min, respectively. The perfusion pressure was kept at 4 mmHg in the portal side and at 25 mmHg at the hepatic artery side. In order to mimic the anastomosis time, the liver grafts were not perfused and were kept for 30 min in room temperature and then were reperfused with autologous blood for 4 h. The liver in the COR group demonstrated increased ATP, decreased lipid peroxidation, enzyme leakage and improved bile production. Minor *et al.*^[39] suggested that starting reoxygenation in a low temperature could reduce oxidative stress injury during reperfusion, and improve mitochondrial function^[40]. Following the previous study Westerkamp *et al.*^[41] investigated COR in a rat DCD model. In this study, the rat DCD livers were subjected to SCS at 4 °C for 6 h and then subjected to COR, HMP or SNP. After 45 min mimic anastomosis time, they were reperfused 2 h with red blood cells and Williams Medium E solution. In the control group, livers were immediately reperfused at 37 °C. Reduced transaminase enzymes level and lipid peroxidation level, superior mitochondrial function, higher bile production, improved bile quality and better preserved bile duct epithelium was observed in the COR group. The COR represented superior liver function compare to the SCS groups but comparable to the HMP and the SNP group.

ABDOMINAL REGIONAL PERFUSION

The main concept of abdominal regional perfusion is to limit deleterious effect of warm ischemia in DCD organs by the abdominal organ perfusion with continuous flow. Abdominal regional perfusion is being done *via* cannulation of femoral artery and vein using cardio pulmonary bypass machine or extracorporeal membrane oxygenation machine. For the first time regional perfusion was performed by a Spanish surgeon at 1989^[42]. The perfusion is being used in two categories

Table 1 Disadvantages of the different methods

Preservation methods	Disadvantages
Persufflation	Not able to assess the viability of the grafts
Hypothermic perfusion	High cost, not able to assess the viability of the graft
Subnormothermic perfusion	High cost, clinical challenging, not able to assess the viability of the graft
Normothermic perfusion	High cost, clinical challenging, the blood supply, the risk of losing the graft in the case of emboli in the system
Gradual rewarming	High cost, clinical challenging, need an accurate machine to be able to change the temperature and pressure
Abdominal regional perfusion	Ethical challenging
Thrombolytic therapies	Risk of severe bleeding

as hypothermic or normothermic perfusion^[43]. One group from West forest University describes perfusing of six DCD livers with hypothermic regional perfusion which was performed at 22 °C. In this study they showed good initial graft survival^[44]. The hospital clinic in Barcelona started using normothermic regional perfusion protocol on human category 2 DCD donors. The recipients were subjected to a median 45 mo follow-up. One year graft survival was 73% while patient survival rate was 81%. In another study a group from La coruna in Spain included category 2 DCD liver donors, they subjected 7 donors to hypothermic regional perfusion and 10 donors to normothermic regional perfusion. The results demonstrated high biliary complication in the recipients (25%) with low rate of five years graft survival^[45].

THROMBOLYTIC THERAPIES (TISSUE PLASMINOGEN ACTIVATOR)

Hashimoto *et al*^[46] suggested that the higher incidence in biliary complications of DCD livers may be related to microthrombi in the peri-biliary plexus. In this study they included 22 patients and assessed the effect of tissue plasminogen activator (TPA) injected into the hepatic artery of donor's during back table. Fourteen recipients out of 22 developed excessive post reperfusion bleeding and 2 patients developed ITBS. The TPA level was investigated in all the patients to find out if there was a correlation between the TPA level and excessive bleeding. They found that TPA level in the patients with bleeding was comparable with those who did not develop bleeding. The patients with excessive bleeding had history of higher previous laparotomy done in the past and higher body mass index, which might be associated with incidence of massive bleeding. In another study Seal *et al*^[47] recently showed that TPA treatment in DCD liver grafts decreases ITBSs occurrence and improves one- and three-year graft survival after transplant. TPA injection was delivered into the hepatic artery during liver transplant in 85 patients and compared to 33 patients who did not undergo TPA treatment. They reported lower occurrence rate of ITBL (16.5% vs 33.3%) and lower intrahepatic constriction in the group that received TPA treatment (3.5% vs 21.2%).

THE DISADVANTAGES OF DIFFERENT PRESERVATION METHODS

The disadvantages of each method are listed in the Table 1.

CONCLUSION

Because of exponential increase in the demand of liver grafts and high mortality on the waitlist, the interest of expanding the suitable organs for transplant has been increased. The optimized use of DCD liver grafts, different *ex-vivo* preservation interventions have been proposed achieving high rates of success. There is enough evidence that these new techniques have potential to improve graft function. Now, it is time for randomized controlled trials and a cost-effective analysis to determine if these techniques will become standard clinical practice.

ACKNOWLEDGMENTS

The authors would like to thank Stefanie Parker for proof-reading and editing.

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P- Reviewer: Balaban YH, Krueel CRP, Kita K, Marino IR, Sugawara Y
S- Editor: Gong XM **L- Editor:** A **E- Editor:** Liu SQ





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