French Editorial Commentary from the ACHBPT

Biliary tract viability assessment and sequential hypothermic-normothermic perfusion in liver transplantation

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We read with great interest the study of Mergental *et al.* (1) reporting the 5-year outcomes of the VITTAL trial (2,3). VITTAL was a prospective, non-randomized, single-arm trial that tested end-ischemic oxygenated normothermic machine perfusion (NMP) with a "back-to-base" strategy to evaluate, and potentially transplant, liver grafts declined by all liver transplantation (LT) centers in the United Kingdom. For a liver to be considered viable, it had to metabolize perfusate lactate to a concentration of ≤2.5 mmol/L within four hours from the start of perfusion, and meet at least two of the following criteria: bile production without a defined quantity; maintenance of perfusate pH above 7.3; glucose consumption in the perfusate; maintenance of stable arterial and portal flow above 150 and 500 mL/min, respectively; maintenance of graft suppleness and homogeneous perfusion (4). Thirty-one discarded human donor livers underwent viability testing by using end-ischemic NMP, of which 22 (71%) livers were subsequently transplanted. The primary outcome of the trial was graft survival rate at 90 days and it was 100%.

The authors reported the long-term outcomes of patients and liver grafts from the VITTAL trial. The graft and patient survival at 1, 3, and 5 years were respectively 91%, 82%, and 82%, and 100%, 91%, and 82%. Among the 22 grafts deemed transplantable, 12 grafts were harvested from donors after brain death (DBD) and 10 grafts were harvested from donors after circulatory death (DCD). Among the 10 DCD livers, three developed non-anastomotic biliary strictures (NAS) (30%) and required retransplantation. The fourth liver retransplantation in the series was performed in a patient who had received a DBD graft and was complicated by hepatic artery thrombosis.

Anastomotic biliary stricture occurred in two cases; each time treated by endoscopic retrograde stenting. Additionally, biliary tract irregularities on magnetic resonance cholangiopancreatography (MRCP), without liver function test alteration, were observed in three cases. At 5 years, four recipients had died, all of which had a functioning graft. Two of them had been retransplanted for NAS. The cause of death was recurrence of primary cancer in three cases and chronic rejection due to poor treatment adherence in one case.

Comments

This study presents the long-term results of liver grafts deemed non-transplantable by conventional criteria but transplanted after assessment via NMP. Authors should be appraised for this high-quality study. However, biliary complication incidence was elevated and two critical points require discussion: (I) the viability criteria applied in this trial; and (II) the exclusive application of NMP at the end of

the ischemic phase.

The viability criteria used in the VITTAL trial

During NMP, the liver is maintained in an almost physiological environment and recovers its metabolic functions. This leads to the restoration of aerobic metabolism, as evidenced by glucose consumption, lactate clearance, maintenance of acid-base balance, and bile production. There are two types of graft viability criteria during NMP: hepatocellular and cholangiocellular viability criteria (5-7). The quality of the graft can be assessed by evaluating: (I) its metabolic function (lactate clearance, pH maintenance, urea and coagulation factors production); (II) its excretory function (bile production, indocyanine green clearance) (8); (III) its appearance, consistency, and hemodynamics (flow, pressure, and resistance of the hepatic artery and portal vein) during perfusion. The function of the biliary epithelium can be assessed by analyzing bile composition (pH, glucose levels, and bicarbonate levels) (9). In the VITTAL trial, only hepatocellular viability was considered for evaluating liver transplantability during NMP although bile composition was studied, and biliary biopsies were performed. These two factors were not considered in the graft evaluation nor in the decision to proceed with transplantation or not and a posteriori, NAS developed in DCD livers that had a biliary pH <7.65 and a biliary bicarbonate level <25 mmol/L. Histological evaluation of these grafts revealed advanced biliary lesions and arterial media necrosis (1).

It has indeed been shown that bile composition during NMP can predict the occurrence of NAS (9,10). Transplanting livers from DCD donors without controlling bile composition during NMP exposes the recipient to NAS (5,6). This could explain the high incidence of NAS in the VITTAL trial (30% retransplantation rate for NAS in the DCD group). These biliary viability criteria were further refined in the DHOPE-COR-NMP trial (10). It had been shown that absolute values of bile pH, bicarbonate, and glucose during NMP may not the most appropriate markers to test cholangiocellular viability and that the delta between bile and perfusate levels of pH, bicarbonate, and glucose should be used to identify bile alkalization and glucose reabsorption by the biliary epithelium (10).

Use of end-ischemic NMP alone

In the VITTAL trial, an end-ischemic NMP was chosen (2). End-ischemic NMP exposes the graft to ischemia-reperfusion injury, to which the bile ducts are extremely sensitive (11). Since the beginning of the VITTAL trial in 2016, the Cambridge team shared a similar experience showing high percentages of biliary complications after NMP of livers from DCD donors (5,6). It has been demonstrated that a short period of hypothermic oxygenated perfusion (HOPE) reduces ischemia-reperfusion injuries (12,13). The Groningen group had shown a beneficial effect of the combination of arterial and portal hypothermic perfusion [Dual Hypothermic Oxygenated Perfusion (DHOPE)] and NMP (DHOPE-NMP) on cholangiocellular function. Biliary bicarbonate concentration was higher in the DHOPE-NMP group compared to the NMP group. Not only do biliary bicarbonates may serve as evidence of good cholangiocellular function but may also serve as protection to the biliary epithelium against the effects of toxic hydrophobic bile salts (14). This phenomenon has been described as the "bicarbonate umbrella" (14). In 2017, the same Groningen group launched the DHOPE-COR-NMP trial (combination of one-hour DHOPE, followed by one hour of controlled oxygenated rewarming, and subsequent NMP), aiming to reduce ischemia-reperfusion injuries at the beginning of NMP (6-8,10). All livers in the DHOPE-COR-NMP trial met the hepatocellular viability criteria used in the VITTAL study, despite the fact that all livers came from high-risk DCD donors whose median age was significantly higher than in the VITTAL study (10). With a median follow-up of 12 months, they observed only one case of post-transplant cholangiopathy after DHOPE-COR-NMP of high-risk DCD liver grafts, and no recipient was retransplanted (10). The same Groningen team has more recently reported its results using the DHOPE-NMP combination (15). One hundred and five procedures were performed to test grafts initially declined for transplantation, 69 livers were deemed transplantable and were transplanted. The graft and recipient survival at 1 and 3 years were respectively 93% and 91%, and 99% and 97%. Two patients (3%) developed NAS and required retransplantation. After these findings, the viability criteria were modified using the delta between bile and perfusate levels of pH, bicarbonate, and glucose rather than their absolute biliary values. Using these cholangiocellular viability criteria, no cases of NAS were observed (16).

Conclusions

NMP is an important tool for evaluating and selecting

donor livers which, based on classical criteria, were initially considered non-transplantable. The VITTAL trial has pushed the boundaries of using these high-risk liver grafts after NMP evaluation. However, end-ischemic NMP alone, as applied in the VITTAL study, does not seem to protect the bile ducts from ischemia-reperfusion injuries, particularly for livers from DCD donors. Therefore, a short period of DHOPE before NMP, along with the use of cholangiocellular viability criteria during NMP, could help reduce post-transplant morbidity and the risk of graft loss due to NAS.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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