Case Report

A marginal liver graft with hyperbilirubinemia transplanted successfully by ischemia-free liver transplantation

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Abstract: The shortage of transplant organs remains a serious issue worldwide, and using liver grafts from extended criteria donors could expand the donor pool. Extended criteria donor liver allografts have a high chance of complications such as primary nonfunction, early allograft dysfunction, and ischemic-type biliary lesions. How to employ these extended criteria donors safely and effectively warrants further investigation. Herein, we report the successful use of a marginal donor liver with hyperbilirubinemia to save the life of an acute-on-chronic liver failure recipient using a new surgical technique: ischemia-free liver transplantation (IFLT). The graft was retrieved for transplantation due to the following reasons: (I) the recipient was in a life-threatening situation and no living donor donation candidate was available; (II) the graft was considered transplantable except for cholestasis; and (III) IFLT could reduce ischemia/reperfusion injury (IRI), resuscitate the allograft *ex situ*, and maintain organ viability before transplantation. The graft was transplanted successfully using the IFLT procedure. Although anatomic biliary stricture occurred after surgery, no IRI-related complications were found during the follow-up. The use of liver grafts from extended criteria donors is safe and effective under IFLT. Additional IFLT clinical studies need to be performed, particularly concerning donor management, graft selection, and *ex situ* resuscitation.

Keywords: Ischemia-free liver transplantation (IFLT); hyperbilirubinemia; extended criteria donors; liver failure; case report

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Introduction

Organ transplantation is a critical life-saving therapy for end-stage organ failure (1). According to data from the World Health Organization (WHO) Global Observatory on Donation and Transplantation (http://www.transplant-observatory.org/), organ shortage is a major limitation for transplantation, and solid organ transplants account for fewer than 10% of the global demand. It is thus crucial to expand the organ donor pool, and various approaches have been attempted, including expanding the organ source pool to deceased donor organ donation, living-related organ donation, split or reduced-size organ transplantation, and the use of extended criteria donors (ECDs) or marginal donors (2,3). Because of the increased mortality of patients on the waiting list, a growing number of ECD grafts are used in liver transplantation (LTx) (4). In human LTx, ischemia/reperfusion injury (IRI) occurring following blood flow restoration can cause damage to the grafts, leading to complications such as early allograft dysfunction (EAD), primary nonfunction (PNF), and ischemic-type biliary

lesions (ITBLs) (5). IRI can also cause damage to other organs, leading to complications such as postreperfusion syndrome (PRS) and acute kidney injury (AKI) (6). The tolerance to hypoxia and IRI in ECD or marginal donor livers is worse than that of high-quality allografts, leading to a higher incidence of IRI-related complications (7,8). To enhance the quality of ECD or marginal allografts, machine perfusion, including hypothermic machine perfusion, normothermic machine perfusion (NMP), and subnormothermic machine perfusion, has been demonstrated to be a viable preservation strategy in LTx (9). The first human LTx with NMP-preserved grafts was reported by Ravikumar *et al.* in 2016, and their results confirmed the safety and feasibility of using NMP in organ transplantation and transportation (10). Subsequently, a clinical randomized controlled trial demonstrated that NMP preservation is associated with a 50% lower level of graft injury and a 50% lower organ discard rate than conventional static cold storage (11). Mechanistic studies have revealed that NMP not only inhibits inflammatory reactions but also promotes graft regeneration in the donor liver, leading to a decreased IRI level (12). Based on the NMP technique and surgical innovation, ischemia-free liver transplantation (IFLT) was established at our institute, theoretically eliminating the effects of donor liver IRI throughout the transplant process. The first case of IFLT involved the successful resuscitation of a donor liver with 85–90% macrovesicular steatosis (13), suggesting its considerable potential in expanding the organ donor pool.

Herein, we report the successful application of a hyperbilirubinemia graft using IFLT and discuss the issues concerning the use of grafts from ECDs, donor management, and the timing of transplantation.

We present the following case in accordance with the CARE reporting checklist (available at http://dx.doi.org/10.21037/atm-20-6296).

Case presentation

A 35-year-old man was diagnosed with chronic viral hepatitis B and was taking entecavir irregularly for 6 years. He had no history of smoking, alcohol consumption, or other types of viral hepatitis. He had been admitted to a local hospital and started to present with symptoms related to acute-on-chronic liver failure (ACLF) for 3 weeks, including jaundice, severe coagulation dysfunction, and refractory ascites. After this, the patient's condition worsened gradually and he was referred to our institute as an LTx candidate. While waiting for a suitable donor liver, he eventually developed gastrointestinal bleeding and grade 4 hepatic encephalopathy before transplantation. His laboratory tests showed severe liver function decompensation [aspartate aminotransferase (AST), 40 U/L; alanine transaminase (ALT), 69 U/L; γ-glutamyltransferase (GGT), 70 U/L; total bilirubin (TBIL), 38.2 mg/dL; direct bilirubin (DBIL), 21.2 mg/dL; international normalized ratio (INR), 3.68; activated partial thromboplastin time, 73.5 s; fibrinogen, 0.85 g/L; prothrombin activity, 18%; hemoglobin, 56 g/L; platelet, 60×10^9/L; white blood cell, 2.62×10^9/L; blood ammonia, 108 μmol/L], and his model for end-stage liver disease (MELD) score was 32. In addition to conventional anti-hepatitis B virus treatment and measures to protect hepatic function, he had undergone plasma exchanges or dialysis treatment 4 times to reduce the toxicity of hyperbilirubinemia and mitigate inflammatory mediators before LTx. The treatment effect was not satisfactory, and LTx was the only promising treatment approach that could provide freedom from life-threatening conditions.

A brain-dead man aged 26 years voluntarily donated his organs. The cause of brain death was severe traumatic brain injury. He had undergone hematoma evacuation and decompressive craniectomy surgery immediately after admission to the local hospital. He remained in a deep coma, with the disappearance of spontaneous respiration and absence of a brainstem reflex after surgery. The declaration of brain death was made by 2 independent qualified neurologists and critical care physicians. The laboratory tests revealed pulmonary infection, hypernatremia, and liver dysfunction. In particular, his serum TBIL level had gradually increased to 14.03 mg/dL. When he was transferred to our hospital, he had been admitted to the local hospital for 25 days. After being transferred to our hospital, enhanced anti-infection and sodium-lowering therapies were initiated, magnesium isoglycyrrhizinate and ursodeoxycholic acid were used to improve liver function, intravenous nutrition was reduced, and enteral nutrition was gradually increased. The indocyanine green retention rate at 15 minutes (ICG15) 7 days before retrieval was 42.5%, and at 1 day before retrieval the rate was 27.5%. The laboratory data before donor organ retrieval are summarized in *Table 1*, and indicated that his liver function was gradually improving, the retrieval should be delayed, and that donor management should be continued. However,

Table 1 Blood biochemical parameters of the 26-year-old brain-dead donor.

Parameters	Days before donor retrieval									Day of retrieval
	30 days	14 days	7 days	6 days	5 days	4 days	3 days	2 days	1 day	
ALT, U/L	128	107	125	158	203	212	180	144	100	84
AST, U/L	227	135	216	410	437	315	183	88	75	61
TBIL, mg/dL	1.11	9.85	13.71	14.03	13.46	14.03	9.64	6.05	5.46	4.88
DBIL, mg/dL	0.57	5.97	8.98	9.02	8.65	8.79	6.06	3.58	3.02	2.63
GGT, U/L	37	51	52	24	21	26	27	26	28	30
PA, mg/L	NA	NA	63	78	113	156	185	186	186	185
Na^+, mmol/L	158	175	160	156	152	151	151	148	136	133

ALT, alanine transaminase; AST, aspartate aminotransferase; DBIL, direct bilirubin; GGT, γ-glutamyltransferase; PA, prealbumin; Na^+, sodium ion; NA, not applicable; TBIL, total bilirubin.

because the condition of the recipient required urgent attention and the donor was young without underlying liver disease, we decided to retrieve the liver from the donor in advance using the IFLT procedure.

Our patient successfully underwent LTx via the IFLT procedure. The liver of the donor was dark brown (*Figure 1A*), and no hepatic artery variant was documented in the computed tomography angiography examination. The pathological findings of a liver biopsy specimen revealed mild cholestasis and hydropic degeneration, without other abnormal findings (*Figure 1B*). The liver graft had undergone NMP for 440 minutes until allograft revascularization. The perfusate components are reported in our previous article (13). The pH value of the perfusate was in the range of 7.16 to 7.30 at the initial stage and maintained at a normal range (7.35–7.45) after 100 minutes. The lactate levels dropped quickly from 8.3 mmol/L to 0.6 mmol/L within 40 minutes and gradually stabilized at approximately 2.0 mmol/L (*Figure 1C*). Bile production was continuous, and the total volume was approximately 23 mL *(Figure 1D*). The pH values of the bile were higher than detected (>7.8). The flow and pressure of both the portal vein and hepatic artery were acceptable throughout the entire IFLT procedure (*Figure 1E* and *F*). The partial pressure of oxygen (pO_2) was stabilized at approximately 250 mmHg, and the partial pressure of carbon dioxide (pCO_2) was stabilized at approximately 35 mmHg during the preservation phase (*Figure 1G*). The TBIL, DBIL, ALT, and AST in the perfusate gradually increased and were acceptable at the end of perfusion (4.19 mg/dL, 3.29 mg/dL, 477 U/L, and 1,154 U/L, respectively; *Figure 1H* and *I*). Taken together, these results suggested efficient NMP and transplantable organ viability. The cold ischemic time and warm ischemic time were both 0 minutes. Cavo-caval anastomosis was performed using a piggy-back technique. Reconstruction of the portal vein and hepatic artery were performed in an end-to-end fashion. The duration of LTx was 8 hours 45 minutes, and the anhepatic phase was 68 minutes. The estimated blood loss was approximately 5,500 mL.

The conventional immunosuppressive regimen in our unit comprises basiliximab, calcineurin inhibitors, and mycophenolate mofetil. Hormones are not routinely used in our center. However, because of the slow decline of bilirubin in the early postoperative period, we used a small dose of methylprednisolone. After methylprednisolone use, bilirubin gradually decreased. The donor's CYP3A5*3 (A6986G) genetic locus was AG, and the recipient's corresponding locus was AA. Tacrolimus was first administered on postoperative day (POD) 4 but a therapeutic level was difficult to attain because of a rapid metabolic pattern. Cyclosporine A was used on POD 14, and the concentration was satisfactory. Rapid recovery of blood coagulation function and liver enzymes after surgery was recorded. His graft function continued to improve, and he was discharged with good graft function on POD 22. Unfortunately, he required a stent to treat anastomotic stricture of the common bile duct using endoscopic retrograde cholangiopancreatography on POD 44, and the stent was removed on POD 321. No PRS, AKI, ITBLs, or rejection occurred after surgery. *Figure 2* shows a summary of his clinical course. At follow-up, the recipient showed good allograft function and has enjoyed a good quality of life for more than 1 year and as of the publication of this

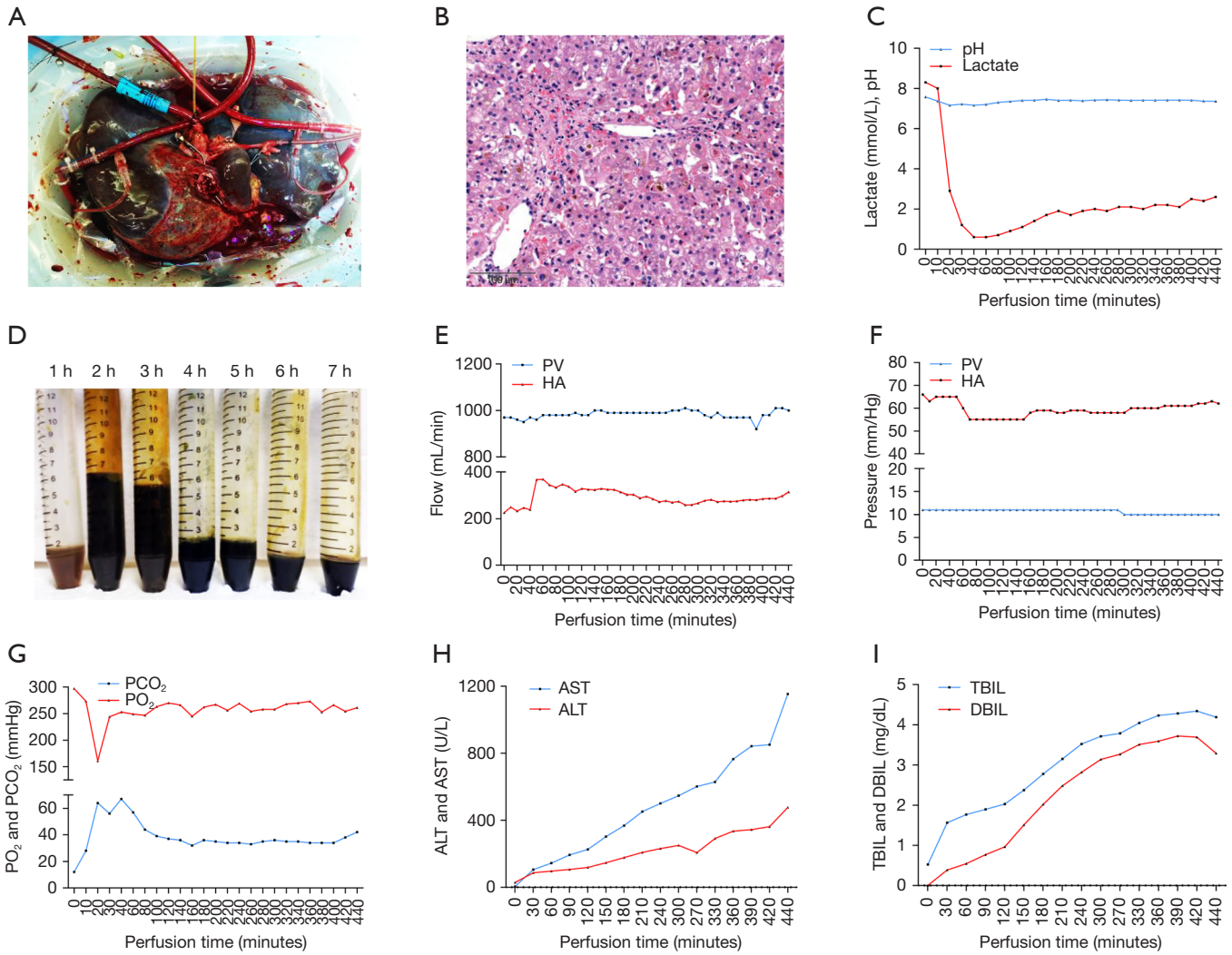

Figure 1 Histopathological and normothermic machine perfusion characteristics of the donor liver. (A) Shows the liver appearance under *ex situ* perfusion; (B) shows histopathological features (hematoxylin-eosin stain, 200×); (C) shows pH values and lactate levels in the perfusate; (D) shows bile production; (E and F) show the flow rates and pressure of the hepatic artery (HA)/portal vein (PV); (G, H, and I) show the O_2 and CO_2 tension and liver function tests [alanine transaminase (ALT), aspartate aminotransferase (AST); total bilirubin (TBIL), direct bilirubin (DBIL)] in the perfusate.

paper.

All the procedures in the studies involving human participants were performed in accordance with the Helsinki Declaration (as revised in 2013), and this study was approved by the ethics committee of The First Affiliated Hospital, Sun Yat-sen University {no. [2019]037}. Written informed consent was obtained from the patient for the publication of this article. The organ used in this study was procured from a brain-dead volunteer donor with written informed consent from all the directive family members.

Discussion

ECD allografts are gradually being accepted for transplantation because of the increasing demand for donor organs. Despite the beneficial effect on reducing wait times, the use of ECD allografts has also been associated with lower post-transplant outcomes caused by their susceptibility to IRI and subsequent decreased functional recovery (14). Although no unified criteria exists for the definition of ECD or marginal livers, steatosis, age, serum sodium, the ICU stay time, and serum bilirubin are frequently adopted

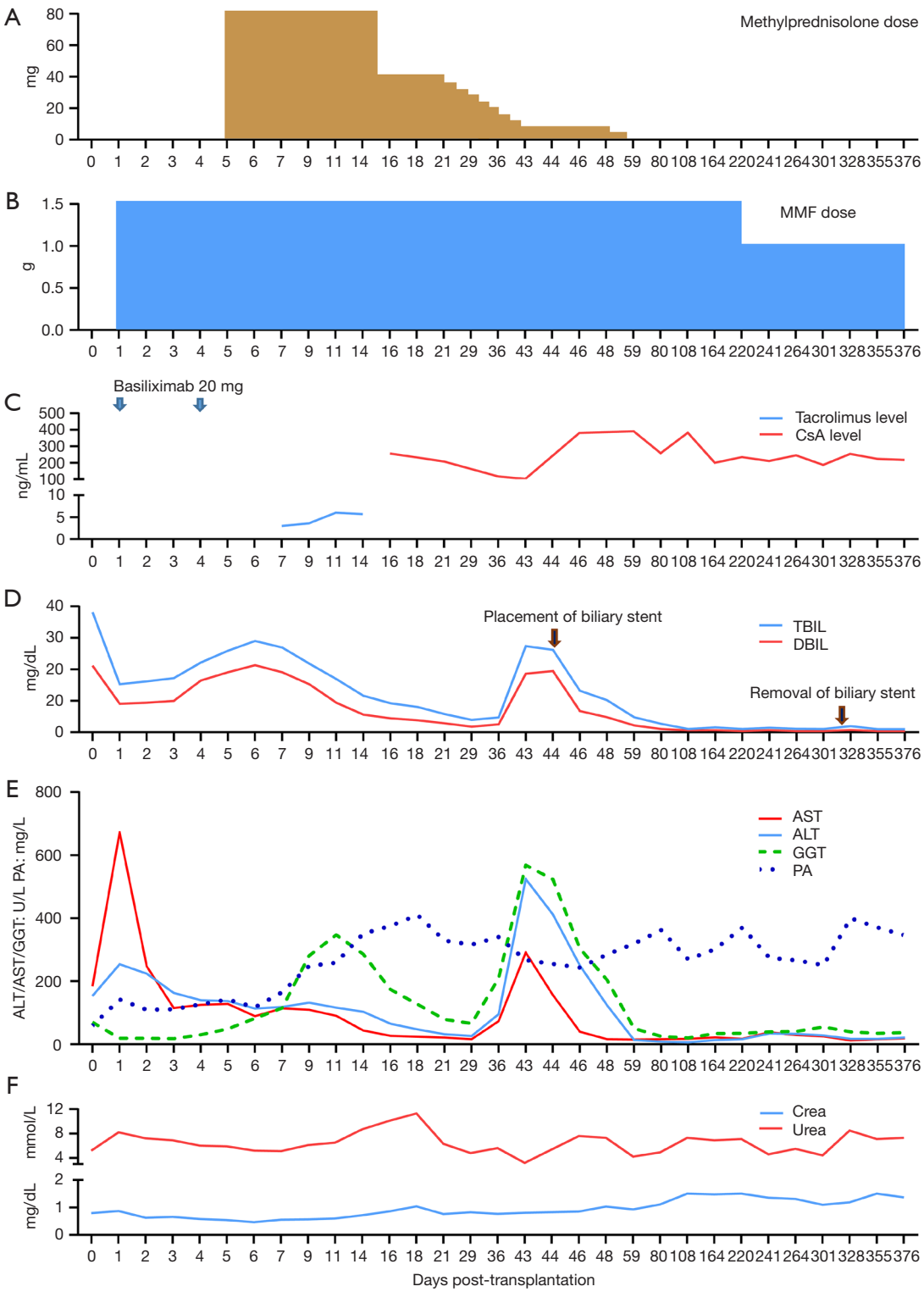

Figure 2 Posttransplant course of the recipient who received a hyperbilirubinemia donor liver during follow-up. (A, B, C, and D) show the methylprednisolone, mycophenolate mofetil (MMF), basiliximab dose, and tacrolimus/cyclosporine A (CsA) levels. (D, E, and F) show the changes in the total bilirubin (TBIL), direct bilirubin (DBIL), alanine transaminase (ALT), aspartate aminotransferase (AST), γ-glutamyl transpeptidase (GGT), prealbumin (PA), creatinine (Crea), and urea.

parameters to evaluate the organ utilization risk at the various transplant centers (15). According to the latest Eurotransplant manual (version 5.0 January 30, 2017, https://www.eurotransplant.org/patients/eurotransplant-manual/), donors with a serum bilirubin level >3.0 mg/dL are considered to be "marginal donors". In more extreme situations, Czerwiński *et al.* reported that livers with a bilirubin level >2 mg/dL from alcohol abuse donors might not be suitable for transplantation because of the high incidence of severe histological changes (16). The donor in our case had a high serum bilirubin level of 4.88 mg/dL on the retrieval day, with a peak serum bilirubin level of 14.03 mg/dL. The ICG clearance test is the most common and convenient approach for the perioperative dynamic evaluation of liver function in the case of hepatectomy and LTx (17). The donor's ICG15 values in our case at –7 days and –1 day before retrieval were far beyond the normal value (<10%). The ICG clearance values may be misguided in the case of hyperbilirubinemia because of the carrier competition (18). Hyperbilirubinemia in our case limited the predictive value of the ICG clearance test. However, the relatively high level of ICG15 still reflected that the donor liver was not in good condition. According to our experience, the donor liver was not suitable at that time for conventional LTx and needed continued maintenance.

We ultimately retrieved and accepted the donation in advance for the following reasons. First, the recipient was diagnosed with ACLF and presented with hepatic coma, severe coagulopathy, and liver disorders, with an urgent need for transplantation. According to previously described diagnostic criteria of ACLF grades, the patient had grade 3 ACLF (liver: serum bilirubin >12 mg/dL; brain: grade IV hepatic encephalopathy; coagulation: INR >2.5). Gustot *et al.* reported that nonremission grade 3 ACLF patients have a very high 28-day transplant-free mortality (96.6%) (19), but no appropriate living donor donation among the family members was found. Over time, he might have lost the chance of transplantation because of the increasing risk of infection, or brain, kidney, and other organ dysfunction. Second, the donor was young without underlying liver disease, and a liver biopsy of the graft showed no abnormal findings other than mild cholestasis and hydropic degeneration. Third, because of the IFLT technique, we could resuscitate the donor liver and assess liver viability *ex situ* under continuous NMP.

NMP has been successfully used to resuscitate ECD or marginal livers, prolong the liver preservation time, and reduce IRI-related complications (11,20,21). The cold ischemia time can be reduced using NMP, while graft ischemia still cannot be fully avoided during the conventional procedure of organ procurement, preparation, and implantation (22). We hypothesized that LTx without graft ischemia might achieve better outcomes. We set up a reliable IFLT procedure after a series of animal experiments supported by NMP and successfully applied it to humans in 2017 (13). During IFLT, the oxygenated blood supply was persistent throughout the whole process of procurement, preservation, and implantation. According to our previous pilot study, the incidence of EAD and the peak levels of liver damage markers significantly declined with the use of IFLT (23). The IFLT procedure has the following advantages: (I) complete avoidance of graft ischemia and IRI, (II) assessment of graft viability before transplantation, and (III) the potential to resuscitate unusable grafts *ex situ*, ameliorating graft damage and enabling subsequent transplantation. Livers were considered transplantable if they met at least 2 of the following criteria during *ex situ* NMP (24): (I) metabolized lactate ≤2.5 mmol/L within 4 hours from the start of the perfusion; (II) bile production; (III) a pH greater than 7.30 in the perfusate; (IV) stable hepatic artery flow (≥150 mL/min) and portal vein flow (≥500 mL/min); (V) homogeneous graft perfusion with a soft consistency of the parenchyma. Although the graft in this case appeared dark brown and biopsy revealed cholestasis, the perfusion parameters met all the above criteria during NMP. The peak AST and ALT within 7 days post-transplantation were 672 and 254 U/L, respectively, and the INR on POD 7 was 1.22. However, the posttransplant bilirubin level decreased more slowly than expected, and the initial dose of 80 mg of methylprednisolone was used to improve liver function according to our previous randomized controlled trial (25). No IRI-related IBTLs were found after follow-up up to 376 days postoperation. The efficacy and safety of IFLT require more in-depth study, and a randomized controlled trial (ChiCTR1900021158) is ongoing in our center.

Currently, more than 80% of organ donations in our center come from brain-dead donors. Nonetheless, brain death is often accompanied by dramatic pathophysiological changes, which, without proper management, can result in the degeneration of organ function before retrieval (26). Brain-dead patients require aggressive and intensive care from the declaration of brain death until organ retrieval, including sustaining normal temperature, infection control, management of the respiratory/circulatory system, and replacement of hormones (27). A previous study showed that

the incidence of early graft loss in donors with a final serum sodium level >155 mmol/L to be significantly elevated, with early graft survival in liver donors with corrected hypernatremia being unaffected (28). Hypernatremia was present in this donor; however, by restriction of the sodium supply, utilization of vasopressin, and nasal feeding with sterile injection water, the serum sodium was successfully reduced to 133 mmol/L. We speculated that the cause of hyperbilirubinemia might have been due to infection and long-term intravenous nutrition at the local hospital. After enhanced anti-infection and enteral nutrition treatment, the donor's bilirubin dropped gradually. Although the bilirubin level fluctuated before retrieval, we speculated that if the maintenance was continued, the bilirubin should continue to decrease. However, organ retrieval using the IFLT technique is also safe and effective under some circumstances, particularly when the recipient is in a life-threatening situation or vital signs of the donor are difficult to maintain.

In conclusion, we presented a case of successful LTx using a hyperbilirubinemia liver graft with an IFLT procedure. Particular attention should be paid to the use of ECD livers and achieving a balance between whether the donor organ is retrieved or continually maintained.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at http://dx.doi.org/10.21037/atm-20-6296

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form available at http://dx.doi.org/10.21037/atm-20-6296). The authors have no conflicts of interest to declare.

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. All procedures performed in studies involving human participants were in accordance with the Helsinki Declaration (as revised in 2013), and this study was approved by the ethics committee of The First Affiliated Hospital, Sun Yat-sen University {no. [2019]037}. Written informed consent was obtained from the patient for the publication of this article. The organ used in this study was procured from a brain-dead volunteer donor with written informed consent from all the directive family members.

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