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High-Dose Tissue Plasminogen Activator Flush in Donation-after-Cardiac-Death Donors May Mitigate Ischemic Biliary Strictures in Liver Transplantation

To the Editor:

The utilization of donation-after-cardiac-death (DCD) livers remains generally low.[1] Concerns raised by clinicians include inconsistent data on optimal donor characteristics, warm ischemic time, and risks of ischemic cholangiopathy.[2] However, many regions have a substantial gap between available organs and listed patients, so the utilization of all available organs would be of obvious benefit. Strategies to address the perceived liabilities associated with DCD organs could influence their utilization in a positive direction.

In our DCD donor surgical technique, tissue plasminogen activator (tPA) is added to normal saline and used as the initial in situ flush after the requisite no-touch period. In brief, 100 mg of lyophilized tPA is reconstituted in 100 mL of sterile water and then diluted in 1 L of room-temperature normal saline. DCD procurement follows the standard protocol in which the donor is terminally extubated and given 30,000 units of intravenous heparin. After asystole, a 5-minute no-touch period commences after which the patient is declared dead if no resumption of cardiac electrical activity or pulsatility occurs.

The recovery surgeon is then called into the operating room and begins rapid organ retrieval by creating a generous midline incision to gain anterior access to the aorta. The aorta is emergently cannulated, and tPA infusion is begun with concomitant cross-clamping of the thoracic aorta. The abdominal organs are flushed with cold University of Wisconsin (UW) solution until the effluent is almost clear. The organs are removed in the usual fashion.

Through the end of July 2015, we had implanted 8 DCD liver grafts that were procured using this specific technique. The mean donor age was 22 years (range 12-31 years), and the mean donor warm ischemic time was 23 minutes (range, 19-29 min). Mean follow-up after transplant was 204 days (range, 31-460 days). Four recipients who were underserved by Model for End-Stage Liver Disease (MELD) score were transplanted without exception points and had a mean laboratory MELD of 20: 3 patients had ethanol cirrhosis, and 1 patient had hepatitis C cirrhosis. Four patients had MELD exception points (mean 24): 2 patients had hepatocellular carcinoma, and 2 patients had biliary cirrhosis and cholangitis. Of the 8 patients, 7 were primary transplants, and one was a retransplant.

Less than 30 minutes from extubation, all DCD donors were declared dead, and the flush was begun according to our protocol. During implantation of the DCD graft in the recipient, our protocol is to infuse 2 mg tPA into the donor hepatic artery prior to starting the hepatic arterial anastomosis. The mean cold ischemia time was 281 minutes (range, 180-353 minutes). Posttransplant, the peak mean aspartate aminotransferase level was 1,505 U/L, and the peak mean alanine aminotransferase level was 739 U/L in the recipients. The bile ducts were reconstructed with either hepaticojejunostomy (2 patients) or choledochocholedocostomy (6 patients).

Six patients had no posttransplant biliary complications. One patient developed biliary ischemic cholangiopathy that was likely not related to the DCD graft. The patient had normal liver enzymes postoperatively and no evidence of biliary pathology but developed a hepatic artery thrombosis (HAT) 30 days posttransplant, possibly attributable to an infected fluid collection adjacent to the arterial anastomosis. He subsequently developed biliary ischemic changes that required percutaneous biliary intervention. He is currently 9 months posttransplant with a normal bilirubin but with an indwelling percutaneous biliary catheter. We believe the biliary complication in this patient was caused by the HAT and was not related to the DCD graft. Another patient developed a mild extrahepatic biliary anastomotic stricture on imaging 14 days after transplant but had a normal total bilirubin. After endoscopic dilation, this patient has not required any further biliary intervention. He is now 10 months posttransplant with normal liver enzymes.

Our preliminary data offer a potential strategy to increase DCD utilization for select patients. Use of tPA in DCD donors has been reported before,[3] but ours is the first report using high-dose tPA at normothermic temperatures. The dose we use is derived from current accepted dosing guidelines for tPA in patients with acute stroke or myocardial infarction. We believe our protocol may achieve more successful thrombolysis in the biliary tree that may mitigate biliary ischemic injury. This concept expands on the Ochsner Medical Center and Toronto General Hospital collective experience that suggests biliary ischemic strictures in DCD grafts are decreased by administering smaller aliquots of in situ tPA to the hepatic artery before reperfusion during the recipient operation.[4]

More data are needed to confirm and standardize the role of an in situ normothermic tPA flush in DCD donors, especially at the histologic level to assess the biliary canalicular arterioles and capillaries. The most accepted theory regarding the role of tPA was advanced by Hashimoto et al who suggested that tPA promoted thrombolysis of microthrombi in the peribiliary circulation.[3] However, their experience relied on the administration of arterial tPA on the back table at cold preservation temperatures (4°C). Infusion of tPA at physiologic temperatures may facilitate the enzymatic thrombolytic process to occur prior to cold flush with UW solution and reduce the risk of platelet clumping caused by the cold preservation solution.

High-dose normothermic tPA flush may be a viable strategy to reliably reduce ischemic cholangiopathy in DCD donor liver grafts and should be studied in a larger cohort.

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Comment on Effective Management of Trigeminal Neuralgia by Neurostimulation

To the Editor:

I am writing regarding the article ''Effective Management of Trigeminal Neuralgia by Neurostimulation'' that was published in the summer 2015 issue of the *Ochsner Journal*.[1]

In the discussion, the author wrote, ''Another procedure used to treat trigeminal neuralgia is gamma knife radiosurgery, a procedure in which the surgeon directs a beam of electricity at the trigeminal nerve and destroys it.''

Gamma knife radiosurgery is a form of stereotactic radiosurgery that employs radiation from cobalt sources, not electricity. And the procedure is intended to damage the trigeminal nerve—not destroy it.

I believe that this clarification on the mechanism of gamma knife radiosurgery is important for general medical practitioners who are not familiar with all options for trigeminal pain control.

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Author's Reply to Dr Rasskazoff

I would like to thank Dr Rasskazoff for reading our article and making these comments. We do agree that the word electricity was not the appropriate word to use here, but we mentioned in the same statement that it is a radiosurgery approach, so we hope this will not confuse our readers. Regarding whether to use the word damage or destroy, I think our readers will understand the meaning and the intention of the procedure with either word.

Thanks again for making this clarification.

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Comment on The Future of Medical Education: All About Being Connected

To the Editor:

I read with great interest your article titled ''The Future of Medical Education: All About Being Connected'' published in 2012, and it resonated that the medical profession remains in the same place 3 years on.[1] Important, clear, and impactful ideas mentioned by the author still remain to be implemented in the core curricula of medical education. It seems the article remains ahead of the game even now.

The author mentions with great emphasis the need to connect with one another—''among nations, systems, organizations, or individuals''—to ensure we benefit from the latest innovations in healthcare and trends in teaching. But what has changed? The world is even more connected now than before. Today about half the adult population owns a smartphone; by 2020, 80% will.[2] Search engines like Google are overtaking clinicians as a primary symptom checker,[3] and healthcare innovations are spinning out one after the other. But still, the medical school curriculum has made little advancement in the approach to teaching.

There is still no collaboration between institutions, and assessments remain to be benchmarked at an international standard. Why does each university continue to develop individual learning materials when a universal platform and sharing of resources could be the key to success? Online lectures, video tutorials, and simulations not only add educational value but also help save time and resources. Why don't we capitalize on the lightning speed of the internet to collaborate and improve the poorly designed e-modules we currently rely on? At my institution, a new scheme has seen students receiving iPads in the clinical years of training, but there is little content to go with them. Technology these

days is more than capable of producing medical simulations for training purposes, but instead of exploiting these developments, we continue to rely on old-school placements in the hope that we get to see certain surgical procedures. I'm not suggesting technology should replace patient contact or hands-on experience, but we should make the most of the opportunities it can provide to supplement our training. After all, isn't the aim to produce world-class physicians?

The technology is here—but why aren't we using it? If this culture changes, I'm sure that we can completely revolutionize the way in which we train and practice in medicine.

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Erratum

Moiz A, Javed T, Bohorquez H, Bruce DS, Carmody IC, Cohen AJ, Staffeld-Coit C, Luo Q, Loss GE Jr, Garces J. Role of special coagulation studies for preoperative screening of thrombotic complications in simultaneous pancreas-kidney transplantation. *Ochsner J*. 2015 Fall;15(3):272-276. Erratum submitted by authors. Author added to byline.

An author was omitted from the author list for this article. Trevor W. Reichman should be listed as eleventh author. His affiliation is Multi-Organ Transplant Institute, Ochsner Clinic Foundation, New Orleans, LA. His author contributions are conceptualization of the project, collection of the data, and critical review of the drafted manuscript.