Clinical Study
Timing of Hepatic Artery Reperfusion and Biliary Strictures in Liver Transplantation

Ganesh Gunasekaran, Jyoti Sharma, Leandro C. Mosna, Roxana Bodin, and David C. Wolf
Division of Hepatobiliary Surgery and Transplantation, Westchester Medical Center, 100 Woods Road, Valhalla, NY 10595, USA

Correspondence should be addressed to Ganesh Gunasekaran; gunasekarang@wcmc.com

Received 24 June 2013; Revised 2 October 2013; Accepted 2 October 2013

Copyright © 2013 Ganesh Gunasekaran et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

During orthotopic liver transplantation (OLT), biliary tract perfusion occurs with hepatic artery reperfusion (HARP), commonly performed after the portal vein reperfusion (PVRP). We examined whether the average time interval between PVRP and HARP impacted on postoperative biliary strictures occurrence. Patients undergoing OLT from 2007 to 2009 were included if they were ≥18 years old, had survived 3 months postoperatively, and had data for PVRP and HARP. Patients receiving allografts from DCD donors were excluded. Patients were followed for 6 months post-OLT. Seventy-five patients met the study inclusion criteria. Of these, 10 patients had a biliary stricture. There was no statistical difference between those with and without biliary stricture in age, gender, etiology, MELD score, graft survival, and time interval between PVRP and HARP. Ninety percent of patients with biliary stricture had a PVRP-HARP time interval >30 minutes, as opposed to 77% of patients without biliary stricture. However, this was not statistically significant. The cold ischemia time was significantly different between the two groups. Time interval for HARP after PVRP did not appear to affect the development of biliary strictures. However, 30 minutes may be suggested as a critical time after which there is an increase in biliary stricture occurrence.

1. Introduction
Orthotopic liver transplantation (OLT) remains the gold standard for treatment of end-stage liver disease (ESLD) despite advances in medical treatment and management of complications [1]. Surgically, OLT involves heptatectomy followed by implantation. Implantation includes reestablishment of three critical structures: the portal vein, the hepatic artery, and the biliary duct in a sequential fashion. Most often, hepatic artery reperfusion (HARP) occurs after portal vein reperfusion (PVRP) and establishes the blood supply to the bile duct epithelium. Postoperative biliary complications may be attributable to hepatic artery thrombosis or stenosis, technical reasons, ischemia-reperfusion injury, and immunological injury. Most common biliary complications include stricture, leak, biloma, and biliary abscess. These complications can be early, those occurring less than 30 days after OLT, or late, those occurring after 30 days [2].

Biliary complications secondary to long warm ischemia times, independent of vascular compromise, have been reported in the literature specifically in recipients who received livers from donation after cardiac death (DCD) donors [3–6]. Ischemic cholangiopathy has been described in 9–50% of DCD recipients with subsequent increased risk for graft loss, retransplantation, and death [3, 6].

Although the PVRP-HARP interval and its effect on biliary complications have been studied before [7], this study aimed to identify the specific PVRP-HARP time interval that is a “cut off” or safe to perform the arterial anastomosis leading to lower postoperative biliary strictures in OLT. We hypothesized that a longer time interval for HARP may result in increased biliary strictures.

2. Methods
We retrospectively reviewed all patients who underwent OLT from January 2007 to December 2009 through the Organ Transplant Tracking Record after study approval from the Institutional Review Board. We obtained information on all
Table 1: Descriptive characteristics of patients with and without biliary strictures undergoing OLT from 2007 to 2009.

| Variable                            | OLT without biliary strictures (𝑁 = 65) | OLT with biliary strictures (𝑁 = 10) | 𝑃 value |
|-------------------------------------|----------------------------------------|-------------------------------------|---------|
| Age, years, mean ± sd (range)       | 55.0 ± 11.3 (18.0–75.0)                | 55.0 ± 9.9 (37.0–70.0)              | 0.99    |
| Male, % (𝑁)                         | 72.3 (47)                               | 80.0 (8)                            | 0.60    |
| Etiology, % (𝑁)                     |                                        |                                     |         |
| HCC                                 | 27.7 (18)                               | 30.0 (3)                            | 0.57    |
| ALF/fulminant                        | 4.6 (3)                                 | 10.0 (1)                            | 0.44    |
| HCV/ETOH                             | 4.6 (3)                                 | 10.0 (1)                            | 0.44    |
| HCV                                 | 21.5 (14)                               | 20.0 (2)                            | 0.63    |
| HBV                                 | 3.1 (2)                                 | 0.0 (0)                             | 0.75    |
| PSC                                 | 3.1 (2)                                 | 0.0 (0)                             | 0.75    |
| NASH                                 | 3.1 (2)                                 | 0.0 (0)                             | 0.75    |
| Cryptogenic                          | 10.8 (7)                                | 20.0 (2)                            | 0.34    |
| MELD, mean ± sd (range)             | 21.4 ± 10.5 (6.0–44.0)                  | 24.3 ± 12.7 (6.0–48.0)              | 0.42    |
| Graft survival, months, mean ± sd (range) | 24.9 ± 9.3 (3.0–45.0)                  | 24.9 ± 9.6 (12.0–40.0)              | 0.99    |
| Alive, % (𝑁)                        | 86.2 (56)                               | 90.0 (9)                            | 0.74    |
| PVRP-HARP, minutes, mean ± sd (range) | 48 ± 29 (10–189)                      | 50 ± 26 (26–119)                    | 0.81    |
| Warm ischemia time (WIT; minutes) mean ± sd (range) | 41.3 ± 7.8 (20–60)                  | 46.8 ± 12.2 (36–69)                 | 0.06    |
| Cold ischemia time (CIT; minutes) mean ± sd (range) | 407.9 ± 126.6 (38–756)                 | 501.5 ± 125.9 (277–631)             | 0.03*   |

*Statistically significant.
The average PVRP-HARP time was 50 minutes for 10 patients with biliary strictures. Figure 1 displays the range of PVRP-HARP time intervals in patients with biliary strictures. Most PVRP-HARP time intervals were larger than 30 minutes (only 1 patient had a PVRP-HARP time interval less than 30 minutes) (Figure 1).

Three categories of PVRP-HARP time intervals were compared between patients with and without biliary strictures including 30 minutes, 48 minutes (the average PVRP-HARP time interval of all OLT), and 1 hour (Table 2). Nine of 10 (90%) patients with biliary strictures had a PVRP-HARP time interval $>30$ minutes, as opposed to 50 of 65 (77%) patients without biliary strictures. However, this was not statistically significant. The cold ischemia time was significantly different between the two groups ($P = 0.03$).

### 4. Discussion

Warm ischemia time is the duration the liver is removed from ice until it is reperfused with recipient blood. During warm ischemia time, the liver is susceptible to both ischemia and eventually reperfusion injury [8]. Although initial hypothermia halts metabolism, slow depletion of cellular energy stores occurs and rewarming at time of reimplantation causes an increase metabolic demands without oxygen and nutrients, leading to structural and functional cellular defects [8]. Thus, due to this accelerated cellular damage during rewarming, a relatively short period of warm ischemia is more harmful to cells than a longer cold ischemia time [8]. One population in which the effect of warm ischemia has been widely studied is the DCD population.

DCD is the fastest growing source of transplanted livers in the US [3]. The first reports of DCD organ procurement were published in 1995 by University of Pittsburgh [9] and Madison, WI [10]. DCD can be either uncontrolled or controlled [4, 11]. In the former patients have unexpected cardiopulmonary arrest and/or unsuccessful resuscitation, and in the latter they undergo planned withdrawal of ventilatory and organ-perfusion support most often in the operating room [4, 11]. Uncontrolled DCD is associated with a severe ischemic injury resulting in inferior recipient outcomes [11]. Initial enthusiasm for DCD was tempered by the less favorable outcomes compared with DBD. Currently, most centers accept controlled DCD livers with their own selection criteria.

With improvements in organ selection, retrieval, preservation, and implantation techniques, biliary complications have dramatically reduced since the 1970s. However, biliary complications still occur 10–30% of OLT, resulting in death for 10% of patients [2, 17–23]. The most common biliary complications are leaks and strictures, but sphincter of Oddi dysfunction, hemobilia, and biliary obstruction from cystic duct mucocele, stones, sludge, or casts are also possible [17, 24, 25]. Similar to other study findings [2], our biliary strictures were primarily treated with ERCP and stenting. Postintervention, our patients did well and likely have a long-term success rate of $>50–70\%$ [26–31].

This study examined the time interval between PVRP and HARP to determine its effect on postoperative biliary strictures in DBD OLT. We found that the length of the interval between PVRP-HARP did not impact the incidence of biliary strictures up to 6 months after OLT. Moreover, none of our 10 patients with biliary strictures had ischemic cholangiopathy, which has been reported in up to 50% of DCD recipients [4, 6, 11–16].

With improvements in organ selection, retrieval, preservation, and implantation techniques, biliary complications have dramatically reduced since the 1970s. However, biliary complications still occur 10–30% of OLT, resulting in death for 10% of patients [2, 17–23]. The most common biliary complications are leaks and strictures, but sphincter of Oddi dysfunction, hemobilia, and biliary obstruction from cystic duct mucocele, stones, sludge, or casts are also possible [17, 24, 25]. Similar to other study findings [2], our biliary strictures were primarily treated with ERCP and stenting. Postintervention, our patients did well and likely have a long-term success rate of $>50–70\%$ [26–31].

This study examined the time interval between PVRP and HARP to determine its effect on postoperative biliary strictures in DBD OLT. We found that the length of the interval between PVRP-HARP did not impact the incidence of biliary strictures up to 6 months after OLT. Moreover, none of our 10 patients with biliary strictures had ischemic cholangiopathy, which has been reported in up to 50% of DCD recipients [4, 6, 11–16]. This may be due to the physiological differences (i.e., longer warm ischemia) in DCD versus DBD organ procurement. Animal models have indicated that dual vessel reperfusion (both vein and artery reperfused at the same time) has higher bile flow and biliary cholesterol than single reperfusion (vein only), leading to better liver function in the former [32]. Our study implies that at least
in terms of biliary complication dual vessel reperfusion is not crucial. Also, variation in timing of hepatic artery preparation (i.e., prior to implantation, after implantation and PVRP or a combination) likely does not affect biliary stricture occurrence postoperatively. Interestingly, almost all our patients with a biliary stricture had a PVRP-HARP time above 30 minutes, although not statistically significant this may be clinically significant with 30 minutes being a critical time after which there is an increase in biliary stricture development.

In our study, longer warm and cold ischemia time, especially the latter, were seen in patients with biliary strictures. These findings are consistent with other studies in DCD OLT, where cold and warm ischemia time were risk factors for predicting postoperative biliary complications [33]. We attempted to determine in this study whether other time-sensitive factors (i.e., PVRP-HARP time interval) impact the development of biliary strictures.

There are some limitations to our study. First, of all the possible OLT patients available for this study, 160, only 75 were met the inclusion criteria. A significant number of these patients were excluded because they lacked PVRP and HARP data values, or the values were not recorded correctly. This was particularly true in the first year of our study, 2007. Secondly, our small sample size prevented the study from having enough power to find any statistical significance in our results. Finally, the cause of biliary strictures in our subjects could be multifactorial, and the retrospective nature of this study further prevents us from drawing any temporal conclusions of causality or generalizing our results to other liver transplant populations. Despite these limitations, this study does give us insight with regard to timing of hepatic artery reperfusion and OLT outcomes.

5. Conclusion

The length of the time interval for HARP after PVRP did not appear to affect the development of biliary strictures. On the other hand, the cold ischemia time did appear to be significant, in accordance with the previous literature [7, 33]. Although no statistically significant difference in PVRP-HARP time was found between the groups with and without biliary strictures, it is possible to suggest a potential critical time of 30 minutes based on the observation that 9 out of 10 biliary strictures occurred when the PVRP-HARP interval was greater than that time. Larger prospective randomized studies with longer follow-up time are needed to determine if the PVRP-HARP time interval impacts postoperative biliary strictures development.

Abbreviations

| Abbreviation | Definition |
|--------------|------------|
| DBD | Donation after brain death |
| DCD | Donation after cardiac death |
| ERCP | Endoscopic retrograde cholangiopancreatography |
| ESLD | End-stage liver disease |
| HARP | Hepatic artery reperfusion |
| OLT | Orthotopic liver transplantation |
| PVRP | Portal vein reperfusion |

References

[1] M. Feldman, L. S. Friedman, and L. J. Brandt, “Liver transplantation,” in Sleisenger and Fordtran’s Gastrointestinal and Liver Disease, vol. 2, chapter 95, Saunders, Philadelphia, Pa, USA, 9th edition, 2010.
[2] M. Wojcicki, P. Milikiewicz, and M. Silva, “Biliary tract complications after liver transplantation: a review,” Digestive Surgery, vol. 25, no. 4, pp. 245–257, 2008.
[3] D. J. Reich and J. C. Hong, “Current status of donation after cardiac death liver transplantation,” Current Opinion in Organ Transplantation, vol. 15, no. 3, pp. 316–321, 2010.
[4] D. J. Reich, D. C. Mulligan, P. L. Abt et al., “ASTS recommended practice guidelines for controlled donation after cardiac death organ procurement and transplantation,” The American Journal of Transplantation, vol. 9, no. 9, pp. 2004–2011, 2009.
[5] H. P. Grewal, D. L. Willingham, J. Nguyen et al., “Liver transplantation using controlled donation after cardiac death donors: an analysis of a large single-center experience,” Liver Transplantation, vol. 15, no. 9, pp. 1028–1035, 2009.
[6] A. I. Skaro, C. L. Jay, T. B. Baker et al., “The impact of ischemic cholangiopathy in liver transplantation using donors after cardiac death: the untold story,” Surgery, vol. 146, no. 4, pp. 543–553, 2009.
[7] M. Cag, M. Audet, A. C. Saouli et al., “Does arterialisation time influence biliary tract complications after orthotopic liver transplantation?” Transplantation Proceedings, vol. 42, no. 9, pp. 3630–3633, 2010.
[8] K. J. Halazun, A. Al-Mukhtar, A. Aldouri, S. Willis, and N. Ahmad, “Warm ischemia in transplantation: search for a consensus definition,” Transplantation Proceedings, vol. 39, no. 5, pp. 1329–1331, 2007.
[9] A. Casavilla, C. Ramirez, R. Shapiro et al., “Liver and kidney transplantation from non-heart beating donors: the Pittsburgh experience,” Transplantation Proceedings, vol. 27, no. 1, pp. 710–712, 1995.
[10] A. M. D’Alessandro, R. M. Hoffmann, S. J. Knechtli et al., “Successful extrarenal transplantation from non-heart-beating donors,” Transplantation, vol. 59, no. 7, pp. 977–982, 1995.
[11] D. P. Foley, L. A. Fernandez, G. Leverson et al., “Donation after cardiac death: the University of Wisconsin experience with liver transplantation,” Annals of Surgery, vol. 242, no. 5, pp. 724–731, 2005.
[12] P. Abt, M. Crawford, N. Desai, J. Markmann, K. Olthoff, and A. Shaked, “Liver transplantation from controlled non-heartbeating donors: an increased incidence of biliary complications,” Transplantation, vol. 75, no. 10, pp. 1659–1663, 2003.
[13] M. E. de Vera, R. Lopez-Solis, I. Dvorchik et al., “Liver transplantation using donation after cardiac death donors: long-term follow-up from a single center,” The American Journal of Transplantation, vol. 9, no. 4, pp. 773–781, 2009.
[14] A. Maheshwari, W. Maley, Z. Li, and P. J. Thuluvath, “Biliary complications and outcomes of liver transplantation from donors after cardiac death,” Liver Transplantation, vol. 13, no. 12, pp. 1645–1653, 2007.
[15] S. Fujita, S. Mizuno, T. Fujikawa et al., “Liver transplantation from donation after cardiac death: a single center experience,” Transplantation, vol. 84, no. 1, pp. 46–49, 2007.
[16] D. J. Reich, “Non-heart-beating donor organ procurement,” in Atlas of Organ Transplantation, A. Humar, W. D. Payne, and A. J. Matas, Eds., pp. 23–33, Springer, London, UK, 2006.
[17] F. Greif, O. L. Bronsther, D. H. van Thiel et al., “The incidence, timing, and management of biliary tract complications after orthotopic liver transplantation,” Annals of Surgery, vol. 219, no. 1, pp. 40–45, 1994.

[18] D. J. Verran, S. K. Asfar, C. N. Ghent, D. R. Grant, and W. J. Wall, “Biliary reconstruction without T tubes or stents in liver transplantation: report of 502 consecutive cases,” Liver Transplantation and Surgery, vol. 3, no. 4, pp. 365–373, 1997.

[19] P. Neuhaus, G. Blumhardt, W. O. Bechstein, R. Steffen, K. Platz, and H. Keck, “Technique and results of biliary reconstruction using side-to-side choledochocholedochostomy in 300 orthotopic liver transplants,” Annals of Surgery, vol. 219, no. 4, pp. 426–434, 1994.

[20] T. P. O’Connor, W. D. Lewis, and R. L. Jenkins, “Biliary tract complications after liver transplantation,” Archives of Surgery, vol. 130, no. 3, pp. 312–317, 1995.

[21] J. M. Rabkin, S. L. Orloff, M. H. Reed et al., “Biliary tract complications of side-to-side without T tube versus end-to-end with or without tt tube choledochocholedochostomy in liver transplant recipients,” Transplantation, vol. 65, no. 2, pp. 193–199, 1998.

[22] B. R. Davidson, R. Rai, T. R. Kurzawinski et al., “Prospective randomized trial of end-to-end versus side-to-side biliary reconstruction after orthotopic liver transplantation,” The British Journal of Surgery, vol. 86, no. 4, pp. 447–452, 1999.

[23] T. H. Welling, D. G. Heidt, M. J. Englesbe et al., “Biliary complications following liver transplantation in the model for end-stage liver disease era: effect of donor, recipient, and technical factors,” Liver Transplantation, vol. 14, no. 1, pp. 73–80, 2008.

[24] J. O. Colonna II, A. Shaked, A. S. Gomes et al., “Biliary strictures complicating liver transplantation: incidence, pathogenesis, management, and outcome,” Annals of Surgery, vol. 216, no. 3, pp. 344–352, 1992.

[25] R. J. Stratta, R. P. Wood, A. N. Langnas et al., “Diagnosis and treatment of biliary tract complications after orthotopic liver transplantation,” Surgery, vol. 106, no. 4, pp. 675–684, 1989.

[26] B. Y. Tung and M. B. Kimmey, “Biliary complications of orthotopic liver transplantation,” Digestive Diseases, vol. 17, no. 3, pp. 133–144, 1999.

[27] S. Jagannath and A. N. Kalloo, “Biliary complications after liver transplantation,” Current Treatment Options in Gastroenterology, vol. 5, no. 2, pp. 101–112, 2002.

[28] B. Macfarlane, B. Davidson, J. S. Dooley et al., “Endoscopic retrograde cholangiography in the diagnosis and endoscopic management of biliary complications after liver transplantation,” European Journal of Gastroenterology and Hepatology, vol. 8, no. 10, pp. 1003–1006, 1996.

[29] A. F. Rossi, C. Grosso, G. Zanasi et al., “Long-term efficacy of endoscopic stenting in patients with stricture of the biliary anastomosis after orthotopic liver transplantation,” Endoscopy, vol. 30, no. 4, pp. 360–366, 1998.

[30] R. V. Mahajani, S. J. Cotler, and M. F. Uzer, “Efficacy of endoscopic management of anastomotic biliary strictures after hepatic transplantation,” Endoscopy, vol. 32, no. 12, pp. 943–949, 2000.

[31] D. A. Schwartz, B. T. Petersen, J. J. Poterucha, and C. J. Gostout, “Endoscopic therapy of anastomotic bile duct strictures occurring after liver transplantation,” Gastrointestinal Endoscopy, vol. 51, no. 2, pp. 169–174, 2000.

[32] D. P. Foley, R. Ricciardi, A. N. Traylor et al., “Effect of hepatic artery flow on bile secretory function after cold ischemia,” The American Journal of Transplantation, vol. 3, no. 2, pp. 148–155, 2003.

[33] M. Gastaca, “Biliary complications after orthotopic liver transplantation: a review of incidence and risk factors,” Transplantation Proceedings, vol. 44, no. 6, pp. 1545–1549, 2012.