Hypothermic perfusion with retrograde outflow during right hepatectomy is safe and feasible

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Background. *In situ hypothermic perfusion during liver resection performed under vascular inflow occlusion decreases hepatic ischemia-reperfusion injury, but technical limitations have restricted its widespread use. In situ hypothermic perfusion with retrograde outflow circumvents these impediments and thus could extend the applicability of in situ hypothermic perfusion. The safety and feasibility of in situ hypothermic perfusion with retrograde outflow were analyzed in selected patients undergoing right (extended) hepatectomy and compared to intermittent vascular inflow occlusion, the gold standard method, in this randomized pilot study.*

Methods. *Patients were first screened for parenchymal liver disease (exclusion criteria: steatosis ≥30%, cirrhosis, or cholestasis). Study participants were randomized intraoperatively to undergo in situ hypothermic perfusion with retrograde outflow (n = 9) or intermittent vascular inflow occlusion (n = 9). The target liver core temperature during in situ hypothermic perfusion with retrograde outflow was 28°C. The primary end point was ischemia-reperfusion injury (expressed by peak postoperative transaminase levels). Secondary outcomes included functional liver regeneration (assessed by hepatobiliary scintigraphy) and clinical outcomes.*

Results. *Peak transaminase levels, total bilirubin, and the international normalized ratio were similar between both groups, although a trend toward more rapid normalization of bilirubin levels was noted for the in situ hypothermic perfusion with retrograde outflow group. Functional liver regeneration as evaluated by hepatobiliary scintigraphy was improved on postoperative day 3 following in situ hypothermic perfusion with retrograde outflow but not after intermittent vascular inflow occlusion. Furthermore, in situ hypothermic perfusion with retrograde outflow (requiring continuous ischemia) was comparable to intermittent vascular inflow occlusion for all clinical outcomes, including postoperative complications and hospital stay.*

Conclusion. *The use of in situ hypothermic perfusion with retrograde outflow appears to be safe and feasible in selected patients with healthy liver parenchyma and may benefit early functional liver regeneration. Future applications of in situ hypothermic perfusion with retrograde outflow include patients with damaged liver parenchyma who would require major hepatic resection with a prolonged vascular inflow occlusion duration. (Surgery 2017;■:■-■.)*

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LIVER RESECTION remains the cornerstone of the curative treatment of primary and secondary hepatic malignancies. Although outcomes after hepatic operation have improved substantially over the past decades, major liver resection (ie, ≥3 Couinaud segments[1]) is still associated with

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considerable morbidity and mortality rates.[2,3] Nevertheless, the boundaries of liver operations are continuously expanding, as is reflected by recent developments such as ALPPS (associating liver partition with portal vein ligation for staged hepatectomy),[4] the advent of laparoscopic liver resection,[5] and the increasing number of major resections being performed.[6] Moreover, these techniques are performed increasingly in patients affected by parenchymal liver disease, such as cirrhosis or steatosis,[7] or in patients with predamaged livers due to neoadjuvant chemotherapy.

In contrast to these operative techniques and criteria of patient eligibility, the risk factors for postoperative complications have remained largely unchanged.[6,8] In addition to parenchymal status per se,[6,8,9] intraoperative blood loss and transfusion requirement strongly augment the risk for postoperative morbidity[6,9] and mortality.[8,9] Vascular inflow occlusion (VIO) is, therefore, used either on demand or routinely during major liver resections to control intraoperative blood loss. Notwithstanding its efficacy in decreasing intraoperative blood loss,[10] VIO inadvertently induces hepatic ischemia-reperfusion (IR) injury as a side effect.[11]

Inasmuch as IR injury negatively affects postoperative liver function[12] and thereby increases the risk of postoperative liver failure,[13,14] much effort has been dedicated to the search for an intervention that improves outcomes in patients subjected to IR injury.[15] In that regard, a modest yet promising body of evidence demonstrates that hypothermic perfusion during liver resection is a feasible strategy to combat IR injury.[16-22]

Although an established aspect of organ preservation in the field of transplantation, the use of hypothermia during liver resection is considerably more complex. In this setting, the desired decrease of liver core temperature is achieved best via in situ hypothermic perfusion (IHP), that is, perfusing the organ with a chilled crystalloid or organ preservation solution. Application of IHP during liver resection has long been limited by the need for antegrade drainage of the perfusate. This requires clamping of the vena cava in addition to VIO (ie, total hepatic vascular exclusion) or a caval flow-preserving ante situm approach to enable effusion of the perfusate through a cavotomy[16,18,22] or via the hepatic veins,[19,20] respectively. Because of the burden and risks associated with both techniques,[20,23] the use of IHP has been restricted to selected patients undergoing highly complex procedures.

To overcome these limitations, a new technique for IHP with preservation of caval flow and retrograde perfusate drainage (IHP-R) was recently reported.[24] In the work presented here, the safety and feasibility of IHP-R were investigated next to intermittent VIO, the gold standard method,[25] in a randomized pilot study with as primary end point hepatic IR injury expressed as peak transaminase levels. Secondary outcomes included the regeneration of postoperative liver function, intraoperative blood loss, and postoperative complications. A total of 18 patients without parenchymal liver disease scheduled for a (extended) right hepatectomy were allocated randomly to undergo IHP-R or intermittent VIO during parenchymal transection.

PATIENTS AND METHODS

Patient inclusion and allocation. The study was approved by an institutional review board and was registered at https://clinicaltrials.gov (NCT01499979). All patients scheduled to undergo an elective right or extended right hepatectomy, defined as any nonanatomical resection encompassing more than 4 Couinaud segments, were considered for participation. Additional inclusion criteria were age ≥18 years, body mass index ≤35 kg/m^2, American Society of Anesthesiologists score I–III, and not having undergone liver surgery in the previous year.

Written informed consent was obtained prior to any study-specific procedure. Patients were screened for the presence of hepatopathologies known to affect outcomes following liver surgery, that is, moderate-to-severe steatosis, cirrhosis, and cholestasis, as described previously.[24] Those who did not meet the screening criteria were excluded from participation in the study. After intraoperative assessment of resectability and feasibility of IHP-R, participants were allocated randomly to the IHP-R (n = 9) or intermittent VIO (n = 9) group using sequentially labeled envelopes generated by an independent third party. The randomization sequence was obtained using GraphPad QuickCalcs (GraphPad Software, La Jolla, CA). All patients were blinded for allocation. An interim analysis was performed by the institutional review board following inclusion and treatment of 10 patients.

Surgical technique. A detailed technical description of IHP-R has been reported previously.[24] Following full mobilization of the right liver lobe, the right hepatic artery and right portal vein branch were dissected, clamped, and cut. Next,