https://doi.org/10.1016/j.hpb.2018.12.012 HPB

ORIGINAL ARTICLE

Complex liver resection under hepatic vascular exclusion and hypothermic perfusion with versus without veno-venous bypass: a comparative study

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Abstract

Background: While hypothermic liver perfusion has been shown to improve parenchymal tolerance to complex resections in patients requiring prolonged hepatic vascular exclusion (HVE), the benefit of associated veno-venous bypass (VVB) in this setting remains poorly evaluated.

Methods: All patients undergoing liver resection requiring HVE and hypothermic liver perfusion for at least 55 min between 2006 and 2017 were retrospectively reviewed. Perioperative outcomes were compared between patients with (VVB+) or without VVB (VVB−).

Results: Twenty-seven patients were analyzed, including 13 VVB+ and 14 VVB−. Median HVE duration was similar in VVB+ and VVB− patients (96 vs. 75 min, respectively). VVB+patients had longer operative time (460 vs. 375 min, $p = 0.023$) but less blood loss ($p = 0.010$). Five (19%) patients died postoperatively from liver failure or sepsis, without difference between groups. Postoperative major morbidity rate was similar between VVB+ and VVB− patients (30% vs. 50%, respectively) such as rates of liver failure, haemorrhage, renal insufficiency and sepsis, but VVB− patients experienced more respiratory complications (64% vs. 15%, $p = 0.012$).

Conclusion: During liver resection under HVE and hypothermic liver perfusion, use of VVB allows for reducing blood loss and postoperative respiratory complications. VVB should be recommended in case of liver resection with prolonged HVE.

Received 21 September 2018; accepted 28 December 2018

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Introduction

Complex hepatic resection for lesions involving hepatocaval confluence or inferior vena cava (IVC) may require total hepatic vascular exclusion (HVE) to improve tumour accessibility and resectability, limit intraoperative blood loss and red blood cells transfusions, and reduce the time of transection.[1–4] HVE includes occlusion of hepatic inflow (clamping of the portal triad) and outflow (clamping of supra- and infra-hepatic IVC) and has already been widely reported in the literature.[5]

HVE leads to a marked reduction in venous return and cardiac output up to 40–60%. The hemodynamic response attempts to alleviate the consequences of reduced venous return by an increase in heart rate and systemic vascular resistance. In adult patients, this response is often insufficient to maintain adequate blood pressure for long periods. This situation demands a close

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This work has been presented at the 13th IHPBA World Congress (Geneva, Switzerland) in September 2018.

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Please cite this article as: Navez J et al., Complex liver resection under hepatic vascular exclusion and hypothermic perfusion with versus without veno-venous bypass: a comparative study, HPB, https://doi.org/10.1016/j.hpb.2018.12.012

and specific anaesthetic monitoring and intervention. In 10–20% of patients HVE is not well supported and must be interrupted because of hemodynamic instability despite pharmacological intervention.[6–8] While HVE is often better tolerated during orthotopic liver transplantation due to frequent portal hypertension and collateral circulation caused by cirrhosis, a prolonged portal vein clamping on non-cirrhotic liver induces splanchnic congestion, visceral oedema, and a decrease in mesenteric arterial blood flow, promoting intestinal ischemia.[9,10] Therefore, a systemic veno-venous bypass (VVB) can be useful to avoid hemodynamic consequences of the “anhepatic phase”, help the patient to better support a long-time procedure, and release the surgeon from time pressure during a delicate procedure.[11–13]

Ischemic hepatocellular injuries and liver tolerance to HVE depend on the duration of the clamping. Normothermic liver ischemia is usually limited to 60–85 min to avoid significant hepatocellular injuries.[14] By using hypothermia, which provides a protection to the liver and reduces hepatocellular damages, the limit duration of hepatic ischemia can be prolonged to up to 2 h and beyond according to the level of hypothermia.[15] Compared to normothermia, hypothermic liver perfusion is associated with a lower postoperative morbidity and less renal and liver failure when HVE lasts more than 60 min.[16]

To the best of our knowledge, no previous work has evaluated the benefits of VVB, if any, on postoperative outcomes in patients undergoing complex liver resection with hypothermic HVE. The present study aimed to report our experience of HVE and hypothermia during hepatectomy and to compare intraoperative and postoperative outcomes of patients according to the use of VVB.

Material and methods

All patients undergoing liver resection under HVE and hypothermic perfusion of the liver, either using veno-venous bypass (VVB+) or not (VVB−), were retrospectively reviewed. The present study being an observational, noninterventional, retrospective study, neither informed consent nor approval of the ethics committee was required to use data from patients’ records according to French legislation. All data were collected anonymously from medical records only. The decision to use VVB depended upon the operating senior surgeon: OS and OSc systematically used VVB for HVE exceeding 1 h whereas SD never used it. Indications for surgery included either benign or malignant lesions of the liver or the IVC. Patients with HVE during less than 55 min were excluded. Long-lasting HVE ($\geq$ 55 min) was anticipated and expected in case of invasion of IVC and/or caval confluence, planned reconstruction of major hepatic veins, and extremely large lesion.

Preoperative management

To determine the resectability of the hepatic lesion and to exclude extrahepatic disease, all patients underwent a preoperative assessment, including thoraco-abdominal computed tomography (CT), hepatic magnetic resonance imaging (MRI), and biopsy of both tumor and underlying liver when radiological diagnosis was uncertain. All cases were discussed at tumour board meetings, which included surgeons, hepatologists, oncologists, radiologists, and pathologists to assess the eligibility of patients for surgery and the eventual need for neoadjuvant treatment. If the volume of the liver remnant was too small, portal vein embolization was performed in the future resected liver. Patients’ operative risk and comorbidities were evaluated using the American Society of Anesthesiology (ASA) physical score.[17]

Anaesthetic and surgical procedures

Each patient was monitored via a central venous line and an arterial catheter. Central venous pressure was kept low (between 2 and 5 mmHg) before vena cava clamping, and then increased by intravenous fluids filling before HVE. Surgical approach was laparotomy through a J shaped incision or a transverse bilateral subcostal incision. Liver tumors were assessed with intraoperative ultrasonography, as well as their relationships to major vessels, and other hepatic lesions not visualized on preoperative workup were soughed. The liver was completely mobilized until controlling infrahepatic and suprahepatic IVC; collaterals were ligated including the right adrenal vein. The parenchyma was transected by using an ultrasonic aspirator (CUSA Excel, Integra Life Sciences, Plainsboro Township, NJ). Small Glissonian pedicles and hepatic veins of less than 3 mm were sectioned after bipolar coagulation and those larger than 3 mm were cut after clipping or ligation. Intermittent Pringle maneuver was used in case of haemorrhagic transection. When dissection became difficult when approaching the hepatocaval confluence or inferior vena cava, HVE was performed. Vascular exclusion was achieved by first clamping the portal triad following by clamping the infrahepatic IVC and then the suprahepatic IVC. In the group VVB−, hepatic refrigeration was performed by using topical cooling (crushed ice or cold water) and by infusing cold saline solution, Institut Georges Lopez (IGL-1) solution, University of Wisconsin (UW) solution or Custodiol, in the portal vein.[7] In the group VVB+, preparation of venous bypass included placement of cannula into the IVC through the femoral vein and into the superior vena cava through either the internal jugular vein or the axillary vein, ideally using a percutaneous approach under ultrasound guidance.[4] Inferior mesenteric vein, when present, was cannulated to allow for including the portal territory blood flow into the venous bypass circuit. When inferior mesenteric vein was absent, for instance in case of prior left colectomy, the initial portion of the portal vein was used to insert a cannula into the SMV. After initiating HVE, the liver was cooled between 18 and 24 °C, using perfusion of preservation solution (Custodiol or IGL-1) by direct cannulation of the pedicular portal vein and topical cooling. In both group, drainage of the liver perfusate was achieved through a cannula placed in the IVC. Vascular reconstruction was performed if needed, by using preferably autologous graft or peritoneal patch, allogeneic grafts and PTFE

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prosthesis in second and last intention, respectively. Before reperfusion, a solution of Methylene blue was injected into the IVC and portal vein to detect vascular leaks and suture them. The liver was rewarmed with saline solution through the portal vein before unclamping the IVC and hepatic pedicle. Closed-suction drains were left in all patients.

Outcome measurements

After surgery, patients were transferred to the intensive care unit for a minimal duration of 24 h. Laboratory tests including blood count, biochemistry, liver function tests and coagulation tests, were daily performed during the first 5 days. Postoperative surgical complications occurring during the first 30 days were graded using Dindo-Clavien's classification.[18] Only relevant complications requiring a specific treatment (at least Dindo-Clavien grade ≥ 2) were considered.

Statistical analysis

All data were expressed as mean and median values with range. Comparison of continuous variables was made using Student's t test or the Wilcoxon U-test where appropriate. Biological data were normalized by using the Box-Cox transformation and were studied by the generalized estimating equation (GEE). We used chi-square with Cook's correction for dichotomous categorical variables, the chi-square test when comparing more than two categorical variables and Smirnov's test for comparing ordered variables. Two-sided $p \leq 0.05$ was considered statistically significant.

Results

Patients' characteristics

From October 2006 to July 2017, 27 consecutive patients underwent liver resection under HVE with hypothermic portal perfusion of the liver, including 13 VVB+ and 14 VVB−. Patients' baseline characteristics are reported in Table 1. There was no difference in age, sex ratio, BMI and preoperative anesthetic risk. The median diameter of the main tumor at imaging was larger in the VVB− group than in the VVB+group ($p = 0.01$). Indications for surgery included primary liver tumors (n = 10), colorectal or neuroendocrine liver metastasis (n = 8), leiomyosarcoma (n = 2), paraganglioma (n = 1) or benign lesions in 6 (Table 2). No patients had cirrhosis.

At preoperative assessment, the future liver remnant volume was less than 30% of the total liver volume in 5 patients who received preoperative right (n = 4) or left (n = 1) portal vein embolization. Transarterial chemoembolization was performed in 2 patients in each group. Regarding vascular imaging, IVC and/or hepatocaval confluence were invaded or in contact with the tumor in 26 cases; the last patient had a very large intrahepatic cholangiocarcinoma in contact with the portal bifurcation.

Operative characteristics

Median operative time was longer in VVB+ patients (460 min, range 350−600) than in VVB− patients (375 min, range 180−652) ($p = 0.02$), but median HVE time was similar between

Table 1 Patient's characteristics

	Total	Group VVB+	Group VVB−	p value
Number of patients (n)	27	13	14	–
Age (years), median (range)	56 (17–79)	61 (28–72)	53 (17–79)	0.135
Sex ratio: male/female (n)	1.5	1.6	1.3	0.836
BMI (kg/m^2), median (range)	24.1 (18.4–32)	24.1 (20.8–32.0)	24.1 (18.4–31.9)	0.725
ASA score, n (%))				
I - II	26 (96%)	13 (100%)	13 (93%)	0.170
III - IV	1 (4%)	0 (0%)	1 (7%)	
Indication for surgery, n (%)				
Benign	6 (22%)	2 (15%)	4 (29%)	0.430
Malignant	21 (78%)	11 (85%)	10 (71%)	
Maximum tumor size (mm), median (range)	83 (30–230)	70 (30–150)	140 (46–230)	**0.013**
Vascular involvement, n (%)				
IVC	24 (89%)	11 (85%)	13 (93%)	0.516
Hepatic vein(s)	24 (89%)	10 (77%)	14 (100%)	0.077
Portal vein	10 (37%)	4 (31%)	6 (43%)	0.536
Portal vein embolization, n (%)	5 (19%)	4 (31%)	1 (7%)	0.134
Transarterial chemoembolization, n (%)	4 (15%)	2 (15%)	2 (14%)	0.956
Neoadjuvant chemotherapy, n (%)	9 (33%)	6 (46%)	3 (21%)	0.193

Significant results in bold. BMI: body mass index; ASA: american Society of Anesthesiology; IVC: inferior vena cava.

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Table 2 Indications for liver resection

	Total (n = 27)	Group VVB+ (n = 13)	Group VVB−(n = 14)
Malignant tumours			
Colorectal liver metastasis	5 (19%)	3	2
Neuroendocrine liver metastasis	3 (11%)	0	3
Hepatocellular carcinoma	4 (15%)	2	2
Intrahepatic cholangiocarcinoma	4 (15%)	3	1
Hepatocholangiocarcinoma	2 (7%)	1	1
IVC leiomyosarcoma	2 (7%)	1	1
Paraganglioma	1 (4%)	1	0
Benign lesions			
Hepatic adenoma	2 (7%)	0	2
Alveolar echinococcosis	2 (7%)	2	0
Giant cavernous hemangioma	2 (7%)	0	2

IVC: inferior vena cava.

Table 3 Intraoperative outcomes

	Total (n = 27)	Group VVB+ (n = 13)	Group VVB−(n = 14)	p value
HVE time (min), median (range)	86.5	96 (58–160)	75 (57–180)	0.181
Operative time (min), median (range)	405	460 (350–600)	375 (180–652)	**0.023**
Resected segments, n (range)	5 (1–6)	5 (1–6)	5 (2–6)	0.413
Type of resection, n (%)				
Major hepatectomy (≥3 segments)	24 (89%)	11 (85%)	13 (93%)	0.519
Major hepatectomy with caudate lobe	17 (63%)	6 (46%)	11 (79%)	0.088
Vascular reconstruction	10 (37%)	6 (46%)	4 (29%)	0.370
Preservation solution, n (%)				
Saline solution	4 (15%)	0 (0%)	4 (29%)	0.112
Custodiol	14 (52%)	7 (54%)	7 (50%)	
IGL-1	7 (26%)	5 (38%)	2 (14%)	
UW	1 (4%)	0 (0%)	1 (7%)	
Unknown	1 (4%)	1 (8%)	0 (0%)	
Blood loss (mL), median (range)	2238	600 (200–2500)	1750 (200–20000)	**0.010**
RBC transfusion, n units, mean (±SD)	2	2 (±1.8)	5 (±5.4)	0.083

Significant results in bold. HVE: hepatic vascular exclusion; IGL: institute George Lopez; UW: university of Wisconsin; RBC: red blood cells.

groups (Table 3). Major hepatectomy was performed in 89% of patients, including nearly two third of them associated with caudate lobe resection. Vascular reconstruction was performed in 37% of patients (6 in VVB+group, 4 in VVB− group, $p = 0.37$), and included caval anastomosis or replacement ($n = 5$), hepatic vein reimplantation or plasty ($n = 3$), portal vein plasty or anastomosis ($n = 3$); one patient had IVC replacement and portal vein anastomosis. Median overall blood loss was greater in VVB− patients ($p < 0.01$) without significant difference in red blood cells units required for transfusion. An abdominal drainage was left in all patients, except one from VVB+group.

Postoperative outcomes

Severe morbidity rates were comparable between both groups (30% in VV + group, 50% in VVB− group, $p = 0.34$) (Table 4). The rates of liver failure, bile leakage, haemorrhage, renal insufficiency, and sepsis were not different between the two groups but VVB− patients experienced more frequently respiratory complications than VVB+ patients (64% vs. 15%, respectively, $p = 0.01$), including pulmonary atelectasia and acute respiratory distress syndrome, treated by non-invasive ventilation with chest physiotherapy and prolonged mechanical ventilation, respectively. None of those patient with

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Table 4 Postoperative outcomes

	Total (n = 27)	Group VVB+ (n = 13)	Group VVB–(n = 14)	p value
ICU stay (days), median (range)	7	9 (4–30)	4.5 (1–50)	**0.042**
Hospital stay (days), median (range)	17.5	16 (12–59)	18.5 (9–66)	0.349
Severe complications (Dindo-Clavien 3/4), n (%)	9 (40.1%)[a]	3 (30.0%)[a]	6 (50.0%)[a]	0.370
Death, n (%)	5 (18.5%)	3 (23%)	2 (14.3%)	0.582
Types of complications:				
Hepatic complications, n (%)				
Liver failure	4 (14.8%)	2 (15.4%)	2 (14.3%)	0.962
Bile leakage	6 (22.2%)	3 (23%)	3 (21.4%)	0.941
Portal thrombosis	1 (3.7%)	1 (7.7%)	0 (0%)	0.317
Ascites	4 (14.8%)	0 (0%)	4 (28.6%)	**0.043**
Hemorrhage, n (%)	3 (11.1%)	0 (0%)	3 (21.4%)	0.089
Metabolic acidosis, n (%)	8 (29.6%)	3 (23%)	5 (35.7%)	0.503
Digestive complications, n (%)	6 (22.2%)	4 (30.7%)	2 (14.3%)	0.327
Perforation	2	2	0	
Ileus	4	2	2	
Respiratory complications, n (%)	11 (40.7%)	2 (15.4%)	9 (64.3%)	**0.012**
Pleural effusion	2	1	1	
Pneumonia	1	1	1	
ARDS	2	0	2	
Pulmonary atelectasia	4	0	4	
Pleuresia	1	0	1	
Sepsis, n (%)	5 (18.5%)	3 (23%)	2 (14.3%)	0.577
Renal insufficiency, n (%)	4 (14.8%)	2 (15.4%)	2 (14.3%)	0.956

Significant results in bold. ICU: intensive care unit; ARDS: acute respiratory distress syndrome.

[a] Postoperative death excluded in the rate.

respiratory complication had underlying chronic pulmonary or cardiac disease, and all were ASA 1 or 2. One VVB+patient with the mesenteric cannula inserted through the portal vein experienced a portal thrombosis on postoperative day 1, immediately repaired by surgical excision and reanastomosis. No gas embolism was observed in both groups. Five patients (18.5%) died postoperatively, including 4 from liver failure and 1 from septic shock after digestive perforation. Mortality rates were similar in both groups. Evolution of liver tests (including AST, ALT, gammaGT, total bilirubin and prothrombin time) during the five days following the procedure was not significantly different between the two groups (Fig. 1). Liver and renal functions tended to normalize at postoperative day 5. Median postoperative ICU was longer in VVB+group compared to VVB− group (9 days vs. 4.5 days, p = 0.04), but median hospital stay was not different (16 days vs. 18.5 days, p = 0.35), respectively. At final pathology, all preoperative diagnosis were confirmed, except in 2 cases for which the initial diagnosis of intrahepatic cholangiocarcinoma was turned into hepatocholangiocarcinoma.

Discussion

While HVE and hypothermic perfusion have been shown to reduce intraoperative bleeding and improve hepatic tolerance to complex hepatic resection, hemodynamic instability can occur in up to 20% of patients due to a marked reduction in venous return because of IVC clamping. To our best knowledge, the present study is the first comparative study on perioperative outcomes of patients undergoing liver resection under HVE and hypothermic perfusion, according to the use or not of VVB. No difference in postoperative morbidity and mortality was observed between groups, but there was a reduced intraoperative blood loss and postoperative respiratory complications when VVB was used.

Despite many improvements and innovations in surgical techniques, complex liver resections under HVE are not without danger and expose to a high risk of morbidity and mortality. In the present series, the rate of 18.5% is high but comparable to the rate reported in the literature, ranging from 10 to 30%.[3,12,19,20] Most of the deaths in our study were caused by liver failure,

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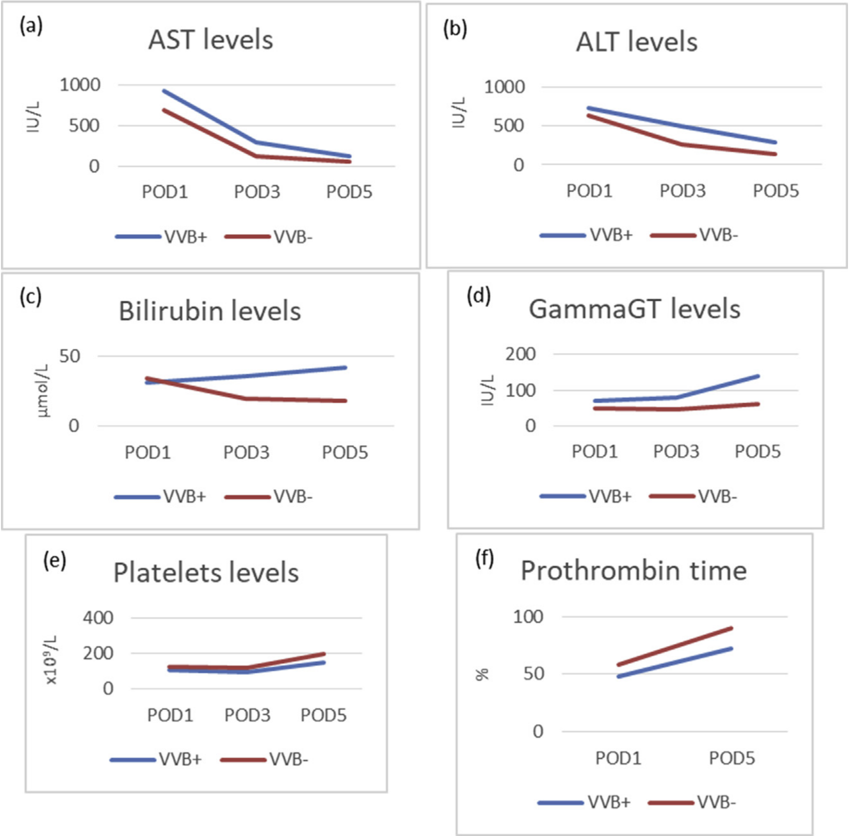

Figure 1 Evolution of postoperative liver function tests at days 1, 3 and 5 in VVB+and VVB – groups: AST levels (a), ALT levels (b), total serum bilirubin levels (c), gammaGT levels (d), platelets levels (e) and prothrombin time (f)

which is the most severe complication, leading to multiorgan failure. Overall, severe postoperative morbidity was 40% and did not differ between groups. However, respiratory complications were more often observed in the group of patients without VVB, including pleural effusion and acute respiratory distress syndrome. Even if we have no explanation for this difference, we hypothesize that a better hemodynamic stability and a lower amount of crystalloid fluid infused to maintain a normal cardiac output in the VVB group, due to a lower amount of blood loss and transfusions (although not always significant), prevent from vascular overload and consequently pulmonary complications.

The risk of developing postoperative failure depends not only upon the duration of liver ischemia, but also on the quality of liver parenchyma and the volume of liver remnant.[21] It is well known that diseased livers, even with steatosis or chemotherapy-associated liver injury, have a reduced tolerance against ischemia and an impaired ability to regenerate after major liver resection.[22,23] In the present study, among the four patients who developed liver insufficiency, two underwent a right extended hepatectomy and two a left extended hepatectomy, including one with a chemotherapy-associated sinusoidal obstruction syndrome. Because of involvement of major vessels, those complex hepatic surgeries often require a major resection of non-tumoral parenchyma that must be taken into consideration as well as underlying liver disease when the procedure is planned.

The use of hypothermic perfusion has been shown to attenuate ischemia-reperfusion injury and hepatocellular damage.[24–26] This protective effect is explained by a decrease in oxygen consumption and metabolic rate due to cooling, which improves hepatocellular viability and attenuates synthesis of proinflammatory proteins during the initial phase of ischemia-reperfusion.[25] Azoulay *et al.* compared postoperative outcomes of patients having HVE with versus without hypothermic portal perfusion.[16] Hypothermia was used when the procedure was planned to last more than 1 h. They found a better tolerance to ischemia in the group with hypothermia, reflected by the difference in the postoperative peak of transaminases, but the rates of postoperative liver failure were not significantly different between the two groups (15% vs. 38% in normothermic group >60 min, p = 0.10). Moreover, the hypothermic HVE group had a lower postoperative morbidity and a better postoperative renal function. In our study, hypothermia was used in all patients, and the major part of the parenchymal transection was performed before HVE to minimize ischemia time. The protective effect of liver hypothermia was observed by the rapid decrease in liver function tests from day 1 to day 5, and we found 14.8% of

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postoperative liver failure rate. In such complex hepatectomies requiring perilous dissection, vascular reconstructions and a prolonged operative time, hypothermic perfusion is mandatory to minimize the risk of hepatic dysfunction and enables to extend the liver ischemia time when necessary.

Duration of HVE has a huge impact on hepatocellular injury. Although some authors reported a clamping time well supported up to 90 min, it has been shown that HVE duration of more than 60 min is associated with higher volumes of transfusion and postoperative complications rates compared to HVE duration of less than 60 min.[16,27] Only HVE of more than 55 min were considered in the present study in order to include all patients with VVB, although this cutoff is a little bit shorter than other series.

The complexity of hepatectomies with major vascular reconstruction for tumors involving the hepatocaval confluence or the IVC may require a long time of HVE, which is not always well supported by patients. First the combination of caval and pedicular clamping dramatically reduces venous return, resulting in a 40–60% decrease in cardiac output.[6] In adult patients, this drop in cardiac output is often associated with a decrease in mean arterial blood pressure that often requires the use of pharmacological support. Additionally, a prolonged clamping of the IVC engenders a renal venous congestion that decreases renal blood flow which, in turn, may promote postoperative kidney dysfunction. Finally, prolonged clamping of the portal vein creates a splanchnic congestion and promotes bacterial translocation. To overcome these major hemodynamic consequences, a specific anaesthetic management is required but is not always sufficient. Clamping of the supracoeliac aorta has been proposed, but worsens renal and intestinal ischemic injuries.[28] The use of VVB for such hepatectomies has been poorly described in the literature, yet it can restore venous return and cardiac output and decrease the risk of renal failure. The protective effect of VVB on kidney function remains however controversial and has only been studied during liver transplantation.[29–31] To avoid portal hypertension and visceral congestion, our technique of VVB in the present study was performed with cannulation of the portal vein through the inferior mesenteric vein.[32] Although we did not observe any difference in postoperative renal, digestive or septic complications in this small retrospective series, we strongly advocate the use of VVB in case of prolonged HVE, hemodynamic intolerance or in patients with underlying poor kidney function, and we encourage the use of VVB in centres performing such complex procedures.

The present study carries a number of limitations. The retrospective design of the study precluded from collecting some hemodynamic, anaesthetic and biological data, which were available only for recent patients and could not be analyzed. Secondly, there may be a selection bias given that the use of bypass was surgeon specific. Finally, the small sample size was accentuated by the selection of only patients with hypothermic perfusion and a HVE superior to 55 min, resulting in possibility of type II error, but that allowed on the other hand, a better homogeneity of the groups regarding complexity of liver resection.

In conclusion, this first comparative study on patients undergoing liver resection under HVE and hypothermic perfusion according to the use of VVB showed a reduction in intraoperative blood loss and postoperative respiratory complications when VVB was used. However, both mortality and overall postoperative morbidity were not different between the two groups. In patients requiring complex liver surgery under HVE exceeding 1 h, we recommend the use of venous bypass.

Acknowledgements

The authors are most grateful to Doctor Francis Zech (Institute of Experimental and Clinical Research, Cliniques Universitaires Saint-Luc, Brussels, Belgium) for statistical analysis.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest

None declared.

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Please cite this article as: Navez J et al., Complex liver resection under hepatic vascular exclusion and hypothermic perfusion with versus without veno-venous bypass: a comparative study, HPB, https://doi.org/10.1016/j.hpb.2018.12.012