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Vascular Occlusion or Not during Liver Resection: The Continuing Story

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Key Words
Vascular occlusion techniques · (Extended) liver resection · Pringle maneuver, continuous or intermittent

Abstract
Background: Vascular occlusion can be applied during liver resection to reduce blood loss. Herein, we provide an update of the current evidence concerning vascular occlusion. ***Methods:*** A systematic literature search was conducted to review the effects of liver in- and outflow occlusion techniques during liver resection, focusing on blood loss and hepatic ischemia-reperfusion injury. ***Results:*** The Pringle maneuver (PM) is effective in controlling blood loss; however, there is no indication for routine vascular clamping during hepatic resection in uncomplicated patients. During complex resections and in patients with abnormal liver parenchyma, the intermittent PM is preferred over continuous clamping. Total hepatic vascular exclusion (THVE) is indicated only in resection of tumors involving the inferior caval vein or the caval hepatic junction. THVE can be applied with the preservation of caval vein flow. This mode of selective hepatic vascular exclusion results in less blood loss in combination with the PM. ***Conclusion:*** If clamping is necessary during complex resections or in abnormal liver parenchyma, intermittent PM is advised. THVE or selective hepatic vascular exclusion may be considered in tumors involving the inferior caval vein or the caval hepatic junction. There is no evidence supporting the use of ischemic preconditioning, maintenance of a low central venous pressure or of pharmacological interventions during liver resection.

Introduction

Excessive blood loss during transection of the liver parenchyma is associated with adverse postoperative outcomes, which may culminate into liver failure especially when a small liver remnant is involved [1]. To combat blood loss during liver resection, various methods of hepatic inflow or simultaneous in- and outflow occlusion techniques have been introduced (fig. 1). Nonselective inflow occlusion is achieved by applying the Pringle maneuver (PM; clamping of the hepatic artery and portal vein in the hepatic pedicle), continuously or intermittently. Selective inflow occlusion is achieved by hemihepatic or segmental occlusion of (branches of) the portal vein or hepatic artery. Simultaneous hepatic inflow and outflow occlusion can be accomplished by total hepatic vascular exclusion (THVE) or selective hepatic vascular exclusion (SHVE). A low perioperative central venous pressure (CVP) has also been suggested to limit blood loss during liver resection [2]. Unfortunately, clamping can lead to negative effects such as hepatic ischemia-reperfusion injury (IRI) [3]. This phenomenon is the result of non-per-

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fusion and consequently, hypoxia of the liver parenchyma during vascular occlusion [3]. To limit this type of injury, several interventions have been devised. These include the intermittent PM (IPM), ischemic preconditioning (IP; a short clamping period followed by reperfusion before continuous clamping), in situ cooling of the liver under THVE, and pharmacological interventions such as the administration of trimetazidine, methylprednisolone, or dextrose [4]. The dilemma in extensive hepatic resection is the desire to control blood loss using vascular occlusion, whilst limiting IRI in the remnant liver. This paper aims at providing an update of the indications and efficacy of different types of vascular occlusion techniques which can be applied during liver resection. The current results of interventions to limit hepatic IRI will also be discussed.

How Much Ischemia Can the Liver Tolerate?

Most methods of IPM involve repeated cycles of occlusion between 15 and 20 min and a period of unclamping of 5 until 10 min [5]. Research has shown that IPM with ischemic intervals of 30 min can also be accomplished effectively and safely in human liver resections [6–8]. In addition, durations of continuous liver ischemia of up to 85–90 min have been reported in patients with normal and cirrhotic livers. There were no correlations between the duration of ischemia and the length of hospital stay, complications, liver failure or death [9, 10]. Thus, the liver seems to tolerate a period of (normothermic) ischemia of up to 90 min. Nevertheless, the liver can tolerate IPM if the duration of accumulated ischemic times is shorter than 120 min (PM for 20 min and a 5-min clamp-free interval) [11]. Patients with an ischemic time of more than 120 min showed less blood loss from the transection area (14 vs. 22 ml/cm^2, $p < 0.05$), but an equal transection time related to the transection area and blood transfusion volume was seen compared to a control group (without IPM). They also showed a lower recovery rate of the arterial ketone body ratio (0.1 vs. 0.65, $p < 0.05$), and higher plasma levels of IL-6 after liver resection (250 vs. 50 pg/ml, $p < 0.05$). These results suggest that the liver can tolerate longer ischemic times of up to 90 min without inducing liver failure.

Low CVP

A low perioperative CVP has been suggested to limit blood loss during liver resection [2, 12]. By lowering the pressure inside the inferior caval vein, the hepatic venous pressure and thus, the hepatic sinusoidal pressure would drop, possibly resulting in less bleeding during resection (672.4 ± 429.9 ml vs. control group: 1,662.6 ± 1,932.1 ml, $p < 0.01$) [2]. In a study by Jones et al. [13], it was found that the volume of blood loss during liver resection correlated with CVP, regardless of using the PM. They reported that a CVP ≤5 cm H_2O resulted in a median blood loss of 200 ml and blood transfusions in only 5% of patients compared to 1,000 ml blood loss and 48% blood transfusions in patients with a CVP >5 cm H_2O (p = 0.0001 and p = 0.0008, respectively). However, the conclusion of a Cochrane review published in 2009 was that even though a low CVP reduces blood loss in comparison to a control group (mean difference –419.35 ml; 95% CI –575.06 to –263.63), it does not lower red cell transfusion requirements (standardized mean difference –0.31; 95% CI –0.65 to 0.03) nor does it seem to decrease intraoperative morbidity or offer any long-term survival benefits [14].

Pringle Maneuver

The PM is achieved by simultaneous clamping of the hepatic artery and portal vein. It is the best known and time-honored method of vascular clamping to control blood loss during liver resection [15]. A recent survey in Europe showed that 71% of hepatic surgeons apply vascular clamping on indication, and that the PM is the most frequently used technique [16]. It has been reported, however, that this method has some potential drawbacks. These include portal vein emboli, spontaneous rupture of the spleen [17], induction of hepatic IRI [3] and decreased time to tumor recurrence [18]. Concerning the latter, a correlation of the use of the PM and decreased time to tumor recurrence has recently been refuted by recent research [19, 20].

It has been shown that the IPM (sequential application of the PM with periods of reperfusion) reduces splanchnic congestion and decreases hepatic IRI [21]. A randomized trial concluded that IPM is better tolerated by the liver than the continuous PM in patients with compromised liver parenchyma, but that in patients with normal parenchyma, there was no significant benefit of IPM. This outcome has been criticized because of the inclusion of patients undergoing standard right hemihepatectomy which usually does not involve resection of a critical mass of the liver [22, 23]. Therefore, IPM is preferred in patients with chronic liver disease.

The optimal cycle of IPM is still a matter of debate. Recent research shows that IPM with ischemic intervals of 30 min induces similar hepatocellular injury as with ischemic intervals of 15 min, determined by cumulative L-FABP levels ($p = 0.378$), and L-FABP levels at any time point ($p = 0.149$) [8]. Furthermore, there were no significant differences in median blood loss [450 (250–1,000) vs. 575 (100–2,300) ml, $p = 0.915$], liver function [postoperative peak bilirubin 37 (14–84) vs. 23 (16–101) μmol/l, $p = 0.670$], morbidity or hospital stay [8 (5–119) vs. 11 (5–53) days, $p = 0.955$] between both groups [8]. Ezaki et al. [24] applied vascular inflow occlusion intermittently in patients with chronic liver disease using a clamping and declamping time of 10–20 and 5–8 min, respectively. Liver function and complications were comparable in this study. In a randomized controlled trial comparing intermittent occlusion with an ischemic interval of 15 min with that of 30 min (each with 5 min of reperfusion), no difference was seen in the bilirubin ratio (serum total bilirubin level on postoperative day 2 divided by the preoperative level: 1.6 ± 0.8 vs. 1.7 ± 0.8, $p = 0.874$), and a similar remnant liver function [postoperative day 7: median total bilirubin 11.9 (5.1–34.2) $\times 10^{-3}$ vs. 13.7 (5.1–61.7) $\times 10^{-3}$ mmol/l, $p = 0.136$] was reported [6]. In all, these results suggest that IPM with ischemic intervals of 30 min can be safely used.

In a randomized clinical trial by Capussotti et al. [25] comparing IPM with 15 min of ischemia and 5 min of reperfusion, with no vascular clamping during liver resection, there were no significant differences in blood loss [184.1 (122.8–245.5) vs. 204.1 (158.4–249.8) ml, $p = 0.653$] and outcomes (mortality 1.6%, morbidity 29.4%). A longer transection time was seen in the patients without vascular clamping (73 vs. 49 min, $p < 0.001$). This study suggests that using optimal intraoperative conditions of preserved venous drainage of the remnant liver and modern tools for parenchymal transection, liver resection can be performed safely without pedicle clamping and with comparable blood loss and morbidity [21], even in patients with a diseased liver [25, 26]. Hence, routine portal triad clamping does not offer any benefit to the patient as regards perioperative outcome [27]. Nevertheless, there are cases involving complex resections and/or abnormal liver parenchyma, in which the amount of blood loss during resection is not acceptable. In such cases, blood loss is a major cause of morbidity and mortality [21]. Because the liver tolerates ischemia better than blood loss [28–30] and the drawbacks of complete inflow occlusion can be restricted, the (intermittent) PM can be applied when necessary, paraphrased as 'it is better to clamp than to bleed'.

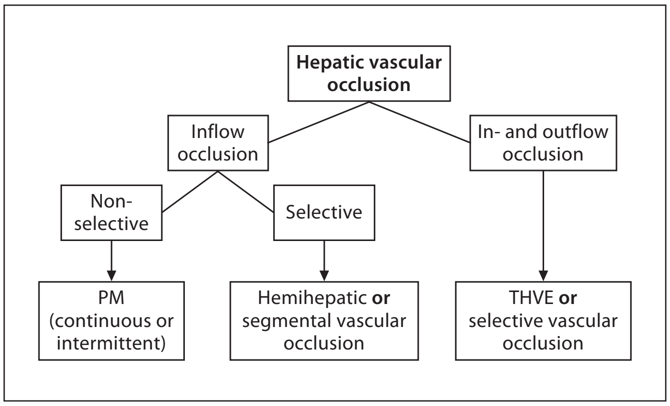

Fig. 1. Vascular occlusion techniques that can be applied during liver resection to reduce blood loss or hepatic IRI.

Selective Inflow Occlusion: Hemihepatic and Segmental Vascular Occlusion

Hemihepatic vascular occlusion has been proposed to reduce hepatic IRI to the remnant liver [31]. This technique selectively cuts off the arterial and venous inflow to the left or right hemiliver, and can be used when resecting parts of the left or right hemiliver such as in resection of the right posterior section (segments 6/7). Figueras et al. [32] compared IPM with intermittent hemihepatic vascular occlusion and found no significant differences in blood loss (mean 671 ± 533 vs. 735 ± 397 ml, $p = 0.54$), or operative time (mean 207 ± 48 vs. 219 ± 45 min, $p = 0.24$). Liang [33] compared IPM with continuous hemihepatic vascular occlusion and also found no significant difference in blood loss, morbidity rate or hospital stay. However, this author did find a longer operating time in the hemihepatic occlusion group [33]. Nevertheless, hemihepatic vascular inflow occlusion was recommended over the PM in a recent prospective randomized controlled trial since this technique is easier to perform and leads to an earlier recovery of postoperative liver function [34].

The segmental vascular occlusion technique involves selective occlusion of the supplying portal branch using an ultrasound guided balloon catheter [15]. This occlusion technique was designed to delineate the portal territory of the tumor in order to help the process of segment-oriented hepatic resection [31]. The outline of the segment can be recognized by demarcation of the liver parenchyma [15]. Injection of methylene blue into the portal vein gives a more precise view of the segmental borders [15].

Selective hemihepatic occlusion and selective segmental occlusion have been introduced to control blood loss during resection whilst not interrupting the blood flow of the complete liver [31]. These methods can also have an advantage in patients in whom anatomic demarcation of the part of the liver to be resected is desired [31]. Application has been suggested beneficial in patients with peripheral hepatic lesions and abnormal liver parenchyma [31]. However, there were no differences found in liver function markers and morbidity between total and selective inflow occlusion in patients with cirrhosis [35]. In all, there is no evidence supporting the use of routine selective vascular inflow occlusion rather than the PM [35].

THVE (Combined with Cold Perfusion)

THVE involves total vascular inflow and outflow occlusion of the liver, resulting in isolation of the liver from the systemic circulation [31]. The hepatic artery, portal vein, suprahepatic inferior caval vein and infra-hepatic inferior caval vein are clamped [15]. The infrahepatic inferior caval vein is clamped above the renal veins and right adrenal vein [15]. However, this surgical process is associated with hemodynamic intolerance in 10–20% of patients due to reduction in cardiac output [15]. Also, in a randomized controlled trial by Belghiti et al. [36], the occlusion times and operative times were significantly longer in the THVE group compared to the Pringle group (42 ± 12 vs. 35 ± 9 min, $p < 0.05$, and 366 ± 106 vs. 301 ± 103 min, $p < 0.05$, respectively) [36, 37]. This was the result of extra procedures such as caval dissection, vascular loading before clamping and three-stage removal of the clamps with intermediate hemostasis [37]. Furthermore, postoperative hospital stay has been found to be significantly longer in the THVE group compared to the Pringle group (mean 22 ± 12 vs. 14 ± 6 days, $p < 0.05$) [36, 37], even in the presence of surgical and anesthetic expertise [15]. Postoperative liver function [10, 38], morbidity [10, 38] and mortality rates [10] were not significantly different between both groups, nor was the amount of intraoperative blood loss (mean THVE: 1,195 ± 1,105 vs. Pringle: 989 ± 1,250 ml) [36]. However, significantly more blood loss during liver transection was reported in the Pringle group than in patients in whom a modified technique of hepatic vascular exclusion was performed (750 ml ± 365 ml vs. 350 ml ± 210 ml), with complete inflow occlusion and dissection of the inferior vena cava below the liver and isolation with a vascular tape [38]. Because of the potential harm in patients with cardiac disease and absence of a significant advantage, THVE cannot be recommended over the PM [35]. Nevertheless, THVE is especially useful in patients with a tumor thrombus in the inferior caval vein [37], and in case of tumor infiltration of the inferior caval vein or caval hepatic junction requiring excision of (part of) the caval vein [15].

Additionally, THVE enables the application of in situ hypothermic perfusion (IHP) of the future remnant liver [15]. During IHP, the liver is perfused with a cold solution, thereby inducing a state of parenchymal hypothermia. Hepatocellular energy demands subsequently fall due to the lower metabolic rate [39]. As a result of that, energy supplies are preserved, the amount of oxidative stress is reduced, and the detrimental late inflammatory response characteristic of I/R injury is hampered [40, 41]. Overall, these effects result in better postoperative recovery, as has been shown by a series of experimental studies conducted in our surgical laboratory [42–45].

However, clinical research published on the topic of IHP during THVE remains limited. Ever since Fortner et al. [46] pioneered the technique in 1974, only three studies have reported the application of IHP during THVE [47–49]. Although all studies state the beneficial effect of IHP on livers subjected to long ischemic intervals and/or those suffering from parenchymal disease, only one included a control group. In 2005, Azoulay et al. [47] published their results on a study comparing IHP during THVE (THVE-IHP) with THVE alone, lasting either <60 or ≥60 min. Interestingly, even though the group that underwent THVE-IHP differed significantly from the control groups in tumor size, the number of resected segments, and total ischemic duration, significant improvements in postoperative outcomes were seen. These improvements comprised a decrease in postoperative complications (THVE-IHP: 1.2 ± 0.9 complications/patient compared to THVE ≥60 min: 2.6 ± 1.8 complications/patient, $p = 0.005$), as well as a vast reduction in AST values postoperatively (THVE-IHP: 450 ± 298 IU/l compared to THVE <60 min: 1,000 ± 808 IU/l, $p = 0.006$, and ≥60 min: 1,519 ± 962 IU/l, $p < 0.001$), and ALT values (THVE-IHP: 390 ± 391 IU/l compared to THVE <60 min: 853 ± 743 IU/l, $p = 0.01$, and ≥60 min: 1,033 ± 861 IU/l, $p = 0.006$). It is, however, difficult to draw firm conclusions about the benefits of IHP from the limited amount of evidence available.

Selective Hepatic Vascular Exclusion

Excluding the liver from the systemic circulation with the preservation of caval flow is known as SHVE [37]. This is achieved by combining vascular inflow occlusion and extrahepatic clamping of the major hepatic veins [37, 50]. The benefit of this method is hepatic vascular occlusion without the hemodynamic and biochemical drawbacks of THVE or blood loss due to venous backflow during the PM [37]. Literature shows that SHVE is just as effective as THVE in controlling blood loss, but leads to fewer complications and a shorter hospital stay [15]. These advantages have recently been confirmed by Zhou et al. [51] and Smyrniotis et al. [52], who reported that SHVE is more effective in controlling blood loss during surgery (SHVE: 650 ± 850 vs. THVE: 850 ± 700 ml, n.s.), reducing complications and hospital stay (SHVE: mean 10 ± 4 vs. THVE: 16 ± 6 days, p = 0.03). However, this technique is technically more demanding than THVE and cannot be used when the tumor involves the caval hepatic junction [31]. Also, bleeding can still occur due to collateral veins between major hepatic veins or incomplete mobilization of the posterior liver plane [31]. Indications for the use of SHVE are complex hepatectomies on compromised liver parenchyma with excessive bleeding despite the use of the PM due to venous backflow or intolerance to THVE due to a poor cardiovascular status [52].

Ischemic Preconditioning

IP is characterized by a short period of ischemia and reperfusion preceding a longer time of ischemia [5]. In studies by Clavien et al. in 2000 [53] and 2003 [54], it was demonstrated that IP (10 min of ischemia followed by 10 min of reperfusion and an ischemic period of 30 min) was associated with significant beneficial effects in patients with steatotic livers as evidenced by reduction in subsequent hepatic IRI, as demonstrated by a reduction in the number of apoptotic sinusoidal lining cells. A similar result was found in the study of Choukèr et al. [55] applying IP in patients with normal liver parenchyma. The latter study also showed better intraoperative hemodynamic stability in patients in whom IP was applied using 10 min clamping followed by 10 min of reperfusion before the PM [55]. Heizmann et al. [56] showed that IP (10/10 min) prior to PM has a protective effect after surgery, because of improvement in liver macrocirculation (p = 0.024) resulting from prevention of portal vein postischemic flow reduction and an increase in arterial perfusion. Petrowsky et al. [57] published an RCT in which IP resulted in similar outcomes as IPM regarding the protective effect against postoperative liver injury, although IP was associated with less blood loss (146 vs. 250 ml, p = 0.008), and a shorter transection time (40.4 vs. 50.6 min, p = 0.002). This outcome is corroborated by the study of Zapletal et al. [58], which reported that IP and IPM show a comparable protective mechanism against IRI regarding the microcirculatory system, although IP leads to a more comprehensive protection on the cellular level. In combination with hepatic vein occlusion, application of IP using 10 min of clamping followed by 10 min of unclamping before continuous SHVE was not recommended by Azoulay et al. [59]. This did not improve liver function (p = 0.2), morbidity or mortality rates (p = 0.5) or IRI [59]. In a Cochrane review published in 2009, comparing IP and continuous vascular inflow occlusion, no differences were found in mortality (RR 1.43; 95% CI 0.29–7.06), liver failure (RR 0.84; 95% CI 0.41–1.71), and other intraoperative morbidity, hospital stay (mean difference –1.43 days; 95% CI –3.52 to 0.66), and operating time (mean difference –14.18 min; 95% CI –34.25 to 5.88) [5].

In conclusion, there is currently no evidence to suggest a protective effect of IP in patients undergoing liver resection under continues vascular occlusion [5, 60–62]. Besides that, the application of IP is not recommended in older patients [63], since (several cycles of) intermittent ischemia has shown to be more protective [57, 64]. Comparing IP and intermittent vascular clamping, it was also demonstrated that both were equally effective when using short periods of ischemia [5]. However, in complex liver resections when the ischemia time exceeded 40 min, intermittent vascular occlusion provided better protection of hepatic cells [21]. This may not be surprising in view of the fact that the IPM can be seen as a repetitive form of ischemic conditioning.

Pharmacological Interventions

Vascular inflow occlusion potentially results in damage of the liver parenchyma by phenomena summarized as IRI. The underlying cause of IRI is complex and involves a multitude of different cell types and signaling mechanisms [3]. Reactive oxygen species and inflammatory mediators, for example, play an important role in IRI [62]. It is not surprising that pharmacological interventions aiming at neutralizing or modulating the pathways of IRI using antioxidants and steroids have been the topic of past and current IRI research [62]. Improved liver function markers and/or reduced liver injury markers indicated that methylprednisolone, trimetazidine, dextrose and ulinastatin could have possible protective effects against IRI in vascular controlled liver resections [4]. However, literature shows no significant differences in mortality, liver failure or peri- or postoperative mortality for any pharmacological intervention [4, 65]. Hence, based on current evidence, it cannot be advised to administer medication with the purpose of limiting IRI in vascular controlled liver resection [65]. The use of these drugs should only be used in well-designed clinical trials before clinical implementation [4, 62, 63].

To summarize, in operations in which blood loss is limited, vascular occlusion is not indicated, as it does not improve patient outcome. In patients in whom excessive blood loss occurs, the PM is indicated. In the case of compromised liver parenchyma, IPM is preferred over continuous inflow occlusion, and ischemic periods of 30 min may be used. Selective hemihepatic and selective segmental inflow occlusion have been suggested to be beneficial in patients with peripheral hepatic lesions to limit the amount of IRI to the entire liver. In uncompromised as well as in cirrhotic livers, however, there is no evidence supporting the use of selective vascular inflow occlusion rather than the PM. If a tumor thrombus is present in the inferior caval vein or if the tumor infiltrates into the inferior caval vein or caval hepatic junction, THVE is particularly useful. Combining THVE with cold perfusion of the liver can lead to improved postoperative liver and kidney function and lower morbidity. Modification of the technique of THVE by extrahepatic occlusion of the hepatic veins (SHVE) may be beneficial in situations where the PM does not sufficiently limit blood loss due to venous backflow, or when THVE is contraindicated due to a bad cardiovascular status. IP, a low CVP and pharmacological interventions show no significant differences in patient outcomes.

Discussion

As mentioned above, using optimal intraoperative conditions, liver resections can nowadays be performed safely without vascular occlusion with comparable blood loss and morbidity [21]. It is reasonable to state that in such cases routine portal triad clamping does not offer any benefit in perioperative outcome to patients [27]. Our present review focuses on clamping methods which may prove necessary in situations where complex resections and/or abnormal liver parenchyma induce excessive bleeding. Control of bleeding in these cases is of great importance because blood loss is a major cause of morbidity and mortality during liver resection.

Vascular clamping during liver resection leads to IRI, but the liver is remarkably tolerant to prolonged periods of ischemia, and vascular occlusion does not seem to cause permanent damage to hepatic tissue [66]. Nevertheless, continuous clamping may combine with other factors resulting in significant liver dysfunction [66]. IPM, causing less IRI compared to the continuous PM [21], can be applied instead. Applying the PM intermittently also has other advantages, such as limiting portal hypertension and thus reducing the chance of spontaneous splenic rupture [17]. Much research has been done to define the optimal cycle of IPM, i.e. the periods of ischemia and subsequent reperfusion. Recent studies have shown that IPM with periods of 30 min of ischemia and 5 min of reperfusion can be used safely.

The decision to apply vascular occlusion during liver resection and determining which clamping method to use is highly dependent on the experience and expertise of the surgical and anesthetic team, and the individual patient. However, it should be emphasized that liver surgeons should be experienced in applying various methods of vascular occlusion, which may be demanded in an array of different situations during liver resection, to prevent massive blood loss. Teaching of vascular clamping techniques should therefore be included in training programs in hepatic surgery.

Conclusion

Vascular clamping during hepatic resection should be reserved for situations in which bleeding cannot be restricted by modern intraoperative conditions. If needed, vascular clamping in the form of the (intermittent) PM can be applied. More complex resections or persistent bleeding may lead to the use of THVE or SHVE. Surgeons should be well informed about the indications and drawbacks of these methods, and expertise is required.

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