

How much ischemia can the liver tolerate during resection?

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Abstract: The use of vascular inflow occlusion (VIO, also known as the Pringle maneuver) during liver surgery prevents severe blood loss and the need for blood transfusion. The most commonly used technique for VIO entails clamping of the portal triad, which simultaneously occludes the proper hepatic artery and portal vein. Although VIO is an effective technique to reduce intraoperative blood loss, it also inevitably inflicts hepatic ischemia/reperfusion (I/R) injury as a side effect. I/R injury induces formation of reactive oxygen species that cause oxidative stress and cell death, ultimately leading to a sterile inflammatory response that causes hepatocellular damage and liver dysfunction that can result in acute liver failure in most severe cases. Since the duration of ischemia correlates positively with the severity of liver injury, there is a need to find the balance between preventing severe blood loss and inducing liver damage through the use of VIO. Although research on the maximum duration of hepatic ischemia has intensified since the beginning of the 1980s, there still is no consensus on the tolerable upper limit. Based on the available literature, it is concluded that intermittent and continuous VIO can both be used safely when ischemia times do not exceed 120 min. However, intermittent VIO should be the preferred technique in cases that require >120 min duration of ischemia.

Keywords: Hepatectomy; ischemia; ischemic preconditioning (IP); oxidative stress; reperfusion injury

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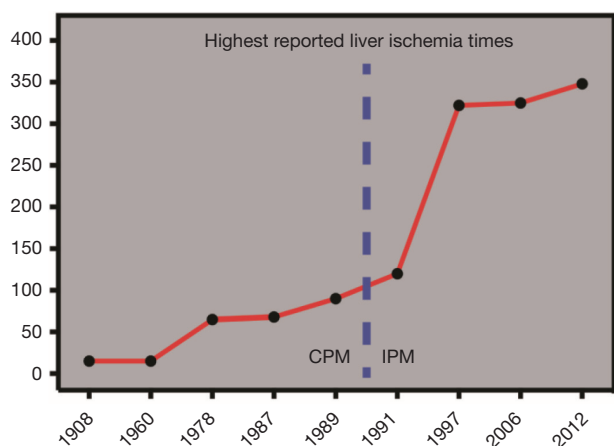
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Introduction

The Pringle maneuver is eponymously attached to the Australian surgeon James Hogart Pringle, who, while working at the Royal Infirmary in Glasgow, in 1908 first reported occlusion of the portal vein and hepatic artery [i.e., vascular inflow occlusion (VIO)] by compressing the hepatoduodenal ligament to control blood loss in trauma patients with a liver laceration (1). The induction of total liver ischemia is inherent to this technique, and for several decades it was believed it could only be applied for 15-20 min. VIO was therefore not extensively used, until Huguet *et al.* claimed that ischemia time in non-diseased livers could be extended to 65 min (2,3). As a result, the use of continuous VIO during resection became more

popular during the 1980s (4) and in 1987 the application of intermittent VIO was first described by Makuuchi *et al.* (5). In this procedure, VIO was applied in cycles of 30 min that were followed by 5 min of reperfusion, which could be repeated in cases that necessitated prolonged VIO.

The main aim of VIO is to reduce intraoperative blood loss and the consequent need for blood transfusion (6), which is a risk factor for postoperative mortality and morbidity (7-9). VIO, however, also results in hepatic ischemia/reperfusion (I/R) injury, which refers to the sterile inflammatory response and hepatocellular damage that are triggered when the hepatic blood (i.e., oxygen) supply is restored after a period of ischemia. Insofar as the duration of ischemia correlates positively with the hallmarks of I/R injury [e.g., ATP depletion and oxidative stress (10-12)],



Year	Ischemia time (min)	VIO technique	Reference
1908	15	CPM	(1)
1978	65	CPM	(2)
1987	68	CPM	(17)
1989	90	CPM	(4)
1991	150	IPM	(18)
1997	201	IPM	(19)
1999	322	IPM	(20)
2006	325	IPM	(21)
2012	348	IPM	(22)

Figure 1 The maximum duration of (cumulative) ischemia time in minutes (y-axis) plotted versus the year of publication (x-axis) (1,2,4,17-22). VIO, vascular inflow occlusion; CPM, continuous Pringle maneuver; IPM, intermittent Pringle maneuver.

animal studies indicate that prolonged ischemia leads to an increased mortality risk (13,14). In addition, livers affected by parenchymal disorders such as (non-)alcoholic fatty liver disease, cirrhosis, and chemotherapy-induced sinusoidal obstruction syndrome are more susceptible to I/R injury and therefore have a lower ischemic tolerance (15,16). As such, the routine use of VIO during liver surgery may be abandoned in the near future. For complex cases that require (on demand) VIO to safely complete parenchymal transection, however, the maximum acceptable duration of hepatic ischemia remains a relevant issue.

In an attempt to address this issue, Gurusamy *et al.* have reviewed the status quo of VIO during liver surgery (6). It was concluded that VIO effectively reduces intra-operative blood loss and decreases blood transfusion requirements, while no negative effects on post-operative mortality and morbidity rates were noted. The use of VIO during liver

resections is therefore generally considered safe. However, since all the studies included used different clamping regimens, no conclusion could be drawn concerning the maximum tolerable ischemia time.

Over the past decades, several reports have challenged the maximum duration of ischemia the liver can tolerate (*Figure 1*). Man *et al.* reported a safe upper limit of 120 min of intermittent VIO in 1999 (23), while in 2012 Torzilli *et al.* claimed that ischemia times exceeding 120 min are well tolerated using this technique (24). In addition, two case reports mention the successful use of exceptionally long durations of liver ischemia: 322 min (20) and 348 min (22), respectively. These reports have reinvigorated the discussion about how much ischemia the liver can actually tolerate.

Nevertheless, the abovementioned reports exclusively cover cases in which the patient was not affected by any type of parenchymal liver disease. This is relevant since several studies indicate that compromised livers poorly tolerate prolonged VIO (25-29). Due to a steep increase in the global prevalence of conditions that underlie parenchymal liver disease such as the metabolic syndrome, VIO is nowadays frequently used in livers with a compromised parenchymal status. Very little data is however available on the effect of prolonged VIO (i.e., >90 min) in this patient category, with only one reported case that describes a cumulative VIO duration of 204 min in a cirrhotic liver (27).

Although several reviews on VIO techniques have been published (30,31), none have focused specifically on the duration of ischemia that the liver can tolerate. In this paper, the relation between parenchymal liver disease and the upper limit of VIO duration is therefore discussed, with specific focus on the use of prolonged (>60 min) ischemia times during liver resection.

VIO techniques

Several techniques to induce VIO during liver surgery have been introduced. Of these, the Pringle maneuver, or hepatic pedicle clamping, is the best known VIO method. A sling is placed around the hepatoduodenal ligament, which comprises both the hepatic artery and the portal vein, and tightened to halt the hepatic blood supply (1). The Pringle maneuver can be used continuously [continuous Pringle maneuver (CPM)] or intermittently [intermittent Pringle maneuver (IPM)]. During IPM, the portal triad is generally occluded for 15-20 min (ischemia) followed by a period of 5-10 min of declamping (reperfusion). Consequently, IPM is applied repeatedly during parenchymal transection.

Table 1 Overview of studies using continuous VIO

Author, year (reference)	Parenchymal status [N]	VIO technique [N]	Groups compared [N]	VIO time (min)	Longest VIO time (min)	Conclusion
Delva <i>et al.</i> 1989 (4)	Cirrhosis [15]	CPM [107]	Cirrhosis [15]	34.1±4.2 [‡]	90	The human liver can tolerate continuous VIO ≤90 min
	Non-diseased [127]	THVE [35]	Non-diseased [127]	32.6±1.2 [‡]		
Huguet <i>et al.</i> 1992 (37)	Non-diseased [53]	CPM [28]	VIO time <30 min [9]	21±4 [§]	85	Non-diseased livers can at least tolerate 60 min of continuous VIO
			VIO time 30-60 min [29]	41±6 [§]		
		THVE [25]	VIO time >60 min [15]	67.5±7.4 [§]		
Hannoun <i>et al.</i> 1993 (25)	Non-diseased [34]	CPM [15]	CPM [15]	70±3 [‡]	127	Continuous VIO may be applied ≤90 min in livers with a healthy parenchyma
		THVE [15]	THVE [15]	72±3 [‡]		
Huguet <i>et al.</i> 1994 (38)	Diseased [9] [†]	CPM [14]	Diseased [9]	64.7±6.8 [‡]	85	Continuous VIO ≤85 min is not a risk factor in healthy livers. Diseased livers are more prone to complications after >60 min of VIO
	Non-diseased [17]	THVE [12]	Non-diseased [17]	68±7.5 [‡]		
Kim <i>et al.</i> 1993 (39)	Cirrhosis [26]	CPM [26]	VIO time >50 min [14]	57.1±8.4 [§]	75	Cirrhotic livers can tolerate VIO ≤50 min
			VIO time <50 min [12]	33.1±3.7 [§]		

[†], chemotherapy-induced liver disease, cirrhosis, or steatosis; [‡], mean ± SEM; [§], mean ± SD. VIO, vascular inflow occlusion; CPM, continuous Pringle maneuver; THVE, total hepatic vascular exclusion.

Another technique for VIO is total hepatic vascular exclusion (THVE) (32). The infrahepatic and suprahepatic vena cava are clamped, as is the portal pedicle, resulting in complete isolation of the liver from the circulation. A similar technique is selective hepatic vascular exclusion (SHVE), also referred to as THVE with preservation of caval flow (33,34). SHVE requires that the liver is disconnected from the vena cava by ligation of the short perforator veins, after which the hepatic veins and the portal pedicle are clamped, thereby inducing hepatic in- and out-flow occlusion with a patent vena cava.

In order to counteract the risks of I/R injury, all techniques for VIO are occasionally combined with ischemic preconditioning (IP). IP is a technique that aims to reduce hepatic I/R injury by inflicting a short ischemic insult followed by a short period of reperfusion prior to a prolonged period of VIO (35,36).

Ischemia times reported using continuous VIO

Continuous VIO is one of the most widely used techniques that aim to reduce blood loss in liver surgery. Multiple studies have been published on continuous vascular occlusion, several of which will be discussed in the following section. The results of these studies are also summarized in *Table 1*. In 1989, the operative management of 142 cases using continuous VIO (THVE, N=35 or CPM, N=107) was reported (4). Liver failure occurred more in patients with cirrhosis (5/15) compared to patients with a non-diseased liver (4/127, P<0.001). The duration of ischemia (mean ± SEM) was similar in patients with non-diseased livers compared to those with cirrhotic livers [(32.6±1.2) vs. (34.1±4.2) min in N=127 and N=15, respectively]. No differences in mortality and morbidity were found between the VIO <45 min (range, 8-44 min, N=119) and the VIO >45 min (range, 45-90 min, N=23) groups. Intergroup

differences in postoperative mortality and morbidity were also not observed in 53 hepatectomies with three groups divided by the duration of VIO [THVE (N=25) or CPM (N=28)] (37). VIO was applied <30 min in group 1 (range, 15-29 min, N=9), 30-60 min in group 2 (N=29), and >60 min in group 3 (range, 60-85 min, N=15). Consequently, it was suggested that the liver could tolerate continuous VIO for >60 min, although no exact maximum duration was specified. When continuous VIO time in 34 patients with uncompromised liver parenchyma was >60 min [THVE (N=15), CPM (N=15) or THVE and CPM sequentially (N=4)] with a mean \pm SEM VIO time of 73.6 \pm 2.5 min (range, 60-127 min), no correlation between the duration of ischemia and postoperative liver injury [aspartate aminotransferase (AST), alanine aminotransferase (ALT)], liver function (bilirubin, prothrombin time), or postoperative complications was seen (25). Accordingly, it was concluded that CPM could be safely applied for up to 90 min in healthy livers. Another study addressing 26 patients who underwent continuous VIO [CPM (N=14) or THVE (N=12)] with ischemia times exceeding 1 h was published in 1994 (38). The mean \pm SEM duration of VIO was 68 \pm 7.5 min in patients with non-diseased livers (N=17) and 64.7 \pm 6.8 min in patients with compromised livers (chemotherapy-induced liver disease, cirrhosis, or steatosis, N=9). Liver failure was seen in 4 patients with cirrhosis, which was reflected by the finding that postoperative morbidity was higher in diseased livers (77.8% vs. 11.8%, $P<0.05$). It was therefore concluded that continuous VIO of ≤ 85 min was not a risk factor in healthy livers, but that diseased livers are more prone to complications after continuous VIO of >60 min. In 26 cirrhotic patients exposed to 50-75 min (group 1, N=14) or 30-42 min (group 2, N=12) of VIO, less blood loss (mean \pm SD) was seen compared with cirrhotic patients operated without VIO (group 3, N=21; 819 \pm 572, 523 \pm 457, and 1,652 \pm 1,240 mL blood loss in group 1, 2, and 3, respectively) (39). Although peak postoperative serum ALT levels were higher in group 1 than in groups 2 and 3 ($P=0.02$), no differences were found in postoperative mortality and morbidity. It was therefore concluded that continuous VIO could be tolerated for about 50 min in cirrhotic livers. However, considering that 12 patients underwent continuous VIO for >50 min, with a maximum of 75 min, cirrhotic livers can possibly withstand the use of CPM for ≤ 75 min.

Taken together, these studies show that continuous VIO can be used for a period up to 90 min in uncompromised livers and to at least 50 min in diseased livers without

increasing mortality and morbidity rates.

Ischemia times reported using intermittent VIO

It was suggested that intermittent VIO reduces I/R injury and could therefore prolong the tolerable ischemia time (5). Several reports using intermittent VIO in either damaged (i.e., cirrhosis, steatosis, or chronic hepatitis) or uncompromised liver parenchyma are highlighted in the next section and are summarized in *Table 2*. Elias *et al.* started to use IPM routinely since 1987 (18). They retrospectively analyzed 20 patients exposed to intermittent VIO of >90 min in cycles of 20 min of ischemia and 5 min of reperfusion (20/5 min cycle). The mean VIO time was 109 min (range, 90-150 min), with a VIO duration of >140 min in two patients. Postoperative complications occurred in 7 patients (28.7%), which is in line with other reports (4,19,40). Total blood loss was the only parameter that positively correlated with prolonged ischemia times. Thus, it was concluded that intermittent VIO might even be safe for ≤ 150 min. In 100 patients with non-diseased and pre-damaged livers (i.e., due to cirrhosis or chronic hepatitis) randomized between IPM (N=50) or no VIO (N=50), mortality and morbidity rates were comparable (19). The median ischemia time was 88 min (range, 24-201 min). Total blood loss was lower in the VIO group (median, 1,280 mL; range, 90-8,500 mL) compared with the control group (median, 1,990 mL; range, 260-13,900 mL; $P<0.001$). It was therefore concluded by the authors that IPM is safe and effective in both compromised and uncompromised livers, but that it should not be applied for >120 min. Subsequently, a group of 12 patients who were operated with cumulative ischemia times of >120 min was compared with this cohort (23). The median ischemia time in this additional group was 134.5 min (range, 123-201 min) and 83 min (range, 24-114 min) in the patients that were randomized to IPM (N=50). A tendency towards lower blood loss was observed for <120 min IPM compared to >120 min IPM [(median, 1,010 mL; range, 230-9,020 mL) vs. (median, 2,030 mL; range, 560-9,420 mL), $P=0.06$]. No differences were found in terms of mortality and morbidity. Based on these results, it was concluded that IPM can be used safely for 120 min without increasing postoperative mortality and morbidity rates in both non-diseased and diseased livers. IPM of >90 min (15/5 min cycles) was retrospectively evaluated in 34 cases by Ishizaki *et al.* (21). In group 1 (N=25), cumulative VIO duration was 90-120 min and in group 2 (N=9), cumulative VIO duration was >120 min

Table 2 Overview of studies using intermittent VIO

Author, year (reference)	Parenchymal status [N]	Groups compared [N]	VIO time, mean \pm SD (min)	Longest VIO time (min)	Conclusion
Elias <i>et al.</i> 1991 (18)	Diseased [13] [†] Non-diseased [7]	IPM [20]	109 \pm 18	150	Intermittent VIO can be used safely \leq 120 min, and might even be safe up to 150 min
Man <i>et al.</i> 1997 (19)	Diseased [59] [†] Non-diseased [41]	IPM [50] No VIO [50]	88 (unknown)	201	IPM can be used safely and effectively in both compromised and uncompromised livers, but should not be applied for >120 min
Man <i>et al.</i> 1999 (23)	Diseased [69] [†] Non-diseased [43]	IPM >120 min [12] IPM <120 min [50] No VIO [50]	134.5 (unknown) 83 (unknown)	201	IPM can be used safely for 120 min without increasing postoperative mortality and morbidity in both non-diseased and diseased livers
Ishizaki <i>et al.</i> 2006 (21)	Diseased [13] [†] Non-diseased [21]	IPM >120 min [9] IPM 90-120 min [25]	176.1 \pm 68 99.4 \pm 8.4	325	IPM can be used safely for >120 min in difficult cases
Torzilli <i>et al.</i> 2012 (24)	Diseased [148] [†] Non-diseased [41]	IPM >120 min [72] IPM 60-120 min [117]	161 \pm 48 86 \pm 17	348	IPM can be safely used >120 min
Wu <i>et al.</i> 1996 (27)	Cirrhosis [83]	IPM >80 min [16] IPM 40-80 min [28] IPM <40 min [39]	110.5 \pm 34.7 58.3 \pm 10.2 25.5 \pm 6.7	204	Carefully selected patients with cirrhotic livers can safely withstand prolonged IPM of >120 min

[†], chemotherapy-induced liver disease, cirrhosis, or steatosis. VIO, vascular inflow occlusion; IPM, intermittent Pringle maneuver.

(range, 120-325 min). There was less blood loss (mean \pm SD) in group 1 (883 \pm 461 mL) compared with group 2 (1,409 \pm 1,039 mL) ($P=0.047$). Moreover, lower peak transaminase levels (mean \pm SD) were noted for group 1 compared with group 2 [AST: (410 \pm 324) *vs.* (966 \pm 590) U/L, $P=0.001$; ALT: (383 \pm 350) *vs.* (913 \pm 690) U/L, $P=0.006$], although peak total bilirubin levels were comparable. Additionally, there were no intergroup differences in postoperative mortality or complications. This was confirmed in 189 patients operated with a cumulative IPM time of >60 min (15/5 min cycles), in which underlying cirrhosis or steatosis was seen in 65 and 83 patients, respectively (24). Patients with ischemia times (mean \pm SD) of 60-120 min (group 1, 86 \pm 17 min, $N=117$) were compared to patients with ischemia times of >120 min (group 2, 161 \pm 48 min, $N=72$), ranging from 120 to 348 min. Peak levels of AST, ALT, and total bilirubin were all higher in group 2 ($P=0.002$, $P<0.001$, $P=0.004$, respectively), but mortality and morbidity rates were similar. Consequently, it was proposed that IPM can be used for >120 min when absolutely necessary, with a reported maximum VIO duration of 325 to 348 min (21,24).

As stated earlier, cirrhotic livers are more susceptible to I/R injury, which limits the maximum VIO duration in these patients (26). Eighty-three patients with cirrhotic livers who did not have ascites, had a serum bilirubin concentration <3.5 mg/dL, and had an indocyanine green clearance rate of less than 40% were divided into three groups: group 1 with <40 min ischemia ($N=39$), group 2 with 40-80 min of ischemia ($N=28$), and group 3 with >80 min of ischemia (range, 84-204 min) ($N=16$) (27). The mean \pm SD cumulative ischemia time was 25.5 \pm 6.7, 58.3 \pm 10.2, and 110.5 \pm 34.7 min in group 1, 2, and 3, respectively. In one patient, a VIO time of 204 min was necessary. Operative blood loss and blood transfusion requirements were higher in group 3 compared to group 1 ($P<0.001$). Peak AST and ALT levels were also higher in group 3 compared with the other study arms (both $P<0.001$). Nevertheless, mortality and morbidity rates were comparable between all groups. Accordingly, it was concluded that carefully selected patients with cirrhotic livers can safely withstand prolonged IPM of >120 min, possibly up to a maximum of 204 min.

Based on the abovementioned results, prolonged IPM can be safely used beyond 120 min in uncompromised

Table 3 Overview of studies comparing intermittent VIO with continuous VIO

Author, year (reference)	Parenchymal status [N]	Groups compared [N]	VIO time, mean \pm SD (min)	Longest VIO time (min)	Conclusion
Belghiti <i>et al.</i> 1999 (28)	Diseased [36] [†]	IPM [44]	46 \pm 18	118	IPM is superior to CPM, especially when underlying liver disease is present
	Non-diseased [50]	CPM [42]	41 \pm 13	67	
Capussotti <i>et al.</i> 2003 (29)	Cirrhosis [35]	IPM [17]	40.4 \pm 11.7	65	Both IPM and CPM are effective in reducing blood loss. There is no difference in the severity of hepatic I/R injury between the two techniques
		CPM [18]	35.5 \pm 13.9	84	

[†], chemotherapy-induced liver disease, cirrhosis, or steatosis. VIO, vascular inflow occlusion; IPM, intermittent Pringle maneuver; CPM, continuous Pringle maneuver; I/R injury, ischemia/reperfusion injury.

livers with a potential maximum duration of 348 min and in thoroughly selected cirrhotic livers with an apparent upper limit of 204 min.

Ischemia times in continuous versus intermittent VIO

Continuous and intermittent VIO have been extensively studied, but few studies have compared the two techniques directly (summarized in *Table 3*). In 1999, IPM (20/5 min cycles, group 1, N=44) was compared with CPM (group 2, N=42) in a randomized clinical trial with a mean duration of VIO of 46 min (range, 20-118 min) and 41 min (range, 16-67 min) in group 1 and 2, respectively (28). Postoperative liver injury markers were similar in both groups, but the correlation between elevation of serum ALT levels and duration of VIO was stronger in group 2 (Pearson's $r=0.68$, $P<0.001$) than in group 1 (Pearson's $r=0.38$, $P<0.01$). This finding suggests that the liver tolerates IPM better than CPM. The overall incidence of postoperative complications was comparable between both groups (30% in group 1 *vs.* 26% in group 2) although a trend was noted towards a higher incidence of acute liver failure in group 2 (4 patients) *vs.* group 1 (0 patients, $P=0.05$). All patients who developed acute liver failure had pre-existent liver disease (cirrhosis or steatosis). Therefore, 3 subgroups were compared with respect to the use of IPM and CPM: patients with healthy livers (group 1, N=50), patients with steatotic livers (group 2, N=11, >20% steatosis), and patients with cirrhotic livers (group 3, N=25). In group 2, the lowest peak prothrombin time was seen following IPM. The use of CPM resulted in significantly higher serum ALT levels in groups 2 and 3 compared with IPM (both $P<0.05$). Higher bilirubin levels in group 3 were found for CPM compared to IPM ($P<0.05$).

The authors therefore concluded that IPM is superior to CPM in terms of parenchymal tolerance to ischemia, especially when underlying liver disease was present. This was however not confirmed in a study with 35 cirrhotic patients comparing IPM (15/5 min cycles) (group 1, N=17) with CPM (group 2, N=18) (29). Only patients aged <75 years with hepatocellular carcinoma and Child Pugh Score A were included. The mean \pm SD VIO time was 40.4 \pm 1.7 min (range, 20-65 min) and 35.5 \pm 13.9 min (range, 16-84 min) in group 1 and 2, respectively. Postoperative complications and mortality were similar ($P=0.2$ and $P=0.1$, respectively). When VIO duration was compared (<30 *vs.* >30 min) instead of VIO technique, patients with >30 min developed more complications (N=8 *vs.* N=0, $P=0.02$). No differences were found in postoperative AST, ALT, prothrombin time, or bilirubin levels. Because approximately 75% of the patients did not receive blood transfusions, it was concluded that both techniques were effective in reducing blood loss and that there was no difference in the severity of hepatic I/R injury. This fueled the discussion that IPM might not be necessary in the cirrhotic liver for ischemia times of up to 60 min.

The effects of prolonged IPM and CPM on hepatic I/R injury were also investigated in two animal models (results are summarized in *Table 4*) (41,42). In swine, 120 min of IPM (12/3 min cycles) was better tolerated than 120 min of CPM (41). Sinusoidal endothelial cell function, reflected by the ability to clear hyaluronic acid from the circulation, was superior in the IPM group. Corroboratively, the extent of hepatocellular necrosis at 6 h of reperfusion was higher in the CPM group. Similar results were obtained in rat models of IPM and CPM (42). Three VIO regimens were compared: IPM in 15/5 min cycle (group 1), IPM in 30/5 min cycle (group 2), and CPM (group 3). Three

Table 4 Overview of preclinical studies comparing intermittent VIO with continuous VIO

Author, year (reference)	Animal	Groups compared [N]	VIO time (min)	Results	Conclusion
van Wagenveld <i>et al.</i> 1999 (41)	Pig	IPM [6]	120	More hepatocellular necrosis in CPM after 6 h of reperfusion	IPM is superior to CPM when prolonged VIO (120 min) is required
		CPM [6]	120	Better sinusoidal endothelial cell function in IPM group	
Chiappa <i>et al.</i> 2001 (42)	Rat	IPM, 15/5 min cycle	60, 90, 120	Higher survival in IPM groups after 120 min VIO	IPM allows longer VIO durations than CPM and therefore is the preferred technique for complex hepatectomies
		IPM, 30/5 min cycle	60, 90, 120	Lower AST and ALT serum levels on POD 1 in IPM groups after 90 or 120 min of VIO	
		CPM	60, 90, 120		

VIO, vascular inflow occlusion; IPM, intermittent Pringle maneuver; CPM, continuous Pringle maneuver; AST, aspartate aminotransferase; ALT, alanine aminotransferase; POD, post-operative day.

different cumulative ischemia times were compared: 60, 90, and 120 min. Survival rates were similar up to 90 min of ischemia. When VIO time was prolonged to 120 min, however, survival was better using IPM (70%, 70%, and 20% in group 1, 2, and 3 respectively, group 1 or group 2 *vs.* group 3, $P < 0.05$). Serum AST and ALT levels were significantly lower on post-operative day 1 following IPM, irrespective of the employed IPM regimen, compared with CPM for both 90 and 120 min of ischemia ($P < 0.05$ for group 1 or group 2 *vs.* group 3). There were no intergroup differences noted when VIO periods of 60 min were compared.

Although the differences are generally small and mostly seen in serum transaminase levels in contrast to mortality and morbidity rates, IPM seems to be better tolerated than CPM in both uncompromised and compromised livers, especially when prolonged ischemia times (>60 min) are necessary.

Ischemia times with IP followed by continuous VIO

IP was first clinically tested by Clavien *et al.* in 1999 in 24 patients undergoing major hepatectomy (35). After that, it became a topic of interest in liver surgery, of which several studies are discussed (also see *Table 5*). Using a standardized CPM regimen of 30 min, Clavien *et al.* found lower post-operative serum ALT and AST levels in the 12 patients

who received IP with CPM (IP-CPM) compared with the 12 patients who received CPM alone (35). This effect was even more pronounced in a small subgroup of patients with steatosis. In a subsequent randomized trial, 100 patients were randomized between IP-CPM (group 1, $N=50$) or CPM alone (group 2, $N=50$) (43). Peak ALT and AST levels were lower in group 1 (406 *vs.* 519 U/L and 364 *vs.* 520 U/L, $P=0.049$ and $P=0.028$, respectively), although mortality and morbidity rates were comparable. Ischemia times of <60 min were associated with better outcomes in group 1. Based on a small subgroup analysis ($N=13$), it was additionally claimed that steatotic livers benefited more from IP than healthy livers. This was evidenced by the considerable reduction in peak transaminase levels seen in fatty livers treated with IP compared to those subjected to CPM alone (363 *vs.* 602 U/L, respectively, $P=0.049$). Guided by these results, IP could be mostly beneficial in ischemia times of ≤ 60 min. Another study found lower serum AST levels on postoperative day 1 in patients operated with IP-CPM ($N=21$) than in patients operated with CPM only ($N=21$), despite the fact that these patients were subjected to longer ischemia times [(54 \pm 19) *vs.* (36 \pm 14) min in IP-CPM and CPM, respectively, $P=0.001$] (44). It is unclear whether the 10 min of IP were added to the cumulative duration of ischemia, but despite this, IP imparted a protective effect given the lower serum AST levels found. One study comparing IP followed by SHVE (group 1, $N=30$) to

Table 5 Overview of studies comparing ischemic preconditioning followed by continuous VIO with continuous VIO only

Author, year (reference)	Parenchymal status [N]	Groups compared [N]	VIO time, mean \pm SD (min)	Longest VIO time (min)	Conclusion
Clavien <i>et al.</i> 2000 (35)	Steatosis [7] Non-diseased [13]	IP-CPM [12] CPM [12]	30 30	30	IP-CPM seems to have a beneficial effect over CPM only
Clavien <i>et al.</i> 2003 (43)	Steatosis [13] Non-diseased [87]	IP-CPM [50] CPM [50]	36 \pm 5.9 35 \pm 6.8	60	IP-CPM seems superior to CPM for VIO durations of <60 min in healthy livers
Nuzzo <i>et al.</i> 2004 (44)	Non-diseased [42]	IP-CPM [21] IPM [21]	54 \pm 19 36 \pm 14*	110 70	IP imparts a protective effect in non-diseased livers despite the longer cumulative VIO time
Azoulay <i>et al.</i> 2006 (45)	Diseased [13] [†] Non-diseased [47]	IP-SHVE [30] SHVE [30]	44.5 \pm 9.2 47.7 \pm 8.3	67	IP does not reduce I/R injury and has no effect on clinical outcomes when used prior to SHVE
Heizmann <i>et al.</i> 2008 (46)	Steatosis (unspecified) Non-diseased (unspecified)	IP-CPM [30] CPM [31]	34 \pm 14 33 \pm 12	82 67	IP-CPM shows benefits over CPM only in routine liver surgery
Arkadopoulos <i>et al.</i> 2009 (47)	Non-diseased [84]	IP-SHVE [41] SHVE [43]	42 \pm 11 42 \pm 10	Unknown	IP prior to SHVE shows a protective effect in non-diseased livers

[†], chemotherapy-induced liver disease, cirrhosis, or steatosis; *, lower duration of VIO, $P < 0.05$. VIO, vascular inflow occlusion; IP-CPM, ischemic preconditioning followed by continuous Pringle maneuver; CPM, continuous Pringle maneuver; SHVE, selective hepatic vascular exclusion; IP-SHVE, ischemic preconditioning followed by selective hepatic vascular exclusion; I/R injury, ischemia/reperfusion injury.

SHVE only (group 2, $N=30$) during major hepatectomies with similar VIO durations [44.5 \pm 9.2 min (group 1) and 47.7 \pm 8.3 min (group 2), $P=0.2$], found comparable peak post-operative (mean \pm SD, group 1 *vs.* group 2) serum AST [(851 \pm 1,733) *vs.* (427 \pm 166) U/L, $P=0.2$], ALT [(717 \pm 995) *vs.* (403 \pm 200) U/L, $P=0.1$], and bilirubin [(63.0 \pm 60.0) *vs.* (81.2 \pm 71.0) μ mol/L, $P=0.3$] levels, as were the severity and number of complications (45). Better clinical outcomes were seen, however, in a randomized controlled trial comparing IP-CPM (group 1, $N=30$) with CPM alone (group 2, $N=31$) (46). Specifically, there was reduced (mean \pm SD) blood loss [(1,280 \pm 910) *vs.* (1,940 \pm 760) mL, $P=0.001$], a lower transfusion incidence (17% *vs.* 48% of patients, $P=0.006$), and a lower complication rate (20% *vs.* 45% overall complications, $P=0.04$) in group 1. Serum ALT and bilirubin levels did not differ between the two groups during the first postoperative week. In a trial in which 84 patients were randomly assigned to IP (10 min ischemia, 15 min of reperfusion) followed by SHVE (group 1, $N=41$) or SHVE alone (group 2, $N=43$), post-operative (day 1; mean \pm SD, group 1 *vs.* group 2) levels of AST [(288 \pm 140)

vs. (498 \pm 255) U/L, $P < 0.05$] as well as the cytokines IL-6 [(177 \pm 88) *vs.* (325 \pm 198) pg/dL, $P < 0.05$] and IL-8 [(219 \pm 112) *vs.* (369 \pm 187) pg/dL, $P < 0.05$] levels were lower in group 1 (47). Mean \pm SD VIO duration was similar in group 1 (42 \pm 11 min) and group 2 (42 \pm 10 min), implying that IP prior to SHVE effectively attenuated I/R injury. In liver biopsies taken at 1 h of reperfusion, the number of apoptotic cells was lower in group 1, further highlighting the protective effect of IP.

All studies discussed above applied IP prior to a period of continuous VIO of <60 min. The protective effect of IP before prolonged (>60 min) ischemia has only been investigated in animal models (summarized in Table 6) (13,48,49). One study assigned 24 pigs to undergo partial liver resection (65%) with IP (10 min ischemia, 10 min reperfusion) followed by 90 ($N=6$, group 1) or 120 ($N=6$, group 2) min of CPM either 90 ($N=6$, group 3) or 120 ($N=6$, group 4) min IPM only (48). Plasma AST and oxidative stress metabolite (i.e., malondialdehyde) levels were lower when IP followed by CPM was compared to IPM only following 90 min of ischemia. However, there

Table 6 Overview of preclinical studies comparing ischemic preconditioning followed by continuous VIO with intermittent VIO or continuous VIO only

Author, year (reference)	Animal	Groups compared [N]	Results	Conclusion
Smyrniotis <i>et al.</i> 2005, (48)	Pig	IP-CPM 90 min [6]	90 min of VIO: lower levels serum AST in IP-CPM	IP-CPM is superior to IPM when VIO duration is \leq 90 min
		IP-CPM 120 min [6]	120 min of VIO: lower levels serum AST in IPM	
		IPM 90 min [6]		
		IPM 120 min [6]		
Rüdiger <i>et al.</i> 2002, (13)	Mouse	IP-CPM 75 min [5]	IP-CPM after 75 min of VIO is superior to CPM (100% vs. 0% survival)	IP-CPM yields better results than CPM only following 75 min of VIO
		IP-CPM 120 min [5]		
		IPM 75 min [5]		
		IPM 120 min [5]	IPM is superior to IP-CPM after 120 min of VIO (71% vs. 14% survival)	IPM is superior to IP-CPM following prolonged (120 min) VIO
		CPM 75 min [5]		
CPM 120 min [5]				
Seyama <i>et al.</i> 2013, (49)	Rat	IPM, 15/5 min cycle [8]	Lower level serum ALT in IPM groups and less necrosis at 3 h reperfusion	IPM is better tolerated than IP-CPM or CPM when VIO is 60 min
		IPM, 10/3.3 min cycle [8]		
		IPM, 5/1.7 min cycle [8]		
		IP-CPM [8]	No differences between IPM groups individually and between IP-CPM and CPM	
		CPM [8]		

VIO, vascular inflow occlusion; IP-CPM, ischemic preconditioning followed by continuous Pringle maneuver; IPM, intermittent Pringle maneuver; CPM, continuous Pringle maneuver; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

was no intergroup difference with respect to the extent of hepatocellular necrosis. When the ischemic insult was extended to 120 min, IPM proved superior to IP-CPM in terms of AST release, plasma malondialdehyde levels, and histological necrosis score. IP-CPM therefore appears more beneficial when the VIO duration does not exceed 90 min, whereas IPM seems preferred when VIO is extended to 120 min. The same conclusions were drawn based on a mouse model comparing IP followed by CPM (group 1), IPM only (group 2), and CPM only (group 3) for VIO times of 75 and 120 min (13). IP-CPM is protective up to 75 min, which was evidenced by the 100% survival 3 days after surgery in groups 1 and 2 *vs.* 0% survival in group 3. When ischemia times were extended to 120 min, a survival rate of only 14% was seen in group 1 *vs.* 71.4% in group 2, and 0% in group 3, indicating that IPM offers the best results when

prolonged VIO is required. These results are supported by a study by Seyama *et al.* (49), in which the severity of hepatic I/R injury was evaluated as a function of five different VIO regimens in rats. Three groups underwent different cycles of IPM [4 15/5 min cycles (group 1), 6 10/3.3 min cycles (group 2), or 12 5/1.7 min cycles (group 3)]. In addition, group 4 received 10 min of IP followed by 60 min CPM and group 5 was subjected to 60 min CPM only. The IPM groups all showed lower ALT levels and less hepatocellular necrosis at 3 h of reperfusion compared with the CPM groups (groups 4 and 5). There were no differences in liver injury when individually comparing the 2 CPM groups (groups 4 and 5) or the 3 IPM groups (groups 1-3). IPM therefore seems better tolerated by the liver than IP-CPM or CPM alone when ischemia times exceed 60 min.

Table 7 Overview of studies comparing ischemic preconditioning followed by intermittent VIO with intermittent VIO only

Author, year (reference)	Parenchymal status [N]	Groups compared [N]	VIO time, mean \pm SD (min)	Longest VIO time (min)	Conclusion
Scatton <i>et al.</i> 2011, (50)	Non-diseased	IP-IPM [41]	45.0 \pm 19.6	96	IP-IPM shows no clinical benefit and should not be preferred over IPM only
		IPM [43]	52.4 \pm 27.7	157	
Winbladh <i>et al.</i> 2012, (51)	Diseased [5] [†]	IP-IPM major [8] [‡]	35 \pm 11	Unknown	The therapeutic value of IP-IPM is questionable
		IPM major [8] [‡]	44 \pm 8		
	Non-diseased [27]	IP-IPM minor [8] [§]	44 \pm 10		
		IPM minor [8] [§]	44 \pm 13		

[†], chemotherapy-induced liver disease, cirrhosis, or steatosis; [‡], major hepatectomy (≥ 3 segments according to Couinaud); [§], minor hepatectomy (≤ 2 segments according to Couinaud). VIO, vascular inflow occlusion; IP-IPM, ischemic preconditioning followed by intermittent Pringle maneuver; IPM, intermittent Pringle maneuver.

Taken together, IP-CPM seems to aggravate I/R injury when ischemic intervals of more than 75 min are used. However, IP may improve post-operative outcomes when applied before a shorter (<75 min) period of continuous VIO.

Ischemia times in IP followed by intermittent VIO

In addition to IP before CPM, two clinical studies also compared the effect of IP (10 min ischemia, 10 min reperfusion) followed by IPM (IP-IPM) to IPM alone (also see *Table 7*) (50,51). One study randomly assigned 84 patients to either IP-IPM (group 1) or IPM (group 2) (50). Ischemia times (mean \pm SD) were similar in both study arms (45.0 \pm 19.6 and 52.4 \pm 27.7 min, respectively). Moreover, there were no differences in the number as well as the severity of postoperative complications or hepatocellular injury markers (e.g., ALT). The second study evaluated the clinical feasibility of IP-IPM (51), postulating that the additional 20 min operating time inherent to IP should be avoided when the therapeutic efficacy of IP-IPM is subpar. Thirty-two patients were therefore divided into 2 experimental groups (N=16/group) based on the planned resection (i.e., major or minor liver resection). Thereafter, each group was randomly divided into 2 groups, receiving either IP-IPM or IPM alone, resulting in 4 groups (N=8/study arm). Microdialysis analysis showed that IP-IPM reduced the hepatic glycogenic activity and lactate formation during and directly after surgery, suggesting that IP alleviated the ischemia-induced metabolic perturbations

seen in the IPM-only groups. However, since clinical outcome parameters such as serum liver injury markers (AST, ALT), serum liver function markers (bilirubin, prothrombin time), and postoperative complications were similar amongst all experimental groups, the therapeutic value of IP-IPM remains questionable.

Discussion

Hepatic I/R injury is still a main concern in liver surgery and a balance between blood loss and I/R injury must be established for every liver resection. VIO effectively reduces blood loss (6) yet induces I/R injury when used for prolonged periods (10,11,14,52,53). In light of this critical trade-off, there is still uncertainty on the maximal duration of VIO that the liver can withstand. This debate is sparked by multiple reports on the safe use of ischemia times of >300 min (20,22,24).

Cirrhotic livers seem to benefit more from IPM. Wu *et al.* (27) performed liver resections in cirrhotic livers using intermittent VIO up to 204 min, whereas Kim *et al.* (39) reported a maximum of 75 min of continuous VIO in cirrhotic patients. Despite that Capussotti *et al.* (29) did not find any differences in clinical outcomes between intermittent and continuous VIO in cirrhotic patients, evidence from animal studies suggests that intermittent VIO in a 15/5 min cycle provides the best protection against hepatocellular injury when the total ischemia time is 60 min (54).

Intermittent VIO has a complication rate that is comparable to continuous VIO (28). The highest complication rates are seen with >60 min of ischemia.

Studies presenting data using continuous VIO report a complication rate of 53-56% (25,37). When IPM was used, complications were seen in 20-65% of patients (18,21,24). A recent systematic review, however, indicated that the complication rate was similar for intermittent and continuous VIO *vs.* no VIO (6). However, no comparison was made between studies with ischemia times of >60 or <60 min, so a meta-analysis should be performed to assess whether intermittent or continuous VIO is preferred for prolonged ischemia times.

Another possibility to decrease I/R injury is IP, which was first described by Clavien *et al.* (35) and was shown to attenuate surgery-induced liver injury in several randomized clinical trials (43,46). In spite of these beneficial effects, combining IP with VIO durations of >60 min seems to be hazardous (13,48) and it is therefore advised to only use IP when parenchymal transection is expected to last <60 min.

Diseased (e.g., cirrhotic or steatotic) livers seem to benefit more from IP than livers with uncompromised parenchyma (55). The ischemia times used in the latter study, however, were extremely short (<20 min). In cirrhotic mice, a protective effect was noted for ischemia times of up to 60 min compared with CPM alone (56). IP has a protective effect before CPM in pre-damaged livers, but should not be used when ischemia times are >60 min.

VIO might lose ground in liver surgery, as some large centers reported using the Pringle maneuver in only 17% of liver resections since 1999 as well as a 35% decrease in its use compared to before 1999 (57). Although 17% is exceptionally low when compared with other studies performed in the last decade (58-60), the routine use of VIO may be omitted in the future. One should, however, note that bleeding complications can occur, in which case the use of VIO is an important tool in order to regain hemodynamic control. VIO will therefore always have a role in liver surgery, although one should always be aware of the consequences of prolonged ischemia. Further evaluation of the pathophysiology of I/R injury and its consequences therefore remains important (61,62), as well as the development of better interventional strategies (53).

There moreover seem to be no strict limitations regarding the duration of ischemia in healthy livers, for ischemia times of more than 300 min have been reported (20-22). Considering that only 3 patients have been exposed to VIO durations of such caliber, it is however difficult to draw definitive conclusions from these reports. These results are nevertheless promising in view of the ongoing progress in hepatic surgery. Furthermore, these data should be kept in

mind when complex hepatic resections are planned and one should not withhold immediately when ischemia times of >120 min are expected during hepatectomies.

To establish the upper limit of hepatic ischemia, more data should be obtained from prolonged ischemia periods in the clinical setting. Since most hepatectomies can be performed within 30-40 min of VIO, it is not feasible to derive these data from randomized controlled trials. The maximum duration of VIO will therefore likely be determined based on case reports and small retrospective studies.

Overall conclusions

Prolonged (≥ 60 min) hepatic VIO (38) can be safely applied using both continuous and intermittent VIO regimens. The latter showed a benefit in terms of intra-operative blood loss and blood transfusion requirements, but did not reduce mortality and morbidity rates (6). Intermittent VIO can safely be applied for >120 min in healthy livers and may even be extended to 300 min when absolutely necessary. In well-selected cirrhotic livers, a cumulative ischemia time of 120 min is considered safe, with an upper limit of at least 200 min. Considering that most parenchymal transections can be completed within 30-40 min, clamping of the hepatic pedicle therefore does not appear to cause additional harm to the liver remnant.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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