Journal of Surgical Research **141,** 247–251 (2007)
doi:10.1016/j.jss.2006.10.054

The Effect of Hepatic Vascular Inflow Occlusion on Liver Tissue pH, Carbon Dioxide, and Oxygen Partial Pressures: Defining the Optimal Clamp/Release Regime for Intermittent Portal Clamping[1]

Adam J. Brooks, F.R.C.S.,[2] John S. Hammond, B.M.B.S., Keith Girling, B.M.B.S., and Ian J. Beckingham, D.M., F.R.C.S.

Department of Surgery and Critical Care, Nottingham University NHS Trust, Queens Medical Centre, Nottingham, United Kingdom

Submitted for publication July 28, 2006

Background. **The optimal duration of hepatic vascular inflow occlusion (Pringle maneuver) and reperfusion during liver resection are not defined. The aim of this study was to describe the changes that occur in liver tissue pH, partial pressure of carbon dioxide (P_LCO_2), and partial pressure of oxygen (P_LO_2) and by using the P_LCO_2 as a predictor of hepatocellular damage define the optimal clamp/release regime for intermittent portal clamping during liver resection.**

Methods. **Continuous pH, P_LCO_2, and P_LO_2 measurements were obtained using a Paratrend multiparameter sensor (Diametrics Medical Inc., Roseville, MN) in 13 patients undergoing elective partial liver resection. Patients were randomly allocated to undergo a 10-min clamp/5-min release regime (group 1) or a 20-min clamp/10-min release regime (group 2).**

Results. **In group 1 (*n* = 6) P_LCO_2 increased and pH decreased significantly after 10 min of clamping and returned to baseline within 5 min of reperfusion. In group 2 (*n* = 7) the P_LCO_2 increased and pH decreased significantly after 10 min of clamping, with a further significant change after 20 min. Following 10 min of reperfusion, pH and P_LCO_2 had not returned to baseline. P_LO_2 did not change significantly with either intermittent portal clamping regime.**

Conclusions. **A reperfusion of 5 min is sufficient to restore the P_LCO_2 and liver tissue pH to normal after 10 min of clamping, but more than 10 min of reperfusion is required after 20 min of clamping. To minimize hepatic ischemia during liver resection, a 10-min clamp/5-min release regime should be used.**

Key Words: **intermittent portal clamping; Pringle maneuver; monitoring; tissue carbon dioxide.**

INTRODUCTION

A number of vascular occlusive techniques have been described to minimize bleeding during liver resection. These include inflow occlusion using hepatic pedicle clamping (Pringle maneuver) and simultaneous inflow/outflow occlusion (total vascular exclusion) [1–5]. Of these, the Pringle maneuver is the method of choice, being better tolerated in the majority of patients [1, 5].

The major complication of hepatic vascular occlusion is hepatic ischemia, which increases with longer and continuous periods of clamping and may manifest in a spectrum ranging from mild dysfunction to lethal organ failure [6–9]. This is particularly true in patients with abnormal liver parenchyma, as this group is acutely sensitive to ischemia [9]. In order to limit hepatic ischemia intermittent portal clamping (IPC) regimes were developed. In a study comparing IPC (15-min clamp/5-min release) with continuous portal clamping (CPC), patients who underwent CPC had significantly higher rates of liver dysfunction than the IPC group [6]. However the optimal clamp release regime has not yet been defined.

Using a Paratrend multi-parameter sensor (Diametrics Medical Inc., Roseville, MN), we have previously reported the changes that occur in pH, P_LCO_2, and P_LO_2 in response to variations in F_iO_2 and end-tidal carbon dioxide and that, upon application of the Prin-

[1] Presented at EHPBA Heidelberg 2005 and published as an abstract in HPB Surg 2005;7:21.

[2] To whom correspondence and reprint requests should be addressed at Department of Surgery, Nottingham University NHS Trust, Queens Medical Centre, Derby Road, Nottingham, NG7 2UH, United Kingdom. E-mail: adam.brooks@nuh.nhs.uk.

0022-4804/07 $32.00

gle maneuver, P_LCO_2 increases with time [10]. In animal models, such prolonged increases in P_LCO_2 are associated with hepatocellular damage [11]. The aim of this study was to describe the changes that occur in liver tissue pH, P_LCO_2, and P_LO_2 during IPC and to define the optimal IPC regime, using P_LCO_2 as a predictor of hepatocellular damage.

METHODS

The study was undertaken at Queens Medical Centre, University Hospital, Nottingham, United Kingdom. Patients with American Society of Anesthesiologists grade >2, preexisting parenchymal liver disease, and nonmetastatic disease were excluded from the study. Following ethical committee approval, 13 patients scheduled for elective liver resection for colorectal metastases gave written, informed consent. Baseline characteristics were collected, and the patients were then randomly allocated to undergo either a 10-min clamp period followed by 5-min reperfusion (group 1) ($n = 6$) or a 20-min clamp period followed by 10-min reperfusion (group 2) ($n = 7$).

All patients underwent a standardized anesthetic, including induction of anesthesia with propofol and maintenance with isoflurane and nitrous oxide in oxygen. An infusion of atracurium was used for muscle relaxation and analgesia was with a continuous thoracic epidural infusion of 0.25% bupivacaine. Central venous pressure was maintained between 0 and 5 mmHg, and blood pressure was maintained within 20% of the preoperative value using an ephedrine infusion at 0-30 mg h^{-1}.

All patients underwent a laparotomy to exclude extrahepatic metastases and intraoperative ultrasound (Aloka, CT) to confirm the number and location of metastases. The Paratrend multiparameter sensor (Diametrics Medical Inc.) was calibrated automatically and inserted as described previously in ref. 9. The probe was sited well away from the tumor mass in the lobe that was to be resected. The measurements were taken before starting the liver resection and during the measurement period no surgical interventions were performed.

The probe required a 20-min period to achieve stable readings. The Pringle maneuver was applied using a Rummel tourniquet secured around the hepatic pedicle. In group 1 the Pringle maneuver was applied for 10 min followed by 5 min of reperfusion; in group 2 the Pringle maneuver was applied for 20 min followed by 10 min of reperfusion. During monitoring of the P_LCO_2, the inspired oxygen concentration ($F_iO_2 = 1.0$), end-tidal CO_2 partial pressure (33.8 mmHg), inspired volatile concentration, and blood pressure were maintained at constant values. Following completion of data collection, the probe was removed and the liver resection commenced. No further readings were taken during the liver resection.

Data were analyzed using the Student's *t*-test and Mann–Whitney test with the Statistical Package for Social Sciences, SPSS (Version 11.0 for Windows; GmbH, Munich, Germany) and are presented as median (IQR) unless otherwise stated.

TABLE 1

Summary of Patient Demographics

	Group 1 Mean (range)	Group 2 Mean (range)
Age	67.3 (55–77)	68.3 (63–75)
Sex		
M	5	5
F	1	2

TABLE 2

Pre-operative and Day 2 Post-operative Bilirubin and ALT Levels for Group 1 and Group 2 Patients

	Group 1		Group 2	
	Mean (SD)	*N*	Mean (SD)	*N*
Preoperative bilirubin (μmol/L)	8.5 (6.0)	4	7.0 (3.34)	5
Preoperative ALT (IU/L)	33.5 (19.1)	4	26.3 (9.6)	5
Day 2 postoperative bilirubin (μmol/L)	37.3 (26.3)	4	71.6 (45.0)	5
Day 2 postoperative ALT (IU/L)	416.5 (298.6)	4	903.4 (933.4)	5

ALT = alanine aminotransferase.

RESULTS

Thirteen patients took part in the study. Their demographics are summarized in Table 1. All patients were scheduled to undergo formal partial hepatectomy for colorectal metastases: group 1 (1 left + 5 right hepatectomies) and group 2 (2 left + 5 right hepatectomies). Insertion and removal of the probe from the liver was associated with only minimal, self-limiting bleeding and no significant morbidity. Pre- and day 2 postoperative liver function tests are summarized in Table 2.

In group 1 the median preclamp pH was 7.03 (IQR 0.18). This decreased significantly to 6.77 after 10 min of clamping ($P = 0.01$). After 5 min of reperfusion the pH had returned to baseline (Fig. 1A). In group 2 the median preclamp pH was 7.29 (IQR 0.08). This decreased significantly to 6.71 (IQR 0.36) after 20 min of clamping ($P < 0.001$) and remained significantly reduced after 10 min of reperfusion ($P = 0.014$) (Fig. 2A).

In group 1 the preclamp median P_LCO_2 was 63.06 (IQR 41.65) mmHg. This increased significantly to 131.75 (IQR 56.48) mmHg ($P = 0.008$) after 10 min of clamping. After 5 min of reperfusion the P_LCO_2 had returned to baseline (Fig. 1B). In group 2 the preclamp median P_LCO_2 was 52.04 (IQR 11.6) mmHg. This increased significantly to 177.17 (IQR 45.4) mmHg ($P < 0.001$) after 20 min of clamping. This was significantly greater than the P_LCO_2 after 10 min of clamping ($P = 0.035$). After 10 min of reperfusion the P_LCO_2 only returned to baseline in two of the seven patients (Fig. 2B).

In group 1 the median preclamp P_LO_2 was 42.04 (IQR 49.35) mmHg. There was no significant change in P_LO_2 after 10 min of clamping or 5 min of reperfusion. In group 2 the median P_LO_2 was 34.53 (IQR 29.47)

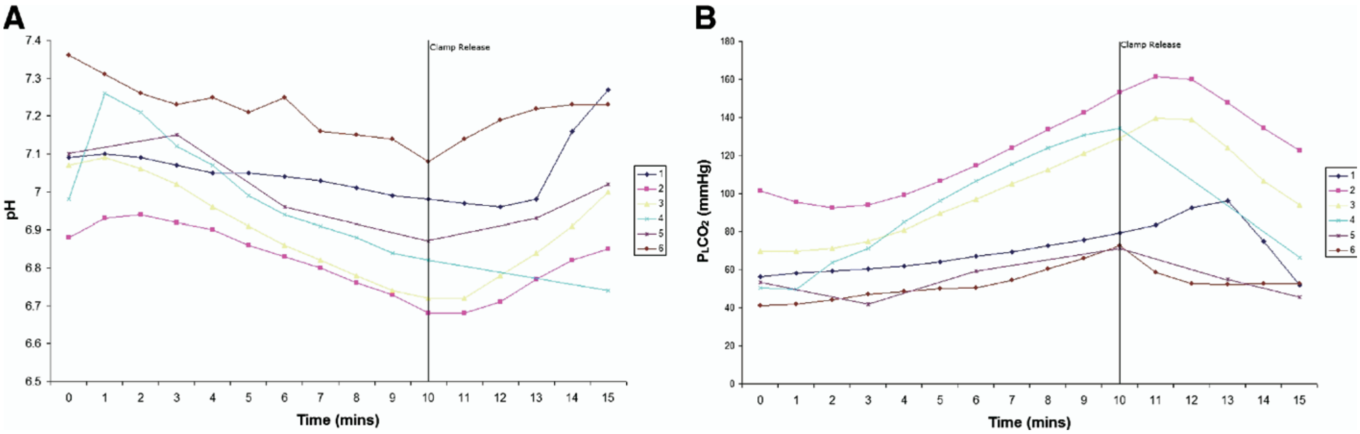

FIG. 1. The liver tissue pH (A) and partial pressure of CO_2 (P_LCO_2) (B) for patients undergoing a 10 min clamp/5 min release IPC regime (Group 1) as measured each minute using the intra-hepatic multi-parameter sensor. The point of clamp release is indicated. (Color version of figure is available online.)

mmHg. There was no significant change in P_LO_2 after 20 min of clamping or 10 min of reperfusion.

DISCUSSION

This study set out to describe the changes that occur in liver tissue pH, P_LCO_2, and P_LO_2 during IPC and, using P_LCO_2 as a predictor of hepatocellular damage, to define the optimal IPC regime. We have previously described the changes in pH, P_LCO_2, and P_LO_2 that occur in response to variations in F_iO_2 and end-tidal CO_2 and have demonstrated that P_LCO_2 increases upon application of the Pringle maneuver [10]. However the effect of IPC on the pH, P_LCO_2, and P_LO_2 in man has not previously been reported.

The Paratrend multi-parameter sensor was originally developed as a tool for continuous intra-arterial blood gas measurement in critically ill patients [12]. The sensor tip comprises a fiber-optic sensor housed within a microporous polyethylene sheath. The probe can be inserted directly into a tissue, where it will provide a continuous measurement of pH, PCO_2, and PO_2 within the interstitial fluid. This approach has been used to study these parameters in a range of tissues (brain, liver, and muscle) in low-flow states [11, 13, 14] and provides a more sensitive measure of end-organ perfusion than conventional systemic markers [15].

We have demonstrated that application of the Pringle maneuver results in an increase in P_LCO_2 and that these changes were mirrored by a decrease in liver tissue pH; that after 10 min of clamping the P_LCO_2 increases and liver pH decreases significantly from baseline, with a further significant change after 20 min of clamping. It also demonstrated that 5 min of reperfusion was sufficient to allow P_LCO_2 and liver pH to return to baseline after 10 min of clamping, but that greater than 10 min of reperfusion were necessary for P_LCO_2 and pH to return to baseline with 20 min of clamping. The study also demonstrated that there were no significant changes to P_LO_2 during 10 or 20 min of clamping.

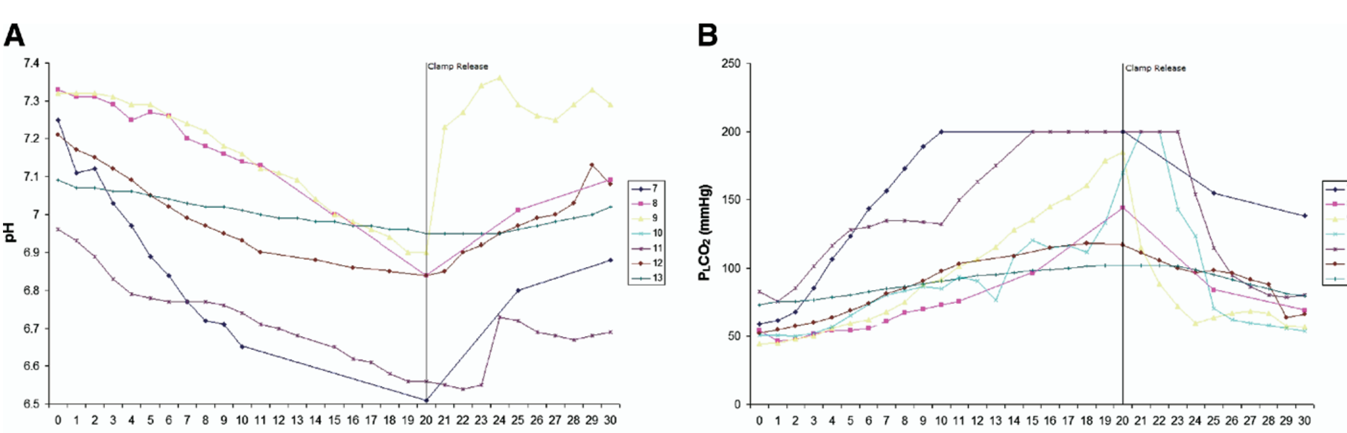

FIG. 2. The liver tissue pH (A) and partial pressure of CO_2 (P_LCO_2) (B) for patients undergoing a 20 min clamp/10 min release IPC regime (Group 2) as measured each minute using the intra-hepatic multi-parameter sensor. The point of clamp release is indicated. (Color version of figure is available online.)

The pathways to hepatic dysoxia following portal claming are complex. After the clamp is applied, aerobic respiration will continue for a period, but as hepatic blood flow is reduced, CO_2 will accumulate and pH will decrease. When oxygen reserves within the liver become critical, anaerobic metabolism will commence, resulting in a further increase in P_LCO_2 and decrease in pH. That P_LO_2 did not change significantly even after 20 min of clamping is perhaps surprising, but is consistent with our findings in previous work [10]. It may be accounted for by incomplete pedicle occlusion, back flow from the hepatic veins, or more likely is related to the attempt to record PO_2 values at the lower limit of the probes sensitivity.

Limitations of this study relate to probe function, patient tolerance, and study design. Due to the fragility of the probe, it was not possible to measure pH, PCO_2, and PO_2 while simultaneously performing the liver resection. Clamp insertion, probe calibration, and data acquisition were undertaken prior to commencing the liver resection. Therefore more prolonged or multiple clamp/release regimes could not be investigated as they would have increased operative time. Other limitations of the probe were that the sensor detected only local changes in pH, PCO_2, and PO_2; hence, the reported values may not be representative of the whole liver. To overcome this limitation, the method of probe insertion was standardized, but ideally it would have been better to use multiple sensors in each patient. The fragility of the probe resulted in some time points being lost. Despite this, 83.4% of the possible data points were obtained. A limitation in the study design was that additional clamping could be used during the resection proper. Therefore it was not possible to interpret the impact of the different IPC regimes on liver dysfunction from the day 2 bilirubin and the alanine aminotransferase values presented.

The significance of P_LCO_2 has been examined in a number of animal models. Desai *et al.* showed that tissue hypercarbia is associated with low-flow states [13], while Soller *et al.* identified the link between tissue $PtCO_2$ and cellular damage and calculated the critical P_LCO_2 at which hepatic cellular death occurs (63.8–75.0 mmHg) in a porcine model of hemorrhage [11]. This study also noted that the duration of tissue hypercarbia was a negative predictor of survival.

Belghiti *et al.* demonstrated in his prospective study of 86 patients that IPC using a 15-min clamp/5-min release regime is significantly better tolerated than CPC [6]. This effect was most evident among patients with underlying parenchymal disease. Similarly, Man *et al.* demonstrated tolerance of intermittent clamp periods up to a cumulative 120 min using a 20-min clamp/5-min release regime. However, after 120 min there was a marked deterioration in liver function [16].

We have demonstrated that the P_LCO_2 increases significantly after 10 min of clamping and that, as occlusion time increases, so too does the time taken for the P_LCO_2 to return to baseline. In 43% of the patient that underwent the 20-min clamp regime the P_LCO_2 was over three times baseline at the end of the clamp period. The maximum measurable PCO_2 using the Paratrend® probe is 199 mmHg. A critical P_LCO_2 value has not been calculated for man, but, using the porcine critical P_LCO_2 value 63.8–75.0 mmHg [11], we see that 71% of patients in group 2 had a P_LCO_2 associated with hepatocellular damage even after 10 min of reperfusion.

This data support the use of an IPC regime during liver resection, to limit tissue hypercarbia and associated hepatocellular damage. It also suggests that occlusion times greater than 20 min are associated with prolonged periods of hypercarbia that require longer periods of reperfusion to return P_LCO_2 to baseline levels. On the basis that duration of hypercarbia is a negative predictor of outcome, these long periods of occlusion should be avoided, particularly in patients with preexisting parenchymal disease.

CONCLUSION

Five minutes of reperfusion is sufficient to restore the P_LCO_2 and liver tissue pH to normal after 10 min of clamping, but more than 10 min of reperfusion is required after 20 min of clamping.

In light of these results, we should consider revising our practice to allow adequate reperfusion times. This can be achieved, using the Pringle maneuver, with a 10-min clamp/5-min release regime.

REFERENCES

1. Belghiti J, Noun R, Zante E, et al. Portal triad clamping or hepatic vascular exclusion for major liver resection. A controlled study. Ann Surg 1996;224:155.
2. Huguet C, Gavelli A, Addario Cheico P, et al. Liver ischaemia for hepatic resection: where is the limit? Surgery 1992;111:251.
3. Edmond J, Schwartz M, Katz E, et al. Total vascular exclusion for major hepatic surgery in patients with abnormal liver parenchyma. Arch Surg 1995;130:824.
4. Man K, Fan ST, Ng IO, et al. Prospective evaluation of Pringle maneuver in hepatectomy for liver tumors by a randomized study. Ann Surg 1997;226:704; discussion 711.
5. Smyrniotis VE, Kostopanagiotou GG, Contis JC, et al. Selective hepatic vascular exclusion versus Pringle maneuver in major liver resections: prospective study. World J Surg 2003;27:765.
6. Belghiti J, Noun R, Malafosse R, et al. Continuous versus intermittent portal triad clamping for liver resection: A controlled study. Ann Surg 1999;229:369.
7. Belghiti J, DiCarlo I, Sauvanet A, et al. A ten year experience with liver resection in 338 patients: Evolutions in indications and of operative mortality. Eur J Surg 1994;160:277.
8. Liu DL, Jeppsson B, Hakansson CH, et al. Multiple system organ damage resulting from prolonged hepatic inflow interruption. Arch Surg 1996;131:442.

9. Teoh NC, Farrell GC. Hepatic ischemia reperfusion injury: Pathogenic mechanisms and basis for hepatoprotection. J Gastroenterol Hepatol 2003;18:891.

10. Brooks AJ, Eastwood J, Beckingham IJ, et al. Liver tissue partial pressure of oxygen and carbon dioxide during partial hepatectomy. Br J Anaesth 2004;92:735.

11. Soller BR, Heard SO, Cingo NA, et al. Application of fiber optic sensors for the study of hepatic dysoxia in swine hemorrhagic shock. Crit Care Med 2001;29:1438.

12. Soller BR. Design of intravascular fiber optic blood gas sensors. IEEE Eng Med Biol Mag 1994;June/July:327.

13. Desai VS, Weil MH, Tang W, et al. Hepatic, renal, and cerebral tissue hypercarbia during sepsis and shock in rats. J Lab Clin Med 1995;125:456.

14. McKinley BA, Ware DN, Marvin RG, et al. Skeletal muscle pH, PCO_2, PO_2 during resuscitation of severe hemorrhagic shock. J Trauma 1998;45:633.

15. Mc Kinley BA, Butler BD. Comparison of skeletal muscle PO_2, PCO_2 and pH with gastric tonometric PCO_2 and pH in hemorrhagic shock. Crit Care Med 1999;27:1869.

16. Man K, Fan ST, Ng IO, et al. Tolerance of the liver to intermittent Pringle manoeuvre in hepatectomy for liver tumors. Arch Surg 1999;134:533.