Effect of graft reperfusion on haemodynamics and gas exchange during liver transplantation†

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Summary

We have documented the changes in gas exchange, haemodynamic state and associated physiological variables which occurred after graft reperfusion in 20 patients undergoing uncomplicated orthotopic liver transplantation. Gas exchange was measured during constant ventilation using a metabolic monitor. After reperfusion, there were increases in $V_O_2$ (mean increase 57 (SD 25) ml min$^{-1}$) ($P<0.001$), $V_CO_2$ (mean increase 38 (17) ml min$^{-1}$) ($P<0.001$) and $P_A_CO_2$ (mean increase 0.88 (0.56) kPa) ($P<0.001$). These were associated with increases in cardiac output (1.2 (1.0) litre min$^{-1}$ m$^{-2}$) ($P<0.001$) and mean pulmonary artery pressure (9 (6) mm Hg) ($P<0.001$). There was a decrease in standard bicarbonate concentration (0.96 (1.6) mmol litre$^{-1}$) ($P<0.02$) and increase in hydrogen ion concentration (0.15 (5.9) mmol litre$^{-1}$) ($P<0.001$) consistent with the release of an acid load from the graft and previously ischaemic tissues. The increases in $P_A_CO_2$ and hydrogen ion concentration were significantly larger in patients in whom venovenous bypass was used during the anhepatic period compared with the “piggyback” surgical technique. We found correlations between the changes in $P_A_CO_2$ and $V_CO_2$ ($r^2=0.25$, $P<0.02$), cardiac output and $V_CO_2$ ($r^2=0.34$, $P<0.01$), and cardiac output and $V_O_2$ ($r^2=0.34$, $P<0.01$). We conclude that major alterations in gas exchange occur after reperfusion which result from alterations in metabolic rate and haemodynamic changes. These may be clinically relevant, particularly in patients at risk of cerebral oedema. (Br. J. Anaesth. 1998; 81: 311–316).

Keywords: liver, transplantation; cardiovascular system; effects; oxygen, consumption; carbon dioxide, elimination

During orthotopic liver transplantation the point at which reperfusion of the donor graft occurs is associated with rapid physiological and metabolic changes. These include an increase in cardiac output, central venous pressure and pulmonary artery pressure, and a decrease in systemic vascular resistance which, when severe, constitute the post-reperfusion syndrome. The causes of these changes are incompletely understood but probably include a sudden increase in venous return, cardiac reflexes and release of substances from the graft itself, such as proinflammatory cytokines and oxygen free radicals. Alterations in metabolic rate also occur as the graft is perfused with oxygenated blood and becomes metabolically active. It has been shown previously that an increase in whole body oxygen consumption occurs after reperfusion which may reflect oxygen uptake by the graft.

However, there are no detailed studies on the alterations in gas exchange which accompany this increase or their relationship to haemodynamic changes and acid–base balance. These are important because they may contribute to potentially fatal complications, such as acute intracranial hypertension, which can occur at this time. Our aim was to describe in detail the complex changes in pulmonary and systemic haemodynamics, gas exchange and metabolic rate which occur after reperfusion to provide a rational approach to the management of the physiological changes which occur at this time.

Patients and methods

We studied prospectively 20 patients, mean age 52 (range 21–67) yr, undergoing orthotopic liver transplantation over a 10-month period. In eight patients venovenous bypass from portal and femoral veins to the axillary vein was used during the anhepatic phase. In the remaining 12 patients the “piggyback” technique was used in which inferior vena caval flow is preserved throughout surgery. With this technique a temporary portacaval shunt was constructed during the anhepatic period and a caval to caval anastomosis fashioned between the donor liver and recipient inferior vena cava. Anaesthesia was maintained with propofol–alfentanil infusion supplemented with midazolam. An infusion of atracurium was used for neuromuscular block and the lungs were ventilated with an air–oxygen mixture using a Servo 900C ventilator. Ventilator settings were adjusted to achieve $P_A_CO_2$ 3.5–4.5 kPa early in the operation and were not altered during the study. All patients received dopamine 3 $\mu$g kg$^{-1}$ min$^{-1}$ and aprotinin at a rate of 500 000 u. h$^{-1}$ after a loading dose of 2 x 10$^6$ u. Arterial, central venous and pulmonary artery pressures were monitored continuously. Cardiac output was measured using an automated thermodilution technique (Baxter Vigilance system, Baxter Healthcare Corp., Irvine, CA, USA). Haemodynamic data were collected con...
Alveolar oxygen pressure \( (P_{A_O}) = P_{O_2} - SVP(H_2O) - P_{ACO_2}/RQ \).

Alveolar to arterial oxygen tension gradient \( (A-a) \) = \( P_{A_O} - P_{A_O} \).

Data were processed using the Fig P for Windows and Minitab statistical packages. Differences between physiological variables before and after reperfusion were compared using the Student’s paired \( t \) test. The relationship between changes in physiological variables at reperfusion was investigated by calculating the Pearson product moment correlation coefficient. \( P < 0.05 \) was considered statistically significant.

**Results**

The indications for surgery were as follows: primary biliary cirrhosis (eight patients), primary sclerosing cholangitis (three patients), alcoholic cirrhosis (four patients), chronic rejection of liver transplant (two patients) and fulminant hepatic failure (three patients). No patients suffered cardiac arrhythmias at reperfusion and there were no cases of primary graft non-function. All patients had successful transplants and were alive at 1 month. Mean time of blood sampling after reperfusion was 28 (SD 11) min. Continuous monitoring of metabolic gas exchange revealed increases in \( V_{O_2} \) and \( V_{CO_2} \) which consistently occurred within 2–3 min of graft reperfusion (fig. 1). Changes in physiological variables at reperfusion are summarized in table 1.

Boluses of epinephrine were required after reperfusion to maintain arterial pressure in 16 patients. The maximum dose required in any patient was 0.8 mg and no patient required infusions of epinephrine or other inotropic drugs. There was no correlation between epinephrine use and haemodynamic or gas exchange changes.
We compared the physiological changes which occurred in patients transplanted using either veno-venous bypass or piggyback surgical techniques. In patients transplanted using the piggyback technique, the increase in $P_{\text{CO}_2}$ and hydrogen ion concentration was less than with venovenous bypass ($P_{\text{CO}_2}$: piggyback mean increase 0.61 (SD 0.41) kPa vs venovenous bypass 1.3 (0.53) kPa ($P<0.02$); hydrogen ion concentration: piggyback mean increase 5.6 (5.5) mmol litre$^{-1}$ vs venovenous bypass 11.7 (4.6) mmol litre$^{-1}$ ($P<0.02$)). Changes in the other measured variables were similar.

There were significant correlations between changes in $P_{\text{CO}_2}$ and $V_{\text{CO}_2}$ ($r^2=0.25$, $P<0.02$), cardiac output and $V_{\text{CO}_2}$ ($r^2=0.34$, $P<0.01$), and cardiac output and $V_O_2$ ($r^2=0.34$, $P<0.01$) (figs 2, 3).

**Discussion**

The principal finding of our study was that reperfusion of the donor graft during liver transplantation was associated with marked changes in gas exchange and metabolic rate. We observed clinically significant increases in $V_O_2$ and $V_{\text{CO}_2}$ which occurred within minutes of removing the vascular clamps and restoring blood supply to the graft. These changes occurred in association with the well-established observation that cardiac output and pulmonary artery pressure increase at reperfusion while systemic vascular resistance decreases.\textsuperscript{1,11,12}

The accuracy of physiological measurements made during a period of rapid change was an important consideration in this study. The validity of thermodilution measurements of cardiac output is...
decreased by rapid changes or fluctuations in blood temperature, and rapid infusion of i.v. fluids, both of which occur frequently at the time of reperfusion. We did not analyse data in the immediate period after reperfusion, and used an automated method of determining cardiac output which has the advantage of eliminating operator error and averaging multiple data points. Bottiger and colleagues showed that the agreement between this method and conventional bolus thermodilution was good during liver transplantation if approximately 30 min had elapsed from reperfusion. Therefore, we consider it unlikely that large errors occurred in measurements of cardiac output in our patients.

The Deltatrac metabolic monitor has been used widely to measure $V_O_2$ in critically ill patients, and during stable laboratory simulations has an accuracy of approximately $\pm 4\%$ for $V_O_2$ and $\pm 3\%$ for $V_CO_2$. Accuracy is reduced in the presence of a high or fluctuating $P_CO_2$, anaesthetic gases or the presence of gas leaks in the circuit, but these were not relevant in this study. The machine calculates $V_O_2$ from $V_CO_2$ and $RQ$ on the assumption that the patient is at steady state, an approach used to avoid the inaccuracies associated with measuring gas volumes in patients undergoing ventilation. We did not alter ventilation during the study, but the significant changes in cardiac output, acid–base status and deadspace ratio which we observed represented disruptions to steady state which may have influenced the validity of $V_O_2$ estimations. Inaccuracy attributable to these factors should decline exponentially with time as a new equilibrium is established after reperfusion. Our data indicate that devices which assume the presence of a steady state when determining $V_O_2$ after graft reperfusion may be inaccurate until an equilibrium has been re-established. The time required for this to occur is unknown and is likely to vary between patients. After changes in ventilation the majority of this process occurs within 20 min and it is likely that errors attributable to haemodynamic, acid–base and deadspace changes were small 30 min after reperfusion assuming the patients were otherwise stable. This conjecture was supported by our observation that $V_O_2$ reached a plateau within 10–15 min, and did not fluctuate significantly in the majority of patients (fig. 1).

The increase in $P_a CO_2$ has several explanations. First, increased aerobic metabolism by the graft resulted in an increase in carbon dioxide production that was not compensated for by increased ventilation, which was intentionally left unchanged. Second, the small decrease in standard bicarbonate concentration indicated an acute metabolic acidosis which probably resulted from the release of an acid load from the graft and other ischaemic tissues. Welte and colleagues found that gastric intramucosal pH decreased during the anhepatic phase of liver transplantation which was consistent with the presence of gut ischaemia, and this resolved after reperfusion. In our patients there was no correlation between the changes in standard bicarbonate or hydrogen ion concentration and $P_a CO_2$, which may indicate that buffering of the acid load was not a major determinant of the change in $P_a CO_2$. Impaired elimination of carbon dioxide may have contributed to the increase in $P_a CO_2$, but despite constant ventilator settings, we observed a small but significant decrease in deadspace ratio and an increase in alveolar ventilation, which would augment rather than impair carbon dioxide elimination. The most likely explanation for these changes was increased pulmonary perfusion and a decrease in the $V/Q$ ratios of non-dependent alveoli, attributable to increased pulmonary artery pressure and cardiac output.

The observed increase in $V_CO_2$ after reperfusion correlated with the increase in $P_a CO_2$. This association was expected under conditions of constant ventilation where, in the absence of severe pulmonary disease, alveolar and arterial $P_CO_2$ are almost identical. Our results also indicate that altered pulmonary blood flow is an important determinant of $V_CO_2$ because we found a strong correlation between changes in cardiac output and $V_CO_2$. This observation is consistent with those made by Shibutani and coworkers in patients undergoing aortic aneurysm surgery in whom decreases in $V_CO_2$ correlated strongly with decreases in cardiac output.

An increase in arterial carbon dioxide tension causes vasodilatation. In patients with acute respiratory distress syndrome, Thorens and colleagues showed that acute hypercapnia, induced over 30–60 min by a reduction in minute ventilation, increased cardiac output and pulmonary artery pressure, and decreased systemic vascular resistance. Although many factors may be important, the similarity between these changes and those occurring in our patients suggest that altered carbon dioxide tension may contribute to the haemodynamic changes which occur after reperfusion during liver transplantation.

A possible clinical relevance of altered carbon dioxide metabolism relates to cerebral blood flow in patients with abnormal cerebral autoregulation or intracranial hypertension, both of which are common in patients undergoing liver transplantation for fulminant hepatic failure. Cerebral oedema and increased intracranial pressure have also been described recently in patients with chronic liver disease. In patients with cerebral oedema, sudden increases in intracranial pressure are well recognized after reperfusion and may lead to coma and death. The exact aetiology of these changes is unclear and is probably multifactorial, but cerebral vasodilatation in response to increased arterial carbon dioxide tension is a possible contributing factor. The cerebrovascular response to acute hypercapnia in patients with normal autoregulation is extremely rapid (\(< 10 s\)). Our data indicate that an increase in minute ventilation is advisable before reperfusion to minimize the risk of carbon dioxide-induced cerebral vasodilatation in patients at risk of cerebral complications.

We found that $P_a CO_2$ and hydrogen ion concentration increased less in patients transplanted using the piggyback technique. Steib and colleagues found that cardiac output and oxygen delivery were higher during the anhepatic phase of transplantation with the piggyback technique compared with venovenous bypass and we have made similar unpublished observations. Better organ perfusion, particularly of splanchnic tissues, during the anhepatic phase of transplantation may account for the smaller acid load released into the systemic circulation at reperfusion with the piggyback technique.

There was a strong relationship between changes
in cardiac output and \( V_{O_2} \) after reperfusion. There are two possible explanations for this: first, \( V_{O_2} \) may be supply-dependent at this time, particularly if the increase in cardiac output improves oxygen delivery to tissues which were ischaemic during the anhepatic period.24 Alternatively, oxygen uptake by the new liver resulting in increased oxygen demand may be the major determinant of cardiac output, and therefore oxygen delivery, after reperfusion. Previous studies have suggested that the change in \( V_{O_2} \) at reperfusion is a clinically useful measure of graft function.15 24 However, several factors could influence \( V_{O_2} \) at this time. In particular, if the change in \( V_{O_2} \) is attributable in part to factors other than metabolism of the graft, such as epinephrine use and oxygen debt in splanchic tissues incurred during the anhepatic phase, the sensitivity and specificity of this test are unlikely to be high. This may explain why some authors have observed a large increase in \( V_{O_2} \) in patients in whom primary liver non-function occurred.25 In most patients the increase in \( V_{O_2} \) was slightly larger than the increase in \( V_{CO_2} \) and this was reflected by a small but statistically significant decrease in RQ. A similar observation was made by Svensson and colleagues4 and it is possible that this occurred because of altered substrate utilization at the tissue level, such as restoration of hepatic lipolysis. An alternative explanation is that the excess oxygen consumption was caused by free radical formation, which consumes oxygen without the production of carbon dioxide. Free radical production has been demonstrated after reperfusion, may continue for up to 24 h, and 2COa may be high. This may explain why some authors have observed a large increase in \( V_{CO_2} \) and \( 2CO_a \) during uncomplicated liver transplantation.24 Alternatively, oxygen uptake by the new liver, and the perfusion of tissues which were ischaemic during the anhepatic period. The magnitude of these changes may be clinically relevant, particularly in the high risk patient in whom cerebral and haemodynamic instability may occur.

References


