Case Report

A case of post-reperfusion syndrome following surgery for liver trauma

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We report the case of a young trauma patient who needed tight perihepatic surgical packing to control bleeding from a ruptured liver. He developed severe cardiovascular and respiratory decompensation on removal of the surgical packs as a result of the post-reperfusion syndrome. He underwent a total hepatectomy and, 35 h later, orthotopic liver transplantation. The pathophysiology of post-reperfusion syndrome is discussed, and its importance to anaesthetists in the non-transplant setting is emphasized.

Keywords: complications, intra-operative; complications, ischaemia-reperfusion injury; complications, post-reperfusion syndrome; complications, abdominal compartment syndrome; liver, hepatectomy; liver, trauma

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The term ‘post-reperfusion syndrome’ was first used by Aggarwal et al. in 1987 to describe the profound changes seen in recipient cardiovascular status following graft reperfusion during liver transplantation. They defined the syndrome as a decrease in mean arterial pressure (MAP) of 30% or more from baseline, for at least 1 min within 5 min of reperfusion of the liver graft. Post-reperfusion syndrome and similar terms have also been used in a wider context to describe any significant deleterious systemic effects following reperfusion of an organ or region of the body after a period of ischaemia. This has been reported following aortic aneurysm repair, release of high pressure in closed body compartments, release of limb tourniquets, organ transplantation, re-establishment of coronary blood flow—medically or surgically, cardiopulmonary bypass and even after generalized shock. Detailed accounts of post-reperfusion syndrome in the anaesthetics literature in the non-liver transplant setting are scarce. This is surprising given that most of these events occur either intra-operatively or during the early postoperative period.

It is important to distinguish between post-reperfusion syndrome and ischaemia-reperfusion injury. Ischaemia-reperfusion injury is now widely accepted to refer to a process of continued or accelerated local damage occurring in a previously ischaemic organ or region of the body following restoration of the blood supply. In this report, we use the term post-reperfusion syndrome to refer to the systemic events that occur after reperfusion of an ischaemic organ. We describe the management of a case of life-threatening cardiovascular and respiratory decompensation that occurred during a second laparotomy for removal of surgical packs in a patient with severe liver trauma.

Case history

A 14-yr-old male (height 187 cm, weight 75 kg) who had been involved in a road traffic accident presented to a district general hospital. On arrival, he was fully conscious and had stable cardiovascular indices. Computerized axial tomography showed a substantial liver laceration in the right lobe. He started showing signs of acute bleeding and was transferred urgently to the operating theatre. Fluid resuscitation continued while the abdomen was opened. Temporary clamping of the portal triad (Pringle manoeuvre) was performed in an attempt to arrest bleeding. However, this was unsuccessful and it proved to be impossible to stop the bleeding by conventional means. The regional liver centre was contacted and a decision taken to pack the liver, close the abdomen and transfer the patient for specialist care. The patient was transferred to this centre soon after the
conclusion of the laparotomy. He remained sedated, paralysed, his trachea intubated and his lungs mechanically ventilated. Up to this time he had received a total of 25 units of blood, 7 units of fresh frozen plasma, 4 units of platelets, 4 litre of colloid and 2 litre of crystalloid.

On admission to our intensive care unit (ICU), 13 h after the original incident, the patient was well oxygenated (FiO₂ 0.28), was cardiovascularly stable without inotropic support and had good urine output. His liver function was mildly impaired, his trachea intubated and his lungs mechanically ventilated. Up to this time he had received a total of 25 units of blood, 7 units of fresh frozen plasma, 4 units of platelets, 4 litre of colloid and 2 litre of crystalloid.

Fourteen hours after admission to our ICU, the patient was well oxygenated (FiO₂ 0.28), was cardiovascularly stable without inotropic support and had good urine output. His liver function was mildly deranged with an international normalized ratio (INR) of 1.74, lactate 2.72 mmol litre⁻¹ and aspartate transaminase (AST) of 129 iu litre⁻¹. Hepatic angiography showed shift and compression of the coeliac axis and hepatic artery, with possible arterial injury controlled by effective packing. An attempt was made to emoblize the superior segmental vessels on the assumption that they were likely to bleed when the packs were removed.

Fourteen hours after admission to our unit, there was an episode of moderate hypotension, which responded well to volume replacement. A catheter was inserted in the left femoral artery to monitor cardiac output using continuous pulse contour analysis (PiCCO, Pulsion Medical Systems, Munich). Further fluid administration was guided by intrathoracic blood volume index estimation and central venous pressure (CVP). Seventeen hours after admission, the patient became oliguric, acidicotic and hyperlactataemic with evidence of deteriorating liver function. Buffer-free continuous veno-venous haemofiltration (CVVH, exchange rate 4.0 litre h⁻¹) employing prostacyclin was commenced. Infusions of norepinephrine 0.05 μg kg⁻¹ min⁻¹ and dopexamine 1 μg kg⁻¹ min⁻¹ were given in an attempt to improve splanchnic circulation. Sedation consisted of fentanyl and lorazepam infusions titrated to optimal effect.

After 27 h in our ICU, the patient was transferred to the operating theatre to explore the abdomen and remove the liver packs. Physiological variables during this time are shown in Table 1 (column A) and Table 2. The CVVH was discontinued. On arrival in the operating theatre, anaesthesia with isoflurane, 50% oxygen in air and a femoral infusion (300 μg h⁻¹) was commenced. Mechanical ventilation of the lungs was volume controlled with a peak inspiratory pressure of 28 cm H₂O. A fall in blood pressure at this point was managed by i.v. colloid administration and by increasing the infusion rate of norepinephrine to 0.12 μg kg⁻¹ min⁻¹. A 7FG cannula was inserted in the left internal jugular vein to provide an additional route for rapid volume transfusion. Arterial pressure was measured from both left radial and femoral arteries simultaneously. Cardiac output was monitored using PiCCO by both intermittent thermodilution technique and continuous pulse waveform analysis.

After opening the abdomen and within 1 min of starting removal of the perihepatic surgical packs, the patient’s MAP dropped to 35 mm Hg, his heart rate rose to 128 beats min⁻¹ and the CVP fell to 12 mm Hg without any significant bleeding. The initial fall in blood pressure was treated with colloids and 100 μg boluses of epinephrine. The norepinephrine infusion rate was increased to 0.35 μg kg⁻¹ min⁻¹ to maintain a MAP of 60 mm Hg after adequate volume replacement (Table 1, column B). The PiCCO monitor indicated a picture of high cardiac index with low systemic vascular resistance index (SVRI). During removal of the surgical packs, the liver was noted to be very dusky, but its colour improved once all the packs had been removed. There was diffuse parenchymal bleeding from the lacerated liver surfaces, and the surgeons attempted to control this by conventional means. However, there was a further fall in blood pressure, still without any evidence of significant blood loss. An epinephrine infusion of 0.2–0.3 μg kg⁻¹ min⁻¹ was added. Peak inspiratory pressure rose steadily to 45 cm H₂O on unchanged ventilator settings and the FiO₂ was increased to 0.9 in order to maintain PaO₂ above 10 kPa. Diagnoses of tension pneumothorax and pericardial tamponade were excluded. Auscultation of the lungs revealed fine crepitations at the bases. The surgeons once again packed the lacerated liver and closed the abdomen.

When abdominal closure had been completed, the patient underwent a thorough physical re-examination on the operating table for evidence of other pathology. A repeat chest x-ray and transthoracic echocardiography were also performed in the theatre. Except for evidence of pulmonary oedema, physical examination, chest X-ray and ECG were unremarkable. Data from the PiCCO monitor continued to indicate that the patient had a high cardiac index with low SVRI.

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<th>A</th>
<th>B</th>
<th>Normal values</th>
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<tr>
<td>Heart rate (beats min⁻¹)</td>
<td>100</td>
<td>128</td>
<td>72</td>
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<tr>
<td>MAP (mm Hg)</td>
<td>50</td>
<td>60</td>
<td>70–105</td>
</tr>
<tr>
<td>Cardiac index (litre min⁻¹)</td>
<td>2.76</td>
<td>5.5</td>
<td>3.5–5.0</td>
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<tr>
<td>CVP (mm Hg)</td>
<td>20</td>
<td>12</td>
<td>0–8</td>
</tr>
<tr>
<td>SVRI (dyn s cm⁻³ m⁻²)</td>
<td>900</td>
<td>650</td>
<td>1250–1750</td>
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<tr>
<td>ITBVI (ml m⁻²)</td>
<td>890</td>
<td>1050</td>
<td>850–1000</td>
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<tr>
<td>EVLWI (ml kg⁻¹)</td>
<td>8</td>
<td>12</td>
<td>3–7</td>
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<thead>
<tr>
<th></th>
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<tr>
<td>Pao₂ (kPa)</td>
<td>14.0</td>
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<tr>
<td>Paco₂ (kPa)</td>
<td>0.28</td>
</tr>
<tr>
<td>PIP (cm H₂O)</td>
<td>4.7</td>
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<tr>
<td>Hb (gm dl⁻¹)</td>
<td>9.5</td>
</tr>
<tr>
<td>INR</td>
<td>3.17</td>
</tr>
<tr>
<td>Lactate (mmol litre⁻¹)</td>
<td>6.01</td>
</tr>
<tr>
<td>AST (iu litre⁻¹)</td>
<td>2022</td>
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A presumptive diagnosis of severe post-reperfusion syndrome was made. At this stage, it became evident that the patient was unlikely to survive more than a few hours, a point of view reinforced by rising pulmonary inflation pressures and deteriorating gas exchange. Urgent discussions between the anaesthetists, operating surgeons and hepatologist were held. All agreed that the only therapeutic option remaining was to undertake a total hepatectomy with a view to delayed liver transplantation, should there be evidence of sustained improvement in the patient’s condition. The mother of the patient was contacted by phone and verbal consent for total hepatectomy obtained.

The abdomen was reopened and the surgical packs were removed once again. The liver, which now looked markedly ischaemic, was completely excised and a porto-caval anastomosis fashioned. During re-opening of the abdomen, the patient developed frank pulmonary oedema with copious quantities of frothy fluid issuing from the endotracheal tube. Following vascular isolation of the liver, there was a rapid improvement in physiological variables, formation of pulmonary oedema fluid reduced markedly and it became possible to reduce the rate of infusion of the inotropes. Thereafter, abdominal closure proceeded uneventfully, with continued improvement in the cardiovascular status. On return to the ICU, CVVH was restarted and an infusion of N-acetyl cysteine was commenced as a free radical scavenger.

A cadaveric liver became available the following day and was implanted into the patient 35 h after total hepatectomy. By 9 h post-transplant it was possible to discontinue all inotropic support and the patient’s trachea was extubated on the eighth day post-transplant. He was discharged from ICU on day 17 but was readmitted on day 19 for respiratory monitoring and administration of continuous positive airway pressure. He remained on the ICU for a further 5 days. Renal function was slow to recover and required CVVH for 22 days. His post-operative course was complicated by methicillin-resistant *Staphylococcus aureus* infection and recurrent episodes of vomiting in the ward. He was discharged home after 43 days in hospital and remained well after 1 yr.

**Discussion**

Acute intra-operative cardiovascular decompensation is not uncommon in patients who have sustained major trauma. More common causes include hypovolaemia, pericardial tamponade, tension pneumothorax, embolism, myocardial injury, sepsis and anaphylactic reactions to drugs or blood products. This patient had sustained liver trauma with possible disruption of the arterial blood supply and had undergone considerable haemorrhaging that could only be controlled by tight packing and arterial embolization. The subsequent clinical course gave rise to serious concern that he had developed hepatic ischaemia. His liver function deteriorated progressively after the first laparotomy and packing. During the second laparotomy, there was visual evidence of liver hypoperfusion, which transiently improved when the packs were removed. However, after removal of the packs, the patient became profoundly hypotensive, despite both adequate cardiac preload and the absence of any significant bleeding. The PiCCO monitor indicated a high cardiac index with a low SVRI that might in part have resulted from mechanical decompression of the splanchnic circulation following pack removal. However, the history, the overall clinical picture and the PiCCO derived variables together suggested that the patient had suffered an ischaemic injury to the liver and had gone on to develop post-reperfusion syndrome. A diagnosis of septic shock could not be excluded with certainty at that time, but the clinical evolution of the case militated against this possibility. Rapid improvement of the patient after de-vascularization of the damaged liver, sustained after hepatectomy, also supported the diagnosis of post-reperfusion syndrome.

Systemic inflammatory response syndrome (SIRS) is common in acute liver failure and may have played a part along with post-reperfusion syndrome in this case. Total hepatectomy is a well-described therapeutic strategy in some patients with acute liver failure and is employed in order to "buy time" until a suitable donor organ has been procured. Hepatectomy appears to interrupt the evolution of life threatening SIRS and multiorgan dysfunction syndrome (MODS) for a brief period (see below). It is also possible that post-reperfusion syndrome itself can lead to SIRS.

The post-reperfusion syndrome is a systemic response to a reperfusion injury, while ischaemia-reperfusion injury is a process of continued or accelerated local damage occurring in a previously ischaemic organ or region of the body following restoration of the blood supply. Ischaemia-reperfusion injury may compromise the viability of the reperfused organ or region, but, in contrast, sustained post-reperfusion syndrome may be immediately life threatening. In the classic descriptions of post-reperfusion syndrome during liver transplantation, various combinations of bradyarrhythmias, hypotension, decreased systemic vascular resistance, increased cardiac filling pressures and high pulmonary arterial pressures were observed. A similar clinical picture is described in non-liver transplant cases. While there are many similarities between the classic descriptions of post-reperfusion syndrome and the clinical picture that developed in this case, severe tachycardia was a significant exception.

Recent evidence suggests that oxygen, reintroduced into the microvasculature, is able to produce a burst of oxygen-derived free radicals. Prolonged hypoxia is known to alter membrane potentials, disturb the distribution of ions, increase intracellular volume, decrease membrane fluidity and impair the cytoskeletal organization of endothelial cells. Many of these endothelial cell responses to hypoxia are exacerbated by reperfusion of the ischaemic vessel bed.
Ischaemia-reperfusion injury causes systemic release of inflammatory mediators, thereby promoting neutrophil activation, enhancing generalized leucocyte and endothelial adhesion molecule expression and enhancing the opportunities for leucocyte–endothelial interaction leading to vascular dysfunction and tissue injury. There is experimental evidence to suggest that tumour necrosis factor α (TNF-α), complement cascade, imbalance of nitric oxide–superoxide dismutase and platelet activating factor also take part in mediating post-reperfusion syndrome in a manner similar to their role in SIRS. Hepatic as well as intestinal ischaemia-reperfusion injury are recognized causes of myocardial, pulmonary and hepatic injury. There have been suggestions that inhibition of xanthine oxidase, an enzyme which enhances free radical generation, can attenuate ischaemia-reperfusion injury. Although there is ample experimental evidence to suggest that free radical scavengers and antioxidants prevent ischaemia-reperfusion injury, research into their effects in preventing post-reperfusion syndrome has been scanty. Moreover, their efficacy in attenuating an existing post-reperfusion syndrome is even more uncertain. However, in retrospect, an attempt could have been made in our case to modulate neutrophil function and adhesion by using N-acetyl cysteine intra-operatively.

Total hepatectomy followed by liver transplantation either immediately or at a later stage is an established method of treatment in acute liver graft failure. This management strategy has been also found to be life saving in fulminant hepatitis patients who developed severe MODS, while awaiting liver transplantation. More recently, unsalvageable liver trauma has been added to the list of indications of total hepatectomy. So far, there have been 13 reported cases of total hepatectomy and liver transplantation performed in trauma patients. In the largest series of eight patients reported by Ringe and Pichlmayr, the indication for the procedure in four patients was uncontrolled bleeding. Other indications for total hepatectomy have been ‘toxic liver syndrome’, massive liver necrosis, hepatic insufficiency, fulminant hepatic failure or portal venous thrombosis. We believe that our case was unique in that total hepatectomy was performed to resolve life-threatening post-reperfusion syndrome. Post-reperfusion syndrome leading to death during surgical unpacking of the abdomen in trauma patients has been reported before.

In this series, 10 patients developed abdominal compartment syndrome (intra-abdominal hypertension, high peak airway pressure and oliguria) and had to undergo decompressive laparotomy. On decompression, four of these patients suffered asystole and did not survive. The authors attributed this to post-reperfusion syndrome.

We believe that our case illustrates a number of important issues. Intraoperative post-reperfusion syndrome can occur in other situations, not just during liver transplantation. The anaesthetics team should be aware of the possibility of post-reperfusion syndrome and its systemic sequelae whenever some sort of re-vascularization or surgical decompression procedure has been undertaken. Deterioration in cardiovascular or pulmonary function following re-establishment of blood supply should be taken very seriously. Appropriate haemodynamic monitoring should be employed and adequate vascular access is imperative in this type of surgical procedure. A modern ventilator, which can accurately deliver high positive end expiratory pressure and pressure controlled ventilation would be useful. At present there is no established method of preventing the occurrence of post-reperfusion syndrome and treatment is essentially supportive.

As liver transplantation becomes more successful, total hepatectomy may become a viable treatment option in unsalvageable liver trauma. However, the risk of donor organ shortage should be carefully weighed against the odds of the patient not surviving without a total hepatectomy. A decision of this nature should be taken by an experienced multidisciplinary liver team, in a unit where transplantation is available. Early referral is important. It is worth noting that all of the reported survivors of aggressive management like this were very young adults with ages ranging from 14 to 24 yr.

References


