J Anesth (2007) 21:513–515
DOI 10.1007/s00540-007-0561-7

Journal of
Anesthesia

Pulmonary hypertension due to unknown causes in liver resection

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Abstract
A 16-year-old male underwent transcatheter arterial embolization against a large hepatic tumor, and was subsequently scheduled for removal of the tumor. Sudden hypotension and tachycardia were observed on removal of the tumor. Massive bleeding or obstruction of the inferior vena cava was expected to develop, but this did not occur because of simultaneous pulmonary hypertension (PH). The development of acute PH due to pulmonary vasoconstriction was suspected. Milrinone and prostaglandin E1 were effective. The same type of PH was again observed during manipulation of the residual portion of the liver. The acute PH was reproducible each time the liver was manipulated, which could suggest that this series of PH was specifically related to the hepatic lesion. A necrotic hepatic lesion might play an important role in disturbing the pulmonary circulation and causing the development of acute PH.

Key words Pulmonary hypertension · Liver resection · Cytokines

Introduction

It is known that sudden intraoperative pulmonary hypertension is mainly caused by acute heart failure [1], pulmonary embolism [2], or anaphylaxis [3]. We experienced a reproducible PH due to unknown causes during liver resection.

Case report

A 16-year-old male, whose weight and height were 47 kg and 167 cm, respectively, was admitted to the hospital because of acute back pain. He showed no physical abnormalities and had a nonspecific medical history. All other laboratory data were also normal. A diagnostic abdominal computer tomographic scan revealed that a tumor occupied a large portion of the left hepatic lobe, but showed no sign of liver cirrhosis. An angiographic examination was peformed and identified bleeding from a liver tumor, which was probably the cause of the back pain. A transcatheter arterial embolization (TAE) was then performed against a hepatic tumor occupying three hepatic segments. Forty days after the TAE, the patient was scheduled for an extended right lobectomy with resection of the retrohepatic inferior vena cava under a partial clamping technique.

Roxatidine (75 mg; H2 blocker) was given orally 2 h prior to admission to the operating room. After anesthetic induction with an intravenous injection of 0.1 mg fentanyl, 100 mg propofol, and 8 mg vecuronium, anesthesia was maintained with a target-controlled infusion system (TE-371; Terumo, Tokyo, Japan) with propofol (the target concentration was set at 3 μg/ml) and 67% nitrous oxide in oxygen. Routine clinical monitoring was carried out, including a three-lead electrocardiogram, noninvasive arterial blood pressure, pulse oximetric pulse wave oxygen saturation (Sp_{O_2}), and end-tidal carbon dioxide concentration (Et_{CO_2}). After the insertion of arterial and central venous catheters, we inserted a pulmonary arterial catheter because of a risk of massive bleeding. We continuously monitored arterial, right atrium, and pulmonary arterial pressures (ABP, RAP, and PAP) and intermittent pulmonary arterial wedge pressure (PAWP) throughout the management procedure.

A blood transfusion was given according to the volume of blood loss during detachment of the liver. The patient's hemodynamic status was stable, although moderate bleeding continued. However, his mean ABP suddenly decreased to 40–50 mmHg and his heart rate increased to 140–150 bpm on removal of the tumor. Simultaneously, his mean PAP increased to more than 40 mmHg (Fig. 1), although his RAP and PAWP did not

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Received: March 28, 2007 / Accepted: July 18, 2007

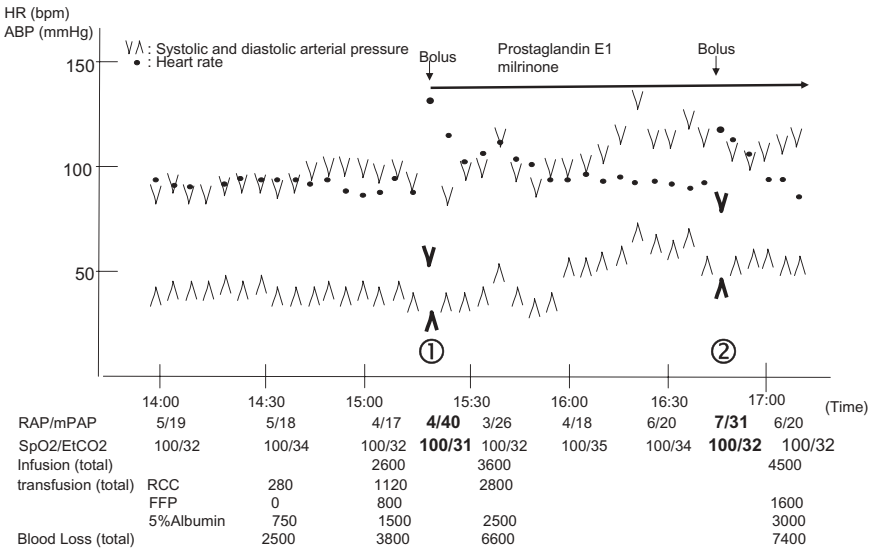

Fig. 1. Intraoperative hemodynamic changes. *ABP*, arterial blood pressure; *HR*, heart rate; *RAP*, right atrium pressure; *mPAP*, mean pulmonary arterial pressure; Sp_{O_2}, pulse oximetric pulse wave oxygen saturation; Et_{CO_2}, end-tidal carbon dioxide concentration; *Bolus*, bolus administration of prostaglandin E1 and milrinone; *RCC*, red cell concentrates; *FFP*, fresh frozen plasma. ① The first episode of acute pulmonary hypertension. ② The second episode of acute pulmonary hypertension

change (5–6 and 10–11 mmHg, respectively). There were no typical signs of left ventricular failure. The Sp_{O_2} value was maintained at 99%–100%, and the Et_{CO_2} value changed very little. Blood gas data also showed normal values. Primary pulmonary vasoconstriction was suspected. We immediately started fluid management and the administration of ephedrine (8 mg) and methoxamine (2 mg) via the central venous infusion line. Our surgeons continued to perform hemostatic manipulation for massive bleeding. We then, started vasodilator therapy with a continuous infusion of prostaglandin E1 (30–50 ng/kg/min) and milrinone (0.5–0.75 μg/kg/min) combined with temporary boluses of a small dose via the pulmonary arterial infusion line. During this treatment, the patient's hypotension and tachycardia also improved. His mean PAP decreased to 25–30 mmHg in 15 min and then returned to the pre-event values. When we carried out hepatic manipulation to confirm the patient's hemostatic status after resection of the liver, we again observed the same type of PH (Fig. 1). His mean PAP returned to normal values in 20 min without the development of severe hypotension and tachycardia, but with boluses of small dosees of prostaglandin E1 and milrinone. Postoperatively, these phenomena were not observed.

Discussion

We experienced a reproducible sudden PH due to unknown causes during a liver resection. It is generally known that intraoperative PH is mainly caused by heart failure [1], pulmonary embolism [2], or anaphylaxis [3]. However, these possibilities did not appear to apply. Regarding heart failure, it is generally considered that PCWP is increased due to pump failure. However, no increase in PCWP was observed in this case. In regard to pulmonary embolism, drastic changes in Sp_{O_2} and Et_{CO_2} values are usually observed, and a capnogram usually shows a typical waveform change. However, these changes were not apparent in this case. At the moment of the acute increase in PAP, we carried out a blood transfusion because of transient massive bleeding. An anaphylactic transfusion reaction might be one possible cause for this phenomenon. However, the patient did not show any other typical clinical signs of an anaphylactic reaction followed by blood transfusion.

Consequently, it was strongly suspected that pulmonary vasoconstriction caused the development of acute PH in our case, although the cause of this pulmonary vasoconstriction is still unknown. RAP should have increased with PH. However, RAP did not increase at that time in spite of the high PAP. It was likely that bleeding masked an increase in RAP. This phenomenon was probably related to various factors, and therefore it might be impossible to determine a specific cause. However, the fact that our case showed reproducible PH during hepatic manipulation would suggest an answer to this question. It is not unreasonable to suppose that hepatic manipulation was at least related to this phenomenon. This patient was suffering from hepatic cell carcinoma, which never produced any vasoactive mediator. Therefore, we would like to consider the possibility that cytokines, which appeared to exist in the hepatic lesion, played an important role in this phenomenon.

Some studies have suggested that an imbalance in the production or metabolism of several vasoactive mediators in the lung may be important in the pathogenesis of primary pulmonary hypertension [4,5]. In general, a number of cytokines play major roles in the response to injury and infection, and also in the development of

organ damage in critically ill patients. These cytokines induce various cytokines by the cytokine network [6]. It has been reported that some cytokines, for example tissue necrosing factor-α (TNF-α) and platelet activating factor (PAF), can induce PH by affecting pulmonary vasculature in certain situations [7].

In this case, preoperative TAE was performed against the hepatic tumor. Thus, the liver probably contained abundant cytokines, particularly TNF-α in the necrotic lesion due to TAE. It is suggested that the release of cytokines from the necrotic lesion during hepatic manipulation and the subsequent activation of the cytokine network might play an important role in the development of this acute PH.

We would also like to suggest the possibility that imbalances the production or metabolism of several vasoactive mediators, for instance endothelin, thromboxane, and prostacyclin, were evoked through endothelial injury due to the release of abundant cytokines in the necrotic hepatic lesion [8–10]. This patient might be more susceptible to this type of imbalance than others. In other words, that could be the reason why all patients undergoing liver resection will not develop PH.

We should note that temporary bolus injections of milrinone and prostaglandin E1, in addition to their continuous infusion via the pulmonary arterial line, were effective in relieving the acute PH in this case. There have been some reports that phosphodiesterase III inhibitors [11] and prostaglandin E1 [12] produce pulmonary arterial relaxation. It is reasonable to think that the modified use of these two drugs provided the rapid onset of their therapeutic efficacy for PH in this case.

In conclusion, we have presented our experience of a reproducible sudden PH due to unknown causes during liver resection. This phenomenon was probably related to various factors. We suggested the possibility that cytokines played an important role in this phenomenon. In addition, phosphodiesterase III inhibitors and prostaglandin E1 were effective.

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