Case Report

Hypoxic hepatitis during the perioperative period in patients with severe pulmonary disease and cor pulmonale

ABSTRACT

Hypoxic hepatitis (HH) is characterized by marked and transient elevations in liver enzyme levels in the absence of other potential causes of liver injury. Although rare, it can occur in the presence of hemodynamic instability and hypoxemia in patients with cor pulmonale. We report two cases of perioperative HH in patients with severe pulmonary disease and cor pulmonale. The first case is of a patient with cor pulmonale who underwent hemiarthroplasty for a femur fracture. Transient hypotension developed during spinal anesthesia and severe hypoxemia were observed in the postoperative period. After surgery, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels suddenly increased to 3740 and 817 U/L, respectively. The second case is of a patient with congestive heart failure and cor pulmonale whose blood pressure and oxygen saturation decreased during induction of general anesthesia and after surgery, and AST, ALT, and lactic dehydrogenase levels increased to 1291, 1292, and 2710 U/L, respectively. The liver enzyme levels normalized within 7–14 days in both cases. We speculate the diagnosis of these cases as HH.

Key words: Anesthesia; cor pulmonale; hypoxic hepatitis; portal congestion

Introduction

Perioperative liver injury is usually related to known liver disease, direct injury due to surgical manipulation, or use of anesthetic drugs.[1] Furthermore, although rare, perioperative hypoxic hepatitis (HH) may develop because of hemodynamic instability or severe hypoxia. It is usually referred to as "ischemic hepatitis" or "shock liver" and manifests as a marked elevation in liver enzyme levels, prolongation of prothrombin time (PT), and increase in the international normalized ratio (INR).

Pulmonary impairments, such as cor pulmonale, can lead to right heart failure and subsequent hepatic circulation congestion. Congestive liver increases the susceptibility to hypoxic damage as it impairs oxygen diffusion from the capillaries to the cells.[2] In addition, the severity of hypoxic damage varies from minimal elevation of liver enzyme levels to fulminant hepatic failure and death.

Here, we present two cases of perioperative HH in patients with severe pulmonary disease and cor pulmonale. We discuss in detail and compare the mechanism of HH in both cases. We also speculate on the etiology of HH and measures for early recovery from HH.

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Hyuckgoo Kim, Sang-Jin Park[1], Deokhee Lee[1]

Department of Anesthesiology and Pain Medicine, Pusan National University Yangsan Hospital, [1]Department of Anesthesiology and Pain Medicine, College of Medicine, Yeungnam University, Nam-gu, Daegu, Republic of Korea

Address for correspondence: Prof. Deokhee Lee, Department of Anesthesiology and Pain Medicine, College of Medicine, Yeungnam University, 170, Hyeonchung-ro, Nam-gu, Daegu 705-703, Republic of Korea. E-mail: dhlee415@ynu.ac.kr

Case Reports

Case 1

A 57-year-old male, weighing 55 kg, was scheduled for bipolar hemiarthroplasty. He had a 10-year history of chronic obstructive pulmonary disorder and cor pulmonale. Preoperative chest radiography revealed severe bronchiectasis with emphysema in both lung fields and pneumonic consolidation in the right lower lung [Figure 1]. Preoperative liver function tests showed normal aspartate aminotransferase (AST) (26 U/L) and alanine aminotransferase (ALT) levels (15 U/L). Other preoperative evaluations were within normal limits.

In the operating room, routine anesthetic monitoring was initiated. Initial vital signs were blood pressure (BP) of 120/70 mmHg, heart rate (HR) of 90 beats/min (bpm), and oxygen saturation of 87%. Spinal anesthesia with 7 mg of 0.5% bupivacaine was administered through a 25-gauge spinal needle at the 4–5th lumbar intervertebral level. Approximately 10 min after intrathecal injection, sensorial block was ascertained using the pinprick test at the 6th thoracic vertebral level. At this time point, systolic BP (SBP) dropped to 80 mmHg; 8 mg of ephedrine was administered intravenously. SBP then recovered to 90–100 mmHg and it was maintained at this level until the end of surgery.

On postoperative day 1 (POD 1), AST and ALT levels suddenly increased to 3740 and 817 U/L, respectively [Table 1]. In addition, PT and INR increased to 24.7 s (normal: 10.4–13.4) and 2.23 (normal: 0.85–1.25), respectively [Table 2]. Arterial blood gas analysis showed pH: 7.380, $PaCO_2$: 59.4 mmHg, PaO_2: 32 mmHg, base excess: 8.8 mM, and SaO_2: 57.9%. Echocardiography revealed distension and enlargement of the right atrium and ventricle with mild pulmonary hypertension (specifically, right ventricular systolic pressure [RVSP]: 37 mmHg, right atrial pressure [RAP]: 10 mmHg, and pulmonary capillary wedge pressure [PCWP]: 14.8 mmHg) [Figure 2]. In addition, global right ventricular hypokinesia accompanied by moderate pulmonary hypertension was observed. Chest computerized tomography revealed pleural effusion in the left lower lung. Ultrasonography of the liver showed an abnormal parenchymal lesion with ascites around the liver and pelvic cavity. Viral hepatitis was ruled out based on blood immunology tests. On POD 9, AST and ALT levels decreased to 47 and 305 U/L, respectively, and normalized on POD 14. The patient was discharged on POD 20.

Case 2

A 55-year-old male, weighing 59 kg, was scheduled for emergent surgery for femur neck fracture. He had earlier been treated for congestive heart failure with cor pulmonale. Preoperative chest radiography revealed bronchiectasis with emphysema and pneumonic consolidation in the right lung with loss of left lung parenchyma and cardiomegaly [Figure 3]. Preoperative echocardiography showed moderate tricuspid valve regurgitation and pulmonary hypertension (specifically, tricuspid valve regurgitation Grade: II, RVSP: 66 mmHg, RAP: 5 mmHg, PCWP: 12.65 mmHg, D-shaped left ventricle, and dilated pulmonary artery). Preoperative liver function tests showed normal AST and ALT levels, 36 and 66 U/L, respectively.

In the operating room, routine anesthetic monitoring was initiated. Initial vital signs were BP: 110/80 mmHg, HR: 130 bpm, and oxygen saturation: 88%. Anesthesia was induced with etomidate 9 mg and rocuronium 50 mg. Immediately before tracheal intubation, BP and oxygen saturation were not checked and HR increased to 140 bpm. Tracheal intubation was performed immediately, and fluid was rapidly administered intravenously. Ephedrine 8 mg was administered but it elicited no response; thus,

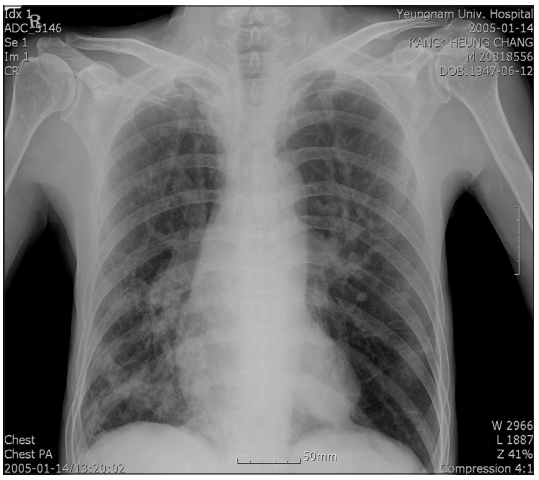

Figure 1: Preoperative chest simple image in case 1. Preoperative image reveals severe bronchiectasis with emphysema in both lung fields and pneumonic consolidation in the right lower lung

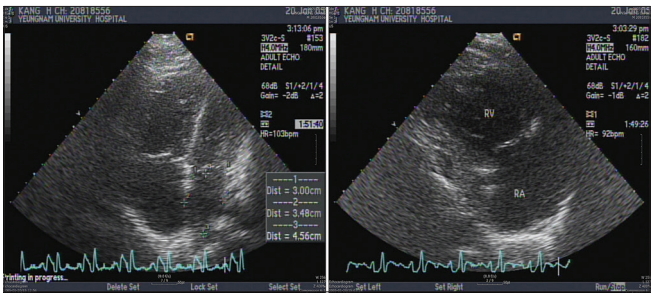

Figure 2: Postoperative transthoracic echocardiography in case 1. Echocardiography reveals distension and enlargement of the right atrium and ventricle with D-shaped left ventricle

Table 1: Pre- and post-operative findings of arterial blood gas analysis and liver function tests

Case 1	pH	PaO_2 (mmHg)	$PaCO_2$ (mmHg)	BE (mEq/L)	SaO_2 (%)	AST/ALT (U/L)
PRE	7.505	61	48.8	14.3	92.7	26/15
POD 1	7.38	32	59.4	8.8	57.9	3740/817
POD 2	7.423	62	53.4	9.6	91.3	3858/2621
POD 3	7.34	48	47.3	−0.7	84.6	568/1292
POD 5	7.488	46	59.8	19.4	83.1	294/1206
POD 9						47/305
POD 14						46/57
Case 2	**pH**	**PaO_2 (mmHg)**	**$PaCO_2$ (mmHg)**	**BE (mEq/L)**	**SaO_2 (%)**	**AST/ALT (U/L)**
PRE	7.427	87.8	42.1	3	97.7	36/66
POD 1	7.429	83.8	43.1	3.7	95.9	1291/1292
POD 2	7.346	101	40.6	2.9	97.7	881/1304
POD 3	7.401	99.1	45	2.6	98.4	316/1027
POD 5	7.414	104	41.6	3.8	97.9	88/498
POD 7	7.377	97.1	46.1	1.7	95.2	53/295
POD 10						36/40

PRE: Preoperative period; pH: Arterial pH; PaO_2: Arterial oxygen tension; $PaCO_2$: Arterial carbon dioxide tension; BE: Arterial base excess; SaO_2: Arterial oxygen saturation; POD: Postoperative day; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase

Table 2: Pre- and post-operative blood test results

Case 1	Hb/Hct (g/dL)	Plt (10^3/μL)	PT/PTT/INR (sec)	Na/K (mmol/L)	D-bil/T-bil/LDH (mg/dL)
PRE	13.6/40.2	249	14.3/39.0/1.11	135/3.2	0.24/0.81
POD 1	13.3/40.9	255	24.7/41.8/2.23	142/4.7	0.36/0.78
POD 2	11.2/34.5	134		137.2/4.53	0.5/1.4
POD 5	12/37.9	140		144/2.5	0.47/1.18/619
POD 9	14/46.2	358		135/3.1	0.49/1.14/635
POD 14	12.4/39.2	311		130/2.9	46/57
Case 2	**Hb/Hct (g/dL)**	**Plt (10^3/μL)**	**PT/PTT/INR (sec)**	**Na/K (mmol/L)**	**D-bil/T-bil/LDH (mg/dL)**
PRE	15.6/45.9	464	11.7/31.8/1.07	130/3.9	0.36/0.56/564
POD 1	14.6/42.9	356	17.4/52.3/1.58	136/4.3	0.82/1.25/2710
POD 2	13.1/39.0	300		142/4.3	0.82/1.63/-
POD 3	12.8/37.3	312		142/4.1	0.85/1.27/-
POD 5	13.9/41.2	365	13.6/32.7/1.24	139/3.7	0.51/0.76/376
POD 9	13.2/38.9	739	13.6/36.5/1.24	137/5.1	0.63/0.38/-
POD 14	12.8/37.3	878		137/4.2	0.23/0.45/439

PRE: Preoperative period; POD: Postoperative day; Hb: Hemoglobin; Hct: Hematocrit; PT: Prothrombin time; PTT: Partial thromboplastin time; INR: International normalized ratio; D-bil/T-bil: Direct bilirubin/total bilirubin; LDH: Lactate dehydrogenase

epinephrine 300 μg was administered intravenously. In addition, 0.1 μg/kg/min of epinephrine and 0.5 μg/kg/min of milrinone were infused intravenously. SBP recovered to 90–110 mmHg, and vital signs stabilized. General anesthesia was maintained with sevoflurane 1–1.5 vol% in 50% O_2. Perioperative transesophageal echocardiography revealed right atrial hypertrophy and enlarged hypokinetic right ventricle. In addition, moderate tricuspid valve regurgitation and pulmonary hypertension with increased central venous pressure were observed.

Following surgery, vital signs were consistently stable with epinephrine, milrinone, and norepinephrine infusion. However, at approximately 18 h after surgery, AST, ALT, and lactic dehydrogenase levels suddenly increased to 1291 U/L, 1292 U/L, and 2710 U/L, respectively [Table 1], and PT and INR increased at 17.4 s (normal: 10.4–13.4) and 1.58 (normal: 0.85–1.25), respectively [Table 2]. Liver enzyme levels finally normalized on POD 10, and thereafter, the patient had an uneventful course.

Discussion

Histopathological confirmation is required for the definitive diagnosis of HH. However, HH can be diagnosed based on a remarkable underlying cardiorespiratory disease and marked elevation of liver enzyme levels, needless of histopathological examination. Therefore, the diagnosis of HH is established using the following three criteria:[3,4] a clinical setting of acute cardiac, circulatory, or respiratory failure; dramatic increase in serum aminotransferase activity to at least 20 times the upper normal limit; and exclusion of other putative causes

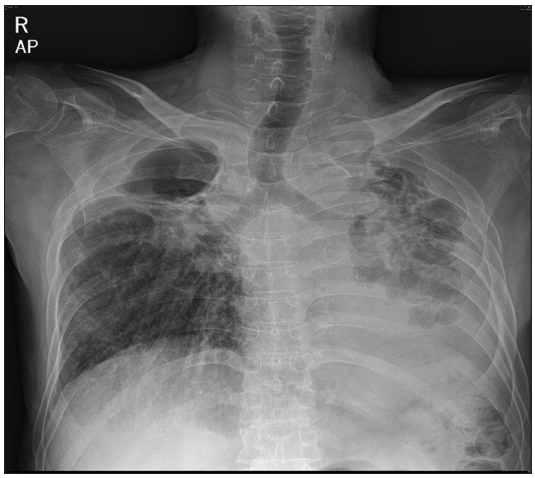

Figure 3: Preoperative chest simple image in case 2. Preoperative image reveals severe bronchiectasis with emphysema in the right lung field and pneumonic consolidation in the right lower lung with loss of left lung parenchyma and cardiomegaly

of liver cell necrosis, such as viral or drug-induced hepatitis. We believe that, in case 1, drug-induced liver injury is very unlikely as regional anesthesia was performed, precluding the use of any volatile or intravenous anesthetic. In case 2, there was no history of exposure to a hepatotoxic drug, and no hepatotoxic medications were administered. Sevoflurane does not have hepatotoxic effects.[5] Furthermore, the biochemical features of anesthetic-induced hepatitis include a prolonged period of hyperbilirubinemia and slow liver enzyme normalization.[3] Therefore, considering their signs and underlying hemodynamic conditions, both patients met the three criteria.

The mechanism of HH differs in both cases: arterial hypoxemia in case 1 and decreased hepatic flow in case 2. However, portal congestion due to cor pulmonale was common in both cases and was key to the development of HH in both cases. Cor pulmonale induces right heart failure and impairs hepatic venous outflow, which leads to portal congestion. Edema in congestive liver disturbs oxygen diffusion in the hepatic lobule.

With regard to portal congestion, the elevated hepatic venous pressure produces massive, prolonged, and constant filtration of fluids across hepatic sinusoids, especially in the centrilobular zone.[6] Resultantly, oxygen transfer to liver cells is impeded by the barrier imposed by the edema fluid. Although this does not decrease oxygen delivery to the liver, oxygen uptake in the liver is reduced because hepatic blood perfusion is disturbed. In addition, transient systemic hypotension occurred during anesthesia in both cases. In case 1, SBP decreased to 80 mmHg for a few minutes because of sympathetic block, and in case 2, BP decreased drastically during anesthesia induction. In both cases, decreased BP may have reduced hepatic blood flow, resulting in inadequate oxygen supply to the liver. Furthermore, systemic hypotension causes hepatic artery constriction by coincidental systemic reflex vasoconstriction. A low SBP of <90 mmHg for 15 min may result in the development of HH.[7]

In case 1, PaO_2 was low preoperatively because of severe pulmonary disease and remained low postoperatively. Therefore, we hypothesize that arterial hypoxemia contributed to the development of HH. In an animal study, extreme hypoxemia was found to induce necrosis of centrilobular liver cells,[8] demonstrating that tissue oxygenation during ischemia or hypoxemia is critical to cellular viability. We believe that, in case 1, combined hepatic arterial hypoxemia and portal congestion effected HH.

HH characteristically resolves within 7–10 days. Although no specific treatment exists for HH, early recognition of the disease and its underlying pathology is crucial to effective management. Stable hemodynamics and appropriate blood oxygenation must be a priority as adequate hepatic blood flow and oxygen supply can ensure recovery of liver function. In case 2, we used vasopressors and inotropes to increase BP. Considering the patient's underlying disease, epinephrine was the drug of choice as it has superior inotropic potency and positively influences right ventricular output.[9] Furthermore, epinephrine has an overwhelming effect on right ventricular output against increased pulmonary arterial pressure.[10]

Conclusion

HH is rarely encountered during the perioperative period, likely induced by transient hemodynamic instability and severe hypoxemia in patients with right heart failure accompanied by cor pulmonale. The fundamental concept of HH is that liver ischemia is caused not only by decreased BP but also by portal congestion and arterial hypoxemia.[3] Anesthesiologists must minimize even transient BP fluctuations and optimize oxygenation during the perioperative period.

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Conflicts of interest
There are no conflicts of interest.

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