Case report: Fatal hepatic failure after aortic valve replacement and sevoflurane exposure

[Présentation de cas : Insuffisance hépatique fatale après un remplacement de la valve aortique et une exposition au sévoflurane]

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Purpose: To report a case of lethal hepatotoxicity possibly caused by sevoflurane.

Clinical features: A 76-yr-old woman with a history of four previous minor surgical procedures developed acute liver failure after general anesthesia with sevoflurane, sufentanil and propofol for aortic valve replacement. After an uneventful procedure the patient was extubated 4.5 hr after surgery. On the second postoperative day, serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) increased. On the third postoperative day liver failure occurred, ALT peaked at 10504 $U \cdot L^{-1}$ and AST at 15516 $U \cdot L^{-1}$, and coagulopathy with an international normalized ratio of 4.6 developed. Liver transplantation was considered but rejected as a therapeutic option. The patient died three days after the operation in multiple organ failure triggered by hepatic failure. Other possible causes for liver failure were excluded.

Conclusions: Sevoflurane hepatitis as a cause for liver failure may be implicated in this patient undergoing valve surgery. Unlike other halogenated anesthetic drugs, sevoflurane is not metabolized to hepatotoxic trifluroacetyl proteins. However, compound A may react with proteins and may be transformed into antigenic material. We suggest that all halogenated anesthetics may be implicated with acute liver injury.

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Éléments cliniques *: Une insuffisance hépatique aiguë s'est développée chez une femme de 76 ans, déjà opérée quatre fois à l'occasion d'interventions chirurgicales mineures, à la suite d'une anesthésie générale avec sévoflurane, sufentanil et propofol lors du remplacement de sa valve aortique. Après une intervention sans particularité, la patiente a été extubée 4,5 h après la chirurgie. Le deuxième jour postopératoire, l'alanine aminotransférase (ALT) et l'aspartate aminotransférase sériques (AST) ont augmenté. L'insuffisance hépatique est survenue le troisième jour après l'opération, et l'ALT et l'AST ont présenté des valeurs maximales de 10504 $U \cdot L^{-1}$ et 15516 $U \cdot L^{-1}$ respectivement. Le même jour, une coagulopathie avec un rapport international normalisé de 4,6 s'est développée. Une transplantation hépatique a été envisagée, mais cette option thérapeutique a été refusée. La patiente est décédée trois jours après l'opération d'une défaillance multisystémique provoquée par l'insuffisance hépatique. D'autres causes possibles de l'insuffisance hépatique ont été écartées.*

Conclusion *: Une hépatite au sévoflurane provoquant une insuffisance hépatique peut être en cause chez cette patiente de chirurgie valvulaire. Au contraire d'autres agents anesthésiques halogénés, le sévoflurane n'est pas métabolisé en protéines de trifluoroacétyl hépatotoxique. Toutefois, le composé A peut réagir avec des protéines et peut être transformé en matériel antigénique. Ce cas laisse à penser que tous les anesthétiques halogénés pourraient causer des lésions hépatiques aiguës.*

Objectif *: Présenter un cas d´hépatotoxicité létale causée probablement par le sévoflurane.*

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MOST halogenated volatile anesthetics, including halothane, enflurane, isoflurane, and desflurane undergo cytochrome P450-mediated oxidative metabolism to form trifluoroacetylate (TFA) hepatic proteins.[1,2] All patients anesthetized with these agents have the potential to form these altered liver proteins that can act as haptens. At re-exposure to any of these halogenated volatile anesthetics, an immune-mediated toxicity may rarely cause volatile anesthetic-induced hepatitis, leading to hepatic injury which may occasionally be fatal.

Sevoflurane does not form TFA-liver proteins. Theoretically, patients sensitized to the other volatile anesthetics could be safely anesthetized with sevoflurane.[2] However, we report a case of lethal hepatic failure in a woman undergoing cardiac surgery with a sevoflurane, sufentanil and propofol anesthesia. Consent for publication of this report received approval from the Institutional Review Board according to German legal practice (Landeskrankenhausgesetz Rheinland-Pfalz).

TABLE

Test	*Preop.*	*EOS*	*Day 1*	*Day 2*	*Day 3*	*Normal value*
ALT	18	14	34	425	10504	0-34 $U \cdot L^{-1}$
AST	27	32	63	588	15516	0-31 $U \cdot L^{-1}$
ALP	54	31	48	103	125	35-104 $U \cdot L^{-1}$
GGT	22	11	25	73	89	0-38 $U \cdot L^{-1}$
LDH	292	257	377	812	12944	0-248 $U \cdot L^{-1}$
Bilirubin	16.8				46.2	0-17 $\mu mol \cdot L^{-1}$
Creatinine	102	78	92	177	327	27-118 $\mu mol \cdot L^{-1}$
INR	0.93	1.27	1.01	1.43	5.30	1.0
Platelets	175	124	124	129	82	150-400 nL^{-1}
WBC	6.1	9.4	14.1	14.1	12.1	4.5-11.0 nL^{1}

Preop. = preoperative values; EOS = end of surgery on admission to the intensive care unit; day 1 = first postoperative day; day 2 = second postoperative day; day 3 = third postoperative day; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ALP = alkaline phosphatase; GGT = gamma glutamyl transferase; LDH = lactate dehydrogenase; bilirubin = total bilirubin; INR = international normalized ratio; WBC = white blood cell count.

Case report

A 76-yr-old, 54 kg, 167 cm woman suffering from combined aortic stenosis/aortic insufficiency was scheduled for aortic valve replacement. She had a history of a previous appendectomy, abdominal hysterectomy, inguinal lymph node excision, and surgery for a humeral fracture. All these surgical procedures had occurred more than ten years previously, hence the medical records of these procedures were unavailable. The patient did not recall any adverse events related to her previous anesthetics. She was otherwise in good health with no history of jaundice or hepatitis. She had never received blood transfusions, had no tattoos, and there was no history of recent travel. She had taken neither acetaminophen nor herbal remedies within the last three months, although she did suffer from mild allergic rhinitis to house dust mite and pollen, and drank 0.2–0.3 L wine per day.

Preoperative coronary angiography demonstrated insignificant coronary artery disease with mild stenosis of the left anterior descending artery < 30%. Her peak transvalvular pressure gradient was 40 mmHg with a mean pressure gradient of 30 mmHg; aortic regurgitation was classified as severe with a pressure half-time of 250 msec. Left ventricular function was moderately reduced; preoperative left ventricular ejection fraction was 47%, left ventricular end-diastolic pressure was 10 mmHg. She was hospitalized for decompensated heart failure one month prior to surgery. During this period her cardiac function recovered with appropriate titration of an angiotensin-converting enzyme (ACE) inhibitor, a diuretic, and digoxin. Two weeks prior to surgery her liver biochemistry values were normal (Table). Plasma antibodies to hepatitis A and hepatitis B surface-antigens were undetectable, nor were antibodies for hepatitis B surface and core-antigens, hepatitis C virus, or human immunodeficiency virus detectable.

On the day of surgery the patient was premedicated with 1 mg of flunitrazepam. Anesthesia was induced with midazolam 5 mg *iv* and sufentanil 50 µg *iv*; endotracheal intubation was facilitated with pancuronium 6 mg *iv*. Anesthesia was maintained with a continuous infusion of sufentanil (total dose including the bolus for induction 3.1 $\mu g \cdot kg^{-1}$), and sevoflurane before and after cardiopulmonary bypass (CPB) up to a maximal end-tidal concentration of 1.0 Vol%. During CPB, sevoflurane was not administered while the patient received a continuous infusion of propofol (total dose 2.4 $mg \cdot kg^{-1}$). A semiclosed circuit (Primus, Dräger Medical, Lübeck, Germany) with soda lime absorbent (Intersorb plus; Intersurgical, Wokingham, UK) was used for low-flow anesthesia with a fresh gas flow of 1 $L \cdot min^{-1}$. Hers was the first case of the day, and fresh CO_2 absorbent was used. Monitoring included an electrocardiogram, a pulse oximeter, a radial arterial line for continuous recording of arterial blood pressure, a central venous line, transesophageal echocardiography and recording of bispectral index.

Cardiopulmonary bypass was performed using mild hypothermia (lowest core temperature 32.4°C), alpha stat, and nonpulsatile flow (2.4 $L \cdot min^{-1} \cdot m^{-2}$). Mean

arterial pressure was maintained between 50–80 mmHg using low-dose norepinephrine (maximal dose 0.12 $\mu g \cdot kg^{-1} \cdot min^{-1}$, total dose 340 μg) for 80 min during CPB and shortly after CPB. Cardiopulmonary bypass lasted 68 min and the aorta was cross clamped for 49 min. A 19-mm Carpentier-Edwards Perimount aortic valve bioprosthesis (Edwards Lifesciences Services, Unterschleissheim, Germany) was implanted. Surgery and anesthesia were uneventful. Intraoperative transesophageal echocardiography confirmed the preoperative diagnosis and showed a good result after aortic valve replacement (peak pressure gradient 14 mmHg, mean pressure gradient 7 mmHg, no aortic regurgitation). Intraoperatively, 1000 mL of Ringer's lactate, 1000 mL of colloid (Voluven, 6% hydroxyethyl starch, MW 130.000 Dalton; Fresenius Kabi, Bad Homburg, Germany), and two units of packed red cells (600 mL) were administered.

Postoperatively the patient was transferred to the intensive care unit (ICU). She was sedated with propofol for two hours and her trachea was extubated 4.5 hr after the end of the procedure. Her blood pressure remained stable throughout, and she did not require any inotropes or vasopressor medications. Postoperative analgesia was provided by patient controlled analgesia with piritramide. She remained in the ICU for 23 hr and was transferred to the intermediate care unit on the first postoperative day. The first postoperative day was completely uneventful.

During the morning of the second postoperative day, serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) values increased to 452 $U \cdot L^{-1}$ and 588 $U \cdot L^{-1}$, respectively and her international normalized ratio (INR) increased spontaneously to 1.43. The patient became acidotic (pH 7.16, pCO_2 26.2 mmHg, pO_2 85.2 mmHg, base excess: $^{-}18$ $mmol \cdot L^{-1}$). Acidosis was corrected by sodium bicarbonate. Twelve hours later the patient deteriorated acutely. Hypotension and oliguria developed and acidosis reappeared. She was transferred back to the ICU, hypotension was treated with volume loading and norepinephrine, and veno-venous filtration was initiated. The patient developed a fever with a maximum temperature of 38.8°C.

On the third postoperative day, the patient deteriorated further. Her ALT and AST values peaked at 10504 $U \cdot L^{-1}$ and 15516 $U \cdot L^{-1}$ respectively, and coagulopathy ensued with an INR of 4.58. She became confused, hypoxemic, and required reintubation. Increasing doses of catecholamines, epinephrine and norepinephrine were needed to stabilize hemodynamics. In this life-threatening situation liver transplantation was considered but rejected by the relatives of the patient. The patient finally died 65 hr after the operation.

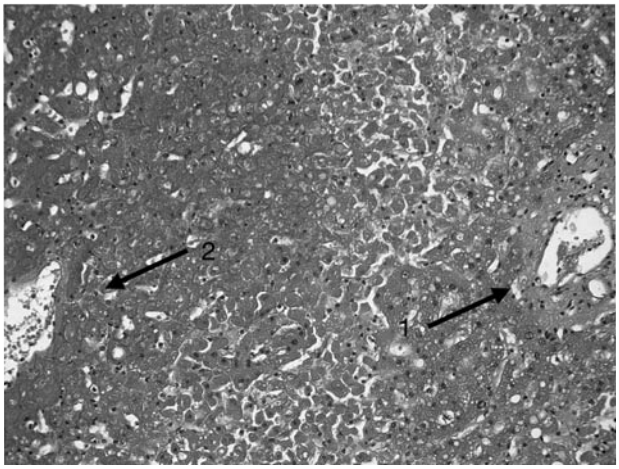

FIGURE 1 Liver section stained with hematoxylin and eosin. In periportal areas (1) there is a narrow edge of vital hepatocytes with vacuoles. Close to the central vein (2) extensive necrosis of hepatocytes is seen.

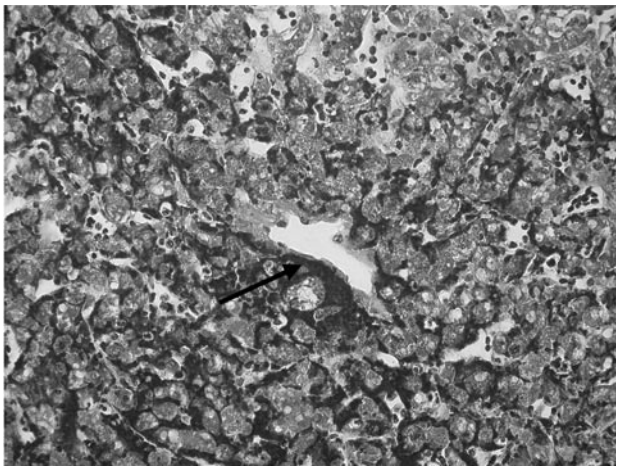

FIGURE 2 Liver section stained with Masson-Goldner. In the centre, a central vein (arrow) with its collagenic fibres is seen. Aggregates of red blood cells are found in between avital hepatocytes partially filled with lipofuscin.

Clinical investigations failed to reveal a cause of acute liver failure other than presumed sevoflurane hepatotoxicity. The patient had no pericardial effusion, no evidence of Budd-Chiari syndrome, no thrombosis of the portal vein and hepatic artery, and no acute viral hepatitis. Autopsy confirmed acute liver dystrophy and multiple organ failure. Histological sections of the liver showed hepatocyte damage in the vicinity of

the central veins. Periportally, a narrow edge of vital hepatocytes with vacuoles was seen (Figures 1 and 2). No infiltration of inflammatory cells was present. These findings confirmed ischemic injury of the liver, however the time of ischemic injury was unclear. On autopsy, there was no pericardial effusion, but there was a pleural effusion of 800 mL on the right side, 200 mL on the left side, and ascites of 350 mL. The heart showed signs of subendocardial ischemia and coronary artery disease with no significant stenosis. The aortic valve prosthesis was competent. The typical signs of generalized hypoperfusion shock were found in the lungs, kidneys, gut and stomach.

Discussion

Hepatic hypoperfusion during CPB and/or after the procedure and/or arterial embolism cannot be completely excluded in a patient undergoing aortic valve replacement.[3] However, throughout the procedure and during the first day after surgery no clinical signs of hypoperfusion were apparent. Repeated clinical examinations showed no evidence of abnormalities in arterial and portal blood flow.

Angiotensin converting enzyme inhibitors are known to cause hepatotoxicity which may progress to liver failure.[4] The ACE-inhibitor induced hepatotoxicity is usually of cholestatic nature.[4] In the case presented, neither laboratory nor histological findings gave evidence of cholestatic liver failure.

The typical clinical features of liver injury in patients anesthetized with halogenated volatile anesthetics include malaise, fever, jaundice, eosinophilia, marked elevations in serum transaminases and, in severe cases, encephalopathy and death.[2,5] This patient developed fever, jaundice, encephalopathy, and marked elevations in ALT and AST, and she finally died on the third postoperative day. Sevoflurane hepatitis as a cause for liver failure cannot be excluded in this complex situation of cardiac surgery using extracorporeal circulation.

The potential for halogenated volatile anesthetics other than sevoflurane to cause hepatotoxicity is related to the degree of their metabolism.[6] Halothane is metabolized up to 20%, enflurane to < 5%, isoflurane to < 1%, and desflurane to 0.02–0.2%.[6,7] The incidence of severe liver injury associated with halothane is in the range of 1 in 6,000 to 1 in 30,000 exposures.[5,6]. Several risk factors for volatile anesthetic-induced hepatitis have been described.[2,5] Re-exposure is the major risk factor, more than 90% of the patients affected will have a history of such previous exposure. Further risk factors include middle-aged patients with a peak incidence between 50 and 60 yr, obesity, female gender, history of drug atopy or multiple drug allergies, and induction of the cytochrome P-450 system by drugs or chronic ingestion of ethanol.[2,5]

The etiology of severe halothane-induced hepatitis is thought to be immunologically mediated.[2,5,6] Halothane is metabolized by the cytochrome P-450 system resulting in the formation of several reactive intermediates, principally trifluoroacetyl chloride,[1,8] which is able to bind to amino groups of proteins. This results in the formation of TFA hepatic proteins.[1,2,8] These TFA hepatic proteins seem to be immunogenic. In sensitized patients these TFA hepatic proteins cause specific antibody and/or T-cell responses leading to hepatic injury of various severities. Martin[2] described volatile anesthetic induced hepatitis as an immune-mediated toxicity occurring in susceptible patients following exposure to a halogenated anesthetic. Cross-sensitization is explained by this immunogenic etiology of volatile anesthetic induced hepatitis. It has been documented to occur with exposure to halothane, isoflurane, desflurane and enflurane.[2,9,10]

Sevoflurane, however, does not form TFA liver proteins.[2,11] Its metabolism does not result in formation of fluoroacetylated liver neoantigens or other reactive molecules.[11] Two to five percent of the administered sevoflurane is metabolized by the cytochrome P-450 system to hexafluoroisopropanol, inorganic flouride and formaldehyde.[11,12] Hexafluoroisopropanol has a low binding affinity to liver proteins and is rapidly gluconurated and eliminated by the kidneys.[12] Kharasch[11] postulated in 1995 that anesthetic metabolism and anesthetic toxicity can no longer be considered synonymous. Martin[2] stated that, theoretically, patients sensitized to other volatile anesthetics could safely be anesthetized with sevoflurane. He did not, however, recommend the use of sevoflurane in a patient with a history of volatile anesthetic induced hepatitis.[2]

There are several reports[12–18] of sevoflurane induced hepatotoxicity, mostly in children, many of them published in Japanese. Compound A (2-fluoromethoxy-1,1,3,3,3-pentafluoro-1-propene) is produced by the reaction of sevoflurane with carbon dioxide absorbents. Its production is increased during low flow anesthesia, closed circuit machines, using high inspired concentrations of the drug,[19] and using soda-lime or Baralyme absorbents.[20] Compound A is nephrotoxic in rats.[21] However, no clinically significant renal effects were found in patients, even with stable renal insufficiency, exposed to compound A during sevoflurane anesthesia.[21] Compound A may also play a key role for the potential hepatoxic effects of sevoflurane.[22] Compound A reacts directly with proteins.

It can transform proteins into antigenic material. In guinea pigs each compound A exposure resulted in increased antibody titers to TFA serum albumin.[22] The humoral immune response to compound A had a similar time course to that observed after halothane exposure.[23] Zheng *et al.*[22] concluded that compound A exposure may pose the same risk of volatile anesthetic induced hepatitis as all other volatile agents. We presume that our patient was cross-sensitized to volatile anesthetics applied during previous surgery, and exposure to compound A resulted in hepatic injury.

We conclude that sevoflurane hepatitis may be implicated in this case of cardiac surgery with extracoporeal circulation. In rodents, repeated exposure to compound A resulted in the same humoral response to TFA serum albumin as with halothane. This case suggests that sevoflurane used in a semi-closed or closed circuit has the rare potential to cause severe hepatic injury as with all other halogented volatile agents, while recognizing that hepatic hypoperfusion and or hepatic embolism can never be excluded from the differential diagnosis in a patient undergoing valvular surgery.

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