

## Diminished Hepatic Arterial Flow during Halothane Administration

JONATHAN L. BENCMOF, M.D.,\* JOSEPH J. BOOKSTEIN, M.D.,† LAWRENCE J. SAIDMAN, M.D.,‡  
RONALD HARRIS, M.D.§

Hepatic injury following halothane anesthesia is rare.<sup>1,2</sup> Whereas hypersensitivity,<sup>3,4</sup> and biotransformation to reactive products,<sup>5,7</sup> which may bind to hepatic microsomes,<sup>8-11</sup> have been considered as causative factors, no report considers decreased blood flow in the hepatic artery. This communication reports the cases of two patients in whom dramatic documented decreases in hepatic arterial blood flow occurred during halothane anesthesia. Hepatitis developed in one patient.

## REPORT OF TWO CASES

*Case 1.* A 26-year-old Caucasian woman was being evaluated for a congenitally absent vagina and uterus with primary amenorrhea, dermoid cyst of the right ovary, hirsutism and acne. Crography, nephrotomography, and ultrasonography showed a right renal mass. During urography she had a questionable episode of urticaria. Arteriography was attempted using local anesthesia, but could not be completed due to lack of patient cooperation. The patient was then scheduled for arteriography with general anesthesia.

History included congenital absence of the left ear, childhood seizures, and mental retardation (mental age approximately 12 to 15 years). The medical history was otherwise negative, and the patient did not drink, smoke, take any medication, or have any allergy other than the possible previous reaction to radio-contrast material. The surgical history consisted of removal of all teeth at some time in the past, for unknown reasons, an appendectomy at the age of 9 years, and enucleation of the left eye for phthisis bulbi, with prosthesis implant, at the age of 24 years. For the latter procedure, anesthesia was induced with enflurane and maintained with halothane for one hour. The patient had no known complication

\* Assistant Professor of Anesthesia.

† Professor of Radiology.

‡ Professor of Anesthesia.

§ Assistant Professor of Radiology.

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TABLE 1. Liver Function Tests Following Angiography Performed during Halothane Anesthesia

Laboratory Test (Normal Values)	Pre-an- gion- gram Values	Post-angiogram Day									
		2	3	4	5	6	7	8	9	10	15
SGOT, IU (10-30)	11	465	1035	855	1089	1350	1660	1580	1045	1015	615
SGPT, IU (10-30)			170	1340	1730	2280	1975	2300	1803	1500	1320
LDH, IU (26-186)	130			650	764	976	878	860	520	650	341
CPK, IU (0-130)				31	22	26	29	18	14	14	22
Alkaline phosphatase, IU (25-85)					98	108	123	122	108	45	102
Bilirubin, $\frac{\text{direct}}{\text{total}}$ mg/100 ml ( $\frac{<0.2}{<1.2}$ )	0.1 0.4		0.7 1.4	0.5 1.1	0.6 1.3	1.0 2.0	1.7 2.7	2.0 3.6	2.5 4.4	2.1 3.5	1.1 2.2
Protime, sec ( $\frac{\text{control}}{\pm 2 \text{ sec}}$ )				11.8 10.4	11.1 10.4	13.3 10.4	12.7 10.9	11.4 10.0	13.0 10.7	12.3 11.5	10.5 10.8
Eosinophils, per cent ( $<3$ )	2		2	5	6	3					

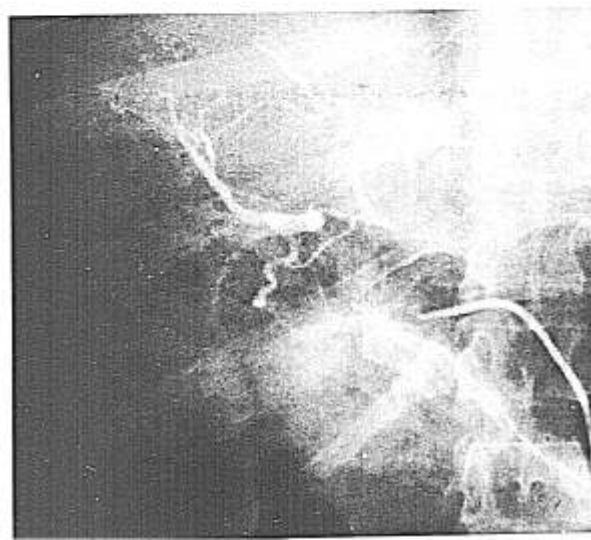
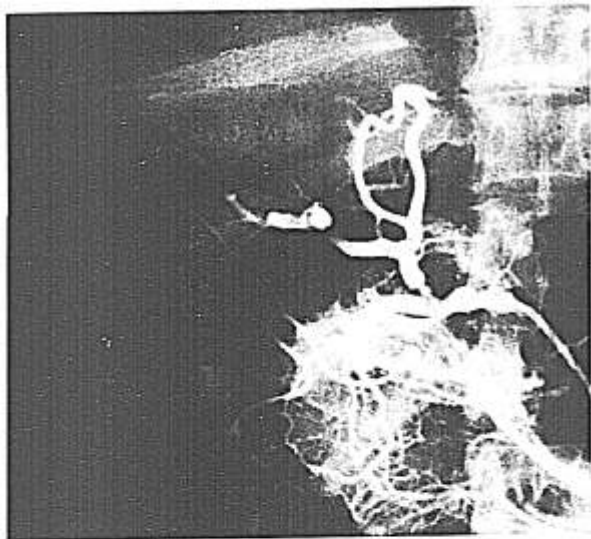


FIG. 1. A. (*above*) Selective hepatic arteriogram 3 seconds after onset of injection. Major hepatic arteries are of normal caliber, except for spasms near the catheter tip. Linear velocity of blood flow in the hepatic artery is extremely slow. B. (*below*) At 8 seconds, contrast medium has cleared from all other opacified branches of the celiac axis, but remains within hepatic arterial branches of normal caliber.

during these hospitalizations. She had never received any blood product, not had she any known contact with patients who had hepatitis.

The patient was childlike in appearance and moderately obese (height 5 feet, weight 170 pounds). The results of physical examination were within normal limits except for the problems cited above. Laboratory studies, including liver function tests (table 1), disclosed no abnormality.

Premedication consisted of atropine, 0.4 mg, im, pentobarbital, 100 mg, im, and meperidine, 50 mg, im. Anesthesia was induced intravenously with thiopental, 250 mg, and diphenhydramine, 25 mg, and maintained with 0.7 per cent halothane, nitrous oxide, 3 l/min, and oxygen, 2 l/min. Blood pressure was 140-110/85-70 mm Hg, pulse 90-120 beats/min with a normal sinus rhythm. Respirations were controlled at 14-16 breaths/min. The patient's color remained good.

Ninety minutes after the onset of anesthesia,

selective hepatic arteriography was performed to identify any metastatic lesions, using 25 ml Renografin-76. Hepatic blood flow was extremely reduced, as judged by marked reduction in linear velocity of flow within hepatic arteries (fig. 1). Velocities of flows in other branches of the celiac axis were normal. Except for some catheter-induced spasm, the major hepatic arterial branches were of normal caliber. The portal vein was not visualized. Administration of halothane was discontinued and anesthesia maintained for the next 30 minutes with nitrous oxide, 3.4 l/min, oxygen, 2 l/min, and thiopental, 100 mg in two divided doses. Diphenhydramine, 25 mg, was given when a rash developed. Blood pressure and pulse were unchanged. Twenty minutes after halothane had been discontinued, repeat hepatic arteriography showed normal flow to the hepatic parenchyma (fig. 2). Some catheter vasospasm continued. The central hepatic artery had diminished slightly in caliber

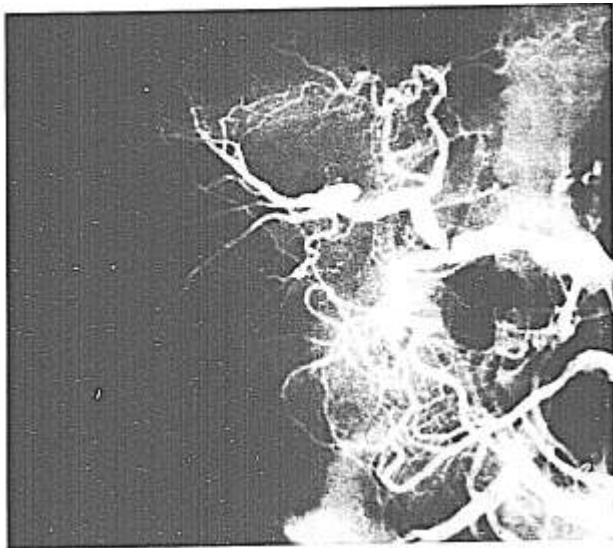


FIG. 2. Repeat hepatic arteriogram after halothane was discontinued. Arteriogram 2 seconds after the onset of injection demonstrates propagation of contrast medium to the periphery of the liver. Serial films demonstrated clearing from the hepatic arteries at rates comparable to those in other celiac-artery branches. Central hepatic arteries are slightly reduced in caliber relative to figure 1A, indicating that the significant vasoconstriction was restricted to small vessels.

compared with the initial study. Ten minutes later, the patient awoke and responded normally to commands.

That evening and for the next four days the patient complained of anorexia, nausea, and vomiting, and had a fever (highest temperature 102.7 F). She was given prochlorperazine, 10 mg, im, with little effect on two occasions. Table 1 shows the temporal sequence of the liver function tests. The greatest changes in these values, except for bilirubin, occurred during the sixth through eighth days after angiography. In spite of abnormal liver function tests, the patient felt and ate well, and remained afebrile from the fifth post-angiogram day. On the eleventh day, final quantitative Australia antigen titer was negative and she was discharged. Throughout her hospital stay several sputum and blood cultures were negative. One non-clean-catch urine specimen yielded moderate numbers of *Escherichia coli*. The patient has remained asymptomatic to the present time (a year post-angiogram).

**Case 2.** A 5-year-old boy who had a three-month history of hypertension was admitted to the hospital for angiography. While taking hydrochlorothiazide, 25 mg *q.d.*, apresoline, 20 mg, *t.i.d.*, and propranolol, 10 mg *t.i.d.*, *p.o.*, his blood pressure had been in the range of 160-180/110-120 mm Hg. Past medical history was negative except for a tonsillectomy-adenoidectomy three months before, which was performed using uneventful halothane-

nitrous oxide anesthesia. Physical examination disclosed no abnormality except a precordial functional murmur. Results of all laboratory studies, including EKG and chest x-ray, were within normal limits.

Premedication consisted of droperidol, 1.5 mg, and fentanyl, 0.03 mg, im. Anesthesia was induced with thiopental, 80 mg, iv, and maintained with 1 per cent halothane and nitrous oxide, 3 l/min, and oxygen, 2 l/min. Throughout the entire 3½-hour procedure blood pressure was in the range of 120-130/70-80 mm Hg, pulse 100-110 beats/min, with a normal sinus rhythm. Respirations were spontaneous, 12-14 breaths/min, and the patient always had good color.

Figure 3 shows the initial abdominal aortogram. No radio-contrast material can be seen in the proper hepatic artery distal to gastroduodenal artery take-off, while all other organ flows in the abdomen appear normal. Figure 4 shows a celiac arteriogram. Blood flow to the liver is markedly reduced and the beaded appearance of the proper hepatic artery is consistent with peripheral vasoconstriction. An accessory hepatic artery, which also had a reduced flow, arose from the superior mesenteric artery. The catheter tip was in the celiac artery, clearly proximal to the area of vasospasm. Selective renal arteriography demonstrated a segmental stenosis. The patient awoke uneventfully and did well post-operatively. Liver function tests after angiography were within normal limits.

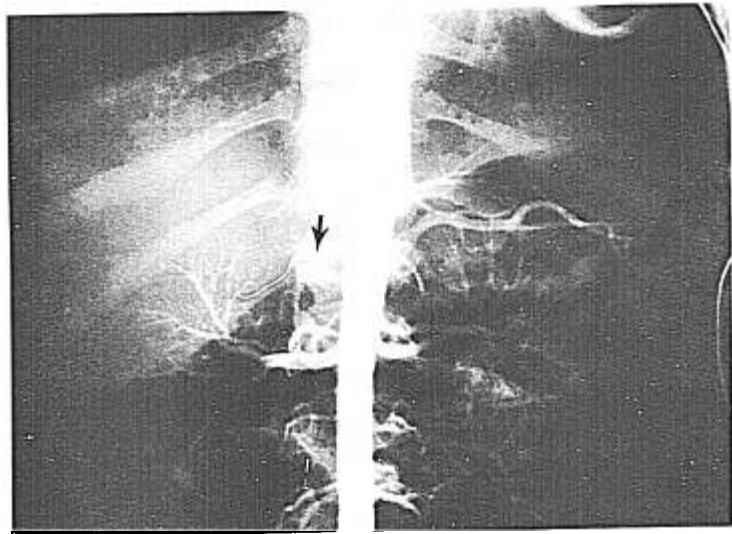


FIG. 3. Survey aortogram performed 45 minutes after induction of halothane anesthesia results in faint opacification of branches of the celiac artery. Contrast medium propagates much further in the splenic artery than in the hepatic artery (arrow).

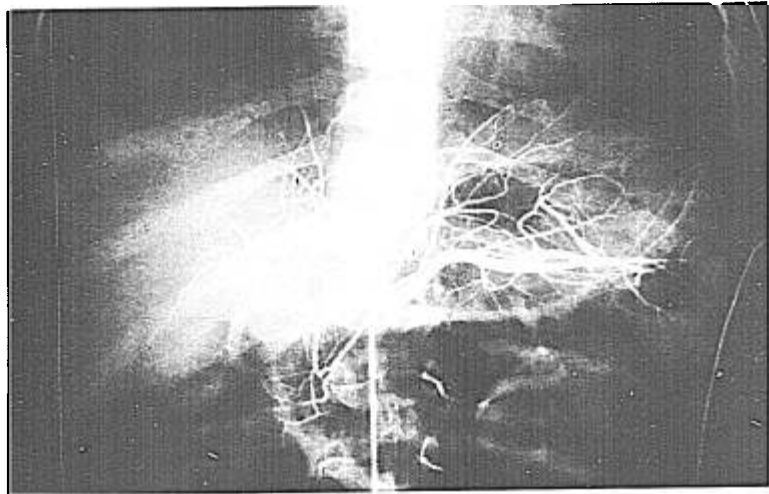


FIG. 4. Selective hepatic arteriogram performed two hours after the onset of anesthesia with halothane. Marked slowing of blood flow in the hepatic artery, relative to the splenic artery, persists. The corrugated appearance of the proper hepatic artery represents a response to slowed flow. The site of obstruction to flow is not demonstrated on the arteriograms, and is presumably beyond the smallest vessels that can be visualized angiographically.

#### DISCUSSION

These case reports document the occurrence of a marked selective decrease in hepatic arterial blood flow during halothane anesthesia. Hepatic arterial blood flow practically ceased, while flows in all the other branches of the celiac axis appeared normal. In Case 1, normal hepatic arterial flow was restored after halothane anesthesia was discontinued. The subsequent hepatitis in this patient was of moderate severity as judged by clinical symptoms and enzymatic changes. In spite of extensive study and review,<sup>2,12,14</sup> a causal relationship between halothane administration and hepatitis is at best unclear. The questions pertinent to this case are: did halothane cause the marked reduction in hepatic blood flow, and did the marked reduction in hepatic blood flow contribute to the development of hepatitis?

In Case 1, a cause-and-effect relationship between halothane and the selective reduction in hepatic arterial blood flow is probable. This contention is supported by the

temporal sequence of events, particularly the disappearance of hepatic vasoconstriction coincident with discontinuation of halothane. A similar severe reduction of hepatic arterial flow occurred in Case 2, and such reductions have also been reported to occur in two children during halothane anesthesia,<sup>15</sup> as well as in a series of adult volunteers during methoxyflurane anesthesia.<sup>16</sup>

The site of significant vasoconstriction was not directly demonstrated on the angiograms. Indeed, the central hepatic arteries were slightly dilated on the hepatic arteriogram with reduced blood flow in Case 1. This indicates that the vasoconstriction was restricted to small peripheral vessels. The smallest arteries visualized angiographically were 1 mm in diameter, and the vasoconstriction was downstream from them. Whether the vasoconstriction was in even smaller arteries, arterioles, or sinusoids, is unknown. That portal flow appeared near normal in Berger's series<sup>15</sup> would argue against hepatic venous constriction as the cause of reduced arterial flow. In case 2 the

beaded appearance of the proper hepatic artery suggests distal obstruction; similar beading is seen in renal, intestinal, or extremity arteries secondary to peripheral obstruction (personal observation, JJB).

It is possible, but highly unlikely, that the observed changes in blood flow in Case 1 were due to catheter-induced vasospasm followed by vascular accommodation. First, similar degrees of catheter vasospasm are present on the arteriograms obtained with and without the presence of halothane, yet the linear velocities of blood flow are markedly different. Second, the catheter also induced vasospasm in the gastroduodenal artery, which showed no reduction in linear velocity of blood flow. Third, similar marked reductions in hepatic arterial blood flow occurred without catheter vasospasm in Case 2, and in Berger's two patients.<sup>15</sup> Last, catheter vasospasm is frequently seen during angiographic procedures but does not impair organ perfusion to anywhere near the extent reported here.

What was the cause of hepatitis in Case 1? Australia antigen has been found in blood of patients who have serum hepatitis, infectious hepatitis, and chronic active hepatitis.<sup>17-19</sup> The failure to demonstrate Australia antigen in the serum of this patient militates against, but does not rule out, the possibility that the hepatitis was viral in origin. She had not received any blood product for years preceding this episode, and no history of hepatitis contact could be elicited. The only non-inhaled drug known to induce hepatitis that the patient received was prochlorperazine. However, prochlorperazine-induced hepatitis is associated with enzymatic changes reflecting intrahepatic cholestasis. Hypoxemia, hypotension and sepsis, which can cause acute hepatitis, were not part of the clinical course.

The severe reduction in hepatic arterial blood flow suggests hypoxia as a mechanism of hepatic injury. There is, however, considerable evidence against the hypothesis that decreased hepatic arterial flow *alone* caused the hepatic injury in Case 1. Extensive investigations of the effects of halothane in man and animals<sup>20-25</sup> have indicated no disproportionate reduction in total hepatic flow relative to cardiac output and oxygen con-

sumption. In Berger's two children,<sup>15</sup> and in our Case 2, severely reduced hepatic arterial flow during halothane anesthesia was not followed by the development of hepatitis or abnormal liver function tests. In Libonati's series of healthy volunteers<sup>16</sup> who had markedly reduced hepatic arterial flows during methoxyflurane anesthesia, no significant adverse functional effect was seen. Tests of hepatic function after anesthesia were not reported, but presumably hepatitis would have been mentioned, had it developed. Last, it is well known that ligation of hepatic arteries centrally is well tolerated in most patients.<sup>26</sup> However, the physiologic implication of distal vasoconstriction, as shown by our angiograms, may be very much different, since collateral arterial circulation would not develop in this situation.

Although hepatic hypoxia is unlikely to be the sole cause of hepatic injury, it may be an important prerequisite. Recent investigations indicate that anaerobic conditions greatly enhance *in-vitro* covalent binding of reactive halothane intermediates to hepatic phospholipids and proteins.<sup>5,9</sup> The binding is irreversible and may impair membrane function, perhaps to the extent of causing cellular injury.<sup>27</sup> Additionally, it has been shown *in vitro* that during hypoxic conditions, defluorination of halothane (by presumably reductive pathways) was significantly increased and was associated with a threefold increase in covalent binding (by presumably reactive products).<sup>10</sup> Furthermore, infusion of the debrominated reduced metabolite  $CF_3CH_2Cl$  into the portal vein of the rat produced centrilobular necrosis.<sup>11</sup> Finally, pretreatment of rats with polychlorinated biphenyls (Arochlor 1254), which enhances both oxidative and reductive pathways in microsomes and induces abnormal cytochrome P-450, has been found greatly to increase covalent binding and hepatic damage following halothane anesthesia, particularly when the rats were hypoxic.<sup>11</sup>

These observations suggest the following hypothetical mechanism for post-halothane hepatic injury in Case 1: Reduced hepatic arterial flow caused hepatic hypoxia. Hepatic hypoxia stimulated reductive pathways of biotransformation, which generated reactive intermediates. The reactive intermediates

bound covalently with microsomes, causing hepatic damage. The first and last steps in this sequence are the most questionable.

The above observations and hypothesis suggest the need for further studies to determine the relationships between all anesthetics, hepatic arterial blood flow, biotransformation, and sensitization phenomena. During these studies two key points should be clarified initially. First, the frequency of severe reductions of hepatic arterial blood flow during anesthesia needs to be determined. Second, once the relationship between anesthesia and reduced hepatic arterial blood flow is further clarified, the relationship between reduced blood flow and hepatitis can be evaluated.

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