

Isoflurane, and Not Halothane, Increases Mesenteric Blood Flow Supplying Esophageal Ileocoloplasty

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Regional ischemia may induce anastomotic leakage or stenosis after esophageal reconstruction using retrosternal interposition of an ileocolic graft. These complications may be related to systemic or local hemodynamic alterations. This study was designed to evaluate the influence of inhalational anesthetic agents on the intestinal circulation supplying these ileocolic grafts. Seven patients (age 30 ± 5 yr, mean \pm standard deviation [SD]) were studied in the immediate postlaparotomy period. Miniaturized Doppler implantable microprobes were sutured to the single artery supplying the graft and connected to an 8-MHz pulsed Doppler flowmeter. Continuous fentanyl infusion ($300 \mu\text{g} \cdot \text{h}^{-1}$) was maintained throughout the study. Measurements were performed at the end of four 30-min periods, which were, successively: first control; isoflurane or halothane anesthesia; second control; and isoflurane or halothane anesthesia. Isoflurane and halothane were administered in cross sequence with end-tidal concentration of 0.8% and 0.5%, respectively, to induce equipotent anesthesia. Both anesthetics induced similar decreases in mean systemic arterial pressure (MAP), cardiac output (CO), and systemic vascular resistance. During isoflurane, mean mesenteric blood flow (MBFm) supplying the graft was increased (+38%; $P < 0.05$), and the mesenteric vascular resistance index (MVRI; -44%; $P < 0.05$) was decreased, leading to an increase in the MBFm/CO ratio ($P < 0.05$). Halothane changed neither the MBFm nor the MBFm/CO ratio, despite a mild decrease in MVRI (-14%; $P < 0.05$). Diastolic blood flow velocity increased significantly (2.3 ± 0.9 vs. $0.8 \pm 0.3 \text{ cm} \cdot \text{s}^{-1}$, $P < 0.05$) only with isoflurane, suggesting a local vasodilation not observed with halothane. Mesenteric vascular effects of isoflurane differed significantly ($P < 0.05$) from those observed with halothane. We conclude that isoflurane and not halothane preferentially vasodilates human mesenteric vessels supplying ileocolic grafts. (Key words: Anesthetics, volatile; halothane; isoflurane. Gastrointestinal tract: esophageal ileocoloplasty; blood flow. Measurement techniques: pulsed Doppler flowmetry.)

ESOPHAGEAL RECONSTRUCTION for repair of esophagogastric injury after lye ingestion may require the interposition of an ileocolic graft.¹ Outcome after this procedure may be compromised by cervical anastomotic

leakage or stenosis, the incidence of which ranges from 33 to 56%.^{2,3} These complications are often related to regional hypoperfusion and ischemia produced by systemic hemodynamic alteration⁴ or impairment of local blood supply.^{3,5} The recent development of implantable Doppler microprobes enabling continuous measurements of regional blood flow^{6,7} provide the opportunity to monitor mesenteric blood flow (MBF) supplying the whole colonic graft in the perioperative period.

Although inhalational anesthesia has been shown to decrease preportal splanchnic blood flow in experimental models,⁸⁻¹⁰ the vascular effects of volatile anesthetic agents on the mesenteric vascular bed have not been reported in humans.

This study was designed to evaluate with implantable Doppler microprobes the effects of isoflurane and halothane anesthesia on the MBF supplying colonic grafts in humans.

Materials and Methods

PATIENTS

Seven patients, 30 ± 5 yr old (mean \pm standard deviation [SD]), were studied after informed consent and Local Ethical Committee approval were obtained. Patients had no history of cardiovascular or respiratory disease. Esophageal reconstruction was scheduled several months after severe caustic burns of the esophagus and stomach. The operative method used¹ consisted in a blunt retrosternal dissection. The mobilized ileocolon was brought through this newly created anterior mediastinal tunnel and anastomosed to the cervical esophagus in an isoperistaltic orientation. Vascular supply of the graft was achieved by the right superior colic artery, a branch of the superior mesenteric artery, as shown by the postoperative angiography in figure 1. The vascular sympathetic afferent supply of the graft was intact, and venous drainage continued into the portal system.

After preanesthetic medication with flunitrazepam (1 mg, intramuscular [im]), induction was performed with thiopental ($3-5 \text{ mg} \cdot \text{kg}^{-1}$, intravenous [iv]). Tracheal intubation was facilitated by pancuronium bromide ($0.1 \text{ mg} \cdot \text{kg}^{-1}$, iv). Anesthesia was maintained with nitrous oxide 60-70% in oxygen and with continuous fentanyl infusion ($300 \mu\text{g} \cdot \text{h}^{-1}$). The cumulative intraoperative fentanyl dose averaged $1,600 \pm 300 \mu\text{g}$ (mean \pm standard

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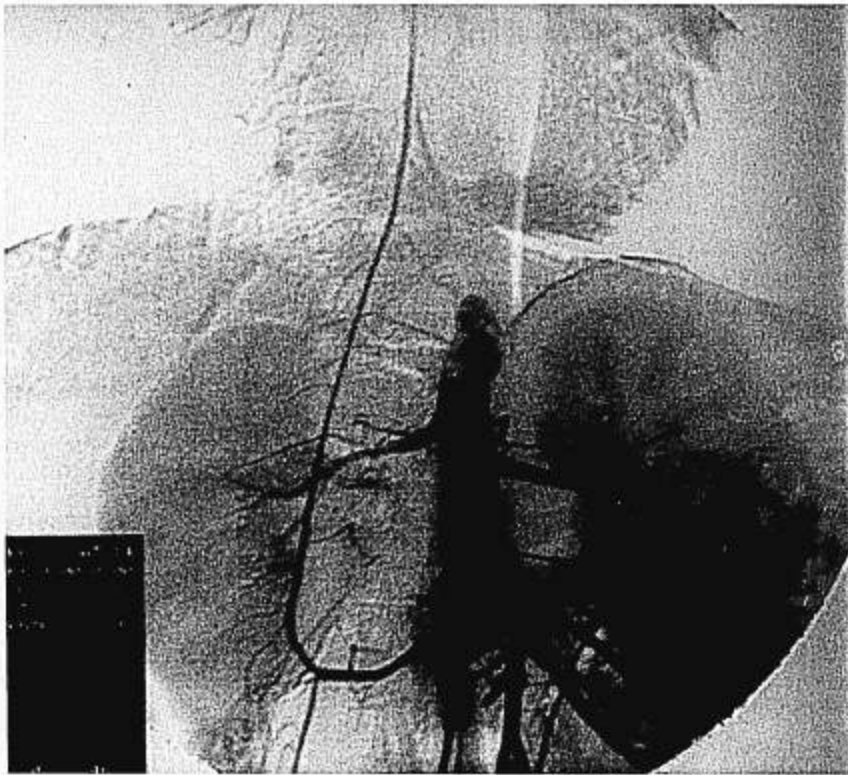


FIG. 1. Example of the postoperative angiographic control of the right superior colic artery supplying the intrathoracic ileocolic graft. Note that collateral flow is absent.

error of the mean [SEM]). Duration of surgery averaged 4 h (range 2–5 h). Lungs were mechanically ventilated *via* an endotracheal tube by a volume cycled ventilator (CPU 1, Ohmeda, Maurepas, France). Minute ventilation and tidal volume were adjusted to maintain arterial carbon dioxide tension (P_{aCO_2}) between 35 and 40 mmHg and to generate the lowest mean airway pressure (8 ± 2 mmHg, mean \pm SD).

SYSTEMIC HEMODYNAMIC PARAMETERS

The following parameters were measured or calculated. Heart rate (HR) by ECG recording; mean systemic arterial pressure (MAP) *via* a radial catheter; and right atrial pressure (RAP), pulmonary arterial pressure (PAP), pulmonary artery occlusion pressure (PAOP) *via* a triple lumen catheter. All end-expiratory pressures were measured using Hewlett-Packard quartz transducers carefully zeroed at the mid-axillary level. Cardiac output (CO) values were obtained by averaging three successive thermodilution determinations (CO computer 9510 A, Edwards Laboratories). The cardiac index (CI) and the systemic vascular resistance index ($SVRI = MAP - RAP/CI$, in $mmHg \cdot l^{-1} \cdot min \cdot m^2 = IU$) were calculated.

MESENTERIC BLOOD FLOW STUDY

The Doppler microprobe design and implantation technique have been described previously.⁶ Briefly, the

probe was 3 mm in width and 4 mm in length. The Doppler crystal was glued to a silicone prism, in such a manner as to obtain an incidence angle of 60° between the ultrasonic beam and the vessel axis. Before implantation, the linearity of each probe response for flow velocities ranging from 5 to $80 \text{ cm} \cdot \text{s}^{-1}$ was verified.⁶ At the end of the surgical procedure, a single-use 8-MHz pulsed Doppler microprobe was sutured to the adventitia of the right superior colic artery near its origin. To facilitate implantation and proper alignment of the probe along the vessel axis, the base of the silicone prism was cut in the shape of a concave gauge adapted to vessel curvilinearity. Four 7-0 sutures, carefully passed through the arterial adventitia and through the silicone prism, facilitated close contact between the probe and the vessel wall, with proper alignment in relation to the vessel axis.

The probe was connected to the Doppler flowmeter *via* leads exiting from the abdomen through the skin. The zero-crossing pulsed Doppler blood flowmeter used in this study has been described and validated previously.^{6,7,11} The main characteristic of this apparatus is the ranged time system of reception, which enables selection of the sample volume size and facilitates its movement across the vessel lumen. The diameter (D) was determined according to the echographic equation: $D = C/2 \times (t_2 - t_1) \times \cos 60^\circ$, where C is the ultrasound speed in biological tissues; $t_2 - t_1$ is the difference between distal (t_2) and proximal (t_1) reception time corresponding to the

vessel walls; and 60° is the angle of incidence of the ultrasonic beam.¹¹ Mean (V_m) and phasic cross-sectional blood flow velocities can be measured. Mean MBF (MBF_m , in $ml \cdot min^{-1}$) was calculated according to the formula: $MBF_m = \pi D^2/4 \times V_m$. Since arterial diameter was assumed to be constant along the cardiac cycle, only maximum systolic (V_s) and end-diastolic (V_d) blood flow velocities were recorded. Since the true back pressure of the flow was impossible to measure, we calculated the index of local mesenteric vascular resistance (MVRI) as the direct ratio: $MVRI = MAP/MBF_m \times 10^{-2}$ (in $mmHg \cdot l^{-1} \cdot min \cdot 10^{-2}$). The probes were removed 3 days later by gentle traction, with no adverse effect.

PROTOCOL

The study began 3 h postoperatively, when hemodynamic conditions had stabilized and clinical and laboratory parameters had been checked (central temperature = $36.3 \pm 0.2^\circ C$; plasma hemoglobin concentration = $11.1 \pm 0.6 g \neq 100 ml$).

During the postoperative and the protocol period, fentanyl was continuously infused ($300 \mu g \cdot h^{-1}$), and the patients' lungs were mechanically ventilated as described earlier. When P_{aCO_2} was between 35 and 40 mmHg, stability was assessed by a continuous monitoring of end-tidal CO_2 concentration (Normocap monitor, Datex).

The following four sets of measurements were performed and data recorded after 30 min of equilibration for each period, which were, successively: first control; isoflurane or halothane; second control; and isoflurane or halothane. Anesthetic sequence was randomly determined so that the nonprimary drug was tested after a second control period during which a zero concentration of the first anesthetic was confirmed. End-tidal concentration of each anesthetic was measured continuously (Normac monitor, Datex) and adjusted to achieve a theo-

retical equipotent concentration (0.65 MAC), which was 0.8% and 0.5% for isoflurane and halothane, respectively.

STATISTICAL ANALYSIS

Measurements during each anesthetic administration were compared to the preceding control period using a Wilcoxon matched-pair test. A Mann-Whitney U test was used to compare data obtained with both anesthetics.

Results

Mean systemic and mesenteric hemodynamic parameters are summarized in table 1. HR, PAP, RAP, and PAOP were not significantly altered in the different protocol situations. Compared to control, CO (-11%, $P < 0.05$; -13%, $P < 0.05$) and MAP (-25%, $P < 0.05$; -19%, $P < 0.05$) decreased significantly during isoflurane and halothane, respectively. There was no significant difference between the two anesthetic agents.

Mean right superior colic artery diameter was 3.1 ± 0.5 mm (mean \pm SEM; range 2-4.7 mm) and did not change significantly throughout the study period. Mesenteric hemodynamic parameters are illustrated in figure 2. Isoflurane induced a large and significant increase in V_m and MBF_m (+38%, $P < 0.05$; range 20-90%) and a decrease in MVRI (-44%, $P < 0.05$), whereas halothane did not change MBF_m despite a decrease in MVRI (-14%, $P < 0.05$). The MBF_m/CO ratio was increased significantly during isoflurane ($P < 0.05$) and did not change with halothane. Moreover, V_d increased with isoflurane (2.3 ± 0.3 vs. $0.79 \pm 0.3 cm \cdot s^{-1}$; $P < 0.05$), whereas it did not change with halothane. V_s values were not altered in each protocol situation. Comparing both anesthetic agents, MBF_m , MBF_m/CO , MVRI, V_m , and V_d variations were significantly different ($P < 0.05$). Figure 3 represents a typical tracing. V_d , which was close to zero in

TABLE 1. Systemic and Mesenteric Hemodynamic Parameters

	C ₁	I	C ₂	H
HR (beats per min)	93 \pm 2	93 \pm 4	91 \pm 4	92 \pm 4
CO ($l \cdot min^{-1}$)	6.4 \pm 0.5	5.6 \pm 0.4*	6.4 \pm 0.4	5.6 \pm 0.4*
MAP (mmHg)	83 \pm 3	61 \pm 2*	78 \pm 3	64 \pm 4.3*
RAP (mmHg)	7.4 \pm 0.9	7.5 \pm 0.9	6.4 \pm 0.6	6.6 \pm 0.6
SVRI IU ($mmHg \cdot l^{-1} \cdot min \cdot m^2$)	20 \pm 2	15 \pm 1*	18 \pm 1	17 \pm 1*
MBF_m ($ml \cdot min^{-1}$)	51 \pm 19	77 \pm 33*†	47 \pm 8	43 \pm 15
MBF_m/CO (%)	0.8 \pm 0.3	1.3 \pm 0.6*†	0.7 \pm 0.3	0.8 \pm 0.3
MVRI IU \cdot 100 ($mmHg \cdot l^{-1} \cdot min \cdot 10^{-2}$)	39 \pm 10	22 \pm 6*†	37 \pm 9	30 \pm 7*
V_m ($cm \cdot s^{-1}$)	8.5 \pm 1.5	12.5 \pm 3.4*†	8.1 \pm 1.5	7.7 \pm 1.3
V_s ($cm \cdot s^{-1}$)	34.5 \pm 4.2	34.4 \pm 4.3	33.6 \pm 4.3	32.7 \pm 4.2
V_d ($cm \cdot s^{-1}$)	0.8 \pm 0.3	2.3 \pm 0.9*†	0.8 \pm 0.4	0.4 \pm 0.2

Values are mean \pm SEM; n = 7.

C₁, C₂ = control; I = isoflurane; H = halothane; HR = heart rate; CO = cardiac output; MAP = mean systemic arterial pressure; RAP = right atrial pressure; SVRI = systemic vascular resistance index; MBF_m = mean mesenteric blood flow; MVRI = mesenteric vascular

resistance index; V_m , V_s , V_d = mean, systolic, and diastolic blood flow velocities, respectively.

* $P < 0.05$ versus C (preceding control period).

† $P < 0.05$ versus H.

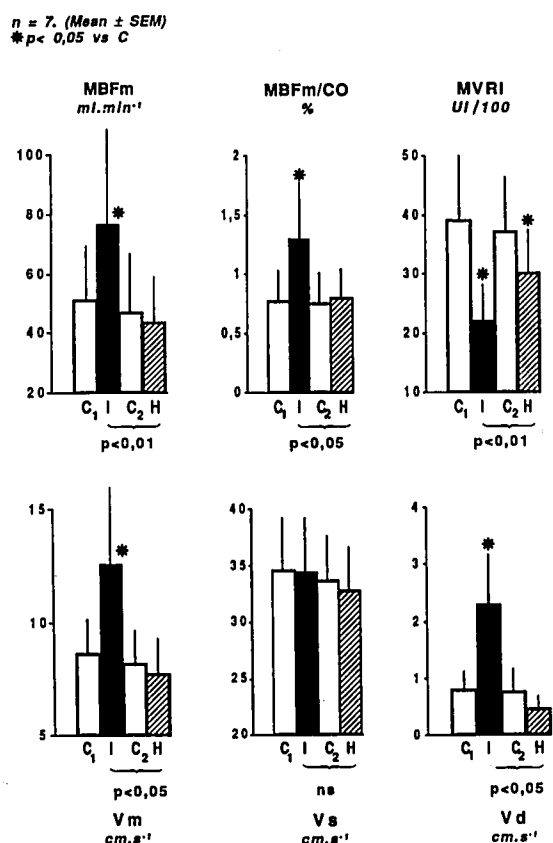


FIG. 2. Mean mesenteric hemodynamic parameters during control periods (C₁, C₂) and during isoflurane (filled bars) and halothane (hatched bars) equipotent anesthesia (0.65 MAC). MBF_m = mean mesenteric blood flow; CO = cardiac output; MVRI = mesenteric vascular resistance index (in mmHg · l⁻¹ · min · 10⁻²); V_m, V_s, V_d = mean, systolic, diastolic blood flow velocities, respectively.

control, increased during isoflurane (fig. 3, arrow) and did not change during halothane.

Discussion

Local complications after esophageal replacement with colonic interposition are relatively frequent and may compromise clinical outcome.²⁻⁴ Since local ischemia may be involved,^{4,5} monitoring of local blood flow may be of interest. Recent advances in Doppler technology enables monitoring of local arterial blood flow during the perioperative period.^{6,7} This study reports the impact of two inhalational anesthetics tested after esophageal replacement by an ileocolic graft. Despite the new anatomic position, MBF_m increased with isoflurane, whereas it did not change with halothane, despite a similar decrease of MAP and CO.

Perioperative measurements of human MBF were not possible until the development of implantable flow probes. The technique used in this study has been described previously⁶ and has been used to measure aortocoronary

bypass flow,⁶ hepatic blood flow after orthoptic liver transplantation,⁷ and renal blood flow after kidney transplantation.¹² This technique has the following advantages: it is a small and portable system allowing bedside measurements; the measurement procedure is simple and rapid; and continuous monitoring can be performed if needed.

The accuracy of the Doppler flow measurement technique has been described previously in experimental¹¹ and clinical studies.^{5-7,12,13} Precise blood flow measurements using this technique require exact determination of vessel internal diameter. Using the same equipment, Levenson *et al.* demonstrated the accuracy of pulsed Doppler diameter measurements, comparing Doppler-determined diameter to the actual diameter of calibrated tubes, using an *in vitro* model.¹¹ The intercept of the linear regression was 0.35 mm, which meant that the Doppler method overestimates the diameter by 0.35 mm. The smallest diameter measured in our study was 2 mm, so that the margin of error may be as high as 17%. Moreover, in our study, comparisons were made between repetitive measurements in the same patient, thereby limiting the impact of a systematic error.

Since intraoperative mesenteric flow measurements cannot be interpreted because of the vascular impact of surgical manipulations, pharmacologic effects of halogenated anesthetics were studied immediately after the sur-

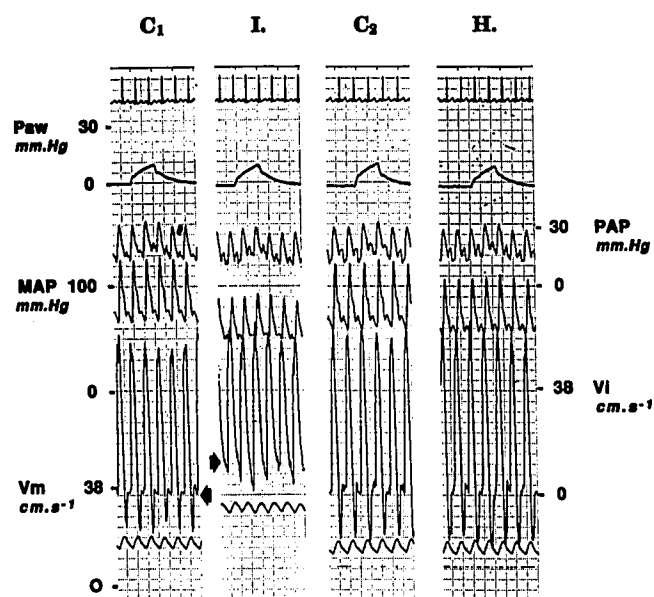


FIG. 3. Typical tracing obtained in one patient during control (C₁, C₂) and either isoflurane (I) or halothane (H) anesthesia. PAW = airway pressure; PAP = pulmonary arterial pressure; MAP = systemic arterial pressure; V_I, V_M = instantaneous and mean cross-sectional blood flow velocities, respectively, in the artery supplying the ileocolic graft. Arrows show the increase in diastolic blood flow velocity observed with isoflurane.

gery. Moreover, the study was conducted during a continuous fentanyl infusion. Thus, the results represent the combined effects of halothane or isoflurane and fentanyl and not the effect of the volatile agent alone.

The hemodynamic stability observed during the two control periods suggests that patients were sedated. It should be mentioned that the control value of MBFm can be influenced by the thoracic position of the graft and its supplying artery.¹³ For this reason, tidal volume was adjusted to be as small as possible to reduce intrathoracic pressure. In addition, PaCO₂ was kept constant because of its major influence on mesenteric hemodynamics.^{14,15}

Isoflurane and halothane induced similar decreases in CO and MAP. SVRI tended to decrease more with isoflurane than with halothane, although the difference was not significant. This effect might suggest that isoflurane has a more pronounced vasodilating action than does halothane. Despite these systemic hemodynamic alterations, which agree with the literature,^{8-10,16-19} isoflurane induced a MBFm increase associated with a local vasodilation. Such an effect was not observed with halothane, despite a mild reduction in local vascular resistance. In a similar protocol, using the same methodology, Payen *et al.* showed an increase in portal blood flow during isoflurane inhalation.²⁰ This supports the current data, despite the impact of surgery on mesenteric vascular tone.^{8,21} In the current study, the MBFm/CO ratio increased with isoflurane and did not change with halothane. The more pronounced regional vasodilation compared to systemic effects during isoflurane suggests that this mesenteric circulation is particularly sensitive to the vasodilation associated with isoflurane. This effect is also demonstrated by the increase in the diastolic component of MBF, which depends on downstream vascular resistances.²²⁻²⁴ Since CO decreased similarly with both anesthetics and only isoflurane increased the partition of flow toward the graft, it is possible that other regional flows are reduced by isoflurane. This reduction may involve the muscle blood flow, as suggested previously.^{10,17,18}

These results differ from those previously reported in animals,^{9,10,25} in which both halothane and isoflurane decreased mesenteric flow proportionate to the systemic effects. This discrepancy may result from the species difference and from the delay with the laparotomy. Nevertheless, in denervated isolated intestinal loops, both isoflurane^{26,27} and halothane²⁶ exhibited direct vasodilation when perfusion pressure was held constant. In the current study, only halothane induced a mild decrease in systemic and mesenteric flows, suggesting that the vasodilating properties of halothane do not compensate for the vasoconstriction induced by laparotomy. Conversely, the vasodilator properties of isoflurane remained intact.

The potential clinical impact of these data for this type of surgery should be assessed by a prospective study to

analyze the eventual benefit, if any, of regional vasodilation.

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