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Halothane, but Not Isoflurane or Enflurane, Protects Against Spontaneous and Epinephrine-Exacerbated Acute Thrombus Formation in Stenosed Dog Coronary Arteries

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Occlusive platelet thrombi periodically form in mechanically stenosed dog coronary arteries producing cyclical blood flow reductions occurring over 4–7 min. Cyclical coronary flow reductions are exacerbated by IV epinephrine 0.4 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 15 min. These flow reductions can be abolished by known inhibitors of platelet function. This study assesses the effect of halothane, isoflurane, and enflurane on spontaneous- and epinephrine-exacerbated cyclical coronary flow reductions. Twenty-three open-chest dogs [1% halothane (n = 5), 0.5% halothane (n = 5), 0.25% halothane (n = 3), 1.5% isoflurane (n = 5), and 2.0% enflurane (n = 5)] with a mechanically stenosed coronary artery showed cyclical blood flow reductions. With 1.0% halothane administration, spontaneous cyclical blood flow reductions were abolished (n = 5), whereas during administration of isoflurane 1.5% (n = 5) and enflurane 2.0% (n = 5) cyclical flow reductions and myocardial ischemia continued. Subsequent administration of halothane in the isoflurane and enflurane groups showed abolition of coronary flow reductions in all animals (n = 10). In eight animals a 15-min epinephrine infusion (0.4 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was given following a control period and again following abolition of coronary flow reductions by halothane 0.5% (n = 5) and halothane 0.25% (n = 3). The magnitude of cyclical blood flow reductions (difference between initial and final coronary flow level of each flow reduction) changed from 52 ± 11 to 61 ± 12 ml/min (NS), and frequency increased from 0.37 to 0.57/min ($P < 0.05$, n = 8) during epinephrine infusion. Halothane abolishes spontaneously occurring cyclical blood flow reductions and prevents epinephrine-induced cyclical blood flow reductions, whereas isoflurane and enflurane do not inhibit spontaneous cyclical coronary blood flow reductions. The effects of halothane on coronary artery thrombus formation in humans are unknown, but additional studies are needed to investigate the effect of halothane and other anesthetic agents on coronary thrombus formation and platelet function in humans. (Key words: Anesthetics, volatile: enflurane; halothane; isoflurane. Blood: platelet function. Heart: coronary occlusion. Sympathetic nervous system, catecholamines: epinephrine.)

WE HAVE previously demonstrated that acute platelet thrombus formation occurs in stenosed dog and pig coronary and rabbit and monkey carotid arteries.[1–4,¶] These developing thrombi produce a gradual decline in measured arterial blood flow, followed by an abrupt return to the control level when the thrombus embolizes distally. This periodic thrombus formation followed by embolization produces cyclical reductions in arterial blood flow, which we call CFR, are defined as "cyclical flow reductions."¶ The intracoronary thrombus at the site of experimental stenosis has been analyzed using light and scanning electron microscopy and confirms the presence of an obstructing thrombus developing during cyclical coronary flow reductions.[5–9] We and others have shown that CFR can be abolished with a variety of platelet-inhibiting drugs, such as aspirin and other nonsteroidal anti-inflammatory agents as well as with prostacyclin, and a monoclonal antibody to the IIb-IIIa platelet membrane receptor.[1,2,6,8,10–14] However, we and others have also shown that when CFR have been abolished with 5 mg/kg of aspirin and other platelet inhibitors, they can be renewed temporarily by infusing epinephrine 0.4 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 15 min.[15,16] Many older surgical patients have significant atherosclerotic arterial disease, which predisposes them to acute thrombotic episodes resulting in perioperative myocardial infarction, cerebrovascular accidents, or acute occlusion of arterial grafts. Increased endogenous catecholamine levels during surgical stress may exacerbate arterial thrombosis. *In vitro* studies have suggested that halothane may inhibit platelet activity. Studies utilizing a halothane atmosphere over samples of platelet-rich plasma or bubbling the agent through platelet-rich plasma demonstrate a dose-related and reversible inhibition of platelet aggregation (light turbidometic method of Born) accompanied by elevation of intraplatelet cAMP levels.[17–19]

In the present study, we investigated the effects of halothane, isoflurane, and enflurane on spontaneous and epinephrine-stimulated thrombus formation and CFR in stenosed canine coronary arteries in an open-chest preparation. The results may offer useful information and direction for future studies of agents that might decrease the risk of perioperative thromboembolic complications.

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¶ Folts JD: Experimental arterial platelet thrombosis, platelet inhibitors, and their possible clinical relevance. Cardiovasc Rev Rep 3:370–382, 1982.

Materials and Methods

Animal Preparation

Twenty-three adult mongrel dogs of either sex, weighing 25–30 kg, were anesthetized with thiamylal sodium, 17.5 mg/kg iv 25 min after receiving morphine sulfate, 3 mg/kg im. Following tracheal intubation, ventilation was controlled with an Ohio positive-pressure ventilator (Ohio Scientific Inc., Aurora, Ohio) and anesthesia was supplemented with 80% N_2O/20% O_2. The dog was given a dose of 10 mg succinylcholine for temporary skeletal muscle relaxation during thoracotomy. Thus, the dog was paralyzed for a short time, during the use of electrocautery when the initial dose of sodium thiamylal was still effective. Sodium thiamylal was given as needed to meet the requirements of general anesthesia. Lack of significant eye reflex and a slack relaxed jaw were periodically checked throughout the day to ensure adequate anesthesia. This protocol was approved by the University of Wisconsin Animal Care Committee. Arterial blood gases were periodically analyzed and changes in ventilation rate were made to maintain normal values. Arterial P_{O_2} levels were maintained above 90 mmHg and Pa_{CO_2} between 30 and 40 mmHg (Corning 175 automatic *p*H/blood gas system; Corning Medical, Corning Glass Works, Medfield, Massachusetts). A thoracotomy was performed at the fifth left intercostal space. The heart was suspended in a pericardial cradle and the left lung retracted, taking care not to obstruct the pulmonary veins.

A saline-filled polyethylene catheter was advanced through a femoral artery to just above the aortic valve and connected to a Statham P 23Db blood pressure transducer (Statham Instructions, Inc., Oxnard, California) for aortic blood pressure measurement. A polyethylene catheter was inserted into the cephalic vein of the front leg for fluid administration and drug infusions.

The proximal circumflex branch of the left coronary artery was separated for 2–3 cm from the surrounding tissue by blunt dissection, tying small side branches where necessary. Care was taken to avoid disturbance of the great cardiac vein. A Statham electromagnetic flowmeter probe of appropriate size was placed around the coronary artery. A Lexan plastic cylinder, 4 mm in length, designed to produce a 60–70% narrowing of the vessel, was then placed around the coronary artery just distal to the flow probe as previously described.[1,2,7,15,¶] A tapered, smooth, nylon fishline was placed between the inside of the obstructing cylinder and the outside of the vessel wall. This can be pulled in either direction to make fine adjustments in the amount of stenosis (fig. 1). A 2-0 Tevdek ligature was placed loosely around the coronary artery distal to the obstructing cylinder to permit temporary complete occlusion for determination of the reactive hyperemic response and for checking flowmeter baseline stability (fig. 1). We have previously demonstrated that an average reduction in coronary artery diameter of 70–75% abolishes the reactive hyperemic response to a 20-s complete occlusion.[2,7,15,20] This amount of stenosis does not significantly reduce control levels of coronary flow. An electrocardiograph lead was sutured to the epicardium in the area supplied by the circumflex artery for surface ECG.

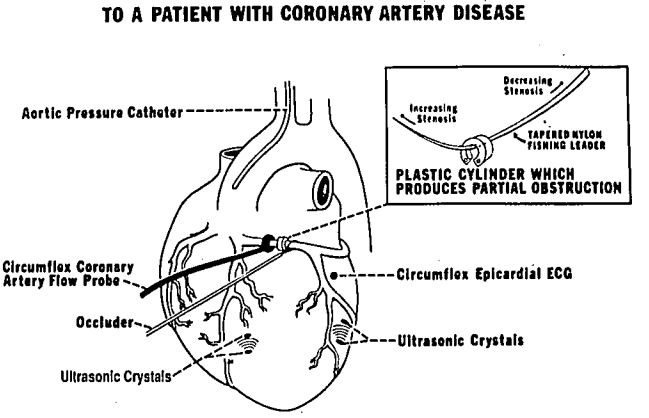

FIG. 1. Technique for producing fixed stenosis in a segment of the left circumflex coronary artery (LCX). A plastic cylinder, 4 mm in length, is placed around the coronary artery, encircling and constricting it producing a 60–70% reduction in diameter. A smooth, tapered, nylon fishline is placed between the inside wall of the plastic cylinder and the outside wall of the coronary artery. The fishline is then pulled in either direction to make slight increases or decreases in the amount of stenosis. Circumflex coronary artery blood flow is measured with an electromagnetic flow probe. Ultrasonic crystals can be placed in the myocardium for measurement of regional segmental dynamics.

Protocol

A 45-min period was allowed for stabilization of the animal preparation, and coronary blood flow was continuously monitored.

When a thrombus begins to form in the stenosed lumen, this increases resistance to blood flow and causes a gradual decline in coronary flow as the thrombus gets larger. As flow declines to near zero, the pressure gradient across the stenosis increases and may force the thrombus through the stenosed lumen, causing it to embolize distally, thus suddenly restoring coronary flow. The thrombus usually does not spontaneously embolize but requires a gentle shaking of the obstructing cylinder, causing the thrombus to embolize, restoring coronary flow, and allowing the experiment to continue.[1,2,7,15,¶] The difference between the initial and final flow level of each cyclical flow reduction is referred to as the CFR magnitude. Spontaneously occurring cyclical reductions in coronary blood flow (CFR) due to periodic acute platelet thrombus formation and embolization in this series of experiments were monitored at a paper speed of 0.10 mm/s on an eight-channel direct

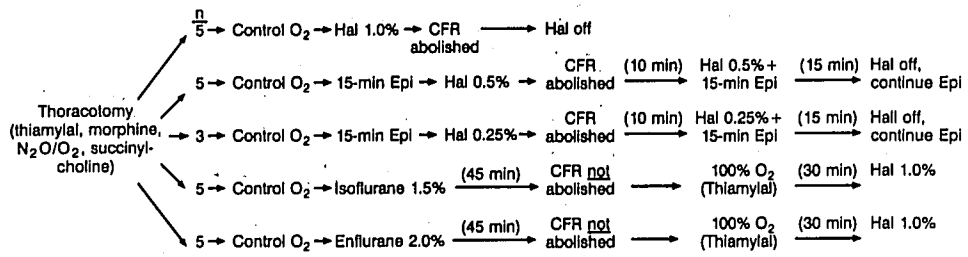

FIG. 2. Flow diagram of protocol described in "Materials and Methods." CFR = cyclical reductions in coronary blood flow.

writing Brush Gould polygraph. CFR, aortic blood pressure, and ECG were recorded continuously, and the effects on coronary flow were noted.

Following the 45-min stabilization period, with the dog receiving N_2O/O_2 and thiamylal anesthesia, the gas mixture was changed to 100% O_2 for 15 min during control measurements before adding halothane, enflurane, or isoflurane at vaporizer settings corresponding to inspired concentrations of halothane 1.0% (n = 5), isoflurane 1.5% (n = 5), and enflurane 2.0% (n = 5) until either CFR were abolished or 45 min had passed. Thirty minutes after discontinuing ventilation with enflurane (n = 5) or isoflurane (n = 5) during ventilation with 100% O_2 (thiamylal anesthesia), halothane was started at 1.0% inspired concentration and the effects on CFR were recorded (protocol, fig. 2). In eight animals following the control CFR period, a 15-min epinephrine infusion (0.4 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was begun to observe effects on CFR. Ten minutes following initial epinephrine infusion, halothane 0.5% (n = 5) or halothane 0.25% (n = 3) ventilation was begun, and the effects on CFR occurrence were monitored. Epinephrine infusion was repeated 10 min after cessation of cyclic coronary flow reductions while the halothane was continued for 15 min and all parameters measured (protocol, fig. 2). Finally, epinephrine infusion was continued after stopping halothane and effects on the occurrence of CFR were evaluated. The epinephrine solution (Elkins-Sinn, Cherry Hill, New Jersey) in normal saline was infused into the leg vein at 0.4 $\mu g \cdot kg^{-1} \cdot min^{-1}$ with a glass syringe and a Harvard infusion pump (Harvard Apparatus Co., Inc., Millis, Washington). The Fluotec vaporizer used (Cyprane Eighty, England) was periodically calibrated with a SARA mass spectrometer.

All values were expressed as the mean ± SD using Student's *t* test for paired comparisons within study groups using each animal as its own control.

Results

Spontaneously Occurring Cyclical Reductions in Coronary Blood Flow

All animals studied (n = 23) with critical coronary artery stenosis exhibited spontaneously forming cyclical reductions in circumflex coronary artery blood flow with representative examples shown on the left of figure 3. Each flow decline was followed by an abrupt restoration of flow because the thrombus embolizes represents a single CFR, with CFR occurring over 4–7 min from control flow to minimal flow levels and continuing unabated following discontinuation of nitrous oxide during control measurements on 100% oxygen. Anesthesia during this period was maintained with supplemental thiamylal in addition to the previous morphine dose. The spontaneously occurring flow reductions occurred repetitively after intracoronary thrombi spontaneously dislodged, due to the pressure gradient that develops across the stenosis causing return of coronary blood flow to control levels or following physical dislodgement of the thrombus by gently shaking the plastic obstructing cylinder to cause dislodgement of the thrombus and restoration of circumflex coronary blood flow. Physically dislodging the thrombus to restore coronary flow has been successfully utilized by other groups using the same model.[6,8–11,13–14,16,21] Furthermore, because all of these groups place the stenosing cylinder distal to the flow measuring probe, whether an

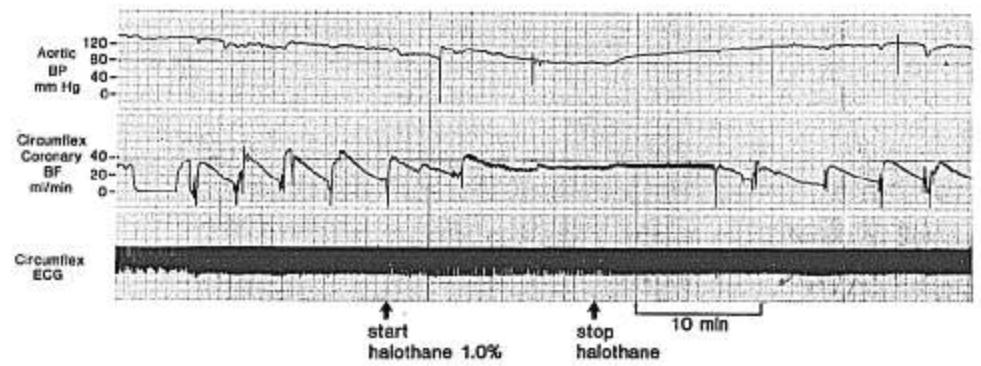

FIG. 3. Effect of 1.0% halothane on spontaneously forming cyclical reductions in coronary blood flow (CFR). At the left of the figure during control CFR a 20-s complete coronary occlusion demonstrates absence of significant reactive hyperemic response (BP = blood pressure, BF = blood flow). This shows that a "critical stenosis" has been produced. Prompt abolition of CFR is seen with halothane ventilation at 1.0%. Paper speed 0.10 mm/s.

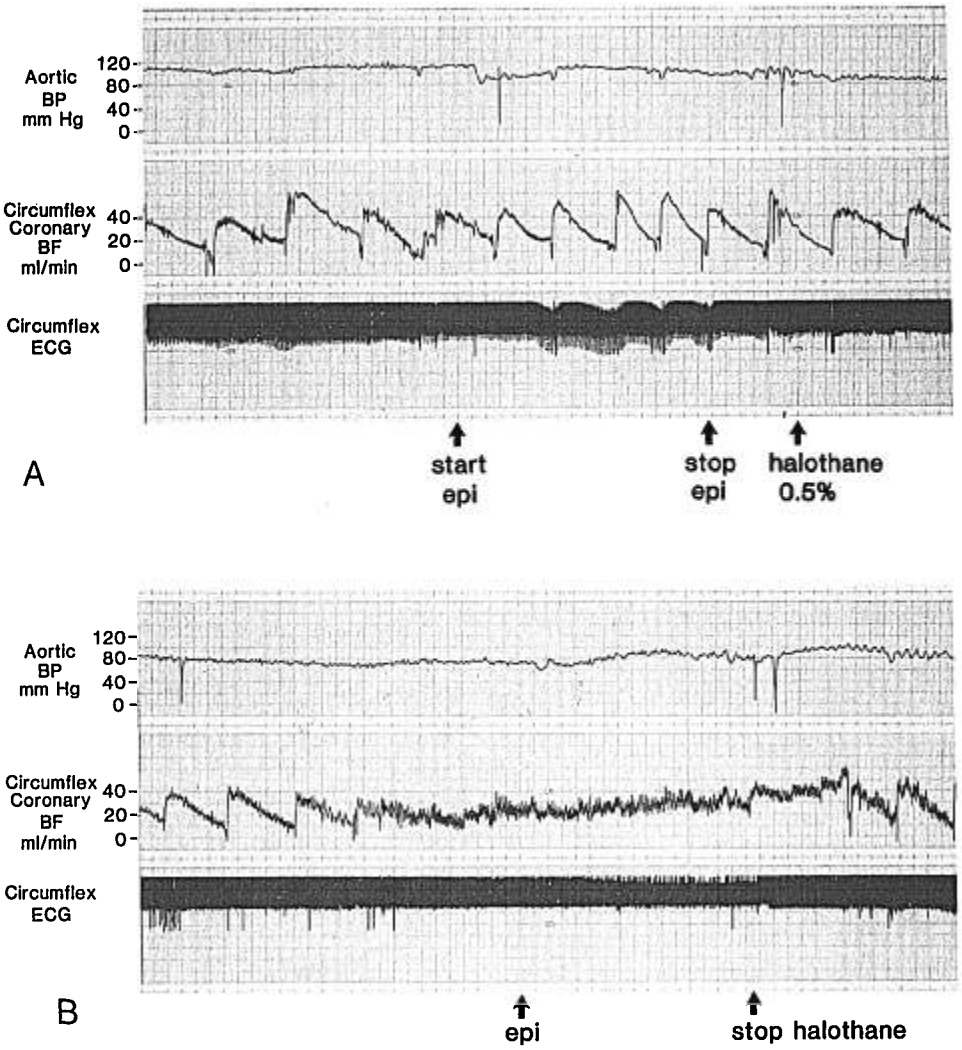

FIG. 4. *A.* Exacerbation of CFR by epinephrine infusion at 4 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 15 min with increased magnitude of CFR and a more rapid decline in coronary blood flow of CFR during epinephrine infusion. Halothane 0.5% ventilation was started at the right. *B.* Continuous recording from figure 4*A* shows abolition of CFR during ventilation with 0.5% halothane in oxygen, which prevented further CFR during repeat epinephrine infusion. Discontinuing halothane while continuing epinephrine infusion produced a rapid recurrence of thrombus-induced CFR.

electromagnetic probe[10,11] or a pulsed Doppler ultrasonic flow probe,[6] none reported any difficulty with the baseline stability when physically dislodging the thrombus by shaking the plastic cylinder.

Effect of Halothane Anesthesia on Spontaneously Forming Cyclical Reductions in Coronary Blood Flow

In five of five animals, halothane (1.0% inspired concentration) produced prompt abolition of CFR caused by intracoronary thrombus formation and embolization. Initial and final coronary artery blood flow measurements of CFR during the control period averaged 48.0 ± 9.24 and 4.79 ± 6.83 ml/min, respectively. Mean aortic blood pressure averaged 126.25 ± 7.50 mmHg with CFR frequency 0.24 ± 0.03 min^{-1}. Halothane 1.0% produced a 27% decline in mean aortic blood pressure and abolished CFR within 5 ± 2 min from onset of halothane ventilation with aortic blood pressure 92.50 ± 27.17 mmHg and coronary blood flow averaging 36.25 ± 11.09 ml/min. No ECG changes indicative of ischemia were seen. While CFR were abolished in the stenosed artery, coronary flow was dependent upon aortic blood pressure because we have previously shown that a "critical stenosis" had been produced and autoregulation is abolished (fig. 3).[2,7,15,20] After discontinuing halothane, mean aortic blood pressure returned to control level within 12 ± 3 min while ventilation was maintained with 100% O_2 and CFR recurred in the stenosed coronary artery.

Effect of Halothane Anesthesia on Epinephrine-Exacerbated Cyclical Reductions in Coronary Blood Flow

In eight of eight animals (halothane 0.5%, n = 5; halothane 0.25%, n = 3), CFR were abolished at low concentrations of inspired halothane, and recurrent CFR during iv epinephrine infusion at 0.4 $\mu g \cdot kg^{-1} \cdot min^{-1}$ did not occur (figs. 4*A*, 4*B*, 5*A* and 5*B*).

Figure 4 shows spontaneously occurring CFR on the left and during the 15-min epinephrine infusion. Epinephrine infusion increased the CFR magnitude only slightly from 52 ± 11 to 61 ± 12 ml/min (NS) and in-

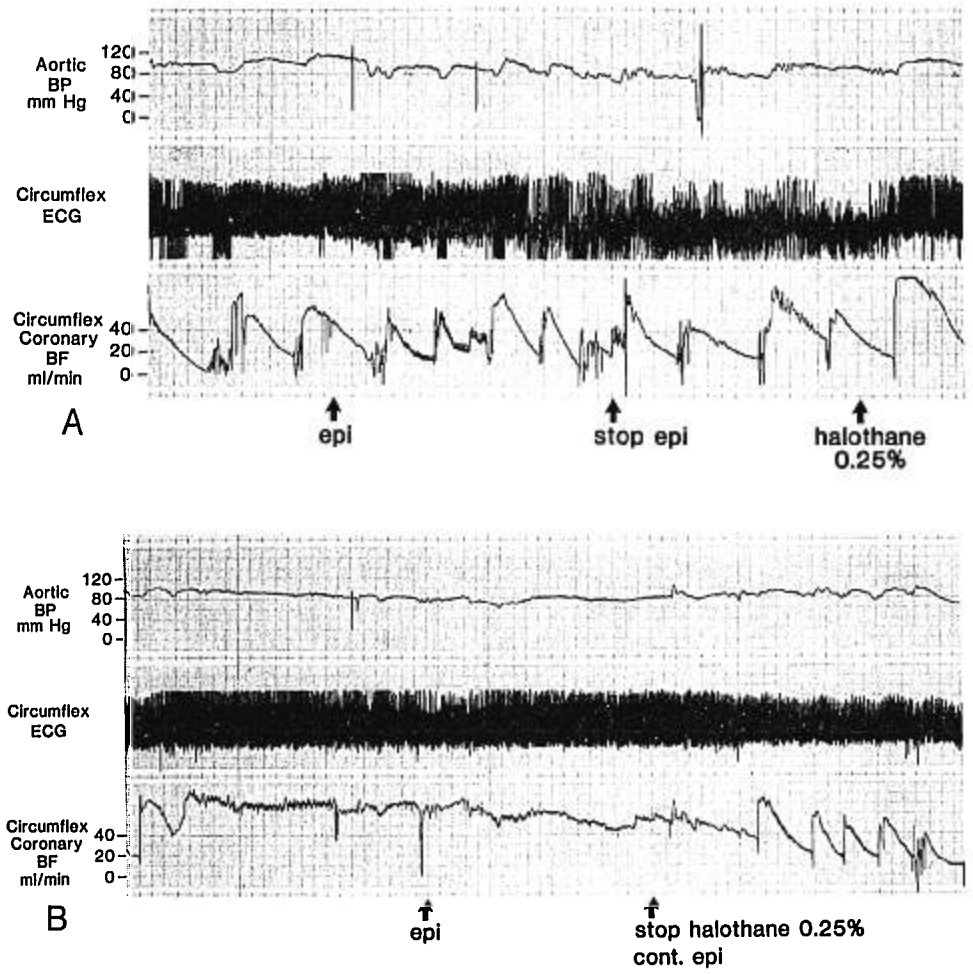

FIG. 5. *A.* A similar record in another animal with low-dose halothane (0.25%) in oxygen. At left control CFR are exacerbated by epinephrine infusion and halothane 0.25% is started at right while CFR continue. *B.* Continuous recording from figure 5*A* during 0.25% halothane shows reversal of a CFR in progress possibly by causing disaggregation of thrombus and prevention of CFR recurrence during epinephrine infusion. Stopping low-dose halothane while continuing epinephrine infusion again allows rapid recurrence of epinephrine-stimulated CFR.

creased CFR frequency from 0.37 ± 0.07 to 0.57 ± 0.09 min^{-1} during epinephrine ($P < 0.05$, n = 8). Following discontinuation of the initial epinephrine infusion in figure 4, halothane 0.5% was started, producing a gradual 30-mmHg pressure decline and abolishing CFR in approximately 20 min. Repeat epinephrine infusion during continued halothane ventilation produced a gradual increase in mean aortic blood pressure toward control level while CFR remained inhibited. Discontinuation of halothane produced recurrence of CFR within 5 min during continued epinephrine infusion and further elevation of arterial blood pressure. Similar results were seen using 0.25% halothane as in figures 5*A* and 5*B*. At 0.25%, halothane, arterial blood pressure was minimally affected, and there was no statistically significant difference in the time after onset of halothane to abolition of CFR compared with 0.5% halothane.

Effect of Enflurane and Isoflurane Anesthesia on Spontaneously Occurring Cyclical Reductions in Coronary Blood Flow

Neither isoflurane nor enflurane produced any significant change in frequency or magnitude of CFR (fig. 6*A*). Initial and final coronary flow during control CFR before isoflurane averaged 54.53 ± 13.61 and 3.60 ± 4.92 ml/min, respectively. Initial and final coronary flow levels during isoflurane averaged 49.63 ± 14.49 and 9.02 ± 5.96 ml/min, respectively. Aortic blood pressure declined from 122.5 ± 14.43 to 75.0 ± 12.91 mmHg during isoflurane while CFR frequency remained unchanged (0.26 ± 0.05 to 0.27 ± 0.04 min^{-1}). Similarly, initial CFR coronary flow levels (53.57 ± 7.77 *vs.* 56.23 ± 12.88 ml/min), final CFR flow levels (1.33 ± 2.97 *vs.* 8.48 ± 12.92 ml/min), and CFR frequency (0.25 ± 0.07 *vs.* 0.22 ± 0.03 min^{-1}) were unchanged by enflurane. Isoflurane 1.5% and enflurane 2.0% produced a gradual 39% and 30% decline in mean arterial blood pressure, respectively, and there was no significant difference between the two agents. After 45 min of using either isoflurane or enflurane with the CFR continuing at the same rate, the agent was discontinued and ventilation was maintained with 100% O_2 for 30 min before halothane was begun at 1.0% inspired concentration. In all animals ventilation with halothane produced abolition of CFR within 15 ± 6 min (fig. 6*B*).

Discussion

This study demonstrates an *in vivo* inhibitory effect of halothane anesthesia on spontaneously forming cyclical

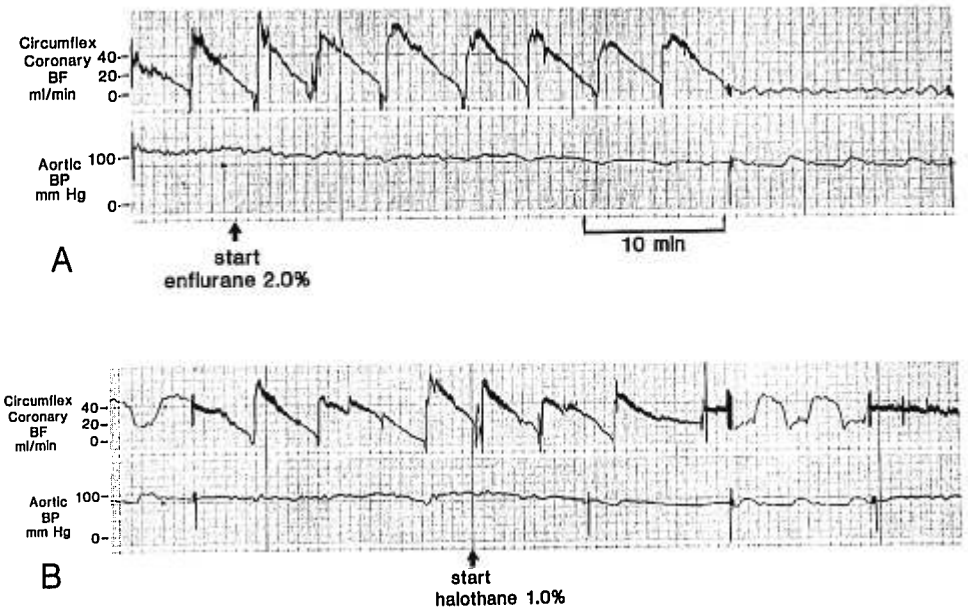

FIG. 6. *A.* The lack of an inhibitory effect of enflurane on the occurrence of CFR. Enflurane 2.0% produced an aortic pressure decline similar to halothane 1.0% and isoflurane 1.5%. *B.* A continuous recording with figure 6*A* showing CFR approximately 30 min after discontinuing enflurane ventilation and following the onset of 1.0% halothane ventilation. Halothane produced abolition of CFR, whereas enflurane showed no inhibitory effect on CFR in the same animal.

coronary blood flow reductions in dogs caused by intracoronary acute platelet thrombus formation at the site of mechanically produced critical coronary stenosis. The finding that halothane, even at subanesthetic levels, reliably abolishes CFR while isoflurane and enflurane had no effect on coronary flow reductions was not expected. The CFR described in this study are in all likelihood caused primarily by intracoronary thrombus formation and not coronary vasospasm because nitroglycerin, a large coronary artery dilator, has no inhibitory effect on CFR.[22] CFR in this preparation can be abolished by aspirin and other nonsteroidal anti-inflammatory agents, whereas epinephrine infusion causes recurrence of CFR in animals treated with aspirin.[15] CFR cause progressive ischemic dysfunction in subendocardial and subepicardial regional contractile function measured with miniature ultrasonic crystals.[23] Scanning electron and light microscopic studies have shown intracoronary platelet thrombus formation in studies using this dog preparation.[5–9] Agents, such as prostacyclin or chlorpromazine and other phenothiazine derivatives, abolish CFR and also prevent recurrence of CFR during epinephrine infusion.[1,**] The exacerbation and recurrence of CFR after aspirin administration or other nonsteroidal anti-inflammatory agents by epinephrine infusion can be attributed to the α_2-adrenoreceptor activation of platelet aggregation and inhibition of platelet adenylate cyclase activity in addition to possible direct membrane effects on calcium transport.[24–27]

Although halothane has been shown to markedly reduce endogenous catecholamine levels in rats,[28] it is unlikely that the inhibition of CFR in the present study is due to reduction in endogenous catecholamine-induced platelet activity because halothane protected against renewal of CFR during exogenous epinephrine infusion. The thrombi producing CFR appear more related to platelet thrombus formation than fibrin clot formation because CFR in this model occur unabated following heparinization of the dogs.[7]

Numerous *in vitro* studies have demonstrated an inhibitory effect of halothane on platelet aggregation and shown that this is related to increased platelet adenylate cyclase activity and intraplatelet cAMP. Recent studies have indicated that halothane selectively attenuates α_2-adrenoreceptor-mediated vasoconstriction.[29] Halothane has been shown to inhibit platelet deposition on PTFE graft material.[30] *Ex vivo* platelet aggregation studies using blood samples drawn during enflurane anesthesia have demonstrated absence of a significant antiplatelet effect.[31] *In vitro* and *ex vivo* platelet aggregation studies have shown no effect of isoflurane on collagen-induced platelet aggregation and a minimal inhibitory effect of isoflurane on ADP-induced platelet aggregation.[32] Impaired platelet aggregation and increased bleeding time have been reported during surgery with halothane anesthesia.[33]

This study demonstrates marked differences in antithrombotic effect of the most commonly used volatile anesthetics. At approximately equipotent doses based on hypotensive effect and MAC differences, halothane produced a reliable abolition of cyclical coronary flow reductions, whereas isoflurane and enflurane had no effect on CFR occurrence. Further studies are needed to investigate the effect of halothane and other agents on thrombus formation, platelet function, and possibly early coronary artery bypass graft patency rates in humans.

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