

Normalization of Cerebral Blood Flow during Prolonged Halothane Anesthesia

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The effects of 150 min halothane (1% inspired in 100% O₂) anesthesia on cerebral blood flow (CBF), cerebral metabolic rate for oxygen (CMR_{O₂}), cerebral vascular resistance (CVR), cardiac output (CO), and cerebral autoregulation of blood flow (CA) were determined in normal goats and in goats following alpha- and beta-receptor blockade. In normal goats, CBF increased significantly from an awake value of $65 \pm 5 \text{ ml} \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1}$ to $135 \pm 12 \text{ ml} \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1}$ following 30 min of halothane anesthesia. After approximately 30 min, CBF began to decrease and approached pre-inhalation levels at 150 min. Cerebral vascular resistance and CMR_{O₂} decreased during the first 30 min of inhalation, but significantly increased over the next 120 min of anesthesia. Cardiac output decreased significantly with induction of anesthesia, remained below awake values throughout the 150 min of halothane inhalation, and returned to pre-inhalation levels following anesthesia. Mean arterial blood pressure (MABP) increased slightly, but not significantly after halothane was terminated.

Alpha- and beta-receptor blockade with phentolamine and propranolol failed to alter the course of CBF, CVR, and CMR_{O₂} throughout the entire experimental period as compared with control values. However, CO failed to return to pre-inhalation levels upon emergence from anesthesia. In addition, MABP was significantly lower than the nontreated goats upon emergence from anesthesia.

Arterial injections of angiotensin (1 μg) were administered periodically during the 150 min of anesthesia in order to challenge CA. Cerebral blood flow increased significantly in both normal and receptor-blocked animals with each angiotensin injection indicating a loss of CA to rapid increases in MABP.

Results from this study indicate that the initial rise in CBF usually associated with halothane inhalation is a transient phenomenon after which CBF gradually returns to control levels over a protracted period of time. The return of CBF to control values is unrelated to CA and is not influenced by alpha- and beta-adrenergic receptor blockade. (Key words: Anesthetics, volatile: halothane. Brain: blood flow; metabolism.)

HEMODYNAMIC ADAPTATION to prolonged inhalation anesthesia is a well-documented observation.^{1,2} Chiefly, the phenomenon is characterized by an initial decrease in cardiac output, stroke volume, contractile force, heart rate, and blood pressure followed by a gradual

return to normal or near normal values with time. The cause of these cardiovascular adjustments following anesthetic-induced disturbance is not known. However, Price and associates demonstrated that beta-receptor blockade in humans prevented the "recovery" of cardiac output, systemic vascular resistance, and dP/dt following three hours of halothane anesthesia.¹ These authors suggested that halothane directly stimulated beta receptors or caused sympathetic stimulation. Although studies have shown that sympathetic activity initially is depressed by halothane, a "sympathomimetic-like" effect for halothane on beta receptors located in bronchial smooth muscle and uterus has been reported.^{3,4}

In previous studies we have observed that cerebral blood flow (CBF) increases dramatically within the first few minutes of halothane inhalation, and thereafter, declines to pre-induction levels.^{5,6} It was the purpose of this study to determine if these changes, or any part of these changes were due to halothane stimulation of autonomic receptors located in the cerebral vasculature.

Methods

The studies were performed with 18 mature female goats weighing 30–35 kg, which were surgically prepared for the continuous measurement of CBF and metabolism in the awake and anesthetized state using a method originally described by Albrecht *et al.*⁵ Briefly, during halothane–nitrous-oxide anesthesia, an electromagnetic flow probe 4 or 5 mm in diameter was surgically placed around an internal maxillary artery. In the goat the internal maxillary artery, a branch of the carotid artery, supplies the entire blood supply to its respective half of the brain. Following this, a $2 \times 1 \text{ cm}$ opening was made along the top and midline of the skull and a catheter was inserted into the superior sagittal sinus for the collection of venous blood samples. The opening was then closed and the catheter secured with dental cement. A thoracotomy was performed and an electromagnetic flow probe (16–18 mm diameter) was placed around the main pulmonary artery for the measurement of cardiac output (CO). Chronic catheters were implanted in both a femoral artery and a femoral vein for arterial blood pressure measurements and blood sampling. Upon completion of the surgical procedure, each animal was permitted to recover for at least ten days before study.

On the day of experimentation, CBF and CO were measured using a Statham #2200® blood flow measur-

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TABLE 1. Cardiovascular Effects of 150 Min of 1% Halothane Anesthesia

	CBF*	CMR _{O₂} †	MABP‡	CO§	CVR¶	SVR**
Awake	65 ± 5	3.84 ± 0.2	94 ± 8	3.2 ± 1.0	11.6 ± 1.5	2.4 ± 0.5
Induction (5 Min)	113 ± 8‡‡	2.89 ± 0.3††	88 ± 5	2.6 ± 0.6††	6.2 ± 0.8††	2.7 ± 0.4
30 Min	135 ± 12††	2.47 ± 0.1††	84 ± 6	2.2 ± 0.5††	5.0 ± 0.8††	3.1 ± 0.5
60 Min	90 ± 11††‡‡	2.83 ± 0.1††	90 ± 4	2.4 ± 0.6††	8.0 ± 1.6††	3.0 ± 0.5
90 Min	81 ± 9††‡‡	2.87 ± 0.2††	93 ± 4	2.5 ± 0.6††	9.2 ± 1.7††	2.9 ± 0.4
150 Min	73 ± 7‡‡	2.96 ± 0.1††‡‡	91 ± 6	2.4 ± 0.6††	9.5 ± 1.5††‡‡	3.0 ± 0.5
Awake	61 ± 5	3.48 ± 0.3	101 ± 9	2.9 ± 0.8	13.3 ± 1.3	2.8 ± 0.6

* Cerebral blood flow in ml · 100 g⁻¹ · min⁻¹; † Cerebral metabolic rate for O₂ in ml · 100 g⁻¹ · min⁻¹; ‡ Blood pressure in mmHg; § Cardiac output in l/min; ¶ Cerebral vascular resistance in dyn · s · cm⁻⁵ × 10⁻⁴; and ** Systemic vascular resistance in dyn · s · cm⁻⁵ × 10⁻³.

†† Significantly changed from awake value; *P* < 0.05, *n* = 8; all values represent means ± SE.

‡‡ Significantly different from 30 min values; *P* < 0.05, *n* = 8.

ing system with electrical zero calibration. Prior to the beginning of each experiment the hematocrit and hemoglobin concentration were determined. After this, 100% oxygen was administered for five minutes via an airtight, rubber-cuffed mask to the animal, which was standing unrestrained, in a yoke and stall. At five minutes, blood samples were drawn simultaneously from a femoral artery and the sagittal sinus while continuously recording CBF. Blood-gas values were measured with an IL 313 analyzer and oxygen content with a Lexicon oxygen analyzer. Cerebral metabolic rate for oxygen (CMR_{O₂}) was derived from the femoral arterial and sagittal sinus oxygen content difference times total CBF divided by brain weight (assuming hemispheric metabolic rate to be representative of the total brain). Total CBF was determined by multiplying the unilateral electromagnetic flow probe measurements by 2, assuming both carotid flows to be equal. After completion of all experiments, the animals were killed and the brains removed for weighing and subsequent final CMR_{O₂} calculations. Upon establishment of awake, control values for CMR_{O₂}, the animals were anesthetized with 1.0% halothane (inspired) in oxygen. Arterial and sagittal sinus blood samples were drawn at 5 min (after which the animals were intubated and mechanically ventilated), and at 30, 60, 90, and 150 min from the start of halothane administration. At 150 min, halothane inhalation was terminated, but the animals continued to breathe oxygen until they regained consciousness. When they regained consciousness (normally about 20 min after halothane termination), final arterial and sagittal sinus blood samples were taken. Throughout the entire experiment, CBF, CO, and mean arterial blood pressure (MABP) were monitored continuously. Blood P_{CO₂} was maintained between 33 and 38 mmHg by adjusting ventilation rate or volume. Body temperature was maintained with a heated water blanket, and the animals were draped during anesthesia. In some animals it was necessary to infuse angiotensin (0.1–0.2 μg/min) in order to maintain a MABP of approximately 80 mmHg

or higher since MABP was a controlled variable in the study. Periodic arterial injections of angiotensin (1 μg) were administered prior to the start of each experiment, throughout the course of halothane anesthesia, and after emergence from anesthesia, in order to assess the status of cerebral autoregulation. Any animal which failed to demonstrate cerebral autoregulation prior to study was excluded.

In ten animals, the above described protocol was repeated except that phentolamine (6 mg) and propranolol (6 mg) were administered intravenously 30 min prior to the induction of anesthesia and again 60 min after the induction of anesthesia. However, a sagittal sinus catheter was implanted and CMR_{O₂} was measured in only five of these animals. Upon completion of these experiments, pressor doses of norepinephrine and isoproterenol were given to test the effectiveness of the alpha- and beta-receptor blockade.

In a separate series of experiments goats were anesthetized with ketamine (3 mg/kg); intubated, and mechanically ventilated for 20 min after which angiotensin (1 μg) was administered and the status of cerebral autoregulation assessed. The latter series of experiments were done to demonstrate that intubation and mechanical ventilation had no effect on cerebral autoregulation.

Statistical significance of the data was determined by *t* test, paired data *t* test, and one-way analysis of variance.

Results

The effects of continuous halothane inhalation on CBF, CMR_{O₂}, CO, MABP, cerebral vascular resistance (CVR), and systemic vascular resistance (SVR) can be seen in table 1. CBF progressively increased during the early phase of anesthesia reaching a maximum elevation approximately 30 min from induction after which CBF slowly decreased to near pre-inhalation values by 150 min. CMR_{O₂} and CVR decreased significantly with induction and reached their lowest point at 30 min and, thereafter, they significantly increased over the remaining 120 min of halothane inhalation. CO fell signifi-

TABLE 2. Cardiovascular Effects of 150 Min of 1% Halothane Anesthesia Following Phentolamine and Propranolol Receptor Blockade

	CBF*	CMR _{O₂} †	MABP‡	CO§	CVR¶	SVR**
Awake (Before receptor blockade)	70 ± 4	3.93 ± 0.3	89 ± 4	3.0 ± 0.9	10.2 ± 0.3	2.4 ± 0.3
Induction (5 Min)	94 ± 7††	2.86 ± 0.5‡‡	92 ± 7	2.5 ± 0.7††	7.8 ± 0.2††	2.9 ± 0.3
30 Min	123 ± 7††	2.04 ± 0.3‡‡	78 ± 8	2.2 ± 0.4††	5.1 ± 0.2††	2.8 ± 0.5
60 Min	78 ± 5	2.31 ± 0.8‡‡	82 ± 5	2.1 ± 0.3††	8.4 ± 0.3††	3.1 ± 0.4
90 Min	67 ± 5	2.57 ± 0.2‡‡	80 ± 6	2.3 ± 0.3††	9.6 ± 0.3	2.8 ± 0.6
150 Min	59 ± 7	2.83 ± 0.4§§	81 ± 6	2.2 ± 0.4††	10.3 ± 0.3	2.7 ± 0.5
Awake	65 ± 8	3.69 ± 0.4	84 ± 6¶¶	2.3 ± 0.5††	10.3 ± 0.4	2.9 ± 0.6

* Cerebral blood flow in ml · min⁻¹ · 100 g⁻¹; † Cerebral metabolic rate for O₂ in ml · 100 g⁻¹ · min⁻¹; ‡ Blood pressure in mmHg; § Cardiac output in l/min; ¶ Cerebral vascular resistance in dyn · s · cm⁻⁵ × 10⁻⁴; ** Systemic vascular resistance in dyn · s · cm⁻⁵ × 10⁻³.

†† Significantly changed from awake value; P < 0.01, n = 10; all values represent means ± SE.

‡‡ Significantly changed from awake value; P < 0.05, n = 5.

§§ Significantly changed from awake and 30 min value; P < 0.05, n = 5.

¶¶ Significantly lower than untreated animals (table 1); P < 0.01, n = 10.

cantly with induction and did not return to pre-anesthesia levels until after anesthesia was terminated.

Administration of phentolamine and propranolol prior to and during the course of anesthesia did not prevent the return of CBF to pre-inhalation levels (table 2). CMR_{O₂} and CVR followed a similar course as was seen in untreated goats. CO fell with induction of anesthesia in a fashion similar to that seen with untreated animals, but unlike untreated animals, CO did not return to awake levels following emergence from anesthesia. In addition, MABP was significantly lower than in untreated goats upon awakening from anesthesia (table 1). The lack of significant blood pressure change to injections of norepinephrine (5.0–7.5 µg) and isoproterenol (1–4 µg) at the end of each experiment demonstrated adequate alpha- and beta-receptor blockade.

Cerebral autoregulation following arterial injections of angiotensin (1 µg/kg) was absent in both control and receptor-blocked animals during the entire period of anesthesia, as was evidenced by abrupt increases in CBF which closely mirrored sudden changes in arterial blood pressure (fig. 1). Similarly, intubated and ventilated goats anesthetized with ketamine displayed normal autoregulatory capability (fig. 2). Impaired or absence of autoregulation was noticed in some animals for up to 240 min following the discontinuance of halothane anesthesia.

Discussion

The cerebral circulation appears to be similar to other hemodynamic parameters in that it tends to return to normal following halothane-induced changes. In the present study, CBF increased dramatically during the first 30 minutes of inhalation, after which it gradually declined over the subsequent two hours of anesthesia. Previous studies also have noted declines in CBF with prolonged periods of anesthesia.^{7–10} However, all of these studies were conducted under different circumstances and in some cases with different anesthetics.

Takeshita *et al.*, in a study of the effects of morphine on CBF and CMR_{O₂} of dogs, observed a time-dependent decrease in CBF that appeared unrelated to the effects of morphine, since control animals demonstrated a similar though smaller decrease (control animals in this case were anesthetized with 0.1% halothane and 70% N₂O).⁷ These authors contend that time alone can cause a progressive fall in CBF as the result of a progressive increase in CVR. They explained that the phenomenon may be due in part by cerebral vasodilatation in response to surgical manipulation of the cerebral circulation which then gradually subsides. However, results from our study do not support this contention. The animals used in our experiments were surgically prepared days prior to study, and therefore, surgical trauma to the cerebral vasculature could be safely excluded as a possible explanation for the significant changes in CBF and CVR seen in our study (tables 1 and 2).

De Valois and Peperkamp studied the prolonged effects of either halothane, or barbiturates on CBF in rabbits.⁸ They found that a 0.5% halothane concentration in 100% oxygen caused a significant drop in CBF reaching its nadir 45 minutes for induction, after which CBF slowly rose over the next 3 hours. When 70% N₂O was added to the inhalation mixture, CBF increased slowly for 3.5 hours and then fell sharply over the next 1.5 hours. Unfortunately, interpretation of these data is complicated by the fact that arterial blood pressure fell significantly in both situations. However, the data do show that CBF has a tendency to return to baseline levels following either upward or downward displacement. This also was suggested by the experiments involving anesthesia with pentobarbital. In this case, De Valois and Peperkamp observed that CBF dropped sharply immediately after administration of pentobarbital and then continually rose to reach control values three hours later.⁸ Again, adequate interpretation of these results is hampered since it is not clear if the CBF data represented fully anesthetized values or were merely reflecting gradual emergence from anesthesia.

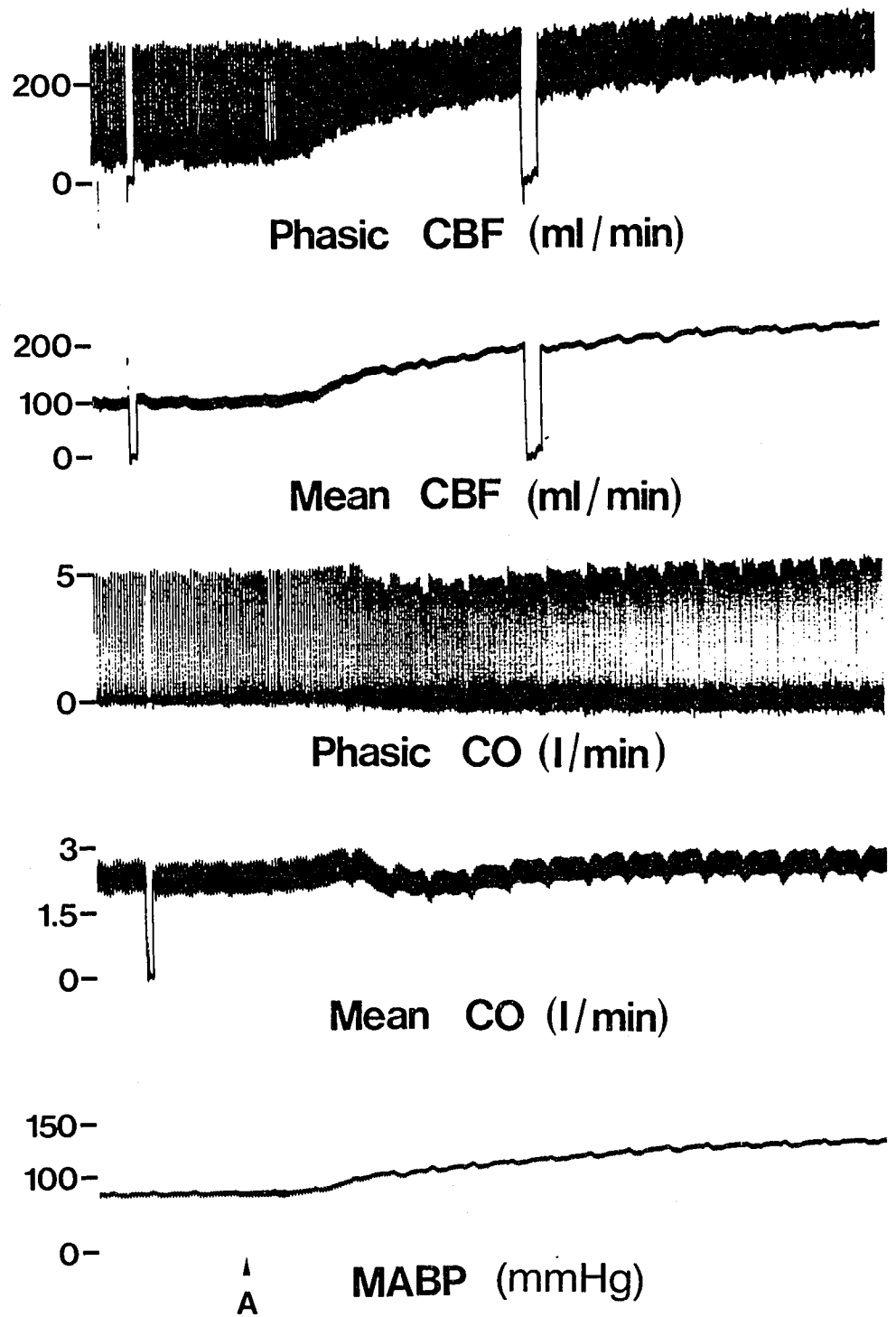


FIG. 1. The effects of 1 μ g angiotensin injected intravenously on MABP and CBF in the mechanically ventilated, halothane-anesthetized goat. Recording speed: 1 mm/s.

The studies by Raichle *et al.* and McDowall *et al.* offer further observations on the long-term effects of anesthesia on CBF.^{9,10} In the latter study, the combination of 0.5% halothane, N₂O, and oxygen produced a significant, progressive fall in CBF in dogs over a 2.5-hour period. However, the periodic removal of N₂O and the substitution of room air for the vaporizing of halothane

caused CBF to alternately rise and fall with each change in the inhalation mixture. Although the removal of N₂O resulted in a slowly rising CBF, the overall direction of blood flow was downward. Raichle *et al.* studied the effects of halothane and oxygen anesthesia on CBF in paralyzed dogs for a period of 5 hours. Again, CBF was seen to decrease progressively throughout the course

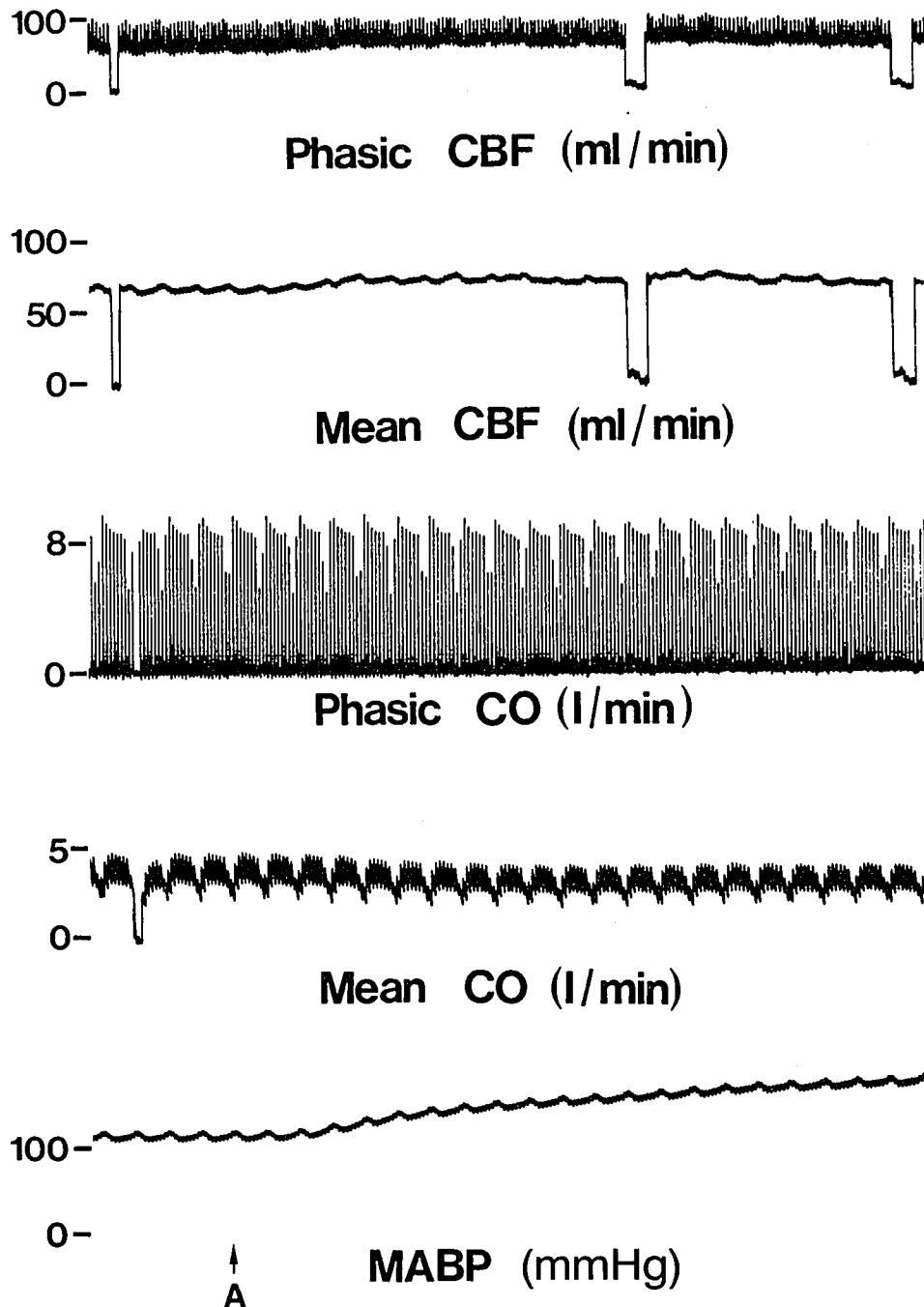


FIG. 2. The effects of 1 μ g angiotensive injected intravenously on MABP and CBF in the mechanically ventilated, ketamine-anesthetized goat. Recording speed: 1 mm/s.

of the study. Despite the downward trend, however, the cerebral vasculature retained its ability to respond to CO_2 . The addition of CO_2 to the inhalation mixture caused significant cerebral vasodilation and a concomitant increase in CBF even after 5 hours of anesthesia.

The greatest difficulty in comparing the results from the previously described studies with data from our study is the lack of unanesthetized, control CBF values and immediate post-induction levels in the earlier reports. These CBF values are important as reference points for determining the trend of CBF throughout

the course of prolonged anesthesia. In our study, CBF was seen to increase substantially above control levels following halothane induction after which it declined. In other words, the course of CBF demonstrated a biphasic response to halothane. Due to the lack of control "reference points," it would appear that the previously described studies may have detected only the declining phase of CBF.

The mechanism by which CBF "adjusts" to anesthetic-induced perturbation is not possible to deduce from the data presented here. However, alpha- and beta-re-

ceptor blockade failed to alter either the increasing phase or the decreasing phase of CBF changes. This would seem to suggest the absence of an adrenergic component to the effect of halothane on CBF. While receptor blockade may not conclusively exclude an adrenergic mechanism, other reports have shown that the cerebral vascular system in the goat shows a high degree of sensitivity to adrenergic agonists and antagonists when administered directly into the cerebral circulation.^{11,12} Of course, it is possible that cholinergic innervation might be responsible for the changes seen in our study. However, cerebral vascular cholinergic nerve endings seem to be involved in cerebral vasodilatory activity if they have any physiologic significance at all.¹³

The failure of receptor blockade to inhibit the progressive return of CBF to normal values during prolonged halothane inhalation is at variance with the report by Price *et al.* for other hemodynamic parameters.¹ These authors demonstrated that the recovery of cardiac output, contractile force, and an increase in SVR during three hours of halothane inhalation was prevented by beta-receptor blockade in humans.¹ We did not see any effects of receptor blockade on CBF and CVR in goats. In addition, we did not see any recovery during anesthesia in CO or SVR in goats with or without receptor blockade. However, in the post-anesthetic period, blocked animals had significantly lower MABP than unblocked animals, and CO failed to return to pre-anesthetic levels.

Perhaps the most interesting observation of our study was that the loss of cerebral autoregulation due to the presence of halothane was of no consequence to the restoration of CBF to pre-inhalation levels. Studies by our laboratory and others have demonstrated that halothane abolishes cerebral autoregulation rendering the cerebral circulation vulnerable to sudden fluctuations in arterial blood pressure.^{14,15} In this study, injections of angiotensin throughout the entire course of anesthesia consistently demonstrated a lack of cerebral autoregulatory response to a pressor challenge even while CVR and CBF were returning to normal values (figs. 1 and 2; table 1). Thus, it is apparent that the restoration of CBF is unrelated to cerebral autoregulation as autoregulation is conventionally viewed. However, other adaptive mechanisms exist which might explain the results of our study. The decline in CBF could be interpreted as tolerance or tachyphylaxis to halothane. It is well-known that if a drug is taken repeatedly it is likely to become progressively less effective, so that the dose has to be increased if the drug's original effect is to be sustained. This phenomenon is known as drug resistance or tolerance (tachyphylaxis, a subcategory of tolerance, is characterized as a rapidly developing form of drug resistance).¹⁶ However, while helpful in a descriptive sense, tolerance is an obscure phenomenon. None-

theless, such a wide ranging adaptive process would have available a variety of active mechanisms to affect it.¹⁶ Presumably, these mechanisms must be integrated in some way to the homeostatic regulatory machinery of the cerebral vasculature and/or brain tissue. Clearly, halothane has a profound effect on brain function and CBF, but it does seem that over a protracted period of time an active adjustment at some level in the cerebral vascular system takes place which counteracts the effects of halothane.

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