The Effects of Methoxyflurane on Arterial Pressure, Preganglionic Sympathetic Activity and Barostatic Reflexes

Per Skovsted, M.D., and Henry L. Price, M.D.†*

The effects of methoxyflurane on arterial pressure and cervical preganglionic sympathetic activity and the responses of these to stimulation of the aortic depressor nerve were studied in cats.

In normal cats end-expired concentrations of methoxyflurane of 0.28, 0.48 and 0.55 per cent produced proportional depressions in arterial pressure. Sympathetic activity was unaffected. The responses of arterial pressure and sympathetic activity to baroreceptor nerve stimulation also were unaffected by methoxyflurane in these concentrations.

In baroreceptor-denervated animals methoxyflurane produced a slight reduction in sympathetic activity, believed to be due to a depressant action on the medullary pressor neurons, an action which in normal animals is counteracted by the reflex response to arterial hypotension. (Key words: Methoxyflurane; Sympathetic nervous activity; Barostatic reflexes; Arterial blood pressure.)

METHOXYFLURANE (Penthrane) produces slight-to-moderate hypotension[1-3] and decreases output,[3, 4] cardiac contractile force[5, 6] and systemic vascular resistance.[3] Limb blood flow has been reported to be unaffected, as is the response of vascular smooth muscle to norepinephrine.[7] The sympathetic nervous system also has been reported to be unaffected by methoxyflurane.[4, 5] Catecholamine concentrations in arterial blood are unchanged but capable of increasing during hypercarbia and hemorrhage.[4] On the other hand, adrenal venous catecholamine concentrations decrease directly in proportion to the depth of anesthesia.[9] In this study direct measurements of preganglionic sympathetic activity and of the response to baroreceptor nerve stimulation have been used to investigate the effects of methoxyflurane on the sympathetic nervous system and barostatic reflexes.

Methods

The subjects of the experiments were 13 cats weighing 1.4 to 3.4 kg. The experimental methods were, in general, those described in the companion paper.[10] Methoxyflurane was delivered from a calibrated Foregger Pentomatic vaporizer. End-expired gas samples were withdrawn manually into a 50-ml syringe (in 5-ml increments) and analyzed for methoxyflurane by gas chromatography.

Experimental Protocol

The cats were prepared as follows.

Eight "normal" animals (in which the left aortic depressor nerve only was divided) were anesthetized with methoxyflurane using an inspired concentration of 1 per cent. After 15 minutes' sympathetic activity (SA), mean arterial blood pressure (MABP) and end-expired methoxyflurane concentration were measured. Inspired methoxyflurane concentration was then raised to 2 per cent, and maintained there for 25 minutes. The measurements were repeated at 30 and 40 minutes (*i.e.*, after 15 and 25 minutes of exposure to 2 per cent methoxyflurane). In cats 1 to 7 a reproducible central nervous system response to baroreceptor nerve stimulation was obtained, and a 15-sec period of stimulation was produced every five minutes throughout the exposure to methoxyflurane. The eighth animal was unresponsive to stimulation. Cats 4, 6 and 7 were subjected to baroreceptor nerve stimulation after denervation also.

Cats 4–8 were subjected to baroreceptor denervation 50 to 60 minutes after discontinuation of methoxyflurane. When the consequent rise in SA and MABP had stabilized

* Research Associate.
† Professor of Anesthesia.
Received from the Department of Anesthesia, University of Pennsylvania, 3400 Spruce Street, Philadelphia, Pennsylvania 19104. Accepted for publication August 19, 1969. Supported (in part) by U.S.P.H.S. Grants GM-15430-02 and 2G-215-11 from the National Institute of General Medical Sciences, National Institutes of Health.

TABLE 1. Effects of Methoxyflurane on Mean Arterial Blood Pressure and Sympathetic Discharge Frequency (impulses/sec) in "Normal" Cats*

	Initial Value	15-Min	30-Min	40-Min	Final Value
			Mean Arterial Blood Pressure (mm Hg)		
Cat 1	140	133	103	56	134
Cat 2	140	130	110	66	145
Cat 3	142	140	96	100	152
Cat 4	135	120	95	78	138
Cat 5	116	95	65	52	125
Cat 6	135	130	85	60	120
Cat 7	112	75	75	78	120
Cat 8	140	105	100	102	146
MEAN	132.5	116.0	91.1	74.0	135.0
SE	4.2	7.9	5.3	6.8	4.4
			Sympathetic Discharge Frequency (impulses/sec)		
Cat 1	6	15	9	6	20
Cat 2	55	55	60	56	50
Cat 3	24	24	19	21	24
Cat 4	12	9	9	8	15
Cat 5	35	40	48	40	80
Cat 6	12	18	20	16	16
Cat 7	60	47	45	48	70
Cat 8	35	44	64	54	56
MEAN	29.9	31.5	34.3	31.1	41.4
SE	7.1	6.0	8.0	7.3	9.2

* Means and standard errors of end-expired methoxyflurane concentrations: 15 minutes, 0.28 ± 0.02 per cent; 30 minutes, 0.48 ± 0.03 per cent; 40 minutes, 0.55 ± 0.02 per cent.

(10 to 15 minutes), methoxyflurane was restarted in a 1 per cent inspired concentration for 15 minutes, continued with a 2 per cent inspired concentration, but for 15 minutes only, then discontinued. Measurements as in the "normal" animals were made after 15 and 30 minutes, and finally an hour after discontinuation of methoxyflurane. Cats 9 and 10 (decerebrated) and 11–13 (spinal cord sectioned) were anesthetized in a similar manner, but methoxyflurane was discontinued after 15 minutes of exposure except in cats 10 and 11. In these two cats the inspired concentration was raised to 2 per cent after 15 minutes of exposure to 1 per cent.

Results

The results in the eight "normal" cats are presented in table 1. The symbol ± is followed by one standard error. The findings in a single animal are shown in figure 1.

NORMAL ANIMALS

Mean arterial blood pressure fell significantly as anesthetic depth increased. After 15 minutes (end-expired methoxyflurane concentration 0.28 ± 0.02 per cent) MABP had fallen from 132.5 ± 4.2 mm Hg to 116.0 ± 7.9 mm Hg ($P < 0.02$); after 30 minutes (end-expired methoxyflurane concentration 0.48 ± 0.03 per cent) it had fallen to 91.1 ± 6.8 mm Hg ($P < 0.05$). After 40 minutes (end-expired methoxyflurane concentration 0.55 ± 0.02 per cent) MABP was 74.0 ± 6.8 mm Hg ($P < 0.05$). Final measurements 60 minutes after discontinuation of methoxyflurane showed MABP 135.0 ± 4.4 mm Hg, indistinguishable from the initial value.

Sympathetic discharge frequency was unaffected by the administration of methoxyflurane. The initial level was 24.1 ± 7.5 impulse/sec; after 40 minutes of methoxyflurane

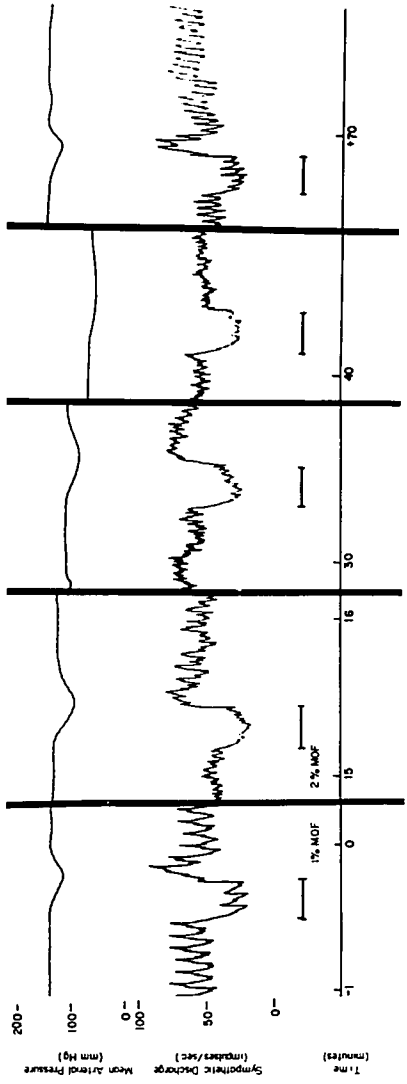

FIG. 1. Effects of increasing depths of methoxyflurane anesthesia on arterial pressure and sympathetic discharge frequency and on the responses of these to a 15-sec period of aortic depressor nerve stimulation in cat 2.

The time scale is minutes of exposure to methoxyflurane. "1% MOF" and "2% MOF" indicate the inspired concentrations of methoxyflurane. Horizontal bars indicate nerve stimulation. +70 min is 70 minutes after termination of methoxyflurane. The sympathetic impulses before and after methoxyflurane occurred in bursts, giving the curve a saw-toothed appearance. During administration of methoxyflurane the pattern of activity changed to more continuous firing even though the total number of impulses remained the same.

TABLE 2. Effects of Methoxyflurane on Mean Arterial Blood Pressure and Sympathetic Discharge Frequency (impulses/sec) in Cats 4–8 before Denervation ("normal") and after Denervation (Denervated)*

	Initial Value	15-Min Value	Per Cent Depression from Control	30-Min Value	Per Cent Depression from Control	Final Value
Mean Arterial Blood Pressure (mm Hg) in "Normal" Cats						
Cat 4	135	120	11.1	95	29.6	138
Cat 5	116	95	18.1	65	24.0	125
Cat 6	135	130	3.7	85	27.0	120
Cat 7	112	75	33.0	75	33.0	120
Cat 8	140	105	25.0	100	28.6	146
MEAN	127.6	105.0	18.2	84.0	28.4	129.8
SE	5.7	9.6	5.1	6.4	1.5	5.2
Mean Arterial Blood Pressure (mm Hg) in Denervated Cats						
Cat 4	195	140	28.2	88	54.1	165
Cat 5	140	117	26.4	76	45.7	150
Cat 6	170	96	43.5	67	60.6	132
Cat 7	142	102	28.1	75	47.2	115
Cat 8	150	102	32.0	90	40.0	182
MEAN	159.4	111.4	31.6	79.2	49.5	148.8
SE	10.4	8.0	3.1	4.3	3.6	11.8
Sympathetic Discharge Frequency (impulses/sec) in "Normal" Cats						
Cat 4	12	9	25.0	9	25.0	15
Cat 5	35	40	−14.3	48	−37.1	80
Cat 6	12	18	−50.0	20	−66.7	16
Cat 7	60	47	21.7	45	25.0	70
Cat 8	35	44	−25.7	64	−82.9	56
MEAN	30.8	31.6	− 8.7	37.2	−27.3	47.4
SE	8.9	7.6	14.3	10.0	22.6	13.6
Sympathetic Discharge Frequency (impulses/sec) in Denervated Cats						
Cat 4	40	34	15.0	30	25.0	46
Cat 5	150	120	20.0	120	20.0	120
Cat 6	30	40	−33.3	25	16.7	30
Cat 7	120	90	25.0	55	54.0	150
Cat 8	110	90	18.2	75	31.8	210
MEAN	90.0	74.8	9.0	61.0	29.5	111.2
SE	23.5	16.4	10.7	17.3	6.6	33.3

* In "normal" cats, end-expired methoxyflurane Concentrations after 15 and 20 minutes were 0.31 ± 0.02 per cent and 0.51 ± 0.04 per cent; in denervated cats, 0.34 ± 0.02 per cent and 0.53 + 0.02 per cent.

it was 24.5 ± 8.0 impulses/sec. A final measurement 60 minutes after discontinuation averaged slightly higher (41.4 ± 9.2), but was not significantly greater than the initial values.

RESULTS AFTER DENERVATION, DECEREBRATION OR SPINAL SECTION

The effects of baroreceptor denervation on MABP and SA can be estimated by compar-

TABLE 3. Effects of Methoxyflurane on Mean Arterial Blood Pressure and Sympathetic Activity in Decerebrated (9,10) and Spinal (11–13) Cats*

	Initial Value	15-Min Value	30-Min Value	Final Value
Mean Arterial Blood Pressure (mm Hg)				
Cat 9	120	64	—	60
Cat 10	96	69	—	85
Cat 11	74	70	—	72
Cat 12	95	86	100	80
Cat 13	135	132	105	110
MEAN (11–13)	101.3	96.0	—	87.3
SE	17.9	18.6	—	11.6
Sympathetic Discharge Frequency (impulses/sec)				
Cat 9	15	13	—	15
Cat 10	12	12	—	9
Cat 11	8	5	—	7
Cat 12	24	26	22	22
Cat 13	15	13	13	10
MEAN (11–13)	15.7	14.7	—	13.0
SE	4.6	6.1	—	4.6

* End-expired concentrations of methoxyflurane in decerebrated cats (9,10) were 0.30 and 0.18 per cent after 15 minutes of exposure to methoxyflurane. In spinal cats (11–13) after 15 minutes the mean end-expired concentration of methoxyflurane was 0.33 ± 0.01 per cent; at 30 minutes values of 0.56 and 0.50 per cent were found.

ing the final values of "normal" cats 4–8 with the initial values after denervation in the same animals (table 2). This also shows the effects of methoxyflurane on SA and MABP before and after denervation. To compare the responses under the two circumstances with different initial pressures and frequency levels, we have expressed the values obtained after 15 and 30 minutes of methoxyflurane as percentage depression from the initial level.

While the responses of both MABP and SA to methoxyflurane in the denervated cats were insignificantly different from normal after 15 minutes of exposure, a trend toward greater depression in both was noted. After 30 minutes of methoxyflurane these differences were significant. SA depression was absent in the "normal" group at 30 minutes (−27.3 ± 22.6 per cent) but after denervation it was significant (29.5 ± 6.6 per cent, $P < 0.02$). MABP at this time showed a 28.4 ± 1.5 per cent reduction under normal circumstances but a 49 ± 3.6 per cent decline after denervation. Final values for MABP were slightly lower, and for SA slightly higher, than the initial level in the denervated group but the changes were not significant.

Table 3 shows the effects of methoxyflurane on sympathetic activity in two decerebrate and three spinal cats, the spinal cats being maintained at almost constant blood pressure levels by infusion of norepinephrine. Both the decerebrate and the spinal cats had responses in sympathetic activity similar to those found in "normal" animals.

Table 4 shows the effects of baroreceptor nerve stimulation on arterial pressure and sympathetic frequency before, during and after exposure to methoxyflurane in all cats studied. It is noticeable that even at an end-expired methoxyflurane concentration of 0.56 ± 0.03 per cent no change occurred in the magnitudes of the blood pressure and frequency responses. In three cats (4, 6, and 7) studied both before and after denervation the MABP response to baroreceptor nerve stimulation was less, and that of SA greater, after denervation than before. However, the reflex

TABLE 4. Effects of Methoxyflurane on the Responses of Arterial Pressure and Sympathetic Discharge Frequency to Aortic Depressor Nerve Stimulation*

	Per Cent Depression									
	Initial Value	5 Min	10 Min	15 Min	20 Min	25 Min	30 Min	35 Min	40 Min	Final Value
Mean Arterial Blood Pressure Response										
Cat 1	22.2	26.0	21.8	19.7	23.0	21.8	19.0	15.0		15.5
Cat 2	20.8	27.3	25.0	28.2	29.1	26.3	23.6	23.8	18.2	18.2
Cat 3	18.7	21.4	21.4	21.4	16.7	14.9	16.7	14.7	14.3	20.9
Cat 4	28.4	34.6	36.0	31.1	35.6	29.1	25.0	22.0	17.6	15.5
Cat 5	8.6	8.3	10.5	10.5	6.3	6.6	5.9	9.8	—	7.8
Cat 6	16.8	11.1	11.0	8.3	10.5	15.7	6.4	6.2	3.5	15.6
Cat 7	13.4	16.3	16.9	12.2	12.9	12.9	13.6	6.5	10.4	17.5
MEAN	18.4	20.7	20.4	18.8	20.6	18.2	15.7	14.0	12.8	15.9
SE	2.4	3.6	3.3	3.3	4.4	3.0	2.9	2.7	2.7	1.5
Sympathetic Discharge Frequency Response										
Cat 1	42.4	50.0	38.5	53.3	48.5	38.9	37.1	25.0		39.1
Cat 2	47.7	35.0	43.6	44.4	56.4	48.1	48.3	48.3	50.0	44.0
Cat 3	37.1	41.7	37.5	33.3	37.2	34.8	36.8	34.8	33.3	29.6
Cat 4	18.4	16.7	20.0	22.2	57.1	35.3	37.5	50.0	50.0	24.5
Cat 5	33.6	40.0	45.0	30.0	33.3	36.4	26.7	31.1		33.3
Cat 6	19.3	27.8	11.1	13.3	11.1	4.8	5.9	10.5	4.4	28.2
Cat 7	60.0	64.0	72.0	73.9	80.0	71.4	60.0	56.4	62.5	61.7
MEAN	36.9	39.3	38.2	38.6	46.2	38.5	36.0	38.6	40.0	37.2
SE	5.7	5.8	7.4	7.7	8.2	7.5	6.4	6.8	10.0	4.8

* End-expired methoxyflurane concentrations at 15, 30 and 40 minutes exposure: 0.29 ± 0.03 per cent, 0.49 ± 0.03 per cent and 0.56 ± 0.03 per cent.

responses were unchanged by methoxyflurane just as during exposure to methoxyflurane in the "normal" state.

Discussion

The finding that the sympathetic activity level was completely unchanged and that arterial pressure progressively declined in the face of increasing depths of methoxyflurane anesthesia confirms the suggestions of others [4-6] that methoxyflurane leaves the sympathetic nervous outflow unaffected. In addition, our use of direct recording methods and our study of the barostatic reflexes in the presence of methoxyflurane permit us to analyze the mode of action and to question why it produces the observed effects.

As part of the experiment we studied the effects of baroreceptor nerve stimulation in three cats both before and after complete baroreceptor denervation and vagotomy. Since in the "normal" cats only one baroreceptor nerve was stimulated, leaving the others as well as the vagi intact, the possibility existed that our stimulus was modified by baroreceptor or chemoreceptor impulses from other buffer nerves and did not represent the response of a single barostatic reflex arc. Furthermore, the reflex changes in arterial pressure which paralleled changes in sympathetic activity during administration of methoxyflurane theoretically could have been caused by increased vagal tone in response to stimulation. These reservations were eliminated by comparing the responses to depressor nerve stimulation before and after denervation in the same animals. Although the reflex response was modified slightly by denervation, the effects of methoxyflurane before and after nerve section were precisely the same.

The basis for our discussion is the concept of Alexander,[11] *i.e.*, that the sympathetic out-

flow is largely controlled by two centers in the medulla oblongata, a tonically-active pressor center and a depressor area excited only by impulses from peripherally located baroreceptors, both centers acting via descending pathways synapsing with spinal vasomotor neurons. Since the effects of methoxyflurane in the two decerebrate and three spinal cats were similar to that found in "normal" cats, any major effect of methoxyflurane on sympathetic activity from centers above the mesencephalon or on the isolated cord apparently was ruled out. Hence we assume that the principal site of action is within the medulla, and therefore that either the pressor or the depressor area (or both) must be affected.

The medullary pressor neurons are believed to be uninhibited after baroreceptor denervation, and they fire at an elevated rate. The response to methoxyflurane in such a preparation represents the effect of the anesthetic on the pressor elements alone. From our data we conclude that these elements are depressed by methoxyflurane. If there were inhibition of the medullary pressor neurons only, the depressor elements remaining unaffected, one could expect an enhanced response to stimulation of the aortic depressor nerve. Since methoxyflurane failed to modify the reflex, we conclude that medullary depressor neurons also are inhibited.

We have left unanswered the question why sympathetic outflow does not decline when intact animals are given methoxyflurane. Our data suggest that arterial hypotension, acting through the intact barostatic reflex arcs, stimulates the sympathetic outflow, maintaining it at a normal level despite the direct medullary depression caused by the anesthetic. In support of this, we have observed that when arterial hypotension is corrected by infusing a vasopressor sympathetic activity falls to an abnormally low level.

Two pieces of evidence from our studies suggest that the level of sympathetic activity reflexly maintained in normal animals has a significant modifying effect in preventing the development of arterial hypotension even more profound than that observed. First, when sympathetic activity was inhibited briefly by stimulating the aortic depressor nerve, the level of arterial pressure was reduced substantially. Second, the degree of arterial hypotension caused by methoxyflurane was more pronounced in baroreceptor-denervated than in "normal" animals. If the same conclusion holds in man, this observation has important clinical implications. It suggests that methoxyflurane will cause an extraordinary degree of arterial hypotension when the barostatic reflexes are weak., as during spinal or epidural anesthesia, following large doses of *d*-tubocurarine, in patients who have had surgical sympathectomy or individuals who have idiopathic postural hypotension.

The authors wish to acknowledge the able technical assistance of Mr. Leo Davidson.

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