Central Sympathetic Excitation Caused by Fluroxene

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

The effects of fluroxene on cervical preganglionic sympathetic nervous activity and arterial pressure and the responses of both to stimulation of the aortic depressor nerve have been studied in the cat. Three concentrations of fluroxene were used: 4, 8 and 12 per cent, end-expired. In normal cats 4 per cent fluroxene affected neither arterial pressure nor sympathetic nervous activity; 8 per cent caused a considerable increase in sympathetic nervous activity without effect on arterial pressure; 12 per cent caused no further change in sympathetic nervous activity, but decreased arterial pressure significantly. Similar responses were observed after decerebration. In baroreceptor-denervated animals increasing depths of fluroxene anesthesia caused a progressive decline in arterial pressure, but did not affect the level of sympathetic nervous activity. Barostatic reflexes were unaffected by fluroxene at 4 per cent, significantly depressed at 8 per cent, and abolished at 12 per cent. It is concluded that fluroxene, like cyclopropane and diethyl ether, causes central sympathetic nervous excitation by depressing medullary depressor neurons. (Key words: Fluroxene; Sympathetic nervous system; Barostatic reflexes; Arterial blood pressure.)

IN ADDITION to providing stable cardiovascular conditions, fluroxene (Fluoromar) is useful because of its low flammability compared with ethyl ether,[1] compatibility with epinephrine,[2] and low solubility coefficient in blood.[3] Early studies of the dog by Krantz *et al.*[1] showed that neither light nor deep fluroxene anesthesia had a significant effect on arterial pressure. Dundee and Dripps[4] confirmed these observations in man; arterial pressure was depressed in only 25 per cent of subjects at deep levels of anesthesia. Bagwell *et al.*[5] demonstrated in dogs only moderate depression of myocardial contractile force with fluroxene concentrations above 6 per cent. Cullen *et al.*[6] found that high fluroxene concentrations increased cardiac output in man. This finding, in addition to the others, suggests an increase in sympathetic activity. The present study represents an attempt to investigate the effect of fluroxene on the sympathetic nervous system.

Methods

The subjects of the experiment were 15 cats weighing 1.4 to 3.8 kg. The methods used are described in the companion paper about ethyl ether. Hypoxia and acidosis were prevented or corrected as described previously. Cats 1 to 10 were considered "normal" (only the left aortic depressor nerve was divided). They were exposed to 5 per cent fluroxene for 12 minutes, after which end-expired fluroxene concentration, mean arterial blood pressure (MABP) and sympathetic nervous activity (SA) were measured. The inspired fluroxene concentration was raised to 10 per cent for 12 minutes and the measurements repeated. The inspired concentration was then raised to 15 per cent for an additional 12 minutes, the measurements repeated, and fluroxene discontinued. Final measurements were made 20 minutes after discontinuation of fluroxene. In cats 4 to 10 baroreceptor denervation was then accomplished, invariably leading to increases in MABP and SA. When the acute changes had subsided the cats were again exposed to fluroxene in the same manner as before.

In cats 4 to 10 baroreceptor denervation was produced by cutting the vagi and right aortic depressor nerves and ligating the carotid arteries below and above the sinus bulb, technically simpler than isolating and section-

* Research Associate.
† Professor of Anesthesia.
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TABLE 1. Effects of Fluroxene on Mean Arterial Pressure (MABP) and Sympathetic Nervous Activity (SA) in "Normal" Cats.

	MABP Response (mm Hg)					
	Control	Initial	4.5 ± 0.2 per cent End-expired Fluroxene	8.2 ± 0.3 per cent End-expired Fluroxene	11.5 ± 0.3 per cent End-expired Fluroxene	Final
Cat 1	98	100	110	98	95	95
Cat 2	163	156	180	160	134	170
Cat 3	138	120	130	110	90	155
Cat 4	127	120	116	130	120	135
Cat 5	140	145	130	110	80	135
Cat 6	132	125	158	160	130	140
Cat 7	136	128	142	148	128	144
Cat 8	103	100	120	105	50	105
Cat 9	137	140	140	136	112	135
Cat 10	142	142	145	138	102	142
MEAN	131.6	127.6	137.1	129.5	103.6	135.6
SE	6.0	5.9	6.6	7.2	8.4	6.9

	Frequency Response (Impulses/sec)					
	Control	Initial	4.5 ± 0.2 per cent End-expired Fluroxene	8.2 ± 0.3 per cent End-expired Fluroxene	11.5 ± 0.3 per cent End-expired Fluroxene	Final
Cat 1	35	25	30	65	77	45
Cat 2	100	70	140	150	120	130
Cat 3	48	50	60	90	95	45
Cat 4	73	75	80	190	180	70
Cat 5	47	35	32	40	50	60
Cat 6	16	12	18	28	30	20
Cat 7	41	40	42	48	82	42
Cat 8	50	40	50	90	85	60
Cat 9	45	40	40	95	110	50
Cat 10	58	40	60	85	125	75
MEAN	51.3	42.7	55.2	88.1	95.4	59.7
SE	7.1	6.0	11.0	15.8	13.3	9.3

ing the sinus nerves. This led to the same result, namely that the barostatic reflex induced by raising the arterial pressure with epinephrine was abolished. Cats 11 to 13 were not given fluroxene before denervation; in these, division of the sinus nerves as well as the vagi and aortic depressor nerves was accomplished, the carotids remaining patent. Two cats were studied after midcollicular decerebration during halothane anesthesia. When decerebrate rigidity occurred, halothane was discontinued and the study proceeded as in "normal" animals except that fluroxene was administered initially in an inspired concentration of 15 per cent for 15 minutes, then discontinued for 15 minutes, after which final control measurements were completed. Following this, baroreceptor denervation was done. Administration of fluroxene was then repeated. In cats 4 to 12 a reproducible response to baroreceptor-nerve stimulation was obtained after denervation. A 15-second stimulation was applied every five minutes throughout the period of exposure to fluroxene.

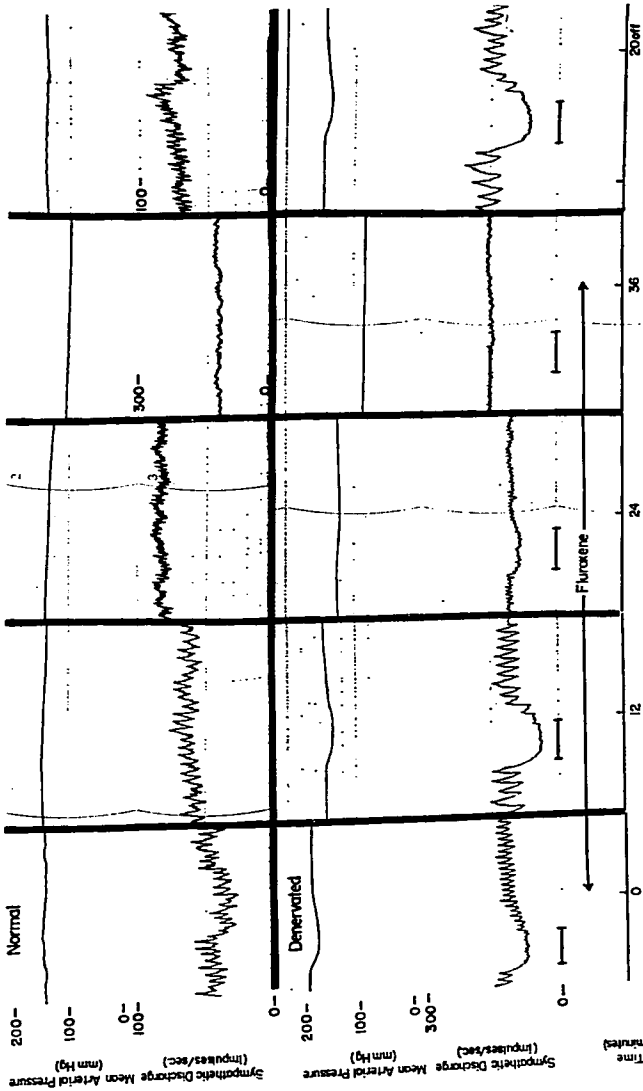

FIG. 1. Tracing from cat 10, showing responses of MABP and SA to increasing fluroxene concentrations in the normal and baroreceptor-denervated state. The solid bar indicates a 15-second baroreceptor nerve stimulation. After 24 minutes of exposure to fluroxene (8 per cent end-expired) sympathetic activity increased in the "normal" state and the normal respiratory pattern of impulse emission changed to continuous firing. At the same time the response to baroreceptor nerve stimulation was markedly reduced. Note change in frequency range in the upper panel. "20 off" indicates findings 20 minutes after discontinuation of fluroxene.

TABLE 2. Effects of Fluroxene on Mean Arterial Pressure (MABP) and Sympathetic Nervous Activity (SA) in Baroreceptor-denervated Cats

	MABP Response (mm Hg)					
	Control	Initial	4.2 ± 0.1 per cent End-expired Fluroxene	8.3 ± 0.2 per cent End-expired Fluroxene	11.5 ± 0.4 per cent End-expired Fluroxene	Final
Cat 4	164	160	165	140	93	168
Cat 5	185	195	150	110	36*	175
Cat 6	163	180	156	120	60	145
Cat 7	159	180	160	125	70	138
Cat 8	141	157	125	80	45*	125
Cat 9	141	155	125	120	76	126
Cat 10	171	186	155	130	79	156
Cat 11	156	142	140	130	100	170
Cat 12	183	190	112	105	65	175
Cat 13	155	150	125	125	125	160
MEAN	161.8	169.5	141.3	117.5	74.9	153.8
SE	4.8	5.9	5.8	5.3	8.3	6.1

	Frequency Response (Impulses/sec)					
	Control	Initial	4.2 ± 0.1 per cent End-expired Fluroxene	8.3 ± 0.2 per cent End-expired Fluroxene	11.5 ± 0.4 per cent End-expired Fluroxene	Final
Cat 4	135	120	130	190	200	150
Cat 5	80	90	65	45	25	70
Cat 6	44	32	27	18	18	55
Cat 7	125	110	90	110	70	140
Cat 8	88	85	60	85	60	90
Cat 9	130	120	90	130	175	140
Cat 10	125	110	105	100	145	140
Cat 11	155	90	100	190	210	220
Cat 12	98	75	80	175	190	120
Cat 13	55	45	12	16	40	65
MEAN	103.5	87.7	75.9	105.9	113.3	119.0
SE	11.5	9.5	11.4	21.0	24.6	15.9

* In animals 5 and 8 fluroxene was discontinued after only 5 minutes of exposure to the 15 per cent concentration because of marked arterial hypotension.

Results

Since in both "normal" and denervated cats the final SA was significantly higher than the initial value ($P < 0.05$) and because in denervated animals the final MABP was significantly lower ($P < 0.001$), all changes in SA and MABP induced by fluroxene have been compared with control levels calculated as the arithmetic means of initial and final values.

Table 1 shows the effects of fluroxene on SA and MABP in "normal" cats 1 to 10. ± indicates one standard error of the mean. At 4.5 ± 0.2 per cent end-expired fluroxene neither MABP nor SA was significantly different from the control level. At 8.2 ± 0.3 per cent, MABP was still unchanged, but SA had increased from 51.3 ± 7.1 imps/sec to 88.1 ± 15.8 imps/sec ($P < 0.01$). At 11.5 ± 0.3 per cent end-expired fluroxene MABP was slightly depressed (from 127.6 ± 5.9 to 103.6 ± 8.4 mm Hg, $P < 0.005$), while SA showed a slight but insignificant further rise (from 88.1

TABLE 3. Effects of Fluroxene on the Responses of Sympathetic Nervous Activity and Mean Arterial Pressure to Baroreceptor-nerve Stimulation

	MABP Response (Per Cent Depression)					
	Control	Initial	4.2 ± 0.1 per cent End-expired Fluroxene	8.3 ± 0.2 per cent End-expired Fluroxene	11.5 ± 0.2 per cent End-expired Fluroxene	Final
Cat 4	11.1	12.2	9.6	14.7	0	10.0
Cat 5	9.7	9.6	7.6	13.8	0	9.7
Cat 7	16.1	14.8	14.8	7.9	3.5	17.4
Cat 8	13.5	15.4	6.7	0	0	11.6
Cat 9	8.9	10.6	5.6	4.0	0	7.1
Cat 10	11.0	10.4	8.3	3.8	0	11.5
Cat 11	7.2	8.9	5.8	1.6	0	5.5
Cat 12	25.1	20.8	9.6	8.7	0	29.3
MEAN	12.8	12.8	8.5	6.8	0.5	12.8
SE	2.0	1.4	1.1	1.9	0.4	2.7

	Frequency Response (Per Cent Depression)					
	Control	Initial	4.2 ± 0.1 per cent End-expired Fluroxene	8.3 ± 0.2 per cent End-expired Fluroxene	11.5 ± 0.2 per cent End-expired Fluroxene	Final
Cat 4	17.3	21.0	17.9	6.7	0	13.5
Cat 5	22.7	16.7	14.3	16.0	7.7	28.6
Cat 7	42.6	45.4	55.6	16.7	3.6	39.7
Cat 8	24.7	25.8	25.0	0	0	23.6
Cat 9	33.2	31.3	29.4	18.5	0	35.0
Cat 10	49.2	36.7	61.9	22.7	0	61.7
Cat 11	28.6	30.9	15.8	4.8	0	26.2
Cat 12	89.4	95.8	45.0	12.1	0	83.0
MEAN	38.5	38.1	33.1	12.2	1.4	38.9
SE	8.2	8.8	6.6	2.7	1.0	8.1

TABLE 4. Effects of Fluroxene on Mean Arterial Pressure (MABP) and Sympathetic Nervous Activity (SA) in Cats 4–10 before and after Denervation

	MABP Response (mm Hg)					
	Control	Initial	4.3 ± 0.2 per cent End-expired Fluroxene	8.1 ± 0.2 per cent End-expired Fluroxene	11.9 ± 0.3 per cent End-expired Fluroxene	Final
"Normal"	131.0 ± 5.0	128.6 ± 5.9	135.9 ± 5.6	132.4 ± 7.4	103.1 ± 11.0	133.7 ± 5.0
Denervated	160.6 ± 6.0	173.3 ± 6.0	148.0 ± 6.2	117.9 ± 7.2	65.6 ± 7.5	147.6 ± 7.4
	Frequency Response (Impulses/sec)					
	Control	Initial	4.3 ± 0.2 per cent End-expired Fluroxene	8.1 ± 0.2 per cent End-expired Fluroxene	11.9 ± 0.3 per cent End-expired Fluroxene	Final
"Normal"	47.1 ± 6.6	40.3 ± 7.0	46.0 ± 7.6	82.3 ± 20.6	94.6 ± 18.8	53.9 ± 7.1
Denervated	103.9 ± 12.9	95.3 ± 11.7	81.0 ± 12.7	96.9 ± 21.3	99.0 ± 27.8	112.1 ± 14.9

± 15.8 to 95.4 ± 13.3 imps/sec). Figure 1 shows a representative example.

Table 2 shows the effects of fluroxene on SA and MABP in cats 4 to 13 after baroreceptor denervation. The SA responses to fluroxene in denervated preparations appeared to be much less uniform than those in "nomal" animals. In some cats high fluroxene concentrations produced increases in activity which declined again after fluroxene was discontinued. In others similar increases occurred but after discontinuation of fluroxene SA continued to increase. Six animals responded to fluroxene either with no change or with declines in SA. In the group as a whole 4.2 ± 0.1 per cent end-expired fluroxene caused a significant decline in SA ($P < 0.001$) compared with the "control" level (mean of initial and final values). Compared with the initial level alone there was no significant change. Neither the intermediate (8.3 ± 0.2 per cent) nor the highest (11.5 ± 0.7 per cent) fluroxene concentration caused a significant change in SA compared with the "control" level. All concentrations caused significant declines in arterial pressure, increasing with concentration. Four per cent fluroxene caused MABP to decrease from 161.8 ± 4.8 mm Hg to 141.3± 5.8 mm Hg ($P < 0.02$). Eight per cent decreased MABP from 141.3 ± 5.8 mm Hg to 117.5 ± 5.3 mm Hg ($P < 0.005$); 11.5 per cent fluroxene reduced MABP to 74.9 ± 8.3 mm Hg ($P < 0.0001$).

Table 3 shows the effects of fluroxene on the responses of SA and MABP to baroreceptor-nerve stimulation in cats 4 to 12. Values are expressed as per cent reduction from control, as described previously. Since the final responses of both SA and MABP were identical to the initial values, these values have been used for comparing the effects of fluroxene on the responses. Four per cent (4.2 ± 0.1) end-expired fluroxene caused no change in the SA response to stimulation of the aortic depressor nerve, although the response of arterial pressure was reduced significantly, from 12.8 ± 1.4 per cent to 8.5 ± 1.1 per cent ($P < 0.02$). Eight per cent (8.3 ± 0.2) fluroxene significantly depressed the responses of both SA (38.1 ± 8.8 to 12.2 ± 2.7 per cent, $P < 0.02$) and MABP (12.8 ± 1.4 to 6.8 ± 1.9 mm Hg, $P < 0.005$).

Twelve per cent fluroxene (11.8 ± 0.2 per cent) abolished the SA responses in six of eight animals. The other two still responded, but the responses were greatly depressed. For the entire group the response was reduced from 38.1 ± 8.8 per cent to 1.4 ± 1.0 per cent ($P < 0.01$). The MABP responses were abolished in seven of the eight animals. For the group, the response fell from 12.8 ± 1.4 per cent to 0.5 ± 0.4 per cent ($P < 0.001$). Figure 1 illustrates the relation between SA and the reflex response in cat 10.

Table 4 shows the mean responses of SA and MABP to fluroxene in the same seven animals before and after denervation. This comparison is made to illustrate the effects of baroreceptor denervation on MABP and SA (as seen by comparing the final values in the normal state with the initial values after denervation) and also to show that the increase in sympathetic nervous activity produced by 12 per cent fluroxene (from 47.1 ± 6.6 to 94.6 ± 18.8 imps/sec) reached a level indistinguishable from that produced by subsequent baroreceptor-nerve denervation (53.9 ± 7.1 to 103.9 ± 12.9 imps/sec). Figures 2 and 3 show the data of table 4 in graphic form.

Both the decerebrate cats responded to fluroxene like the "normal" animals. Sympathetic response frequency in cat 14 increased from 58 to 108 imps/sec; in cat 15, from 22 to 54 imps/sec at end-expired fluroxene concentrations of 10.7 and 10.3 per cent. After denervation, the responses to 11 per cent end-expired fluroxene were an increase from 102 to 120 imps/sec in one cat and a decrease from 48 to 30 imps/sec in the other.

Discussion

Our analysis is based on the hypothesis of Alexander,[7] namely, that sympathetic activity normally depends upon the net outflow of two antagonistic centers in the medulla oblongata. One center contains tonically-active pressor neurons; the other contains depressor neurons which are activated only by impulses from peripheral stretch-sensitive receptors located in major vascular areas. Both centers act finally

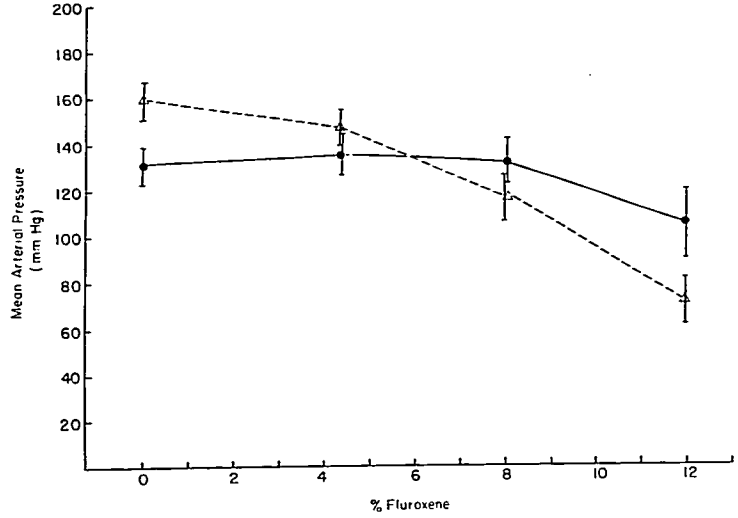

FIG. 2. Effect of fluroxene on mean arterial blood pressure. ● Mean response of cats 4 to 10 in the "normal" state. △ Mean response of cats 4 to 10 after denervation. Vertical bars represent ±1 SE.

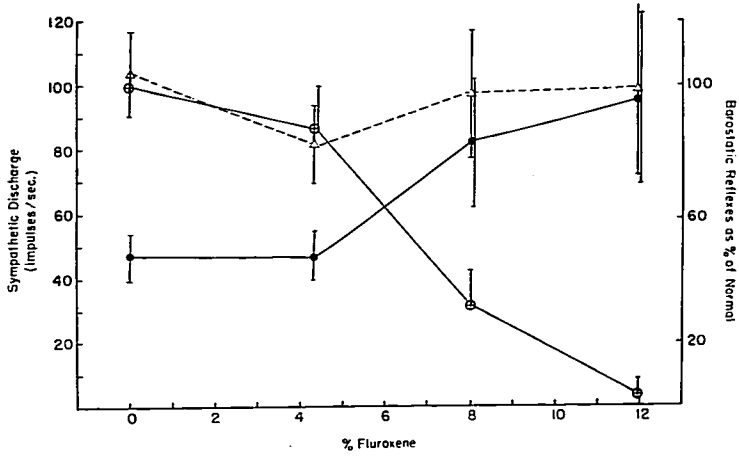

FIG. 3. Effects of fluroxene on sympathetic discharge and barostatic reflexes. ● Mean response of cats 4 to 10 in the "normal" state. △ Mean response of cats 4 to 10 after denervation. Vertical bars represent ±1 SE. ⊕ Frequency response to aortic depressor nerve stimulation. The initial response was set arbitrarily at 100.

via sympathetic vasomotor neurons in the spinal cord. Since the response to fluroxene in the decerebrate animals was identical to that in normal animals a major excitatory effect on sympathetic centers above the mesencephalon apparently has been ruled out.

Since it is not known whether responses in the acutely-sectioned cord are normal, we chose instead to study the same animals before and after baroreceptor denervation, accepting the latter results as indicative of anesthetic actions on the medullary and spinal "pressor" neurons. Fluroxene failed to change the rate of sympathetic discharge in denervated animals. From this we conclude that the pressor neurons are largely unaffected. However, although fluroxene failed to change the total number of emitted impulses it, like ether, strikingly changed the pattern of emission from normal (respiratory) bursts to almost-continuous firing (see fig. 1). Presumably this change resulted from depression of the medullary respiratory center.

The progressive decline in arterial pressure with increasing depth of anesthesia presumably represents a direct cardiovascular depressant action. In the "normal" cat 4 per cent fluroxene had no effect on arterial pressure or on sympathetic nervous activity, while 8 per cent increased sympathetic activity significantly, an action that could not be considered the result of either anoxia or acidosis, but must have been caused by the agent *per se*. This activation apparently compensated for the direct depressant cardiovascular action of increased fluroxene concentration, since arterial pressure remained unchanged at 8 per cent (unlike the response in denervated preparations). At 12 per cent fluroxene (end-tidal) there was an insignificant increase in sympathetic nervous activity over that observed at 8 per cent. However, arterial pressure declined, suggesting direct cardiovascular depression by fluroxene that was no longer effectively counteracted by further increase in sympathetic outflow. The evidence that the barostatic reflexes were unaffected by fluroxene at 4 per cent (where sympathetic nervous activity was unchanged), depressed at 8 per cent (where sympathetic nervous activity increased) and abolished in most animals by 12 per cent leads us to believe that the increase in sympathetic nervous activity which fluroxene caused in the "normal" cat resulted directly from suppression of the barostatic reflex (*i.e.*, from depression of the medullary depressor neurons). Support for this conclusion is that the administration of fluroxene and baroreceptor denervation elevated sympathetic nervous activity to the same degree. Therefore, fluroxene, like cyclopropane [8] and ether,[9] apparently elevates sympathetic outflow not by reflex (barostatic) activation but by causing failure of the reflex.

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