# *Myocardial Function and Metabolism in the Methoxyflurane-depressed Canine Heart*

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In an intact closed-chest dog preparation, 2–3 MAC (0.44 per cent alveolar) methoxyflurane markedly decreased left ventricular function and myocardial blood flow, efficiency, and oxygen uptake. A negative myocardial excess lactate and unchanged cardiac output–myocardial blood flow ratio suggested adequate myocardial oxygenation. The significant correlation between myocardial blood flow and mean aortic blood pressure in the depressed heart may indicate a loss of metabolic control of coronary perfusion. Myocardial uptake of nonesterified fatty acids, lactate, and pyruvate decreased with myocardial depression. Although there was little glucose utilization in the depressed hearts, arterial glucose was low in contrast to the arterial level with halothane. Consequently, altered myocardial glucose metabolism cannot be postulated as a mechanism in the cardiac depression produced by methoxyflurane. (Key words: Methoxyflurane; Negative inotropy (or decreased myocardial contractility); Myocardial blood flow; Glucose; Nonesterified fatty acids; Lactate; Pyruvate; Oxygen uptake; Excess lactate; $^{85}$Krypton; Dye dilution; Cardiac output.)

ALTHOUGH myocardial depression has been recognized as a feature of all potent inhalation anesthetics for decades,[1–3] the mechanisms involved are still ill-defined. Recently, interference in myocardial glucose metabolism has been implicated in the negative inotropic effect of halothane.[4, 5] Because the cardiodynamic effects of methoxyflurane are similar to those of halothane,[6] myocardial dynamics and substrate utilization after administration of methoxyflurane have been studied, using the same experimental design and techniques.[7]

In spite of the demonstration of greatly decreased coronary blood flow during halothane anesthesia,[7–10] several studies have suggested that the simultaneous decreases in cardiac work and oxygen demand result in adequate oxygen delivery to the depressed hearts.[7–9] This aspect of the effect of methoxyflurane has also been investigated and compared with the results seen with halothane.

## Methods

The basic protocol has been reported.[7] Male mongrel dogs weighing 20.4 to 24 kg were screened and inoculated for distemper and hepatitis before admission to the program. They were followed for at least three weeks prior to the experiment, with complete blood counts and a standard vivarium diet, to ensure that they were in good health. After an overnight fast, they were brought to the laboratory without medication. A cuffed orotracheal tube was placed with the aid of 10 mg/kg thiopental and 0.5 mg/kg succinylcholine. The dogs were ventilated with methoxyflurane vaporized in oxygen from a calibrated vaporizer ‡ through a nonrebreathing valve by a Bird Mark IV anesthesia ventilator. Expired $CO_2$, continuously monitored by an infrared analyzer,§ was kept at about 4 per cent. In addition, frequent measurements of arterial *p*H, $P_{CO_2}$ and $P_{O_2}$ were made. Esophageal temperature was measured with a thermistor probe and maintained near 37 C by external heating. Goodale–Lubin dacron cardiac catheters ¶ were placed with fluoroscopic guidance, as follows: through femoral cutdowns, a 9-fr, 80-cm catheter in the thoracic aorta and a 7-fr, 80-cm catheter in the right atrium; through a carotid cutdown, a 9-fr, 50-cm catheter in the left ventricle; through the external jugular vein, a 6-fr, 80-cm catheter in the great cardiac vein (the major venous drainage from the left ventricle) through the coronary sinus. Aortic,

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‡ Foregger Company, Smithtown, New York.
§ Beckman/Spinco, Palo Alto, California.
¶ U. S. Catheter Industries, Glens Falls, New York.

right atrial and left ventricular pressures were transduced by Statham strain gauges and recorded with an electrocardiogram on a Sanborn 350 polygraph. The maximum rate of rise (dp/dt) of the left ventricular pressure pulse was derived by an R-C circuit and also recorded. At least 90 minutes elapsed between the end of catheterization and recording of the measured variables. Two concentrations of methoxyflurane were used: the least concentration which would prevent the animal from responding to a painful stimulus or breathing against the ventilator (minimal alveolar concentration, or MAC); and the highest concentration that would allow a mean aortic pressure of about 60 torr. The order of dose administration was alternated to minimize the effects of sequence. At the time of the testings, high-speed polygraph recordings were made. Cardiac output was determined in duplicate by the indicator-dilution method using indocyanine green ** injected into the right atrium, with sampling from the thoracic aorta through a constant-withdrawal Gilford densitometer system. Calculation was facilitated by a Sanborn 130 cardiac-output computer. Left ventricular myocardial blood flow was estimated from the coronary venous washout curve of $^{85}$krypton.[11] Simultaneous aortic and coronary venous blood samples were taken for measurement of oxygen tensions and contents, pH, $P_{CO_2}$, hematocrit, glucose, nonesterified fatty acids (NEFA), lactate, and pyruvate, by methods described previously.[7] Methoxyflurane concentrations were measured by gas chromatography. End-tidal gas was sampled at room temperature from the expiratory limb of the nonrebreathing system by means of a gas-tight microsyringe. One-milliliter samples of expired air were injected directly into a gas chromatograph for methoxyflurane analysis.†† The columns consisted of copper tubing, 2 meters × 6.35 mm, packed with 20 per cent SE-30 silicone gum rubber on Gas Chrom Q. The column temperature was 150 C, and the carrier gas was helium at an inlet pressure of 2.4 atm and a flow rate of 100 ml/min. A dual hydrogen flame ionization detector was operated with hydrogen at 2 atm pressure and a flow rate of 60 ml/min; the scavenger gas was air at 2 atm pressure and a flow rate of 470 ml/min. The inlet block, the outlet block, and the detector were operated at 200 C. Under these conditions methoxyflurane had a re-

TABLE 1. Physiologic Variables

| | MAC (Mean ± SE) | 2-3 MAC (Mean ± SE) |
|---|---|---|
| Per cent alveolar methoxyflurane | 0.20 ± 0.01 | 0.44 ± 0.01 |
| Temperature (C) | 37.2 ± 0.2 | 37.4 ± 0.3 |
| Hematocrit (per cent) | 44 ± 0.9 | 42.2 ± 1.1 |
| Arterial pH | 7.37 ± 0.02 | 7.36 ± 0.02 |
| Arterial carbon dioxide (torr) | 31.3 ± 0.9 | 32.4 ± 1.4 |
| Arterial oxygen (torr) | 464 ± 20 | 448 ± 21 |

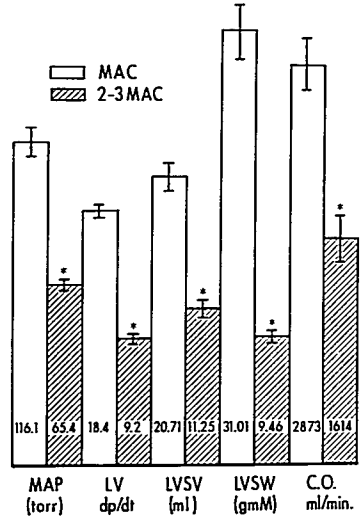


FIG. 1. Cardiodynamics after administration of methoxyflurane (mean ±SE). MAP = mean aortic pressure; LV dp/dt = maximum rate of rise of left ventricular pressure; LVSV = left ventricular stroke volume; LVSW = left ventricular stroke work; C.O. = cardiac output.
* $P < 0.05$.

** Cardio-Green, Hynson, Westcott and Dunning, Baltimore, Maryland.
†† Microtek 2500R, Mikrotek Instrument Corporation, Baton Rouge, Louisiana.

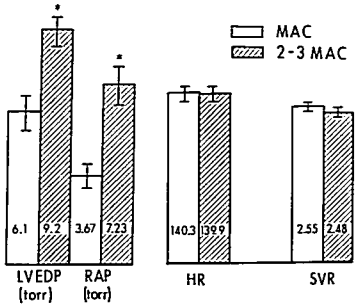


FIG. 2. Cardiodynamics after administration of methoxyflurane (mean ±SE). LVEDP = left ventricular end-diastolic pressure; RAP = right atrial pressure; HR = heart rate; SVR = systemic vascular resistance.
* $P < 0.05$.

tention time of 33 seconds. The detector output was displayed on a potentiometric recorder and integrated simultaneously with a disc integrator. Assays of gas samples were performed alternately with assays of known amounts of methoxyflurane vapor in air. Standards were prepared by allowing an appropriate amount of methoxyflurane to vaporize in a stoppered volumetric flask. One hundred-microliter volumes were withdrawn from the flask and tested alternately with the breath samples. The amount of methoxyflurane in a breath sample was calculated by relating peak height to that of the mean of the standards for any given experiment. Blood removed for sampling was replaced by blood previously drawn from the same animal. During the procedure, 0.9 per cent saline solution, 5 ml/kg/hour, was infused. Statistical analysis was done with Student's *t* test for paired samples and the product–moment correlation coefficients.[12]

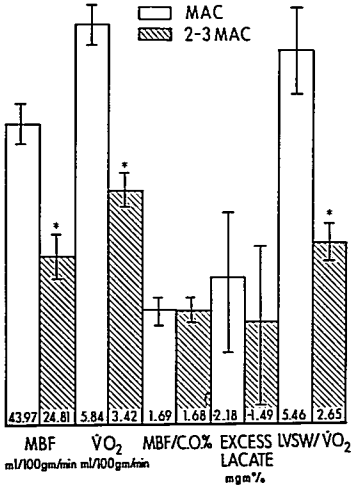


FIG. 3. Kinetics of oxygen utilization with methoxyflurane (mean ±SE). MBF = myocardial blood flow; $\dot{V}_{O_2}$ = myocardial oxygen uptake.
* $P < 0.05$.

## Results

In the nine dogs studied, the control (or MAC) alveolar methoxyflurane concentration was 0.20 per cent, which agrees with the previously-reported MAC for dogs of this drug.[13] The myocardial depressant dose averaged 0.44 per cent, or 2–3 MAC. Esophageal temperature, arterial hematocrit, *p*H, $P_{CO_2}$, and $P_{O_2}$ were unchanged by 2–3 MAC methoxyflurane (table 1).

Although no direct measurement of myocardial contractility was made, the marked decrease in the indices of left ventricular function (fig. 1) with increased filling pressures and unchanged heart rate and calculated systemic vascular resistance (fig. 2) strongly suggest a negative inotropic effect of 2–3 MAC methoxyflurane. Myocardial blood flow and oxygen uptake also decreased, although the ratio of myocardial blood flow to total cardiac output did not change, nor was there any myocardial excess lactate at either MAC or 2–3 MAC methoxyflurane (fig. 3). The left ventricular stroke work-to-myocardial oxygen uptake ratio decreased along with ventricular function, suggesting a decrease in ventricular efficiency (fig. 3).

The arterial level, myocardial A-V difference, and myocardial uptake of NEFA declined with the high methoxyflurane concentrations (fig. 4). Myocardial uptake of lactate and pyruvate decreased also, but there was no significant change in the arterial level or myocardial A-V difference with either substrate (fig. 5). No significant differences between the effects of MAC and 2–3 MAC methoxy-

flurane on the arterial level, myocardial A-V difference, or uptake of glucose were found (table 2). Coronary venous glucose concentrations were higher than arterial concentrations in five of nine dogs at MAC and in six of nine at 2–3 MAC methoxyflurane (in a sense, these animals "produced" glucose). The overall picture of glucose metabolism in the dog heart anesthetized with methoxyflurane was one of little or no glucose uptake.

## Discussion

The cardiodynamic effects of 2–3 MAC halothane[7] closely resembled those seen in the present study of methoxyflurane (fig. 6). Halothane MAC was 0.63 per cent, and the depressant dose was 1.63 per cent alveolar, or 2–3 MAC. The myocardial blood flow-to-cardiac output ratio with halothane was 1.52 per cent at both MAC and 2–3 MAC.

No myocardial excess lactate was produced by the halothane-depressed heart, in spite of the marked decreases in myocardial blood flow and oxygen uptake. Although the metabolic effects of halothane were not as great as those of methoxyflurane, they were in the same directions: there was little glucose uptake, and "production" occurred in a number of animals;

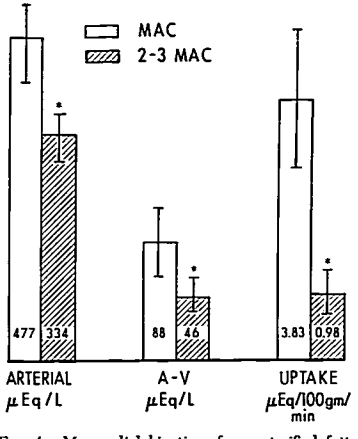


FIG. 4. Myocardial kinetics of nonesterified fatty acids with methoxyflurane (mean ±SE). * $P < 0.05$.

NEFA uptake fell, while arterial level did not change with halothane; lactate and pyruvate uptake decreased although the lactate change was not significant.

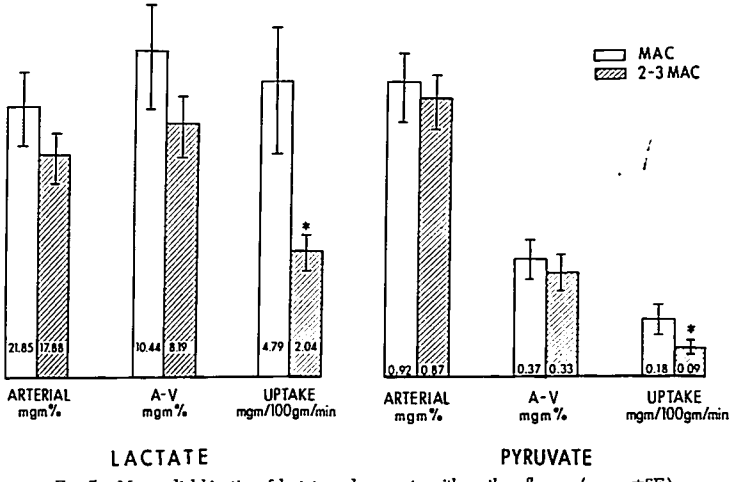


FIG. 5. Myocardial kinetics of lactate and pyruvate with methoxyflurane (mean ±SE). * $P < 0.05$.

TABLE 2. Myocardial Glucose Kinetics after Administration of Methoxyflurane

| | MAC (Mean ± SE) | 2-3 MAC (Mean ± SE) |
|---|---|---|
| Arterial glucose (mg/100 ml) | 84.4 ± 4.8 | 75.8 ± 4.9 |
| | (n = 4) | (n = 3) |
| *With uptake* | | |
| Arterial | 86.5 ± 7.6 | 71.3 ± 7.3 |
| Uptake/100 gm/min | 2.32 ± 0.5 | 1.66 ± 0.3 |
| A-V | 6.00 ± 2.1 | 7.30 ± 1.9 |
| | (n = 5) | (n = 6) |
| *With "production"* | | |
| Arterial | 82.8 ± 5.9 | 78 ± 6.2 |
| Production/100 gm/min | 2.99 ± 1.06 | 2.44 ± 0.4 |
| A-V | −5.8 ± 1.5 | −9.7 ± 1.1 |

In our laboratory, deep halothane anesthesia in the dog has consistently lowered the arterial hematocrit,[7, 14] whereas there was no change with methoxyflurane. If this change with halothane is related to a dilating effect on the spleen of deep halothane anesthesia, as we have postulated, methoxyflurane either has no effect on the canine spleen or causes splenic contraction at both low and high concentrations.

The effects of halothane and methoxyflurane on the arterial levels of glucose and NEFA appear to differ. Although arterial glucose levels with the two anesthetics did not differ at MAC and 2–3 MAC, the levels with halothane were higher (>100 mg/100 ml) than those with methoxyflurane.[7] In unpublished work in dogs, we have observed that blood glucose levels in dogs rise during administration of halothane, while falling or remaining constant with methoxyflurane. Inasmuch as myocardial glucose uptake is dependent on the arterial glucose level,[15] little uptake would be expected at the arterial glucose levels seen with methoxyflurane. At the arterial glucose levels produced by halothane, the myocardial uptake should have been significant. Consequently, it is not possible from this experiment to speculate about the role of myocardial glucose metabolism in the negative inotropic effect of methoxyflurane. While halothane did not affect NEFA levels,[7] methoxyflurane produced a significant decrease. Myocardial NEFA uptake decreased significantly with myocardial depressant doses of both halothane and methoxyflurane. Inasmuch as lipids are the predominant myocardial fuel in the fasting state,[15] this is to be expected, just as is the decreased oxygen consumption.

The reason for the different effects of the two drugs on arterial hematocrit, glucose, and NEFA is not apparent. Sympathetic stimulation usually produces a rise in NEFA, glucose,[16] and hematocrit (presumably from splenic contraction in the dog), so that this mechanism cannot be implicated. The metabolic results may be related to an effect on the hormonal control of metabolism (insulin, growth hormone and cortisol)[17] or hepatic glycogen–glucose dynamics.

Another major difference between the two anesthetics is the difference between the effects of the order of dose administration. In each study, the high concentration (2–3 MAC) was administered first in half the animals. Statistical analysis of the results with halothane revealed no difference resulting from the order of dosage. With methoxyflurane, however, several effects seemed to vary with the order of dosage. When 2–3 MAC methoxyflurane was administered first, the difference between left ventricular function at MAC and that at

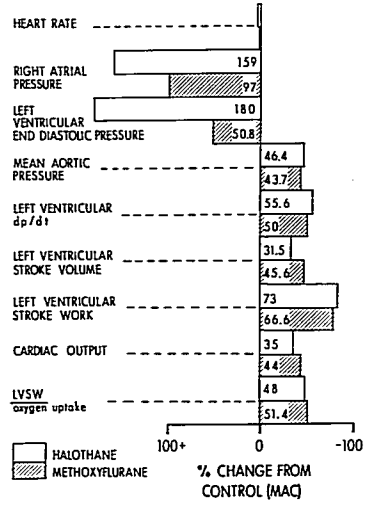


FIG. 6. Comparison of the cardiodynamic effects of MAC 2–3 halothane with those of MAC 2–3 methoxyflurane.

TABLE 3. Effect of Sequence on the Myocardial Functional and Metabolic Effects of Methoxyflurane

| | MAC Administered First (n = 4) | | 2-3 MAC Administered First (n = 5) | |
|---|---|---|---|---|
| | MAC (Mean ± SE) | 2-3 MAC (Mean ± SE) | MAC (Mean ± SE) | 2-3 MAC (Mean ± SE) |
| Mean aortic pressure (torr) | 121.5 ± 5.8 | 58.5 ± 5.75* | 111.8 ± 2.18 | 73.6 ± 2.24* |
| Left ventricular dp/dt | 21.5 ± 0.8 | 8.25 ± 0.82* | 16.0 ± 0.9 | 11.2 ± 0.3* |
| Left ventricular stroke volume (ml) | 21.46 ± 3.13 | 8.70 ± 1.03* | 20.1 ± 2.24 | 14.93 ± 1.29* |
| Left ventricular stroke work (gm m) | 33.91 ± 5.27 | 7.35 ± 7.04* | 28.69 ± 3.01 | 13.34 ± 1.43* |
| Cardiac output (ml/min) | 2792 ± 467 | 1186 ± 144* | 2944 ± 320 | 2065 ± 186* |
| Left ventricular end-diastolic pressure (torr) | 5.38 ± 1.47 | 9.63 ± 1.85* | 6.6 ± 1.15 | 8.4 ± 0.9* |
| Right atrial pressure (torr) | 2.13 ± 0.6 | 6.28 ± 0.75* | 4.9 ± 0.9 | 7.0 ± 1.3* |
| Heart rate (beats/min) | 132.5 ± 12.4 | 143.7 ± 8.55 | 146.6 ± 2.4 | 138.2 ± 2.46 |
| Systemic vascular resistance | 2.83 ± 0.43 | 2.88 ± 0.58 | 2.32 ± 0.27 | 2.01 ± 0.13 |
| Myocardial blood flow (ml/100 g/min) | 46.51 ± 3.12 | 20.19 ± 2.1* | 41.92 ± 4.8 | 29.90 ± 0.9* |
| $Vo_2$ (ml/100 gm/min) | 6.23 ± 0.4 | 2.83 ± 0.27* | 5.52 ± 0.33 | 3.88 ± 0.3* |
| Arterial glucose (mg/100 ml) | 95 ± 4.4 | 75 ± 6.4* | 76 ± 5.4 | 80.8 ± 5.4 |

* $P < 0.05$.

2–3 MAC was less than when MAC methoxyflurane was given first (table 3). The same was true of myocardial blood flow and oxygen uptake. Since the alveolar anesthetic concentrations, esophageal temperature, and blood gases were not significantly changed by the sequence, it would appear that circulatory depression is related in some small degree to the duration of methoxyflurane administration. Although the rate of equilibration of the vapor is very slow with the very high blood–gas partition coefficient, 90 minutes were allowed between dose changes and, in most cases, the alveolar concentrations had been steady for 60 minutes before testing. MAC 2–3 methoxyflurane given after MAC methoxyflurane produced a significant decrease in arterial glucose, while when MAC 2–3 methoxyflurane was administered first, glucose levels were unchanged (table 3). It appears that duration was more important than level of anesthesia in this regard.

A statistically significant correlation between mean aortic pressure and myocardial blood flow was seen with 2–3 MAC methoxyflurane, but not with 2–3 MAC halothane or MAC methoxyflurane or halothane[7] (fig. 7). This observation suggests that coronary perfusion is passively dependent on the aortic pressure head during deep methoxyflurane anesthesia while maintaining some independent metabolic control during halothane and light methoxyflurane anesthesia. The maintenance of the myocardial blood flow–cardiac output ratio and the lack of myocardial excess lactate indicate that myocardial oxygenation was grossly adequate with 2–3 MAC methoxyflurane[18] (as was the case with 2–3 MAC halothane[7]).

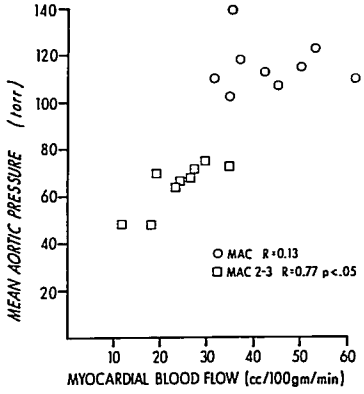


FIG. 7. Correlation between aortic pressure and myocardial blood flow after administration of methoxyflurane. R = correlation coefficient.

Saito suggested that methoxyflurane increased coronary vascular resistance and decreased the cardiac output–coronary blood flow ratio in the dog.[10] He used an open-chest bypass preparation with basal barbiturate anesthesia, short-term administration of methoxyflurane with a semiclosed circle absorption system, and no measure of blood or alveolar methoxyflurane concentrations. Consequently, it is difficult to compare our results.

## Conclusion

The myocardial dynamic and metabolic effects of 2–3 MAC methoxyflurane resemble those of 2–3 MAC halothane. Arterial glucose levels were low, however, so that the interference in myocardial glucose metabolism found with halothane cannot be postulated as a mechanism of the cardiac depression of methoxyflurane. Although the methoxyflurane-depressed heart appeared to be adequately oxygenated, the dependence of myocardial blood flow on aortic pressure indicates a loss of the intrinsic metabolic control of coronary perfusion.

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## Drugs

**METHOXYFLURANE TOXICITY** Serum levels of inorganic fluoride and nonvolatile organic fluoride were elevated in a patient who had methoxyflurane anesthesia for a bilateral nephrectomy. The concentrations of both types of fluoride were significantly reduced by extracorporeal hemodialysis. (*Taves, D. R., and others: Toxicity Following Methoxyflurane Anesthesia. III. Hemodialysis of Metabolites, J.A.M.A. 214: 96 (Oct.) 1970.*)