The Effects of Halothane and Cyclopropane on the Maximum Acceleration of Left Ventricular Ejection and the Tension–Time Index in Dogs

Ben F. Rusy, M.D., John E. Moran, M.D.,† Steven Fox‡*

In chronically prepared dogs the maximum acceleration of ejected left ventricular blood ($\dot{Q}_{max}$) and the tension–time index (TTI) were used as correlates of left ventricular myocardial contractility and integrated wall tension, respectively. These variables were measured in the conscious animal and at end-expired air concentrations of 1, 1.5, and 2 per cent halothane and 20, 25, 30, and 35 per cent cyclopropane. $\dot{Q}_{max}$ was depressed 65 per cent by 1.5 per cent halothane and 35 per cent by 30 per cent cyclopropane. TTI was decreased 29 per cent by halothane and increased 47 per cent by cyclopropane. Cyclopropane decreased myocardial contractility more than has been previously reported in studies in which this variable was evaluated from the relationship between ventricular stroke work and filling pressure. The divergent effects of halothane and cyclopropane on TTI suggest that left ventricular oxygen consumption may be greater during the administration of cyclopropane. (Key words: Anesthetics; Cardiac contractility; Cyclopropane; Halothane; Left ventricular ejection; Myocardial oxygen consumption; Tension–time index.)

THIS REPORT describes the effects of halothane and cyclopropane on the maximum acceleration of left ventricular ejection ($\dot{Q}_{max}$) and the tension–time index (TTI). Values were obtained by an experimental method suitable for measurements in conscious as well as anesthetized animals.

$\dot{Q}_{max}$ correlates closely with the contractile state of the left ventricle,[1] while TTI is an index of integrated myocardial wall tension.[2] The myocardial contractile state and wall tension are the most important physical factors which determine left ventricular oxygen consumption.[3] It was thought that the simultaneous examination of these variables, in terms of their above-mentioned correlates, would provide additional knowledge for evaluating the effects of halothane and cyclopropane on cardiac function.

Methods

Healthy mongrel dogs weighing 12 to 15 kg were selected on the basis of their ability to lie quietly on their sides on the experimental table. With the dogs under pentobarbital anesthesia and during mechanical ventilation with air right thoracotomy and pericardiotomy were performed aseptically. An electromagnetic flow probe (In-Vivo Metric Systems) was placed on the ascending aorta just distal to the coronary ostia. A polyethylene catheter (PE 330) with stylet was implanted in the left atrium according to the method of McQuarrie.[4] The catheter and flow probe connector were exteriorized through the skin between the scapulae. After closure of the incision the dogs were allowed to convalesce for at least a week, and usually longer, during which time they were trained to lie on their sides in the laboratory.

During an experiment, cardiac output, instantaneous aortic flow and its derivative, left

* Associate Professor, Anesthesiology and Pharmacology.

† Resident in Anesthesiology. Dr. Moran died suddenly on March 15, 1970, while a Fellow in the Anesthesia Research Training Program.

‡ Medical student.

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¶ Halothane supplied through the courtesy of Ayerst Laboratories.

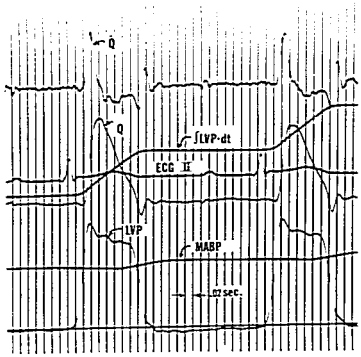

FIG. 1. A portion of a typical record from an unanesthetized dog, showing mean femoral arterial blood pressure (MABP), instantaneous left ventricular pressure (LVP), tension-time per beat ($\int$ LVP ·dt), lead II of the electrocardiogram (ECG II), instantaneous ascending aortic flow (Q), and acceleration of left ventricular ejected blood ($\dot{Q}$).

ventricular pressure and its integral, mean femoral arterial pressure, and lead II of the ECG were recorded. A typical record is shown in Fig. 1.

Ascending aortic flow (Q) was measured by connecting the flow probe to a Medicon K-2000 electromagnetic flow amplifier. A baseline for flow was established by assuming zero flow in the aortic root during diastole. Also obtainable (not shown in Fig. 1) from the flowmeter was average ascending aortic flow ($\overline{Q}$). The flowmeter sensitivity was determined by equating $\overline{Q}$ with the cardiac output (CO) measured by the dye dilution (Cardio-green) method. The dye dilution technique for determining CO was used only to calibrate the flowmeter, following which $\overline{Q}$ was taken as the measure of CO.

The first time derivative of flow ($\dot{Q}$) was obtained by continuous electronic differentiation of Q. The differentiator had an R-C time constant of 0.66 msec and was calibrated by substituting a 10-Hz triangular wave (Hewlett-Packard Low Frequency Function Generator) for the flow signal. Since Q is directly proportional to the velocity of ascending aortic blood, its first time derivative, $\dot{Q}$, is correspondingly related to the acceleration of blood ejected by the left ventricle. The maximum value of acceleration, $\dot{Q}_{max}$, correlates closely with the inotropic state of the left ventricle.

Mean femoral arterial pressure (MABP) was obtained by means of a Statham P23-Db pressure transducer connected to a plastic needle placed percutaneously in the femoral artery using per cent lidocaine anesthesia. Total peripheral resistance (TPR) was computed as the ratio of MABP (mm Hg) to cardiac output (l/min). Left ventricular pressure (LVP) was obtained via another P23-Db transducer connected to a catheter which was inserted through the implanted atrial catheter into the left ventricle. The integral of left ventricular systolic pressure with respect to time, $\int$LVP ·dt, has units of mm Hg × sec/beat and was derived continuously by electronic means. Integrated systolic left ventricular pressure per minute (the tension-time index) was computed by multiplying the average pressure–time per beat over 15 consecutive beats by the heart rate. Data were recorded on an Electronics for Medicine DR-8 recorder.

These data were obtained in the conscious, quietly resting dog (control) and during the administration of 20, 25, 30 and 35 per cent cyclopropane and 1, 1.5 and 2 per cent halothane. In a given animal, experiments with each anesthetic were separated by at least two days. Anesthetic concentrations were verified by infrared analysis of end-expired air. At each end-expired concentration a plateau was maintained for 15 minutes before data were collected. The anesthetics were administered from a nonrebreathing system (Ruben valve) through an endotracheal tube with cuff. Respirations were controlled (Bird, Mark 4), so that end-expired P_{CO_2} ranged from 25 to 35 mm Hg. Other than halothane or cyclopropane, the only drug administered was succinylcholine, used to prevent spontaneous movements and ventilation which sometimes occurred at the lesser anesthetic concentrations. It was usually given in a single dose of 20 mg intravenously at the start of the procedure, and data were not recorded until at least 30 minutes after its administration. In separate experiments we found that the administration of succinylcholine during steady anesthetic states occasionally produced small changes in the measured variables, which subsided well

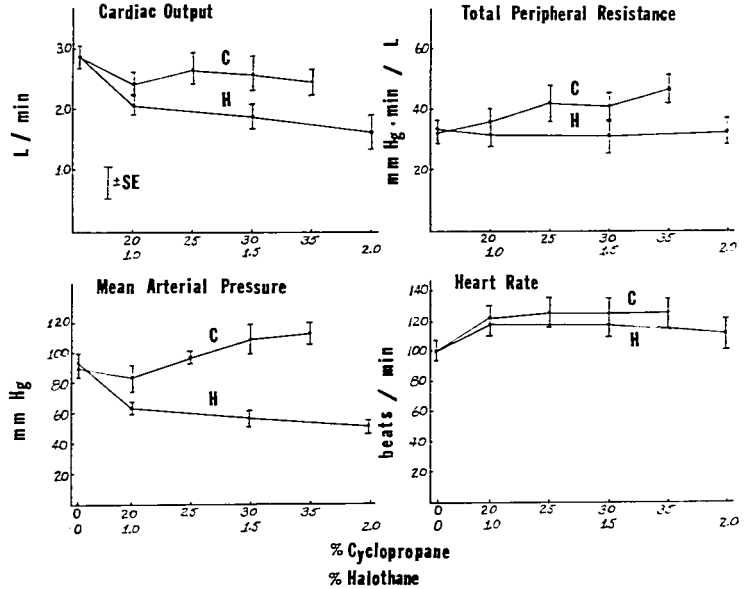

FIG. 2. Effects of cyclopropane (C) and halothane (H) on cardiac output, mean arterial pressure, total peripheral resistance, and heart rate in eight dogs. Unanesthetized control values appear at the extreme left. Percentages of cyclopropane and halothane are plotted on the abscissa.

within 30 minutes. Experiments with both anesthetics were successfully carried out in eight dogs.

Results

Dose–response curves for the effects of cyclopropane (C) and halothane (H) on CO, MABP, TPR, and heart rate are shown in figure 2. Values represent the average responses of the same eight dogs to the two anesthetics. Multiples of MAC[5] for both anesthetics are plotted in opposition along the abscissa of each curve, although no claim for their equipotency is made.[6]

Cardiac output was depressed 29, 34, and 41 per cent below the unanesthetized (control) value by 1, 1.5, and 2 per cent halothane, respectively ($P < 0.01$). There was a small but not significant depression of CO at every concentration of cyclopropane. MABP was depressed significantly ($P < 0.001$) by all concentrations of halothane. It was depressed 50 per cent below control by 2 per cent halothane. Blood pressure was increased by all concentrations of cyclopropane except 20 per cent, with which a 6 per cent decrease was observed. These changes in pressure were not significant, except for the 24 per cent increase ($P < 0.05$) observed with 35 per cent cyclopropane. TPR was increased by cyclopropane, but not significantly except at 35 per cent cyclopropane, with which a 44 per cent increase ($P < 0.02$) was observed. There was a slight, but not significant, decrease in TPR at every concentration of halothane. Heart rate was increased slightly by both anesthetics, although this effect was not significant.

The effects of cyclopropane and halothane on $\dot{Q}_{max}$ and TTI are shown in figure 3. $\dot{Q}_m$

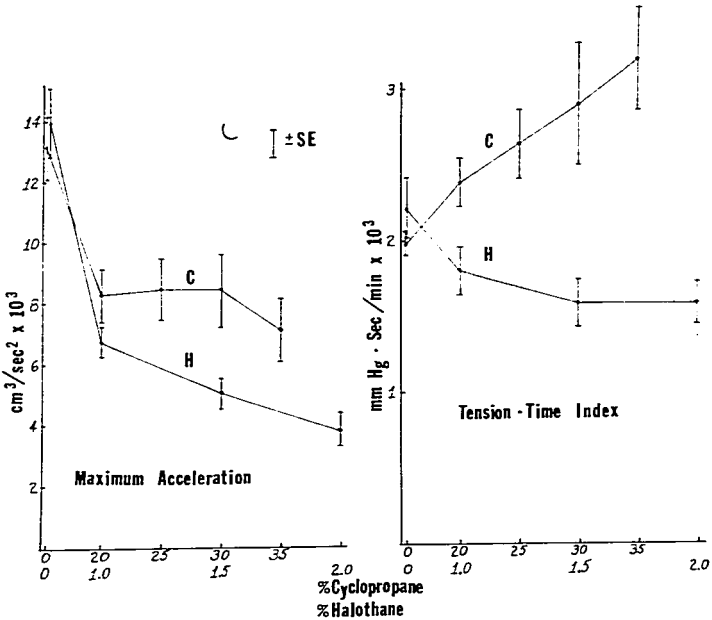

FIG. 3. Effects of cyclopropane (C) and halothane (H) on maximum acceleration of left ventricular ejected blood and tension–time indices in eight dogs. Unanesthetized control values are at the extreme left. Percentages of cyclopropane and halothane are plotted on the abscissa.

was decreased significantly by all concentrations of each anesthetic. The decreases below control ranged from 35 to 45 per cent ($P < 0.02$) for cyclopropane and from 52 to 79 per cent ($P < 0.001$) for halothane. TTI was significantly increased above control by every concentration of cyclopropane. The increases were 20, 34 ($P < 0.05$), 47, and 62 ($P < 0.02$) per cent, respectively, for 20, 25, 30, and 35 per cent cyclopropane. TTI decreased 20, 29, and 29 per cent with 1, 1.5, and 2 per cent halothane. The decreases were significant ($P < 0.02$) at 1.5 and 2 per cent halothane.

Discussion

Our data indicate that the contractility of the left ventricle, measured in terms of $\dot{Q}_{max}$, is decreased by cyclopropane, albeit not to the same extent as by halothane. $\dot{Q}_{max}$ has been shown by Noble and his associates[1] to correlate well with the contractile state of the left ventricle. It is little affected by changes in end-diastolic pressure, *i.e.*, preload,[1] or by changes in aortic pressure, *i.e.*, afterload.[1,7] The finding of decreased contractility with cyclopropane differs from the observations of Price *et al.*[8] and Etsten and Shimosato,[9] who found little or no change. This may be related to the fact that these investigators based their conclusions largely on the observation that cyclopropane elicited only a minor change in the relationship between ventricular stroke work and end-diastolic pressure. This relationship, the ventricular function curve (VFC), can be altered by changes in aortic pressure (afterload) in the absence of any change in the ventricular contractile state.[10] Since aortic

pressure is frequently elevated[11, 12, 13] by cyclopropane, the interpretation of the VFC is rendered complex, and it is not easy to determine that changes in ventricular contractility have or have not occurred. Had our dogs not been completely at rest during the control (conscious) measurements of $\dot{Q}_{max}$, these would have been high, and we might then have overestimated the depression of contractility caused by anesthesia. We do not believe that this occurred, since our resting values for $\dot{Q}_{max}$ and for heart rate and MABP agree very closely with those observed by Noble *et al.*[1], who felt that their dogs were genuinely at rest. In addition, the degree of cardiovascular depression we observed with halothane was not different from that described by Eger *et al.*[14] for man and by Merin[15] for the dog. For these reasons we believe that the depression of contractility we found for cyclopropane was real.

In these experiments halothane depressed myocardial contractility to a significantly greater degree than cyclopropane at all anesthetic concentrations studied. It is important to examine this effect of halothane, since it might be associated with a depression of CO sufficient to cause peripheral tissue underperfusion and hypoxia. While we did not perform blood gas analysis, the depression of CO we found agrees closely with that observed by other investigators who did obtain blood gas data. The 41 per cent decline of CO we found at 2 per cent halothane is similar to the 50 per cent depression found by Eger *et al.*[14] for the same end-expired halothane concentration in man. At 1.5 per cent halothane we found a 34 per cent depression of CO, which agrees very closely with the decrease observed by Merin[15] for 1.6 per cent halothane in dogs. These investigators found little or no acidosis, and their studies suggest that the rather marked decreases in CO seen during halothane anesthesia in the healthy man or dog are not associated with generalized tissue hypoxia. It cannot be assumed that the results in patients with heart disease would be the same. No data describing the effect of halothane alone in this type of patient are presently available. It is interesting to note that cyclopropane, administered to healthy man, does not decrease CO nearly as much as does halothane, but does cause the same or even more acidosis.[13]

TTI increased for cyclopropane and decreased for halothane. The increases ranged from 20 to 62 per cent for 20 to 35 per cent end-expired cyclopropane and were significant at all depths of anesthesia examined. We have described TTI as an index of integrated myocardial wall tension. This is not rigorously true, since we derived it simply as the integral of left ventricular systolic pressure, while wall tension is a function of both ventricular pressure and radius.[16] Very little information about heart size during anesthesia is available. We did not measure it in this study but, in independent unpublished observations of left ventricular end-diastolic volume (LVEDV) at several depths of cyclopropane and halothane anesthesia using a cineradiographic technique, we found that LVEDV increased with both anesthetics and that the increases were greatest with cyclopropane. This would increase the integrated wall tension above the value derived by considering pressure only. For halothane, wall tension would shift upwards closer to control, while for cyclopropane it would shift still further above control.

Left ventricular oxygen consumption ($M\dot{V}_{O_2}$) is determined chiefly by the contractile state and integrated wall tension.[2, 3, 17, 18] The relative importance of each factor is not clearly understood at present. Some work demonstrates that tension plays the major role,[18] while other work suggests equal roles for the two factors.[2, 19] With respect to halothane, the indices of contractile state and integrated tension were decreased, suggesting that $M\dot{V}_{O_2}$ was decreased; this is in agreement with the findings of Merin[15] and Theye,[20] who measured $M\dot{V}_{O_2}$ directly. The situation with cyclopropane is not as easily assessed since the indices of contractile state and integrated tension were changed in opposite directions. If it is assumed that these variables are of equal importance in determining $M\dot{V}_{O_2}$, then our data suggest that $M\dot{V}_{O_2}$ was increased at cyclopropane concentrations above approximately 25 per cent (1.4 MAC). If it is assumed that tension plays the major role, $M\dot{V}_{O_2}$ probably was increased with all concentrations of cyclopropane.

It should be stressed that we have used indirect methods to determine the effects of halothane and cyclopropane on $M\dot{V}_{O_2}$. While direct measurements of this variable confirm

our findings with halothane, such measurements are not presently available for cyclopropane, and they will have to be made before any definite statement about the effects of this agent on $M\dot{V}_{O_2}$ can be made. Our findings certainly suggest that $M\dot{V}_{O_2}$ increases during cyclopropane anesthesia, however. We feel that these factors should be considered in the evaluation of the effects of cyclopropane and halothane on the heart.

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Drugs

HYPERTONIC MANNITOL Administration of hypertonic mannitol (10 per cent) or hypertonic saline (2.25 per cent) to healthy subjects produces a significant increase in serum potassium regardless of preceding potassium intake. This increase may be associated with EKG changes suggestive of hyperkalemia. The changes in serum potassium occur in hydropenic and hydrated healthy men and are independent of changes in serum sodium concentration produced by infusions. Similar increases in serum potassium are also produced by expansion of the extracellular fluid volume by isotonic mannitol, but not by isotonic or hypertonic bicarbonate solution or by isotonic saline. In addition to other complications of hypertonic mannitol administration, the possibility of worsening hyperkalemia in patients with renal failure or other diseases associated with increased serum potassium must be considered. (*Moreno, M., and others: Increase in Serum Potassium Resulting from the Administration of Hypertonic Mannitol and Other Solutions, J. Lab. Clin. Med. 73: 291 (Feb.) 1969.*)