Left Ventricular Function and Compliance in Swine during Halothane Anesthesia

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Halothane (0.05–1.7 vol per cent end-tidal) in nitrous oxide (N_2O), 60 per cent: oxygen (O_2), 40 per cent was administered to nonmedicated, closed-chest pigs. Ventricular function was analyzed from cardiac output (thermodilution) and left ventricular (LV) pressure indices. Ventricular volumes and compliance were estimated from single and biplane LV angiography. In separate experiments, the effects of N_2O, time, and the angiographic dye injections were shown to be minimal. Halothane caused dose-dependent decreases in aortic blood pressure, cardiac output, peak first derivative of left ventricular pressure (LV dP/dt), the in-vivo maximum velocity of fiber shortening (V_{max}), and ejection fraction; non-dose-dependent decreases in heart rate and circumferential fiber shortening rate. Although a pronounced dose-related negative inotropic effect of halothane in the pig heart was demonstrated, there was no definite effect on ventricular pressure-volume relationships (compliance). If there was any such effect of halothane, it was obscured by the cardiac depression produced. (Key words: Anesthetics, gases: nitrous oxide. Anesthetics, volatile: halothane. Heart: cardiac output; compliance, ventricular; myocardial function, anesthetics; vascular pressures.)

THE DOSE-DEPENDENT negative inotropic effect of halothane on the heart has been well documented in a number of species.[1-5] However, the ventricular pressure–volume relationships are less clear. Studies in anesthetized and awake dogs have been few and their results conflicting.[3,6,7] In addition, there is little information about the dose–effect of halothane on ventricular function in swine.[8,9] Inasmuch as the swine is finding increasing use as a cardiovascular model, we believed that delineation of ventricular function and pressure–volume relationships during exposure to various concentrations of halothane was necessary.

Materials and Methods

Thirteen young Yorkshire-bred pigs (20–25 kg) were anesthetized with halothane administered by a face mask. A catheter was inserted into an ear vein for infusion and drug administration. Following tracheal intubation, the lungs were ventilated with a volume-cycled ventilator adjusted to maintain a constant end-expired carbon dioxide concentration and arterial blood carbon dioxide tension. Halothane was delivered from a calibrated vaporizer in a mixture of nitrous oxide and oxygen. The inspired concentration of oxygen was adjusted to maintain the arterial blood oxygen tension above 100 torr. End-tidal gas was sampled in a flask especially designed for halothane analysis by gas chromatography. Body temperature was controlled by external heating and was monitored with a Swan-Ganz thermodilution catheter placed percutaneously in the pulmonary artery (via a femoral vein). Fluid balance was maintained by pump infusion of 0.9 per cent sodium chloride at 60 ml/hour.

Other catheters placed percutaneously included a Thompson-Telco tip manometer in the left ventricle (via the right carotid artery) for high-fidelity pressure measurement; an 8F angiographic catheter in the left ventricle (via the left carotid artery) for contrast injection; and a 7F fluid-filled catheter in the thoracic aorta (via a femoral artery) for pressure measurement and blood sampling. During the catheterization, the animals were anesthetized with halothane and nitrous oxide N_2O aided by succinylcholine infusion (2–3 mg/kg/hour). Upon completion of the catherization, the halothane was discontinued. After at least 60 min, the first measurements were made.

During a measurement run, the following sequence was followed: blood sampling, thermodilution cardiac output measurement in duplicate; measurement of vascular and cardiac pressures for at least three respiratory cycles; collection of an end-tidal gas sample for halothane measurement; left ventriculography by the injection of Urografin®, 0.8 ml/kg, with a mechanical ECG-triggered syringe while the respirator was momentarily turned off. Following control measurements, the order of administration of the higher halothane concentrations was randomized. At least 45 min were allowed for equilibration to the changed anesthetic level.[10] Succinylcholine was not given, but the saline infusion was continued. In four additional young pigs, the effects of nitrogen (N) and N_2O at the same halothane concentrations were compared. The order of administration of halothane and the carrier gases was randomized. To assess the effects
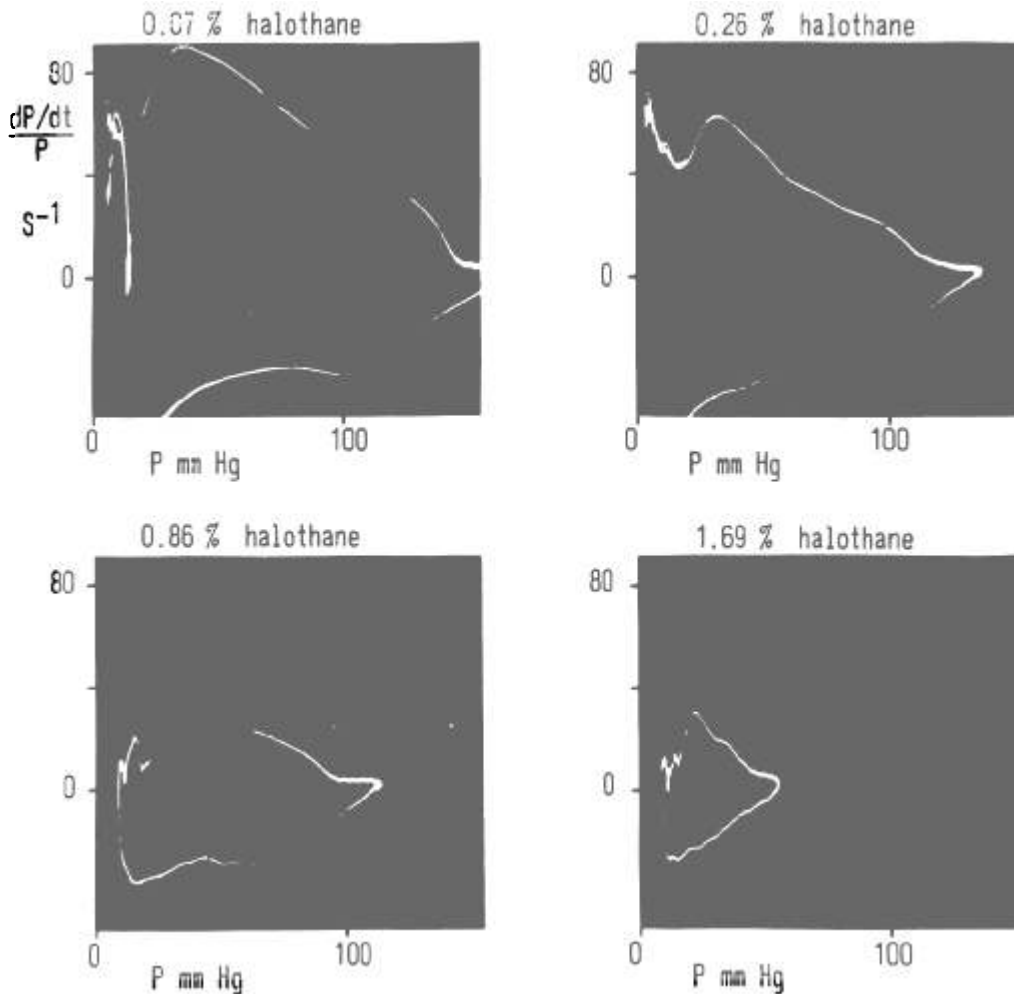
Fig. 1. These phase plane photos of LV dP/dt/P *vs.* P for the four indicated halothane concentrations illustrate the concomitant decreases in dP/dt/P and aortic end-diastolic pressure with no systemic change in LVEDP. The chronological order of the halothane concentrations is .07, .86, .26, and 1.69 per cent.

of time and the repeated injections of radiopaque contrast medium, the halothane–N_2O concentration was kept constant in two more young pigs and measurements were made over four hours.

The following definitions or techniques were used for quantitation of the results.

1) Mean aortic pressure (MAP) was calculated electronically with a Thompson-Telco M-52 preamplifier through a Statham P23Db transducer.

2) End-diastolic pressure (EDP) was defined as the pressure at which maximum rate of tension development (dP/dt) exceeds 200 torr/sec after the a wave, but before P exceeds the maximum a wave pressure.

3) Peak first derivative of left ventricular pressure (peak LV dP/dt) was calculated electronically with an effective bandwidth (−3dB) of 50 Hz from the tip manometer; divided by the instantaneously developed left ventricular pressure (LV dP/dt/P); and displayed as a function of the left ventricular pressure on a Textronics oscilloscope.[11] The maximal velocity of left

ventricular fiber shortening (V_{max}) was determined by extrapolating the downslope of the LV dP/dt/P *vs.* left ventricular pressure (LVP) back to the ordinates (0 LVP) (fig. 1). The calculation assumes a constant series elastic modulus of one.

4) Cardiac output (CO) was determined by the thermal dilution technique[12] but exponential extrapolation was not employed.

5) End-diastolic volume (EDV): all volumes were calculated by the area–length method of Dodge in either biplane (frontal–lateral) or single plane (right anterior oblique, RAO–30 degrees) corrected for nonparallel beam distortion.[13]

$$V = \frac{\pi}{6} Lm^2$$

where M = 4 A/πL, A is the planimetered area, L the major axis. End-diastole was taken as the frame coming closest in time to end-diastole as defined above for EDP.

6) Ejection fraction (EF) was calculated as

$$EF = \frac{EDV - ESV}{EDV}$$

where end-systolic volume (ESV) is taken as the LV volume at moment of closure of the aortic valve as defined by the aortic and LV pressure recordings.

7) Compliance (Comp) was calculated as

$$\frac{(EDV - BDV)/EDV}{DPC}$$

where BDV is taken as the LV volume when LV pressure is minimum, i.e., at the beginning of passive filling, DPC is the corresponding diastolic-pressure change.

8) Circumferential fiber shortening rate (CFSR) was taken as

$$CFSR = \frac{(M_{ed} - M_{es})/M_{ed}}{\Delta T}$$

where M is the effective minor axis ($= 4A/\pi L$) at end-diastole and end-systole, respectively. ΔT is the corresponding time interval.

9) Peripheral resistance (PVR) was estimated by

$$PVR = \frac{MAP}{CO} \text{ expressed in dyne cm}^{-5} \text{ sec}$$

The Student t test for paired data was used to test for the significance of differences in mean values under control conditions, and at the low, medium, and high halothane concentrations. $P < .05$ (two-sided) was taken as the minimum level for significance.

Results

Body temperature, arterial blood-gas, end-expired CO_2, arterial blood pH, and hemoglobin values did not vary significantly within the low-, medium- or high-halothane concentration groups (table 1). Arterial blood pH and body temperature at the low halothane

concentration did show statistically significant decreases from the control condition. The differences are small, however, and of questionable physiologic import.

There were highly significant negative correlations between halothane concentrations and mean aortic pressure, peak LV dP/dt, cardiac output, and ejection fraction (table 2). Less impressive correlations were seen between halothane concentrations and circumferential fiber shortening rate and compliance. When the data were grouped according to control and low, medium and high halothane concentrations, the latter two variables differed significantly only between control and higher halothane concentrations, but not within the higher concentrations (table 3).

Heart rate, peripheral resistance, and end-diastolic pressure showed no significant difference among the groups. End-diastolic volumes remained remarkably constant except for the small but significant increase between the low and medium halothane concentrations (table 3).

For purposes of illustration, figure 1 shows the dP/dt/P vs. P plot for four concentrations of halothane. In chronological order, the halothane concentrations were 0.07, 0.86, 0.26 and 1.60 per cent. This illustrates that concomitant decreases in dP/dt/P together with aortic end-diastolic pressure, but with little systematic change in LV end-diastolic pressure.

The comparative effects of N_2O-O_2-halothane and N_2-O_2-halothane anesthesia were investigated in four pigs. As shown in table 4, two concentrations of halothane were tested: low, 0.80 per cent (with N_2) and 0.77 per cent (with N_2O); and high, 1.42 per cent (with N_2) and 1.36 per cent (with N_2O). There was no statistically significant difference in any of the controlled variables (except pH_a at low concentrations of halothane) when eqiuvalent concentrations of nitrogen and nitrous oxide were compared (table 4). The only significant difference in the hemodynamic and ventriculographic values when nitrogen and nitrous oxide were compared as carrier gases for halothane

TABLE 1. Controlled Variables (Mean ± SE)

	Control	Low Halothane Concentration	Medium Halothane Concentration	High Halothane Concentration
Halothane (per cent end-tidal)	.12 ± .04	.61 ± .06*	1.05 ± .06*	1.63 ± .09*
Hemoglobin (g/dl)	12.8 ± .6	12.5 ± .5	11.9 ± .9	12.0 ± .7
CO_2 (per cent end-tidal)	4.4 ± .2	4.3 ± .1	4.4 ± .1	4.4 ± .2
Temperature (C)	37.4 ± .2*	37.0 ± .3	37.0 ± .3	37.1 ± .3
pH_a	7.50 ± .02*	7.47 ± .02	7.45 ± .01	7.45 ± .02
Pa_{CO_2} (torr)	34.2 ± 1.7	34.2 ± 2.2	35.3 ± 2.8	35.7 ± 2.2
Pa_{O_2} (torr)	120 ± 6	135 ± 8	127 ± 7	126 ± 10
O_2 saturation$_a$ (per cent)	96 ± .2	96 ± .2	96 ± .2	96 ± .33

*$P < 0.05$ vs. next halothane concentration.

was the decrease in dP/dt at high halothane concentrations. There was a suggestion that N_2O, 50–60 per cent, decreased aortic and ventricular blood pressures at both high and low halothane concentrations and decreased stroke volume and circumferential fiber shortening rate at low halothane concentrations. Ventricular pressure–volume relationships were not different with use of the two carrier gases.

The only consistent hemodynamic change with time and injection of the contrast medium was a slight decrease in LV dP/dt. There was little change in ejection fraction, circumferential fiber shortening rate, end-diastolic pressure, aortic blood pressure, or heart rate.

Discussion

The first four experiments employed the biplane apparatus (frontal and lateral projections), with special attention given to segmental kinesis. In all cases (20 ventriculograms), a dose-dependent, uniform hypokinesis was observed. Hence, we adopted single-plane

(RAO projection) films for subsequent volumetric determinations.

The first run in each experiment was the control (0 per cent inspired halothane for 45 min). To have allowed sufficient time later for randomized controls (with complete halothane washout) would have prolonged the experiment beyond the time where a stable preparation was likely. Following the control run, the remaining halothane concentrations were randomized to eliminate the effects of time and the contrast material. Furthermore, since the animal was paralyzed with minimal anesthesia (N_2O, 65 per cent, and residual halothane in the control period), it is possible that the control data are from a hyperactive preparation. However, the control (halothane, 0.12 per cent) values for cardiovascular dynamics in our experiments are very similar to those demonstrated by Sawyer et al. in slightly larger (32-kg) conscious, trained miniature pigs.[8] Nevertheless, the control data should be interpreted cautiously. This is especially true for compliance

TABLE 2. Correlation between Halothane (H) Concentrations (Per Cent End-tidal) and Measured Hemodynamic Values

	Linear Regression Equation				Correlation Coefficient
Heart rate (HR) (beats/min)	HR =	129	−	11.4 × H	.28*
Mean aortic blood pressure (MAP) (torr)	MAP =	128	−	46.1 × H	.86*
Left ventricular end-diastolic pressure (LVEDP) (torr)	EDP =	8.75	+	.63 × H	.070
Peak left ventricular dP/dt (torr/sec)	LV dP/dt =	2,281	−	1,224 × H	.69*
Cardiac output (CO) (l/min)	CO =	3.34	−	1.01 × H	.72*
Left ventricular end-diastolic volume (LVEDV) (ml)	EDV =	56.0	−	5.4 × H	.27
Ejection fraction (EF)	EF =	.42	−	.12 × H	.705*
Left ventricular diastolic compliance (Comp) (l/torr)	Comp =	.046	−	.016 × H	.406*
Left ventricular circumferential fiber-shortening rate (CFSR) (l/sec)	CFSR =	.748	−	.25 × H	.608*
Peripheral (systemic) vascular resistance (PVR) (dyne cm⁻⁵ sec)	PVR =	41.8	−	4.3 × H	.21

$* P < 0.05.$

TABLE 3. Hemodynamic Results (Mean ± SE) for Halothane–N_2O Anesthesia in 11 Pigs

	Control	Low Halothane Concentration	Medium Halothane Concentration	High Halothane Concentration
Halothane (per cent end-tidal)	.12 ± .04	.61 ± .06*	1.05 ± .06†	1.63 ± .09‡§
Heart rate (beats/min)	120 ± 9	117 ± 6	118 ± 8	111 ± 7‡
Mean aortic blood pressure (torr)	127 ± 8	98 ± 5*	75 ± 5†	55 ± 4‡§
Left ventricular end-diastolic pressure (torr)	8 ± .8	9.5 ± 1.6	9.2 ± 2.4	10.4 ± 1.5
Peak left ventricular dP/dt (torr/sec)	2,500 ± 400	1,080 ± 79*	730 ± 57†	560 ± 57‡§
Extrapolated maximum velocity of fiber shortening (l/sec)	74 ± 8	43 ± 3*	40 ± 3	30 ± 2‡§
Cardiac output (l/min)	3.3 ± .3	2.54 ± .2*	2.1 ± .1†	1.7 ± .2‡§
Left ventricular end-diastolic volume (ml)	60 ± 3	60 ± 4	63 ± 4†	62 ± 4
Ejection fraction	.44 ± .02	.32 ± .02*	.27 ± .014	.24 ± .015§
Left ventricular diastolic compliance (l/torr)	56 ± 9	29 ± 5*	28 ± 4.2	25 ± 2.6
Left ventricular circumferential fiber-shortening rate (l/sec)	.75 ± .07	.51 ± .04*	.42 ± .03	.38 ± .04
Peripheral (systemic) vascular resistance (dyne cm⁻⁵ sec)	3,350 ± 430	2,990 ± 170	3,210 ± 390	2,890 ± 310

* $P < 0.05$ for control vs. low halothane concentration.
† $P < 0.05$ for low vs. medium halothane concentration.

‡ $P < 0.05$ for medium vs. high halothane concentration.
§ $P < 0.05$ for low vs. high halothane concentration.

TABLE 4. Biochemical and Hemodynamic Results (Mean ± SE) for Halothane–N_2 and Halothane–N_2O Anesthesia in Four Pigs

	Low Halothane Concentration		High Halothane Concentration	
	N_2	N_2O	N_2	N_2O
Halothane (per cent end-tidal)	.80 ± .02	.77 ± .10	1.42 ± .07	1.36 ± .17
Temperature (C)	37.9 ± .25	37.8 ± .12	37.8 ± .19	37.8 ± .23
pH_a	7.40 ± .04	7.45 ± .03*	7.46 ± .03	7.47 ± .01
Pa_{CO_2}	40 ± 1.7	39 ± 1	38 ± 0.8	38 ± 1.1
Pa_{O_2}	177 ± 24	199 ± 26	192 ± 19	192 ± 25
Fi_{O_2}	.47 ± .05	.49 ± .04	.45 ± .01	.42 ± .01
Hemoglobin (g/dl)	12.8 ± .5	12.5 ± .3	12.8 ± .2	12.4 ± .2
CO_2 (per cent end-tidal)	5.0 ± .2	4.8 ± .1	4.9 ± .1	5.1 ± .1
Heart rate (beats/min)	126 ± 13	129 ± 10	128 ± 14	119 ± 12
Cardiac output (l/min)	2.22 ± .36	2.18 ± .42	1.79 ± .56	1.49 ± .36
Left ventricular end-diastolic pressure (torr)	4.0 ± 2.8	4.4 ± 2.6	4.5 ± 1.3	5.9 ± 2.0
Mean aortic blood pressure (torr)	81 ± 6	73 ± 6	53 ± 3	42 ± 5
Peak left ventricular dP/dt (torr/sec)	838 ± 63	813 ± 89	613 ± 83	458 ± 59*
Peripheral (systemic) vascular resistance (dyne cm^{-5} sec)	2,940 ± 465	2,860 ± 620	2,710 ± 540	2,560 ± 320
Left ventricular end-diastolic volume (ml)	46 ± 4	44 ± 4	47 ± 2	49 ± 2
Ejection fraction	.37 ± .02	.34 ± .03	.26 ± .03	.25 ± .02
Left ventricular diastolic compliance (l torr)	34 ± 8	28 ± 4	24 ± 8	19 ± 6
Left ventricular circumferential fiber-shortening rate (l/sec)	.68 ± .09	.57 ± .08	.44 ± .06	.44 ± .04

* $P < 0.05$ vs. N_2.

and CFSR, which changed significantly from control to low halothane concentration, but showed no subsequent change (table 3).

Nitrous oxide has direct cardiovascular effects in man. Alone or in combination with narcotic analgesics it depresses ventricular function.[14,15] When N_2O is added to halothane anesthesia, the effect is predominantly one of systemic vasoconstriction, without evidence of a negative inotropic effect.[16] In dogs both a negative inotropic[17] and vasoconstrictive[18] effects have been seen. Since our control condition was N_2O anesthesia, we did not wish to change the background for the halothane administration. In view of the documented effects of N_2O reported above, it seemed prudent to measure the effects separately in four pigs. The hemodynamic differences were minimal, but there did appear a pattern suggesting a somewhat more depressed myocardium with N_2O–halothane than with N–halothane (table 4). The effects of halothane with the two gases were essentially the same, however. Consequently, we are confident that the effects we are reporting represent a true halothane influence.

Two pigs were studied to document the effects of the duration of anesthesia and the radiopaque contrast material used for making all the left ventricular volume measurements. The contrast material is hypertonic, and its short-term effect on circulation (0–20 min) has been adequately documented.[19,20] In man, this was reflected by transient (3 min) increases in blood volume, heart rate, stroke volume, and cardiac output, which returned to normal in 20 min. Kloster found return to nearly basal values within 5 min for mean pressure and pulse rate.[19] In our study we

allowed 30–45 min for equilibration to new halothane concentrations, which should have been more than sufficient to allow for return to basal values following injection of the contrast material. The data for the two pigs suggest that there was some deterioration of the preparation, but that the effect was not great. This bias, such as it is, appears to have been most sensitively reflected in the isovolumic pressure-derived data (peak dP/dt). Hence, simply varying the order of halothane concentrations would be sufficient to remove the source of bias. Furthermore, in the main study group, only four injections of contrast medium were used, in a deliberate effort to minimize the total dose of contrast material.

Heart rate was not significantly affected by increasing halothane concentrations when the data were grouped (table 3). However, there was a weak correlation between heart rate and end-tidal halothane concentration as calculated by linear regression analysis (table 2). The dose-dependent decreases in aortic blood pressure and cardiac output were apparent by both methods of analysis (tables 2 and 3). That the decreases were equivalent is indicated by the lack of change in peripheral resistance, which also suggested that the effects were cardiac in origin.

Sawyer et al. demonstrated that halothane decreased aortic blood pressure and cardiac output in miniature swine, but they did not measure contractile performance and looked at only one concentration of halothane.[8] They allowed hypoventilation so that Pa_{CO_2} increased by 35 per cent, which may have affected the cardiovascular dynamics. In addition, they used 100 per cent oxygen as the carrier gas. Consequently,

comparison is difficult. Nevertheless, our findings are consistent with theirs, and go further to elucidate the dose-dependent relationship and the importance of other variables.

The decreases in cardiac output and mean aortic blood pressure can be explained by the well-documented direct negative inotropic effect of halothane on the myocardium.[2–4,21] The 75 per cent decrease in LV dP/dt and a 62 per cent decrease in V_{max} during the administration of high concentrations of halothane confirm this. Since V_{max} has been shown to be less dependent on changes in afterload than peak dP/dt,[22,23] and since we found such a marked decrease in aortic blood pressure with halothane, there is some justification to believe that V_{max} more accurately reflects the actual effect of halothane on contractile performance. There is a suggestion that preload may have increased with halothane, since both end-diastolic pressure and end-diastolic volume showed increases (albeit insignificant). However, the effect cannot have been large, and the direction was such that the contractile performance of the heart should have been increased rather than decreased. Consequently, there is no reason to believe that change in preload influenced the measurement of ventricular function. The ventriculographic data are also consistent with a negative inotropic effect. The circumferential fiber shortening data showed a negative correlation with halothane concentrations (table 2), but this did not prove to be statistically significant when the data were grouped (table 3). We found a significant decrease in the ejection fraction with halothane, averaging 0.44 under control conditions and decreasing to 0.24 at the high halothane concentration (tables 2 and 3). Hamilton et al. reported ejection fractions of 0.28 under control conditions and 0.09 with halothane, 1.8 per cent, in dogs, but their control was a barbiturate-anesthetized animal with an already low value, and they employed the thermodilution technique, which is known to underestimate ejection fraction.[6] Although the control ejection fraction that we report is lower than that normally found in man, it is consistent with findings in other studies of pigs (unpublished data). So far as we are aware, direct determinations of ejection fraction during halothane anesthesia have not been described elsewhere.‡ The decrease in ejection fraction is entirely consistent with the responses found for heart rate, cardiac output, and end-diastolic volume. That is, end-diastolic volume increased slightly and stroke volume (judged inde-

pendently from thermal-dilution cardiac output and heart rate measurements) decreased significantly.

There was no statistically significant change of end-diastolic pressure or end-diastolic volume at any halothane concentration. The apparent increase in volume is well within the measurement error. Rusy et al. saw dose-related increases in end-diastolic volume from an awake control state in dogs.[7] Hamilton et al. reported small increases in end-diastolic volume with increasing halothane concentrations that were significant only at the highest concentration (1.8 per cent end-tidal).[6] Vatner and Smith reported small but significant increases in both left ventricular end-diastolic pressure and end-diastolic diameter when halothane, 2 per cent, was compared with 1 per cent and with the awake control condition in chronically instrumented dogs.[3]

A direct negative chronotropic effect of halothane has been clearly demonstrated.[24] However, the evidence in the intact animal is inconsistent. Sawyer reported that heart rate was unchanged with halothane in pigs.[8] Rusy's awake dogs had a tachycardia that was not changed by halothane anesthesia.[7] Vatner and Smith[3] and Merin et al.[5] reported increased heart rate in dogs. End-diastolic diameters and pressures all increased in spite of increased heart rate in the latter two studies. Although there was a correlation between heart rate and EDV in this study, it was small (r = 0.36). From the grouped data (table 3), there was no change in heart rate at the time that EDV increased (low–medium) or when compliance decreased (control–low). Consequently, we doubt that heart rate played a role in the volume–pressure relationships.

Compliance showed a significant decrease with halothane, from control to the low halothane concentration, but no further decrease for medium and high halothane concentrations (table 3). Hamilton et al. reported that ventricular compliance did not change with increasing halothane concentrations in the dog.[6] On the basis of a study of rat heart trabeculae, Goldberg et al. concluded that "halothane reduced compliance by a direct action on the mechanism responsible for this property of the myocardium."[2] No quantitative comparison can be made between compliance measured in intact swine and compliance of rat trabeculae, but the directions of the changes are the same.

It is well known that the nonlinear filling curve of the ventricle dictates that compliance must decrease with increasing EDP.[25–27] Indeed, there was a significant correlation between compliance and EDP in this study. We found Comp = .0487 − .00172 × EDP. The standard error of the estimate is .0204 torr^{-1}, and r = .40, with the probability of r = 0 being less than .005. That is, compliance decreases as EDP increases, as expected from results of previous studies of the isolated heart.[28,29] Furthermore, since we found no

‡ Since the preparation of this manuscript, three studies in man measuring end-diastolic ventricular dimensions and/or ejection fraction by means of echocardiography during halothane anesthesia have been published.[30–32] End-diastolic dimensions decreased,[31] did not change,[30] or increased.[32] Ejection fraction decreased.[30,31]

systematic change in end-diastolic volume or pressure with halothane, the pressure–volume filling curve goes through the same point at end-diastole. Thus, our compliance data approximate the slope at this point, and this slope does not appear to have been affected by halothane at low, medium, or high concentrations. It seems likely, therefore, that compliance changes in the intact animal observed by others following halothane administration may well have been due to EDP changes. We cannot state that there is no direct effect of halothane on compliance, but it is clear that what change did occur was accounted for by the change in EDP. This necessitates that if the direct effect of halothane on LV compliance or wall stiffness is to be determined, great care must be taken to maintain constant EDP, as compliance shows greater sensitivity to EDP than it does to halothane. Changes in contractile performance, heart rate, and end-diastolic pressure themselves have effects on compliance. In order to be certain that there was a direct effect of halothane (or any other intervention), these variables would have to be kept constant. This is patently impossible with a potent negative inotropic drug like halothane.

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