Isoflurane and halothane impair both systolic and diastolic function in the newborn pig

M. Ruth Graham MD FRCPC, Darren B. Thiessen BSc BA,
W. Alan C. Mutch MD FRCPC

Purpose: Volatile anaesthetics have considerable effects on diastolic relaxation in the adult myocardium. We hypothesized that isoflurane (I) and halothane (H) may have even greater effects on diastolic function in the newborn, as the newborn heart has increased passive stiffness and altered calcium handling relative to the adult. Using a newborn pig model, we compared I and H at three clinically relevant concentrations with respect to both systolic and diastolic function.

Methods: Sixteen newborn pigs were randomized for study at control (background fentanyl $100 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$ and 0.5, 1.0 and 1.5 MAC of I ($n = 8$) or H ($n = 8$). Temperature, arterial blood gases, and LVEDP were controlled. Left ventricular pressure (LVP) was monitored continuously and LV anterior-posterior dimension was determined by using sonomicrometry crystals. Systolic function was assessed by peak positive dP/dT (dP/dT_{max}) and the slope of the end-systolic pressure-dimension (ESP-D) relationship. Diastolic relaxation was given by peak negative dP/dT ($-dP/dT_{\text{max}}$) and the time constant for ventricular relaxation (τ). Left ventricular stiffness was calculated from the slope of the end-diastolic pressure-dimension (EDP-D) relationship.

Results: At equal MAC concentrations, I and H were identical

in effect for every variable studied. Systolic function was depressed at all anaesthetic concentrations. Control dP/dT_{max} ($1:1815 \pm 561$ (SD) $\text{mmHg} \cdot \text{sec}^{-1}$, H: 1841 ± 509) decreased to 832 ± 341 with 1.5 MAC I and 691 ± 127 with 1.5 MAC H ($P < 0.05$ vs control). ESP-D slope decreased from $62 \pm 31 \text{ mmHg} \cdot \text{mm}^{-1}$ at control to 15 ± 11 with 1.5 MAC I and from 79 ± 16 to 37 ± 15 with 1.5 MAC H ($P < 0.05$ vs control). Diastolic function was affected only at higher MAC anaesthesia. Control τ increased from $18.0 \pm 6 \text{ msec}$ to 29.1 ± 7.5 with 1.5 MAC I and from 20.8 ± 5.9 to 30.0 ± 11.3 with 1.5 MAC H ($P < 0.05$). EDP-D slope was increased at both I and 1.5 MAC anaesthesia. EDP-D slope increased from $0.16 \pm 0.24 \text{ mmHg} \cdot \text{mm}^{-1}$ at control to 0.58 ± 0.46 with 1 MAC I and from 0.16 ± 11 to 0.50 ± 0.35 with 1 MAC H. The $-dP/dT_{\text{max}}$ decreased at every MAC level of anaesthesia.

Conclusion: These combined systolic and diastolic effects help to explain the increased sensitivity of the newborn myocardium to volatile anaesthetics.

Objectif: Les anesthésiques volatils ont un effet considérable sur la relaxation diastolique du myocarde adulte. Nous avons émis une hypothèse selon laquelle l'isoflurane (I) et l'halothane (H) pourraient avoir un effet encore plus important sur la fonction diastolique du nouveau-né, parce que la rigidité cardiaque passive du nouveau-né est plus grande et que son utilisation du calcium diffère de celle de l'adulte.

Méthodes: Seize porcelets nouveau-nés ont été répartis aléatoirement pour étude de contrôle (fond de fentanyl $100 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$), et à 0,5 MAC, 1 MAC et 1,5 MAC de I ($n = 8$) ou de H ($n = 8$). La température, les gaz artériels et la pression ventriculaire télédiastolique gauche ont été contrôlées. La pression du ventricule gauche (VG) a été monitorée en continu et la dimension antéro-postérieure du VG déterminée à l'aide de cristaux sonométriques. La fonction systolique a été évaluée avec le dP/dt maximal (dP/dt_{max}) et la courbe de la dimension télésystolique. La relaxation diastolique a été mesurée par le dP/dt maximal négatif ($-dP/dt_{\text{max}}$) et la constante de temps (τ). La rigidité ventriculaire gauche a été calculée à partir de la pente de la relation pression télédiastolique-dimension.

Key words

ANAESTHESIA: newborn;
ANAESTHETICS, VOLATILE: halothane, isoflurane;
HEART: diastole, relaxation rate, systole.

From the Department of Anaesthesia, University of Manitoba, Winnipeg, Manitoba, Canada.

Address correspondence to: Dr. Ruth Graham, LB-315, Lennox Bell Lodge, Department of Anaesthesia, Health Sciences Center, 60 Pearl St., Winnipeg, Manitoba, Canada R3E 1X2.

Phone: (204) 787-1797. Fax: (204) 787-4291.

Internet: graham@bldghsc.lanl.umanitoba.ca

R. Graham is a recipient of the Canadian Anaesthetist's Society Research Award.

Accepted for publication 26th December, 1995.

Résultats: A MAC égal, I et H ont été identiques pour toutes les variables étudiées. La fonction systolique était déprimée à toutes les concentrations. Le dP/dt_{max} de contrôle ($I: 1815 \pm 561$ (ET) $mm \cdot Hg \cdot sec^{-1}$, $H: 1841 \pm 509$) a diminué à 832 ± 341 avec 1,5 MAC I et à 691 ± 127 avec 1,5 MAC H ($P < 0,05$ vs contrôle). La pente de la relation pression télédiastolique-dimension a diminué de 62 ± 31 $mmHg \cdot mm^{-1}$ (contrôle) à 15 ± 11 avec 1,5 MAC I et de 79 ± 16 à $37 \pm$ avec 1,5 MAC H ($P < 0,05$). La fonction diastolique n'était affectée que par l'anesthésie à des MAC plus élevés. Le contrôle τ a augmenté de $18,0 \pm 6$ msec à $29,1 \pm 7,5$ avec 1,5 MAC $\pm$ et de $20,8 \pm 5,9$ à $30,0 \pm 11,3$ avec 1,5 MAC H ($P < 0,05$). La pente de la relation pression télédiastolique-dimension a augmenté sous anesthésie à I et à 1,5 MAC. Elle a augmenté de $0,16 \pm 0,24$ $mmHg \cdot mm^{-1}$ (contrôle) à $0,58 \pm 0,46$ avec 1 MAC I et de $0,16 \pm 11$ à $0,5 \pm 0,35$ avec 1 MAC H. Le $-dP/dt_{max}$ a diminué sous anesthésie à chacun des niveaux de MAC.

Conclusion: Ces effets systoliques et diastoliques combinés aident à comprendre la plus grande sensibilité du myocarde néonatal aux anesthésiques volatils.

Volatile anaesthetics have important effects on ventricular diastolic function in the adult myocardium.¹⁻³ Similar studies in the newborn are lacking but, since the immature heart differs both ultrastructurally and functionally, anaesthetic effects on diastole may be even more pronounced.

Diastole involves both ventricular relaxation and filling. Relaxation is an energy dependent process requiring sarcoplasmic reticulum (SR) mediated removal of calcium from the cytosol and may be described by the peak rate of decline of left ventricular pressure ($-dP/dT_{max}$) or by the time constant for isovolumic relaxation (τ).³⁻⁶ Diastolic stiffness is best described by the slope of the end-diastolic pressure volume relationship.⁴⁻⁶ Both components need to be determined to completely characterize diastolic function.

With one exception,¹ studies in adults document a prolongation of τ with exposure to both isoflurane and halothane.^{3,6,7} Effects on diastolic stiffness are less clear; a number of studies indirectly suggest a decrease in compliance with halothane^{3,8} while others document no effect with either agent.⁹⁻¹¹

In the newborn, the amount of SR is reduced and less able to sequester calcium.^{12,13} Krane and Su¹⁴ demonstrated a greater depression of SR calcium uptake and release by halothane in the immature myocardium compared to the adult, which suggests impaired diastolic relaxation. Palmisano *et al.*¹⁵ have shown a prolongation of τ with both halothane and isoflurane anaesthesia in isolated infant rabbit hearts, with halothane producing the greater effect. No study, to date, has examined ven-

tricular filling effects in newborns, but the noncontractile component of the myocardium is proportionately greater in infants than adults, which functionally translates into increased passive stiffness.¹⁶ Thus, diastolic stiffness may be affected to a greater extent in this age group.

The present study examined the effects of halothane and isoflurane on systolic function and both compartments of diastole in a newborn pig model. We used the slope of the end-systolic pressure dimension relationship as an index of maximal elastance, to characterize systolic function^{17,18} and the slope of the end-diastolic pressure dimension relationship as an index of stiffness.³⁻⁶ We hypothesized that these agents would be depressant to both systolic and diastolic function. Comparisons were made at equal MAC concentrations, to determine if differences between the two agents existed.

Methods

After receiving institutional animal care committee approval, sixteen pigs, one to three days of age were studied. Ketamine (10 $mg \cdot kg^{-1}$) and atropine (0.02 $mg \cdot kg^{-1}$) *im* were given as a premedication. The animals were placed supine, and during surgical preparation, anaesthesia consisted of fentanyl (100 $\mu g \cdot kg^{-1} \cdot h^{-1}$), N_2O 50% in O_2 and pancuronium (0.1 $mg \cdot kg^{-1} \cdot hr^{-1}$). The trachea was intubated with a Sheridan endotracheal tube and the lungs ventilated with a tidal volume of $10-15$ $ml \cdot kg^{-1}$ and a rate sufficient to maintain arterial PCO_2 within the normal range. Animals were randomized to two groups; Group I (isoflurane) ($n = 8$, 1.73 ± 0.2 kg) and Group H (halothane) ($n = 8$, 1.75 ± 0.3 kg). A Beckman LB2 gas analyzer, calibrated for the anaesthetic agent used, monitored inspired/expired anaesthetic agent concentrations from the distal gas sampling port. Rectal temperature was monitored and maintained at $38^\circ C$ by a radiant heater, heating pad and passive humidification of the inspired air.

The femoral artery was catheterized to monitor arterial pressure (P_{art}). Through the femoral vein, a 4F balloon tipped catheter was advanced into the inferior vena cava, above the level of the diaphragm. The position was verified post mortem. A Millar Mikro-tip 3F catheter was passed retrograde via the left carotid artery into the apex of the left ventricle for continuous measurement of intracavitary pressure (P_{lv}).

Through a sternotomy, the pericardium was reflected so that the pressure surrounding the heart was atmospheric. Left ventricular dimension was determined in the anterior-posterior (A-P) plane by ultrasonic crystal transducers positioned on the endocardial surface through a stab wound and secured by a purse string

suture. Cardiac dimensions were obtained from the transit time of ultrasonic bursts between the transducer pair. The crystal pair was connected to a calibrated sonomicrometer (Sonomicrometer 120, Triton). Surface electrocardiographic (ECG) leads were placed and pacing wires attached to the right atrium and connected to a Grass S88 stimulator. The animals were then allowed a 30 min stabilization period.

The ECG, P_{art} , P_{lv} and A-P dimension were recorded continuously on a Hewlett-Packard eight channel chart recorder, and intermittent measurements were stored on computer (IBM 386) using a data acquisition package (Advanced Codas, Dataq Instruments).

Protocol

In each group, measurements were made at baseline (background of fentanyl, N_2O discontinued) and then at 0.5, 1.0 and 1.5 MAC of the anaesthetic in random order in each group. The MAC for halothane and isoflurane is 0.90% and 1.48% respectively in newborn swine.¹⁹ A 15 min period with stable end-tidal gas concentrations was maintained prior to data collections. Atrial pacing at 180 beats $\cdot$ min⁻¹ was initiated if heart rate decreased below this value to control for potential rate effects on τ , and LV end diastolic pressure (LVEDP) maintained at ± 2 mmHg of the control value with fluid administration or withdrawal as required.

At each anaesthetic concentration, a recording of at least 30 heartbeats was made at end expiration. The balloon tip of the IVC catheter was then inflated for approximately 30 sec to decreased left ventricular filling transiently so that a range of LV pressures at decreasing LV dimensions could be obtained.

The LV pressure tracing was differentiated by computer software (Advanced Codas) and peak positive and negative dP/dT determined. The following parameters were then determined at each anaesthetic concentration:

1 Systolic indices

- (i) Positive dP/dT_{max} (averaged over 30–50 heartbeats)
- (ii) The slope of the end-systolic pressure A-P dimension (ESP-D) relationship was determined from plotting P_{lv} against A-P dimension for the entire cardiac cycle over successive beats of decreasing dimension obtained during IVC occlusion (see Figure 1 and Figure 2). End-systole was defined as the point in the cardiac cycle where the LV pressure-dimension product was maximal.³² A plot of end-systolic pressure vs the corresponding dimension yielded a straight line. Linear regression analysis determined the slope of this relationship.

FIGURE 1 A representative example of the LVP vs A-P dimension loops obtained with decreasing venous return to the heart by inflation of the IVC balloon under control conditions. The interrupted line is the linear regression of the ESP-D points obtained, the slope of which is an index of contractility. The EDP-D regression has been omitted for clarity. ESP-D slope = 79.3 mmHg $\cdot$ mm⁻¹ ($R^2 = 0.71$, $n = 20$), EDP-D slope = 0.10 mmHg $\cdot$ mm⁻¹ ($R^2 = 0.63$, $n = 21$).

FIGURE 2 A representative example of the LVP vs A-P dimension loops obtained during 1.5 MAC halothane anaesthesia in the same animal as Figure 1. ESP-D slope = 23.5 mmHg $\cdot$ mm⁻¹ ($R^2 = 0.77$, $n = 15$), EDP-D slope = 0.15 mmHg $\cdot$ mm⁻¹ ($R^2 = 0.91$, $n = 16$).

2 Diastolic indices

- (i) Negative dP/dT_{max} (averaged over 30–50 heartbeats)
- (ii) Tau (τ) was calculated from the decline in the LV pressure trace according to the equation: $P_t = P_0 e^{-t/\tau}$ where P_t is LV pressure at any time, t , and P_0 is LV pressure at time zero. Maximal $-dP/dT$ defines end ejection and hence the beginning of

TABLE I Temperature, blood gas and end-tidal anaesthetic concentrations

Variable	Isoflurane				Halothane			
	Control	0.5 MAC	1.0 MAC	1.5 MAC	Control	0.5 MAC	1.0 MAC	1.5 MAC
ETanaesth	0	0.74 ± 0.02	1.40 ± 0.04	2.2 ± 0.05	0	0.45 ± 0.06	0.93 ± 0.05	1.40 ± 0.8
TEMP °C	37.9 ± 0.5	37.0 ± 0.4	37.9 ± 0.4	38.0 ± 0.5	38.1 ± 0.9	38.3 ± 0.6	38.3 ± 0.6	38.2 ± 0.5
PO ₂	337 ± 105	326 ± 107	301 ± 126	308 ± 106	289 ± 93	302 ± 89	328 ± 105	293 ± 106
PCO ₂	34.4 ± 3.7	35.7 ± 4.0	35.4 ± 4.1	34.2 ± 4.0	36.6 ± 3.3	36.7 ± 3.0	36.6 ± 3.6	37.8 ± 7.9
pH	7.43 ± 0.07	7.41 ± 0.07	7.40 ± 0.06	7.42 ± 0.08	7.44 ± 0.04	7.40 ± 0.03	7.41 ± 0.07	7.38 ± 0.11

n = 8; Values represent mean ± S.D., both groups

TABLE II Haemodynamic measurements

Variable	Isoflurane				Halothane			
	Control	0.5 MAC	1.0 MAC	1.5 MAC	Control	0.5 MAC	1.0 MAC	1.5 MAC
MAP	64.2 ± 10.6	44.6 ± 9.3*	36.3 ± 7.8*	31.6 ± 8.7*	68.4 ± 13.8	51.8 ± 7.3*	43.7 ± 6.3*	35.3 ± 7*
LVEDP	7.4 ± 3.1	7.8 ± 2.8	8.6 ± 2.8	7.7 ± 3.5	7.3 ± 4.8	8.8 ± 6.0	7.7 ± 4.4	7.8 ± 5.0
HR	218 ± 19	189 ± 6	188 ± 7	186 ± 9	214 ± 18	197 ± 8	194 ± 10	197 ± 16

n = 8; mean ± S.D., both groups

**P* < 0.05 vs control

isovolumic relaxation. Therefore, $-dP/dT_{\max}$ was used to determine zero time and LV pressure measurements were collected until 20% of $-dP/dT_{\max}$ was reached. The natural logarithm of P_i was then plotted vs time (300 samples $\cdot$ sec⁻¹) and τ was defined as the negative reciprocal of the slope, determined by linear regression analysis of the transformed data according to the equation: $\ln P_i = -t/\tau + \ln P_0$. Using a computer software package developed in this laboratory, τ was calculated as the mean value during 20–30 consecutive heartbeats at each anaesthetic concentration.

- (iii) LV diastolic stiffness was determined from the LVEDP A-P dimension relationship, obtained from the same curves in 1 (ii) above. Similar to the technique of Green *et al.*,⁹ the monoexponential relationship between LVEDP and A-P dimension was analyzed by least squares regression using the equation: $P_{lv} = Ce^{Kp \cdot D}$ where C = a derived constant, Kp = chamber stiffness and D = the dimension corresponding to a given P_{lv} . Kp , the slope of the log normalized data, was used as an index of ventricular stiffness.

Statistical analysis

Indices of diastolic and systolic function were compared at each MAC level of anaesthesia within and between groups by analysis of variance for repeated measures.

Post hoc comparisons were made within and between groups with the least squares means test and significance accepted at the *P* < 0.05 level.

Results

Temperature, blood gas and end-tidal anaesthetic concentrations are listed in Table I and were well controlled between groups.

Haemodynamics (Table II)

The mean values for MAP, LVEDP and HR at each MAC concentration studied in both groups are listed in Table II. Mean arterial pressure was not different at control between groups and was decreased compared with control with both anaesthetic agents at every MAC concentration studied. The difference in MAP between concentrations or groups of anaesthetic was not significant. The LVEDP and HR were not different within or between groups at any concentration of anaesthetic studied.

Systolic indices (Table III)

Positive $dP/dT_{\max}$ fell significantly from control at every MAC level of anaesthesia, with no differences found between isoflurane or halothane.

The ESP-D slope was different between the isoflurane and halothane groups at control. ESP-D slope decreased from control with increasing concentration of anaesthetic, and the decrease was parallel between

TABLE III Systolic measurements

Variable	Isoflurane				Halothane			
	Control	0.5 MAC	1.0 MAC	1.5 MAC	Control	0.5 MAC	1.0 MAC	1.5 MAC
+dP/dT	1815 ± 561	1179 ± 366*	978 ± 321*	832 ± 341*	1841 ± 509	1075 ± 201*	877 ± 144*	691 ± 127*
ESP-D SLOPE	62 ± 31	29 ± 13*	25 ± 14*	15 ± 11*	79 ± 16†	37 ± 10*	41 ± 15*	37 ± 15*

n = 8 mean ± S.D., both groups.

**P* < 0.05 vs control

†*P* < 0.05 control halothane vs control isoflurane

Table IV Diastolic measurements

Variable	Isoflurane				Halothane			
	Control	0.5 MAC	1.0 MAC	1.5 MAC	Control	0.5 MAC	1.0 MAC	1.5 MAC
-dP/dT	1680 ± 511	1133 ± 422*	1009 ± 350*	823 ± 382*	1747 ± 488	1198 ± 203*	1058 ± 179*	822 ± 180
τ	18.0 ± 6.0	22.3 ± 4.9	24.3 ± 5.5	29.1 ± 7.5*	20.8 ± 5.9	26.8 ± 10.5	26.6 ± 8.0	30.0 ± 11.0
EDP-D SLOPE	0.16 ± 0.24	0.20 ± 0.16	0.58 ± 0.46*	0.45 ± 0.35*	0.16 ± 0.11	0.14 ± 0.06	0.50 ± 0.35*	0.46 ± 0.38

n = 8 mean ± S.D., both groups.

**P* < 0.05 vs control

groups. Therefore, although control values differed, the response in this variable to increasing anaesthetic concentrations did not differ between groups.

Diastolic indices (Table IV)

Negative dP/dT_{max} decreased from control at every MAC level of anaesthesia, with no differences between either agent or dose. The time constant for isovolumic relaxation was prolonged only at the highest concentration of anaesthetic studied in both groups, with no difference demonstrated between groups. Diastolic stiffness was increased at 1.0 and 1.5 MAC for both anaesthetics, with no differences between groups.

Discussion

The present study shows that isoflurane and halothane are equally cardiodepressant in newborn swine. Systolic function was impaired at every level of anaesthesia studied, while diastolic relaxation and compliance were affected at deeper levels of anaesthesia only. Initially anticipating a 20% difference in τ between groups, our pre-experiment power analysis indicated that 15 animals would be required in each group. We terminated the experiment after studying eight animals in each group as repeated power analysis at this point, using the actual differences in τ seen, indicated that at least 47 animals in each group would be required for significance (α = 0.05, β = 0.2, power = 80%).

Systolic effects

Increased sensitivity of the immature myocardium to inhaled anaesthetics is well supported by the present

study. The +dP/dT_{max} (a load sensitive measure of contractility) and the slope of the end-systolic pressure-dimension (a load insensitive measure of contractility) decreased significantly with both anaesthetic agents at 0.5 MAC. The dP/dT_{max} decreased by 33.9% and 39.5% with isoflurane and halothane respectively, while ESP-D slope decreased by 52% and 54% respectively. These results were obtained in an open chest preparation that included a background infusion of fentanyl. It is possible that the combination of an inhaled agent and fentanyl may have had synergic or additive effects to explain these profound effects on systolic function at such low anaesthetic concentrations. However, studies examining cardiac effects of fentanyl alone, or in combination with isoflurane do not bear this out.²⁰⁻²² Alternatively, the manipulation of the heart required to insert the sonomicrometry crystals may have decreased myocardial reserve or species variation in volatile anaesthetic sensitivity may exist to account for the profound effects seen.

We were unable to demonstrate a difference in systolic effect between the two anaesthetics in our newborn model. Despite the difference in ESP-D slopes at control, the statistical analysis used, which takes the initial difference into account, showed a parallel and equal response to increasing anaesthetic concentration between groups. These findings agree with most experimental evidence regarding the immature myocardium. Baum and Klitzner showed that action potential duration was affected equally by isoflurane and halothane in the neonatal myocardium,²³ and Bosnjak *et al.* showed that both agents produced similar inhibition of voltage

dependent calcium channels.²⁴ Echocardiographically, Murray *et al.* showed that 1.0 MAC halothane and isoflurane decreased CO, SV and ejection fraction to a similar degree in newborns.²⁵ Schieber documented a decrease in dP/dT of 55% at 1.3 MAC isoflurane and halothane, in concurrence with that seen in the present study.²⁶ Finally, Lerman *et al.* in a newborn swine preparation demonstrated an equivalent depression of cardiac index with exposure to 1.5 MAC isoflurane or halothane.¹⁹

Palmisano *et al.* did however, show a differential effect between the two agents when examining LV developed pressure and peak positive dP/dT in isolated infant rabbit hearts.¹⁵ As these measures of contractility are load dependent, it is possible that loading conditions may not be comparable between this *in vitro* preparation and the *in vivo* situation. Alternatively, the assessment of contractility may be different *in vivo*, where additional factors, such as autonomic nervous system effects may play a role.^{27,28}

At the subcellular level, isoflurane has been shown to have a predominant effect on sarcolemmal Ca⁺⁺ flux, while halothane has effects on both sarcolemmal and sarcoplasmic reticulum Ca⁺⁺ handling.^{23,24,29} As the adult myocardium is predominantly dependent on SR Ca⁺⁺ flux for excitation-contraction coupling, the potentially different effects between agents in the adult population may be explained by this mechanism. The newborn myocardium, with its relatively undeveloped SR and T-tubular system is much more dependent on transsarcolemmal Ca⁺⁺ flux for excitation-contraction.¹³ As both agents inhibit transsarcolemmal Ca⁺⁺ flux to the same extent, a differential sensitivity may be less apparent in the newborn myocardium.

Diastolic effects

Anaesthetic effects on diastolic relaxation have been well documented in adults.^{1-3,6} The present study extends these findings to the neonatal myocardium with comparable results.

Pagel *et al.* reported an increase in τ from 22 ms at baseline to 36 and 34 msec with 1.5 MAC isoflurane and halothane, a 61% and 51% increase respectively, in adult hearts.³ The prolongation of τ in the neonatal pig heart at equivalent MAC concentrations is of similar magnitude, 60% and 44% respectively in the present study. This is in contrast to Palmisano *et al.*, the only other investigators to examine anaesthetic effects on diastolic relaxation in an isolated infant preparation. Their results suggest that halothane impairs diastolic relaxation to a greater extent than isoflurane.¹⁵ Again the difference between *in vitro* vs *in vivo* preparation may account for these differences.

Prolongation of τ has been shown to be load dependent,³⁰ with systolic load the most important factor.³¹ As systolic load decreases with both volatile anaesthetics (manifested indirectly by the decrease in arterial blood pressure), then τ should decrease with increasing anaesthetic concentration if the effect were solely load dependent, an effect opposite to that observed. Numerous other studies have suggested that τ increases with increasing preload. Gaasch elegantly demonstrated that this is the case only if the increase in preload is translated into an increase in systolic load.³¹ As preload did not change in the present study and systolic load actually decreased, loading conditions cannot explain the prolongation of τ observed.

As relaxation rates are dependent on active removal of Ca⁺⁺ from the cytosol, the documented anaesthetic effects on transsarcolemmal Ca⁺⁺ movement are a more likely explanation for the results obtained.

The major new finding in the present study is that of halothane and isoflurane on intrinsic ventricular distensibility of the newborn myocardium at concentrations greater than 1 MAC, manifested by an increase in the slope of the LVEDP-A-P dimension relationship. This cannot be accounted for by an alteration in steady state EDP as this was maintained at a stable level throughout the experiment. In the adult literature, isoflurane has not been shown to alter ventricular distensibility by an invasively derived measure of either regional or chamber stiffness.³ Likewise, using invasively derived measures of passive ventricular filling, halothane does not affect ventricular distensibility,^{9,10} although compliance may be apparently decreased secondary to changes in LVEDP.^{8,32} Thus, the results obtained are unique to this population.

A valid criticism of the present study is the use of only one cardiac dimension – the internal A-P diameter, to assess changes in ventricular stiffness. The use of a single measure of dimension does not allow for complete characterization of geometry changes within the ventricle, and as such cannot be extrapolated to a true pressure volume determination. Ideally, a better measure of volume would include dimension measurements in three planes. In preliminary studies, however, this proved to be too traumatic to the very small ventricle of a day-old piglet. Despite these limitations, Rankin *et al.* have shown in an adult dog preparation, that although shape changes occur within the left ventricle, the internal minor axis dimension (that used in the present study) accounted for 87% of the stroke volume displacement, while the major axis (apex-to base) shortening contributed only 9% to the total volume displaced.³³ As well, the minor axis is least influenced by LV volume changes associated with septal shifts due to right ven-

tricular volume changes. Alternatively, the conductance catheter technique has been shown to provide accurate measures of ventricular volume.³⁴ Cassidy *et al.* were able to validate this technique in two-week-old piglets.³⁵ However, the size of the conductance catheter (6F) precludes its use in neonatal piglets at the present time.

Diastolic stiffness may be altered by two mechanisms. Weiss *et al.* theorized that the time available for diastolic relaxation may be insufficient, if the subsequent systole occurred before 3.5 relaxation half-times,³⁶ resulting in an increase in EDP at the same end diastolic volume. Alternatively, an increase in stiffness may occur by an increase in resting tension throughout diastole.³⁷ The former mechanism is heart rate dependent while the latter is rate independent. In the present study, τ increased from 20 msec at control to 30 msec at 1.5 MAC anaesthesia while heart rate was maintained at approximately 180 beats $\cdot$ min⁻¹ or 333 msec $\cdot$ cardiac cycle. Diastolic time varied between 150–180 msec under these circumstances. If τ is used as an overapproximation of relaxation half-time,¹³ then at any anaesthetic concentration studied, diastolic time was always sufficient to allow for 3.5 times the relaxation half-time. Therefore, insufficient time for relaxation cannot explain the result obtained.

Thus, it appears that the increase in stiffness seen in the present study represents a true change in ventricular distensibility with exposure to higher concentrations of inhaled anaesthetics. Validation through alternative measures of ventricular volume would appear to be warranted.

In conclusion, the most commonly used inhalational anaesthetics have effects on both systolic and diastolic function in a newborn pig model with a background infusion of fentanyl. Although the preparation cannot be directly compared with the normal human newborn, the combined effects seen on both components of cardiac function at higher concentrations of anaesthesia may help to explain the clinical observation that newborns tolerate inhaled anaesthetics poorly at concentrations greater than approximately 0.5 MAC. There appears to be no advantage of one volatile agent over the other in this regard.

Acknowledgements

The authors gratefully acknowledge the statistical analysis performed by M. Cheang M. Math and the editorial comments of D.B. Craig M.D. FRCPC.

References

- 1 Humphrey LS, Stinson DC, Humphrey MJ, *et al.* Volatile anesthetic effects on left ventricular relaxation in swine. *Anesthesiology* 1990; 73: 731–38.
- 2 Swanson CR, Muir WW III. Simultaneous evaluation of left ventricular end-systolic pressure-volume ratio and time constant of isovolumic pressure decline in dogs exposed to equivalent MAC halothane and isoflurane. *Anesthesiology* 1988; 68: 764–70.
- 3 Pagel PS, Kampine JP, Schmeling WT, Wartler DC. Alteration of left ventricular diastolic function by desflurane, isoflurane and halothane in the chronically instrumented dog with autonomic nervous system blockade. *Anesthesiology* 1991; 74: 1103–14.
- 4 Plotnick GD. Changes in diastolic function – difficult to measure, harder to interpret (Editorial). *Am Heart J* 1989; 118: 3; 637–41.
- 5 Pagel PS, Grossman W, Haering JM, Wartler DC. Left ventricular diastolic function in the normal and diseased heart. Perspectives for the anesthesiologist (Part 1). *Anesthesiology* 1993; 79: 836–54.
- 6 Pagel PS, Grossman W, Haering JM, Wartler DC. Left ventricular diastolic function in the normal and diseased heart. Perspectives for the anesthesiologist (Part 2). *Anesthesiology* 1993; 79: 1104–20.
- 7 Doyle RL, Foëx P, Ryder WA, Jones LA. Effects of halothane on left ventricular relaxation and early diastolic coronary blood flow in the dog. *Anesthesiology* 1989; 70: 660–6.
- 8 Moores WY, Weiskopf RB, Maysinger M, Utley JR. Effects of halothane and morphine sulphate on myocardial compliance following total cardiopulmonary bypass. *J Thorac Cardiovasc Surg* 1981; 81: 163–70.
- 9 Greene ES, Gerson JJ. One versus two MAC halothane anesthesia does not alter the left ventricular diastolic pressure-volume relationship. *Anesthesiology* 1986; 64: 230–7.
- 10 Brower RW, Merin RG. Left ventricular function and compliance in swine during halothane anesthesia. *Anesthesiology* 1979; 50: 409–15.
- 11 Van Trigt P, Christian CC, Fagraeus L, *et al.* The mechanism of halothane-induced myocardial depression. *J Thorac Cardiovasc Surg* 1983; 85: 832–8.
- 12 Nakanishi T, Okuda H, Kamata K, Abe K, Sekiguchi M, Takao A. Development of myocardial contractile system in the fetal rabbit. *Pediatr Res* 1987; 22: 201–7.
- 13 Kaufman TM, Horton JW, White DJ, Mahony L. Age-related changes in myocardial relaxation and sarcoplasmic reticulum function. *Am J Physiol* 1990; 259: H309–16.
- 14 Krane EJ, Su JY. Comparison of the effects of halothane on skinned myocardial fibers from newborn and adult rabbit: II. Effects on sarcoplasmic reticulum. *Anesthesiology* 1989; 71: 103–9.
- 15 Palmisano BW, Mehner RW, Stowe DF, Bosnjak ZJ, Kampine JP. Direct myocardial effects of halothane and isoflurane. *Anesthesiology* 1994; 81: 718–29.
- 16 Heymann MA. Fetal and neonatal circulation. In: Adams

- FH, Emmanouilides GC, Reimenschneider TA (Eds.). *Heart Disease in Infants, Children and Adolescents*. Baltimore: William & Wilkins, 1989; 24–34.
- 17 Suga H, Sagawa K, Kostiuk DP. Controls of ventricular contractility assessed by pressure-volume ratio, $E_{\max}^1$. *Cardiovasc Res* 1976; 10: 582–92.
 - 18 Sagawa K. The end-systolic pressure-volume relation of the ventricle: definition, modifications and clinical use (Editorial). *Circulation* 1981; 63: 1223–7.
 - 19 Lerman J, Oyston JP, Gallagher TM, Miyasaka K, Volgyesi GA, Burrows FA. The minimum alveolar concentration (MAC) and hemodynamic effects of halothane, isoflurane, and sevoflurane in newborn swine. *Anesthesiology* 1990; 73: 717–21.
 - 20 Schieber RA, Stiller RL, Cook DR. Cardiovascular and pharmacodynamic effects of high-dose fentanyl in newborn piglets. *Anesthesiology* 1985; 63: 166–71.
 - 21 Yaster M, Koehler RC, Traystman RJ. Effects of fentanyl on peripheral and central hemodynamics in neonatal lambs. *Anesthesiology* 1987; 66: 524–30.
 - 22 Weiskopf RB, Eger EI III, Holmes MA, et al. Cardiovascular actions of common anesthetic adjuvants during desflurane (I-653) and isoflurane anesthesia in swine. *Anesth Analg* 1990; 71: 144–8.
 - 23 Baum VC, Klitzner TS. Excitation-contraction coupling in neonatal myocardium: effects of halothane and isoflurane. *Developmental Pharmacology and Therapeutics* 1991; 16: 99–107.
 - 24 Bosnjak ZJ, Supan FD, Rusch NJ. The effects of halothane, enflurane and isoflurane on calcium current in isolated canine ventricular cells. *Anesthesiology* 1991; 74: 340–5.
 - 25 Murray DJ, Forbes RB, Mahoney LT. Comparative hemodynamic depression of halothane versus isoflurane in neonates and infants: an echocardiographic study. *Anesth Analg* 1992; 74: 329–37.
 - 26 Schieber RA, Namnoum A, Sugden A, Shiu GK, Orr RA, Cook DR. Hemodynamic effects of isoflurane in the newborn piglet: comparison with halothane. *Anesth Analg* 1986; 65: 633–8.
 - 27 Merin RG, Basch S. Are the myocardial functional and metabolic effects of isoflurane really different from those of halothane and enflurane? *Anesthesiology* 1981; 55: 398–408.
 - 28 Kato M, Komatsu T, Kimura T, Sugiyama F, Nakshima K, Shimada Y. Spectral analysis of heart rate variability during isoflurane anesthesia. *Anesthesiology* 1992; 77: 669–74.
 - 29 Lynch C III, Frazer MJ. Depressant effects of volatile anesthetics upon rat and amphibian ventricular myocardium: insights into anesthetic mechanisms of action. *Anesthesiology* 1989; 70: 511–22.
 - 30 Raff GL, Glantz SA. Volume loading slows left ventricular isovolumic relaxation rate. Evidence of load dependent relaxation in the intact dog heart. *Circ Res* 1981; 48: 813–24.
 - 31 Gaasch WH, Carroll JD, Blaustein AS, Bing OHL. Myocardial relaxation: effects of preload on the time course of isovolumetric relaxation. *Circulation* 1986; 73: 1037–41.
 - 32 Goldberg AH, Phear WPC. Halothane and paired stimulation: effects on myocardial compliance and contractility. *J Appl Physiol* 1970; 28: 391–6.
 - 33 Rankin JS, McHale PA, Arentzen CE, Ling D, Greenfield JC, Anderson RW. The three-dimensional dynamic geometry of the left ventricle in the conscious dog. *Circ Res* 1979; 39: 304–13.
 - 34 Baan J, van der Velde ET, de Bruin HG, et al. Continuous measurement of left ventricular volume in animals and humans by conductance catheter. *Circulation* 1984; 70: 812–23, 1984.
 - 35 Cassidy SC, Teitel DF. The conductance volume catheter technique for measurement of left ventricular volume in young piglets. *Pediatr Res* 1992; 31: 85–90.
 - 36 Weiss JL, Frederikson JW, Weisfeldt ML. Hemodynamic determinants of the time-course of fall in canine left ventricular pressure. *J Clin Invest* 1976; 58: 751–60.
 - 37 Serizawa T, Vogel WM, Apstein CS, Grossman W. Comparison of acute alterations in left ventricular relaxation and diastolic chamber stiffness induced by hypoxia and ischemia. *J Clin Invest* 1981; 68: 91–102.