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The Effects of Halothane and Pentobarbital on the Threshold of Transpulmonary Passage of Venous Air Emboli in Dogs

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The influence of halothane, pentobarbital, and their interaction on the passage of air across the pulmonary circulation was studied in 12 dogs using transesophageal M-mode echocardiography for air detection in the left atrium and/or aorta. Air was detected in the left atrium and/or aorta after pulmonary artery air injection of 0.04 ml/kg during 1% halothane anesthesia (n = 5). Addition of pentobarbital changed the threshold to 1.0 ml/kg. During pentobarbital anesthesia with and without halothane (n = 7), the thresholds were 1.1 and 1.2 ml/kg, respectively. The authors conclude that the threshold for transpulmonary passage of venous air is higher during anesthesia with pentobarbital with or without halothane than during anesthesia with halothane alone. (Key words: Anesthetics, intravenous: pentobarbital. Anesthetics, volatile: halothane. Embolism: air. Measurement techniques: echocardiography.)

THE LUNG ACTS AS a physiological filter for venous air emboli. This filtering ability can be impaired by overloading the pulmonary vessels with gas infusion,[1–5] arteriovenous shunts,[6] pulmonary O_2 toxicity,[3] and the use of vasodilators.[2] Clinically, Marquez *et al.* reported paradoxical air embolism without evidence of intracardiac septal defects.[7] Butler and Hills, using doppler ultrasound, demonstrated that aminophylline, a presumed pulmonary vasodilator, profoundly reduced the threshold dose of intravenously injected air required for air emboli to pass into the systemic circulation through the pulmonary vascular bed in a pentobarbital-anesthetized dog.[2] Subsequently, Drummond has asked whether volatile anesthetics which have vasodilating effects might also enhance the passage of venous air through the pulmonary circulation.[8]

Using transesophageal M-mode echocardiography, we have studied the effects of halothane, pentobarbital, and their interaction on the transpulmonary passage of venous air embolism in dogs.

Materials and Methods

Twelve mongrel dogs weighing between 7 and 12 kg were studied. Animal care followed the institutional guidelines for animal experimentation. Anesthesia was induced with ketamine hydrochloride (10 mg/kg), xylazine hydrochloride (2.0 mg/kg), and atropine sulfate (0.05 mg/kg) intramuscularly, and the dogs were placed in a supine position. After endotracheal intubation, the dogs were mechanically ventilated with a mixture of oxygen/nitrogen (1:1) to achieve a Pa_{CO_2} of 35–40 mmHg. To maintain immobilization, the dogs were paralyzed with pancuronium bromide (0.2 mg/kg), and supplemental doses were administered every hour. Esophageal temperature was maintained at 37.5 ± 0.5° C with a heating blanket.

A 7-F Swan-Ganz® thermodilution catheter (Edwards Laboratories, Inc., Santa Ana, California) was inserted into the main pulmonary artery through the femoral or external jugular vein for pressure measurement. Through the same vein, another catheter was inserted into the right atrium to measure central venous pressure. An arterial catheter was inserted in the femoral artery for pressure measurement and blood sampling. A 3.5 MHz transesophageal M-mode echocardiographic probe (Aloka Industries Ltd., Tokyo) interfaced with an echoinstrument (Model SSD-110S, Fukuda Denshi Inc., Tokyo) was inserted into the esophagus for air detection.[9,10] The probe was positioned at a level where the left atrium and the aortic cavity could be visualized simultaneously.

Dogs were randomly separated into two groups after the induction of anesthesia. Group 1 dogs (n = 5) breathed 1% halothane for 30 min, after which air embolization was instituted as described below. Pentobarbital (15 mg/kg) was then administered in addition to halothane anesthesia for 30 min, and air embolization was repeated. Group 2 dogs (n = 7) received pentobarbital (20 mg/kg) for 30 min prior to air embolization. One percent halothane was added, and air embolization was repeated after 30 min of halothane-pentobarbital anesthesia.

Following a 30-min stabilization period, control hemodynamic measurements were made, and 0.2 ml/kg air was injected over 5 s through the pulmonary artery port of the Swan-Ganz® catheter to avoid passage through possible intracardiac septal defects. The presence of air in the left atrium and/or the aorta was validated by a scratch-like or fluff-like echocardiogram (fig. 1). If no air was detected, an additional bolus of 0.5 ml/kg of air was injected, and the dose was increased by increments of 0.5 ml/kg until air was detected in the

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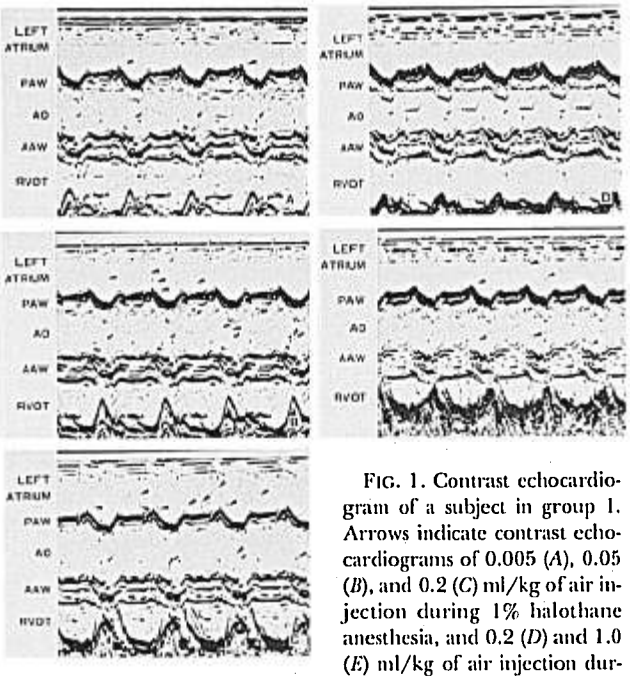

FIG. 1. Contrast echocardiogram of a subject in group 1. Arrows indicate contrast echocardiograms of 0.005 (*A*), 0.05 (*B*), and 0.2 (*C*) ml/kg of air injection during 1% halothane anesthesia, and 0.2 (*D*) and 1.0 (*E*) ml/kg of air injection during 1% halothane plus pentobarbital anesthesia. As the volume of air injected was increased, the amount detected on the echocardiogram increased during halothane anesthesia (*A–C*). Note that, after pentobarbital administration, no air was detected in (*D*), and that seen on the echocardiogram of *E* was similar to that of *C*, in spite of the fivefold increase in dose of air injected. PAW = posterior aortic wall; AO = aortic root; AAW = anterior aortic wall; RVOT = right ventricular outflow tract.

left atrium and/or the aortic cavity. At least 20 min was allowed between incremental air injections. If an air echocardiogram was detected after 0.2 ml/kg of air injection, decreasing doses of 0.1, 0.05, 0.025, 0.01, and 0.005 ml/kg of air were subsequently injected. The minimum quantity of injected air required for detection in the left atrium or/and the aorta was regarded as the threshold value for transpulmonary passage of venous air. In a preliminary study, we injected twice at the same volume, and confirmed the reproducibility of the threshold value. However, to prevent excessive accumulation of air, this study was carried out once at each volume.

TABLE 1. The Threshold Values for Transpulmonary Passage of Venous Air Emboli (ml/kg)

Group 1			Group 2		
Dog No.	H	HB	Dog No.	B	BH
1-1	0.1	1.0	2-1	1.5	1.5
1-2	0.01	1.0	2-2	1.5	1.0
1-3	0.01	1.0	2-3	1.5	1.5
1-4	0.01	1.0	2-4	1.0	1.0
1-5	0.005	1.0	2-5	1.0	1.0
			2-6	1.0	1.0
			2-7	1.0	1.0
Mean	0.04	1.0		1.2	1.1
S.D.	±0.04	±0.0*		±0.3*	±0.2*

H = halothane; HB = halothane plus pentobarbital; BH = pentobarbital plus halothane; B = pentobarbital.
* $P < 0.05$ compared with variable under "H."

Mean arterial pressure (MAP), central venous pressure (CVP), mean pulmonary arterial pressure (MPAP), heart rate (HR), and standard ECG lead 2 were monitored before and after air injections. Cardiac output was measured only before the first air injection, because injection of fluid into the pulmonary artery might have affected deformation and pulmonary distribution of air bubbles.

Data Analysis

All reported values are presented as mean ± SD. Hemodynamic data were analyzed statistically using analysis of variance (ANOVA) techniques followed by paired and nonpaired Student's *t* test corrected for multiple comparisons. Threshold values were analyzed statistically using Kruskal-Wallis test followed by multiple comparisons of Hollander and Wolfe. A probability of less than 0.05 was considered significant.

Results

The quantity of air required for passage of air to the systemic circulation is shown in table 1. With 1% halothane anesthesia, the threshold was 0.005–0.1 ml/kg, whereas, with pentobarbital anesthesia, it was significantly greater, *i.e.*, 1.0–1.5 ml/kg. The addition of pentobarbital to halothane anesthesia raised the threshold to that of pentobarbital alone (group 1). When halothane was added to pentobarbital anesthesia, the threshold was not statistically different from pentobarbital alone (group 2).

Control hemodynamic data before venous air injection are shown in table 2. MAP during pentobarbital anesthesia was significantly higher than that with pentobarbital plus 1% halothane (group 2), halothane alone, and halothane plus pentobarbital (group 1). There were no significant differences in all the other hemodynamic parameters examined. Hemodynamic data during the injection and recovery period of air embolism for groups 1 and 2 are shown in tables 3 and 4, respectively. As indicated, there was a significant increase in MPAP during the injection of large volumes of air (0.5 ml/kg or greater), and the increment in MPAP was proportional to the amount of air injected.

Discussion

The hazard of paradoxical air embolism in patients undergoing surgery in the sitting position who did not

TABLE 2. Control Physiologic Data

	Group 1		Group 2	
	H	HB	B	BH
MAP (mmHg)	70 ± 7*	71 ± 8*	118 ± 4	87 ± 18*
HR (beats/min)	96 ± 12	98 ± 11	112 ± 22	101 ± 12
CVP (mmHg)	1.3 ± 0.8	1.8 ± 1.1	2.0 ± 0.9	1.5 ± 0.6
MPAP (mmHg)	9.8 ± 1.1	10.4 ± 1.8	12.0 ± 1.6	11.6 ± 1.6
CO ($l \cdot min^{-1} \cdot kg^{-1}$)	0.14 ± 0.03	0.16 ± 0.03	0.17 ± 0.02	0.15 ± 0.02
Pa_{O_2} (mmHg)	284 ± 13	283 ± 8	278 ± 20	270 ± 14
PVR ($dyn \cdot sec \cdot cm^{-5}$)	650 ± 180	720 ± 290	510 ± 60	560 ± 70

Values are mean ± SD. Abbreviations are the same as in table 1. * $P < 0.05$ compared with variable under "B."

TABLE 3. Cardiovascular Data for Group 1

	H								HB							
	MAP		HR		CVP		MPAP		MAP		HR		CVP		MPAP	
Dose of Air (ml/kg)	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
0.005	69	6	97	14	0.7	0.3	9.8	1.3								
0.01	70	5	98	13	0.6	0.4	10.3	1.7								
0.025	70	3	97	13	0.7	0.7	10.0	1.4								
0.05	70	8	100	14	1.3	1.1	10.3	1.7								
0.1	69	7	99	13	1.2	0.8	10.4	1.5								
Recovery	69	7	97	17	1.2	0.8	9.0	4.5								
0.2	77	14	99	14	1.6	0.9	11.4	2.3								
Control	70	7	96	12	1.3	0.8	9.8	1.1	71	8	98	11	1.8	1.1	10.4	1.8
0.2									71	8	99	11	1.9	1.0	11.0	1.9
Recovery									71	8	98	11	1.8	1.1	11.0	1.4
0.5									66	8	98	12	2.1	1.2	13.4	2.5*
Recovery									66	7	100	13	1.8	1.2	12.0	1.4
1.0									60	11	101	12	2.2	0.8	15.8	2.9*
Recovery									68	7	98	12	2.0	1.1	12.8	1.3

Abbreviations are the same as in table 1. * $P < 0.05$ compared with control.

have evidence of intracardiac shunt was reported by Marquez *et al.*[7] They pointed out that the minute size of air bubbles would lead to transpulmonary passage of venous air, which, in sufficient volume, might be clinically catastrophic. Butler and Hills[5] and Katz *et al.*[11] have demonstrated the transpulmonary passage of venous air emboli in dogs anesthetized with pentobarbital[5] or halothane.[11] They noted that the passage of venous air into the systemic circulation occurred at a volume of 0.35 $ml \cdot kg^{-1} \cdot min^{-1}$ and a total dose of 240

TABLE 4. Cardiovascular Data for Group 2

	MAP (mmHg)				HR (beats/min)				CVP (mmHg)				MPAP (mmHg)			
	B		BH		B		BH		B		BH		B		BH	
Dose of Air (ml/kg)	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Control	118	4	87	18†	112	22	101	12	2.0	0.9	1.5	0.6	12.0	1.6	11.6	1.6
0.2	118	4	87	19†	111	22	101	12	2.0	0.9	1.5	0.6	13.7	2.5	12.6	2.5
Recovery	114	8	86	13†	110	19	103	17	1.9	1.0	1.8	0.6	12.6	2.0	11.7	1.7
0.5	114	10	86	14†	108	19	102	17	1.9	0.8	2.2	0.4*	27.3	2.9*	14.3	2.6
Recovery	114	11	86	14†	114	19	101	16	1.9	0.8	1.9	0.8	12.3	1.6	12.1	1.7
1.0	109	18	78	21†	117	13	105	20	2.2	1.2	2.8	0.8*	23.7	2.1*	18.7	3.4*†
Recovery	114	12	84	18†	112	13	101	15	1.7	1.0	2.0	0.6	13.1	1.3	12.3	1.5
1.5	100	24	61	14†	114	6	95	5	3.7	1.4	3.5	0.5*	27.3	0.5*	21.0	3.1*†
Recovery	113	7	77	3†	110	16	90	6	2.0	0.9	2.2	0.8	13.7	0.6	13.0	1.7

Abbreviations are the same as in table 1.
* $P < 0.05$ compared with control.
† $P < 0.05$ compared with variable during "B."

TABLE 5. Transesophageal Echocardiogram Detection of Transplumonary Passage of Venous Air Emboli in the Left Atrium and the Aorta

Dose of Air (ml/kg)	Group 1				Group 2			
	H		HB		B		BH	
	LA	Ao (n)	LA	Ao (n)	LA	Ao (n)	LA	Ao (n)
0.005	1	0 (5)						
0.01	3	2 (5)						
0.025	3	2 (5)						
0.05	4	2 (5)						
0.1	5	4 (5)						
0.2	5	4 (5)	0	0 (5)	0	0 (7)	0	0 (7)
0.5			0	0 (5)	0	0 (7)	0	0 (7)
1.0			5	2 (5)	4	2 (7)	5	3 (7)
1.5					3	2 (3)	2	1 (2)

Abbreviations are the same as in table 1. Note that, in many cases (12/24), air was detectable in the left atrium only. In no case was air detectable in the aorta but not the left atrium.

± 31 ml during pentobarbital anesthesia,[5] and at 0.30 $ml \cdot kg^{-1} \cdot min^{-1}$ and a total dose of 180 ± 24 ml during halothane anesthesia,[11] respectively. They concluded that the threshold for air passage was relatively lower during halothane anesthesia as compared to pentobarbital, based on a significant difference in the total dose of air required for detection of air in the systemic circulation. The results of our study support this conclusion, and show an even more marked difference in the threshold dose during pentobarbital and halothane anesthesia. During halothane anesthesia, venous air passed to the systemic circulation at minimal doses of air (0.1–0.005 ml/kg), while, during pentobarbital anesthesia, the threshold was 1.0 ml/kg. As in previous studies,[5,11] no significant difference in hemodynamic parameters were observed between the two groups at minimal dose air injections (tables 2–4).

Since the pathophysiology of a bolus air injection is different from that of slow air infusion,[12] it is difficult to compare the absolute threshold level determined in previous studies with our results. In contrast to previous studies, we observed a remarkable difference in the threshold during the two anesthetic regimens. We suggest that the reason for this difference reflects differences in injection technique (bolus *vs.* continuous infusion), site of air injection (pulmonary artery *vs.* external jugular vein), and site of air detection. The latter may be important, since the technique used in our study, left atrial and aortic echocardiography, is probably more sensitive than the abdominal aortic doppler ultrasound technique used in previous studies. This difference is illustrated by the finding that, in many instances, air was detectable in the left atrium only, and in no case was air detectable in the aorta but not the left atrium (table 5). Use of a less sensitive technique, such as doppler ultrasound, would, therefore, overestimate the threshold dose required for transpulmonary air passage.

The mechanism by which anesthetics influence the threshold for transpulmonary passage of venous air embolus is unknown, but may be mediated through effects on pulmonary blood flow at the level of the arteriole, shunt vessels, or capillary. Since the arteriole is the major determinant of pulmonary vascular resistance, one might expect an arteriolar effect to be reflected in changes in PVR. However, we observed no difference in PVR during halothane and pentobarbital anesthesia (except during injection of very large volumes of air which independently raised MPAP (tables 2–4). Similar findings were reported by Butler and Hills[5] and Katz *et al.*,[11] who observed no significant difference in MPAP, PVR, and CO in the two anesthetic groups. The lack of anesthetic effect on PVR suggest that the observed differences in the threshold for transpulmonary passage of air are not due to arteriolar effects.

A possible anesthetic effect on arteriovenous shunt was suggested by Cheney *et al.*, who measured shunt fraction in awake and halothane-anesthetized dogs,[13] and during venous embolism in pentobarbital-anesthetized dogs[14] using a radioactive microsphere technique. They observed no difference in shunt fraction in air-breathing, halothane, or pentobarbital-anesthetized dogs. During venous embolism, pentobarbital caused a 2.5-fold elevation of PVR relative to control, with no effect on CO or shunt fraction. These data suggest that there is a commensurate increase in shunt resistance during venous embolism with pentobarbital anesthesia. Increased shunt resistance by pentobarbital might explain the increased threshold for transpulmonary air passage during pentobarbital or combined halothane-pentobarbital observed in our study. To our knowledge, there are no studies directly examining the effect of halothane on shunt flow or resistance, or of anesthetic effects on capillary flow dynamics during pulmonary embolism.

In summary, we found that the threshold for transpulmonary passage of venous air was significantly higher during pentobarbital or combined pentobarbital-halothane anesthesia, as compared with halothane anesthesia alone. In the absence of air-breathing control subjects, it is difficult to determine whether the effect of pentobarbital is to raise the threshold level relative to control or whether halothane acts to decrease the threshold for transpulmonary air passage. However the finding that the addition of pentobarbital to halothane anesthesia increased the threshold to the same level as pentobarbital alone might suggest a threshold-increasing effect of pentobarbital and a null-effect of halothane. With regard to the mechanism for this difference, we observed no differences in pulmonary vascular

resistance during halothane and pentobarbital anesthesia, suggesting that other effects, perhaps on shunt or capillary flow dynamics, may be important.

The clinical significance of these findings is unknown because of uncertainties regarding the applicability of our findings to humans and a lack of information concerning the incidence and morbidity of systemic air embolism in surgical and anesthetic practice. However, there are a number of well-documented clinical reports demonstrating the catastrophic outcome of arterial air embolus.[7,10,15] The incidence of air embolus may be better clarified in the future with combined use of intraoperative monitoring techniques, such as doppler, transcutaneous oximetry, or end-tidal carbon dioxide concentration.[16] The well-recognized sequelae of venous air embolism include hypoxemia, right heart failure, and paradoxical embolism. Our data suggest that pentobarbital or combined pentobarbital-halothane anesthesia may protect against the latter complication relative to halothane alone. This potential prophylactic effect may merit consideration among the many factors involved in selection of an anesthetic regimen, particularly in operations at high risk for venous air embolism, such as right ventriculotomy, craniotomy, angiocardiography, and retroperitoneal insufflation.

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