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EFFECTS OF TRIMETAPHAN AND NICARDIPINE ON EXPERIMENTAL PULMONARY AIR EMBOLISM IN DOGS

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Abstract: Experimental study of air embolism was conducted to elucidate the effects of trimetaphan (TMP) and nicardipine (NCP) on the hemodynamics and the minimum air volume capable of penetrating from pulmonary artery to systemic circulation (the threshold air volume) in dogs. Existence of air bubbles in the left atrium or the aorta were visually confirmed using transesophageal echocardiography. The 14 dogs were classified into two groups, TMP group and NCP group. Air embolisms were produced by air infusion through an inserted pulmonary artery catheter. The threshold air volume under TMP administration was significantly attenuated compared with control (without TMP); these median± quartile deviation (Q.D.) values were 0.50±0.19 ml/kg in control, 0.20±0.15 ml/kg in 15% mean artery pressure (MAP) reduction ($p<0.01$ vs. control) and 0.10±0.04 ml/kg in 30% MAP reduction ($p<0.01$ vs. control). There was no significant diffesence in the threshold air volume under NCP administration. Mean pulmonary arterial pressure (MPAP) was significantly decreased after TMP administration; these mean±standard deviation (S.D.) were 17.0±2.6 mmHg in control, 14.6±1.7 mmHg in 15% MAP reduction ($p<0.05$ vs. control) and 14.1±2.4 mmHg in 30% MAP reduction ($p<0.05$ vs. control). There was no significant MPAP change in NCP group. All MPAP values were significantly increased after air injection. The increasing rate in NCP group tended to be higher than in TMP group: 48.8% in NCP and 33.9% in TMP at 15% MAP reduction, and 44.5% in NCP and 32.5% in TMP at 30% MAP reduction. We concluded that NCP and TMP had different responsibility to the stimuli of air embolism, and NCP would be a more optimal vasodilator than TMP during neurosurgical procedures in the sitting position.

Index Terms

air embolism, transesophageal echocardiography, dogs, trimetaphan, nicardipine

INTRODUCTION

The lung has an important non-respiratory function as a blood filter. It captures and deals with accidental clots or air arriving through the pulmonary atrery[1]. This important protective function is affected by several factors: therapeutic vasodilators[1], oxygen[2], arteriovenous shunt in the lung[3] or volume overload infusion in the pulmonary vasculature[4]. When the air volume exceeds a certain level, that is the threshold air volume, paradoxical air embolism occurs[5]. The threshold air volume is the minimum volume of air flowing from the pulmonary artery to the systemic circulation via the pulmonary vascular network. Clinically, Marqes et al.[6] reported this paradoxical air embolism without any evidence of intracadiac septal defect. Butler and Hills[1] using doppler ultrasound demonstrated that aminophylline caused reduction of threshold

air volume coming from the venous system to the systemic circulation. Echocardiography has been extensively utilized for detecting air embolism in the cardiovascular system[7]. Transesophageal echocardiography is one of the most sensitive methods for detecting intracardiac air embolism[8], and this procedure has been established as the most useful method for the detection of paradoxical air embolism[9]. It was reported that the threshold air volume coming from the pulmonary artery to the left heart system in dogs is elevated with halothane, and reduced with pentobarbital administration, using transesophageal M-mode echocardiography[10]. Vik et al.[11] with using transesophageal B-mode echocardiography reported on air passing through the pulmonary circulation in swine. Since induced hypotension using vasodilators has been carried out in the sitting position of neurosurgery, air embolism was produced passively in this surgery. Most of the air that entered the pulmonary artery was filtered in the vascular network of the lungs and eliminated to alveolar space[12]. However, if a small amount of air infiltrates to the pulmonary vein, paradoxical air embolism would develop. This paradoxical air embolism is considered as a rare complication but it may have serious consequences. If some vasodilators dilate the pulmonary vasculatures, paradoxical air embolism may be more likely to develop. It is thesefore important to determine the safety of vasodilative agents with regard to paradoxical air embolism during induced hypotension in the sitting position. In the present study, we attempted to elucidate the effects of two vasodilators, trimetaphan (TMP) and nicardipine (NCP), on the threshold air volume of transpulmonary passage using transesophageal echocardiography, and on the reactivity of the pulmonary vasculature to air embolism in dogs.

MATERIALS AND METHODS

The 14 mongrel dogs weighing 6.0～10.5 kg (mean±S.D.: 7.7±1.5 kg) were studied. Animal care followed the institutional guidelines for animal experimentation. Dogs were divided into two groups at random according to the vasodilator used: TMP group (n=7) and NCP group (n=7). Anesthesia was induced with ketamine hydrochloride (15 mg/kg) and atropine sulfate (0.05 mg/kg) intramuscularly. The dogs were placed in a supine position and intubated, followed by the intravenous injection of pentobarbital (15 mg/kg) and pancuronium bromide (0.2 mg/kg). Anesthesia was maintained with a continuous infusion of pentobarbital (5 mg/kg/h) and pancuronium bromide (0.2 mg/kg/h). The dogs were mechanically ventilated with a volume regulated ventilator, the inspired oxygen fraction by the air mixture being maintained at 0.3-0.4%, and the arterial PaCO2 at 35-45 mmHg. A 7-F thermodilution pulmonary artery catheter was inserted into the pulmonary artery through the right external jugular vein for pressure measurement and air injection. Through the same vein, another catheter was inserted near the right atrium to measure central venous pressure and for the injection of cold saline for cardiac output measurement. Arterial catheter was inserted into the femoral artery for pressure measurement and blood sampling. Blood temperature was maintained at 37.5±0.5℃ with a heating blanket. A transesophageal echocardiographic probe (5 MHz VST-936-5, Aloka Industries Ltd., Tokyo, Japan) interfaced with an echoinstrument (Model SSD-620, Aloka Industries Ltd., Tokyo, Japan) was inserted into esophagus for air detection. The probe was positioned at a certain level where the left atrium or the aortic cavity could be visualized. Air bubbles after passing through the pulmonary circulation were recog-

nized on the echocardiogram as high-intensity, very fine spots in the left atrium and/or the aorta in both M- and B- mode, compared with the air in the right ventricle and the pulmonary artery, in which air bubbles were visualized as scratch-like or fluff-like in M-mode and as high -intensity spots in B-mode. These image patterns were classified as positive only when they were identified clearly by two or more expert observers, and other images were regarded as negative. The echocardiogram was recorded by a videotape recorder, and it was used repeatedly for confirmation. After 30-minute period for stabilization, hemodynamic variables including heart rate (HR), mean arterial pressure (MAP), central venous pressure (CVP), mean pulmonary arterial pressure (MPAP), and pulmonary artery wedge pressure (PAWP) were measured and defined as control value (C0). In the first stage, 0.2 ml/kg air was infused at a rate of 5 ml/min through the pulmonary artery portion of the pulmonary arterial catheter to avoid passage through possible intracadiac septal defects, and to determine whether the presence of air could be detected in the left atrium and/or the aorta, and hemodynamic measurements were made. The hemodynamic variables at this stage were defined as C0air. When the presence of air in the left atrium and/or the aorta was detected and the image was defined as positive after 0.2 ml/kg air injection, the volume of air was decreased to 0.1, 0.05, 0.025 and 0.01 ml/kg until the presence of air could no longer be detected. The last detected value was used as the threshold volume. When the presence of air in the left atrium and/or the aorta was not detected and the image was defined as negative after 0.2 ml/kg air injection, the volume of air was increased to 0.5, 1.0 and 1.5 ml/kg until the presence of air was detected. The first detected value was used as the threshold air volume. A minimum recovery period of 20 min was settled to allow MPAP to return the control value after each air infusion, and hemodynamic variables were measured before and after each air infusion. TMP was then infused continuously until MAP was decreased to 15% reduction of the control value (C0). After stabilization of the hemodynamic state, homodynamic variables were measured and these values were defined as C15. Following these measurements, determination of threshold volume of transpulmonary passege of air was performed according to the protocol described. Hemodynamic measurements at 0.2 ml/kg air infusion were performed and hemodynamic values were defined as C15air. The TMP dose were elevated until MAP decreased to 30% reduction of control (C0) and obtained values were defined as C30. Determination of the threshold air volume and hemodynamic measurements were performed as above. With 30% reduction of MAP, the hemodynamic values with 0.2 mg/kg air injection were defined as C30air. These procedures were repeated in each dog in the NCP group. The increasing rates of MPAP were calculated to represent the reactivity of the pulmonary vasculature to air embolism as two vasodilators evaluation. The increasing rate of MPAP was calculated with the following equation:

$$\frac{\text{MPAP (C15air or C30air)} - \text{MPAP (C15 or C30)}}{\text{MPAP (C15 or C30)}} \times 100\ (\%)$$

DATA ANALYSIS

Data analysis was performed with a computerized statistical analysis package (Stat Flex, View Flex Inc., Tokyo). The changes of the threshold air volumes of air did not show normal

distribution by $\chi 2$-test for goodness of fit, and were analyzed by Mann-Whitney test. Data were presented as median±quartile deviation (Q.D.). The changes of MPAP were not a nomal distribution by $\chi 2$-test for goodness of fit, and were analyzed by Wilcoxon test. Data were presented as mean±standard deviation (S.D.). Significance was defined as $p<0.05$.

RESULTS

The threshold air volumes of the tranpulmonary passage are shown in Table 1. In the TMP group, the threshold air volumes with TMP infusion were significantly lower than in control (without TMP); these median±Q.D. values were 0.50±0.19 ml/kg in control, 0.20±0.15 ml/kg in 15% MAP reduction ($p<0.01$ vs. in control) and 0.10±0.04 ml/kg in 30% MAP reduction ($p<0.01$ vs. in control). In the NCP group, there was no significant difference between with NCP infusion and without NCP; these median±Q.D. values were 0.50±0.50 ml/kg in control, 0.50±0.88 ml/kg in 15% MAP reduction and 0.50±0.88 ml/kg in 30% MAP reduction. The changes of MPAP before air infusion in the two groups are indicated in Fig. 1. These results demonstrated the MPAP change caused by each vasodilator itself. There was no significant difference in control values between the two groups. The MPAP were significantly decreased after TMP administration; these mean±S.D. were 17.0±2.6 mmHg in control (C0), 14.6±1.7 mmHg in 15% MAP reduction (C15) ($p<0.05$ vs. C0) and 14.1±2.4 mmHg in 30% MAP reduction (C30) ($p<0.05$ vs. C0). There was revealed no significant MPAP change in NCP administrated group; these mean±S.D. were 16.3±3.9 mmHg in control (C0), 16.9±5.3 mmHg in 15% MAP reduction (C15) and 17.9±7.6 mmHg in 30% MAP reduction (C30). Alteration of MPAP produced by 0.2 ml/kg air infusion in 15% MAP reduction with TMP and NCP are shown in Fig. 2 (C15 and C15air). All MPAP values were increased significantly after air

Table 1. Threshold air volume following trimetaphan (TMP) and nicardipine (NCP) administration

	TMP				NCP		
	COair	C15air	C30air		COair	C15air	C30air
dog 1	1.00	0.50	0.20	dog 1	0.50	0.50	0.50
2	0.50	0.50	0.20	2	0.50	0.50	0.50
3	0.50	0.20	0.10	3	0.20	0.20	0.50
4	0.50	0.50	0.20	4	1.00	1.00	0.50
5	1.00	0.20	0.10	5	0.50	0.50	0.20
6	0.50	0.20	0.10	6	0.50	0.50	1.00
7	0.50	0.20	0.05	7	0.50	1.00	1.00
median	0.50	0.20*	0.10**	median	0.50	0.50	0.50
Q.D.	0.19	0.15	0.04	Q.D.	0.50	0.88	0.88

COair : threshold air volume before vasodilator administration
C15air : threshold air volume in 15% mean artery pressure (MAP) reduction with vasodilator
C30air :threshold air volume in 30% MAP meduction with vasodilator
*: $p<0.05$, **: $p<0.01$ significant difference versus control (COair)
Q.D.: quartile deviation

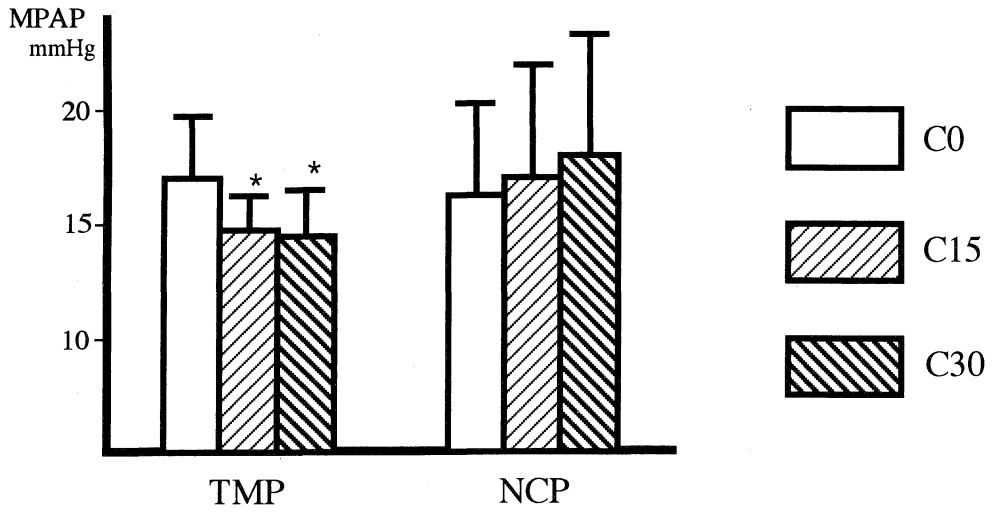

Fig. 1. Mean pulmonary artery pressure (MPAP) following trimetaphan (TMP) and nicardipine (NCP) administration before air infusion.
C0 : MPAP before vasodilator
C15 : MPAP after 15% reduction mean artery pressure (MAP) with vasodilator
C30 : MPAP after 30% reduction MAP with vasodilator
* : $p<0.05$ significant difference versus control (C0)

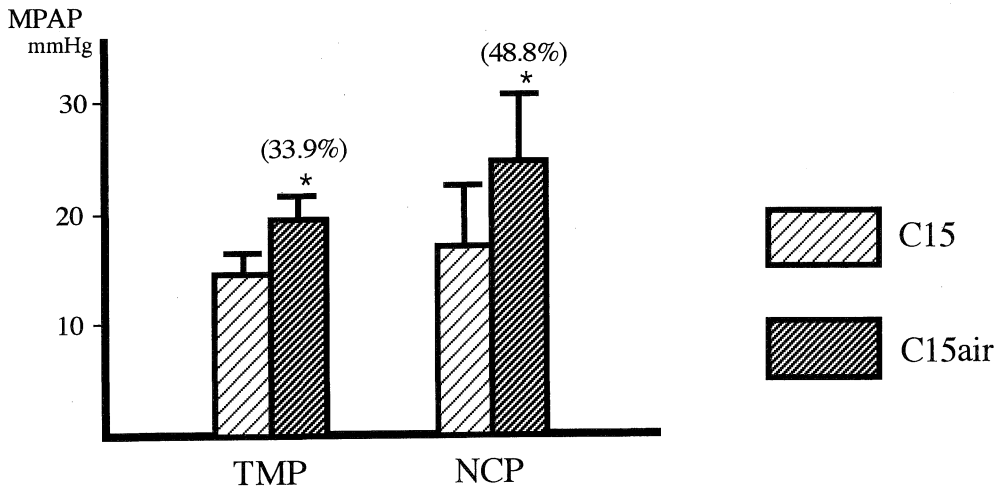

Fig. 2. Mean pulmonary artery pressure (MPAP) responses with air infusion (0.2ml/kg) under 15% mean artery pressure (MAP) reduction with vasodilator.
C15 : MPAP after 15% MAP reduction with vasodilator
C15air : MPAP at 0.2mg/Kg air infusion under 15% MAP reduction with vasodilator parenthesis values indicated MPAP increasing ratio after air infusion
* : $p<0.05$ significant difference versus control (C15)

infusion; the MPAP values after infusion with TMP administration were 19.4 ± 2.2 mmHg (C15air) ($p<0.05$ vs. C15) and with NCP administration were 24.6 ± 6.2 mmHg (C15air) ($p<0.05$ vs. C15). The MPAP in 30% MAP reduction is shown in Fig. 3 (C30 and C30air). All MPAP values were increased significantly after air infusion; the MPAP values with TMP

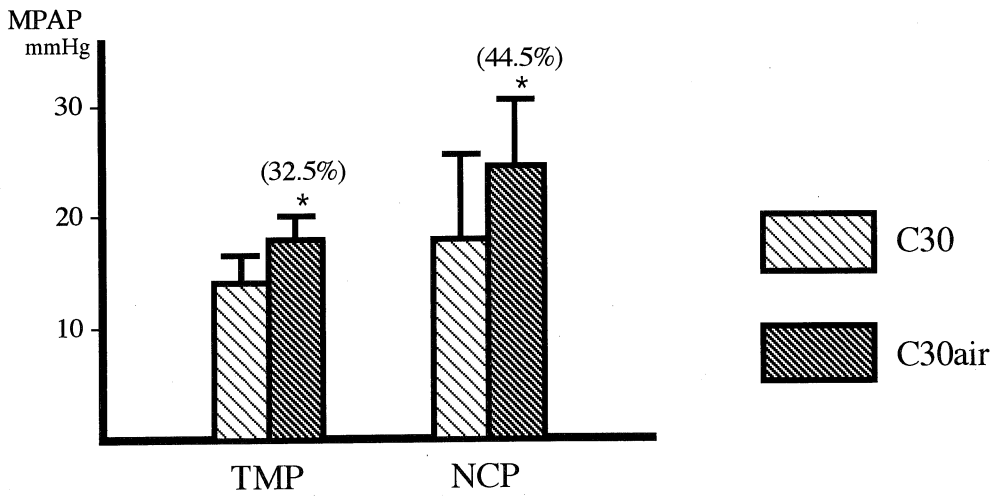

Fig. 3. Mean pulmonary artery pressure (MPAP) responses with air infusion (0.2ml/Kg) under 30% mean artery pressure (MAP) reduction with vasodilator.
C30 : MPAP after 30% MAP reduction with vasodilator
C30air : MPAP at 0.2mg/Kg air infusion under 30% MAP reduction with vasodilator parenthesis values indicated MPAP increasing ratio after air infusion
* : $p<0.05$ significant difference versus control (C30)

administration were 18.0±2.0 mmHg (C30air) ($p<0.05$ vs. C30) and with NCP administration were 24.7±7.1 mmHg (C30air) ($p<0.05$ vs. C30). The increasing rate of MPAP revealed no significant difference between the two drugs, but the NCP group had a tendency to be higher than the TMP group in the increasing rate of MPAP ; these values were 48.8% in NCP and 33.9% in TMP at 15% MAP reduction, and 44.5% in NCP and 32.5% in TMP at 30% MAP reduction.

DISCUSSION

We used transesophageal echocardiography for air detection in the left atrium and/or aorta. Air bubbles were recognized as specific pattern in the contrast echocardiogram. In venous air embolism, air bubbles were visualized as rather large contrast-echo images in right ventricle outflow tract and pulmonary artery, but after passing through the pulmonary circulation bobbles became smaller, and on the echocardiogram the contrast-echo image became more like fine spots. On the M-mode images were demonstrated as fine spots combined with a few scratch-like echoes.

Therefore the recognition of air in the left atrium and aorta was more difficult compared with the venous side. We identified and confirmed the contrast echo air images by examining the continuous change of the echocardiogram. M-mode echocardiography was more effective for this purpose because this echo-mode was available to retain a continuous image for several seconds on one screen. This study examined which vasodilators affect the pulmonary vasculature and air passage from the pulmonary artery to the systemic circulation. We have

obtained the following three results from the present study: (1) the threshold volume of air coming from the venous system into the left heart system was significantly decreased with TMP compared with NCP, this meant that in the pulmonary artery air passed more easily into the pulmonary vein under treatment with TMP than with NCP; (2) TMP produced a significant MPAP reduction, but the change in the NCP group was not significant. These reaults agree with previous investigations[13,14,15]; (3) there was individual tendency in the increasing rate of MPAP during air embolism between two vasodilators, although this difference was not remarkable. The first and third results may indicate that the reactivity to air on the pulmonary vasculature differed according to the vasodilator used. During air embolism, MPAP elevation results from mechanical obstruction caused by the embolism itself and from vasoconstriction caused by humoral or neural factors reacting to air in the same manners to microemboli[16]. Pulmonary vasoconstriction is developed in hypoxia[17]. Vasodilators have been shown to inhibit this hypoxic pulmonary vasoconstriction[13,18,19] by the process of direct dilation of the vascular smooth muscle. Delcroix et al. reported that hydralazine decreased the elevation of pulmonary arterial pressure after embolization by 100-μm diameter beads but had no effect after 1000-μm beads embolization[20]. It may be that the constrictive reaction occurs in the small-diameter vessels. We confirmed that the diameter of most air bubbles in this study after shaking in vitro were from 40 to 200 μm with microscopic examination. In vivo, the air bubbles would be reduced in size by mixing in the flow of the pulmonary circulation until 25 μm diameter or less, as in the report of Presson et al.[12]. We speculated that during air embolism air would reach capillaries with diameters of 25 μm or less. In Delcroix's report[20] hydralazine dilated small pulmonary vessels 100 μm or less in diameter, and our results may indicate that TMP dilates more peripheral pulmonary vessels. Some vasodilators may have the effect of blunting the constrictive reaction of arterioles and capillaries, whose diameters may be as small as 100 μm. Hence if a vasodilator is used during air embolism, the constrictive reaction to air may be attenuated, and entrained air may flow to more peripheral pulmonary vessels. If the air volume is large and the vasodilating effect of the drug is strong, paradoxical air embolism may occur. This study revealed that TMP produced greater capability to paradoxical air embolism than NCP in the case of accidental large volume air infusion.

In conclusion, we recognized different reactivity to air embolism on the pulmonary vasculatures in two vasodilators; nicardipine would be a more optimal vasodilator than trimetaphan during surgery in the sitting position.

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