J Anesth (1994) 8:125–131

Journal of
Anesthesia

Original articles

Effects of phenylephrine and ephedrine on pulmonary arterial pressure in patients with cervical or lumbar epidural anesthesia, or enflurane anesthesia

MAKOTO TANAKA[1] and SHUJI DOHI[2]

[1] Department of Anesthesiology and Critical Care Medicine, The Johns Hopkins Hospital, [2] Department Anesthesiology and Critical Care Medicine, Gifu University School of Medicine, 40 Tsukasamachi, Gifu City, Gifu, 500 Japan

Abstract: The authors studied systemic and pulmonary hemodynamic changes with ephedrine (EP) or phenylephrine (PH) when used to normalize arterial hypotension resulting from acute sympathectomy due to cervical or lumbar epidural anesthesia, or enflurane anesthesia in 52 patients. Both EP (0.2 ± 0.05 mg·kg^{-1}) and PH (0.025 ± 0.008 mg·kg^{-1}) produced a significant increase in pulmonary arterial pressure (PAP) with a concomitant increase in arterial pressure (AP). In the patients anesthetized with cervical epidural block and NO_2–O_2, systolic PAP increased from 22 ± 5 to 28 ± 8 mmHg with EP and from 23 ± 6 to 32 ± 10 mmHg with PH in response to approximately 30 mmHg increase of AP, and the ratio of the increment of systolic PAP to systolic AP (ΔPAP/ΔAP) was 0.15 ± 0.08 with EP and 0.20 ± 0.13 with PH ($P < 0.05$); these changes did not differ significantly from those observed in the patients having lumbar epidural or enflurane- N_2O–O_2 anesthesia. The influence on cardiac output (CO) differed significantly between EP and PH; EP increased CO in all three groups ($P < 0.05$), while PH did not elicit any significant changes in CO. A significant relationship between PAP and AP was found in patients given EP; the regression equation was $\Delta PAP = 0.22 \times \Delta AP\text{-}2.9$ ($r = 0.77$). The relationship in patients given PH was less significant ($r = 0.38$). The results indicated that EP and PH elicit pulmonary hypertensive effect similarly in the patients with a high level of epidural anesthesia and that although both drugs act differently (EP mainly due to increases in the blood flow and PH solely due to its pulmonary vasconstrictive action), the increases in PAP were predictable, to some extent, from the increase of AP in anesthetized humans without predominant cardiopulmonary disorders.

Key words: Lung, Pulmonary arterial pressure, Sympathetic nervous system, Epidural, Ephedrine, Phenylephrine

Address correspondence to: S. Dohi

Received for publication on March 17, 1992; accepted on July 13, 1993

Introduction

More than 30 years ago, Aviado [1] reviewed the cardiovascular effects of 26 pressor agents including ephedrine and phenylephrine used in clinical practice. He pointed out at that time that no definitive information regarding their effects on pulmonary circulation existed in humans. Since then the pulmonary circulation has been shown to differ from the systemic circulation with respect to its autonomic regulation [2], and newly developed sympathomimetic amines such as dopamine and dobutamine have been examined with regard to their effects on the human pulmonary circulation for the last 15 years. However, the pulmonary hemodynamic effects of bolus pressor agents when used for the correction of arterial hypotension, as may accompany acute sympathectomy or a relative overdose of an anesthetic drug, are still unknown.

Ephedrine and phenylephrine are well-known to produce a certain increase in systemic arterial pressure. With respect to autonomic regulation of the pulmonary circulation [2] as well as pressor agent's characteristics [3], they may affect pulmonary vasculature differently and significant differences between the pulmonary arterial pressure responses to ephedrine and those to phenylephrine seem likely as well. Phenylephrine acts as a vasoconstrictor under resting pulmonary vascular tone in a dose-related fashion in the cat [2,3]. Ephedrine, on the other hand, was once speculated to increase pulmonary arterial pressure (PAP) entirely due to increased pulmonary blood flow in the dog [1,4]. These suppositions on PAP may differ significantly in the presence of pulmonary and cardiac sympathectomy. However, as far as we know, this has also not been confirmed in anesthetized humans. Therefore, in the present study, we examined the effects of EP and PH on pulmonary arterial pressure in comparison with systemic arterial pressure in patients, mechanically ventilated and anesthetized with either cervical or

lumbar epidural block, or enflurane in addition to N_2O and O_2.

Materials and methods

Fifty-two adult patients (44 men and 8 women, 35–80 years of age, Table 1) who were indicated to have both arterial and pulmonary arterial pressure catheters in place during anesthesia were included in the present study. They included lung lobectomy or pneumonectomy, liver lobectomy, and total cystectomy for which both arterial and pulmonary arterial pressure lines are routinely indicated in our institution. All patients belonged to ASA class II, and those with cardiovascular complications and/or chronic obstructive lung diseases were excluded from the present study. We divided the patients into three groups as follows: Cervical epidural + N_2O + O_2 (group I), lumbar epidural + N_2O + O_2 (group II), and enflurane + N_2O + O_2 (group III). We only used ephedrine or phenyleprine when arterial blood pressure decreased to below 80% of its resting awake value in each patient. The protocol of this study was approved by our local review committee of the University of Tsukuba Hospital.

All patients were premedicated with diazepam (5–10 mg) p.o. or i.m. 90 min or 45 min before the arrival to the operating room, respectively. In the operating room, each patient had an ECG monitor (lead II or V), a peripheral i.v. catheter and an arterial catheter in the left radial artery. Patients who were indicated to have cervical or lumbar epidural anesthesia for their surgery had an epidural catheter (18G, nylon cath, approximately 5 cm cephalad) at C_7-T_1, or L_{1-2}, respectively. After the epidural catheter's position was confirmed by a 3-ml test dose, the patients received 8–10 ml of a 1.5% lidocaine solution containing epinephrine (1/200 000) for cervical epidural and 10–15 ml of that for lumbar epidural anesthesia through the catheter in place in the supine position. Analgesic levels confirmed by the pinprick test were C_3 to T_7 for group I and did not extend above T_5 for the lumbar groups.

General anesthesia was then induced with thiamylal, 4–5 mg·kg^{-1}, iv, and then each patient's trachea was intubated with the facilitation of succinylcholine chloride, 1 mg·kg^{-1}, or pancuronium, 6 mg i.v., in all 52 patients. In four of these patients, fentanyl (20 μg·kg^{-1}) and pancuronium (0.1 mg) were supplemented prior to the induction of general anesthesia and tracheal intubation. A flow-directed, balloon-tipped catheter (PAC, 7.5 Fr, American Edwards Lab., Santa Anna, CA, USA) was directed into the pulmonary artery through the right internal jugular vein. Anesthesia was maintained with nitrous oxide and oxygen using a semiclosed circle system and a total fresh gas inflow of 6 l·min^{-1} with F_iO_2 of 0.33–0.5. All patients were mechanically ventilated with a tidal volume of 10–15 ml·kg^{-1}, respiratory rates of 10–12 breaths·min^{-1} to maintain $Paco_2$ in the physiological range (35–42 mmHg). Rectal temperature was kept in normal ranges. ECG, heart rate (HR), arterial blood pressure (AP), pulmonary arterial pressure (PAP), right atrial pressure (RAP), and end-tidal carbon dioxide concentration ($ETco_2$; Narmocap, Datex, Helsinki, Finland) were continuously measured and recorded on a polygraph (Sanei, Tokyo, Japan). Each patient received 8–10 ml·kg^{-1} of lactated Ringer's solution during the study.

Before the initiation of surgical procedures and when AP had decreased in each patient, a bolus injection of either phenylephrine (PH, 2.5 ± 0.8 μg·kg^{-1}) or ephedrine (EP, 0.20 ± 0.05 mg·kg^{-1}) was carried out arbi-

Table 1. Types of anesthesia, drugs, number of patients, patients' profiles, resting awake arterial pressure (AP), and Pao_2, $Paco_2$, pHa just before EP or PH Injection of the six groups of patients

Anesthetic techniques	Drugs	No. of patients Male/Female (44/8)	Age (years)	Body weight (kg)	Height (cm)	Resting awake values of systolic AP (mmHg)	Arterial blood gas during anesthesia		
							Pao_2 (mmHg)	$Paco_2$	pHa
Group I									
Cervical epidural + N_2O, O_2	Ephedrine	7/2	60 ± 10	50 ± 13	151 ± 7	138 ± 9	167 ± 36	41 ± 5	7.39 ± 0.04
	Phenylephrine	9/1	60 ± 15	59 ± 11	162 ± 8	134 ± 12	159 ± 37	39 ± 4	7.39 ± 0.03
Group II									
Lumbar epidural + N_2O, O_2	Ephedrine	8/1	53 ± 14	56 ± 11	158 ± 11	120 ± 9	169 ± 24	35 ± 4	7.42 ± 0.05
	Phenylephrine	8/0	53 ± 11	58 ± 7	165 ± 3	119 ± 11	169 ± 13	35 ± 5	7.43 ± 0.06
Group III									
Enflurane + N_2O, O_2	Ephedrine	5/3	68 ± 8	52 ± 4	156 ± 6	136 ± 15	149 ± 30	36 ± 6	7.43 ± 0.04
	Phenylephrine	7/1	65 ± 10	57 ± 8	161 ± 9	134 ± 17	157 ± 33	37 ± 2	7.44 ± 0.03

trarily through the peripheral venous line. Pulmonary artery occluded pressure (PAOP) and cardiac output (CO) were measured prior to the injection in all patients by inflating the balloon of the PAC with 1.5 ml of air. CO was measured by the thermodilution technique in triplicate with 10 ml of iced 5% dextrose solution with a CO computer (COM-1, American Edwards Lab.) and the average value was taken as a representative. During the continuous measurements of ECG, AP, PAP, RAP, HR, and $ETco_2$, PAOP, and CO measurements were repeated when AP seemed to reach a maximum following the administration of either pressor agent.

From the continuous recordings, the response time defined from the injection of drugs until the maximum responses were obtained in AP and PAP (TmAP and TmPAP, respectively) and the ratio of the increment of systolic PAP to systolic AP ($\Delta PAP/\Delta AP$) in both PH and EP groups were also calculated. For statistical analyses, analysis of variance and then Student's *t*-test for paired comparisons were used to assess the hemodynamic effects of the drugs. Student's unpaired *t*-test was also used to compare the responses between the patients receiving EP and PH. P values less than 0.05 were considered statistically significant. We also analyzed data to provide a linear regression equation with the least-square method relating increment of PAP and the other variables such as control PAP or PVR, AP, changes in CO, or the pulmonary vascular pressure gradient (PAP-PAOP). All values were represented as mean ± SD.

Results

There were no significant differences in preinjection values of HR, systolic AP, systolic PAP, RAP, PAOP, systemic vascular resistance (SVR), pulmonary vascular resistance (PVR), Pao_2, $Paco_2$, and pHa either between the PH and EP groups in each anesthetic regimen or among the six groups (Tables 1, 2). However, the mean values of CO in both enflurance groups were significantly lower than the others (Table 2).

PH produced significant increases in AP as expected, and the increases were always associated with concomitant increases in PAP, RAP, PAOP, SVR and PVR in all three groups (Fig. 1, and Table 2). As seen in Fig. 1, the increases of AP following PH were biphasic and those of PAP were almost exclusively monophasic. The maximum values for each were adopted at the point of the second peak of AP. Only HR had decreased significantly compared with the preceding measurement. On the other hand, EP increased all of the variables, but the increase in PAP occurred slowly compared with that of the PH group.

Since no statistically significant difference in any response was found among the six groups of patients, the differences were compared between the responses to EP and those to PH en bloc for the results. The mean ratio for increment of systolic PAP to increment of systolic AP ($\Delta PAP/\Delta AP$) was statistically different between the patients who received EP and PH (0.14 ± 0.4 *vs* 0.19 ± 0.06, $P < 0.01$). The response time defined as the duration between drug administration and the maxi-

Table 2. sAP, sPAP, HR, CO, RAP, PVR and the ratio of the increment of sPAP to that of sAP ($\Delta PAP/\Delta AP$), prior to and after the administration of ephedrine (EP) or phenylephrine (PH) in the three groups of patients

		sAP (mmHg)	sPAP (mmHg)	HR (BPM)	CO (l/min)	RAP (mmHg)	PAOP (mmHg)	SVR (dyn.sec/cm^5)	PVR (dyn.sec/cm^5)	$\Delta PAP/\Delta AP$ (ranges)
Group I-EP	Before	99 ± 13	22.3 ± 4.9	73 ± 12	5.1 ± 2.1	2.0 ± 3.2	3.3 ± 4.4	1193 ± 407	133 ± 80	0.15 ± 0.08
	After	139 ± 14**	28.3 ± 7.6**	83 ± 16**	6.3 ± 2.4**	2.8 ± 4.5	4.1 ± 6.0	1276 ± 338	146 ± 107	(0.03–0.24)
Group I-PH	Before	98 ± 17	23.3 ± 5.9	78 ± 13	5.6 ± 2.3	1.9 ± 4.0	5.7 ± 5.4	1067 ± 359	104 ± 45	0.20 ± 0.13
	After	142 ± 26**	31.6 ± 9.5**	73 ± 13**	5.8 ± 2.3	2.9 ± 4.2*	9.7 ± 8.6*	1502 ± 583**	136 ± 53*	(0.08–0.52)
Group II-EP	Before	97 ± 16	23.9 ± 6.2	71 ± 16	6.3 ± 1.4	1.8 ± 4.8	6.5 ± 7.4	780 ± 273	94 ± 47	0.16 ± 0.09
	After	143 ± 24**	31.8 ± 9.1**	76 ± 19**	6.9 ± 1.3*	2.6 ± 5.4	8.1 ± 8.1	1086 ± 254**	117 ± 52	(0.08–0.33)
Group II-PH	Before	90 ± 21	21.0 ± 7.0	74 ± 13	6.5 ± 1.0	2.1 ± 6.8	6.6 ± 2.7	670 ± 275	94 ± 53	0.20 ± 0.13
	After	131 ± 28**	31.1 ± 6.5**	68 ± 13**	6.2 ± 1.6	5.4 ± 7.4**	9.8 ± 6.3*	1093 ± 404**	156 ± 42**	(0.05–0.42)
Group III-EP	Before	83 ± 9	19.6 ± 4.2	71 ± 19	3.8 ± 0.8	2.4 ± 2.9	5.4 ± 3.3	1287 ± 303	127 ± 24	0.17 ± 0.09
	After	143 ± 19**	31.4 ± 10.9**	76 ± 15*	4.7 ± 1.3**	3.3 ± 3.5	7.5 ± 3.1	1740 ± 426	154 ± 40	(0.03–0.33)
Group III-PH	Before	92 ± 18	20.6 ± 4.6	74 ± 11	4.0 ± 0.6†	2.0 ± 2.6	3.6 ± 2.4	1307 ± 228	133 ± 50	0.17 ± 0.09
	After	130 ± 20**	26.9 ± 6.7**	65 ± 7**	3.8 ± 0.5†	3.31 ± 2.6*	4.6 ± 2.6**	1977 ± 286**	193 ± 91*	(0.11–0.31)

sAP, systolic arterial pressure; sPAP, systolic pulmonary arterial pressure; HR, heart rate; CO, cardiac output; RAP, right atrial pressure; PAOP, pulmonary artery occluded pressure; SUR, systemic vascular resistance; PUR, pulmonary vascular resistance; ΔPAP, change in pulmonary arterial pressure; ΔAP, change in arterial pressure.
* $P < 0.05$ *vs* Before; ** $P < 0.01$ *vs* Before; † $P < 0.05$ *vs* groups I and II (before).
Values are expressed as mean ± SD.

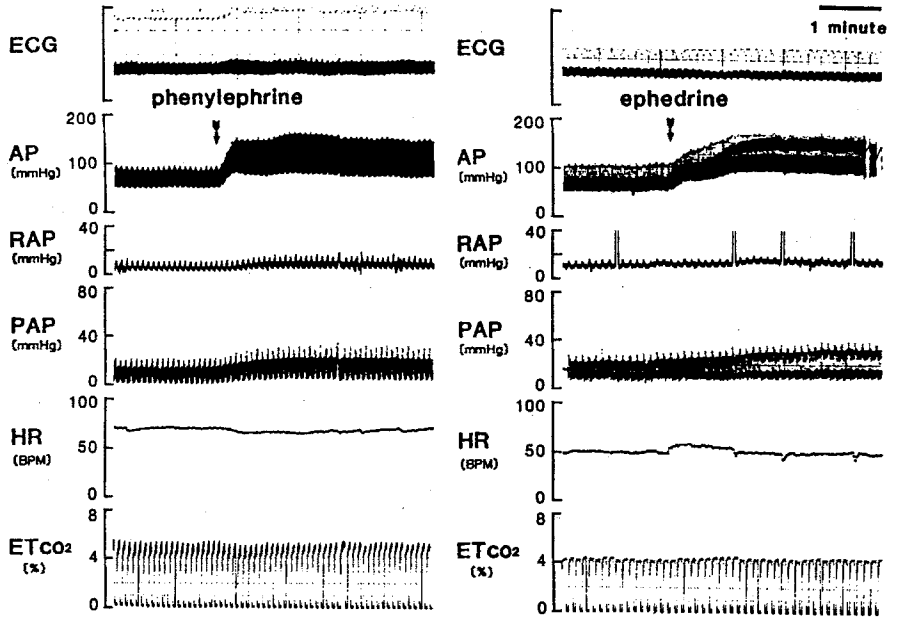

Fig. 1. Demographic polygraph tracings of ECG, arterial pressure (*AP*), right atrial pressure (*RAP*), pulmonary arterial pressure (*PAP*), heart rate (*HR*), and $ETco_2$ before and after phenylephrine (*left*) and ephedrine (*right*)

mum response in sAP and sPAP differed significantly between the patients received EP and PH; the mean values of TmAP and TmPAP following PH were 1.5 ± 0.7 min and 1.7 ± 0.9 min, respectively, with a correlation coefficient (r) of 0.83 between TmAP and TmPAP measured, whereas EP resulted in TmAP of 1.8 ± 0.8 min and TmPAP of 2.9 ± 1.3 min ($P < 0.01$, s PH), showing a large discrepancy with r of 0.51. There was a significant correlation between PAP and AP with EP ($r = 0.77$) but not with PH ($r = 0.38$) (Fig. 2).

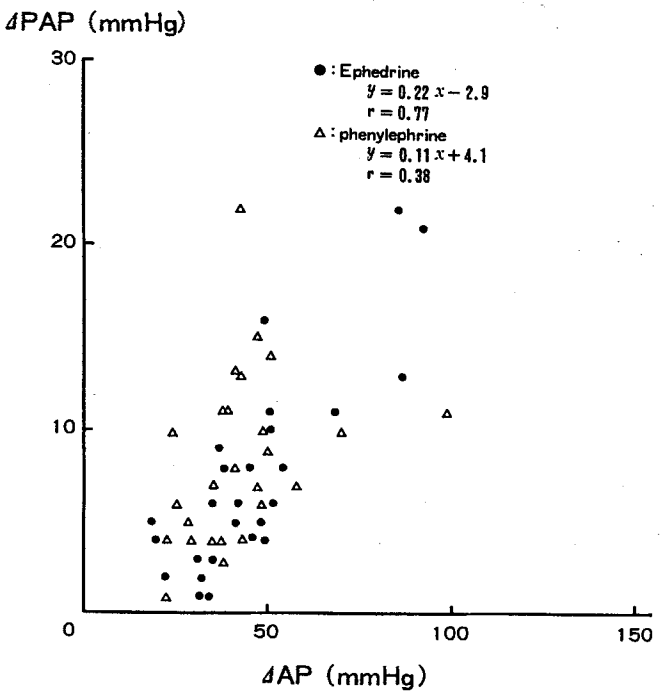

Fig. 2. Correlation between the increments of systolic PAP (sPAP) and systolic AP (sAP) following phenylephrine (*triangles*) and ephedrine (*circles*)

No correlation was found between the peak increment of sPAP and increment of CO following either EP or PH (Fig. 3). The increases in sPAP correlated neither preinjection values of sPAP, sAP, SVR nor PVR. No responses in AP and PAP following EP and PH differed significantly among the patients with cervical and lumbar epidural anesthesia, and general anesthesia alone.

No arrhythmia was observed in any patient following either agent.

Discussion

The results of the present clinical study indicate that both PH and EP elicit a significant increase in PAP by different mechanisms in anesthetized humans irrespective of the presence or absence of pulmonary and cardiac sympathectomy. PH increased AP and PAP in almost parallel fashion; i.e., they reached their maximum responses in about the same time course, but it took markedly longer for PAP to reach the maximum with EP than for AP. Furthermore, the ratio of the increase of PAP to the increase of AP was significantly greater with PH than that with EP. These results indicate that there must be different mechanisms involved in their hypertensive actions on human pulmonary circulation as assumed in the early studies [1].

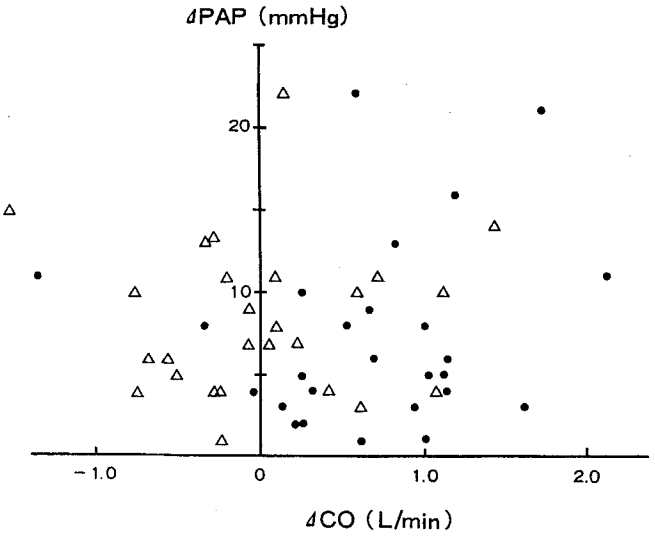

Fig. 3. No correlation between the increments of sPAP and cardiac output following phenylephrine (*triangles*) and ephedrine (*circles*)

Effects of phenylephrine on PAP

PH causes arterial constriction and thus the increment of AP and SVR; these are considered to be largely due to its direct vasopressor action which is mediated through α-adrenoceptors of the peripheral vessels. Although it is still unclear whether or not α-adrenoceptors are present in the human pulmonary vasculature, PH seemed to affect it directly [1]. PH has also been reported to cause venoconstriction and augment venous return in small doses in sympathectomized dogs during spinal anesthesia [6] and in humans anesthetized with nitrous oxide, morphine, and oxygen [7]. Nevertheless, in healthy volunteers anesthetized with halothane, PH-induced increases in AP were accompanied by a marked reduction in CO (5.2–4.0 $l \cdot min^{-1}$) and elevated PAOP (11–17 mmHg) [8]. Probably this can be explained by the fact that venous constriction might transiently increase venous return, but favorable effects on CO may be limited by baroreceptor-mediated reflex bradycardia. In the present results, we observed variable changes rather than a significant decrease in CO. In addition, PH can offset the anesthesia-induced reduction in systemic vascular resistance and augment venous return by producing α-adrenergic stimulation. Furthermore, PH-induced bradycardia is less in the presence of epidural anesthesia [9,10]. These are also responsible for the variable changes in CO caused by pH. Since a recent report demonstrated that α-adrenoceptors exist in human ventricular myocardium and PH per se produces positive inotropic action in the presence of β-blocking agent [11], one may assume that PH increases CO directly in patients with acute cardiac sympathectomy by epidural anesthesia. Thus, we cannot exclude the possibility that the increase in CO following PH in some patients might be responsible, in part, for the increase in PAP. However, the increase in sPAP was by 47%, but CO did not change significantly. Therefore, the increase in PAP appears to be largely due to the direct vasoconstricting action of PH on the pulmonary vasculature [12]. This is compatible with an experimental observation by Hyman et al. [2,3] who demonstrated the existence of α-adrenoceptors in feline pulmonary vasculature through which PH increases PVR in a dose-related fashion under resting pulmonary vascular tone.

Effects of ephedrine on PAP

The response of PAP to EP was considerably different from that to PH, mainly in the time course and the reactivities. EP possesses the property to stimulate β-adrenoceptors directly and thus has a positive inotropic and chronotropic action [5,13] which augments CO and HR as observed in the present study. Aviado and Schmidt [4] observed the variable responses of the pulmonary vasculature to EP in nine anesthetized dogs with open chest preparation where PVR decreased in four, increased in three, and remained unchanged in two dogs. Aviado [1] had speculated that the pulmonary hypertensive action of EP is solely due to increased pulmonary blood flow, and a recent animal study indicated that changes in PAP are largely flow-dependent and depend on preexisting pulmonary vascular tone [14]. In the present results in humans, however, the degrees of the increased PAP were not correlated with the increase in CO (Fig. 3), baseline PVR, or PAP. Therefore, direct pulmonary vasoconstriction might have occurred, to some extent, with EP as well, and that the increment of CO could contribute more to the pulmonary hypertensive action of EP as compared with PH.

Role of basic anesthesia

In addition to cardiac output, there are many factors known to affect PAP including gravity [15], lung volume (mechanical ventilation) [16], hypoxia [17], hypo- or hypercapnia [18,19], acidosis [20], the presence of anesthesia [21], hypertension [22], or lung diseases [23]. Any of these may modulate the pulmonary vascular responses to two pharmacological agents. In the present study, however, although there were some differences in HR, other factors that might have contributed to the PAP responses to PH and EP were either absent or similarly present in both groups. Cervical epidural anesthesia, utilized in the group I patients, could affect the resting pulmonary vascular tone [24] and modify the pulmonary vascular responses to pressor agents as well. It is reported in experimental animals that sympathetic

α- and β-adrenergic blockade appears to produce pulmonary vasodilatation [25]. On the other hand, when pulmonary vascular tone is high, adrenoceptor-mediated responses are reportedly enhanced [3].

Although it was not our primary aim to examine whether or not pulmonary sympathectomy at the spinal cord level affects the PAP responses to PH and EP, we found no significant difference in the increase of PAP as well as in the ΔPAP/ΔAP ratios between the patients with cervical and those with lumbar epidural anesthesia. This agrees with a report that chronic chemical sympathectomy did not cause any difference between pulmonary and systemic hemodynamic response to hypoxia [26,27]. However, another sympathetic drug is reported to increase AP, CO and PAP caused by dopamine to a greater extent during than before thoracic epidural anesthesia in awake humans [28]. Therefore, further studies may be needed before elucidating the effect of epidural anesthesia with pulmonary sympathetic block on the PAP responses to PH and EP. In addition, since lidocaine has been reported to actively constrict the pulmonary vessels [29] and to enhance pulmonary vasoreactivity to catecholamines [30], it is possible that the absorbed and circulating lidocaine following its epidural injection might also modify the PAP responses. No significant difference in the responses to EP between lumbar epidural and general anesthesia suggests that such interactions are not involved in the present results in any important way. However, since we studied patients who had light general anesthesia in addition to a high level of epidural anesthesia, both suppositions concerning the neural and systemic effects of epidural lidocaine on the pulmonary circulation need to be evaluated. Furthermore, the situation in which AP decreased below approximately 80% of control in the present study, could also modulate the mode of PAP and AP responses to the pressor agents.

The pulmonary circulation is significantly affected by a number of drugs currently used to treat congestive heart failure and hypotension during anesthesia [31,32]. Although it is recommended that a partial adrenergic agonist such as ephedrine more ideally corrects the non-cardiac circulatory perturbations [33], the present results indicate that EP increases PAP similarly to PH when used for normalizing arterial hypotension. The PAP increase in response to both agents can be predicted, to some extent, by the concomitant increase in AP; the PAP increase in response to PH was more than those to EP, 1.9 and 1.4 mmHg increase per 10 mmHg increase in AP, respectively. Neither of these increases may be obvious clinically in patients who are preoperatively evaluated to have no cardiovascular complications. Since we found no significant differences in the responses of PAP to EP and PH among the patients who had either cervical epidural, lumbar epidural, or enflurane anesthesia without having any surgical stimulation, it is assumed that preexisting pulmonary vascular tone is unlikely to be an important factor in determining the responses. Rather, the PAP responses to either agent appear to differ in individual patients with different pulmonary vascular reactivity to the agents, and probably in the dosage that augments right and left ventricular performance. In addition, it seems likely that under the condition in which pulmonary tone could be elevated by fluid infusion [28], pharmacological agents [30,34], hypoxia [17,35], or surgical stimulation, the PAP response to sympathomimetic amines is enhanced markedly. Further, the pulmonary circulation represents a critical vascular bed in certain disease states [22,23]. We, therefore, suggest that it is not appropriate to extend the present suppositions to patients with borderline right ventricular strains, pulmonary hypertension [23,36] systemic hypertension [22] and/or surgical stimulation. In such cases, PAP should rigorously be monitored in the patients' management when the usage of the pressor agents is anticipated during anesthesia.

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