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Changes in Pial Vessel Diameter during Hemorrhagic or Drug-induced Hypotension in the Cat

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Abstract Changes in pial vessel diameter during hypotension induced by hemorrhage, trimethaphan, or nitroprusside were studied in 21 cats anesthetized with halothane (0.9%, end-tidal). Pial arteries and veins were measured by immage-splitting technique and were each divided into three groups according to the reference diameter: I; 24-50 μm, II ; 51-100 μm, III ; 101-352 μm. The mean arterial pressure was reduced to approximately 50 torr by either hemorrhage or administration of the drugs. Diameters of arteries increased during hypotension induced by hemorrhage, trimethaphan, or nitroprusside. During hypotension induced by hemorrhage or nitroprusside, dilatation of smaller arteries dilated more than larger ones. During trimethaphan-induced hypotension, dilatation of arteries was independent of vessel size. Consistent and significant dilatation of all veins was observed only during nitroprusside-induced hypotension. CO_2 responsiveness of arteries to hypercapnia was reduced during hemorrhagic or trimethaphan-induced hypotension while it was maintained during nitroprusside-induced hypotension. Changes in diameter of arteries in response to hypercapnia during nitroprusside-induced hypotension were significantly more than those during trimethaphan-induced hypotension. These findings indicated the differential effect of trimethaphan and nitroprusside on pial arteries and veins.

Key words: Brain; pial vessel diameter, Hypotension; hemorrhage, trimethaphan, nitroprusside

Introduction

Trimethaphan (TMP) and nitroprusside (NTP) are commonly used in anesthetic practice for induced hypotension. The differential effects of these drugs on cerebral hemodynamics[1], metabolism[2], oxygenation[3] and electrical activity[4] have been reported, particularly on cerebral hemodynamics. Previous study from the author's laboratory[1] showed that NTP significantly increased cerebrospinal fluid pressure (CSFP) without changes in cerebral blood flow (CBF) while TMP did not cause any significant changes in both CSFP and CBF. This study on NTP suggested that there was no consistent relationship between CSFP and CBF, despite the common belief[5] that the qualitative effect of drugs on CSFP can be predicted from the drug's effect on CBF and cerebral vascular resistance. One approach to clarify the underlying mechanisms for the differential effect of the drugs is direct observation

of cerebral vasculature.

It has been well known that alterations of $PaCO_2$ cause changes in CBF and cerebral vascular resistance. The CO_2 responsiveness has been examined during hypotension because intended or accidental changes in $PaCO_2$ could occur during hypotension in anesthetic practice. Along this line, Gregory et al[6] recently reported that responsiveness of CBF to hypocapnia was maintained during NTP-hypotension but not TMP-hypotension. However, they found no significant changes in measured vascular diameter produced by CO_2 during either technique of hypotension. These findings necesscitated to evaluate effects of TMP and NTP on pial arteries and veins, and to examine diameter change by CO_2 during drug-induced hypotension.

Materials and Methods

This study was performed in 21 cats of either sex weighing 1.8 to 4.3 kg. Anesthesia was induced with halothane, 5% and N_2O, 50%, in oxygen in a cage. Succinylcholine, 50 mg, was injected intramuscularly to facilitate tracheal intubation. Anesthesia was maintained with halothane, 1.5 to 2%, and N_2O, 60%, in oxygen. Muscle relaxation was maintained with intramuscular pancuronium, 0.3 mg/kg, every 30 min, and lactated Ringer's solution was infused at a rate of 5 ml/kg/h. Ventilation was controlled with a Harvard pump to maintain normocapnia ($PaCO_2$ 30±1 torr), throughout the surgical preparation. Both femoral veins were cannulated for drug administration and fluid infusion. A catheter was passed through one femoral artery into the abdominal aorta for continuous measurement of blood pressure (Statham p 23 ID). Mean arterial pressure (MAP) with zero reference at the level of external auditory meatus was recorded on a polygraphrecorder (Nihon Kohden, RM-6000). A second catheter was passed through another femoral artery for blood sampling and blood removal, for controlled hemorrhage.

After completion of vessel cannulation, the cats were placed in a prone position with the head supported by bilateral ear bars, and skin of the head was incised along the midline. A burr hole of 1.5 cm diameter was made using a dental drill over the left parietal cortex with its center on a line drawn between the external auditory meatuses and 1.5 cm lateral to the midline. The dura was opened and reflected. The exposed brain was covered with a thin plastic sheet (Melinex, ICI). The space under the sheet was filled with fluid identical in ionic composition to cerebrospinal fluid of the cat. After completion of surgical preparation, N_2O was substituted for nitrogen, and inspired halothane concentration was reduced to 1.0% and maintained for the remainder of the experiment. The mean duration of surgery was about 3 h. After opening the dura, at least 1 h was allowed to elapse before measurements.

The brain surface was illuminated with a cold light source (Volpi, Intralux). Vessel diameters were measured using microscope (Nicon, SMZ-10) with digital gauge (Ozaki MFG., Model D-10S) and digital counter (Ozaki MFG., Model D-5S)[7]. Rectal temperature was maintained at 37±0.1°C with a heating blanket throughout the experiment. Other measurements included $PaCO_2$, PaO_2, pH (Radiometer, ABL-2), Hb (cyanmethohemoglobin method), end-tidal halothane concentration (gaschromatograph, Shimazu, GC-4A). From one cat 4 to 5 vessels in each artery and vein with different sizes were selected at random for each measurement. Diameters measured during normocapnic normotension were taken as reference. Reference diameters of arteries and veins ranged from 26 to 352 μm and from 24 to 315 μm, respectively. Both arteries and veins were divided into three groups according to the reference diameters (Ⅰ, Ⅱ and Ⅲ). Thereafter, diameters during hypercapnia were measured 10 min after addition of 3% CO_2 to inspired gases. After the measurement during hypercapnia, CO_2 was withdrawn. Diameters during normocapnia were measured again 15 min after withdrawal of CO_2, and were taken as control diameter before induced hypotension. Again, both arteries and veins were divided into three groups according to the control diameters (Ⅰ, Ⅱ and Ⅲ). Thereafter, MAP was gradually reduced to 50 torr at a slower rate than 10 torr/min by blood removal (hemorrhage group, 7 cats), by infusion of TMP (TMP group, 7 cats), or by infusion of NTP (NTP group, 7 cats). TMP was infused at a maximum rate of 10 mg/kg/min and NTP was infused in a total dose of less than 1 mg/kg. In the hemorrhage group, 23±1 ml/kg of blood was removed.

Measurements during normocapnic hypotension were done at 5 and 15 min after the start of induced hypotension. Thereafter, measurements during hypercapnic hypotension were done 10 min after addition of 3% CO_2 to inspired gases as done at normotension.

Each vessel group consisted of 10 vessels, and all vessel diameters at each specific time were measured in duplicate within 2 min. In order to facilitate analysis, standardized per cent changes; per cent change in diameter divided by pressure change and per cent change in diameter divided by $PaCO_2$ change, were calculated. Results were analyzed using Student's t test for paired data, and two way analysis of variance with critical difference testing for standardized per cent changes among hemorrhage, TMP and NTP group. $P<0.05$ was considered to be significant.

Results

The physiological variables are summarized in table 1. The values of MAP during normocapnic hypotension shown in the table were obtained 15 min after the start of induced hypotension, and those at hypercapnia were obtained 10 min after the addition of 3% CO_2. Mean MAP during hypotension in all groups was maintained at approximately 50 torr. There was no significant change in MAP during hypotension with hypercapnia except in the TMP group. Addition of 3% CO_2 caused an increase in the overall mean $PaCO_2$ by 18±1 torr. Mean PaO_2 was maintained from 206 to 257 torr during both normotension and hypotension. Table 2 summarizes changes in diameters of pial vessels 5 and 15 min after the start of induced hypotension. During drug-induced hypotension, all groups of arteries significantly dilated at 5 and 15 min, but during hemorrhagic hypotension artery I and II dilated significantly. During hemorrhagic hypotension, vein I and II dilated. With NTP all veins dilated significantly, while there was no change with TMP. Table 3 shows % change /△ pressure torr. Dilatation in artery I and II during TMP-hypotension was less than that during hemorrhagic hypotension. Dilatation in artery I and II during NTP-hypotension was more than that during TMP-hypotension. Dilatation of smaller arteries was more than that of larger arteries with hemorrhage and NTP, while dilatation of arteries with TMP was independent of vessel size. Venous dilatation with NTP was significantly pronounced more than with hemorrhage or TMP.

Table 4 summarizes changes in vessel diameter in response to hypercapnia during normotension and hypotension. All arteries dilated with hypercapnia during normotension as well as during hypotension induced by either hemorrhage or NTP. During normotension, veins dilated with or without statistical significance, while during hypotension no significant changes occurred in any of the groups. Table 5 shows % change /△ $PaCO_2$ torr. During normotension smaller arteries dilated more with hypercapnia than larger ones. The responsiveness of arteries to hypercapnia during hypotension was significantly less than during normotension with hemorrhage and TMP. Changes in diameter of veins in response to hypercapnia were reduced during hypotension induced by hemorrhage, TMP or NTP.

Discussion

The present study clearly demonstrated the differential effect of techniques for induced hypotension on diameters of the pial arteries and veins. Relationship of vessel size to response to change in hemorrhagic hypotension was recently reported by Kontos et al[8] and MacKenzie et al[9]. However, there is a discrepancy between the two studies. MacKenzie et al[9] observed consistent and progressive increase in size of the arterioles (50 μm) when MAP was reduced from 100 to 40 torr while Kontos et al[8] were unable to note any dilatation of the smaller arteries (42±1.0 μm) when MAP was reduced from resting level to 90 torr;

Table 1 Physiological Variables

	Hemorrhage n=7				Trimethaphan n=7				Nitroprusside n=7			
	Normotension		Hypotension		Normotension		Hypotension		Normotension		Hypotension	
	Normo-capnia	Hyper-capnia	Normo-capnia	Hyper-capnia	Normo-capnia	Hyper-capnia	Normo-capnia	Hyper-capnia	Normo-capnia	Hyper-capnia	Normo-capnia	Hyper-capnia
MAP (torr)	106± 1	111± 5	51± 1	54± 1	92± 4	89± 3	52± 1	48± 1#	99± 9	101±10	49± 2	49± 2
$PaCO_2$ (torr)	32± 2	45± 1*	30± 2	47± 3#	31± 1	49± 2*	31± 2	54± 5#	32± 1	50± 2*	32± 1	49± 2#
PaO_2 (torr)	206±12	221±12	257±22	224±17	240±21	234±19	209±22	217±21	218±24	221±29	221±29	208±12
pH	7.39±0.02	7.27±0.02*	7.42±0.02	7.25±0.01#	7.39±0.03	7.24±0.03*	7.38±0.04	7.19±0.03#	7.39±0.03	7.25±0.02*	7.39±0.02	7.22±0.01#
Hb (g/dl)	12.2±0.8		9.8±0.5†		13.8±0.8		13.5±1.0		12.5±0.9		12.2±0.7	
Rectal temperature (°C)	37.4±0.4		37.7±0.3		37.7±0.2		37.3±0.3		37.2±0.3		37.2±0.3	
Halothane (end-tidal %)	0.88±0.06		0.86±0.07		1.01±0.06		0.93±0.03		0.91±0.07		1.00±0.10	

Values represent means±SEM.

* Significantly different from normocapnia at normotension ($P<0.05$).

\# Significantly different from normocapnia at hypotension ($P<0.05$).

† Significantly different from normotension ($P<0.05$).

Table 2 Pial Vessel Diameter during Induced Hypotension

		Hemorrhage n=7			Trimethaphan n=7			Nitroprusside n=7		
$PaCO_2$ (torr)		31±2			31±2			32±1		
Time (min)		Control	5	15	Control	5	15	Control	5	15
MAP (torr)		108± 5	63± 5*	51± 1*	89± 3	56± 3*	52± 1*	92± 8	56± 4*	49± 2*
Artery (μm)	I	39± 2	53± 3*	63± 4*	46± 2	55± 4	58± 3*	36± 3	50± 3*	65± 5*
	II	62± 5	83± 6*	92± 5*	67± 3	75± 6*	78± 6*	53± 2	61± 3*	71± 4*
	III	201±24	217±30	224±30	157±13	177±18*	184±17*	180±19	197±22*	201±22*
Vein (μm)	I	43± 3	49± 3*	49± 3	39± 3	46± 4	43± 3	45± 4	67± 6*	72± 5*
	II	79± 4	80± 6	85± 5*	72± 5	76± 9	78± 7	74± 5	95± 7*	101± 9*
	III	153± 9	152± 9	155±10	141±10	144±10	142±10	157±26	191±26*	195±26*

Values represent mean±SEM.
* Significantly different from control ($P<0.05$).

Table 3 Changes in Pial Vessel Diameter during Induced Hypotension (% Change/△Pressure torr)

		Hemorrhage n=7		Trimethaphan n=7		Nitroprusside n=7	
Time (min)		5	15	5	15	5	15
Artery	I	0.90±0.24°	1.18±0.16°	0.35±0.25#	0.70 ±0.11#	0.85±0.18†°	1.48±0.29*†°
	II	0.78±0.20°	0.86±0.13°	0.24±0.17	0.43 ±0.14	0.73±0.35†	1.00±0.29†
	III	0.16±0.10	0.20±0.09	0.38±0.08	0.47 ±0.07	0.37±0.12#	0.36±0.09
Vein	I	0.28±0.14	0.21±0.10	0.57±0.29	0.32 ±0.15	1.38±0.34#†	1.50±0.26†°
	II	0.05±0.08	0.12±0.15	0.12±0.25	0.21 ±0.18	1.04±0.23#†	1.04±0.21†
	III	−0.02±0.07	0.04±0.06	−0.02±0.18	0.002±0.08	0.96±0.18#†	0.81±0.14†

Values represent mean±SEM.
* Significantly different from value at five min ($P<0.05$).
# Significantly different from hemorrhage at corresponding time ($P<0.05$).
† Significantly different from trimethaphan at corresponding time ($P<0.05$).
° Significantly different from group III ($P<0.05$).

Table 4 Changes in Pial Vessel Diameter with Hypercapnia

		Hemorrhage n=7				Trimethaphan n=7				Nitroprusside n=7			
		Normotension		Hypotension		Normotension		Hypotension		Normotension		Hypotension	
$PaCO_2$ (torr)		32± 2	45± 1*	30± 2	47± 3#	31± 1	49± 2*	31± 2	54±5#	32± 1	50± 2*	32± 1	49± 2#
Artery (μm)	I	35± 2	63± 4*	63± 4	73± 5#	43± 3	60± 3*	58± 3	60± 4	38± 3	55± 4*	65± 5	82± 8#
	II	68± 3	97± 7*	92± 5	104± 7#	75± 3	102± 6*	78± 6	84± 5	68± 3	82± 3*	71± 4	87± 5#
	III	210±25	251±30*	224±30	258±33#	171±15	212±18*	184±17	189±15	202±20	229±25*	201±22	235±26#
Vein (μm)	I	40± 3	51± 4*	49± 3	51± 6	41± 3	52± 4*	43± 3	47± 3	48± 4	57± 3*	72± 5	73± 5
	II	82± 5	84± 4	85± 5	85± 5	74± 5	97± 9*	78± 7	80± 7	83± 4	93± 5*	101± 9	97± 9
	III	157± 9	170±10*	155±10	156±12	145± 9	158±12	142±10	145±10	169±25	187±27*	195±26	197±23

Values represent means±SEM.
* Significantly different from normocapnia at normotension ($P<0.05$).
# Significantly different from normocapnia at hypotension ($P<0.05$).

Table 5 Changes in Pial Vessel Diameter with Hypercapnia during Induced Hypotension (% Change/△$PaCO_2$ torr)

		Hemorrhage n=7		Trimethaphan n=7		Nitroprusside n=7	
		Normotension	Hypotension	Normotension	Hypotension	Normotension	Hypotension
Artery	I	6.15±0.78°	0.85±0.31*	3.41±0.81#°	0.06±0.28*	2.74±0.29#°	1.70±0.39†
	II	2.78±0.31	0.97±0.36*	1.70±0.28#	0.31±0.22*#	1.18±0.22#	1.17±0.34†
	III	1.87±0.54	1.00±0.30*	1.56±0.22	0.08±0.16#*	0.70±0.14#†	0.90±0.13†
Vein	I	1.65±0.48	0.12±0.41*	2.93±0.90°	0.77±0.26*°	1.41±0.53	0.21±0.26*
	II	0.34±0.22	−0.09±0.24	1.51±0.41#	0.12±0.24*	0.81±0.19	−0.09±0.20*†
	III	0.61±0.19	0.04±0.27*	0.53±0.24	0.01±0.10*	0.64±0.13	0.25±0.15*

Values represent mean±SEM.
* Significantly different from normotension in eachgroup ($P<0.05$).
# Significantly different from hemorrhage group ($P<0.05$).
† Significantly different from trimethaphan group ($P<0.05$).
° Significantly different from group III ($P<0.05$).

however, the smaller arteries dilated more vigorously than the larger ones at MAP of 50 torr. Although direct comparison of the present results with theirs is difficult because in this study the measurement during hypotension was made only at MAP of approximately 50 torr, the present findings are in agreement with the general conclusion extracted from both studies.

It has been reported that cerebral vascular resistance, at least one-third, is located in the precapillary sphincter and arterioles[9]. The present observation would implicate that the smaller arteries might be the principal resistance in the cerebral circulation. Changes to a lesser degree in the diameter of veins than those of arteries indicate insignificant contribution of the veins to autoregulatory response to hemorrhagic hypotension. An explanation for the lesser reactivity of larger arteries would be the dual effects theory proposed by Harper and Veshmukh[10]. They suggested that the larger vessels are more likely to be affected by neurogenic mechanisms, whereas the smaller vessels are more responsive to the metabolic demands of cerebral tissue. The finding which supports this proposal is that phenoxybenzamine will dilate larger vessels further when administered at MAP of 40 torr[9]. Thus, an increased sympathetic discharge accompanied by hemorrhagic hypotension would appear to limit the larger vessel response to the low MAP. Changes in vessel diameter during TMP-hypotension were different from those observed during hemorrhagic hypotension. TMP is known to interrupt adrenergic control of peripheral arteries due to blockade of sympathetic ganglia[11], and the cerebral circulation would appear to be no exception to this property. Therefore, it was suggested that greater increase in diameter of the artery Ⅲ during TMP-hypotension than during hemorrhagic hypotension and independent dilatation of arteries on vessel size during TMP-hypotension results from a blockade of resting sympathetic discharge in the larger arteries. Dilatation of artery I and Ⅱ during TMP-hypotension was less than that during hemorrhagic hypotension. This suggested that autoregulatory response of smaller arteries during TMP-hypotension was reduced by this drug, which may cause metabolic disturbance in the cerebral tissue[2]. The most striking difference among three techniques for induced hypotension was significant dilatation of the veins during NTP-hypotension, suggesting the direct dilatatory action of this drug on the veins[12]. Tateishi[1] resported that TMP did not change CBF and CSFP, while NTP caused an increase in CSFP without change in CBF. He stated that the dilatation of resistance vessels may not cause an increase in CSFP in normal intracranial compliance, while the dilatation of capacitance vessels may cause an increase in CSFP. The latter may be the case during NTP-hypotension, although definite conclusion can only be drawn from simultaneous measurement of CSFP and vessel diameter in the closed cranial cavity.

Dependence of arterial response to hypercapnia during normotension on vessel size had been documented[13] and reconfirmed with the present study. With hypercapnia the smaller arteries responded more vigorously than the larger ones. Wei et al[13] suggested that the differential responsiveness to CO_2 might be related to difference in the response of the larger vessels to sympathetic activation. It appears that the lesser response of the larger vessels is, to a major extent, due to neurogenically induced vasoconstriction which partially abolishes the vasodilatatory effects of CO_2 exerted by its local action .Harper and Glass[14] demonstrated that CO_2 responsiveness of CBF was abolished during hemorrhagic hypotension at MAP of 50 torr in the dog, while Häggendal and Johansson [15] observed some residual CO_2 responsiveness during hemorrhage at MAP of 60 torr in

the dog. Gregory et al[6] reported that during TMP-hypotension (36 torr) CBF did not decrease despite of hypocapnia. Contradictory results have been reported by Hamer et al[16] who showed that 5 % CO_2 increased CBF during TMP-hypotension (40 torr) in the dog. These discrepancies may be due to the different level of hypotension, or due to differencies in the method for CBF measurement. Russell[17] found that arteries did not dilate with hypercapnia during hemorrhagic hypotension at MAP of 30 to 40 torr in the rabbit. Gregory et al[6] found that there were no changes in diameter produced by CO_2 during either TMP-or NTP-hypotension (36 torr). In this study, however, CO_2 responsiveness was better maintained during hypotension with NTP than with TMP, when it was judged by the standardized per cent change in vessel diameter. The MAP in this study higher than that in their study may be the cause of difference (50 vs. 36 torr). It has been assumed that the absence of response to hypercapnia during hypotension is due to maximum dilatation of the vessels in response to the low MAP[6]. However, this is not likely because the difference of CO_2 responsiveness of arterial diameter exists between NTP-and TMP-hypotension at comparable level of MAP. One of the possible explanations would be that during TMP-hypotension a metabolic acidosis occurred in the cerebral extracellular fluid that abolished any response to hypercapnia, the pH being below the range of vascular responsiveness[6]. In the case of NTP, the metabolic acidosis might have been less severe due to better maintained cerebral perfusion[3], so that arteries could further dilate because the pH of the extracellular fluid could still change with alteration of $PaCO_2$ within the responsive range. The second explanation would be that TMP may be capable of pharmacologically denervating the cerebral vessels and changing the normal response to hypercapnia. It has been reported that hypercapnia produced reflex cerebral vasodilatation through arterial chemoreceptors and surgical removal of this pathway produced a decreased dilator response to hypercapnia[18].

Direct comparison of changes in the vessel diameter produced by hypotension and/or hypercapnia between the hemorrhage group and the other drug groups cannot be made, since occasional statistical differences were present. The reason for this difference is not known, but may be due to the different duration of surgery and anesthesia before measurement, although the vessels were selected at random and the experiments were performed in random order. However, there is no significant difference of control MAPs between the drug groups and background anesthesia was the same in all cats. Therefore, the difference between the TMP- and NTP-hypotension is exclusively the result of the drug's effect.

In conclusion, TMP and NTP have the differential effect on pial arteries and veins. CO_2 responsiveness of arteries was abolished during TMP-hypotension, but was maintained during NTP-hypotension.

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