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CO_2 Reactivity of Cerebral Vasospasm After Aneurysmal Subarachnoid Haemorrhage

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Summary

CO_2 reactivity of the brain vessels was investigated in 33 patients (Grade I–III after Hunt and Hess) with cerebral vasospasm after an aneurysmal subarachnoid haemorrhage (SAH) and after early operation within 72 hours. In all cases, transcranial Doppler sonography was used to measure flow velocities in the middle cerebral artery (MCA) and internal carotid artery (ICA) and vasomotor reactivity to CO_2 changes.

Vasospastic conditions lead to higher flow velocities through the narrow segment, lower peripheral stream resistance due to the poststenotic pressure drop and lower vasodilating capacities of arterioles under hypercapnia. In severe vasospastic conditions, the peripheral stream bed is already maximally dilated and the hypercapnic response is weak. On the other hand, the peripheral vascular bed reacts normally to hypocapnia in all vasospastic situations. Our results point out two dangerous conditions of vasospastic disease:

1) exhaustion of peripheral vasodilating capacities, and

2) hyperventilatory therapy.

Both of these situations can result in a reduction of CBF to brain tissue, mainly for two reasons:

1) In the former, a further increase in vasospasm cannot be compensated for anymore when the peripheral arterioles are maximally dilated, and

2) in the latter, hypocapnia produces a strong peripheral vasoconstrictor response with further reduction of CBF.

Keywords: Aneurysm; autorregulation; CO_2 reactivity; subarachnoid haemorrhage; transcranial Doppler sonography; vasospasm.

Introduction

Cerebral vasospasm (VSP) is one of the main complications after aneurysmal subarachnoid haemorrhage (SAH)[16]. Vasospasm has a typical course in onset and strenght[11] and is dependent on the amount of blood in the subarachnoid space[26] and on age. As is well known, vasospasm is only an angiographic image of basal cerebral arteries. In actuality, it is an oedema and thikkening of vessel walls, leading to stenosis of the vessel lumen. There are three haemodynamic effects resulting from the stenosis: 1) an increase in blood flow velocity through the narrow vessel segment, 2) a drop in poststenotic pressure, and 3) poststenotic dilation due vessel wall vibration[7, 10, 33].

The blood flow velocity increase can be easily measured with TCD atraumatically and correlates well with the increase of vessel stenosis [1, 11, 29, 33]. The poststenotic pressure drop cannot be measured directly, but we have an indirect parameter. As is well known, the peripheral vascular bed (arterioles) reacts very rapidly to vascular pressure changes, due to intact autoregulation [10, 30]. In low pressure vascular systems, the arteriolar diameter is dilated with a low stream resistance[8]; in high pressure vascular systems, the distal arterioles are constricted with higher stream resistance. Using the transcranial Doppler flow profile, we can get an impression of the amount of stream resistance in different vascular beds[25, 28]. There are different indicators of stream resistance, such as the pulsatility index or the stream resistance index according to Pourcelot[28]. The different resistance indices depend on the relation of diastolic to systolic blood flow velocity.

Peripheral vascular bed dilation is the compensatory answer to the pressure drop after the spastic segment, so that sufficient cerebral blood flow (CBF) can be maintained over the critical level[9, 15, 17, 20, 26, 27, 32]. When the compensatory capacity of the vasoregulatory mechanisms has been exhausted, CBF decreases, and VSP consequently becomes clinically symptomatic[4, 22, 23, 24]

CO_2 Reactivity

Changes in arterial pCO_2 influence brain perfusion. Hypercapnia leads to increased, hypocapnia to de-

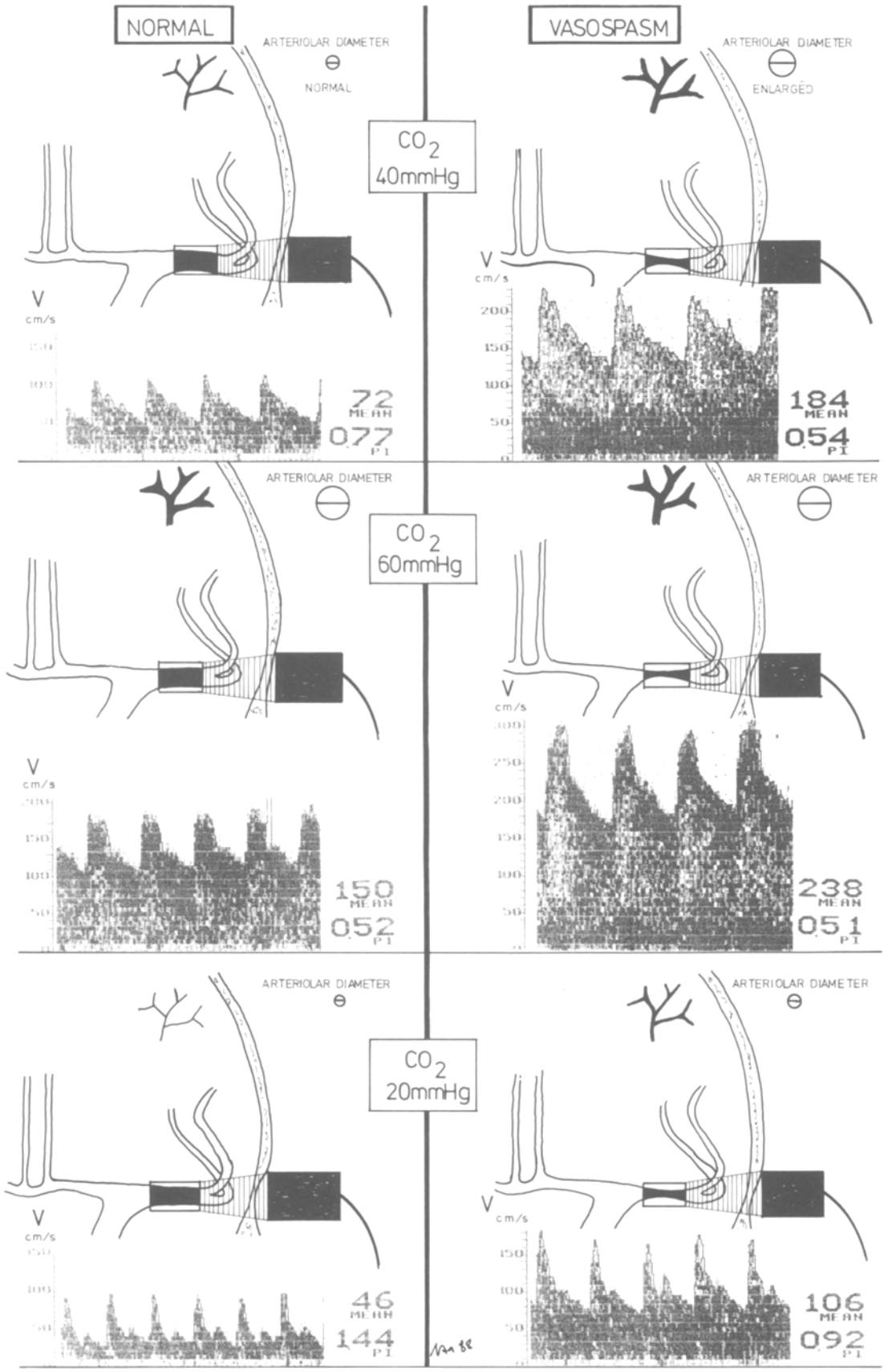

Fig. 1. CO_2 reactivity in normal and severe vasospastic conditions with schematic drawings of the diameter of basal middle cerebral arteries and peripheral arterioles

Table 1. *Mean Values of Flow Velocity Under Normal and Different Vasospastic Conditions and Their Changes During Hypercapnia and Hypocapnia*

		pCO_2: 40 mmHg	pCO_2: 60mmHg	pCO_2: 20mmHg	VASCULAR—REACTIVITY $\frac{\%\Delta V}{\Delta pCO_2}$ HYPERCAPNIA	HYPOCAPNIA
normal conditions 50–80cm/s n = 20	MEAN	58 — 70 — 84	104 — 136 — 166	22 — 41 — 66	2.0 — ↑4.7% — 7.5	0.71 — ↓2.1% — 3.0
	SYST.	90 — 108 — 130	140 — 182 — 220	54 — 84 — 110	1.3 — ↑3.4% — 5.2	0 — ↓1.1% — 2.1
	DIAST.	36 — 47 — 60	76 — 99 — 120	14 — 21 — 48	2.0 — ↑5.6% — 6.8	0.31 — ↓2.8% — 3.6
	P. I.	0.68 — 0.87 — 0.98	0.42 — 0.61 — 0.72	0.83 — 1.54 — 1.71		
mild VSP 80–120cm/s n = 12	MEAN	85 — 98 — 118	132 — 144 — 156	50 — 54 — 58	2.6 — ↑2.3% — 5.2	1.1 — ↓2.2% — 2.0
	SYST.	100 — 130 — 150	160 — 185 — 210	98 — 99 — 100	2.2 — ↑2.1% — 5.5	0.1 — ↓1.2% — 0.4
	DIAST.	44 — 64 — 75	100 — 104 — 108	25 — 29 — 34	2.1 — ↑3.1% — 7.2	1.1 — ↓2.7% — 3.2
	P. I.	0.62 — 0.67 — 0.72	0.54 — 0.56 — 0.62	0.92 — 1.29 — 1.09		
moderate VSP 120–160cm/s n = 11	MEAN	124 — 140 — 158	176 — 192 — 224	78 — 97 — 118	0.5 — ↑1.9% — 3	1.1 — ↓1.5% — 1.8
	SYST.	170 — 198 — 220	230 — 258 — 300	125 — 168 — 206	0.8 — ↑1.6% — 2	0.1 — ↓0.8% — 1.3
	DIAST.	92 — 115 — 125	120 — 158 — 161	50 — 66 — 80	0.3 — ↑1.0% — 2.5	1.4 — ↓2.1% — 2.5
	P. I.	— 0.59 — 0.73	0.52 — 0.52 — 0.66	0.86 — 1.05 — 1.33		
severe VSP >160cm/s n = 10	MEAN	184 — 214 — 250	238 — 253 — 280	106 — 136 — 172	0.6 — ↑0.9% — 1.4	1.5 — ↓1.8% — 2.1
	SYST.	240 — 285 — 300	300 — 304 — 315	180 — 208 — 260	0 — ↑0.5% — 1.2	0.5 — ↓1.1% — 1.5
	DIAST.	130 — 171 — 226	170 — 194 — 238	70 — 96 — 120	0.2 — ↑0.7% — 1.5	1.7 — ↓2.2% — 2.3
	P. I.	0.31 — 0.53 — 0.64	0.31 — 0.43 — 0.54	0.66 — 0.82 — 1.03		

creased perfusion[4, 5, 24, 25, 30]. Angiographically, the diameters of the basal arteries remain stable under varying pCO_2[3, 17]. The flow velocity changes measured in these vessels by Doppler sonography must therefore be due to regulations in the peripheral vascular territory where arterioles constrict under hypocapnia (flow deceleration in the basal artery) and dilate under hypercapnia (flow acceleration in the basal artery)[4, 12, 13, 14, 25, 29, 30].

Materials and Methods

We studied the pCO_2-dependent changes in blood flow velocity using a 2 MHz transcranial Doppler device with integrated frequency analyzer*. The insonation technique and the Doppler device have been described elsewhere[1, 2, 11, 12, 13, 25].

To obtain normal values, the CO_2 reactivity of healthy volunteers with ages between 20 and 30 years were investigated using transcranial Doppler sonography. The mean values are listed in Table 1.

Thirty-three patients with vasospastic conditions after an aneurysmal SAH and after early operation within 72 hours were investigated (Table 2). The patients were graded neurologically using the Hunt and Hess scale[18] in Grades I to III (Table 3). Patients with mass-occupying haemorrhages or infarction due to surgery or vasospasm seen in CT were excluded.

The amount of vasospasm is classified into three groups, according to flow velocities: mild vasospasm

Table 2. *Location of Aneurysm (n = 33)*

Arterial location of aneurysm	Cases
Middle cerebral	12
Anterior communicating	10
Posterior communicating	5
Internal carotid (bifurcation)	4
Basilar	1
Posterior inferior cerebellar	1

* EME Company, Ueberlingen, West Germany.

Table 3. *Transcranial Gradings of Vasospasm (VSP) and Neurological State*

Amount of VSP	Hunt/Hess grading scale		
	I	II	III
Mild VSP n = 12 80–120 cm/s	2	8	2
Moderate VSP n = 11 120–160 cm/s	4	5	2
Severe VSP n = 10 more than 160 cm/s	1	8	1

Table 4. *Mean Intracranial Pressure (ICP), Mean Arterial Systemic Pressure (SAP) and Cerebral Perfusion Pressure (CCP) Under Various pCO_2 Levels (n = 5)*

pCO_2 (mm Hg)	38 ± 2	60	20
Mean ICP (mm Hg)	5	38	− 5
Mean SAP (mm Hg)	90	116	65
CCP (mm Hg)	85	78	70

with flow velocities between 80–120 cm/s, moderate vasospasm with flow velocities between 120–160 cm/s and severe vasospasm with flow velocities over 160 cm/s (Tables 1 and 3). All measurements refer to MCA at 5 cm or to ICA at 5.5–6 cm recording depth. In each case, we evaluated the systolic, diastolic and mean flow velocity and the pulsatility index (PI). In addition, we calculated the systolic, diastolic and mean flow velocity reactivity, defined as the percentage flow velocity change divided by the pCO_2 decrease (hypocapnia) or increase (hypercapnia)[13, 21, 25, 31]. During examination of the CO_2 reactivity, the patient breathes via a Y-shaped mouthpiece, through which the inhaled and exhaled lots of air are separated from each other. End-exspiratory pCO_2 of the exhaled air is measured by an infrared analyzer**. The recording starts under normocapnia (pCO_2 38 ± 2 mm Hg). Hypocapnia is induced by spontaneous hyperventilation; step-wise reduction of end-exspiratory pCO_2 drops to 19–22 mm Hg. Hypercapnia is induced by application of an air-CO_2-mixture. End-exspiratory pCO_2 is raised in steps to over 60 mm Hg.

** Normocap Datex Instrumentations Corp., Helsinki, Finland.

MCA blood flow velocity was measurd continuously. Each time, 2 minutes after a certain steady-state is reached, the corresponding flow velocities are documented.

During this manoeuvre in 5 cases the intracranial pressure (ICP) was recorded using unilateral Gaeltec probes*** which had been inserted epidurally over the frontal convexity. The systemic arterial pressure (SAP) was measured continuously through an arterial catheter in the radial artery as well as the heart rate. The signals were recorded on computer-generated printouts (Fig. 3).

Results

Normal Values

In cases of healthy people and normocapnic conditions, the mean flow velocity in the middle cerebral artery (MCA) at a recording depth of 50 mm was 70 cm/s with a pulsatility index (PI) of 0.87 (Table 1). Under hypercapnic conditions (60 mm HgpCO_2), the mean flow velocity increased up to 136 cm/s and the PI dropped to 0.61 with a systolic value of 182 cm/s and a diastolic one of 99 cm/s (Figs. 1 and 2). This situation is, therefore, the maximal dilation state that a healthy peripheral vascular bed can reach. To get a better idea of this phenomenon, we can say that in normal individuals the mean flow velocity increases 4.7% for each mm Hg of rising pCO_2, the systolic flow velocity 3.4% and the diastolic flow velocity 5.6%. This is the so-called vascular reactivity (Table 1).

During hyperventilation the pCO_2 decreases, and at 20 mm Hg, a mean flow velocity of 41 cm/s can be recorded with a PI of 1.54; systolic and diastolic flow velocity were respectively 84 and 21 cm/s (Figs. 1 and 2). Under these hypocapnic conditions, the vascular reactively during progressive pCO_2 changes from 40 to 20 mm Hg was represented by a 2.1% decrease for the mean flow velocity, by a 1.1% decrease for the systolic flow velocity and by 2.8% for the diastolic flow velocity (Table 1).

Vasospastic Conditions

The severity of vasospasm did not correlate well with the clinical state (Table 3). Some patients with mild vasospasm had Hunt and Hess grading of III, while some patients with severe vasospasm had Hunt and Hess grading I.

*** Gaeltec probes manufactured by Medical Measurements, Inc., Hackensack, New Jersey.

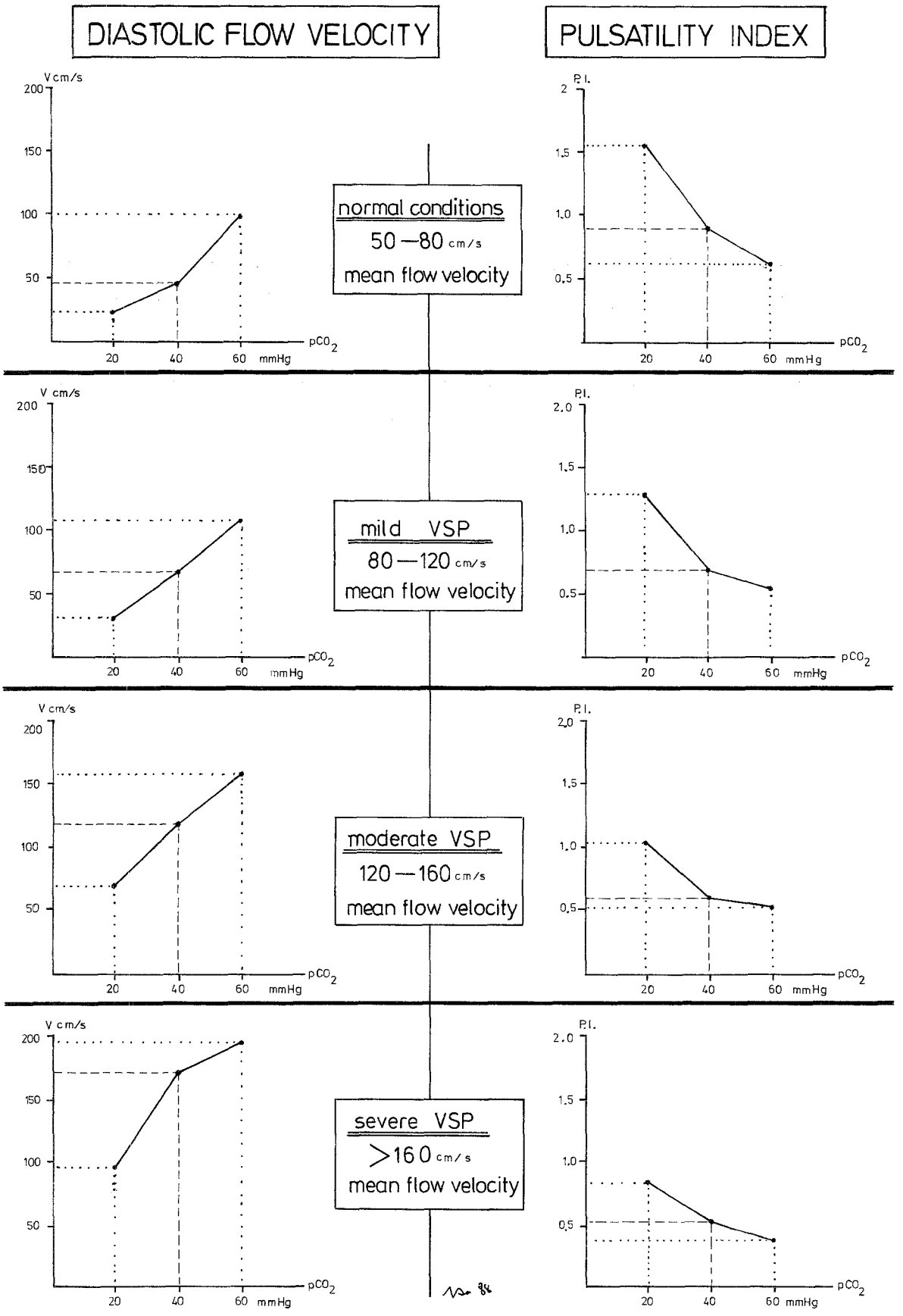

Fig. 2. Mean values diastolic flow velocity and pulsatility index (PI) under CO_2 reactivity improvement in normal and different vasospastic conditions

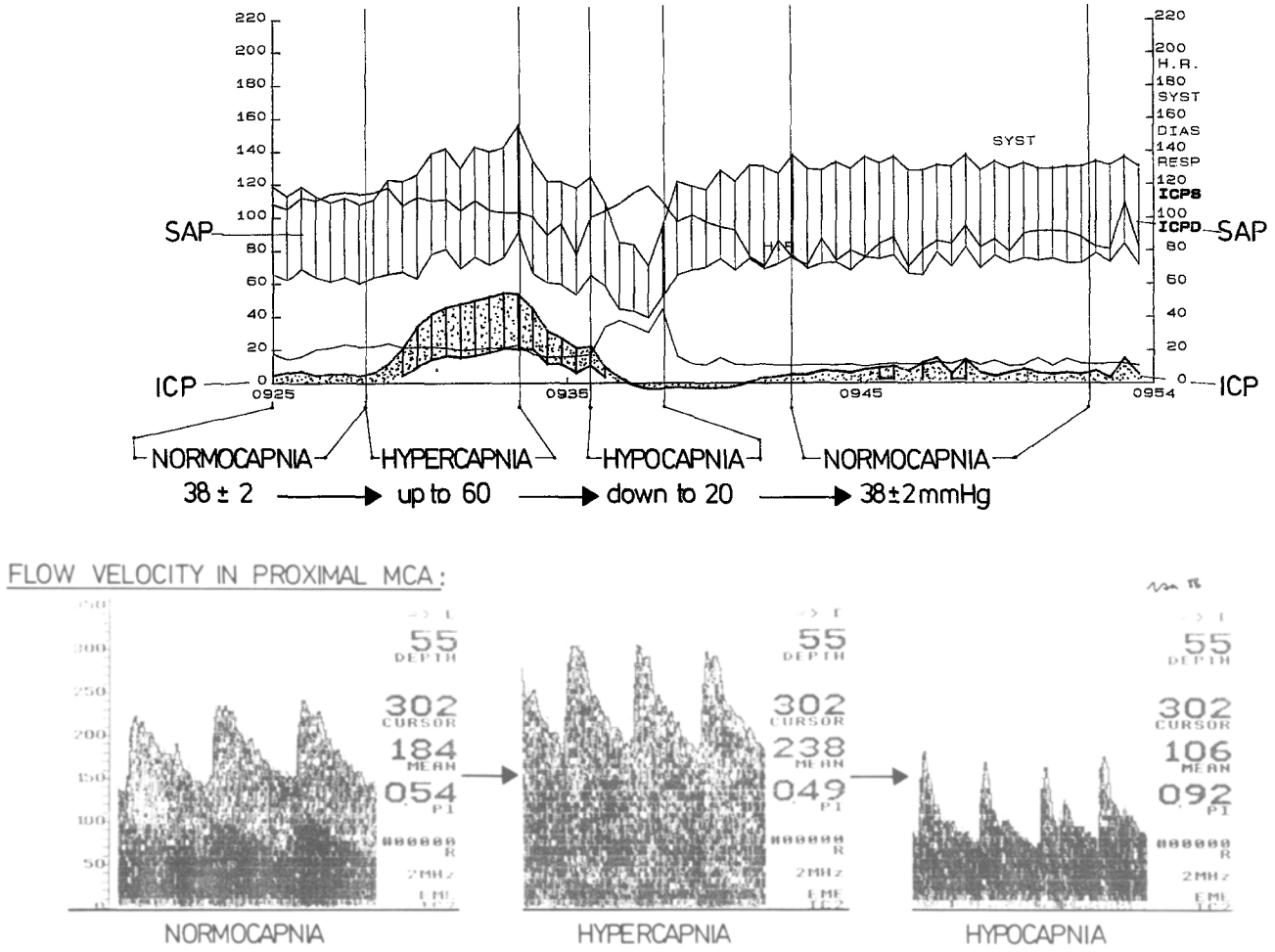

Fig. 3. CO_2 reactivity of flow velocity in middle cerebral artery (MCA) in severe vasospasm and its correlation with intracranial pressure (ICP) and systemic arterial pressure (SAP) (computer printout)

1. Mild Vasospasm:

In mild vasospasm and normocapnic conditions, the mean flow velocity was 98 cm/s with a lower PI of 0.67. Under hypercapnia, the mean flow velocity increased to 144 cm/s with a PI of 0.56.

The increase of flow velocity for each mm Hg of rising pCO_2 was limited to 2.3%. With hyperventilation, the mean flow velocity decreased to 54 cm/s with an unchanged vascular reactivity of 2.2% for each mm Hg of decreasing pCO_2. Still, the stream resistance does not rise up the levels seen under normal conditions, reaching only a PI of 1.29. Obviously, this is a sign of slight limitaion of the arteriolar reactivity (Fig. 2, Table 1).

2. Moderate Vasospasm:

There is a further increase of mean flow velocity in moderate vasospasm from 120—160 cm/s with mean values of 140 cm/s under normocapnia. The pulsatility index is further decreased to 0.59, showing diminished stream resistance. During hypercapnia, the mean flow velocities rise up to 192 cm/s with a limited reactivity rate of 1.9% for each mm Hg of rising pCO_2. With hypocapnia up to 20 mm Hg, the mean flow velocity decreased to 97 cm/s with a further decrease of vascular reactivity of 1.5% for each mm Hg of changing pCO_2. The resistance index during hypocapnia is furthermore diminished to 1.05, showing that arterioles can constrict further under these conditions (Fig. 2, Table 1).

3. Severe Vasospasm:

In severe vasospastic conditions, our patients mean flow velocity at 38 ± 2 mm Hg pCO_2 was 214 cm/s with a PI of 0.53, even lower than in healthy individuals under hypercapnia. We can presume that their peripheral vascular bed was maximally dilated and had

no chance of further dilation even under hypercapnic conditions.

According to this observation, the PI at 60 mm Hg pCO_2 was only a little lower (0.43) than that recorded at 38 ± 2 mm Hg pCO_2 (0.53). Of course, vascular reactivity was also quite far from normality during CO_2 inflation: the mean flow velocity increased only 0.9% for each mm of rising pCO_2, reaching a value of 253 cm/s; systolic flow velocity increased 0.5% with a maximal peak of 304 cm/s; diastolic flow velocity increased 0.7% with a maximal value of 194 cm/s.

The peripheral vascular bed seemed to be exhausted in its vasodilating capacities, but its response to vasoconstrictor stimuli was not so weak. In fact, the PI variations during hypocapnia were pronounced: from 0.53 (38 mm Hg pCO_2) to 0.82 (20 mm Hg pCO_2); the comparative evaluation of vessel reactivity in normal and severe vasospastic conditions supports this observation even more: a 2.1% decrease of mean flow velocity in healthy people and a 1.8% decrease in vasospastic conditions; a 1.1% decrease of systolic flow velocity in healthy people and 1.1% in vasospastic conditions; a 2.8% decrease of diastolic flow velocity in healthy people and 2.2% in vasospastic conditions. It is quite clear that vasoconstrictory response during severe vasospasm is almost normal (Figs. 1 and 2; Table 1).

4. Time Course of CO_2 Reactivity:

The normalization of severe vasospasm over two to four weeks in the basal cerebral artery was followed by a parallel improvement of the peripheral haemodynamic situation of arteriolar reactivity. The CO_2 reactivity improved over the moderate and mild vasospastic condition and reached normal conditions when the mean flow velocity had also normalized.

5. CO_2 Reactivity and Intracranial Pressure (ICP) and Cerebral Perfusion Pressure (CCP):

In 5 patients, intracranial pressure as well as systemic arterial pressure were monitored during CO_2 reactivity, so that cerebral perfusion pressure could be calculated (mean SAP − mean ICP = mean CCP). During hypercapnia up to 60 mm Hg pCO_2, the mean ICP rose about 660% ± 32 and the mean SAP rose about 29% ± 8, so that the CPP was reduced by about 8% + 1.5. In hypocapnic conditions up to 20 mm HgpCO_2, the mean ICP was reduced by about 200% + 15 and the mean SAP was lowered about by 28 ± 6, therefore reducing the mean CCP by about 18% ± 3 (Fig. 3).

Discussion

The amount and evolution of vasospasm can be easily recorded with transcranial Doppler sonography as the increase in flow velocity correlates very well with the grade of the narrow segment of basal cerebral arteries[1, 11, 29]. According to other authors, we have refined the categorization of the Doppler flow velocites for clinical practice in low, moderate and severe vasospasm[11, 29]. Only MCA and the supraclinoid portion of the interal carotid artery (ICA) were recorded, as it is known that in A1 and P1 segments, the flow velocity shows only minor changes[11]. All recordings were done after clipping the aneurysm during early operation (in the first 72 hours after SAH) as it is known that vasospasm occurs after 4 to 5 days following SAH[15, 16, 29].

CO_2 reactivity evaluation of brain vessels in patients with vasospasm after an aneurysmal SAH have enhanced the following haemodynamic findings:

1) a pre-existant vasodilation of arterioles due to the poststenotic pressure fall, with weak further dilating capacity under hypercapnia, and

2) a quite normal vasoconstrictor response under hypocapnia.

The most meaningful parameters in detecting the stream resistance and vasomotor response of the peripheral vessels are the PI values and the diastolic flow velocity changes under hyper- and hypocapnia[6, 7, 25]. Until now, the PI was not taken into consideration for evaluating the extent of vasospasm. A PI around 0.5 seems to represent the state of maximal peripheral vasodilation, since it was reached by healthy people during hypercapnia, and it seems evident that the starting normocapnic PI value of patients with severe vasospasm is very close to that value. The vessels are already maximally dilated and cannot dilate more (Fig. 2). This fact is proven by comparing the diastolic reactivity in healthy people with that in severe vasospastic conditions. In the former, diastolic flow velocity rises 6.2% for each mm of pCO_2 increase, while in the latter it can rise only 0.7%. On the other hand, peripheral vasoconstrictor response under hypocapnia is preserved and is very similar in normal and severe vasospastic conditions (2.7% for each mm CO_2 decrease in healthy people versus 2.0% in severe vasospastic conditions)[4, 32] This observation means that vasoconstrictor capacity is quite strong, even if it cannot produce peripheral stream resistance as high as in normal subjects (see PI values), but this is due to the pressure drop after the vasospastic segment and not to a weaker vasoconstrictor response.

Our findings suggest that when the peripheral vascular bed has already reached its utmost dilating capacities, the CBF is close to being critical, even if the amount of vasospasm in basal vessels does not appear so severe. At this time, in fact, a moderate reduction of the basal vessel lumen with a further peripheral pressure drop cannot be compensated for anymore and leads to ischaemia. On the other hand, vasospastic conditions do not become too dangerous if peripheral vasodilating capacities are preserved.

Our investigations have shown that flow velocities of patients with severe vasospasm can be reduced by severe hyperventilation. This is very dangerous because the volume flow as well as the CPP is reduced, which jeopardizes brain tissue. Therefore, severe hyperventilation and hypocapnia (as is often found in these patients) is dangerous, as is also a decrease of systemic arterial pressure in vasospastic conditions (Fig. 3, Table 4).

As soon as the vasospastic situation in the basal vessels improves, diastolic flow velocity reactivity and pulsatility index values under the CO_2 conditions normalize, proving that the previous weak response to hypercapnia was transient and caused by a critical haemodynamic situation.

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