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A Severe Vicious Cycle in Uncontrolled Subarachnoid Hemorrhage: the Effects on Cerebral Blood Flow and Hemodynamic Responses upon Intracranial Hypertension

Chain-Fa Su[1], Yi-Ling Yang[2], Ming-Che Lee[3], and Hsing I Chen[4]

[1]*The Division of Neurosurgery and* [3]*General Surgery*
Department of Surgery and [4]*Institute of Medical Science*
Tzu Chi Hospital and University
Hualien
and
[2]*Institute of Biotechnology*
National Chia-Yi University
Chia-Yi, Taiwan, R.O.C.

Abstract

In subarachnoid hemorrhage (SAH), Cushing postulated that the increase in systemic arterial pressure (SAP) in response to elevation of intracranial pressure (ICP) was beneficial to cerebral perfusion. However, in uncontrolled SAH, the increased SAP may cause more bleeding into the subarachnoid space and further increase the ICP. We created an animal model to simulate SAH by connecting a femoral arterial catheter to the subarachnoid space. The global cerebral blood flow (CBF) was measured with a venous outflow method. The purposes were to observe the CBF change under the simulated SAH, and to evaluate the effects of an adrenergic blocker and a vasodilator. In addition, spectral analysis of the aortic pressure and flow was employed for the analysis of hemodynamic changes at various ICP levels. When the femoral arterial blood was allowed to flow into the subarachnoid space, the ICP was elevated. The Cushing response to increased ICP caused an increase in SAP. A vicious cycle was generated between ICP and SAP. The CBF under the vicious cycle was greatly depressed. The dog developed pulmonary edema (PE) within 5 mins. An α-adrenergic blocker (phentolamine) and a vasodilator (nitroprusside) were beneficial to the reduction of SAP and ICP, improvement of CBF, and prevention of PE. Hemodynamic analysis revealed that graded increases in ICP caused increases in SAP, total peripheral resistance, arterial impedance, and pulse reflection with decreases in stroke volume, cardiac output and arterial compliance. The hemodynamic changes may contribute to acute left ventricular failure that leads to pressure and volume loading in the lung circulation, and finally acute PE.

Key Words: cushing response, intracranial pressure, systemic arterial pressure, cerebral blood flow, hemodynamic changes, vicious cycle, adrenergic blocker, vasodilator

Introduction

Subarachnoid hemorrhage (SAH) is a serious clinical problem and requires intensive care (13, 27, 28). Cushing, in the early 20th century (8, 9), found that intracranial hypertension (ICH) provoked systemic hypertension in dogs. Many laboratories including ours, have investigated the cardiovascular

Corresponding author: Hsing I Chen, MD, Ph.D. Professor, Institute of Medical Science and Department of Physiology, Tzu Chi University, 701, Section 3, Chung-Yang Road, Hualien 97004, Taiwan, R.O.C. Phone: 886-3-8560824, Fax: 886-3-8573053, E-mail: chenhi@mail.tcu.edu.tw
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and pulmonary sequelae following ICH in animal and human subjects (1-3, 6, 13-16, 18, 27, 29). Cushing postulated that the increase in systemic arterial pressure (SAP) was beneficial to the cerebral perfusion in the face of ICH. Intracranial hypertension or hemorrhage caused by cerebral compression and rupture of cerebral vessels or aneurysm could result in severe outcome (3, 18). The increased SAP may create more bleeding into the subarachnoid space and thus forms a vicious cycle between intracranial pressure (ICP) and SAP. Whether the cerebral perfusion under this condition is retarded or improved is unknown. In the present study, we designed a method that simulates SAH in anesthetized dogs. We found that the marked SAP elevation in response to ICH may even be detrimental to brain perfusion. Termination of the vicious cycle at the right time, use of sympathoadrenergic blocker, and vasodilator can prevent the advancement of the vicious cycle and improve the cerebral blood flow (CBF). In addition, the hemodynamic changes including the steady and pulsatile components were determined under various levels of ICP.

Materials and Methods

Preparation for SAH and Measurement of CBF

Mongrel dogs weighing 10 to 12 kg were used. They were kept in the University Animal Center for more than 10 days after they were purchased from the National Animal Center. A high nutritional diet was given. The use and experimentation of the animals were approved by the University Committee of Laboratory Animal Center. For the acute experiments, the dog was anesthetized with an intraperitoneal sodium pentobarbital (40 mg/kg). Figure 1 illustrates the experimental set-up for a simulation of SAH. The skull in the temporal region was drilled to open a small hole in order to insert two silicon tubings (internal diameter 2 mm) into the subarachnoid space. One cannula was used to measure the ICP. Another was connected to a femoral arterial catheter. The second silicon tubing was inserted into the transverse venous sinus through the cisterna magna to drain the cerebral outflow (26). The latter was measured with an electromagnetic flowmeter (Carolina Medical Electronics Inc., King, NC., USA). The venous outflow was collected in a reservoir which was placed in a constant temperature (37 ± 1°C) water bath. The venous blood was returned to a cannulated femoral vein through a roller pump. The femoral arterial catheter was used to produce SAH. The silicon tubing from the femoral artery to the subarachnoid space was initially clamped. The release of the clamp allowed the femoral arterial blood to flow into the subarachnoid space and thus created a condition similar to

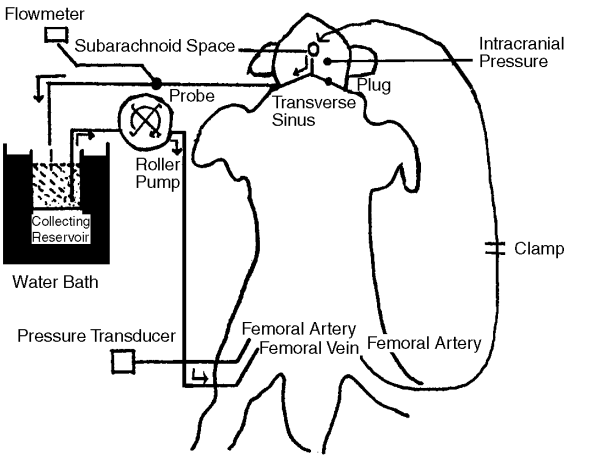

Fig. 1. A schematic representation of the experimental set-up for a simulation of subarachniod hemorrhage (SAH) and measurement of cerebral blood flow (CBF).

clinical SAH. The SAP was recorded from a side arm near the femoral arterial catheter. ICP and SAP were monitored with pressure transducers and recorded on a polygraph recorder (Power Lab, AD Instruments, Mountain View, CA., USA). Bilateral cervical vagus nerves were isolated at the neck region for subsequent section in order to avoid the vagal influence. Fluid or drugs were administered from a side arm close to the femoral vein catheter. Heparin (1000 unit/kg) was given for anticoagulation.

At the end of the experiment, the lung was removed, weighed and inspected grossly. Histological examinations were performed using tissue section and stain with hematoxylin and eosin (H&E).

Measurement and Analysis of Steady and Pulsatile Hemodynamic Parameters

In another series of experiments, the steady and pulsatile hemodynamic parameters were determined. A Millar catheter with two high-fidelity pressure sensors and one flow velocity sensor (Millar Instruments Inc, Model SPR-407, Size 5-6 F) was used to measure the aortic pressure and flow. The catheter was inserted via an isolated carotid artery into the ascending aorta. A lead II electrocardiography (ECG) was also monitored. The aortic pressure, flow wave, and ECG were continuously displayed on polygraph and tape recorder (TEAC, Model MR-30) for off-line analysis.

Several previous studies from our laboratory have described the analysis and calculation of arterial hemodynamic parameters (4, 19, 24). The steady components included aortic pressure (AP), heart rate (HR), stroke volume (SV), cardiac output (CO), and total peripheral resistance (TPR). Spectral analysis

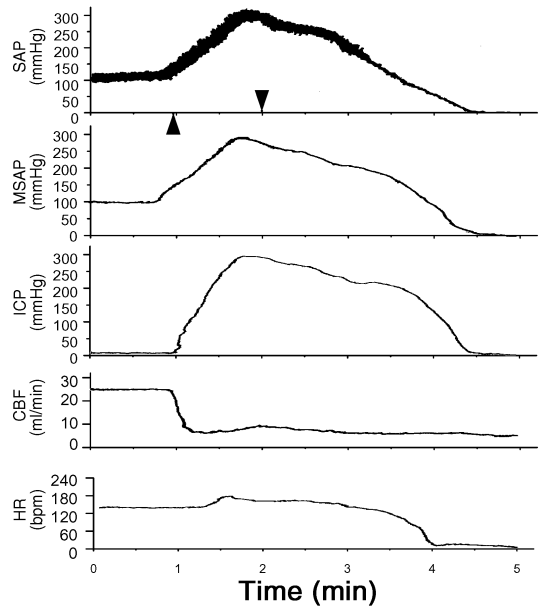

Fig. 2. The changes in systemic arterial pressure (SAP), mean SAP (MSAP), intracranial pressure (ICP), cerebral blood flow (CBF), and heart rate (HR) in an anesthetized and vagotomized dog following SAH. The clamp between the femoral artery and subarachnoid was released (arrow) to allow the femoral arterial blood to flow into the subarachnoid space. Note the marked increases in SAP, ICP with a decline in CBF. The clamp was applied at 1 min later (second arrow). The abbreviations in the other figures are the same as those in this Fig.

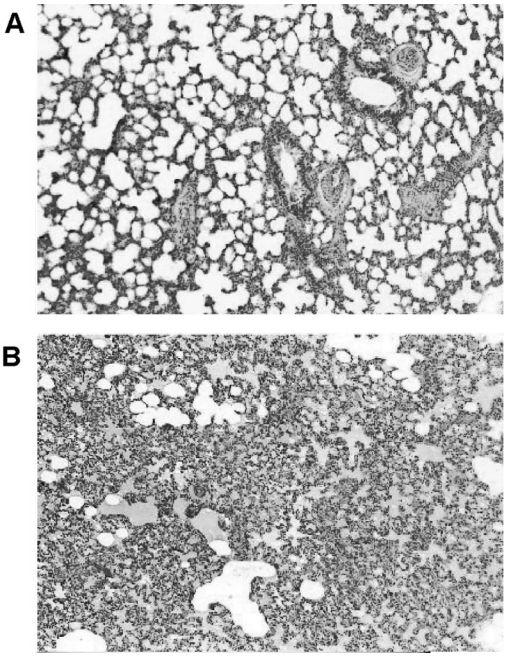

Fig. 3. Histopathological micrography (A and B, hematoxylin and eosin stain, original magnification ×100) in a representative dog. Before or without induction of simulated subarachnoid hemorrhage (SAH). The histological picture showed normal alveolar configuration (A). Following uncontrolled SAH, severe lung edema was observed (B). The normal alveolar structure was disappeared.

was used to obtain the pulsatile hemodynamic parameters such as aortic characteristic input impedance (Zc), compliance (C), forward pulse wave (P_f), and pulse wave reflection (P_b).

In this series of experiments, the ICP was elevated by slow infusion of arterial blood into the subarachnoid space. Intracranial pressure was maintained at 50, 100, and 150 mmHg to observe the changes in hemodynamic parameters at various extents of ICH.

Statistical Analysis

All data are expressed as mean ± SE. One-way analysis of variance and Scheffe's comparison were used to evaluate differences related to groups receiving different interventions and hemodynamic parameters at various levels of ICP. A P value of less than 0.05 was considered to be statistically significant.

Results

SAH on the ICP, HR, and CBF

Figure 2 illustrates the changes in SAP, ICP, HR, and CBF in a representative dog with bilateral cervical vagotomy. Vagotomy was done to avoid the interference of bradycardia on the SAP changes. The release of the clamp (arrow) caused bleeding from the femoral artery into the subarachnoid space. The insult increased the ICP and generated a Cushing response causing an increase in SAP. A vicious cycle was produced between ICP and SAP. In 10 dogs, the SAP and ICP reached a peak level at 258 ± 12 mmHg. At this time, CBF was dramatically reduced to nearly zero. The clamp was applied within 1 minute (arrow) to stop the vicious cycle. However, it was too late. The CBF improvement was only slight, and the animal died with rapid decreases in SAP and HR. Subsequently, pulmonary edema (PE) developed in these dogs as evidenced by the increase in lung weight (LW). The average LW was 187 ± 19 g (mean ± SE, n = 10). The LW/body weight ratio (LW/BW ×100) was 1.72 ± 5.4 (mean ± SE, n = 10). The values are significantly higher ($P < 0.01$) than the normal values (LW, 57 ± 13 g; LW/BW ×100, 0.58 ± 0.23) obtained in 10 dogs sacrificed under deep anesthesia. Pathological examination also revealed hemorrhagic edema in the lung (Fig. 3).

Figure 4 shows clamping the femoral arterial catheter to the subarachnoid space at 10 seconds after

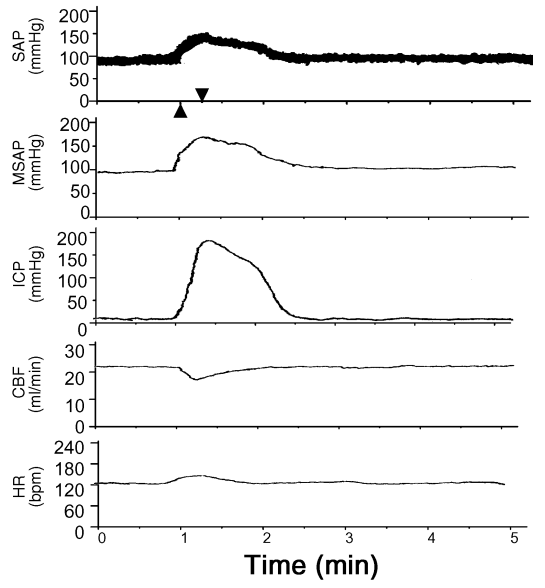

Fig. 4. The figure shows that release (first arrow) of the arterial clamp causes increases in SAP, MSAP, and ICP. Application of the clamp (second arrow) 10 sec later was able to stop the vicious cycle between the SAP and ICP. Note that the CBF was decreased slightly soon after the clamp release, but became stable after the application of the clamp.

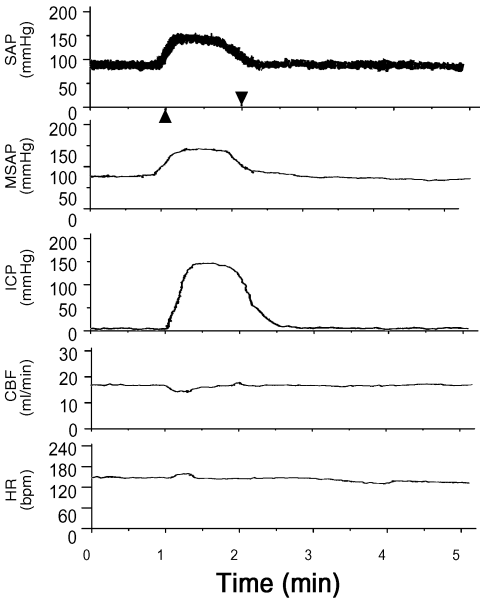

Fig. 5. The effects of an α-adrenergic, phentolamine, on the changes in SAP, MSAP, ICP, and CBF. Phentolamine infusion was able to reduce the increases in SAP and ICP and to improve the CBF.

the release of the clamp. Termination of the vicious cycle achieved at this point when SAP and ICP had not yet reached the maximum. The CBF decreased slightly and then became stable again. In 10 dogs, the SAP and ICP reached a peak at 151 ±21 mmHg. The level was significantly less than that in the case of clamping the catheter at one min after the release of the clamp ($P < 0.01$). After a slight decrease at the onset of clamp release, the CBF stabilized at a level of 18.4 ± 4.8 ml/min, which was close to the normal level (21.4 ±5.2 ml/min, $P > 0.05$). Figures 5 and 6 demonstrated, respectively the effects of an α-adrenergic blocker, phentolamine (10 mg/kg/min) and a vasodilator, nitroprusside (30 mg/kg/min), on the interaction of ICP, SAP, and CBF. Phentolamine and nitroprusside were infused through the femoral vein three mins before the release of the clamp and continuously throughout the course of 5 min. These two agents reduced the increase in SAP and ICP. Accordingly, the CBF was depressed only slightly. In 10 dogs with the use of phentolamine, the maximal increases in ICP and SAP were 148 ±22 mmHg, and the CBF was 17.2 ±3.8 ml/min. In 10 other dogs, nitroprusside infusion caused the ICP and SAP levels to remain stable at 154 ± 19 mmHg and CBF at 16.8 ± 2.8 ml/min.

When the vicious cycle between SAP and ICP was stopped at the right time (10 seconds), lung edema did not occur. The average LW and LW/BW

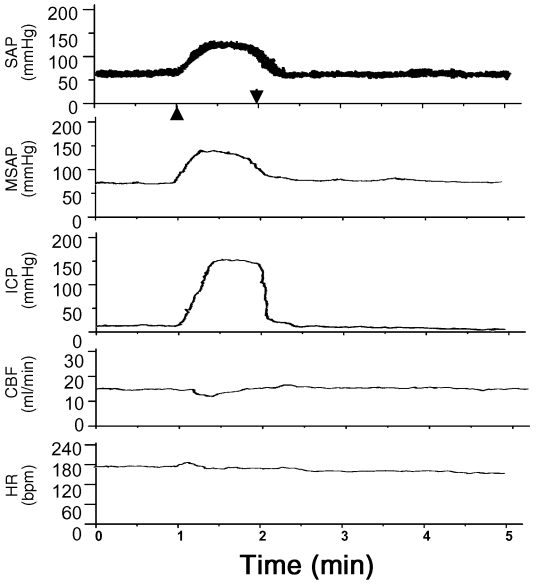

Fig. 6. The effects of a vasodilator, sodium nitroprusside, on the changes in SAP, MSAP, ICP, and CBF. Nitroprusside infusion exerted effects similar to that of phentolamine infusion.

ratio ×100 were 62 ± 14 g and 0.62 ± 0.25, respectively. These values were not significantly different from the normal values ($P > 0.05$). The use of phentolamine and nitroprusside also prevented the development of lung edema. The LW and LW/BW ratio ×100 were 58±5 and 0.60±0.10, respectively with the use of phentolamine (n = 10), and 59 ± 11 and 0.61 ± 0.19,

Table 1. The arterial hemodynamics of steady component at various levels of intracranial pressure

	Aortic pressure (mmHg)			PP	HR	SV	CO	TPR (×100)
	APs	APm	APd	(mmHg)	(beats · min^{-1})	(ml)	(ml · min^{-1})	(Dyne · s · cm^{-5})
ICP (mmHg)								
Control	116 ± 6	93 ± 4	81 ± 4	35 ± 3	124 ± 12	15.8 ± 2.2	1959 ± 44	3703 ± 32
50	142 ± 8*	115 ± 7*	102 ± 6*	40 ± 5	121 ± 11	14.3 ± 2.8	1716 ± 32*	5227 ± 44*
100	163 ± 9*	128 ± 8*	111 ± 7*	52 ± 5*	103 ± 12*	11.2 ± 2.4*	1154 ± 42*	8652 ± 52*
150	186 ± 10*	149 ± 7*	130 ± 6*	56 ± 6	101 ± 14	9.4 ± 2.2	949 ± 36*	12325 ± 40*

APs, APm, APd, aortic pressure corresponding to systolic, mean and diastolic pressure; PP, pulse pressure; HR, heart rate; SV, stroke volume; CO, cardiac output; TPR, total peripheral resistance; ICP, intracranial pressure. Data are mean ± SE (n = 10). *$P < 0.05$ *vs*. the values at lower ICP

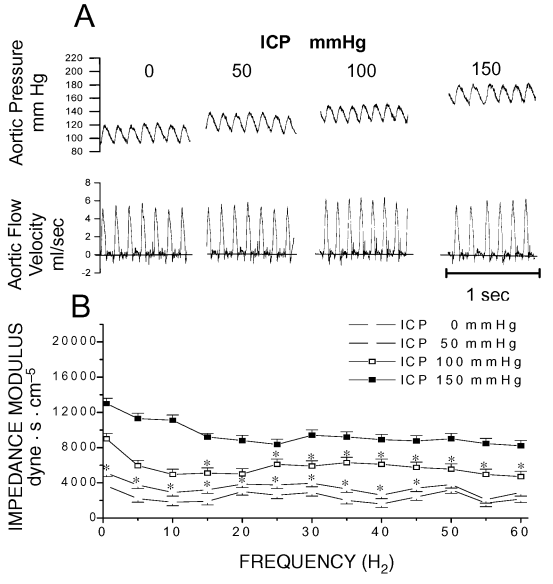

Fig. 7. The aortic pressure and flow waves (A) and impedance modulus (B) at various levels of ICP.

respectively, with the use of nitroprusside (n = 10). These values essentially did not differ from the normal values ($P > 0.05$). Chest radiography and pathological examination did not reveal significant lung changes.

Hemodynamic Responses to Various ICH

Figure 7A depicts the changes in aortic pressure (AP) and aortic flow (AF) waves in a representative dog subjected to various levels of ICP. The arterial pressure was progressively elevated when ICP was increased from control (close to 0 mmHg) to 50, 100, and 150 mmHg. Table 1 summarizes the hemodynamic parameters of steady components including aortic pressure (AP) at the systolic, mean and diastolic phases, pulse pressure (PP), HR, stroke volume (SV), cardiac output (CO), and total peripheral resistance (TPR). Intracranial hypertension significantly increased the AP and TPR. The increase in PP was significant at an ICP of 100 mmHg. The HR and SV were significantly reduced at an ICP of 100 mmHg. Cardiac output was reduced at ICP levels of 50, 100 and 150 mmHg. Figure 7B shows the impedance modulus plotted against frequency. The impedance modulus was also elevated at various ICP levels. Zc, Cm, P_f, and P_b were used to represent the hemodynamics of pulsatile components (Table 2). With the increase in ICP, the Zc, and P_b were significantly elevated, while P_f was decreased. When ICP was increased above 100 mmHg, the arterial compliance at mean AP (Cm) was reduced to about one-third of the value at ICP of control level. The data indicates that ICH affects both the steady and pulsatile hemodynamics.

Discussion

The Vicious Cycle Between SAP and ICP during SAH

The Cushing response of SAP to increased ICP was later demonstrated as a consequence of central sympathetic activation, which causes systemic vasoconstriction that results in systemic hypertension (2, 3, 5, 6). In addition to a significant brain stem damage caused by ICH and uncal herniation, various complications such as cerebral vasospasm, pulmonary edema, and myocardium damage might be caused by ICH (2, 3, 13, 23, 27). The original concept of the Cushing response that an increase in SAP was beneficial to brain perfusion was challenged by the present experiment. We found that bleeding into the subarachnoid space created a vicious cycle between ICP and SAP. In other words, the increase in arterial pressure caused more SAH. The more severe the SAH, the worse the CBF. We have demonstrated probably one of the most dramatic positive feedback in an extreme pathophysiological condition of uncontrolled SAH. This

Table 2. The arterial hemodynamics of pulsatile component at various levels of intracranial pressure

	Zc (Dyne · s · cm^{-5})	Cm (ml · mmHg)	Pf (mmHg)	Pb (mmHg)
ICP (mmHg)				
Control	264 ±26	1.9 ±0.2	23.4 ±1.6	16.8 ±1.2
50	348 ±22*	1.1 ±0.4*	19.2 ±1.2*	24.6 ±1.4*
100	424 ±30*	0.6 ±0.5*	16.4 ±1.1*	32.8 ±2.0*
150	562 ±42*	0.5 ±0.6	12.2 ±1.0*	42.6 ±2.2*

Zc, characteristic input impedance; Cm, arterial compliance at mean aortic pressure; P_f and P_b, forward and backward components of pressure wave; ICP, intracranial pressure. Data are mean ± SE (n = 10). *$P < 0.05$ *vs*. the values at lower ICP

vicious cycle was detrimental to the cerebral perfusion. Termination of the vicious cycle at the right time can prevent the decline in CBF. This practice in clinical condition is not easy to achieve, because the procedure has to be accomplished within minutes or even seconds. In clinical practice, the formation of a clotting thrombosis and/or cerebral vasospasm can stop the bleeding from the disrupted aneurysm or traumatic large arterial vessels. In the present study, we used heparin to avoid clotting and α-adrenergic blocker as well as vasodilator to minimize cerebral vasoconstriction or vasospasm. It is noteworthy that the ICP elevated to a level as high as 258 mmHg. This remarkable high level of ICP may be unusual in general clinical practice. The classic Cushing studies, he elevated the ICP above 120 mmHg (8, 9). In our previous animal study (6), we elevated the ICP to a level above 175 mmHg for the analysis of systemic and pulmonary hemodynamics in response to ICH. We also revealed in a recent clinical report that in some cases with rupture of cerebral myocotic aneurysm, the ICP reached a level as high as 180 mmHg and the patients developed fulminant PE (18). We would like to stress that a high ICP may occur in certain cases with SAH, albeit not common. It is also possible that patients with blood coagulation disorder may develop uncontrolled SAH with an extreme high ICP. These cases might have died of cerebral ischemia or pulmonary edema before reaching the hospital. Finally, we used the uncontrolled SAH model on purpose to create a vicious cycle between ICP and SAH. Although the model may not be highly relevant to clinical practice, it provides a pathophysiological model for the understanding of the occurrence of a positive feedback leading to severe vicious cycle.

Our experimentation also suggest that in the case with suspected SAH, the use of α-adrenergic blockers and vasodilators may be a choice for the prevention of severe SAH and decrease in CBF. In support of the contention of our findings, several previous studies suggested that an increase in SAP enhanced the cerebral vasospasm and worsened the perfusion (21, 22). Many laboratory studies also recommended the use of isoproterenal, phenoxybenzamine, and other vasodilators to reduce the SAP that improved CO and CBF during SAH (11, 12). In contrast, acute hypertension induced by dopamine caused CBF reduction in case of SAH (10).

Early work from our laboratory (1-3, 5) found that ICH induced by cerebral compression resulted in severe systemic and pulmonary hypertension followed by fulminating pulmonary edema in rats. These changes were abolished by sympathoadrenergic blocking agents such as ganglionic blockers (hexamethonium and pentolinium), neuronal blocker (bretylium), norepinephrine depleter (reserpine), and α-adrenergic blockers (phentolamine and phenoxybenzamine). There is evidence that the increase in blood norepinephrine and epinephrine concentrations results in a severe outcome in a traumatic brain injury (32).

Many hemorheological studies (17, 25, 30, 31) have demonstrated the detrimental effect of the increase in SAP caused by SAH, ICH, and cerebral ischemia. Hypervolemic hemodilution may reduce the hematocrit and blood viscosity that are thought to improve cerebral perfusion. On the other hand, a large amount of fluid transfusion tends to increase the SAP and to decrease the CBF. These studies support the contention that systemic hypertension is harmful to cerebral perfusion, particularly in cases with a big aneurysm rupture and uncontrollable SAH.

Hemodynamic Responses to Increased ICP

In the present study, we used spectral analysis of the AP and AF waves for a complete assessment of the steady and pulsatile hemodynamics. The results demonstrated that ICH affected both steady and pulsatile components of the arterial hemodynamics. At each level of ICP (50, 100, and 150 mmHg) the AP and TPR were markedly increased. At an ICP of 150 mmHg,

CO was reduced to less than half of the value at the baseline ICP (Table 1). The Zc and Pb were more that twice the baseline value, while arterial compliance (Cm) and forward wave (P_f) were reduced to about 30% and 50% of the baseline value, respectively (Table 2). This study further confirmed that systemic vasoconstriction and hypertension were the major hemodynamic changes in response to ICH following ICH due to SAH or other causes (12, 14, 15). In an early study (2), the mechanism of volume and pressure loading in the pulmonary circulation following ICH was investigated. Measurements of the aortic and pulmonary flow revealed that a dramatic decrease of aortic flow with a slow fall in the pulmonary flow caused volume accumulation in the lung. Right and left heart bypass preparations were also used to demonstrate that the decrease in left ventricular output was the major cause leading to pulmonary hypertension and edema. A total heart bypass preparation was utilized to find that ICH caused increases in vascular resistance with decreases in vascular capacity of the systemic and pulmonary circulations (6). The mechanism of ICH-induced decrease in cardiac output remains unclear. In the present study, the decrease in CO was accompanied by increases in TPR, Zc, and P_b, and a decrease in P_f. Severe vasoconstriction of the large and small vessels may account for these hemodynamic changes. The left ventricle pumps in the face of high resistance, impedance, and backward wave. In this condition, a dramatic decrease in cardiac output may ensue. In connection with the present study, Chern *et al*. and Hu *et al*. (7, 20) used spectral analysis of the arterial pressure and CBF in normal subjects and patients with carotid stenosis. They found that CBF autoregulation in response to orthostatic changes was present in normal subjects, but was impaired in patients with carotid stenosis.

In summary, we created an animal model that simulates severe uncontrollable SAH. In uncontrolled SAH, the increased SAP caused more bleeding into the subarachoid space and thus generated a vicious cycle between ICP and SAP. Under this condition, the CBF was severely depressed. An α-adrenergic blocker (phenotolamine) and a vasodilator (nitroprusside) were effective in reducing the vicious cycle and improving the cerebral perfusion. Hemodynamic analysis revealed that ICH caused marked increases in total peripheral resistance, characteristic impedance, and pulse wave reflection while accompanied with decreases in stroke volume, cardiac output and arterial compliance. These changes may result in acute left ventricular failure and may be the cause of acute pulmonary edema.

Acknowledgments

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