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Title : TREATMENT OF SUBARACHNOID HEMORRHAGE-INDUCED VASOSPASM: INCREASE IN CEREBRAL BLOOD FLOW (CBF) BY THE SIMULTANEOUS INFUSION OF ANGIOTENSIN II AND SODIUM NITROPRUSSIDE

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**Introduction.** Cerebral vasospasm complicating subarachnoid hemorrhage (SAH) remains a major cause of morbidity and mortality following ruptured intracranial aneurysm. No pharmacologic therapy has proven effective in preventing or reversing vasospasm in order to prevent subsequent cerebral infarction. The use of pressor agents has proven ineffective in increasing CBF in vasospasm patients because of cerebral autoregulatory processes which serve to keep CBF within narrow limits, despite wide fluctuations in peripheral pressure. The systemic infusion of vasodilators such as sodium nitroprusside (SNP) or nitroglycerin (NG) lowers blood pressure and may dilate the cerebral vasculature but has little effect on overall CBF. The direct administration of vasodilators into the carotid artery elevates CBF while avoiding systemic hypotension (1,2), but this route of therapy poses too great a risk of thrombosis and cerebral embolization to consider the use of intracarotid infusions in vasospasm patients. The sought after therapy for SAH-induced vasospasm should involve the peripheral intravenous administration of agents which specifically elevate CBF, while maintaining systemic pressure, in order to increase perfusion of the compromised areas of brain. We report that the simultaneous peripheral administration of angiotensin II (angio) and SNP elevates CBF, and appears to have potential as a therapeutic regimen for SAH-induced vasospasm.

**Methods.** Studies were performed in 10 mature female goats weighing 30-35 kg prepared according to the method of Reimann et al (4). Briefly, extracerebral branches of the carotid are tied off or thrombosed and an electromagnetic flow probe placed around the internal maxillary artery to enable the continuous measurement of CBF in the awake and unrestrained state. Systemic arterial pressure is measured by means of a femoral artery catheter. Intracranial pressure (ICP) is monitored by a catheter placed into the lateral ventricle. Two i.v. lines are placed to allow the simultaneous infusion of two drugs.

**Results.** The infusion of SNP, 34±6 µg/kg/min. lowers mean arterial pressure by 33%, while intracranial pressure (ICP) is significantly increased from 16±2 to 23±3 torr (P<0.01) as has been reported previously (3). CBF was essentially unchanged, at 72±9 ml/min. The additional infusion of angiotensin, 0.1±0.03 µg/kg/min. normalized BP and markedly increased CBF to 110±13 ml/min., a 99% increase by paired-sample

analysis, compared to control (P<0.01). ICP was not increased further by the infusion of the two drugs as compared to ICP with SNP alone.

**Discussion.** Angiotensin II increases BP through a generalized vasoconstriction, but the cerebral vasculature remains relatively unaffected (4). Nevertheless, angiotensin-induced hypertension is associated with little increase in CBF because of autoregulation (1). The infusion of SNP produces a universal vasodilation, and is known to impair the autoregulation of CBF (1,5). SNP alone produces little change in CBF, probably because pressure and cerebrovascular resistance decrease to a similar degree. The infusion of angiotensin during SNP infusion increases BP by peripheral vasoconstriction, which passively increases flow into the SNP-dilated cerebral vasculature. Previous attempts to increase CBF by using phenylephrine as the pressor agent along with SNP (6) or NG (7) have failed, probably because phenylephrine constricts the cerebral vasculature (8). The effect of the combined administration of angiotensin and SNP on the perfusion of an area of brain affected by vasospasm is yet to be determined. Furthermore, in the case of a patient with vasospasm, the increase in ICP associated with the increased CBF might prove deleterious. Nevertheless, this combination of angiotensin and SNP seems to merit clinical trial in the therapy of SAH-induced vasospasm since it represents a documented method of specifically and dramatically increasing CBF by means of a peripheral infusion.

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	BP	ICP	CBF
Control	103±4 (12)	16±7 (7)	63±8 (10)
SNP 34µg/k/m	71±4	23±3	72±9
% Change	(-33±4)	(+52±10)	(+25±12)
SNP + Angio 0.1µg/k/m	100±5	26±4	110±3
% Change	(-3±8)	(+71±17)	(+99±17)