Title: TREATMENT OF SUBARACHNOID HEMORRHAGE WITH THE CALCIUM ENTRY BLOCKER NIMODIPINE AFFECTS PULMONARY GAS EXCHANGE IN PATIENTS REQUIRING CONTROLLED MECHANICAL VENTILATION

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Introduction. Acute microsurgical repair of ruptured cerebral aneurysms abolishes the risk of recurrent bleeding. However, the incidence of delayed ischemic deficits due to vasospasm cannot be substantially reduced. The lipophilic calcium antagonist nimodipine, a compound of the dihydropyridine group, is one of the few drugs which induce a net increase in cerebral blood flow without a pronounced effect on total peripheral resistance (1). - The exact mechanism by which alveolar hypoxia acts within the lung to elicit pulmonary arterial vasoconstriction is still unknown but hypoxic vasoconstriction might induce membrane depolarization and transmembrane influx of extracellular calcium. In fact, calcium antagonists have been shown to inhibit hypoxic pulmonary vasoconstriction in isolated rat lungs (2). The goal of the present study was to determine 1.) whether and under what conditions prophylaxis or treatment of cerebral vasospasm after subarachnoid hemorrhage with nimodipine could cause disturbances in pulmonary gas exchange and 2.) whether the induced changes could be ameliorated by intensifying the applied respiratory therapy.

Methods. 19 patients, 36-78 years old, with angiographically and computertomographically ascertained subarachnoid hemorrhage were included in the present investigation. The clinical grade on admission according to the Hunt and Hess classification was between I and IV. 9 patients had to be mechanically ventilated (Dräger UV$_2$, F_iO_2 = 0.4-0.5, PEEP = 5 cm H_2O). Arterial, pulmonary arterial and central venous pressures were measured direct and registered continuously together with the ECG. The alveolo-arterial oxygen gradient ($AaDO_2$), the alveolo-arterial oxygen quotient ($Q = P_AO_2-P_aO_2/P_AO_2$) and the pulmonary shunt fraction (Q_S/Q_t) were calculated. Nimodipine was given in doses of 0.25, 0.50 and 0.75 µg/kg/min iv. If the administration of nimodipine was associated with a deterioration in arterial oxygenation, the respiratory therapy was modified either by increasing PEEP to 10 cm H_2O or by changing the inspiratory:expiratory ratio from 1:2 to 2:1 (inversed ratio ventilation). Informed consent of the patients or their closest relatives and institutional approval were obtained. Statistical significances were calculated using the analysis of variance.

Results. In contrast to the spontaneously breathing patients, nimodipine decreased pO_2 but increased $AaDO_2$ and Q in the ventilated subjects (Table). In the 4 patients with a Swan-Ganz catheter Q_S/Q_t rose by maximum values of 134±43% ($p<0.01$). These changes could partly be reverted by augmented PEEP or by inversed ratio ventilation.

Discussion. Nimodipine appears to have little effect on pulmonary gas exchange in the presence of normal ventilation-perfusion ratios in spontaneously breathing patients. However, subarachnoid hemorrhage is frequently associated with arterial hypoxemia due to pulmonary shunting, either as a result of true shunt or a ventilation-perfusion imbalance, necessitating the use of artificial ventilation. Our study indicates that nimodipine given under these conditions can alter pulmonary gas exchange supposedly by causing a disproportionate decrease in vascular resistance in hypoventilated areas of the lung. This observation is in good agreement with the concept that the mechanism of hypoxic pulmonary vasoconstriction depends on transmembrane influx of extracellular calcium. Thus, in patients with compromised pulmonary function requiring vasospasm prophylaxis or therapy with nimodipine after subarachnoid hemorrhage, the mode of artificial ventilation has to be adjusted in order to achieve the best matching of ventilation and perfusion.

	NIMODIPINE (µg/kg/min)			
	Control	0.25	0.50	0.75
	n=9	n=9	n=9	n=6
HR min^{-1}	72±6	83±7	86±11	86±11
MAP mmHg	86±6	87±4	87±5	86±6
ZVD mmHg	6±1	6±1	7±1	7±1
PO_2	131±10	110±6*	92±6*	101±6*
$AaDO_2$	98±16	143±23+	184±30+	165±20*
Qx100	41±6	55±5+	65±5*	61±4*

Means ± SEM; + $p<0.05$, * $p<0.01$

References. 1) Harris RJ, Branston NM, Symon L et al.: The effects of a calcium antagonist, nimodipine, upon physiological responses of the cerebral vasculature and its possible influence upon focal cerebral ischaemia. Stroke 13: 759-766, 1982.
2) McMurthy IF, Davidson AB, Reeves JT et al.: Inhibition of hypoxic pulmonary vasoconstriction by calcium antagonists in isolated rat lungs. Circ Res 38: 99-104, 1976.