Title: THE EFFECT OF CAPTOPRIL ON TACHYPHYLAXIS TO SODIUM NITROPRUSSIDE.

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Introduction. Sodium nitroprusside (SNP), a well known direct-acting peripheral vasodilator, is widely used in anesthesia for induction and maintenance of controlled hypotension. Problems associated with its clinical use include resistance, tachyphylaxis and cyanide toxicity. Tachyphylaxis has been postulated to occur because of reflex activation of the sympathetic nervous system via baroreceptors or by increases in plasma renin activity.[1,2] Captopril inhibits angiotensin converting enzyme and blocks the formation of angiotensin II. The effects of blocking the renin-angiotensin system with captopril on SNP-induced hypotension and tachyphylaxis were studied. The contributory roles of plasma renin activity (PRA), angiotensin I (AI) norepinephrine (NE), epinephrine (EPI), and acid base status pH, $NaHCO_3^-$ used were also investigated.

Methods. Two groups of 7 adult male New Zealand White rabbits were anesthetized with up to 2.5% halothane in O_2 by mask. After 1.0 mg/kg succinylcholine iv, the rabbits were intubated and ventilated to maintain a normal pCO_2. Following cannulation of the femoral artery and vein the rabbits were maintained on a vecuronium drip and 0.75% end-tidal halothane. After a 45 min stabilization period, study rabbits were given 1 mg/kg iv captopril in 3-3.5 ml of saline. Control rabbits received saline alone. SNP was delivered by controlled infusion to reduce the mean arterial blood pressure (MAP) by 40% and maintain it at this level for 120 min or up to a total dose of 12 mg/kg SNP (marked tachyphylaxis). A second dose of captopril or saline was given after 60 minutes hypotension. Arterial blood samples were drawn 30 and 1 min prior to and at 30, 60, 90 and 120 min during the hypotension and again 30 min into the recovery period. Blood samples were replaced with equal volume of Hespan^R. Arterial blood samples were assayed for NE, EPI, AI and PRA as well as pH, pCO_2 and pO_2. Any metabolic acidosis was corrected with sodium bicarbonate. Arterial blood pressure, heart rate (HR) end-tidal CO2 and halothane were recorded continuously. Data was normalized using log conversions based upon kurtosis and skew testing. Statistical tests were done using the BMDP statistical packages. Tests included analysis of variance for repeated measures, Bonferroni modified t-test, and stepwise regression analysis. $p < 0.05$ was considered statistically significant.

Results. After a 30 minute stabilization period for both groups, the starting MAP (Control = 80 + 8.4 mmHg, Captopril = 85 $\pm$ 9 mmHg) and HR (Control = 310 $\pm$ 18 bpm, Captopril = 314 $\pm$ 22 bpm) were not significantly different between the groups. MAP did not differ significantly between the groups throughout the protocol, nor did the initial dose of SNP required to induce a 40% hypotension. In the control group, 6 out of 7 rabbits reached marked tachyphylaxis, with the mean SNP dose increasing 36 fold. In the captopril group, none of the rabbits demonstrated tachyphylaxis. In the control group, the amount of SNP required to maintain a 40% reduction in MAP correlated with circulating NE levels ($p < 0.01$) and not with log PRA (Fig, Table). In the captopril group, there was no correlation of the amount of SNP required (to maintain a 40% reduction in MAP) with log NE, log EPI, AI or log PRA levels (Table).

Discussion. This study confirms previous findings of the correlation between circulating NE levels and the amount of SNP required to maintain a desired level of hypotension.[3] Tachyphylaxis correlated with CA levels over a broad range and not with changes in PRA. Other investigators have emphasized the renin-angiotensin systems role in attenuating tachyphylaxis to SNP[2]. This study finds no correlation between the amount of SNP required and measures of either renin-angiotensin (AI, PRA) or the sympathetic nervous system (NE, EPI) in captopril treated rabbits. PRA levels rose sharply after captopril administration, and remained high despite declining requirement of SNP. The levels of CA in the captopril group never rose significantly above resting control values. This could imply that captopril acts on both the renin-angiotensin system as well as the adrenergic system.

References:

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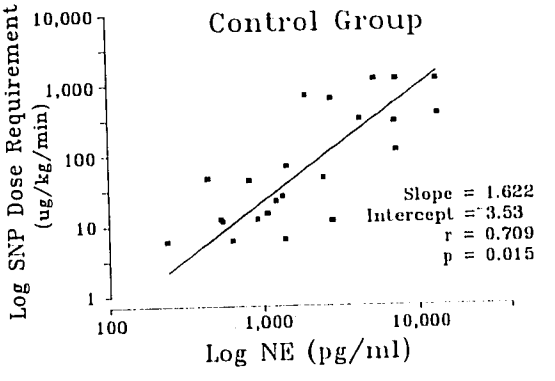
3. Bloor BC, Snipper DM, Stead SW, Van Etten AP, Flacke WE: The Effect of Halothane Concentration on Tachyphylaxis on Sodium Nitroprusside. Anesth 85(3):A569, 1986.



	Control		Captopril	
	r	p	r	p
Log NE	0.7086	< 0.01	0.289	NS
Log EPI	0.3193	NS	0.576	NS
Log PRA	0.0626	NS	0.136	NS
Log AI	0.2940	NS	0.226	NS
Log pH	0.2806	NS	0.270	NS
Log HCO_3	0.4018	NS	0.195	NS