Title: VASOPRESSOR CLEARANCE AND PHARMACODYNAMICS DURING NITROPRUSSIDE INFUSION - COMPARISON OF LEFT ATRIAL AND SYSTEMIC VENOUS ADMINISTRATION

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Introduction. The vasodilators presently available for the treatment of pulmonary hypertension also significantly dilate the systemic circulation, causing unwanted systemic hypotension when high dosages are required. Sympathomimetic agents may be used to ameliorate systemic hypotension. However, their usefulness is limited by the occurrence of pulmonary vasoconstriction resulting from α-receptor stimulation (1). Left-atrial administration of systemic vasoconstrictors has been used to minimize concomitant pulmonary vasoconstriction (2). This should be most effective when systemic clearance of the vasoconstrictors is high. This study was designed to measure vasoconstrictor clearance during simultaneous vasodilator administration; simulating the clinical situation.

Methods. After approval by the institutional Animal Use and Care Administrative Advisory Committee, 6 dogs were given isoflurane anesthesia and had the following lines implanted: flow-directed pulmonary artery thermodilution catheter, left carotid arterial catheter, and left atrial catheter. Then after a one-hour stabilization period, administration of left atrially (LA) administered vasoconstrictors (in random order) ensued-epinephrine (0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$) norepinephrine (0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$), dopamine (8.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$) and phenylephrine (1 $\mu g \cdot kg^{-1} \cdot min^{-1}$) each for 15 minutes, with concomitant intravenous (IV) administration of nitroprusside to minimize hemodynamic changes. Then drug administration was shifted to a systemic vein in the same order with the same dose of nitroprusside. Hemodynamic measurements and blood samples for vasopressor levels were obtained after a control period and at the end of each infusion period. Arterial blood gases, body temperature, and end-tidal isoflurane concentrations were closely controlled. Catecholamine concentrations were measured by radioenzymatic assay. Two-tailed paired t-testing was used for statistical comparisons.

Results. (table) Comparing IV and LA administration of the catecholamines, systemic vascular resistance (SVR), pulmonary vascular resistance (PVR), cardiac output (CO), and mean systemic arterial pressure (MAP), did not change significantly. Hemodynamics also did not significantly differ when comparing IV to LA administration of phenylephrine (percent change [mean ± SD]: SVR 18 ± 32, PVR 15 ± 50, CO 0 ± 36, MAP 9 ± 18). Peripheral clearance was high, resulting in lower pulmonary arterial concentration of the catecholamines when the agents were delivered through the LA. The lower pulmonary clearance resulted in similar systemic arterial concentrations, whether the drug was given through the LA or IV.

Discussion. Low pulmonary clearance of the catecholamines means that systemic hemodynamics will be similar whether the drug is administered LA or IV. Higher peripheral clearance should result in less of an increase in PVR when the vasoconstrictor is administered LA, and dopamine may have predominately vasodilatory effects if it reaches the pulmonary artery in quantities sufficient only to stimulate dopaminergic receptors (3). Studies in animals with elevated PVR will be required to see if this is, indeed, true. Another study showed approximately 50% higher peripheral clearance, but with up to 11-fold faster average infusion rates (4). Peripheral clearance may be concentration-dependant.

References.

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	NOREPINEPHRINE	EPINEPHRINE	DOPAMINE
Clearance (percent) Mean ± SD			
Peripheral	46.8 ± 9.0^	43.8 ±12.1^	48.1 ± 13.3^
Pulmonary	21.8 ± 7.3	7.1 ± 7.2	13.2 ± 8.2
Clearance (ml/min)			
Peripheral	1691 ± 545*	2141 ± 964^	2239 ± 484^
Pulmonary	993 ± 625	462 ± 583	799 ± 801
Intrinsic Clearance (ml/min)			
Peripheral	3304 ± 1227^	4003 ±1990^	4587 ± 1538^
Pulmonary	1315 ± 839	539 ± 708	986 ± 1034
Hemodynamic Change - IV vs LA Administration (%)			
SVR	-3 ± 33	9 ± 27	7 ± 20
PVR	7 ± 46	1 ± 56	36 ± 98
CO	19 ± 28	5 ± 31	3 ± 21
MAP	8 ± 13	6 ± 11	8 ± 10
Pulmonary Artery Concentration (pg/ml)			
LA delivery	479 ± 149*	644 ± 419*	30916 ± 8024*
IV delivery	905 ± 249	1083 ± 630	63343 ±13144
Control	72 ± 33	110 ± 47	130 ± 47
Systemic Artery Concentration (pg/ml)			
LA delivery	909 ± 303	1113 ± 523	60228 ±13500*
IV delivery	705 ± 141	992 ± 539	55027 ±12984
Control	69 ± 52	109 ± 65	163 ± 158

* = $p < .05$ ^ = $p < .01$
comparing peripheral vs. pulmonary clearance
or LA vs. IV delivery