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 hypertension when high doses are required. Sympatholytic agents may be used to ameliorate systemic hypertension. However, their usefulness is limited by the occurrence of pulmonary vasoconstriction resulting from sympathetic arousal (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 vasoconstrictor 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 catheterization 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. Ephedrine (0.1 μg·kg⁻¹·min⁻¹), norepinephrine (0.05 μg·kg⁻¹·min⁻¹), dopamine (8.5 μg·kg⁻¹·min⁻¹) and phenylephrine (1 μg·kg⁻¹·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), arterial oxygen saturation (SaO₂), and 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 ± 30, 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, though 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 vasoconstrictor effects if it reaches the pulmonary artery quantitatively 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-dependent.

References.

norepinephrine epinephrine dopamine

Clearance (percent) Mean ± SD
Pulmonary 46.8 ± 9.0* 43.8 ± 12.1* 48.1 ± 13.3* 21.8 ± 7.3 7.1 ± 7.2 13.2 ± 8.2
Clearance (ml/min)
Pulmonary 1691 ± 545* 2141 ± 964* 2239 ± 484* 993 ± 625 462 ± 583 799 ± 801
Intravascular Clearane (ml/min)
Pulmonary 3304 ± 1227* 4003 ± 1990* 6587 ± 1338* 1315 ± 839 539 ± 708 986 ± 1034
Hemodynamic Change – IV vs LA Administration (Δ)
SVR -5 ± 33 -9 ± 27 7 ± 20
PVR 7 ± 46 1 ± 56 36 ± 98
CO 19 ± 28 5 ± 31 3 ± 21
MAP 12 ± 13 6 ± 11 8 ± 10
Pulmonary Artery Concentration (ng/ml)
LA delivery 479 ± 169* 644 ± 619* 10916 ± 8024* 905 ± 249 1083 ± 630 63343 ± 313144
Control 72 ± 33 110 ± 47 130 ± 47
Systemic Artery Concentration (ng/ml)
LA delivery 590 ± 303 1113 ± 523 60228 ± 133500* 705 ± 141 992 ± 539 55027 ± 129286
Control 69 ± 52 169 ± 65 163 ± 158

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