TITLE: HEPARIN: A MYOCARDIAL DEPRESSANT?
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Heparin, a potent anticoagulant, is widely used in prophylaxis and treatment of thromboembolic problems in pulmonary embolism, deep vein thrombosis, disseminated intravascular coagulation as well as in cardiovascular surgery. Clinically, other than bleeding tendency and heparin-induced thrombocytopenia and thrombosis syndrome, it is generally perceived to be a safe drug. Recently, studies of adverse effect of protamine administration following conclusion of cardiopulmonary bypass have raised the question of the role of protamine-heparin complex. This study was designed to investigate effects of heparin infusion alone on contractility of the denervated rabbit myocardium.

Nine New Zealand white rabbits, weighing 2-3 kg were anesthetized with 45 mg/kg intravenous pentobarbital. The heart was immediately removed. The first septal perforator of the left coronary artery was cannulated with a small polyethylene tube (PE-50) and perfused with warmed (37°C) oxygenated modified Kreb-Ringer bicarbonate buffer (KRB) solution at 1 ml/gm/min. The septum was then dissected out and suspended from a Grass FT03 tension transducer. The other two corners were fixed with tension by opposing clamps through which a 5-volt/5 msec electrical stimulation was given from a Grass stimulator at 1.6Hz. The peak developed tension (PDT) and the maximal acceleration (dT/dt) were recorded. After reaching fully stabilized contractions for at least 30 min., perfusion of heparin diluted in KRB solution was started with doses of 1, 10, 20, and 40 U/ml, respectively. Each dosage was given for 10 min, and the plain oxygenated KRB solution was perfused in between as the control. The PDT and dT/dt were circulated as % of control values. The results were analyzed with paired t-test.

Fig. 1 shows progressive decrease of PDT with heparin infusion as the concentration increases. Fig. 2 shows similar pattern of decreases in dT/dt. All the changes are significant as compared to the control with the exception of 1 U/ml.

Although no adverse cardiac effect other than anaphylactic shock has been described, heparin in our study causes a dose-dependent depression of myocardial contractility in denervated rabbit hearts, particularly at higher concentration.

References

1. J Thorac Cardiovas Surg, 1985, 89:63-70
2. Cardiovascular Research, 1979, 13:254-259

Fig. 1

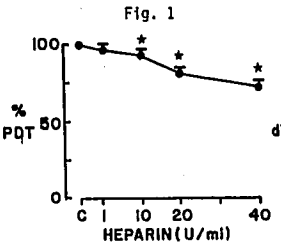
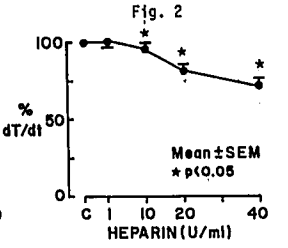


Fig. 2



TITLE: THE DOSE DEPENDENT EFFECT OF DOPAMINE ON HYPOXIC PULMONARY VASOCONSTRICTION IN ANESTHETIZED SHEEP
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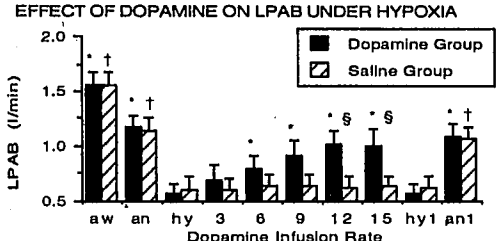
INTRODUCTION: The effects of dopamine on hypoxic pulmonary vasoconstriction (HPV) are controversial (1,2). The usage of different doses and isolated lung models makes it difficult to compare the results of various studies. The present investigation was designed to determine, *in vivo*, the direct pulmonary vascular effects of dopamine in several, clinical doses. METHOD: Chronically instrumented sheep (n=6) were anesthetized with 1.6% (endtidal) halothane and intubated, through a tracheotomy, with a modified double lumen tube. Lungs were ventilated separately with 100% O_2 by using slaved dual Siemen's Servo (900C) ventilators. A total tidal volume of 15 ml/kg with a PEEP of 5 cm H_2O was kept constant. Left pulmonary artery blood flow (LPAB) was measured by an ultrasonic transit time flow probe. After stabilization of hemodynamics, baseline data were recorded. Then the left lung was ventilated with a nitrogen (95%)-CO_2 (5%) mixture. The sheep received randomized infusions of 3,6,9,12,15 µg/kg/min of dopamine or 0.9% NaCl first, then the other drug. Between the dopamine and saline infusions both lungs were ventilated with 100% O_2. Data were collected 20 minutes after each administration. Statistical evaluation was performed by using the Dunnet's test and paired t-test, with significance at $p<0.05$. RESULTS: Left pulmonary blood flow was markedly reduced by N_2-CO_2 insufflation. Dopamine increased this blood flow significantly from 0.57±0.09 to 1.07±0.15 at an infusion rate of 15 µg/kg/min. Left pulmonary vascular resistance index (lpvi) increased significantly from 0.60±0.08 to 1.40±0.20·10^3 dynes·cm·$^{-5}$/m^2 at hypoxia. Dopamine significantly decreased lpvi to 0.8±0.1·10^3 dynes·cm·$^{-5}$/m^2 at an infusion rate of 9 µg/kg/min. Cardiac index (CI) and pulmonary artery pressure (PAP) increased significantly at an infusion rate of 15µg/kg/min from 4.2±0.2 under HPV to 6.5±0.6 l/min/m^2 and 18.6±0.6 to 21.7±1.1 mmHg, respectively. CI also rose significantly at rate of 9 and 12 µg/kg/min. The shunt fraction increased from 30±2 to 43±2% during HPV at an infusion rate of 15 µg/kg/min dopamine. Infusion of NaCl 0.9% had no effect on LPAB, LPVI, CI, PAP and did not increase the shunt fraction. CONCLUSION: Dopamine inhibits HPV in anesthetized sheep. Administration of dopamine to critically ill patients with HPV can be detrimental and shpuld be used carefully.

References

1. Crit. Care Med., 10:371-374, 1982
2. Am. Rev. Respir. Dis. 138:29-35, 1987

EFFECT OF DOPAMINE ON LPAB UNDER HYPOXIA



* p<0.05 vs hy within dopamine group † p<0.05 vs hy within saline group
§ p<0.05 between groups aw = awake an = anesthesia without hypoxia
hy = anesthesia with hypoxia an1, hy1 = an and hy after dopamine infusion