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Title : NITROGLYCERIN TREATMENT IN HYPERTENSIVE RATS

Authors : William E. Hoffman, Ph.D., Susan Polk, M.D., Everett McKissic, M.D., Audrey Holland, B.A., David J. Miletich, Ph.D., and Ronald F. Albrecht, M.D.

Affiliation : Department of Anesthesiology, Michael Reese Hospital & Medical Center, Chicago, Illinois 60616

Introduction. Intraoperative hypertension increases bleeding, fluid exudation and edema, elevates intracranial pressure and increases the risk of stroke and myocardial infarction. Blood pressure levels may be controlled by i.v. infusions of nitroglycerin (NTG). Besides the treatment of intraoperative hypertension, NTG has also been used to treat cerebral and myocardial ischemia in unanesthetized patients. In experiments reported here we tested the cardiovascular and regional hemodynamic effects of nitroglycerin in the unanesthetized and halothane anesthetized spontaneously hypertensive rat (SHR) compared to their normotensive Wistar Kyoto (WKY) controls.

Methods. Three month old male SHR and WKY rats were used in these experiments. Rats were anesthetized with halothane and implanted with femoral artery and vein and left ventricle catheters. Rats tested in an unanesthetized state were allowed 4 hours to recover from the effects of the anesthetic before testing. Anesthetized rats were mechanically ventilated. Arterial pCO₂ levels were adjusted to 35-40 torr and body temperature was maintained at 37°C. Unanesthetized rats were tested with radioactive microspheres in a control state and during an i.v. infusion of 25 and 100µg/kg/min of nitroglycerin. Anesthetized SHR and WKY rats were tested with microspheres in an anesthetized state alone (0.5% halothane in 100% oxygen, paralyzed with pancuronium) and during a NTG induced hypotension of 70 mmHg and 45 mmHg (MBP). Blood samples were taken during microsphere injections and used to calculate cardiac index and total peripheral resistance. Tissue blood flow and vascular resistance during control and nitroglycerin tests were calculated from gamma activity in tissue and blood samples. Statistical tests included t-test comparisons between SHR and WKY at each data point and a repeated measures analysis of variance comparing the effect of nitroglycerin treatment between groups.

Results. Under control conditions in unanesthetized rats, SHR were significantly hypertensive compared to WKY. Cardiac index and brain, heart, kidney, intestine, muscle, paw and skin blood flows were not different between the 2 groups. Similar

doses of i.v. NTG produced moderate decreases in blood pressure and increases in cardiac index in unanesthetized SHR and WKY. During NTG infusions, increases in tissue blood flow in brain, heart, kidney, intestine, and paw tissues were similar between SHR and WKY.

Anesthetized SHR had significantly greater vascular resistance in heart, and all non-vital tissues (intestine, muscle, skin and paw) compared to WKY. Controlled hypotension induced with nitroglycerin in anesthetized rats resulted in significant increases in cardiac index and tissue blood flow in all tissues except kidney in both SHR and WKY. The vasodilator action of nitroglycerin at a given pressure level was significantly greater in heart, muscle, intestine and paw tissues in SHR compared to WKY.

Discussion. These results indicate that in an unanesthetized state, NTG has little effect on blood pressure of either hypertensive or normotensive rats. NTG infusions under these conditions did produce a significant increase in cardiac index and tissue blood flow in brain, heart, kidney, intestine and paw tissues in both SHR and WKY. These data are consistent with results of Vatner et al (1) who reported that NTG has only moderate hypotensive effects in the unanesthetized animal due to reflex stimulation of the cardiovascular system.

Here we have observed that controlled hypotension with NTG does not lead to hypoperfusion of vital tissues in either SHR or WKY even at 45 mmHg. While vascular resistance is higher in SHR than in WKY under anesthetized conditions, these differences are abolished when pressures are brought to similar hypotensive levels with nitroglycerin. These data indicate that hypotensive drug treatment in young healthy SHR hypertensive animals is a relatively safe treatment.

Reference.

1. Vatner, S.F., M. Pagni, J.D. Rutherford, Millard, R.W., and Manders, T: Effects of Nitroglycerin on Cardiac Function and Regional Blood Flow Distribution in Conscious Dogs. *Am. J. Physiol.*, pp H244-252, 1978.

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