TITLE: HEMODYNAMIC EFFECTS OF NITROGLYCERIN IN HUMAN PULMONARY HYPERTENSION

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INTRODUCTION: The goal of vasodilator therapy in pulmonary hypertension (PH) is to decrease pulmonary vascular resistance and pulmonary artery pressure while maintaining systemic arterial pressure. Although many agents have been effective in small series, problems with lack of efficacy and with systemic hypotension are common [1,2]. Nitroglycerin (NTG) differs from other vasodilators in having relatively weak systemic arterial dilating properties. NTG may be an effective pulmonary vasodilator in patients with PH[3,4]. This study examines the acute hemodynamic effects of NTG in patients with symptomatic PH.

METHODS: Ten patients with an average age of 40 years (range 9-67) were studied. The etiologies of PH were primary PH (4 patients), cystic fibrosis (2 patients), prior cardiac shunt, restrictive lung disease, obstructive lung disease, and idiopathic pulmonary hemosiderosis. Following written informed consent, a triple-lumen thermistor-tipped flow-directed pulmonary artery catheter and a radial artery catheter were percutaneously inserted. One hour later baseline measurements were obtained including heart rate, mean pulmonary artery pressure (MPAP), pulmonary artery wedge pressure (PAWP), mean arterial pressure (MAP), central venous pressure (CVP), cardiac output (CO) by thermodilution technique using 10 ml iced saline, pulmonary vascular resistance (PVR), systemic vascular resistance (SVR), systemic arterial oxygen tension (PO_2), and arteriovenous oxygen content difference ($AVO_2\Delta$). NTG was then begun at 0.5 µg/kg/min and increased to 0.75, 1, 2, and 4 µg/kg/min unless hypotension (MAP < 70 mmHg), arrhythmias, or adverse symptoms occurred. Hemodynamic measurements were repeated after 15 minutes at each dose. In 8 of the 10 patients baseline measurements were repeated one hour after discontinuing NTG. NTG ointment (usually 2 inches) was then topically applied and one hour later a final set of measurements was obtained. The protocol was approved by the institution's committee on human subjects. Statistical analysis was by Student's t-test for paired data with $P < 0.05$ considered significant.

RESULTS: The average final dose of NTG was 3 µg/kg/min (range 0.75-4). NTG decreased PVR 36%, MPAP 19%, MAP 15%, PVR 27%, CVP 35%, and $AVO_2\Delta$ 14%; NTG increased cardiac output 18% (Table). PVR decreased more than 25% in 8 of the 10 patients; MPAP decreased at least 5 mmHg in 9 patients. The changes in both PVR and MPAP were dose-related in all patients. There were no significant changes in heart rate, PAWP, or arterial PO_2. NTG produced mild hypotension (MAP 60-70 mmHg) in 3 subjects; no therapy other than discontinuing NTG was required. There were no complications in any patient from the study. Baseline measurements after discontinuing NTG did not differ significantly from control values. NTG ointment resulted in a 27% decrease in PVR ($P < 0.05$), a 14% decrease in MPAP ($P < 0.01$), and an 11% increase in cardiac output. There were no other significant effects of topical NTG. Nine patients were treated with long-acting nitrates. There was major symptomatic improvement in 4 patients, probable improvement in 2 patients, and no improvement in 3 patients.

DISCUSSION: Intravenous and topical NTG were effective in the treatment of both primary and secondary PH producing a reduction in PVR and MPAP and an increase in cardiac output while maintaining an acceptable blood pressure. These results extend our previous findings in 9 other patients where NTG decreased PVR 40% and MPAP 15% and increased cardiac output 40%[3]. In contrast to results with other vasodilating agents[1,2], NTG did not produce dangerous hypotension, tachycardia, or arrhythmias. The improved therapeutic ratio of NTG relates to the relative weakness of its systemic arterial dilating effects so that NTG produces preferential pulmonary vasodilation. We believe intravenous NTG is the best available agent for assessing the reactivity of the pulmonary circulation and for acutely treating PH. Adverse effects, should they occur, are unlikely to have major consequences since the duration of action of intravenous NTG is short. Further study of the effects of chronic nitrate treatment in PH are required.

REFERENCES:

1. Packer M, Greenburg B, Massie B, Dash H: Deleterious effects of hydralazine in patients with pulmonary hypertension. N Engl J Med 306:1326-1331, 1982
2. Hermiller JB, Bambach D, Thompson MJ et al: Vasodilators and prostaglandin inhibitors in primary pulmonary hypertension. Ann Intern Med 97:480-489, 1982
3. Pearl RG, Rosenthal MH, Schroeder JS, Ashton JPA: Acute hemodynamic effects of nitroglycerin in pulmonary hypertension. Ann Intern Med 99:9-13, 1983
4. Zaloga GP, Chernow B, Hott MR et al: Effect of vasodilators on pulmonary vascular resistance in patients with pulmonary hypertension. Clin Pharm 2:265-268, 1983

TABLE 1

	BASELINE	NITROGLYCERIN
PVR ($dyn \cdot s \cdot cm^{-5}$)	1066 ± 210	684 ± 149**
MPAP (mmHg)	51.2 ± 5.6	41.5 ± 5.4**
CO (l/min)	3.64 ± 0.49	4.30 ± 0.51**
HR (beats/min)	87 ± 6	90 ± 7
MAP (mmHg)	87 ± 4	73 ± 3**
SVR ($dyn \cdot s \cdot cm^{-5}$)	1890 ± 274	1382 ± 185**
PAWP (mmHg)	9.0 ± 1.0	8.5 ± 1.4
CVP (mmHg)	12.6 ± 3.1	8.2 ± 2.8**
PO_2(mmHg)	62 ± 2	60 ± 5
$AVO_2\ \Delta$ (ml/dl)	6.6 ± 0.9	5.7 ± 0.7*

*$P < 0.05$ compared to baseline; **$P < 0.01$.