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Effect of Glyceryl Trinitrate on Pulmonary Vasculature of Anesthetized Dogs.* (28263)

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Following administration of glyceryl trinitrate (GTN) pulmonary artery pressure has been observed to increase, decrease, or remain unchanged. Since GTN is a smooth muscle relaxant, like the nitrites, the expected response is a decrease in vessel tone with reduction of pulmonary artery pressure. The variation from this expected result has been attributed to effects on the heart or systemic circulation(1) or to an anomalous action of vasoconstriction on pulmonary blood vessels (2). In the present study, 2 types of cardiac by-pass experiments were used to demonstrate the direct effect of GTN on the pulmonary blood vessels and to clarify the effects of extrapulmonary factors in the pulmonary vascular response.

Methods. Eighteen mongrel dogs weighing 10 to 20 kg were studied under pentobarbital (25 mg/kg) or chloralose (80 mg/kg) anesthesia. A left thoracotomy was performed and all animals were studied with chest open and on positive pressure respiration. Polyethylene catheters were placed in the pulmonary artery, left atrium, distal aorta and endotracheal tube. Pressures were recorded with strain gauge transducers and a multichannel direct writing oscillograph. A Walton-Brodie strain gauge arch was sutured to the surface of the right ventricle for observation of changes in myocardial contractile force. Single injections of GTN (25 or 50 μg/kg) were given into the right ventricle or main pulmonary artery.

After control injections with instantaneous and mean pressure recordings, the right or left ventricle was by-passed using a mechanical pump previously described(3). The pump maintains a constant preset output against resistances up to 700 mm Hg and delivers pulsatile flow at a preselected stroke volume and rate which can be varied over a wide range. The pump inlet was connected to the left or right atrium and output to the descending thoracic aorta or main pulmonary artery respectively. The left or right ventricle was thus eliminated from the general circulation.

With the mechanical pump in place, similar injections and recordings were performed as in the control animals. In selected cases flow was measured with an ultrasonic flowmeter connected into the tube leading from the left atrium to the ventricular by-pass pump.

Results. In 12 control animals with intact circulations, following injection of GTN into the right ventricle or main pulmonary artery, there was a delay of 6 to 12 seconds before the onset of systemic hypotension. During this time there was no change or a slight fall in pulmonary artery pressure. As systemic pressure declined, however, pulmonary artery mean pressure rose an average of 2 mm Hg above baseline values in 11 of the 12 animals (Table I) with a simultaneous increase in myocardial contractile force and heart rate (Fig. 1). After the systemic pressure

TABLE I. Effect of GTN on Mean Pulmonary Artery Pressure in 12 Dogs Before and After Left Ventricular By-Pass.

	Before L.V. by-pass		With L.V. by-pass	
Dog No.	Max △ P, mm Hg	% change	Max △ P, mm Hg	% change
1	+4	+18	−6	−19
2	+2	+11	−5	−17
3	+2	+33	−3	−23
4	+2	+29	−2	−11
5	+2	+40	−2	−12
6	+2	+22	−1	− 7
7	+2	+40	−2	−15
8	+2	+14	−6	−25
9	+1	+ 5	−2	− 9
10	+3	+16	−6	−18
11	0	0	−4	−20
12	+1	+ 6	−2	−11
	+2 ± 1		−3 ± 2	

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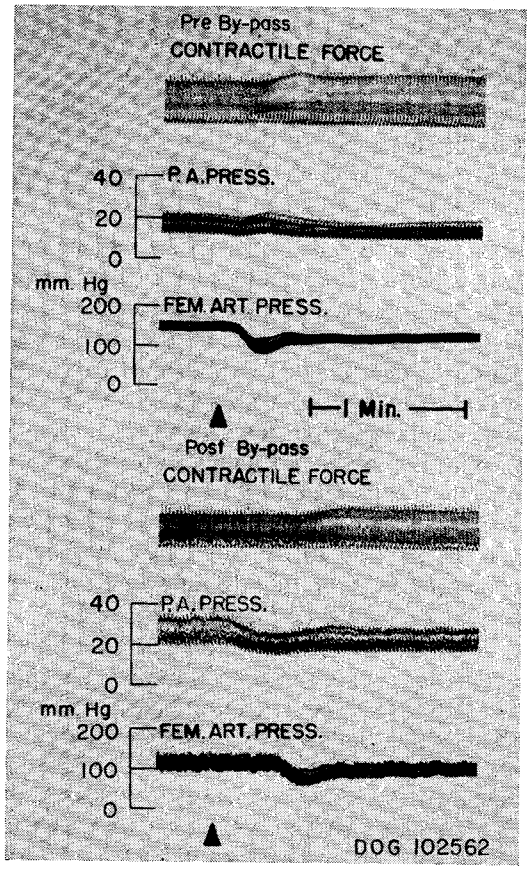

FIG. 1. Representative tracings of myocardial contractile force, pulmonary artery pressure, and femoral artery pressure taken before (top 3 tracings) and after (lower 3 tracings) left ventricular by-pass. Arrows mark time of injection of GTN 25 μg/kg into right ventricle.

reached its lowest values (at 15-34 seconds) all parameters gradually returned to baseline values. The left atrial pressure followed the changes in pulmonary artery pressure but were smaller.

After left ventricular by-pass the initial interval from the time of injection of GTN to the onset of systemic hypotension was prolonged an additional 9 to 29 seconds. During this initial interval while the drug was still confined to the pulmonary circuit there was now a consistent and significant fall in pulmonary artery pressure (Table I). As systemic pressure fell there was an increase in myocardial contractile force and a slight rise in pulmonary artery pressure (Fig. 1). There were no associated changes in left atrial or endotracheal pressures. When flow was measured in the left atrial tube as an indication of total pulmonary blood flow, there was no change or a minimal increase of up to 50 cc/min.

In 6 animals with right ventricular by-pass and constant flow into the lungs, pulmonary artery pressure decreased following the injection of GTN. There was no rise in pulmonary artery pressure coincident with the fall in systemic pressure as seen in the control animals.

Discussion. The response of the pulmonary circulation to vasodilating agents is, as a general rule, moderate. Pulmonary vasodilatation when present can easily be obscured by action of the drug on other segments of the circulation or heart. With the technique of left ventricular by-pass, due to the prolonged circulation time from the left atrium to aorta, the pulmonary circuit can be isolated for a short interval in time from the systemic circulation without disruption of blood flow or nerve supply to the lungs. The direct action of the drug on the pulmonary blood vessels following injection into the main pulmonary artery or right ventricle can be seen before it reaches the systemic circulation or heart(4).

Following GTN injection into the right ventricle or main pulmonary artery with the mechanical pump connected between the left atrium and aorta there was an interval of 15 to 41 seconds before any evidence of drug effect was noticeable on the systemic circulation. During this time while GTN action was confined to the pulmonary circuit there was a consistent and significant fall in pulmonary artery pressure without change in left atrial pressure or change in flow from the left atrial tube. This decrease in pulmonary artery pressure immediately following GTN administration indicates a direct effect of the drug to decrease pulmonary vascular resistance.

In animals with an intact circulation, the increase in pulmonary artery pressure after injection of GTN has been explained on the basis of increased pulmonary blood flow(5). To test this hypothesis experimentally the mechanical pump which was set to deliver a fixed stroke volume at a fixed rate was substituted for the right ventricle and baseline

pressures recorded. The remainder of the circulation was left intact. Following injection of GTN into the pump outflow, essentially the main pulmonary artery, no rise above baseline pulmonary artery pressure was seen. In fact the pulmonary artery pressure, left atrial pressure and pressure fall across the lungs decreased. This indicates that the increased pulmonary artery pressure seen with the intact right ventricle is due to increased blood flow. At this time, after injection of the drug, the pulmonary vascular resistance is in fact decreased. The increased myocardial contractile force and tachycardia seen coincident with the increase in pulmonary artery pressure also are consistent with an associated increased output from the right ventricle.

Summary. The effect of GTN on tne pulmonary vasculature was tested in animals with an intact circulation, with a mechanical pump substituted for the left ventricle and with the pump by-passing the right ventricle. The results of the experiments indicate that in anesthetized dogs the direct effect of GTN in the pulmonary circuit is to decrease pulmonary vascular resistance. The observed increase in pulmonary artery pressure in intact dogs following the injection of GTN is due to increased pulmonary blood flow.

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