

Effect of Organic Nitrates on Coronary Flow.*

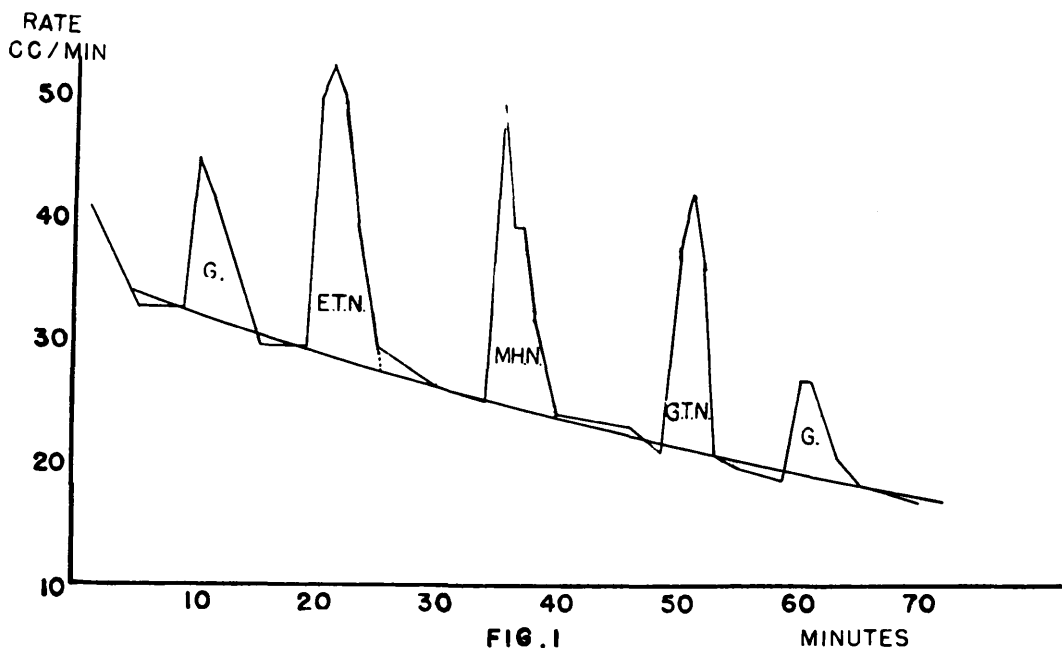
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Erythrol tetranitrate and mannitol hexanitrate,[†] since their introduction by Bradbury,¹ have been used to some extent in the prophylactic treatment of patients with angina pectoris; and glycerol trinitrate has received extensive study both experimentally² and clinically.³ This study was undertaken to determine the comparative effects of these 3 drugs

on the coronary flow through the isolated rabbit heart.

Method. A modified Langendorff preparation of young and vigorous rabbit hearts was used. The hearts were perfused with Locke's solution containing 1% dog serum,⁴ and 0.1% glycine⁵ and adjusted to a pH of 7.4. A constant perfusion pressure of 60 cm of



Graph of Coronary Flow Rate. A typical experiment showing the increase in flow produced by the 3 nitrates with a glycerine control at the beginning and the end. G = glycerine, E.T.N. = erythrol tetranitrate, M.H.N. = mannitol hexanitrate, and G.T.N. = glycerol trinitrate. Base line is indicated.

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† Due to the chemical instability of mannitol hexanitrate, this compound was obtained in the form of maxitate, a stabilized preparation furnished by the R. J. Strassenburg Company, and was extracted with ether and suspended in glycerine. A suspension seemed necessary since it was so insoluble in non-toxic solvents.

¹ Bradbury, J. B., *Brit. Med. J.*, 1895, **2**, 1213.

² Katz, L. N., Lindner, E., Weinstein, W., *Arch. Internat. de Pharmacodyn. de Therap.*, 1938, **59**, 399.

³ Riseman, J. E. F., and Brown, M. G., *Arch. Int. Med.*, 1937, **60**, 100.

⁴ Wedd, A. M., *J. Pharm. and Exp. Therap.*, 1936, **57**, 179.

⁵ Hermann, G., Dechard, G., and Erhard, P., *Proc. Soc. Exp. Biol. and Med.*, 1935, **32**, 547.

TABLE I.
Average Net Increase in Volume and Rate of Coronary Flow* Produced by Various Nitrates.

	Avg area under curve, cm ²	Standard deviation	Avg rate, cc/min	Standard deviation
Mannitol Hexanitate	.29	.09	.044	.020
Erythrol Tetranitrate	.31	.21	.040	.030
Glycerol Trinitrate	.25	.16	.036	.024

*The area under the curve represents the volume of the increase in flow over the base line values. The average increase in rate is the area divided by the duration of the increase. The net values represent the increase over the control glycerine curves. These data represent averages from 17 experiments.

water and a constant temperature of 32°C were maintained throughout the experiment. The effects of solutions (a) of 40% erythrol tetranitrate and (b) of glycerol trinitrate in glycerine were compared to those produced by a fine suspension of 40% mannitol hexanitate[†] in glycerine. Since there was no sharp drop in the coronary flow after the addition of the suspension it was believed that there was no demonstrable plugging of the capillaries. One milliliter of each of these solutions was injected over a period of 3 minutes into the perfusion fluid just above the heart. Only 3 drug tests were made on each heart; however, glycerine controls were run at the beginning and end of each experiment (Fig. 1). Since the activity of the heart and the rate of coronary flow gradually decreased both during these experiments and during control runs in which no drug was added, a base line was drawn along this fall. Comparative values for the 3 drugs were obtained by estimating with a planimeter the area of the increase above the base line following each drug. This determined the volume of the increment in coronary flow caused by the nitrate. Since the solvent, glycerine, produced some increase in the coronary flow, the net increase caused

by each nitrate was determined by subtracting from the figure for each drug that for the glycerine curve next to it. For the second nitrate test an average of the 2 glycerine values was used.

Results. Erythrol tetranitrate, glycerol trinitrate and mannitol hexanitate in these isolated hearts produced an increase in the flow of fluid through the coronaries which varied from 20 to 60%. The response differed considerably from heart to heart, and as a rule varied directly with the vigor and activity of the individual hearts. The maintenance of a regular heart rate by rhythmic electrical stimulation in 9 experiments did little to reduce this variability. However, in each separate heart the response to each of the 3 drugs was of the same order of magnitude, and any effect of the spontaneous decrease in cardiac activity upon the coronary response was obviated by injecting the nitrates in different order in different experiments. The slight differences between the effects of the 3 nitrates shown in their average volume and rate increments (Table I) are not significant.

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