J. Pharm. Pharmacol. 1979, 31: 810–813 Received March 26, 1979

Direct and reflex effects of nitroglycerin on the blood volume distribution, evaluated by regional weighing in the cat

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The effects of nitroglycerin on the blood volume distribution were studied with a method of regional weighing in the anaesthetized cat. An i.v. bolus injection of nitroglycerin produced a dose-dependent decrease in arterial pressure accompanying a decrease in the thoracic blood volume. The latter change was associated with blood volume increases principally in the abdomen, and slightly in the hindquarters. Elimination of the cardiovascular reflex effects by carotid sinus denervation and cervical vagotomy significantly enhanced and prolonged the following changes: the hypotension, the decrease in thoracic blood volume and the volume pooling in the abdomen. The magnitude of increase in hindquarters blood volume was not significantly affected by the denervation procedures, but the duration was much prolonged. The results indicate that the major site of nitroglycerin-induced venous pooling is in the splanchnic circulation. The peripheral venous pooling is produced at the expense of a decrease in the central or pulmonary blood volume. The secondary reflex adjustments tend to minimize the direct effects of nitroglycerin on the blood pressure and blood volume distribution.

Nitroglycerin or nitrites induce a decrease in venous tone or an increase in regional blood volume in the human forearm (Wilkins et al 1937; Mason & Braunwald 1965; Campion et al 1970), feline hindquarters (Ablad & Mellander 1963) and canine splanchnic circulation (Chen 1978). The effects of nitroglycerin in producing ventricular unloading and relieving angina pectoris have been mainly attributed to its predominant action on the venous system (Ganz & Marcus 1972: Miller et al 1976). In patients receiving nitrite treatment, orthostatic syncope occurs as a consequence of severe decline in central venous pressure and venous return (Weiss et al 1937). However, it remains controversial with respect to the sites of venous pooling produced by nitroglycerin in the whole body. Ablad (1963) found that nitrite decreased the pulmonary blood volume without a change in the total blood volume. On the contrary, Ferrer et al (1966) demonstrated that nitroglycerin caused a decrease or no change in the splanchnic blood volume accompanying venous pooling in the pulmonary circulation.

To investigate the instantaneous effects of nitroglycerin on the blood volume distribution, we use a simple and non-invasive method (Fell & Rushmer 1961; Fell 1964) that records the changes in regional weights of the head, thorax, abdomen and hindquarters. The effects are compared before and after carotid sinus denervation and cervical vagotomy to delineate the simultaneous cardiovascular reflex effects on the direct action of nitroglycerin.

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MATERIALS AND METHODS

The experiment was conducted in 12 cats of either sex, 2·2–2·8 kg (means $\pm$ s.e. = 2·4 $\pm$ 0·3 kg). The animal was anaesthetized with an intraperitoneal injection of chloralose 40 mg kg^{-1} and urethane 400 mg kg^{-1}. The brachial artery was cannulated to measure the arterial pressure with a Statham P23Db transducer. Electronic resistance-capacitance filter with 2 s time constant was used to derive the mean arterial pressure. Heart rate was monitored with a Grass 7P4F tachograph triggered by the arterial pulses. A jugular vein was catheterized for administration of drug. The vagus nerves and carotid sinus regions were isolated or exposed for easy access to sinoaortic denervation during the experiment. Tracheal intubation was performed to provide positive-pressure ventilation with ambient air by a Harvard Apparatus respirator. Throughout the experiment, the body temperature was maintained at about 38 °C with a heating lamp.

The method of regional weighing for measurement of blood volume distribution has been described previously (Fell & Rushmer 1961; Fell 1964). The cat was placed on its side on four wooden scale platforms under the head, the chest (at heart level), the abdomen (at kidney level) and the hindquarters.

The body was tied loosely to the platforms with adhesive tapes. Each platform was suspended by means of wire cradle and a single strand of wire on the lower lug of a force-displacement transducer (Grass FT10). A counterbalancing system was fastened to the upper lug of the transducer to enhance the stability and sensitivity. Calibration was done by placing a known weight over one scale platform after the cat was suspended on the system. Recordings were made on a Grass 7 polygraph. The animal was paralysed with i.v. succinylcholine, 4 mg kg^{-1}, to avoid spontaneous movements during the experiment. All the cables and cannulae that connected to the animal were suspended and fixed in order to exert minimal strain on the scale system.

When cervical vagotomy and carotid sinus denervation were to be done, a small table was used to support the animal. After the denervation procedure was completed, the table was removed and the recording system was allowed to stabilize.

Nitroglycerin (Nitrostat, Parke-Davis) was injected intravenously. Fresh tablets (0·6 mg each) were dissolved in 0·9% NaCl (saline) immediately before use. A given dose of bolus injection was contained in 0·5–0·8 ml solution. The same amount of saline solution without nitroglycerin did not produce any change in the regional weights.

RESULTS

An intravenous bolus injection of nitroglycerin produced hypotension and tachycardia. There was a transient decrease in the thoracic weight accompanying an increase in the abdominal weight. When the changes were returning to the control level, a reciprocal fluctuation in the thoracic and abdominal weights was usually observed. The changes in head and hindquarters weights were slight (Fig. 1A). After carotid sinus denervation and cervical vagotomy (Fig. 1B), the baseline heart rate and arterial pressure were both elevated. The same dose of nitroglycerin did not induce a change in heart rate. The hypotension, as well as the regional weight changes in the thorax and abdomen, became more pronounced and prolonged. Furthermore, the reciprocal fluctuation in the thoracic and abdominal weights, if present before the denervation procedures, was no longer observed.

In 12 cats, the changes in heart rate, arterial pressure and regional weights produced by nitroglycerin, 20 μg kg^{-1}, are summarized in Fig. 2. The magnitude of change is expressed by the maximal (peak) response, and the duration by the time constant (T). The latter is defined as the interval

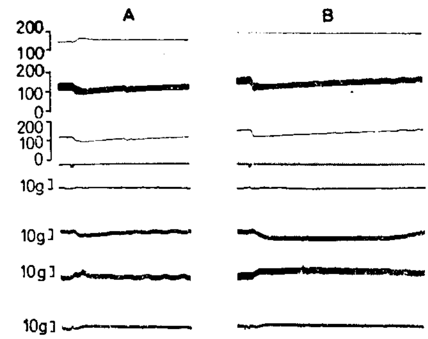

FIG. 1. The effects of nitroglycerin before (A) and after (B) carotid sinus denervation and cervical vagotomy. The tracings downward are: heart rate in beats min^{-1}, pulsatile and mean arterial pressure in mm Hg, timers with 5 s scale and mark indicating the time of nitroglycerin injection in a dose of 20 μg kg^{-1}, regional weight changes in the head, thorax, abdomen and hindquarters. Note the decrease in thoracic weight accompanying an increase in the abdominal weight. In B, tachycardia is not observed, whereas the hypotension and the thoracic and abdominal weight changes become more evident both in magnitude and duration.

between the time of maximal response and the time when the response is reduced to 37% of the maximum value. Either before or after carotid sinus denervation and cervical vagotomy, the change in head weight was not significant. The decrease in thoracic weight was accompanied by an increase in

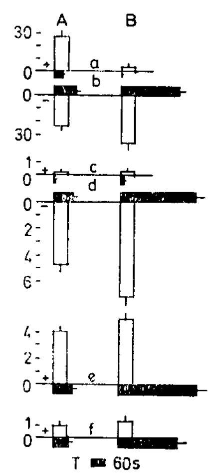

FIG. 2. The maximal changes (open blocks) and the time constants (solid blocks) produced by nitroglycerin at 20 μg kg^{-1} in 12 cats before (A) and after (B) carotid sinus denervation and cervical vagotomy. a: heart rate in beats min^{-1}. b: arterial pressure in mm Hg. c–f: weight changes in the head, thorax, abdomen and hindquarters. + = increase and − = decrease. The vertical and horizontal bars denote the s.e. of the means for the maximal change and the time constant, respectively.

the weight principally in the abdomen (about 85%), and slightly in the hindquarters (about 15%). Carotid sinus denervation and vagotomy significantly enhanced the extent of hypotension ($P < 0{\cdot}001$), the decrease in thoracic weight ($P < 0{\cdot}001$) and the increase in abdomen weight ($P < 0{\cdot}01$). The time constants for the above changes were greatly increased ($P < 0{\cdot}001$). Although the maximal value of weight increase in the hindquarters was little affected by the denervation procedures ($P > 0{\cdot}1$), the time constant was increased approximately 4-fold ($P < 0{\cdot}001$).

Either before or after carotid sinus denervation and cervical vagotomy, the nitroglycerin-effects on the arterial pressure, weight changes in the thorax, abdomen and hindquarters were dose-dependent (Fig. 3). At each dose (10, 20, 40 and 60 μg kg^{-1}), elimination of the baroreceptor and cardiopulmonary receptor reflexes significantly increased the maximal responses except for the weight change in the hindquarters.

DISCUSSION

Studies in the regional circulations have indicated that nitroglycerin or nitrites cause arteriolar and venous dilatation (Ablad & Mellander 1963; Mason & Braunwald 1965; Campion et al 1970; Chen 1978). The action of nitroglycerin on the venous capacitance vessels has been advocated to be the primary mechanism by which this agent reduces the ventricular dimensions, cardiac output and myocardial oxygen consumption (O'Rourke et al 1971; Aronow 1972; Vatner et al 1978). Åblad & Mellander (1963) and Ablad (1963) have found that the nitrites do not significantly change the transcapillary fluid exchange and the total intravascular blood volume. The results of the present investigation reveal that venous pooling caused by nitroglycerin occurs mainly in the splanchnic vascular beds, and slightly in the hindquarters. The instantaneous effects of nitroglycerin in increasing the peripheral blood volume are accompanied by a reduction of the blood volume in the heart-lung region.

The method of regional weighing used in the present study was first designed by Fell & Rushmer (1961). This simple and non-invasive technique is useful for the gross observation of distribution in regional blood volume. From a quantitative point of view, this method does not measure the amount of change in blood volume of a certain area precisely. One of the major problems is that the blood volume change in organs adjacent to the diaphragm, such as the liver, is reflected not only in the abdominal scale, but also in the thoracic scale (Fell & Rushmer 1961). If we assume that nitroglycerin causes significant venous pooling in the liver, the change will lead to an underestimation of the blood volume decrease in the thoracic region and also of the blood volume increase in the abdominal region. In addition to the interaction between scales, the observed change in regional weight does not indicate the blood volume change in a particular circulation, rather it represents the net change in all the tissues and organs above that scale. These limitations should be kept in mind when comparisons are made between our data and the results of others. In the canine whole splanchnic circulation perfused with a constant arterial inflow, Chen (1978) found that nitroglycerin in doses of 30–60 μg kg^{-1} injected intra-arterially produced an increase in the abdominal vascular capacity by 4–5 ml kg^{-1} weight. In the present study, the same dose range (after carotid sinus denervation and vagotomy) caused an increase in the abdominal weight by 5·7–6·4 ml (Fig. 3), which corresponds to a value of 2·4–2·7 ml kg^{-1} weight. In the feline hindquarters and human forearm, the maximal venous pooling was 0·1–0·4 ml per 100 g tissue weight (Ablad & Mellander 1963; Mason & Braunwald

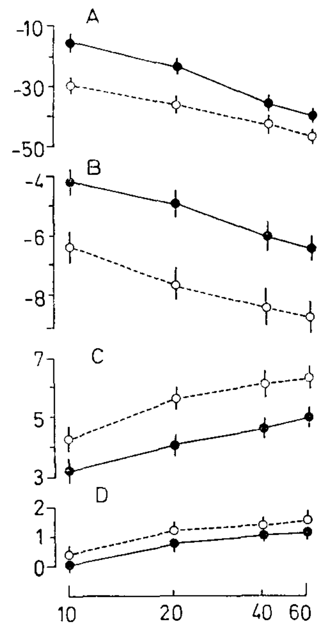

FIG. 3. The dose-response curves of nitroglycerin in 12 cats before (solid circles and solid lines) and after (open circles and dashed lines) carotid sinus denervation and cervical vagotomy. A: change in arterial pessure (mm Hg). B-D: weight changes (g) in the thorax, abdomen and hindquarters. Abscissa: nitroglycerin (μg kg^{-1}, i.v.).

1965). Our data indicated a maximal amount of volume increase in the hindquarters by 1·4 ml. The hindquarters weigh about 26% of the body weight. The total amount of 1·4 ml is normalized to a value of 0·22 ml per 100 g tissue, which is within the range of changes reported previously.

In contrast to the findings of the present investigation, Ferrer et al (1966) have reported that in man nitroglycerin causes a net increase in the pulmonary blood volume associated with a decrease in the splanchnic blood volume. Several investigators (O'Rourke et al 1971; Vatner et al 1978) have suggested that the secondary reflex adjustments tend to minimize and even reverse the direct effects of nitroglycerin. Vatner et al (1978) have also pointed out that different responses to nitroglycerin can be observed especially when the haemodynamic parameters are measured intermittently rather than continuously. We have demonstrated in this experiment that the nitroglycerin-effects on the blood pressure and blood volume distribution become more prominent both in magnitude and duration after carotid sinus denervation and vagotomy. Furthermore, the reciprocal fluctuation in the weights between the thoracic and abdominal scales usually seen before the denervation procedures (Fig. 1A) probably reflects the interaction between the direct and the reflex effects following nitroglycerin administration. When the experimental subjects are not anaesthetized, the secondary reflex adjustments could be more powerful. If the measurements are made intermittently such as those reported by Ferrer et al (1966), some unexpectable results opposite to the direct effects of nitroglycerin may be obtained.

Acknowledgements

The study was supported by National Science Council (Republic of China) and J. Aron Charitable Foundation (U.S.A.). The authors are grateful to Dr. C. Y. Chai for his suggestion and encouragement, to Mr. S. D. Tzeng and Miss H. C. Chen for their technical assistance.

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