Orthostatic Influences on Cardiovascular Responses to Nitroglycerin in Conscious Dogs

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Abstract □ The influence of body position change on the arterial pressure and heart rate responses produced by acute short-acting and sustained-release dosage forms of nitroglycerin was evaluated in a series of chronically prepared, conscious beagle dogs. The upright repositioning of the dog to 60° from horizontal markedly enhanced the hypotensive and bradycardic responses produced by both dosage forms. Since it has been suggested that the lowering of arterial pressure is an essential component resulting in the therapeutic usefulness of nitroglycerin in angina pectoris, the experimental orthostatic model could be a sensitive procedure for the laboratory assessment of drugs of this class.

Keyphrases □ Nitroglycerin—effect of body position on cardiovascular response, short-acting and sustained-release dosage forms, dogs □ Cardiovascular response—nitroglycerin, influence of body position, short-acting and sustained-release dosage forms, dogs □ Vasodilators—nitroglycerin, effect of body position on cardiovascular response, short-acting and sustained-release dosage forms, dogs

In pentobarbital-anesthetized dogs, sublingual nitroglycerin doses as high as 1.95 mg (3/100 gr) were devoid of apparent coronary flow effects, although they lowered the mean arterial pressure significantly (1). However, the intravenous administration of 0.65 mg of nitroglycerin to the anesthetized dog did produce a significant, although short-duration, coronary dilatation associated with a hypotensive and tachycardic response. These findings supported postulates (2) regarding the therapeutic effectiveness of nitroglycerin against anginal pain in humans. Based upon these experimental results with pentobarbital-anesthetized dogs (2), the three important aspects of the pharmacological action of nitroglycerin were: (*a*) a reduction of cardiac work secondary to a lowering of arterial pressure, (*b*) a concurrent dilatation of the coronary vessels, and (*c*) an indirect reduction in myocardial oxygen consumption due to decreased cardiac work.

According to Bernstein *et al.* (3), the therapeutic usefulness of nitroglycerin in angina pectoris is due to its ability to increase coronary blood flow and simultaneously to decrease the cardiac work. However, they did not demonstrate a statistically significant change in myocardial blood flow following sublingual nitroglycerin. Similarly, the therapeutic effects of nitroglycerin were suggested to be due to its coronary flow and blood pressure effects, although sublingual administration failed to demonstrate a significant coronary flow effect in 14 of 15 anesthetized dogs examined (4).

Large intravenous doses (0.22–1.3 mg) of nitroglycerin increased coronary vasodilatation, which endured for longer than 16 min in conscious, trained dogs (5). However, according to Melville (6), the coronary vasodilatation afforded by nitroglycerin is a minor factor in its antianginal action. The results of a subsequent study (1) supported this speculation, since the sublingual nitroglycerin dosage form failed to alter significantly the coronary flow of anesthetized dogs while consistently depressing the arterial blood pressure.

An accurate, reliable, and convenient method was needed for the assessment of both acute and sustained-release coronary dilators of the nitroglycerin type. In view of the apparent and more selective effect of this agent upon blood pressure levels of anesthetized dogs, use of the conscious dog preparation while upright (orthostatic) should fulfill this methodological requirement. A series of experiments was performed to examine the ability of oral nitroglycerin, in sublingual and sustained-release dosage forms, to alter the systolic and diastolic arterial pressures and heart rates in conscious beagle dogs while in the horizontal and upright (60° from horizontal) body positions. This report describes the experimental method and the results obtained with these two dosage forms of nitroglycerin.

EXPERIMENTAL

Six male and female beagle dogs, 8.1–12.2 kg, were used. These dogs had not been previously treated with nitroglycerin or other vasodilators of this class, although they had been used repeatedly over the years for behavioral and psychopharmacological evaluations (7, 8).

Each dog previously had been surgically prepared (9) with externalized bilateral carotid artery loops to allow for the direct measurement of systolic and diastolic arterial pressure while conscious. Direct arterial pressure measurements were obtained by cannulation of one externalized carotid artery and subsequent connections of the cannula[1] supplying input into an arterial pressure coupler[2] of the recorder. Patency of the cannula was maintained with an infusion pump producing a slow volume, retrograde intraarterial infusion of physiological saline through the pressure transducer into the dwelling arterial cannula.

Beat-to-beat heart rate level was determined concomitantly through bipolar silver–silver chloride electrodes positioned and affixed to the skin surface over the sternum. These electrodes were suitably connected to a cardiotachometer coupler[3] of the recorder and supplied a lead I electrode[4] selection to drive the cardiotachometer. Respiration was monitored indirectly through a pneumotachograph belt placed around the thoracico-abdominal region of the dog's body. This pneumotachograph belt was connected to a low level pressure transducer[5], supplying input into a pressure coupler[6] of the recorder. All recording was performed by a dynograph[7] using a paper speed of 2.5 mm/sec.

Two dosage forms of nitroglycerin were evaluated: a sublingual

[1] Type P-23AA Statham pressure transducer.
[2] Type 9872.
[3] Type 9853.
[4] Wilson.
[5] Statham type P-32BB.
[6] Type 9872.
[7] Beckman type R.

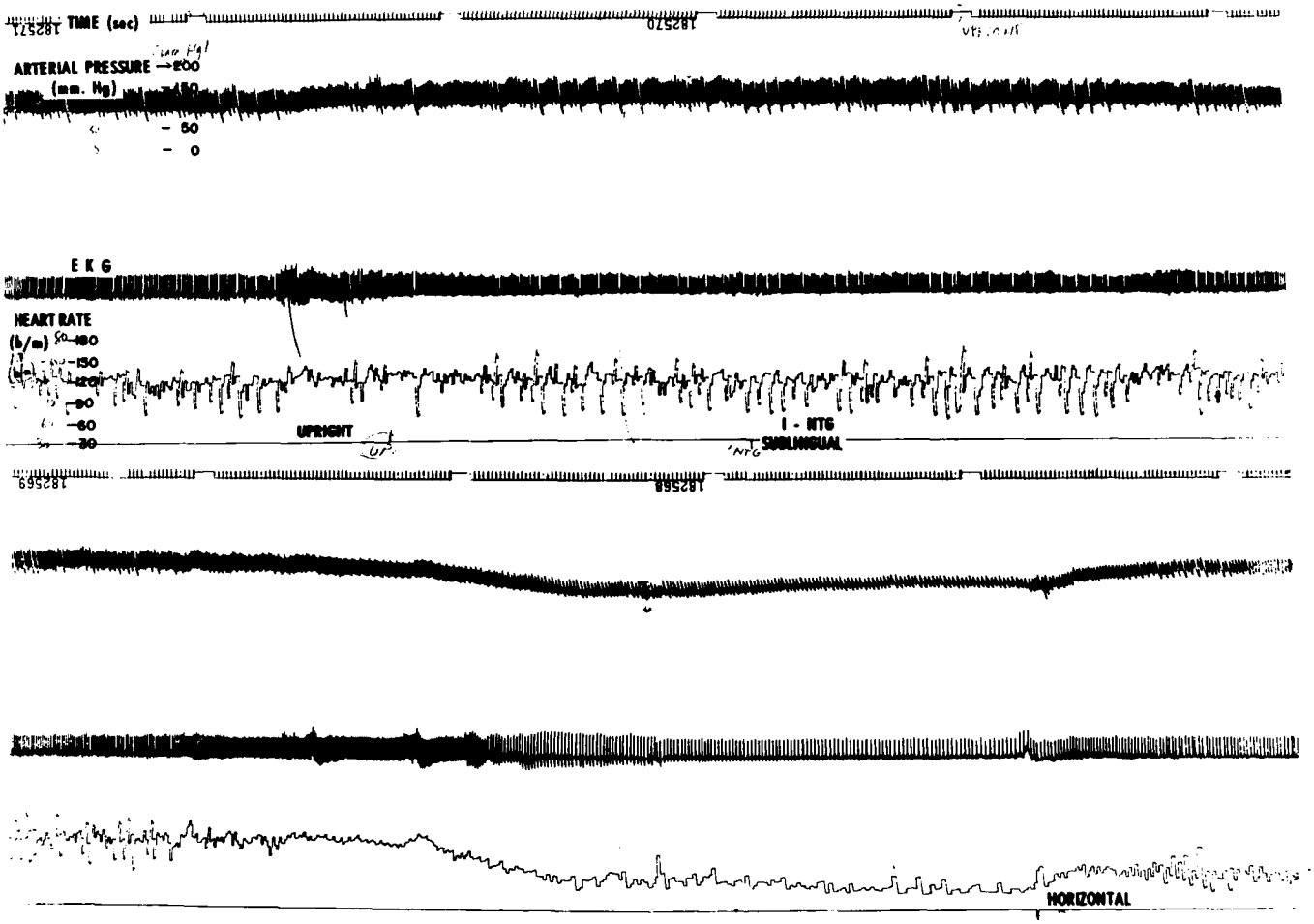

Figure 1—*Arterial pressure (mm Hg) and heart rate (beats per minute) effects of acute sublingual nitroglycerin (0.65 mg) to conscious beagle dogs while upright. Upper and lower records are continuous.*

form containing 0.6 mg (1/100 gr)/tablet and a sustained-released form[8] containing 6.5 mg (1/10 gr)/capsule. Single or multiple amounts of each dosage form were employed and evaluated for their cardiovascular effects.

Because of the minimal response induced by sublingual nitroglycerin in the normotensive dogs while horizontal, four dogs were trained to remain in an upright position (approximately 60° from horizontal) with the aid of a chest sling. This procedure enhanced the amplitude of the hypotensive response to the sublingually administered nitroglycerin and was also the method used to evaluate the effectiveness of the sustained-release form.

Simply, the procedure was to raise-tilt (upright) the dog for 5-min intervals at fixed times of −10, +5, +20, +35, +50, +65, +85, +105, +125, +155, and +185 min after administration of the sustained-release oral capsule. In experiments with the sublingual dosage form, the animal was upright when the tablet was placed in the lip-sac and remained upright for 5 min thereafter. For control purposes, 0.25-gr saccharin tablets, which approximated the size of the sublingual form of nitroglycerin, were similarly placed in the lip-sac while identical manipulations (*e.g.*, body position change) were applied.

The data were analyzed for statistical significance using the matched-pair *t* test (10), with each animal serving as its own control.

RESULTS AND DISCUSSION

The influence of sublingual nitroglycerin on systolic/diastolic arterial pressure and heart rate in two conscious dogs maintained in a horizontal body position was evaluated. The data indicated that the low sublingual dose of one nitroglycerin tablet (0.65 mg) did not produce an apparent lowering of the normotensive arterial pressure nor have an appreciable effect upon the heart rate. The pretreatment systolic/diastolic arterial pressure and heart rate were 150/80 mm Hg and 150 beats/min, respectively, and changed randomly.

The sublingual placement of three nitroglycerin tablets (1.95 mg) in two dogs maintained in a normotensive horizontal position did produce a discernible lowering of arterial pressure level, with an apparently greater effect on the systolic phase than on the diastolic phase of the hypotensive response. A tachycardic response was associated with the blood pressure lowering response. Four minutes after placing the three nitroglycerin tablets in the lip-sac of the dog's mouth, there was a 20-mm Hg lowering of systolic arterial pressure, a 10-mm Hg depression of the diastolic pressure, and an associated 18-beats/min increase in heart rate.

The effects of sublingual nitroglycerin on systolic/diastolic arterial pressure and heart rate in two conscious beagle dogs with orthostatic hypertension maintained by upright body position also was examined. The enhanced arterial pressure lowering effects produced by one nitroglycerin tablet (0.65 mg), sublingually, while the dog was maintained in an upright body position is illustrated on Fig. 1. Within 2 min postadministration, the upright systolic/diastolic pressures were reduced from a control of 160/90 to 140/85 mm Hg with no apparent associated effect upon heart rate. Both the systolic and diastolic arterial pressures continued to decrease over the next 3 min (5 min after nitroglycerin lip-sac placement), at which time maximum depression to 60/30 mm Hg was reached. Heart rate was decreased by this nitroglycerin treatment from a control of 105 beats/min to a 5-min posttreatment level of 60 beats/min. Both the depressed arterial pressure and heart rates returned toward normal when the animal was returned to the normal horizontal body position.

[8] Nitrobid, Marion Laboratories, Kansas City, Mo.

Table I—Arterial Pressure (mm Hg) and Heart Rate (Beats per Minute) Effects of Extended Duration Form of Nitroglycerin in Six Conscious Beagle Dogs while in an Upright Body Position

Minutes after Treatment	Treatment: Control Systolic	Control Diastolic	Control Heart Rate	19.5 mg Sustained-Release Nitroglycerin Systolic	19.5 mg Sustained-Release Nitroglycerin Diastolic	19.5 mg Sustained-Release Nitroglycerin Heart Rate
0	135	75	105	160	90	90
20	140	85	99	140	85	87
35	135	85	99	115[a]	70[b]	78
50	145	90[b]	96	120[b]	80	102
65	135	85	96	120[b]	85	87
80	140	85	84[b]	115[a]	80	75[b]
100	140	85	99	110[a]	80	84
120	150	90[b]	90	120[b]	90	99
140	145	90	90	115[b]	80	78[b]
160	155[b]	95[b]	87[b]	120	90	96
180	160[b]	95[b]	90	130	95	93

[a] $p \leq 0.01$. [b] $p \leq 0.05$.

The placement of a saccharin tablet into the lip-sac area of the dog did not produce a discernible blood pressure or heart rate response when the dog was in either the upright or horizontal body position.

Furthermore, the effects of oral administration of a sustained-release preparation of nitroglycerin on the systolic/diastolic arterial pressure and heart rate in two conscious beagle dogs in an upright body position were investigated. The oral administration of a 6.5-mg sustained-release capsule was devoid of an apparant effect upon systolic/diastolic arterial pressure and heart rate over the 180-min observation period.

The oral administration of three sustained-release capsules (total nitroglycerin dose of 19.5 mg) resulted in a systolic depressor response when the animal was in either body position, although the response was enhanced when the dog was upright. These data, summarized in Table I, reveal that there was a discernible lowering of systolic arterial pressure within 20–30 min after drug administration; a peak effect of −40 mm Hg was reached at 115 min when the dog was in the upright position, and a peak effect of −20 mm Hg appeared at 35 min when the dog was in the normal horizontal body position. The diastolic pressures obtained when the animals were in either body position were not appreciably altered by the drug treatment.

Table I also contains data of the influence on systolic/diastolic pressures of repeated body position changes with no drug treatment in accordance with the schedule used when nitroglycerin was administered. Examination of these data reveals that repeated positional change from horizontal to upright was not associated with a reduction in arterial pressure over time but, in fact, demonstrated a 25-mm Hg increase in the systolic component of the orthostatic pressor response.

The findings from this study support the speculation that an essential component of the pharmacological action of nitroglycerin is a lowering of the arterial pressure. In many studies, any observed coronary dilatation was always associated with a lowering of existing arterial pressure (1, 4). The corollary that the lowering of arterial pressure by nitroglycerin is always associated with a coronary vasodilatation is, however, not true.

In this study, the ability of nitroglycerin in an acute sublingual dosage form, or in a sustained-release form, to lower the arterial pressure in conscious beagle dogs was markedly accentuated when the dog was maintained in an upright body position. The procedure of repositioning the dog to an upright body position for 5-min intervals was performed at a frequency not exceeding one episode every 15 min. The dog was maintained upright with the use of a chest sling which fit under the forearms, over the sternum, and suspended from the top beams of the Pavlov stand. There was no response fatigue when the dogs were challenged with body repositioning every 15 min over 3 hr.

The enhanced arterial pressure lowering response to the vasodilator, nitroglycerin, accomplished by placing the conscious dog in an upright body position could be a useful technique not only for the evaluation of vasodilators of this drug class but also for the study of the physiological mechanisms in orthostatic hypotension or hypertension.

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