Potentiation of Adrenergic Venomotor Responses in Dogs by Cardiac Glycosides

By David Brender, M.B., Paul M. Vanhoutte, M.D., and John T. Shepherd, M.D.

ABSTRACT

Acetylstrophanthidin, 0.3 to 10 µg/ml, caused contraction of helical strips of the dog cutaneous vein in an organ bath at 37°C. A latent period of 12 to 60 minutes preceded the contraction. During this time, the vein exhibited a progressive increase in response to transmural electric stimulation and added norepinephrine. As the dose of acetylstrophanthidin was increased, the latent period shortened and the increased response during the latent period was potentiated. When the contraction caused by 10 µg/ml was maximal, no additional contraction occurred with electric stimulation; the response to electric stimulation was only partially restored by the repeated washing out of the drug, despite relaxation of the strip to almost base-line tension. Since transmural electric stimulation causes contraction by release of tissue catecholamines, these experiments demonstrate that digitalis glycosides sensitize the cutaneous veins of the dog to adrenergic stimulation. This was confirmed in dogs anesthetized with pentobarbital. Intravenous injections of acetylstrophanthidin and digoxin, in doses too small (12.5 to 15.5 µg/kg) to cause direct constriction of the lateral saphenous vein, potentiated the constriction of this vein caused by electric stimulation of the lumbar sympathetic chain.

ADDITIONAL KEY WORDS acetylstrophanthidin and veins digoxin and veins norepinephrine potentiation cutaneous veins

Although there is agreement that digitalis glycosides have a direct constrictor effect on resistance vessels of the systemic circulation (1-5), opinions differ on the action of these drugs on veins. Some investigators (4, 6, 7) found evidence for a direct venoconstrictor effect of digitalis glycosides, but this was not confirmed by other workers (5, 8).

In the present study, we examined in vitro the effects of acetylstrophanthidin on helical strips from the cutaneous veins of the dog. Doses of 0.3 to 10 µg/ml caused the strips to contract; the contraction was preceded by a latent period of 12 to 60 minutes. During the latent period there was a progressive increase in the contraction caused by electric stimulation, the magnitude of the increase being directly related to the dose of acetylstrophanthidin. This potentiating effect of the cardiac glycosides was confirmed in intact dogs; intravenous administration of acetylstrophanthidin or digoxin, in doses too small to have a direct action on the lateral saphenous vein, potentiated the constriction of this vein caused by electric stimulation of the lumbar sympathetic chain.

Methods

IN-VITRO STUDIES

Segments of the lateral saphenous or cephalic veins were removed from dogs (20 to 25 kg) anesthetized with thiopental (20 mg/kg) and chloralose (80 mg/kg) phenobarbital sodium (60 mg/kg), or ether. The veins were placed in physiologic salt solution of the following composition (mM): NaCl, 119; KCl, 4.7; KH₂PO₄, 1.18; MgSO₄, 1.17; NaHCO₃, 14.9; dextrose 5.5; sucrose, 50; CaCl₂, 1.6; and calcium disodium ethylenediaminetetraacetate.
outflow (femoral vein) pressures—was a measure of tone in the vein wall. The venous perfusion fluid was maintained at 37°C.

The other end was connected to a force transducer (Grass Model FT 03) whose electric activity, representing tension of the strip, was recorded on a direct pen-writing recorder (Grass). The transducer was mounted on a movable support that allowed fine adjustment of the strip length.

After an equilibration period (30 to 60 minutes), the strips were placed at the optimal point of their length-active tension curve (11) on the basis of a standard stimulus of transmural electric stimulation (12). Two rectangular platinum electrodes (20 by 4 mm surface, 0.5 mm thick) were adjusted parallel to the vein strips. The electric impulses consisted of square waves (10 v, 2 msec) from a direct-current power supply with switching transistor (RCA 2N 3055) triggered by a stimulator (Grass Model SD5).

A stock solution of acetylstrophanthidin (Sandoz) was prepared by dissolving 1 mg of the powder in 10 ml of the salt solution. Between experiments, the solution was kept at 5°C. All "concentrations" refer to final concentrations in the muscle bath.

**IN-VIVO STUDIES**

To examine the effect of therapeutic doses of digitalis glycosides on the cutaneous veins in vivo, dogs (16 to 20 kg) were anesthetized with pentobarbital sodium (20 mg/kg), intubated, and artificially ventilated with 100% oxygen via a respirator (Harvard). A catheter for injection of drugs was introduced into the right external jugular vein in the neck and positioned with its tip in the right atrium.

Heart rate was calculated from the electrocardiogram, which was recorded continuously after glycoside injection.

The left lateral saphenous vein was cannulated at the ankle and, by means of a roller pump, perfused at constant flow with blood taken from the median sacral artery, as described previously (13). Since blood flow through the vein was constant, the driving pressure—that is, the differences between inflow (perfusion) and outflow (femoral vein) pressures—was a measure of tone in the vein wall. The venous perfusion fluid was maintained at 37°C.

Aortic pressure was measured through a catheter inserted through the left brachial artery.

All pressures were measured by strain-gauge transducers (Statham Model P23De) and recorded on a visual recorder (Honeywell 1508 Visicorder).

**Sympathetic Stimulation.**—The lumbar sympathetic trunk was exposed and stimulated (Grass stimulator Model SD5) via a platinum bipolar electrode placed between the fifth and sixth lumbar ganglia. The trunk was crushed opposite the second and third lumbar ganglia, and all rami communicantes were divided. A stimulus of 10 v was applied for 1 msec (it has been shown previously [13] that this voltage produces a stimulus of supraliminal intensity). Stimulation frequencies ranged from 1 to 10 cps.

**Drugs.**—1. Acetylstrophanthidin (Lilly). For right atrial injection, the stock solution (0.5 mg/ml) was diluted in 0.9% NaCl solution to give a solution of 0.025 mg/ml. For intravenous injection, the stock solution was added into the pump tubing upstream from the roller pump to ensure adequate mixing.

2. Digoxin (Lanoxin, Burroughs-Wellcome). The stock solution (0.25 mg/ml) was diluted in 0.9% saline to give a solution of 0.025 mg/ml for right atrial injection.

**Results**

**EFFECT OF ACETYLSTROPHANTHIDIN ON CUTANEOUS VEIN STRIPS**

**Response to Continuous Low-Frequency Electric Stimulation.**—Figure 1 shows records from a representative experiment. When acetylstrophanthidin was added to the bath at 1 μg/ml there was no increase in base-line tension of the strip over the ensuing 10 minutes. When the same dose of acetylstrophanthidin was added during a constant electric stimulus, within 20 seconds there was a further increase in tension. When the electric stimulus was discontinued but the acetylstrophanthidin remained in the bath, the strip relaxed and the tension decreased to the prestimulation level. In veins taken from seven other dogs, the mean additional increase in contractile response in the presence of acetylstrophanthidin at 1 μg/ml, expressed as a percent of the contractile response to electric stimulation (10 v, 0.5 cps), was 126% (range, 67% to 217%).

**Response to Repetitive Electric Stimulation.**—In vein strips from eight dogs, an electric
stimulus (10 v, 1 to 5 cps, 10 seconds) was applied before and 8 minutes after the addition of acetylstrophanthidin. There was no effect on base-line tension during this time, but the contractile response to the electric stimulus was augmented. This increase in contractile response, expressed as a percent of the control response, averaged 93% (range, 25% to 125%) in six experiments using a dose of 1 μg/ml. In one strip, the increase in response was 150% with 3 μg/ml, and in another strip was 158% with 10 μg/ml. In every case, the augmentation of the response to electric stimulation was gradually abolished by re-

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**Figure 1**
Effect of acetylstrophanthidin on tension response of saphenous vein strip before (Top) and during (Bottom) electric stimulation. Note return of tension to prestimulation levels when electric stimulus was switched off.

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**Figure 2**
Response of two strips from same saphenous vein to same electric stimulus. Top, Contractile responses of control strip remained unaltered. Bottom, Progressive increase in contractile response of other strip after addition of acetylstrophanthidin (1 μg/ml) to bath.
Effect of different doses of acetylstrophanthidin on response to electric stimulation, at 5-minute intervals, of saphenous vein strips from four dogs (10 v, 5 cps, 10 seconds). Each symbol represents one dog; each type of line represents one dosage.

The progressive potentiation of the contractile response to electric stimulation was related to the dose of acetylstrophanthidin, as shown in experiments on strips from 10 of these 15 dogs. In each experiment, the strip was exposed to two or three different concentrations of acetylstrophanthidin, the order of administration of the doses being randomized. Figure 3 illustrates four typical experiments from this series. The degree of potentiation of the response to electric stimulation increased with the dose of acetylstrophanthidin. Each point on the graph represents an increased contractile response with no increase in baseline tension in the vein strip.

Figure 3 also shows that with the lower doses of acetylstrophanthidin (0.3 and 1.0 µg/ml) repeated washing of the strip with fresh physiologic saline solution. In control strips, the response to repetitive electric stimulation was unaltered by repeated washing with fresh solution.

The relationship between augmentation of the reaction, time of appearance of the effect, and the dose used was examined in experiments in which the electric stimulus (10 v, 2 to 5 cps, 10 seconds) was applied at a constant interval (5 minutes). Figure 2 shows records from a representative experiment. Two strips cut from the same vein were studied simultaneously in different organ baths. After the control response to electric stimulation, acetylstrophanthidin (1 µg/ml) was added to one bath. Within 3 minutes, the contractile response to the same electric stimulus was increased, and a progressive augmentation of this response occurred with time. For the period shown, there was no increase in base-line tension in the strip after acetylstrophanthidin. The contractile responses of the other strip (control) to the same electric stimulus remained unaltered during this time. Similar results were obtained using pairs of strips from each of the 15 dogs in this series. Also, no differences were seen between the responses of lateral saphenous or cephalic veins.

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Increased response to electric stimulation, followed by constrictor response, after addition of acetylstrophanthidin, 10 μg/ml, to strips from two different veins. Even after repeated washing with physiologic saline solution (at each break in trace), there is only partial recovery of reactivity to electric stimulation.

µg/ml) a near-maximal potentiation of the contractile response to electric stimulation, without any increase in base-line tension, was reached 20 to 30 minutes after addition of the drug. For six of these dogs, a “frequency-response curve” was constructed at this time and was compared to the curve obtained before addition of acetylstrophanthidin (Fig. 4).

In a series of experiments on veins from four additional dogs, acetylstrophanthidin was also shown to augment the response of the strips to norepinephrine. In these dogs, the increase in contractile response to norepinephrine, 0.1 µg/ml, expressed as a percent of the control response, averaged 47% (range, 43% to 55%) 3 minutes after addition of acetylstrophanthidin, 10 µg/ml.

Prolonged Exposure.—The effect of prolonged exposure of saphenous vein strips to acetylstrophanthidin was examined in veins from 12 dogs. Representative tracings from
two such experiments are shown in Figure 5. The addition of acetylstrophanthidin, 10 μg/ml, caused an augmentation of the response to electric stimulation, as before, but after about 20 minutes there was a gradual contraction of the strip, and during this time, the response to electric stimulation decreased.

When the contractile response to acetylstrophanthidin reached a plateau, electric stimulation failed to elicit any further contraction. Repeated washing of the strip with fresh physiologic saline solution at this time caused a gradual relaxation with reappearance of response to electric stimulation. However, even after repeated washing over several hours with the saline solution and despite the return of the resting tension of the strip to control levels, the response to electric stimulation remained depressed. In the 12 experiments, the response to electric stimulation after the control resting tension was achieved was 30% (range, 18% to 38%) of that before exposure to acetylstrophanthidin.

The time of onset of the contractile response to acetylstrophanthidin was related to the dose, occurring 12 to 20 minutes after 10 μg/ml (in 10 dogs) and 40 to 60 minutes after 1 μg/ml (10 dogs).

Two strips were cut from each saphenous vein from six dogs, and the responses of the pairs of strips were studied simultaneously in different organ baths. The records obtained in a representative experiment are shown in Figure 6. After the control response to electric stimulation, acetylstrophanthidin, 10 μg/ml, was added to both baths. To one strip, electric stimuli were applied every 5 minutes; the other strip was not stimulated. There were no significant differences between the responses of the two strips when comparing the time to onset of contraction (P > 0.3), time to peak contraction (P > 0.1), and contractile response expressed as a percent of the response to electric stimulation before addition of acetylstrophanthidin (P > 0.8). These data demonstrated that the repeated electric stimulation was not influencing the contractile response to acetylstrophanthidin.

Effect of Intravenous Injection of Acetylstrophanthidin.—In eight dogs, 0.25 mg of acetylstrophanthidin was injected into the pump circuit perfusing the left lateral saphenous vein during stimulation of the left lumbar sympathetic chain. Records from a representative experiment are shown in Figure 7. When the lumbar sympathetic chain was stimulated at low frequency (10 v, 2 cps, 6
minutes), a vasoconstrictor response occurred, indicated by the increase in saphenous driving pressure, which rapidly reached a plateau. When the electric stimulus was stopped, the vein relaxed and driving pressure decreased to the prestimulation base line. Injection of acetylstrophanthidin at this time had no effect on the venous driving pressure, but when the lumbar chain was again stimulated beginning 10 minutes after the injection, vasoconstrictor response was slightly increased. Injection of acetylstrophanthidin during the stimulation resulted in a further increase in driving pressure, beginning about 30 seconds after injection. When the electric stimulus was discontinued, the vein relaxed and the driving pressure decreased to its prestimulation base line. This increase in driving pressure, expressed as a percent of the venoconstrictor response to lumbar sympathetic stimulation, averaged 153% (range, 100% to 208%) in the eight experiments. The time needed for the acetylstrophanthidin to pass from the injection site to the vein through the pump circuit was 30 seconds, as shown by the vasoconstrictor response to 20 μg of norepinephrine injected at the same site.

Effect of Right Atrial Injections of Digoxin and Acetylstrophanthidin.—When 0.25 mg of digoxin was injected into the right atrium, there was a potentiation of the saphenous venomotor response to lumbar sympathetic stimulation (10 cps, 15 seconds) (Fig. 8). An augmentation of the vasoconstrictor response to lumbar stimulation was observed as early as 3 minutes after the injection of digoxin, and this increased progressively over the ensuing 40 to 50 minutes. In the five dogs in this group, the increase in constrictor response, expressed as a percent of the control vasoconstriction induced by lumbar stimulation, averaged 28% (range, 11% to 57%) 15 minutes after digoxin injection. The maximal response was reached at 25 to 35 minutes after digoxin and averaged 59% (range, 30% to 100%). In three dogs, the saphenous venomotor response to lumbar sympathetic stimulation was determined before and after right atrial injection of 0.25 mg of acetylstrophanthidin. The maximal increases in response occurred 15 to 20 minutes after injection and, expressed as percent of the control vasoconstriction, were 25%, 57%, and 200%. In these three dogs and one other, the lumbar sympathetic chain was stimulated before and 20 minutes after injection of acetylstrophanthidin, at frequencies of 1, 2, 6, and 10 cps until, at each frequency, the maximal increase in saphenous driving pressure was attained. In every instance except two (dog 4 at 1 cps; dog 3 at 10 cps), the increases in driving pressure were greater after acetylstrophanthidin (Table 1).

Discussion
The in-vitro studies demonstrated a direct vasoconstrictor effect of acetylstrophanthidin. At doses of 0.3 to 10 μg/ml, a latent period preceded the contraction, and during this time, the responses to electric stimulation and

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added norepinephrine were augmented. The glycoside acetylstrophanthidin was chosen for the in-vitro studies because its short action and ease of washout from the tissue allowed repeated injections without the problem of accumulation. Because all strips were placed at the optimal point of their length-active tension curves (11), valid comparisons could be made between the reactions of veins taken from different dogs. That this is so is shown in the experiments illustrated in Figures 5 and 6, in which the time courses of the increased reactivity of the strips and of the contractile response to a dose of acetylstrophanthidin are remarkably similar, both in veins taken from different dogs and also in two strips from the same vein studied simultaneously in different organ baths.

The ability of acetylstrophanthidin to cause venoconstriction directly confirms the early observations by Franklin (6) that digitalis causes contraction of isolated rings from different veins in the sheep. More recently, Matthews and Sutter (14) showed that the anterior mesenteric vein of the rabbit responded to ouabain in doses of 10 μg/ml by a small immediate contraction, followed by relaxation and a secondary marked contraction beginning 1 hour after addition of the drug. That the latent period preceding the contraction is related to the dose of acetylstrophanthidin is also indicated by the findings of Briggs and Shibata (15). They showed that, in the rabbit aorta, ouabain at 1 μg/ml produced a “variable and delayed” contractile response and that a concentration of 100 μg/ml resulted in more rapid and consistent responses.

We found no evidence for a direct venoconstrictor effect in the intact anesthetized dog given acetylstrophanthidin or digoxin in doses of 12.5 to 15.5 μg/kg either into the right atrium or directly into the blood perfusing the saphenous vein. This is in agreement with the data of Solti and Iskum (8) and of Glover and associates (5), who found that strophanthidin and ouabain, respectively, had no direct venoconstrictor effect in man, even in large doses.

The doses of both acetylstrophanthidin and digoxin used by us are well within the therapeutic range usually described for dogs (16-18). We found no change in heart rhythm or mean aortic pressure after injection of acetylstrophanthidin or digoxin. A difference in doses used may explain the difference between our results and those of Ross and associates (7), who found evidence for a generalized venoconstriction in the dog after administration of acetylstrophanthidin, 100 to 125 μg/kg. The rapid distribution and excretion of a fairly small dose of acetylstrophanthidin in the intact animal presumably also explains the absence of the constrictor response that occurs in an organ bath.

The augmented response to electric stimulation and to norepinephrine during the latent period preceding contractile response to acetylstrophanthidin was related to the dose of acetylstrophanthidin and could be demonstrated whether the drug was administered before or during electric stimulation. Leonard (1) demonstrated a similar potentiation by strophanthidin of the contractile response to electric stimulation in strips of rabbit carotid artery. Holman and McLean (19) showed that cocaine potentiated the response of the superior mesenteric vein of the sheep to
electric stimulation and mentioned that ouabain (10^{-7} g/ml) had a similar effect. Transmural electric stimulation of the cutaneous vein, as applied in our experiments, has been shown (19-21) to cause contraction by a release of catecholamines from the sympathetic nerve terminals remaining in the vascular wall. Our data therefore demonstrate that, in addition to its own, more delayed, constrictor effect, acetylstrophanthidin has a rapid potentiating effect on the response of venous smooth muscle to adrenergic stimulation. The finding that the contractile response to added norepinephrine is similarly augmented by acetylstrophanthidin is additional evidence for this potentiation.

This potentiating effect of acetylstrophanthidin was reversible if the drug was washed out before a marked contractile response occurred. On the other hand, if the vein strip remained in prolonged contact with the acetylstrophanthidin, the response to electric stimulation decreased progressively and only partial recovery of the reactivity could be attained with repeated washing with physiologic saline solution. This depression of reactivity following the contractile response to acetylstrophanthidin is in marked contrast to the increased reactivity seen during the latent period preceding contraction. The explanation for this phenomenon is at present uncertain.

In the intact dog, even after the relatively small doses of acetylstrophanthidin and digoxin used, the vеноconstrictor response to lumbar sympathetic chain stimulation was augmented. As in the in-vitro experiments, the potentiation could be demonstrated whether the drug was administered before or during electric stimulation. This confirms the conclusions drawn from the in-vitro experiments that cardiac glycosides markedly potentiate the reactions of venous smooth muscle to sympathetic nerve activity, a factor which may be important in the overall hemodynamic effect of these commonly used therapeutic agents.

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