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**Research Article**

The coronary vasoconstrictor properties of digitals were evaluated in 61 anesthetized, openchest dogs after coronary sinus cannulation and under conditions of a constant heart rate (atrioventricular pacing) and near-constant blood pressure. The contribution of alpha adrenergic receptor stimulation to the digitalis-induced increase in coronary vascular resistance (CVR) was examined. With Na pentobarbital anesthesia (16 dogs), intravenous acetylstrophanthidin (0.5 mg) caused a significant ($P$<0.05) rise in CVR from 1 through 9 min after injection. The peak increase was +11±2% SE of the control of 1.8±0.2 mm Hg/cm$^3$/min. The mean time to peak effect was 3 min, and to recovery was 21 min. Prior alpha adrenergic receptor blockade with phenoxybenzamine in 11 animals reduced ($P$<0.05) the acetylstrophanthidin-induced peak of CVR and substantially decreased ($P$<0.05) the time to recovery (5 min). Intravenous digoxin (1.0 mg) with Na pentobarbital anesthesia (five dogs) had no significant effect on CVR. However, with chloralose and urethane anesthesia (nine dogs) the same dose of digoxin produced a significant rise in CVR from 3 through 30 min. The peak increase was +20±3% of control (1.4±0.1 mm Hg/cm$^3$/min). One-third the dose of intravenous digoxin (0.35 mg) produced a 9.5±1.0% increase in CVR (five additional dogs). Myocardial oxygen consumption did not change significantly in nine dogs after intravenous digoxin. In 10 additional dogs pretreated with phenoxy-benzamine and in 7 dogs pretreated […]



# The Neurogenic Vasoconstrictor Effect of Digitalis on Coronary Vascular Resistance

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ABSTRACT The coronary vasoconstrictor properties of digitalis were evaluated in 61 anesthetized, open-chest dogs after coronary sinus cannulation and under conditions of a constant heart rate (atrioventricular pacing) and near-constant blood pressure. The contribution of alpha adrenergic receptor stimulation to the digitalis-induced increase in coronary vascular resistance (CVR) was examined. With Na pentobarbital anesthesia (16 dogs), intravenous acetylstrophanthidin (0.5 mg) caused a significant ($P < 0.05$) rise in CVR from 1 through 9 min after injection. The peak increase was +11±2% SE of the control of 1.8±0.2 mm Hg/cm$^3$/min. The mean time to peak effect was 3 min, and to recovery was 21 min. Prior alpha adrenergic receptor blockade with phenoxybenzamine in 11 animals reduced ($P < 0.05$) the acetylstrophanthidin-induced peak of CVR and substantially decreased ($P < 0.05$) the time to recovery (5 min). Intravenous digoxin (1.0 mg) with Na pentobarbital anesthesia (five dogs) had no significant effect on CVR. However, with chloralose and urethane anesthesia (nine dogs) the same dose of digoxin produced a significant rise in CVR from 3 through 30 min. The peak increase was +20±3% of control (1.4±0.1 mm Hg/cm$^3$/min). One-third the dose of intravenous digoxin (0.35 mg) produced a 9.5±1.0% increase in CVR (five additional dogs). Myocardial oxygen consumption did not change significantly in nine dogs after intravenous digoxin. In 10 additional dogs pretreated with phenoxybenzamine and in 7 dogs pretreated with mecamylamine, the increase in CVR did not occur after 1.0 mg of intravenous digoxin. Thus there is a coronary vasoconstrictor effect of intravenous acetylstrophanthidin and digoxin, of rapid onset, which is mediated through alpha adrenergic receptor stimulation.

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## INTRODUCTION

A direct vasoconstrictor effect of digitalis has been established in a number of organ systems (1, 2) and has been postulated for the heart (3). Recently, a neurogenic vasoconstrictor effect of digitalis, mediated through alpha adrenergic receptor stimulation, has been described in resting skeletal muscle (4); the magnitude of this effect is substantially greater than the direct effect of the drug (4). These findings coupled with the demonstration of the existence of alpha adrenergic receptors in the coronary vasculature (5, 6) suggest that digitalis might have a neurogenic vasoconstrictor effect in the heart. The purpose of this communication is to present data documenting the existence of a neurogenic coronary vasoconstriction produced by both acetylstrophanthidin and digoxin. The data also characterize the time course and magnitude of this effect.

## METHODS

The experiments were performed in 61 mongrel dogs weighing between 20 and 24 kg. All 18 dogs used to study the effect of acetylstrophanthidin and 5 dogs receiving digoxin were anesthetized with intravenous sodium pentobarbital (30 mg/kg). Of the remainder of the animals 36 were anesthetized with intravenous chloralose (60 mg/kg) and urethane (600 mg/kg) and 2 were anesthetized with intravenous morphine $SO_4$ (25 mg/kg, a dose substantially greater than that used in clinical cardiac surgery [7]). After the induction of anesthesia an endotracheal tube was inserted. The animals were ventilated with a Harvard positive pressure respirator (Harvard Apparatus Co., Inc., Millis, Mass.) at a rate between 14 and 18 cycle/min with a mixture of 95% oxygen and 5% carbon dioxide. The blood from one blood donor dog was used for each experiment. Donor dogs weighing between 24 and 27 kg

were anesthetized with intravenous sodium methohexital (Brevital, Eli Lilly and Company, Indianapolis, Ind.) (25 $cm^3$ of 1% solution in saline). Each was heparinized and exsanguinated from one femoral artery while receiving an intravenous infusion of 500 $cm^3$ of lactated Ringer's solution. 12.5 $cm^3$ of sodium bicarbonate (44 meq/12.5 $cm^3$), 20 $cm^3$ of heparin (1000 U/$cm^3$), and 50 $cm^3$ of 50% glucose were added to the collected blood.

In the operative animals, a right thoracotomy was performed. Care was taken during the surgery to prevent damage to the neural supply (both sympathetic and vagal) to the heart. Coronary sinus blood flow was measured by the method described by Gregg and Fisher (8). A wide-bore (Bardic #16) cannula (C. R. Bard, Inc., Murray Hill, N. J.) was inserted through the right atrial appendage and ligated in place in the most distal end of the coronary sinus. (Fig. 1). The cannula was held in a horizontal position by a brace. This prevented motion that might lead to transient occlusion of some of the small venous tributaries emptying into the coronary sinus near the right atrium. The position of the cannula was noted at post-mortem examination to assure that there was no occlusion of these small tributaries. Coronary sinus outflow was measured by direct collection of venous blood in graduated cylinders. In nine dogs coronary sinus pressure was monitored with a Statham P23Db transducer (Statham Instruments, Inc., Oxnard, Calif.) and remained constant (within 1 cm $H_2O$ of the control value) throughout each experiment. The control values were always between +1 and −3 cm $H_2O$. The coronary sinus effluent was pumped into the venous side of the pressure column and returned to the operative animal.

In an effort to maintain systemic blood pressure constant, a vertical overflow column, shown in the upper right of Fig. 1, was connected to the femoral arteries of the dog. Overflow blood from the column was returned to the animal via the femoral veins. This column contained arteriovenous shunts at several levels. For a given experiment, a level was selected that would allow some arteriovenous shunting before the start of the collection of experimental data. Thus, a tendency toward a slight increase or a slight decrease in the dog's systemic blood pressure resulted in an increase or a decrease in shunting and, within certain limits, a near-constant systemic blood pressure. Because the pressure could not be increased if it fell below the shunt level, a lowering of arterial pressure was evident in the latter part of some experiments. To counteract this tendency, in four animals receiving digoxin after ganglionic blockade and in two receiving acetylstrophanthidin, blood previously circulated through the experimental system was added when necessary to maintain a near-constant pressure. Coronary vascular resistance (CVR)[1] was calculated as the ratio of mean aortic pressure and coronary sinus blood flow. Changes in CVR were expressed as percent changes from control.

In order to maintain a constant heart rate and interval between atrial and ventricular pacing, pacing electrodes were sutured on the epicardial surface of the right atrium and right ventricle and atrioventricular sequential pacing was employed (Medtronic Model 5837 A-V pulse generator, Medtronics, Inc., Minneapolis, Minn.). The interval between atrial systole and ventricular systole was set at 75 ms for all experiments. A heart rate was chosen slightly above the intrinsic rate to allow consistent atrioventricular capture. In most instances this was 150 beats/min.

[1] *Abbreviation used in this paper:* CVR, coronary vascular resistance.

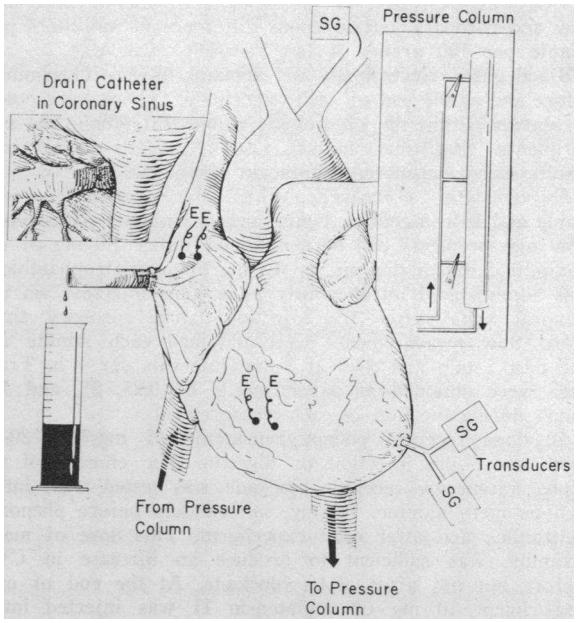


FIGURE 1 Schematic diagram of the canine preparation used for the experiments. A view of the posterior surface of the heart showing the catheter ligated in place near the orifice of the coronary sinus is in the insert on the upper left. The column which was used to maintain systemic pressure at a near constant level is shown on the upper right. SG, strain gauge; E, pacing electrode. See text for details.

Left ventricular pressure was measured via a short rigid wide-bore cannula placed through the apical dimple and sutured in place. The distal end was connected to two pressure transducers. All pressures were monitored with Statham P23Db pressure transducers. An electrocardiogram, systemic blood pressure, full left ventricular pressure, left ventricular diastolic pressure, the first derivative (dp/dt) of the full left ventricular pressure, and right atrial pressure were recorded on a Sanborn Model 350 oscillograph (Hewlett-Packard Co., Waltham Div., Waltham, Mass.). The frequency response of the pressure measurement system was linear up to 30 cycle/s. The rate of rise of left ventricular pressure (dp/dt) was obtained by R. C. electronic differentiation of the full left ventricular pressure. Calibration of the dp/dt differentiator was accomplished by supplying a wave form at known slope to the differentiating circuit, which has a time constant of 0.001 s and a cutoff at 160 cycle/s.

In three animals receiving 1.0 mg of digoxin intravenously, in four animals receiving 0.35 mg of intravenous digoxin, and in two animals receiving 1.0 mg of digoxin with morphine anesthesia, myocardial oxygen consumption data were obtained. In these experiments coronary arterial and venous blood was pumped at a known constant rate through a Guyton arteriovenous $O_2$ analyzer[2] calibrated for each experiment by blood gas determinations done by the method of Van Slyke and Neill (9). The continuous recording of the analyzer permitted on-line documentation of steady states in coronary arteriovenous $O_2$ difference.

[2] Oxford Instrument Co., Jackson, Miss.

$MVO_2$ was expressed as the product of minute coronary flow and coronary arteriovenous difference in milliliters per minute per 100 grams of left ventricle (wet wt).

Blood gases, electrolytes, and hematocrit were determined before and at the end of each experiment. These were noted to remain within the physiologic range throughout the experiments. Statistical analysis used Student's $t$ test and results were considered significant when $P < 0.05$.

*Experimental procedure.* When the preparation was stable and 10 consecutive 1-min control coronary sinus blood flow measurements had been obtained, either 1.0 mg of digoxin, 0.35 mg of digoxin, or 0.5 mg of acetylstrophanthidin was administered intravenously as a bolus injection via the femoral vein. After the injection 1-min coronary sinus blood flow measurements were obtained each minute for the first 5 min and then at 5-min intervals for 1 h. Tracings were obtained at paper speeds of 0.25, 25, and 100 mm/s during the time of each measurement.

10 dogs received phenoxybenzamine (5 mg/kg) 20–30 min before the injection of digoxin. The efficacy of the alpha adrenergic receptor blockade was tested with intravenous methoxamine, 1.0 mg, immediately before phenoxybenzamine and after each experiment. This dose of methoxamine was sufficient to produce an increase in CVR before but not after alpha blockade. At the end of each experiment 10 mg of angiotensin II was injected intravenously to exclude the possibility that the coronary vascular bed was nonspecifically unreactive to vasoconstrictor stimuli other than adrenergic receptor stimulation. In each instance the angiotensin produced an increase in CVR.

Ganglionic blockade was achieved in seven dogs with intravenous mecamylamine (5 mg/kg) before the intravenous administration of digoxin. Bilateral carotid occlusion before and after mecamylamine was employed to test the block. This maneuver resulted in consistent increases in left ventricular dp/dt and decreases in left ventricular end diastolic pressures before, but not after, the blockade. The block was also tested in similar fashion 30 min and 1 h after the injection of digoxin. The presence of alpha adrenergic activity was documented at the end of the experiment by the response of CVR to 1.0 mg of intravenous methoxamine.

In the experiments that evaluated the effect of acetylstrophanthidin on CVR, 0.5 mg of this drug was administered intravenously to 16 dogs after a suitable control period, and hemodynamic observations were made for up to 30 min after injection. To achieve alpha adrenergic receptor blockade 11 of the same dogs subsequently received phenoxybenzamine (5 mg/kg). The alpha block was tested with intravenous methoxamine as previously described. 20–30 min after phenoxybenzamine a second intravenous injection of acetylstrophanthidin was given and the above hemodynamic observations were followed for up to 20 min.

## RESULTS

*Acetylstrophanthidin.* In 16 dogs anesthetized with sodium pentobarbital, intravenous acetylstrophanthidin (0.5 mg) resulted in an increase in CVR from the 1st through the 21st min after injection. The effect was significant through the 9th min. The peak increase in CVR was + 11±2% SE at 3 min. The mean control resistance was 1.8±0.2 mm Hg/cm$^3$/min. The upper panel of Fig. 2 shows the mean data. After alpha adrenergic receptor blockade with phenoxybenzamine in 11 of the same dogs and in 2 additional dogs that had not received a prior injection of acetylstrophanthidin, intravenous acetylstrophanthidin resulted in an increase in CVR only from the 1st through the 3rd min after injection and only to + 7±1% above control (Fig. 2). Both the peak effect and duration of effect were significantly less after alpha adrenergic blockade. Table I shows the associated hemodynamic data. There was no significant change in arterial pulse pressure or in right atrial pressure. The mean pulse pressure in the control period was 25.4±0.4

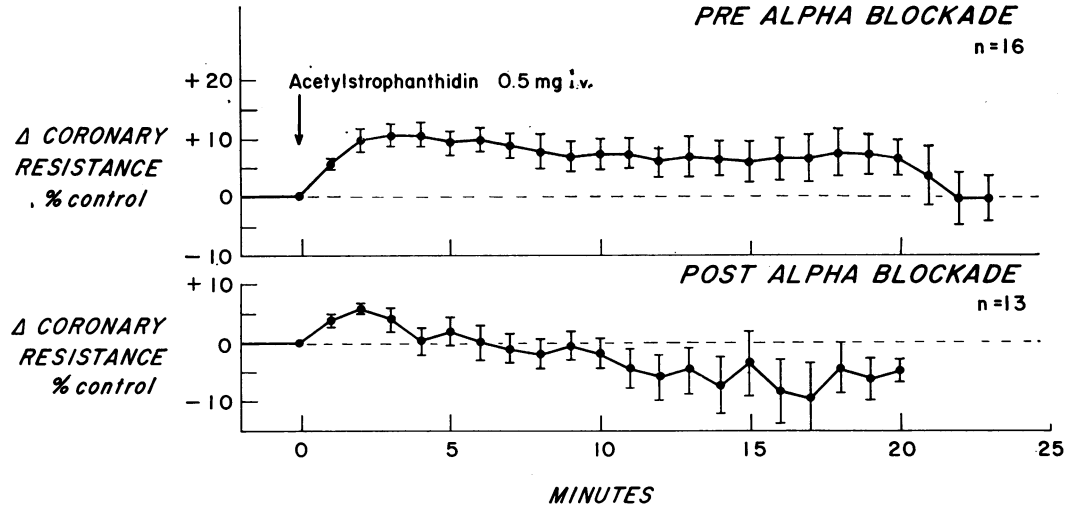


FIGURE 2 The effect of intravenous acetylstrophanthidin before and after alpha adrenergic receptor blockade. Note the sustained increase in CVR, which is secondary to alpha adrenergic receptor stimulation.

TABLE I

*Acetylstrophanthidin Data, after Intravenous Acetylstrophanthidin*

| | Control | 3 min | 9 min | 20 min |
|---|---|---|---|---|
| Before alpha adrenergic blockade | | | | |
| ΔCVR, *% control* | 100 | +11±2 | +6±3 | +7±4 |
| MAP, *mm Hg* | 74±5 | 75±3 | 70±5 | 73±6 |
| LV dp/dt, *mm Hg/s* | 2,200±500 | 2,200±500 | 2,300±550 | 1,900±350 |
| LVEDP, *cm $H_2O$* | 12±1 | 12±1 | 10±1 | 10±2 |
| Heart rate, *beats/min* | 137±6 | 137±6 | 137±6 | 137±6 |
| After alpha adrenergic blockade | | | | |
| ΔCVR, *% control* | 100 | +3±2 | 0±3 | −4±2 |
| MAP, *mm Hg* | 71±4 | 69±4 | 70±4 | 74±6 |
| LV dp/dt, *mm Hg/s* | 3,200±600 | 3,100±550 | 2,700±600 | 2,700±500 |
| LVEDP, *cm $H_2O$* | 10±1 | 9±1 | 9±1 | 9±2 |
| Heart rate, *beats/min* | 134±6 | 134±6 | 134±6 | 134±6 |

MAP, mean aortic pressure; LV dp/dt, the peak first derivative of left ventricular pressure; LVEDP, left ventricular end-diastolic pressure.

and 26.0±1.0 mm Hg 3 min after the injection of acetylstrophanthidin. The corresponding right atrial pressures were 5.7±1.5 and 5.8±1.4 cm $H_2O$. Three separate injections of the vehicle alone (30% ethanol, adjusted for pH) resulted in no change in CVR.

To evaluate whether tachyphylaxis to acetylstrophanthidin could explain the marked dimunition of response to the second injections of the drug, which were given after alpha adrenergic blockade, two dogs were given two injections of acetylstrophanthidin 1 h apart without alpha blockade. The resistance changes were similar after each injection, with an increase in CVR virtually identical to that noted in animals receiving only one injection of acetylstrophanthidin without alpha blockade. Two additional dogs received alpha blockade at the beginning of the experiment and then received an injection of acetylstrophanthidin as the initial administration of the drug. In the latter two dogs the peak increase in CVR was only +7% and +4% at 1 min and 3 min after injection, respectively. In both animals the elevated resistance had returned to control by 4 min. These experiments indicated that tachyphylaxis to acetylstrophanthidin could not explain the difference in CVR between alpha blocked and non-alpha blocked animals.

*Digoxin.* In five dogs anesthetized with sodium pentobarbital, intravenous digoxin (1.0 mg) had no significant effect on CVR. Fig. 3 shows the results.

In nine dogs anesthetized with chloralose and urethane, which have less of a neural depressant effect, intravenous digoxin resulted in an initial decrease (−5±2% SE of control) at 1 min followed by a prolonged rise from 3 to 30 min in CVR (Fig. 4). The peak value was +20±3% of control ($P < 0.01$). The mean time to this peak was 10 min after injection. From 30 min through 55 min the mean resistance remained above control, but this elevation was not statistically significant. The mean control resistance was 1.4±0.1 mm Hg/cm³/min.

Mean aortic pressure was 89±6 mm Hg during the control period and, although it fell slightly, it remained within 6 mm Hg of control until 30 min after injection. Mean pressures at 30, 45, and 60 min were 83±5, 73±6, and 69±6 mm Hg, respectively. The mean pulse pressure was 25.2±0.6 mm Hg during the control period and 25.4±0.3 mm Hg 10 min after the injection of digoxin. Control dp/dt was 4,500±400 mm Hg/s and was 4,300±400, 4,400±300, 3,900±400, and 3,800±600 mm Hg/s at 15, 30, 45, and 60 min, respectively. Control left ventricular end diastolic pressure was 6 cm $H_2O$ and remained within ±2 cm $H_2O$ of this level throughout. The mean right atrial pressure was 12.3±3.7 cm $H_2O$ in the control period and 12.2±3.8 cm $H_2O$ 10 min after the injection of digoxin. The mean heart rate was 150 beat/min and was maintained constant.

Four separate intravenous injections of the vehicle alone (40% propylene glycol, 10% ethanol) into each of four animals resulted in no change in CVR.

In the two dogs anesthetized with intravenous morphine $SO_4$ there were substantial increases in CVR after

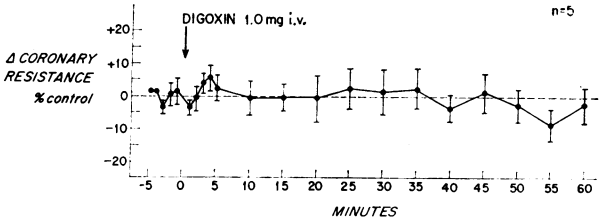


FIGURE 3 The effect of intravenous digoxin on CVR under conditions of sodium pentobarbital anesthesia. Note the lack of a significant change in CVR.,

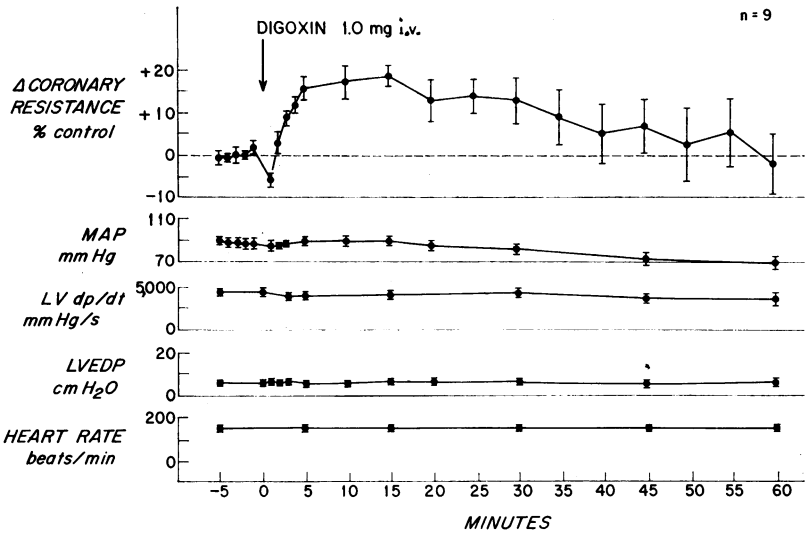


FIGURE 4 The effect of intravenous digoxin (1.0 mg) on CVR under conditions of chloralose and urethane anesthesia. Note the initial decrease followed by a sustained increase in CVR after the intravenous administration of the drug. MAP, mean aortic pressure; LV dp/dt, the peak of the first derivative of left ventricular pressure; LVEDP, left ventricular end-diastolic pressure.

1.0 mg of intravenous digoxin. Peak increases in resistance were 22 and 29% from control resistances of 1.4 and 1.4 mm Hg/cm$^3$/min respectively. Table II contains the data.

In five dogs anesthetized with chloralose and urethane 0.35 mg of intravenous digoxin, one-third of the above dose, also produced an increase in CVR peaking at $+9.5\pm1.0\%$ of control ($P < 0.01$) at 12 min after the injection (Fig. 5 and Table III). This increase in CVR was from a mean control resistance of $1.6\pm0.1$ mm Hg/cm$^3$/min.

To exclude the possibility that the changes in CVR could have been secondary to decreases in myocardial oxygen consumption, observations were made in three additional dogs receiving 1 mg of intravenous digoxin and anesthetized with chloralose and urethane, in the two dogs anesthetized with morphine after 1 mg of intravenous digoxin, and in four of the dogs receiving 0.35 mg digoxin (chloralose and urethane anesthesia). The data for the dogs anesthetized with chloralose and urethane are given in Tables III and IV. In none of the above dogs was there an appreciable decrease in myocardial oxygen consumption at the time of peak vascular resistance increase. In one animal anesthetized with

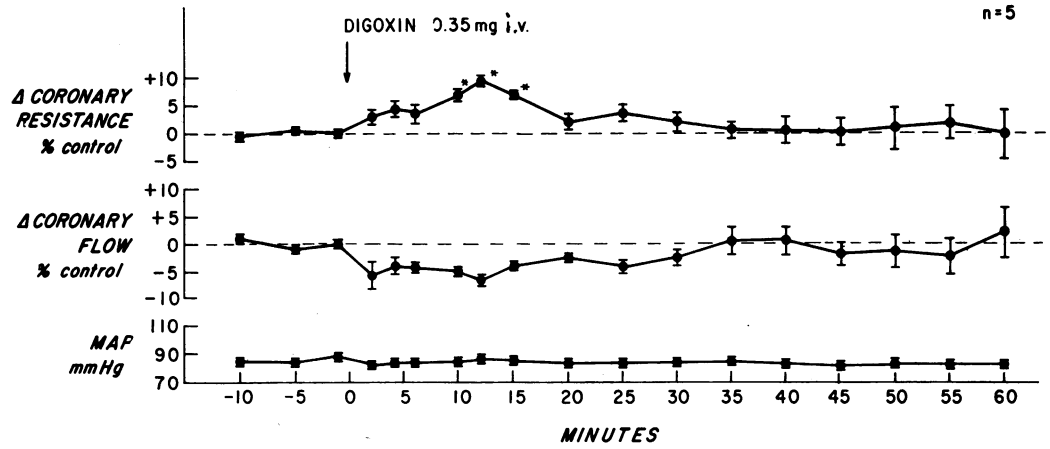


FIGURE 5 The effect of intravenous digoxin (0.35 mg) on CVR, coronary blood flow, and mean aortic pressure (MAP) under conditions of chloralose and urethane anesthesia. The asterisks denote a significant increase in CVR.

TABLE II

*Digoxin Data Obtained with Morphine Anesthesia*

| Time | ΔCVR | Coronary flow | MAP | LV dp/dt | LVEDP | HR |
|---|---|---|---|---|---|---|
| *min* | *% control* | *ml/min/ 100 g LV* | *mm Hg* | *mm Hg/s* | *cm $H_2O$* | *beat/min* |
| Dog 1 | | | | | | |
| Control | 0 | 53 | 81 | 3,525 | 8 | 135 |
| 7.5 | 7.0 | 51 | 83 | 4,150 | 8 | 135 |
| 10 | 1.9 | 53 | 83 | 4,275 | 7.5 | 135 |
| 20 | 22.2 | 44 | 83 | 3,900 | 7.5 | 135 |
| 30 | 15.3 | 47 | 83 | 3,525 | 8.5 | 135 |
| 40 | 9.8 | 49 | 83 | 4,150 | 7.0 | 135 |
| 50 | 5.4 | 51 | 83 | 3,775 | 5.0 | 135 |
| Dog 2 | | | | | | |
| Control | 0 | 66 | 78 | 2,900 | 6 | 135 |
| 7.5 | 18.3 | 57 | 79 | 2,575 | 6 | 135 |
| 10 | 17.9 | 55 | 78 | 2,675 | 6.5 | 135 |
| 20 | 24.5 | 52 | 77 | 2,800 | 5.5 | 135 |
| 30 | 29.1 | 51 | 78 | 3,050 | 6 | 135 |
| 40 | 18.7 | 53 | 75 | 3,650 | 6.5 | 135 |
| 50 | — | — | — | — | — | — |

HR, heart rate; MAP, mean aortic pressure; LV dp/dt: the peak first derivative of left ventricular pressure; LVEDP, left ventricular end-diastolic pressure.

morphine, $M\dot{V}O_2$ by direct Van Slyke determination was 6.6 ml/min/100 g 15 min after injection, when vascular resistance had increased 21.5%, compared with a control $M\dot{V}O_2$ of 6.7 ml/min/100 g. In the other dog there was a slight decrease in $M\dot{V}O_2$ from 6.8 to 6.5 ml/min/100 g 25 min after injection, when vascular resistance was 20.1% above the control level. These findings were associated with only small changes in mean ejection rate from 0.145 to 0.143 s/beat and 0.172 to 0.170 s/beat, respectively.

After alpha adrenergic blockade (10 additional dogs), intravenous digoxin (1.0 mg) resulted in an initial decrease in CVR (− 6±3% of control) at 1 min followed by no significant change in mean CVR (Fig. 6). The mean control resistance was 1.0±0.2 mm Hg/cm³/min. This was not significantly lower than in the dogs that had not received an alpha receptor blockade. Control mean aortic pressure was 78 mm Hg, and was 70 mm Hg at 5 min, and 60 mm Hg at 30 min. In three animals that maintained their aortic pressures at near constant levels (83±5 mm Hg control; 78±5 mm Hg after 10 min) the change in CVR was not significant (+ 5±10%) at 10 min after injection; in these three animals mean control CVR was 1.2±0.3 mm Hg/cm³/min. Mean heart rate was 145 beat/min and constant.

After ganglionic blockade with mecamylamine (seven dogs), intravenous digoxin (1.0 mg) resulted in an initial dip (− 5±2% of control) at 1 min, followed by no significant change in mean CVR (Fig. 7). The mean control resistance was 1.4±0.1 mm Hg/cm³/min, again not significantly different from the animals without blockade. Control mean aortic pressure was 75 mm Hg and was constant through 20 min after which it rose slightly to 76 mm Hg at 30, and 83 mm Hg at 60 min.

TABLE III

*Mean Data Obtained from 0.35 mg Digoxin i.v. Experiments*

| Time | LV dp/dt | LVEDP | Systolic ejection period | HR | $M\dot{V}O_2$ |
|---|---|---|---|---|---|
| *min* | *mm Hg/s* | *cm $H_2O$* | *s* | *beat/min* | *ml/min/100 g LV* |
| Control | 2,800±441 | 8.2±1.1 | 0.187±0.008 | 145±4 | 8.2±0.4 |
| 12 min | 2,960±450 | 8.1±1.4 | 0.187±0.006 | 145±4 | 8.3±0.3 |
| 60 min | 3,080±359 | 10.2±1.5 | 0.186±0.006 | 145±4 | 9.6±0.3 |

$n$ = 5; HR, heart rate; MAP, mean aortic pressure; LV dp/dt, the peak first derivative of left ventricular pressure; LVEDP, left ventricular end-diastolic pressure.

TABLE IV

*Myocardial Oxygen Consumption Studies (1.0 mg Digoxin i.v.)*

| Time | Dog. 1 | | | | Dog 2 | | | | Dog 3 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Δ Coronary resistance | Coronary flow | $M\dot{V}O_2$ | Systolic ejection period | Δ Coronary resistance | Coronary flow | $M\dot{V}O_2$ | Systolic ejection period | Δ Coronary resistance | Coronary flow | $M\dot{V}O_2$ | Systolic ejection period |
| *min* | *% control* | *ml/min* | *ml/min/100 g* | *s* | *% control* | *ml/min* | *ml/min/100 g* | *s* | *% control* | *ml/min* | *ml/min/100 g* | *s* |
| Control | 0 | 45 | 3.8 | 0.180 | 0 | 66 | 4.6 | 0.145 | 0 | 79 | 2.6 | 0.190 |
| 7.5 | 8.2 | 40 | 3.6 | 0.180 | 8.5 | 60 | 4.5 | 0.150 | 10.0 | 75 | 2.7 | 0.190 |
| 10 | 7.7 | 43 | 4.1 | 0.180 | 7.4 | 61 | 4.6 | 0.145 | 4.3 | 76 | 2.8 | 0.190 |
| 15 | 9.8 | 41 | 3.8 | 0.175 | 0.3 | 61 | 4.6 | 0.140 | 0.6 | 77 | 2.8 | 0.185 |
| 18 | 6.5 | 39 | — | 0.175 | 5.9 | 66 | 4.7 | 0.145 | 4.2 | 76 | 2.8 | 0.190 |
| 20 | 4.3 | 38 | 3.7 | 0.175 | 5.3 | 68 | 4.8 | 0.150 | 1.9 | 76 | 2.8 | 0.190 |
| 25 | 0 | 38 | 3.8 | 0.175 | −8.7 | 67 | 4.8 | 0.150 | 4.2 | 76 | 2.8 | 0.195 |
| 30 | 3.8 | 35 | 3.8 | 0.175 | −7.5 | 67 | 4.6 | 0.150 | −0.7 | 78 | 2.9 | 0.190 |
| 50 | −9.8 | 38 | 4.0 | 0.180 | −15.0 | 74 | 5.1 | 0.140 | 0.8 | 78 | 2.9 | 0.200 |

The absolute control CVR's for dogs 1, 2, and 3 were 1.8, 1.2, and 1.2, respectively.

In three of the dogs in which control mean aortic pressure was comparable to the mean pressure in the unblocked animals, i.e., 82, 98, and 85 mm Hg, CVR changed little (i.e. + 6%, − 0%, and + 0%) at 10 min after injection. Control left ventricular dp/dt was 2,250 ±375 mm Hg/s and remained constant through 30 min, after which it rose to 2,750±500 mm Hg/s at 45 and 60 min. Mean left ventricular end diastolic pressure remained consistently at or below 10 cm $H_2O$. The mean heart rate was 150 beat/min and constant.

In two additional dogs the intravenous injection of 1 mg of digoxin after bilateral vagotomy was still associated with a substantial increase in vascular resistance, suggesting that the heart and lungs are unlikely sites for afferent receptors. In these animals the increases in CVR at 10 min after injection were + 14% and + 15%.

## DISCUSSION

These data suggest that both intravenous acetylstrophanthidin and intravenous digoxin have acute coronary vasoconstrictor properties. The vasoconstriction is primarily neurogenic and is largely mediated via alpha adrenergic receptor stimulation. This alpha adrenergic effect appears to be a major mechanism, whereby digitalis increases CVR.

The alpha receptor-mediated vasoconstriction occurs within several minutes after the intravenous administration of digoxin and acetylstrophanthidin, a time substantially before the established increase in inotropic effect of these drugs (10). The vasoconstrictor effect is sustained, with coronary resistance maintained substantially above control levels. It is during this time period

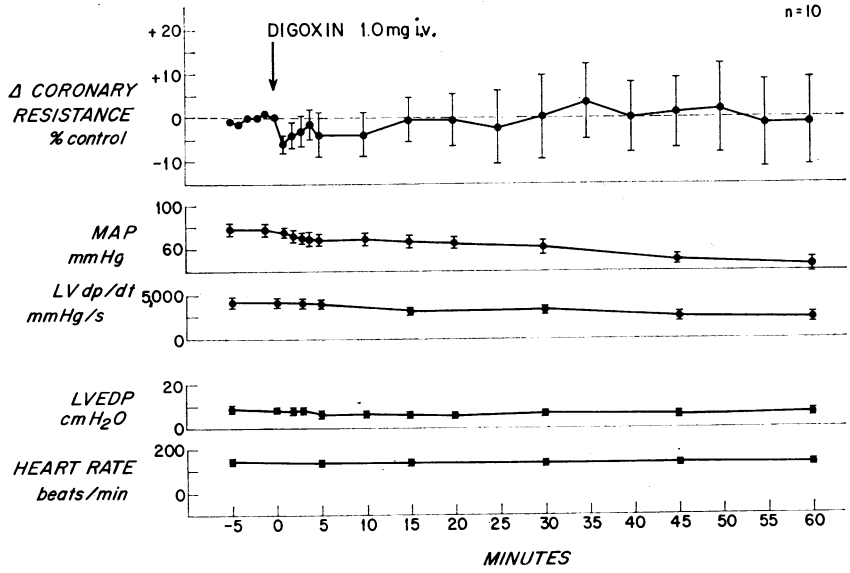


FIGURE 6 The effect of intravenous digoxin on CVR after alpha adrenergic receptor blockade under conditions of chloralose and urethane anesthesia. Note the lack of a significant increase in CVR after intravenous digoxin. Abbreviations as in Fig. 4.

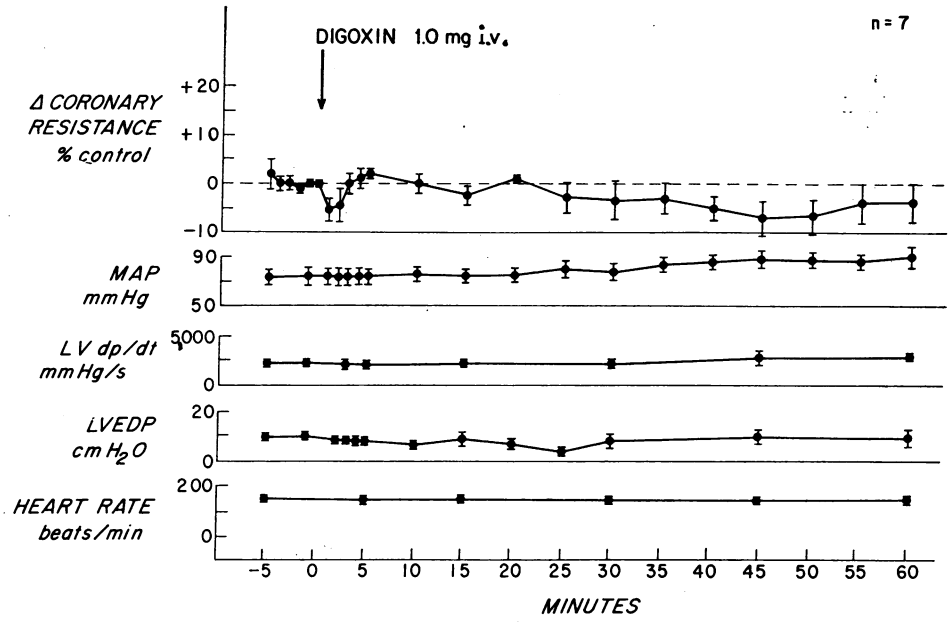


FIGURE 7 The effect of digoxin on CVR after ganglionic blockade under conditions of chloralose and urethane anesthesia. Again note the lack of a significant increase in CVR after intravenous digoxin. Abbreviations as in Fig. 4.

that other investigators have described the appearance of ischemic pain (11), cardiac arrhythmias (12), and in several instances acute pulmonary edema (12, 13) in patients after intravenous digitalization; these complications accompanying digitalis administration may be related, at least in part, to alpha adrenergic vasoconstriction of the coronary vasculature. The increase in vascular resistance then diminishes at a time which corresponds to the greatest increase in the positive inotropic effect of the digitalis preparation being used (10).

The present data indicate that this alpha constrictor effect on coronary vasculature is mediated via the efferent limb of the sympathetic nervous system. The site of action of digoxin and acetylstrophanthidin appears to be at, or proximal to, the sympathetic ganglia. The data from a recent study from our laboratory (4) demonstrating the predominance of a neurogenic effect of acetylstrophanthidin on skeletal muscle vascular resistance helps to localize further this site of action. In that study vagotomy or carotid body denervation did not alter significantly the magnitude of the vasoconstrictor effect in skeletal muscle, suggesting that the heart and lungs or the carotid bifurcations were unlikely sites for afferent receptors. This evidence, in conjunction with the present study, suggests that the site of action of digoxin and acetylstrophanthidin-induced coronary vasoconstriction is most likely to be in the central nervous system or at sympathetic ganglia. However, exact localization remains to be determined.

The results of the present study are consonant with the coronary vasoconstrictor properties of ouabain after intravenous administration described by Vatner, Higgins, Franklin, and Braunwald (3) and by Bloor, Walker, and Pensinger (14). The present data suggest the mechanism whereby coronary vasoconstriction was demonstrable in the experiments by the former authors in conscious dogs but not in the same dogs anesthetized with sodium pentobarbital. As neurogenic and possibly central nervous system effects are being evaluated, the type of anesthesia employed is important. Since sodium pentobarbital has been shown to have significant central nervous system, sympathetic nerve, and ganglionic depressant effects (15, 16), it is likely that the neurogenic vasoconstrictor effect on CVR of ouabain in their study was reduced by barbiturate anesthesia. Chloralose and urethane, which has been used only in animal experiments because of its late toxic manifestation, has less of a central nervous system depressant effect. Our study compares the influence of either chloralose and urethane or morphine anesthesia with that of pentobarbital on the coronary vasoconstrictor effect of digoxin. The finding that the neurogenic effect of digoxin was demonstrable with the former but not with pentobarbital anesthesia is consistent with the neural depressant effect of barbiturates.

The lack of a significant increase in left ventricle dp/dt after the digitalis preparations used in the present experiments is most likely secondary to two factors. First, Daggett and Weisfeldt (17) have shown that the administration of digitalis in dogs anesthetized with

chloralose and urethane and not in congestive heart failure results in reflex withdrawal of cardiac beta adrenergic receptor activity in the heart and no net change in contractility. As already mentioned, it is likely in the present study and in the experiments by Daggett and Weisfeldt that reflex neurogenic activity was maintained intact with the anesthesia used. The findings of Vatner, Higgins, Patrick, Franklin, and Braunwald (18) are consistent with this, in that these authors found that ouabain exerts little inotropic effect in conscious dogs but a significant effect in dogs anesthetized with pentobarbital, which would presumably depress reflex nervous system activity more than chloralose and urethane. It is of interest in this regard that a recent report by Lipp, Denes, Gambetta, and Resnekov (19) emphasized that in patients with acute myocardial infarctions without clinical congestive failure, intravenous digoxin did not change significantly either the stroke index or diastolic pulmonary artery pressure. Second, mean arterial blood pressure decreased in some of the experiments in the present series with a resultant decrease in left ventricle dp/dt. It should be emphasized, however, that the early alpha constrictor effect occurs in the coronary vasculature at a time when there are no associated hemodynamic changes (Fig. 4).

Thus, intravenous acetylstrophanthidin and digoxin result in acute coronary vasoconstriction, which is largely mediated via the alpha adrenergic system. This emphasizes the physiologic importance of alpha adrenergic receptors in the coronary vasculature and describes an important pharmacologic effect of digitalis.

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