Effects of Acetylstrophanthidin on Coronary Vascular Resistance and Myocardial Oxygen Consumption

By John A. Waldhausen, M.D., James W. Kilman, M.D., Thomas L. Herendeen, M.D., and Francis L. Abel, M.D., Ph.D.

The primary clinical indication for digitalis therapy is congestive heart failure and the inotropic effect of digitalis preparations has been demonstrated in both experimental animals and man. However, studies by Ross et al. have shown that digitalis affects not only myocardial contractility but also total peripheral resistance. In view of the latter effects, we have to consider the possibility that digitalis may have a direct action on the coronary vascular bed. Since coronary artery disease frequently accompanies or directly causes congestive heart failure, any action of digitalis on the coronary vascular bed might be of clinical importance.

Previous studies of the effects of digitalis preparations on coronary flow have been inconclusive. Frank et al. found that strophanthin decreased coronary blood flow in the intact anesthetized dog; whereas, in a similar experiment acetyldigitoxin increased flow and digitoxin had no effect. Dearing et al. found no change of coronary flow in the dog with therapeutic doses of digitalis. Page et al. demonstrated an increase of coronary resistance following administration of ouabain. Cardiac oxygen consumption was maintained at the expense of a decrease in coronary venous oxygen saturation. In contrast, strophanthus, as studied by Bing et al., had no significant effect on coronary vascular resistance or oxygen consumption.

The present studies were undertaken in an attempt to control some of the factors known to influence coronary flow and resistance, i.e., changes of myocardial contractility and cardiac output (systemic flow). In these experiments the response to acetylstrophanthidin was studied in the empty fibrillating heart while systemic blood flow was kept constant.

Methods

Thirty-one mongrel dogs weighing from 11.1 to 24.4 kg were anesthetized with 30 mg/kg sodium pentobarbital intravenously. A right thoracotomy was performed; the superior and inferior vena cava and femoral artery were cannulated (fig. 1). Heparin (3 mg/kg body wt) was given intravenously. Complete cardiopulmonary bypass was established, using an occlusive, precalibrated Sigmamotor pump and rotating disc oxygenator. The left atrium and ventricle were drained into the extracorporeal system. A cannula, placed in the right atrium and ventricle, drained into a calibrated reservoir attached to the venous end of the oxygenator. The pulmonary artery was occluded. Total systemic flow was maintained constant with the aid of an electromagnetic flowmeter and averaged 100 ml/min/kg body wt. Pressures in the central aorta, right atrium, and left ventricle were measured by Statham pressure transducers and were recorded continuously on a multichannel oscillograph. Body temperature was kept between 36 and 38°C by means of a heat exchanger in the arterial line. Right heart venous return (coronary blood flow) was measured at five-minute intervals by noting the rate of change of pressure in the bottom of the reservoir when the outflow was occluded. Arterial and

*Kindly supplied by Eli Lilly Company, Indianapolis, Indiana.
FIGURE 1

Diagram of preparation used to study effects of acetylstrophanthidin on coronary circulation. Systemic venous blood is diverted to a venous reservoir and oxygenated in a rotating disc oxygenator. After passing through a heat exchanger it is pumped into the aorta (A) through a femoral artery. Coronary venous return is drained from the right ventricle (RV) and right atrium (RA) into a calibrated reservoir. Left ventricle (LV) and left atrium (LA) are decompressed. Pulmonary artery (PA) is ligated. Systemic flow is monitored by an electromagnetic flowmeter.

right heart venous blood samples were obtained during the control period, at one minute after injection of acetylstrophanthidin, and between 15 and 20 minutes after injection. Blood oxygen content was determined spectrophotometrically. The digitalis preparation was injected into the arterial end of the oxygenator after the observed parameters had stabilized. In 14 animals, given from 0.021 to 0.083 mg/kg acetylstrophanthidin, ventricular fibrillation was induced and maintained with a 3 volt, 60 cycle alternating current applied directly to the myocardium. In eight animals, 0.041 mg/kg acetylstrophanthidin was given but the empty heart was allowed to beat. Although the therapeutic and mean lethal doses of acetylstrophanthidin have not been standardized for the dog, bio-assay in cats would suggest that the lower two doses given in this study were in the therapeutic range. The electrocardiogram was recorded in order to reveal any evidence of digitalis toxicity indicated by cardiac arrhythmias. Myocardial contractility was measured by means of a Walton-Brodie strain gauge arch sutured to the left ventricle. In three dogs, prior to the injection of acetylstrophanthidin, but after ventricular fibrillation was induced, ganglionic blockade was produced with 4 mg/kg hexamethonium, and then maintained by constant infusion of 0.2 mg/kg/min of this drug into the arterial end of the oxygenator. In two other animals with ventricular fibrillation, the heart was denervated through a sternum-splitting incision. In three additional animals a bilateral adrenalectomy was done prior to the study.

Results

In all 14 dogs in which ventricular fibrillation was induced and acetylstrophanthidin given, there was an initial rise of coronary vascular resistance and a fall of coronary blood flow (fig. 2, upper panel). Coronary constriction was maximal at one minute after injection and lasted approximately five min-

FIGURE 2

Effects of acetylstrophanthidin on coronary blood flow (CBF) and coronary resistance (CR) in ventricular fibrillation. Upper panel: acetylstrophanthidin, 0.083 mg/kg. Middle panel: acetylstrophanthidin, 0.041 mg/kg. Lower panel: acetylstrophanthidin, 0.021 mg/kg.
utes. This was followed by a significant drop of resistance with a concomitant rise in coronary blood flow, which persisted for the remainder of the period of observation (up to one hour). The degree of initial constriction and subsequent dilatation was directly related to the amount of acetylstrophanthidin given. Simultaneously with the changes noted in the coronary vascular bed, the systemic vascular resistance increased 44% (fig. 3) and then gradually returned to the control value.

When 0.083 mg/kg acetylstrophanthidin was given, the maximum initial rise in coronary vascular resistance averaged 56% above control while coronary blood flow fell by an average of 16%. The average maximal fall in coronary resistance, which occurred from 15 to 25 minutes after the injection of 0.083 mg/kg acetylstrophanthidin, was 47% at which time coronary blood flow averaged 92% above control. Upon injection of 0.041 mg/kg acetylstrophanthidin, coronary resistance rose initially by an average of 25% and blood flow fell by 13%. The peak rise in flow averaged 66% with a fall in resistance of 35%. With the injection of 0.021 mg/kg the initial rise in coronary resistance averaged 32% and the coronary flow fell by 13%. The maximum secondary coronary dilatation was 32% and coronary flow rose by 46%.

In two dogs in which total cardiac denervation was performed prior to perfusion and induction of ventricular fibrillation, the injection of 0.041 mg/kg acetylstrophanthidin produced effects similar to those observed in dogs with intact sympathetic and parasympathetic nerves (table 1). Likewise, there was no significant difference in the results obtained from three animals that had ganglionic blockade produced with hexamethonium. Bilateral adrenalectomy did little to alter the changes in coronary vascular resistance.

In nine animals a normal heart beat was maintained. Cardiac arrhythmias suggesting digitalis toxicity were not seen in this group of animals. The initial coronary constriction lasted longer than in fibrillating hearts, and

<table>
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<th>Associated procedure</th>
<th>Expt. no.</th>
<th>Coronary resistance per cent of control 1 min</th>
<th>Coronary resistance per cent of control 15 min</th>
<th>Coronary blood flow per cent of control 1 min</th>
<th>Coronary blood flow per cent of control 15 min</th>
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Effects of Acetylstrophanthidin on Coronary Circulation

| TABLE 1 |

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the degree of constriction was more severe (fig. 3). The maximum average increase of resistance was 63% above control with a fall in coronary flow of 13%. The secondary coronary dilatation, noted in the fibrillating hearts, was present to a lesser degree in the beating hearts, and coronary vascular resistance had returned almost to the control state within 20 minutes after the injection of acetylstrophanthidin. Myocardial contractility, measured by a strain gauge arch, increased in all animals studied and averaged 31% above control. Myocardial oxygen consumption was decreased usually in transient fashion during the initial constriction phase of the vascular response to acetylstrophanthidin. Subsequently the oxygen consumption increased, reaching values 50 to 100% greater than control in the period 20 to 25 minutes after injection of the drug as shown in table 2.

Discussion
The study of a pharmacologic preparation such as digitalis, with relation to its effects on coronary circulation, is hindered because several of the determinants of coronary blood flow are altered by the drug. It is well established that coronary resistance rises with an increase of ventricular contraction which may be produced by digitalis preparations. Similarly, cardiac output and aortic pressure, which may be affected by digitalis, influence coronary flow. In the present preparation an attempt was made to keep mechanical activity of the nonworking heart at a constant level. Because the right atrial pressure was maintained at 0 mm Hg or even slightly below by adjusting the tip of the catheter draining the right heart, the amount of work expended in pumping blood into the venous reservoir was probably not significant even in the beating heart. To eliminate most of the effects of ventricular contraction on coronary blood flow, ventricular fibrillation was induced in one group of animals. Systemic flow was maintained constant with a mechanical pump. Al-

<table>
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<th>Dosage</th>
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though the determination of coronary blood flow by the method described omits measurement of coronary blood draining into the left ventricle by the Thebesian veins and by arterio-luminal and sinusoidal vessels, this amount is probably insignificant when compared with the volume returning to the right heart.18

The initial rise in coronary vascular resistance and fall in coronary blood flow is similar to the increase of total peripheral resistance noted in all animals given digitalis preparations as previously reported.8 An increase of renal vascular resistance has also been noted.19 It is apparent from these and other studies20 that this effect of digitalis is due to direct stimulation of vascular smooth muscle and that denervation and ganglionic blockade do not abolish the constriction.

Following the initial vasoconstriction in the fibrillating heart, there is a prolonged fall in coronary vascular resistance and a rise in coronary blood flow. Associated with these changes is a rise in myocardial oxygen consumption. Since digitalis increases myocardial contraction in the beating heart, as measured by the Walton-Brodie strain gauge arch (fig. 3), and since fibrillation, when present, appears grossly more vigorous after acetylstrophanthidin, an increase of oxygen consumption would be expected.21 However, the relationship of oxygen consumption to coronary blood flow is not clearly established.22

Kahler et al.22 observed a rise in myocardial oxygen consumption when coronary blood flow in a nonworking heart was increased or vice versa. Berne28 and his co-workers found that epinephrine and norepinephrine produced a secondary coronary vasodilatation concomitant with an increase of myocardial oxygen consumption. They ascribed the increase of coronary blood flow to an increased oxygen consumption and were able to inhibit the rise in blood flow by stopping the heart with potassium chloride. However, potassium chloride may affect not only the membrane of the myocardial cell but that of the coronary smooth muscle as well. Perhaps isolation of coronary vascular strips with direct applications of digitalis preparations would indicate whether the late vasodilatation of the coronaries with acetylstrophanthidin is primary or secondary.

The animals with beating hearts showed initial coronary vasoconstriction, but this was prolonged in comparison with the fibrillating hearts. Although only minimal vasodilatation was noted in the beating hearts, there was a rise in myocardial oxygen consumption. Much of the lack of vasodilatation can be attributed to the increase of myocardial contraction from acetylstrophanthidin (fig. 3), producing an increased mechanical resistance to coronary flow and thus modifying the coronary vasodilator effect of acetylstrophanthidin.

Ganglionic blockade and cardiac denervation did not abolish the changes in coronary blood flow and myocardial oxygen consumption produced by acetylstrophanthidin. In view of the studies of Leonard20 it is evident that the initial constriction is a direct action of the drug on the smooth muscle of the vessel. In addition, autonomic reflexes did not take part in the increase of coronary blood flow noted approximately 10 minutes after injection of acetylstrophanthidin, because cardiac denervation did little to alter the response.

To exclude an endogenous release of epinephrine, which also produces a similar effect on the coronary circulation, a bilateral adrenalectomy was performed prior to the administration of the digitalis preparation. No significant difference in the response of the coronaries to the drug was noted.

These studies indicate that digitalis preparations produce a transient rise in coronary vascular resistance due to a direct action on the vessel. This period of vasoconstriction is followed by a period of sustained increase of coronary blood flow. Myocardial oxygen consumption is increased in association with the increased flow. Since coronary blood flow is dependent on several factors which are altered by digitalis, particularly ventricular contraction, the increase of coronary blood flow may vary in magnitude.
Summary

The effects of acetylstrophanthidin on coronary circulation were studied in 31 dogs. Coronary blood flow was measured in empty beating hearts or in fibrillating hearts by collecting coronary venous return during perfusion of the systemic circulation (cardiopulmonary bypass). In 14 animals with ventricular fibrillation, acetylstrophanthidin caused an initial coronary constriction and fall in coronary blood flow. This was followed, after approximately 10 minutes, by a significant drop in resistance and a rise in coronary blood flow which persisted for the remainder of the experiment. Associated with the increase of blood flow was an increase of myocardial oxygen consumption. This effect was not abolished by ganglionic blockade, cardiac denervation or bilateral adrenalectomy.

In nine dogs with beating but empty hearts, after the initial constriction of the coronary vessels, there was only a small change in coronary blood flow and resistance, although myocardial oxygen consumption was increased. The lack of coronary vasodilatation was attributed to increased mechanical resistance due to the augmented force of contraction produced by the drug.

References

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JOHN A. WALDHAUSEN, JAMES W. KILMAN, THOMAS L. HERENDEEN and FRANCIS L. ABEL

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