Extracardiac and Coronary Vascular Effects of Digitalis

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The administration of digitalis glycosides causes a variety of extracardiac effects. In both normal human subjects and in other species, digitalis increases smooth muscle tone of resistance and capacitance vessels. The vasoconstriction is mediated, in part, by a direct action of these glycosides on smooth muscle and, in part, by an increase in alpha-adrenergic tone. Constriction of coronary and splanchnic vessels may lead to myocardial or mesenteric ischemia. In contrast to normal subjects, patients with congestive heart failure demonstrate arteriolar and venodilation in response to these glycosides, possibly because the myocardial effect, to increase cardiac output and peripheral blood flow, overcomes the vasoconstrictor properties of these drugs. Other important actions of digitalis glycosides occur in the central nervous systems. Their effects on the area postrema of the medulla oblongata are largely responsible for the alpha-adrenergic–mediated peripheral vasoconstriction, as well as the nausea and vomiting that frequently accompany digitalis intoxication. Actions of glycosides on the cerebral cortex are responsible for the wide range of neurotoxic effects that range from visual disturbances and headaches to seizures and coma. Finally, peripheral neurologic effects of digitalis glycosides on baroreceptor and cardiac afferent fibers may: 1) improve the depressed function of these receptors in the situation of heart failure, and 2) reflexly lower peripheral vascular resistance, thereby partially preventing the vascular constrictor action of these glycosides.

Peripheral Circulation

Studies in Experimental Animals

Arterioles. The intraarterial or intravenous injection of ouabain in anesthetized pigs, rabbits and dogs causes local vasoconstriction and an increase in total peripheral vascular resistance (2–5). Differences between various cardiac glycosides appear to exist, because digoxin does not alter systolic blood pressure or systemic vascular resistance (4). Acetylstrophanthidin administered to conscious dogs causes an increase in myocardial contractility but does not alter systemic or pulmonary vascular resistance (6–8). However, ouabain causes a nonuniform regional circulatory effect in the conscious dog (9). For instance, there is an initial vasoconstriction followed by a more prolonged vasodilation in the mesenteric vascular bed and a prolonged constriction in the renal and iliac circulations. Although normotensive dogs respond to intravenous digoxin with sustained vasoconstriction, animals made hypotensive by hemorrhage develop a short-lived vasoconstriction followed by a more prolonged period of vasodilation (10). The mechanism of the vasoconstriction is alpha-adrenergic, whereas the vasodilation in hypotensive animals is cholinergic.

Studies on the regional circulatory response to digitalis glycosides have revealed an alpha-adrenergic vasoconstrictor component in the hindlimb, skeletal muscle and mesenteric circulations (10–14). In contrast to the action of other vasoconstrictor agents, such as catecholamines, angiotensin II, prostaglandin F2α, dopamine and vasopressin, digoxin infused into the mesenteric artery of dogs decreases blood flow and reduces oxygen consumption of the gut (14). Oxygen consumption is reduced because the small increase in

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arteriovenous oxygen extraction does not fully compensate for the reduced blood flow. Other studies have shown that mesenteric vascular resistance increases after the administration of digoxin in dogs that have a proximal mesenteric artery stenosis (12).

Thus, although there is some variation in the effect of different cardiac glycosides, most compounds cause arteriolar vasoconstriction in normotensive animals. This effect is observed in the skeletal muscle and splanchnic circulation. This increase in smooth muscle tone is mediated, in part, by an increase in alpha-adrenergic stimulation and, in part, by direct effects on vascular smooth muscle as discussed subsequently.

Veins. Tainter and Dock (15) and Rodman and Pastor (16) suggested that venous pooling occurred in the splanchnic circulation after the administration of cardiac glycosides. Later studies using high doses of acetylstrophanthidin, an aglycone, showed that in the dog this pooling was associated with an increase in portal vein pressure (5,17-19). However, a more recent examination of the capacitance vessels in dogs has shown that ouabain actually decreases total peripheral vascular capacity, characterized by a reduction in splanchnic and extrasplanchnic blood volumes (20). The decrease in splanchnic blood volume occurs despite an increase in transhepatic resistance. Although alpha-adrenergic blockade prevents the increase in transhepatic resistance, it does not reduce the generalized venoconstriction. This observation suggests that the effect of digitalis on total vascular capacity is mediated by a direct action on vascular smooth muscle. Thus, ouabain causes constriction of splanchnic and extrasplanchnic capacitance vessels of the dog. However, acetylstrophanthidin administration increases transhepatic venous resistance, an action which may overcome the splanchnic constriction and lead to pooling of blood in this circulation.

Studies in Patients

Arterioles and veins. The finding of arteriolar constriction in animals has been confirmed in patients undergoing open heart surgery during constant perfusion of the systemic circulation (21). Thus, both acetylstrophanthidin and lanatoside-C increase systemic vascular resistance by an average of 23%. The change in arteriolar resistance is of earlier onset and shorter duration than the inotropic action of digitalis glycosides. Ouabain induces both direct arteriolar and venoconstriction in the forearm of normal subjects (22). In contrast, patients with congestive heart failure demonstrate both venodilation and arteriolar dilatation in response to ouabain (22). Although the mechanism for the digitalis-induced vasodilation is not entirely understood, it may stem from the observation that there is a high arteriolar and venous tone at rest consequent to increased neurohumoral activity present in heart failure (23). Thus, the improved cardiac output and peripheral blood flow consequent to the effect of digitalis on the myocardium lowers sympathetic tone. The reduction in sympathetic tone presumably is greater than the direct vasoconstrictor action of digitalis, and therefore leads to a net decrease in arteriolar and venous vascular resistance. Another possible explanation for the observed vasodilation is that digitalis may either stimulate or sensitize arterial baroreceptor and cardiac afferents to reflexly lower peripheral vascular resistance (see following for detailed explanation).

Mesenteric circulation. Digoxin administration has been found to reduce splanchnic blood volume in subjects without heart disease (24,25). The fact that rapid digitalization occasionally leads to the development of acute pulmonary edema in some patients with heart disease is thought to be secondary either to: 1) the peripheral arteriolar vasoconstrictor effect of this drug, which becomes manifest before its positive inotropic action, or 2) a translocation of blood volume from the splanchnic to the pulmonary circulation (26,27). It is likely that the extracardiac arteriolar effects of digitalis in human beings prevent an increase in cardiac output in healthy patients, despite an increase in myocardial contractility.

Digitalis administration has been associated with mesenteric infarction, which, in some instances, results in fatal hemorrhagic necrosis of the gut (28,29). In this regard, long-term administration of digitalis glycosides has been associated with chronic ischemia of the gut (29,30). Additionally, malabsorption syndromes have been found in some patients with congestive heart failure who are being treated with digitalis glycosides (31,32). These mesenteric syndromes may result from the arteriolar vasoconstriction caused by the cardiac glycosides that has been amply demonstrated in animal preparations, as described previously.

Coronary Circulation

Ouabain causes a short duration (<30 minutes) constriction of coronary arteries in anesthetized dogs (33,34), healthy human subjects (35,36) and patients with coronary artery disease (37). The increase in coronary vascular resistance can be prevented if ouabain is injected slowly over a 2 minute period rather than rapidly over a 10 second period (35). Coronary flow at rest is reduced and coronary vascular resistance is increased in patients with coronary disease after a 5 minute infusion of 1 mg of digoxin (38). The human myocardium has been shown to produce lactate and, in certain circumstances, an increase in left ventricular end-diastolic pressure occurs after rapid infusion of ouabain (15 µg/kg body weight) (35). This observation has been confirmed in dogs that, under the condition of global myocardial ischemia, may develop an alpha-adrenergic-mediated increase in coronary vascular resistance, an increased left ventricular end-diastolic pressure and subsequent ventricular fibrillation after injection of 0.5 mg of acetylstrophanthinidin (39). These effects are thought to represent an increase in myocardial ischemia.
Investigators have speculated that the increase in myocardial ischemia associated with digoxin administration in the presence of a small infarction is consequent to an augmentation of myocardial oxygen demands (40). On the other hand, it is possible that the coronary vasoconstrictor effect of digitalis glycosides leads to a worsening of ischemia with subsequent deterioration of myocardial performance (35,39).

However, in most patients with coronary artery disease without heart failure, the effect of a slow infusion of a digitalis glycoside on myocardial ischemia is thought to represent a trade off between the decrease in end-diastolic volume versus the increased contractile state and associated increase in afterload with little effect on coronary vascular resistance (36,38,41). In the presence of congestive heart failure, the decrease in end-diastolic volume and improved contractility serve to reduce wall tension and myocardial oxygen consumption, thereby offsetting the effect of the increased contractile state, which augments myocardial oxygen consumption.

Smooth Muscle of the Gastrointestinal Tract

Some of the more debilitating side effects associated with digitalis are nausea, vomiting and diarrhea (42). The digitalis glycosides have been demonstrated by radiographic techniques to increase visceral smooth muscle tone and decrease the transit time through the gastrointestinal tract (43). These effects on visceral smooth muscle have been demonstrated to occur in several other organs, including the isolated uterus, vas deferens, bronchial smooth muscle and gallbladder, after exposure to digitalis glycosides (44). With respect to the gastrointestinal tract, there appears to be an order of sensitivity with the rectum being most sensitive, teniae coli of the colon somewhat less sensitive, the ileum still less sensitive and gastric strips the least sensitive (45).

The Kidney

Cardiac glycosides produce diuresis and natriuresis through a direct action on the kidney (46–50). In part, the natriuretic effect may be mediated through inhibition of sodium reabsorption in the distal nephron (51). The natriuretic effect of ouabain varies depending on the intrarenal distribution of filtered sodium at the time of the experiments (52). The diuretic action of digitalis glycosides is dependent on its effect on the membrane adenosine triphosphate (ATPase) system (53,54).

The Endocrine System

Long-term therapy with digitalis can cause gynecomastia in men and breast enlargement in women (55–57). This side effect can be accompanied by pain. It is associated with an elevation in the serum estrogen level and a decrease in serum leutinizing hormone and plasma testosterone (58). Also, it has been suggested that the structural similarity between digitalis glycosides, their metabolites and estrogen causes this disturbing side effect (59).

Mechanisms Underlying the Extracardiac and Toxic Actions of Digitalis

There appear to be several important mechanisms through which digitalis glycosides exert their extracardiac effects. These include: 1) a direct smooth muscle action, 2) an indirect effect on smooth muscle mediated by direct stimulation of the central nervous system to increase alpha-adrenergic tone, and 3) an indirect effect caused by reflex stimulation of baroreceptor and cardiac afferent nerve endings.

Direct smooth muscle effects of digitalis. Many of the cardiovascular, circulatory and gastrointestinal effects of digitalis appear to be caused by a direct action on smooth muscle. For instance, isolated human crural arteries and veins develop long-lasting contractions in the presence of digoxin (60). These contractions are not diminished by alpha-adrenergic blockade but can be abolished by the calcium entry antagonist, nifedipine. The contractile response of aortic strips to electrical stimulation can be potentiated with ouabain (61). Furthermore, the contraction caused by noradrenaline is potentiated by ouabain (61).

Potentially, there are three mechanisms by which the digitalis glycosides may increase smooth muscle tone. All three mechanisms lead to an increase in intracellular calcium concentration and, therefore, contraction of the smooth muscle cells. The first mechanism is an inhibition of the Na⁺-K⁺ ATPase pump. This leads to an increase in the intracellular sodium concentration, which then leads to decreased calcium efflux through a sodium-calcium exchange mechanism (62). A second potential mechanism is an inhibition of the electrogenic Na⁺-K⁺ pump in vascular smooth muscle, which leads to a slight depolarization of the smooth muscle fibers, thereby increasing calcium conductance across the cell wall or releasing stored calcium from inside the cell or from the cell wall (63–65). A third mechanism that has been suggested is a Na⁺-K⁺ ATPase-dependent pump which, when inhibited, causes the release of catecholamines that, in turn, induce contraction of the vascular smooth muscle (66,67).

Currently, there is information suggesting that both of the first two mechanisms, that is, inhibition of the Na⁺-K⁺ ATPase pump and an electrogenic pump effect, may mediate the increase in vascular tone after the administration of digitalis glycosides (68,69). However, the third mechanism, that is, local release of catecholamines stimulated by the glycosides, appears unlikely to play a major role because prior depletion of catecholamines with reserpine or denervation does not alter the effect of ouabain (70,71).

Central nervous system effects of digitalis glycosides. Abundant evidence is available demonstrating that digitalis glycosides exert part of their extracardiac effects...
through an action on the central nervous system (70). For instance, the alpha-adrenergic-mediated increase in coronary vascular resistance caused by highly polar cardiac glycosides can be abolished by brainstem transection 2 mm below the obex (71). Such information suggests that the cardiac glycosides increase alpha-adrenergic tone by stimulating the area postrema of the medulla, a region that is devoid of a blood-brain barrier (71). This is the same region that is thought to be responsible, in part, for the arrhythmias, nausea and vomiting that can occur after the intravenous injection of a cardiac glycoside (72–75).

In 1785, Withering (1) described several symptoms of digitalis intoxication resulting from large and repeated doses of foxglove. These included “sickness, vomiting, purging, giddiness, confused vision, objects appearing green or yellow . . . .” Other complications of digitalis intoxication include weakness, headache, fatigue, nocturnal confusion, delirium, disorientation, nightmares, delusions, hallucinations, acute mania or depression, paresthesias, neuralgias, and myalgias (59,76–81). Up to 20% of patients receiving digoxin became intoxicated (82). In one study (83) of an epidemic of digitalis intoxication caused by a packaging error, 95% of the patients had fatigue, 95% visual complaints, 82% muscular weakness, 80% nausea, 80% anorexia, 65% psychiatric disturbances, 65% abdominal pain, 59% dizziness, 54% dreams, 45% headache, 41% diarrhea, 40% vomiting and 9% chest pain. Visual symptoms described are blurring, dimness, scotoma, flickering or flashing lights of yellow, green or red colors, cycloplegia, ambylopia, diplopia and blindness; they occur in 11 to 95% of patients, particularly in cases of digoxin intoxication (79,83–86).

Many of these toxic effects of digitalis glycosides probably result from their profound excitatory effects on nerve cells. These compounds exert a disorganizing influence on the central nervous system and enhance neural activity, in part by lowering the nerve membrane threshold for depolarization. For instance, ouabain and strophanthidin injected intravenously or applied topically to the brain decrease the seizure threshold and increase duration of seizures evoked by electrical stimulation of the sensory cortex (87). Perfusion of the lateral ventricles of the cat with ouabain causes a large dose-dependent release of 5-hydroxytryptamine (5-HT) which can be blocked by 5-HT-specific antagonists (89). This has led to the speculation that 5-HT plays a major role in the genesis of cardiac-glycoside-related neurotoxicity. Other studies have suggested that these compounds increase the central nervous system dopamine content and that this action may be related to their toxic effects (90).

Thus, many of the toxic actions of digitalis glycosides are caused by their effects on cortical and medullary regions of the central nervous system. These effects may be mediated by an alteration in one or more of the neurotransmitters. However, further work is necessary to establish the exact mechanism of action of cardiac glycosides on the central nervous system.

**Effects of digitalis glycosides on baroreceptor and cardiac afferent nerve endings.** Digitalis glycosides have an interaction with the afferent endings located in the carotid sinus region as well as those innervating the heart (91–96). For instance, digitalis increases the discharge rate of afferent nerve fibers located in the carotid sinus nerve (92,93). Both chemoreceptor and baroreceptor afferents are located in this nerve. In addition, the electrical activity of vagal afferent fibers innervating the myocardium is increased by digitalis glycosides (95). Because stimulation of any of these afferents generally causes reflex cardiovascular depression, one might speculate that the direct vascular and central nervous system-mediated vasoconstrictor effects, in part, are limited by these reflexes. Alternatively, the arteriolar vasodilation observed after administration of cardiac glycosides to patients with congestive heart failure may occur, in part, through their effects on baroreceptor and cardiac afferent nerve endings (21). Investigators also have speculated that the pooling of blood in splanchnic veins leads to a decrease in venous return, a beneficial effect that could be ascribed to a reflex action of these cardiac glycosides (5,20). Finally, activation of cardiac receptors has been associated with a reduction in the secretion of antidiuretic hormone (97). Thus, stimulation of these receptors by cardiac glycosides could decrease the secretion of antidiuretic hormone and increase the excretion of both sodium and free water (98).

**Patients with congestive heart failure demonstrate a reduced discharge activity of vagal afferent nerves innervating the heart** (98–101). Because the digitalis glycosides sensitize these receptors to discharge more vigorously to stimuli such as elevations of left atrial pressure, these drugs may be important in restoring a more normal neurohumoral state in such patients (95,102). In addition, by reducing the circulating level of plasma antidiuretic hormone, these drugs may partially restore the renal function in patients with congestive heart failure. Therefore, in addition to the important inotropic effects of cardiac glycosides, these drugs may improve the clinical condition of patients with heart failure by stimulating baroreceptor and cardiac afferent nerves to reduce the excessive vasoconstriction in resistance and capacitance vessels and to enhance excretion of salt and free water.

**Conclusions**

Digitalis glycosides have a plethora of cardiac and extracardiac effects. Although some of the extracardiac effects, such as nausea, vomiting, abdominal pain, malabsorption syndromes, gynecomastia and central nervous system symptoms can be very disturbing to patients, these drugs generally appear to improve cardiovascular function. Cardiac glycosides exert important arteriolar and venoconstric-
tor effects in patients without congestive heart failure. The origin of these effects is mediated through a direct action of glycosides on vascular smooth muscle and an indirect action caused by stimulation of the medullary brainstem centers. An important but less well studied mechanism of action appears to involve reflexes originating in the heart and baroreceptor regions. In normal subjects these reflexes may reduce the direct peripheral vasoconstrictor response, but in patients with heart failure, these reflexes probably assist in restoring the cardiovascular homeostasis by promoting a diuresis, reducing the exaggerated neurohumoral discharge and possibly transiently reducing venous return, which in turn reduces the degree of pulmonary congestion. Thus, although Withering described the therapeutic usefulness of foxglove extracts 200 years ago, only recently have we come to appreciate some of the more diverse and important extracardiac manifestations of this drug.

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