Digitalis: A Neuroexcitatory Drug

INVESTIGATORS studying digitalis in experimental animals have long appreciated the crucial role of the autonomic nervous system in its cardiac effects. Recent studies on the transplanted human heart have demonstrated that at least some major electrophysiologic actions of digitalis are totally abolished by denervation, suggesting that "indirect" neural effects of the drug may be more important than the more widely understood "direct" cardiac effects.\(^1\)\(^2\) Appreciation for the significance of the neural role in digitalis actions suggests important implications for clinical therapy and research directions.

Three neural effects of digitalis have been well documented in animal studies: vagomimetic actions, sensitization of baroreceptors, and (in large doses) sympathetic stimulation. Only the first of these has been widely appreciated in clinical literature. Therapeutic doses of digitalis enhance vagal tone, and as a consequence the following responses may occur: 1) slowing in sinus rate, 2) slowing of atrioventricular conduction, 3) decrease in the automaticity of atrial ectopic pacemakers, and 4) decrease in the refractory period of atrial muscle cells. The third effect is presumably responsible for the therapeutic efficacy of these agents in paroxysmal atrial tachycardia caused by ectopic foci, while the latter three account for their effectiveness in atrial flutter and fibrillation.

Direct evidence for the vagomimetic effects of digitalis has been derived by monitoring spontaneous activity in cardiac vagal fibers during administration of various digitalis preparations.\(^3\)\(^4\) The contribution of this vagomimetic action to the above noted atrial and atrioventricular nodal electrophysiologic effects has been documented in animal studies wherein vagal effects were blocked with vagotomy or atropine.\(^5\)\(^6\) Such studies have also demonstrated the important role of vagomimetic effects in speeding atrial and slowing ventricular rates in atrial flutter.\(^7\)\(^8\) In humans, the contribution of vagomimetic effects on atrial automaticity and atrioventricular conduction has been documented by atropine pretreatment.\(^9\)\(^10\) More recently, confirmation of animal electrophysiology studies has been obtained in humans with transplanted hearts.\(^1\)\(^2\) These patients do not exhibit slowing in ventricular rate when digoxin is administered during atrial flutter.\(^1\) Furthermore, atrial flutter does not progress to atrial fibrillation, but instead conversion to sinus rhythm occurs (probably reflecting direct digitalis effects to lengthen atrial muscle cell refractory period). Finally, patients with transplanted hearts do not exhibit slowing in sinus rate during digoxin administration, although their sinus rates may be faster than 100 beats/minute.\(^1\)

A second neural effect of digitalis, well documented in experimental studies, but rarely considered in clinical literature, is sensitization of the carotid sinus baroreceptors.\(^17\) At the same level of blood pressure, the digitalized subject develops more afferent activity along carotid sinus nerves than the subject without digitalis, resulting in increased efferent vagal activation\(^8\) and withdrawal of sympathetic tone.\(^18\) This interaction between digitalis and baroreceptors may have important therapeutic consequences. First, it may explain at least in part the vagomimetic effect described above. Second, the withdrawal of cardiac sympathetic tone resulting from baroreceptor activation might contribute to the ability of digitalis to convert paroxysmal atrial tachycardia, atrial flutter, and atrial fibrillation to sinus rhythm. It may also help explain the interesting observation that digitalis has an

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antiarrhythmic effect in patients with ventricular arrhythmias in whom sympathetic tone might contribute to ventricular ectopy.

The third and most controversial neural effect of digitalis is its sympathomimetic action. While low doses inhibit sympathetic outflow because of the baroreceptor effect, large digitalis doses have been demonstrated in animal studies to excite the central nervous system, resulting in enhanced sympathetic outflow and cardiac arrhythmias. Experimental evidence for this effect includes the following: 1) increased neural traffic to the heart in the presence of arrhythmogenic doses of the drug; 2) blockade of these digitalis-induced neural effects by spinal cord transection, or cardiac denervation resulting in a significant increase in the digitalis dose required to produce ventricular arrhythmias; and 3) the ability of digitalis to lower the threshold for hypothalamic stimulation to cause arrhythmias. This latter effect has been demonstrated in an experimental model wherein electrical stimulation of the cat hypothalamus resulted in increased traffic along cardiac-bound sympathetic nerves, followed temporally by arrhythmias. The central nervous system excitatory effects of large doses of digitalis are not confined to cardiac sympathetic nerves, but can also be measured in phrenic and peripheral sympathetic nerves, suggesting that generalized excitation of brain stem nuclei is induced.

These three types of neural effects are so significant in experimental studies that they must be considered at least as important as the better known "direct" effects. The latter are responsible for the positive inotropic effect of digitalis and contribute to its arrhythmogenic actions. "Direct" effects are also said to be involved in digitalis-induced slowing in sinoatrial nodal rate, and slowing in atrioventricular conduction. However, recent experimental and clinical evidence with preparations isolated from neural influences suggests that the ability of digitalis to reduce sinus rate and to slow atrioventricular conduction are due entirely to neural actions of the drug. The relative contributions of neural and "direct" actions of digitalis in the generation of toxic arrhythmias has yet to be determined, but the importance of the former has almost certainly been underestimated.

Recognition of the significance of the nervous system in the cardiovascular actions of digitalis may enhance one's ability to use these drugs safely and effectively. The drug effects may be related to, and hence predictable by, the status of the autonomic nervous system. For example, evidence suggests that patients with cardiovascular disease have impaired vagal function. As a consequence, such patients may not exhibit the vagomimetic effects observed in normal patients, and either sympathetic inhibition or sympathetic activation may predominate, depending on the dose of digitalis employed. This prediction might explain the observation that patients with diseased hearts exposed to toxic levels of digitalis develop premature ventricular depolarizations, while patients with normal hearts tend to develop atrioventricular conduction disturbances.

Surgical and pharmacological interventions may also alter autonomic neural status and affect digitalis actions. The effects of cardiac transplantation have been considered above. Patients being treated for hypertension are frequently given sympatholytic drugs (reserpine, guanethidine, alpha methyl dopa, propranolol, or clonidine). In such patients, the ventricle should be more protected from the deleterious arrhythmogenic effects of digitalis. However, the atrioventricular conducting system should be more sensitive to the effects of digitalis, because part of the normal drug action (withdrawal of sympathetic tone) is already present before the drug is administered. Therefore, addition of digitalis in usual doses to the patient on reserpine might result in heart block and sinus bradycardia. These effects have indeed been reported in patients on reserpine and guanethidine. Furthermore, some of the sympatholytic drugs (e.g., reserpine, bretylium) when given by the parenteral route release significant amounts of norepinephrine and this abrupt release in the presence of digitalis might result in tachyarrhythmias. These results have also been reported.

Understanding of and therapy for digitalis toxicity are also facilitated by consideration of the role of the autonomic nervous system. The extracardiac manifestations of digitalis toxicity such as gastrointestinal, visual, and neurologic disturbances occur with a frequency similar to that of cardiac arrhythmias, and with similar doses. They appear to be due to an interaction of digitalis with central nervous system structures such as the chemoreceptor trigger zone and visual cortex. Just as activation of the central chemoreceptor trigger zone might influence gastrointestinal motility, central sympathetic activation appears to result in increased sympathetic traffic to the heart, resulting in arrhythmias. Thus, cardiac arrhythmias and extracardiac manifestations of digitalis toxicity, which are not dissociable by dose may both be results of digitalis neurotoxicity. The specific efficacy of diphenylhydantoin against digitalis-toxic ventricular arrhythmias is therefore not surprising, since in addition to its well known cardiac effects, it is an antiarrhythmic agent with prominent actions in the central nervous system. When digitalis toxicity results in atrioventricular block, as it
usually does in the normal heart, therapy with atropine has been demonstrated to be effective.48

Appreciation for the important neural role in the cardiovascular effects of digitalis suggests several directions for future research. First, although no major differences among digitalis compounds has yet been documented (except for pharmacokinetics), such differences may exist in their neural activation. Recent evidence suggests that digitalis compounds differ in the relative role of the sympathetic nervous system in their cardiotoxicity,49, 50 and in their capacity to activate the parasympathetic nervous system.51 Second, the role of the sympathetic nervous system in digitalis cardiotoxicity suggests new therapeutic modalities. One approach that has been effective experimentally is the use of central nervous system depressants to counteract digitalis-induced ventricular arrhythmias.52, 53 Third, since central nervous system activation seems important, and perhaps even causative in digitalis cardiotoxicity, new digitalis derivatives which do not cross the blood-brain barrier might be found which would retain direct inotropic properties without electrophysiologic toxicity.

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Circulation. 1975;52:739-742
doi: 10.1161/01.CIR.52.5.739

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