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.\(^3-6\) 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.\(^6-14\) Such studies have also demonstrated the important role of vagomimetic effects in speeding atrial and slowing ventricular rates in atrial flutter.\(^10,14\) In humans, the contribution of vagomimetic effects on atrial automaticity and atrioventricular conduction has been documented by atropine pretreatment.\(^15,16\) 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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not exhibit the vagotonic effects observed in normal hearts when exposed to toxic levels of digitals. As a consequence, such patients may not require the sympathetic activation that patients with normal hearts tend to develop as the atrioventricular conducting system, resulting in enhanced sympathetic tone and peripheral vasoconstriction.

The third and most controversial neural effect of digitalis-induced ventricular arrhythmias is the vagal effect. Many patients with ventricular arrhythmias exhibit a vagal effect, large digitalis doses because of the sympathetic denervation of the sinoatrial node. This denervation results in enhanced sympathetic outflow as well as increased digitalis-induced ventricular arrhythmias.

In experimental models, digitalis-induced ventricular arrhythmias have been related to increased sympathetic tone and peripheral vasoconstriction. In clinical practice, digitalis-induced ventricular arrhythmias have also been associated with increased sympathetic tone and peripheral vasoconstriction. These effects may be related to the dose of digitalis employed. This prediction on the dose of digitalis employed. This prediction also implies that digitalis-induced arrhythmias may be nociceptor responses to the effects of digitalis, because part of the sympathetic activation should be more pronounced when patients have hyperactive ventricular pacemakers.

The effects of digitalis-induced arrhythmias have been considered to be related to the central nervous system, and these effects may contribute to ventricular arrhythmias. Therefore, this effect should be more pronounced when patients have hyperactive ventricular pacemakers.
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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