Digoxin
A Neurohormonal Modulator in Heart Failure?
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Digitalis preparations have been in clinical use for more than 200 years. Despite extensive clinical use, controversy persists as to the precise indications for digoxin therapy in patients with chronic heart failure who are in sinus rhythm.1

Clinical Use of Digitalis Glycosides
The potential benefit of digoxin therapy in heart failure patients is thought to be related to its positive inotropic effect that increases cardiac output and thereby decreases ventricular filling pressures.2 Although digoxin is undoubtedly an inotropic agent in tissue preparations,3 this effect, in contrast to other inotropic agents, is not consistently translated into improved hemodynamics in the intact animal or in humans.4 For example, in normal volunteers5 or in patients with left ventricular dysfunction and normal6 or normalized hemodynamics with other therapies,7 no significant increase and even a decrease8 in cardiac output may occur. This paradox was initially attributed to peripheral vasoconstrictor9,10 effects of digitalis compounds that increase afterload and thereby attenuate or mask its inotropic effect. However, peripheral vasoconstriction is transient11 and is manifested only after rapid intravenous administration of digitalis preparations and does not fully explain the failure to augment cardiac function in patients with normal hemodynamics.

In contrast, when digoxin is given acutely to patients with left ventricular systolic dysfunction and abnormal central hemodynamics,12-14 there is a significant increase in cardiac output and a decrease in pulmonary capillary wedge pressure and systemic vascular resistance. It appears, therefore, that the acute hemodynamic response to digoxin is inversely proportional to the degree of underlying hemodynamic impairment.7

Several studies have shown that long-term digoxin therapy improves left ventricular function and is clinically beneficial in patients in sinus rhythm with symptomatic heart failure caused by systolic dysfunction.15-20

Neurohormonal Activation in Heart Failure
One of the distinguishing features of patients with heart failure is activation of neuroendocrine systems.21 Although not all indexes of neuroendocrine activation correlate with the severity of hemodynamic abnormalities,22 recent evidence suggests that the magnitude of increased central sympathetic neural outflow is closely correlated with impairment of cardiac performance in patients with chronic heart failure.23 An excessive increase in sympathetic outflow results in release of atrial natriuretic peptide. Release of atrial natriuretic peptide may thereby limit the extreme vasoconstrictor effects of the sympathetic activation, possibly by sensitizing the baroreceptors24 and inhibiting any adrenergically mediated activation of the renin-angiotensin-aldosterone system.25 In both experimental and human heart failure, there is significant impairment of cardiopulmonary baroreflex mechanisms26 with reduced sensitivity of atrial stretch receptors.27 In dogs, baroreceptor abnormalities may precede the development of overt heart failure.28 Although in humans, these abnormalities may occur soon after a cardiac insult,29 baroreflex responsiveness is most impaired in patients with severe ventricular dysfunction.30 Reversal of experimental heart failure is associated with normalization of baroreceptor function.31 An attenuation of the ability of baroreceptors to modulate excessive activation of the sympathetic nervous system may result in increased serum norepinephrine concentration, arginine vasopressin release, and activation of the renin-angiotensin-aldosterone system.26 These effects may exacerbate or aggravate heart failure and can result in downregulation of the β-adrenergic receptors,32 which in turn decrease myocardial response to compensatory sympathetic stimulation. New data suggest that therapy with angiotensin converting enzyme inhibitors that are known to improve survival in heart failure patients attenuate neuroendocrine activation.33 Similarly, a negative inotropic agent such as a β-adrenergic blocker that possesses the capability of decreasing the adrenergic receptor stimulation may also improve symptoms34 and survival35 in heart failure patients. In contrast, an improvement in
hemodynamics in response to an inotropic\textsuperscript{36} or vasodilator\textsuperscript{37} agent that may occur at the expense of increased activation of the neuroendocrine systems may adversely affect prognosis. Thus, current clinical data suggest that a desirable agent to treat heart failure is likely to be one that improves hemodynamics without further activation of the neuroendocrine systems. It should be recognized, however, that the clinical benefits from such an agent may not always run in parallel with an improvement in hemodynamics.

**Digoxin as a Neurohormonal Modulating Agent in Heart Failure**

Digoxin improves cardiac function in patients with abnormal hemodynamics. In addition to its inotropic effects, recent evidence suggests that digoxin may attenuate, directly or indirectly,\textsuperscript{38} the neuroendocrine abnormalities in patients with heart failure. This, in turn, could theoretically improve and prevent further deterioration of cardiac function even when there is not a significant improvement in hemodynamics.

It is known that digitalis can exert sympatho-inhibitory,\textsuperscript{38} sympathoexcitatory,\textsuperscript{29} and direct vasoconstricting effects.\textsuperscript{40} The relative predominance of these differing effects in response to digitalis may depend on the degree of activation of the neuroendocrine systems\textsuperscript{40} or the dose used.\textsuperscript{41} The first indication of this in humans derived from seminal observations by Mason and Braunwald,\textsuperscript{10} who compared the effects of digitalis glycosides in normal humans with heart failure patients. In this study,\textsuperscript{10} the intravenous administration of ouabain to normal subjects produced forearm arterial and venous vasoconstriction, whereas administration to patients with heart failure resulted in peripheral vasodilatation.

The neurohormonal actions of digoxin may be particularly important because the progression of heart failure is thought to be related to chronic and unopposed excessive activation of the sympathetic nervous system.\textsuperscript{42} This sustained activation may be related to failed intrinsic vasodilatory factors such as atrial natriuretic peptide\textsuperscript{43,44} and/or significant impairment of tonic inhibitory cardiopulmonary and arterial baroreflex regulator mechanisms in heart failure patients.\textsuperscript{45}

Because survival in heart failure is inversely related to the serum concentration of norepinephrine\textsuperscript{46} and plasma renin activity,\textsuperscript{47} it is possible that interventions that restore the baroreflex function (resulting in decreased norepinephrine serum concentrations)\textsuperscript{48} and allow upregulation of \(\beta\)-adrenergic receptors may improve prognosis in heart failure patients.\textsuperscript{26} This is supported by the findings of the Cooperative North Scandinavian Enalapril Survival Study,\textsuperscript{33} which demonstrated that the addition of an angiotensin converting enzyme inhibitor to conventional therapy markedly reduced mortality in severe heart failure. In this study, the neuroendocrine activation was reduced by enalapril therapy after 6 weeks of therapy, suggesting that the effect of angiotensin converting enzyme inhibitors on mortality may be related to the inhibition of neuroendocrine activation. Although it is possible that the inhibitory effects of the neuroendocrine systems by enalapril are related to improved hemodynamics resulting from its vasodialatory effects, it is likely that angiotensin converting enzymes have a direct effect on neuroendocrine activation because angiotensin II can attenuate baroreceptor sensitivity.\textsuperscript{49}

Available data suggest that acute administration of digitalis preparation contributes to the attenuation of neuroendocrine abnormalities noted in heart failure.\textsuperscript{30}

**Plasma Renin Activity**

Plasma renin activity is a negative prognostic predictor, particularly for death resulting from progression to end-stage heart failure.\textsuperscript{47} Acute administration of digoxin decreases plasma renin activity,\textsuperscript{13,50} which in turn decreases angiotensin II and aldosterone levels. This decrease in renin synthesis and secretion in response to digoxin may be related to an increase in cardiac output,\textsuperscript{13} a direct effect on the kidney,\textsuperscript{51} inhibition of sympathetic activity,\textsuperscript{52} or activation of atrial natriuretic peptide.\textsuperscript{53} Whatever the mechanism, a reduction in activation of the renin-angiotensin system may be associated with an improvement in prognosis of heart failure patients.\textsuperscript{33,54}

**Atrial Natriuretic Peptide**

Atrial natriuretic peptide is secreted in response to activation of receptors in the right and left atria by mechanical stretch.\textsuperscript{55} This is potentiated by activation of the neuroendocrine systems.\textsuperscript{56} Once released, atrial natriuretic peptide exerts a potent direct vasodilatory and natriuretic action by virtue of its ability to increase intracellular cyclic guanosine monophosphate.\textsuperscript{57} Atrial natriuretic peptide suppresses synthesis of renin and opposes the systemic vasoconstrictor action of angiotensin II, the ability of angiotensins to stimulate thirst, and secretion of aldosterone and vasopressin.\textsuperscript{58,59} Plasma atrial natriuretic peptide is elevated in chronic heart failure\textsuperscript{60} and provides significant independent prognostic information.\textsuperscript{61} In addition, there is a blunted response to high circulating levels of atrial natriuretic peptide in heart failure patients that may be related to its receptor downregulation.\textsuperscript{62} Enhanced degradation\textsuperscript{43} of endogenous atrial natriuretic peptide in heart failure and an intracellular defect that prevents mediation of the hormonal signal into biological action in the presence of experimental heart failure\textsuperscript{63} may also contribute to the attenuated renal natriuretic response in heart failure. Recent data indicate that the level of plasma atrial natriuretic peptide may be used as a means for assessing the efficacy of treatment.\textsuperscript{64} Ouabain can cause increased secretion of atrial natriuretic peptide from atrial cardiocyte culture.\textsuperscript{65} This may be a partial explanation of the diuresis that frequently follows cardiac glycoside administration in heart failure.\textsuperscript{66} The effects of digoxin on atrial natriuretic peptide secretion and utilization remain to be investigated.
Serum Norepinephrine Levels: Efferent Sympathetic Nerve Activity

Norepinephrine levels, a reflection of increased sympathetic outflow, are important in patients with heart failure. Response to therapy, manifesting by clinical improvement, often results in a decrease in serum norepinephrine concentration. In contrast, an increase in norepinephrine levels, regardless of the type of therapy, is associated with a very poor prognosis. Acute digoxin administration decreases norepinephrine serum concentration in patients with severe heart failure. This appears to be related to the acute hemodynamic effects of the drug and correlates with the increase in cardiac output. Recent studies also demonstrate that intravenous administration of a rapidly acting digitalis preparation (Cedilanid-D) produces a prompt and early inhibition of efferent sympathetic nerve activity in heart failure patients. This sympathoinhibitory action precedes any observed hemodynamic effect of the agent. Evidence that this sympathoinhibitory effect is not solely related to the inotropic action of digoxin is supported by the finding that administration of similar inotropic doses of dobutamine to a comparable group of heart failure patients does not attenuate sympathetic nerve activity to muscle. Although there are no data on chronic effects of digoxin on serial serum norepinephrine concentrations or sympathetic nerve activity in patients with heart failure, preliminary studies in animals suggest that such a chronic effect is likely. The potential for digitalis glycosides to produce a net sympathoinhibitory versus sympathoexcitatory response in different models may also be a dose-dependent phenomenon. Lopez et al have shown that intracarotid administration of low-dose ouabain in dogs produces peripheral vasodilation, whereas higher doses produce vasoconstriction.

Effects of Digitalis on Baroreflex Mechanisms

Digitalis glycosides alter arterial baroreflex mechanisms as well as cardiopulmonary reflexes in animal experiments and in humans. Heart failure is associated with blunting of baroreflex mechanisms. These defects are likely to contribute to the continuous and excessive sympathetic nervous system activity that occurs in heart failure patients and may thereby contribute to downregulation of cardiac receptors. Although the exact mechanisms remain unclear, in experimental heart failure the abnormality in baroreceptor function may be related to excessive activation of the sodium-potassium ATPase pump. When ouabain is perfused through the carotid sinus in dogs with pacing-induced heart failure and decreased sensitivity of the carotid sinus baroreceptors, there is a decrease in this excessive activation of the sodium-potassium ATPase pump resulting in increased sensitivity of these baroreceptors. It is possible that in addition to inhibiting the sodium-potassium ATPase pump, digitalis compounds increase baroreceptor sensitivity via direct stimulation of receptors or by an improvement in contractility resulting in a lower cardiac filling pressure and an increase in systemic blood pressure. A change in baroreceptor sensitivity is not always seen in response to digitalis preparations. For example, when a low concentration of ouabain was administered in normal dogs, no change was noted in the carotid sinus baroreceptor sensitivity. However, it has been shown that high concentrations of cardiac glycosides can augment baroreceptor discharge sensitivity in normal animals. Perfusion of the isolated carotid sinus regions of cats and rabbits with low concentrations of ouabain caused no significant change in baroreceptor sensitivity. Experimentally, it appears, then, that the response to the digitalis preparation may be dose dependent, different from one species to another, and dependent on the state of the baroreceptor function. In normal and heart failure patients, cardiac glycosides have shown to augment the baroreceptor sensitivity. Ferguson et al studied patients with moderate to severe heart failure and observed a normalization of forearm vascular response to lower body negative pressure in response to digitalis glycosides and suggested that these effects were due to acute normalization of impaired baroreflex mechanisms in these patients. In addition, more recent studies demonstrate that intravenous administration of Cedilanid-D produces rapid and profound attenuation of sympathetic nerve activity that precedes the observed hemodynamic action of the agent. It is not known from this study if digitalis has a direct sympathoinhibitory effect or may be due in part to an increase in systolic aortic pressure, although the mean aortic pressure and diastolic pressure remain unchanged. The fact that the decrease in sympathoexcitatory effects preceded the change in systolic pressure suggests a sensitizing effect on afferent baroreflex mechanisms. These findings are supported by the clear evidence of sympathoinhibition induced by digitalis glycosides in animal studies.

The demonstration of the autonomic action of digitalis in humans has been limited only to acute studies. Whether or not chronic administration of therapeutic doses of digitalis in humans produces significant and sustained effects on neurogenic mechanisms remains unclear. However, experimental studies in dogs demonstrate that chronic administration of digoxin produces a sustained potentiation of the vagally mediated cardiopulmonary baroreflex.

Conclusions

Available data suggest that digoxin, in addition to its inotropic effects, has potentially beneficial neurohumoral modulating effects by blunting excess neuroendocrine activation directly or by mediating baroreflex mechanisms. Uniquely, the digitalis preparation may increase cardiac contractility not at the expense of an increase in sympathetic outflow and levels of circulatory vasoactive hormones that are noted with
some inotropic agents. This is of particular importance because inotropic agents or vasodilators that improve hemodynamics at the expense of an increased adrenergic receptor stimulation may adversely affect prognosis. There may be a dissociation between hemodynamic and neuroendocrine effects in response to digitalis preparations. This may be important because activation of the neuroendocrine system may be present in patients with left ventricular dysfunction and normal hemodynamics who usually do not improve their hemodynamic parameters in response to digoxin. If long-term studies confirm that digoxin modulates the excessive neuroendocrine activation noted in asymptomatic left ventricular dysfunction or overt heart failure, this therapy may be used not only to improve hemodynamics but also to slow the process of progressive deterioration of cardiac function noted in this condition.

Despite these theoretical benefits, the main question that remains is related to the effects of digoxin therapy on mortality. The US National Heart, Lung, and Blood Institute and the Department of Veteran Affairs Cooperative Studies Program are presently conducting a double-blind randomized trial of patients with heart failure to assess the effect of digoxin on mortality. It is anticipated that approximately 7,000 patients with chronic heart failure will participate in this study. The completion of this important trial is expected in 1995. In parallel with this, prospective placebo-controlled trials are required to assess the long-term neuroendocrine effects of digoxin in patients with heart failure.

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Circulation. 1991;84:2181-2186
doi: 10.1161/01.CIR.84.5.2181

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