Differential Effects of Digitalis on Chemoreflex Responses in Humans

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**Abstract** To investigate the effects of digitalis on chemoreflexes in humans, we measured muscle sympathetic nerve activity (microneurography), minute ventilation, oxygen saturation, end-tidal carbon dioxide, mean arterial pressure, heart rate, and central venous pressure during stimulation of peripheral chemoreceptors with hypoxia, during stimulation of central chemoreceptors with hypercapnia, and during a cold pressor test before and after digitalis and placebo in 10 healthy volunteers on two different days (randomized, double-blind, crossover design). Digitalis did not affect baseline measurements significantly. Despite similar changes in oxygen saturation and end-tidal carbon dioxide during hypoxia and hypercapnia with both placebo and digitalis, digitalis significantly potentiated overall ventilatory responses to hypoxia (+67±12% before versus +98±3% after digitalis; mean±SEM; P<.01) but did not affect the response to hypercapnia. Sympathetic nerve activity increased by 25±9% during hypoxia before digitalis and 30±10% during hypoxia after digitalis (P=NS) and increased by 38±18% during hypercapnia before digitalis and 26±11% during hypercapnia after digitalis (P=NS). Digitalis did not significantly change responses to the cold pressor test. Placebo had no effect on ventilatory and sympathetic nerve activity responses. We conclude that digitalis selectively augments ventilatory responses to peripheral chemoreceptor stimulation by hypoxia. Hypertension. 1994;23:302-307.

**Key Words** • chemoreceptors • sympathetic nervous system • digitalis • ventilation • apnea

Digitalis glycosides have been shown to potentiate sympathoinhibitory baroreceptor reflex mechanisms. This potentiation may in part explain the reduction in central sympathetic outflow and other beneficial effects of digitalis in patients with heart failure.

Studies on the effects of digitalis on sympathoexcitatory chemoreflexes are few and limited to work in animals. Quest and Gillis found that digitalis resulted in increases in carotid sinus nerve activity. Elimination of chemoreceptors with intracarotid acetic acid produced smaller increases in carotid sinus nerve discharge, suggesting that digitalis excited both chemoreceptor and baroreceptor afferents. Schmitt et al specifically examined the effects of digitalis on chemoreceptor carotid sinus afferent nerve activity and noted that intracarotid injection of digitalis increased chemoreceptor firing. McQueen and Ribeiro subsequently reported that digitalis both increased tonic carotid body discharge and augmented the neural responses to hypoxia. We are unaware of studies in humans investigating the effects of digitalis on chemoreflex function.

Using direct intraneural measurements of sympathetic efferent activity to muscle blood vessels in humans (microneurography), we have previously reported that both hypoxia (peripheral chemoreceptor stimulation) and hypercapnia (primarily central chemoreceptor stimulation) increase sympathetic nerve activity (SNA) in humans. Increased minute ventilation, as well as baroreceptor reflex activation (by raising blood pressure), inhibits these sympathetic responses. There is considerable selectivity in this inhibition, in that responses to hypoxia are inhibited more than the responses to hypercapnia.

We investigated the effects of digitalis on ventilatory, sympathetic, and hemodynamic responses to peripheral (hypoxic) and central (hypercapnic) chemoreceptor stimulation and contrasted these responses with the effects of digitalis on the response to a cold pressor stimulus (a nonspecific sympathoexcitatory stimulus).

**Methods**

**Subjects**

Ten normal volunteers (9 males, 1 female; age, 22.7±2.1 years) were studied with digitalis and placebo on two different days (range, 12 to 72 days between studies) in a double-blind, randomized fashion. All subjects were studied without sedation in the supine, postabsorptive state and were free of cardiovascular or other systemic diseases based on medical history and physical examination. All were nonsmokers and were on no medications. Informed written consent was obtained. These studies were approved by the Human Subjects Review Committee of the University of Iowa.

**Measurements**

Blood pressure was measured with a Physio-Control Lifesat 200 semiautomated sphygmomanometer. Heart rate (electrocardiogram), breathing pattern (pneumograph), O2 saturation (Nellcor N-1100 C pulse oximeter), end-tidal CO2 (47210 A capnometer, Hewlett-Packard Co), central venous pressure, and SNA to muscle were recorded on a 2800 S recorder (Gould Electronics Inc). Ventilatory rate and minute ventila-
tion were monitored with an LS-75 ventilation monitor (Bourns).

Microneurographic recordings of SNA to muscle were obtained from a sympathetic nerve fascicle in the peroneal nerve posterior to the fibular head. This technique has been validated and extensively described in studies from our laboratory and elsewhere. In brief, recordings were obtained by percutaneous insertion of tungsten microelectrodes into sympathetic fascicles in the peroneal nerve. The electrodes were connected to a preamplifier, and the nerve signal was fed through a band-pass filter and routed through an amplitude discriminator to a storage oscilloscope and loudspeaker. For recording and analysis, the filtered neurogram was fed through a resistance-capacitance integrating network to obtain a mean voltage display of the neural activity. Standard criteria for acceptance of a recording of muscle SNA were achieved in all subjects. Sympathetic bursts were identified by inspection of the mean voltage neurogram, and sympathetic activity was calculated as bursts per minute x mean burst amplitude and expressed in arbitrary units. Prior studies in our laboratory determined an intraobserver variability of 5% and interobserver variability less than 10% in this calculation of SNA.

**Procedures**

Measurements were taken before and during exposure to the following gas mixtures via a mouth piece; a nose clip was used to ensure exclusive mouth breathing: 10% O₂ in nitrogen with added CO₂ to maintain isocapnia (isocapnic hypoxia), and 7% CO₂ in oxygen (hyperoxic hypercapnia). At least 20 minutes was allowed between exposures to the different gas mixtures. A cold pressor test (CPT) was performed as a nonspecific sympathoexcitatory stimulus to serve as an internal control. The CPT consisted of immersing the subject's hand into ice water for 2 minutes. Ventilatory responses to the CPT were not measured. Subjects were randomly allocated to receive digitalis or placebo first in a balanced design so that five subjects received digitalis on the first study day and placebo on the subsequent study day, and five subjects received placebo on the first study day and digitalis on the subsequent study day. Data analysis was carried out before unblinding. The order of experimental interventions was randomized between subjects, but the same order was performed before and after drug administration on both study days.

**Protocol**

Studies were initiated after a 20-minute rest period during which all subjects were familiarized with the experimental techniques. The standard protocol used for chemoreflex studies in our laboratory was adhered to. Subjects underwent measurement of baseline variables for 3 minutes while breath-
mean arterial pressure, minute ventilation, and SNA increased significantly. Central venous pressure and end-tidal CO\textsubscript{2} did not change (Table 1, Fig 1).

Administration of digoxin did not significantly affect baseline values (Table 1). Hypoxia after digoxin produced a similar decrease in O\textsubscript{2} saturation, from 99\%±0.3\% to 85±0.8\% (P<.01), and similar increases in heart rate. SNA increased by 30±10\% compared with an increase of 25±9\% before administration of digoxin (P=NS) (Fig 1). The increase in minute ventilation was significantly augmented after digoxin (98±13\%) compared with before (67±12\%, P<.01) (Fig 1). Blood pressure during hypoxia after digoxin was 84±4±1.2 compared with 81.7±1.4 mm Hg with hypoxia before digoxin (P=NS). End-tidal CO\textsubscript{2} and central venous pressure did not change significantly during postdigitalis hypoxia.

Hypoxia produced similar changes in O\textsubscript{2} saturation, end-tidal CO\textsubscript{2}, SNA, minute ventilation, heart rate, and mean arterial pressure before and after placebo (Table 1, Fig 1). Except for a slight increase in mean arterial pressure, placebo had no effect on baseline variables (Table 1).

Effects of Digitalis on Responses to Hypercapnia

During hypercapnia before digoxin, end-tidal CO\textsubscript{2} increased from 41±0.3 to 54±0.3 mm Hg (P<.01), and mean arterial pressure, central venous pressure, heart rate, O\textsubscript{2} saturation, minute ventilation, and SNA increased significantly (Table 2, Fig 2).

Administration of digoxin did not significantly affect baseline values (Table 2). After digoxin, hypercapnia resulted in an increase in end-tidal CO\textsubscript{2}, from 41±0.3 to 53±0.3 mm Hg (P<.01), with increases in mean arterial pressure, heart rate, and O\textsubscript{2} saturation similar to those before digoxin. Central venous pressure did not change significantly during hypercapnia after administration of digoxin. SNA increased by 26±11\%, compared with an increase of 58±18\% before administration of digoxin (P=NS) (Fig 2). The response of minute ventilation with an increase of 232±32\% after digoxin was not different, compared with an increase of 242±54\% before the drug (Fig 2).

Placebo had no significant effect on baseline variables and did not alter the responses of hemodynamics, minute ventilation, and SNA during hypercapnia (Table 2, Fig 2).

Effects of Digitalis on Responses to Apnea During Hypoxia and Hypercapnia

To minimize the sympathetic inhibitory effect of ventilation on sympathetic responses to hypoxia and hypercapnia, we examined the effect of a brief period of apnea on SNA during both hypoxia and hypercapnia before and after digoxin. During hypoxia before digoxin, apnea increased SNA by 329±49\% compared with apnea on room air. After administration of digoxin, apnea during hypoxia increased SNA by 508±250\% compared with apnea on room air (P=.15). During hypercapnia the SNA response to apnea was 184±45\%.

\begin{table}
\begin{tabular}{|l|c|c|c|c|c|c|c|c|}
\hline
\textbf{Measurement} & \textbf{Before Digitalis} & \textbf{After Digitalis} & \textbf{Before Placebo} & \textbf{After Placebo} \\
\hline
\textbf{MAP, mm Hg} & 81.0±1.5 & 86.2±1.7 & 81.8±1.5 & 86.6±1.6 & 81.8±2.8 & 87.1±3.0 & 83.7±2.3 & 88.4±2.1 \\
\textbf{CVP, mm Hg} & 4.6±0.3 & 5.6±0.4 & 4.3±0.6 & 4.6±0.5 & 5.1±0.5 & 5.6±0.6 & 4.7±0.6 & 5.1±0.8 \\
\textbf{HR, bpm} & 65.8±4.4 & 72.1±4.1 & 61.6±4.6 & 67.0±4.4 & 64.8±3.1 & 70.6±3.1 & 61.1±2.8 & 67.7±4.0 \\
\textbf{\(V_E\), L/min} & 7.0±0.7 & 21.2±1.2 & 7.5±0.8 & 23.8±1.8 & 7.7±0.5 & 24.9±1.9 & 8.4±0.7 & 26.3±1.9 \\
\textbf{O\textsubscript{2} saturation, \%} & 99±0.4 & 100±0 & 99±0.3 & 100±0.1 & 99±0.6 & 100±0.2 & 99±0.6 & 100±0.4 \\
\textbf{Pco\textsubscript{2}, mm Hg} & 41±0.5 & 54.0±3 & 41±0.3 & 53±0.3 & 41±0.6 & 54±0.5 & 40±0.8 & 53±0.5 \\
\textbf{SNA, U/min} & 167±26 & 222±35 & 157±30 & 203±46 & 187±32 & 260±31 & 181±43 & 231±34 (n=8) \\
\hline
\end{tabular}
\caption{Effects of Digitalis and Placebo on Hemodynamic, Ventilatory, and Sympathetic Nerve Responses to Hypercapnia}  
\end{table}

\textit{MAP} indicates mean arterial pressure; \textit{CVP}, central venous pressure; \textit{HR}, heart rate; \textit{bpm}, beats per minute; \textit{\(V_E\)}, minute ventilation; \textit{Pco\textsubscript{2}}, end-tidal carbon dioxide; and \textit{SNA}, sympathetic nerve activity. \textit{n}=9 except where noted.

\*P<.05, control vs hypercapnia.
before digitalis compared with 144±47% after digitalis (n=8, P=NS) (Fig 3). In accordance with our earlier findings, the elimination of ventilation by apnea increased the SNA response to hypoxia more than it did the SNA response to hypercapnia.

Placebo did not alter the effects of apnea on SNA responses to hypoxia and hypercapnia.

Effects of Digitalis on Responses to the Cold Pressor Test

To assess for specificity of effects of digitalis on chemoreflex-mediated mechanisms, we examined responses to the non-chemoreflex-mediated CPT before and after administration of digitalis and placebo in nine subjects (Table 3). All subjects were able to tolerate the CPT for 2 minutes without undue distress. The CPT resulted in significant increases in mean arterial pressure, heart rate, and SNA. Neither digitalis nor placebo had any significant effect on these responses.

Discussion

The novel finding in this study is that digitalis selectively potentiates the ventilatory response to hypoxia but not hypercapnia in healthy humans. Sympathetic nerve responses to hypoxia after digitalis are not increased significantly. These studies are the first in humans examining the effects of digitalis on chemoreflex stimulation and confirm earlier animal studies suggesting that digitalis sensitizes peripheral chemoreceptors. Differences in stimulus intensity during hypoxia with and without digitalis cannot explain our findings, because if anything, oxygen saturation during hypoxia averaged 85% after digitalis compared with 83% without digitalis. Our data further indicate that this sensitization selectively affects peripheral but not central chemoreceptors and predominantly potentiates the ventilatory responses. Placebo had little effect on responses to hypoxia or hypercapnia, indicating that these responses are highly reproducible in the short term.

In addition, these data confirm our earlier findings that the inhibitory effect of ventilation on SNA more potently influences the response to hypoxia than the response to hypercapnia. Elimination of the ventilatory response (by apnea) is associated with a greater sympathetic response during hypoxia (increase of 329%) than during hypercapnia (increase of 184%), despite the sympathetic response to hypoxia and free breathing (increase of 25%) being less than the sympathetic response to hypercapnia and free breathing (increase of 38%).

Hypoxia primarily activates peripheral chemoreceptors in the carotid bodies, whereas hypercapnia acts via central chemoreceptors located on the ventral surface of the medulla. Changes in CO2 levels can influence the effects of hypoxia on chemoreflex responses. Approximately 12% of the ventilatory response to hypercapnia is mediated by peripheral chemoreceptors. We sought to minimize these factors first by maintaining isocapnia during hypoxia, and second by maintaining hyperoxia during hypercapnia.

Both hypoxia and hypercapnia elicit increases in sympathetic activity and ventilation in humans. The ventilatory response is predominant and inhibits the sympathetic response; this inhibition affects the sympathetic response to hypoxia more than the response to hypercapnia. Baroreceptor reflex activation induced by increases in blood pressure also inhibits sympathetic responses to hypoxia more than it does the responses to hypercapnia. These differential interactions may be because thoracic, baroreceptor, and peripheral chemoreceptor afferents relay in close proximity in the region of the nucleus tractus solitarius.

These interactions may also help explain the lack of significant potentiation of the sympathetic responses to hypoxia after digitalis, despite the increased ventilatory response. First, the ventilatory response to hypoxia is predominant and inhibits the sympathetic response. Second, digitalis has a sympathoinhibitory baroreceptor-sensitizing effect and baroreceptor reflex activation also inhibits the sympathetic response to hypoxia. We speculate that both the higher ventilatory response and the increased baroreceptor reflex sensitivity after digitalis would oppose any increased sympathetic activation resulting from digitalis-induced peripheral
potentiation of central chemoreceptor responses as potentiation may explain the increased ventilatory re-

ability that chronic digitalis administration may allow peripheral but not central chemoreflex responses may in part be explained by the anatomic location of the peripheral chemoreceptors in the carotid bodies, which may have been evident with a milder degree of hyper-

The mechanism of peripheral chemoreflex potentiation after digitalis is not known. The absence of poten-
tiated responses to hypercapnia and the CPT suggests that digitalis does not induce a generalized reflex hy-

response to exercise in patients with heart failure receiv-

ing digitalis therapy.23 Potentiated ventilatory responses to hypoxia may also be beneficial to patients with chronic obstructive lung disease and blunted hypoxic ventilatory drive, especially if these patients have coex-

isting heart failure. It is also possible that digitals may favorably influence the Cheyne-Stokes breathing pat-

tern noted in patients with severe heart failure; this considera-

tion would be important in understanding the reasons for the beneficial effects of digitals in heart failure patients and deserves further study.

Spontaneously hypertensive rats24,25 and hypertensive humans19,26 have potentiated chemoreflex responses to hypoxia. Hypertension is also associated with higher levels of endogenous digitalis-like substances.27,28 We speculate that the potentiation of peripheral chemoreflex responses by endogenous digitalis-like substances may help explain the increased chemoreflex responses to hypoxia in patients with essential hypertension.

Acknowledgments

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