Digitalis and Baroreceptor Reflexes in Man

ALBERTO FERRARI, M.D., LUISA GREGORINI, M.D., MARIA CARLA FERRARI, M.D., LAURA PRETI, M.D., AND GIUSEPPE MANCIA, M.D.

SUMMARY  Data in animals indicate that large amounts of digitalis potentiate arterial baroreflexes and that this factor may be important for the cardiovascular effects of the drug. To determine if arterial baroreflex potentiation also exists after administration of therapeutic doses of digitalis in man, we studied how stimulation and deactivation of arterial baroreceptors by phenylephrine and nitroglycerin injection affect heart rate and how stimulation and deactivation of carotid baroreceptors by neck suction and pressure affects blood pressure and heart rate. The study was performed in 29 normotensive or hypertensive subjects before and after injection of Lanatoside C (0.8 mg i.v.). Baroreceptor stimulation reduced heart rate and blood pressure, while baroreceptor deactivation increased both of these variables. The bradycardic and hypotensive effect of baroreceptor stimulation increased significantly after digitalis both in normotensive and hypertensive subjects. However, the tachycardic and hypertensive responses to baroreceptor deactivation were not affected by digitalis. Thus, therapeutic doses of digitalis in man enhance baroreceptor reflexes, and both the heart rate and the blood pressure reflex effects are involved. However, the enhancement occurs to a marked degree only with baroreceptor stimulation and is not evident with baroreceptor deactivation.

EVIDENCE from experimental animals indicates that digitalis increases the effectiveness of the arterial baroreceptor reflexes and suggests that this may be important in the clinical action of the drug. First, administration of ouabain in anesthetized cats and dogs is followed by an increased firing of the aortic and the carotid baroreceptors. Second, injection of phenylephrine in anesthetized dogs increases the depressor response that can be obtained by stimulation of baroreceptors in isolated carotid sinus preparations. Third, the bradycardia induced by digitalis in anesthetized dogs is evident when the baroreceptors are intact, but not after sinoaortic denervation.

However, most of the studies we have mentioned have made use of doses of digitalis compounds that are greater (and often markedly so) than the doses used therapeutically. Most important, the only evidence on the effect of digitalis on baroreflexes in man are reports that digitalis may potentiate the bradycardia induced by baroreceptor stimulation, but perhaps only to a minor degree. The present study was undertaken to examine the effects of clinical doses of digitalis on human baroreceptor reflexes. We examined the reflex effects induced by baroreceptor stimulation and those resulting from baroreceptor deactivation below the existing stimulus. By using different techniques we studied both the heart rate and the blood pressure influences of the baroreflex. Our results demonstrate that digitalis has a major action on the cardiac and vascular component of the baroreflexes in man. However, this action is more complex than could be anticipated from the animal studies, as it occurs when baroreceptors are stimulated but not when they are deactivated.

Methods

We studied 29 subjects of both sexes (mean age 41.6 ± 2.5 years, range 21–59 years) who were hospital inpatients with either normal blood pressure or with uncomplicated essential hypertension. None of the subjects had signs of myocardial failure and none had received antihypertensive or other cardiovascular drugs in the preceding 3 weeks. Each gave free consent to the study after its nature and purpose were explained.

Measurements

Pulsatile arterial blood pressure was measured by a catheter (1.7 mm o.d., 11 cm long) placed percutaneously into a brachial artery and connected to a strain-gauge transducer system with an optimal frequency response curve up to 20 Hz. Mean arterial pressure was obtained by electronic damping of the pulsatile signal and by integration of the pulsatile trace over consecutive periods of 10 seconds. An ECG trace (usually lead 2) was recorded throughout the study for calculation of the RR intervals. Heart rate was also continuously measured by a cardiocrometer, the signal for which was derived either from the R wave or from the pulse-pressure signal.

Methods for Studying Arterial Baroreflexes

Two methods were used to study arterial baroreceptor reflexes. In the first, which is currently used, i.v. phenylephrine and nitroglycerin are injected to increase and reduce arterial blood pressure, thus stimulating and deactivating all arterial baroreceptors and causing reflex increases and decreases in RR interval. In our study we injected intravenously a bolus of 50–100 μg of phenylephrine, which induced a progressive rise in systolic and diastolic pressures with a maximal increase of 20–30 mm Hg above the pressure values before the injection, and a bolus of 100–150 μg of nitroglycerin, which induced a progressive fall in systolic and diastolic pressures, with...
a maximal reduction of 15–20 mm Hg below the pressures before the injection.

The other method was the variable-pressure neck chamber, which permits the study of reflex changes in arterial blood pressure as well as in RR interval in response to selective stimulation and deactivation of the carotid sinus baroreceptors. We have given a detailed description of this method elsewhere.10–12 Briefly, it consists of a collar extending inferiorly to the shoulders and superiorly to a plane intersecting the chin, the ear lobe and the occiput. The pneumatic pressure within the collar can be altered in a positive and a negative direction, the alteration being transmitted to the neck tissues outside the carotid sinuses in the respective amount of 86% and 64%.10 Thus, the positive and negative neck pressure applications cause, respectively, a reduction and an increase in carotid transmural pressure, resulting in deactivation and stimulation of the carotid sinus baroreceptors with respect to the existing stimulus. In the present study the alterations in pneumatic pressure were induced rapidly (90% of the change completed in less than 1 second) and were maintained constant for 2 minutes. The increase and the decrease in neck tissue pressure that were obtained were 30.8 ± 1.1 and 29.8 ± 1.1 mm Hg, respectively, before digitalis and 31.2 ± 1.2 and 29.2 ± 1.0 mm Hg after digitalis.

We investigated subjects with normal cardiac function because the injection of phenylephrine caused similar increases in blood pressure before and after administration of digitalis in these patients, achieving comparable baroreceptor stimulation in the two conditions. In preliminary trials, this could not be obtained in patients with heart failure, in whom the phenylephrine injection caused blood pressure to increase less before than after digitalis, probably because in the former condition the heart had less ability to sustain an increased afterload.

Protocol

The study was made with the subjects in a supine position and began with the insertion of the arterial and the venous catheters, which was made under local anesthesia with 2% lidocaine. A 20-minute rest period was allowed to reduce possible emotional factors involved in the cannulation and to achieve satisfactory basal conditions. In 22 subjects arterial blood pressure was increased by phenylephrine and decreased by nitroglycerin, the two drugs being administered in a random order and with an interval of 10 minutes. Lanatoside C was subsequently injected intravenously at a dose of 0.8 mg, followed by an interval of 40–45 minutes to allow the drug to have its effects,13 after which phenylephrine and nitroglycerin were administered at the same doses.

In a separate group of seven subjects, the 20-minute interval after the insertion of the catheters was followed by application of one positive and one negative neck pressure, performed in a random order and separated by a 10-minute interval. Lanatoside C, 0.8 mg, was then injected intravenously and, after an interval of 40–45 minutes, the positive and negative pressure applications were repeated at the same magnitude and with the same sequence as before.

Throughout the study pulsatile arterial pressure, mean arterial pressure, arterial pressure integrated over consecutive periods of 10 seconds, heart rate and ECG were continuously recorded on a Grass polygraph. The recording was made at low speed (50 mm/min), except during the administration of phenylephrine and nitroglycerin, when a high speed (100 mm/sec) of recording was used to allow precise calculation of systolic pressure values and RR intervals during the change in pressure induced by the drugs.

Data Analysis

The data from the injection of phenylephrine and nitroglycerin were analyzed as described by Smith et al.9 and by Pickering et al.9 Systolic pressure was measured during the increase or the decrease induced by phenylephrine and nitroglycerin, each value being related to the RR interval on the next cardiac cycle. Linear regression lines based on 12–17 values were obtained between these two variables, the regression coefficients (i.e., the slope of the regression lines) indicating sensitivity of the reflex. Only subjects in whom there was a close significant correlation (p < 0.01) between the changes in systolic blood pressure and in RR interval both before and after administration of digitalis were considered. This happened in 18 of the 22 subjects with phenylephrine and in 20 of the 22 subjects with nitroglycerin. This technique has given reproducible results in short- and long-term studies.11–15 Within each subject the regression coefficients obtained with either phenylephrine or nitroglycerin before and after administration of digitalis were compared by covariant analysis.16 For the whole group, regression coefficients were compared by t test for paired observations.

The data obtained with the neck chamber were analyzed as previously described.11,12 Mean arterial pressure and RR intervals were calculated as follows. A control period was obtained by averaging the values occurring during the 30 seconds preceding the alterations in neck chamber pressure and an early response was considered which was the average of the values occurring between the fifth and the fifteenth second that followed the alterations in neck chamber pressure. A late or steady-state response was also considered by averaging the values of the last 30 seconds of the neck chamber pressure alterations. These two responses allowed us to take into account both the initial and the late and steady-state effects of the changes in carotid baroreceptor activity.11,12 Data from each individual were pooled to obtain mean and standard error values for the whole group of subjects. The t test for paired observation was used to evaluate effects of digitalis on the responses to stimulation and deactivation of carotid sinus baroreceptors. The early and the steady-state responses were analyzed separately. Values are mean ± SEM.
Results

Phenylephrine (18 subjects)

These data are shown in table 1. In the control period the average value for mean arterial pressure was 112 mm Hg and the RR interval was 823 msec. The rise in pressure induced by phenylephrine caused a progressive lengthening of the RR interval in all subjects. The regression coefficient of RR interval on systolic pressure (expressing the sensitivity of the baroreflex) was on average 8.13 (range 2.67-15.40).

Digitalis had no significant effect on basal mean arterial pressure but caused a significant increase in basal RR interval ($p < 0.001$). There was no significant difference in the rate or magnitude of the rise in blood pressure induced by the same dose of phenylephrine before and after digitalis. After digitalis, however, the sensitivity of the baroreflex was increased. Covariant analysis showed that the magnitude of the regression coefficient was significantly greater in 16 of the 18 subjects (fig. 1) and a significant increase was also found for the whole group by paired $t$ test. The average of the individual regression coefficients after digitalis was 11.83, an increase of 43% over the value before digitalis (fig. 2).

Two further points were analyzed. First, a correlation was sought between the increase in RR interval observed after digitalis in the basal period and the increased slope of the baroreflex response induced by the drug. No significant correlation was found ($r = 0.285$; NS). Thus, the bradycardic action of digitalis was not related to the effect of the drug on the arterial baroreflexes.

Second, no significant correlation was found between the increase in the slope of the baroreflex response induced by digitalis and the value of the slope before digitalis ($r = 0.322$; NS). Thus, the extent of the baroreflex potentiation did not seem to depend on having originally a more or less powerful baroreflex function.

Nitroglycerin

Data for nitroglycerin are shown in table 2. In the control period the average value for mean arterial pressure was 106 mm Hg and the RR interval was 802 msec. The fall in pressure induced by nitroglycerin caused a progressive shortening of the RR interval in all subjects. The regression coefficient of RR interval on systolic pressure (i.e., the baroreflex sensitivity) was an average 4.93 (range 1.86-18.20).

<table>
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<th>Table 1. Reflex Increase in RR Interval Induced by Increasing Arterial Blood Pressure with Phenylephrine in 18 Subjects Studied Before and After Administration of Digitalis</th>
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Data are expressed in each subject as linear relationships between rise in systolic pressure and lengthening in RR interval induced by the injection of phenylephrine, each systolic pressure value being related to the next RR interval value. $p$ refers to the difference between the regression coefficients before and after digitalis, estimated by covariant analysis in individuals and by $t$ test in the group as a whole.

Abbreviations: MAP = mean arterial pressure; RR = RR interval; regr. coeff. = regression coefficient.
Figure 1. Effects of increasing systolic blood pressure by phenylephrine on the RR interval before and after administration of digitalis. The increase in systolic pressure caused a linearly related lengthening of the RR interval. The slope of the relationship, i.e., the regression coefficient, is significantly greater after than before digitalis administration.

As described in the previous section, administration of digitalis was followed by no change in basal arterial pressure and by an increase in basal RR interval (p < 0.005). There was no significant difference in the rate or magnitude of the fall in blood pressure induced by the same dose of nitroglycerin before and after digitalis. In contrast with the results with phenylephrine, however, the sensitivity of the baroreflex as estimated by nitroglycerin was not affected by digitalis. In six subjects, the regression coefficient was significantly increased, in six it was unchanged and in eight it was significantly reduced. The average value for the regression coefficient obtained with nitroglycerin was 0.96 ± 0.17 before digitalis and 0.99 ± 0.12 after digitalis.

Figure 2. Effects of baroreceptor stimulation (phenylephrine) and baroreceptor deactivation (nitroglycerin) on RR interval in the control condition and after digitalis administration. The histograms represent the averages (± SEM) of the regression coefficients of each subject.

Figure 3. Hemodynamic changes induced by stimulating (upper panel) and deactivating (lower panel) carotid sinus baroreceptors by means of negative and positive neck-chamber pressures. Data are average (± SEM) changes from control values in seven subjects who were studied before and after administration of digitalis. C = control values; E = early response; and SS = steady-state responses. Basal mean arterial pressure and basal RR interval were, respectively, 117.2 ± 6.1 mm Hg and 772 ± 29 msec before digitalis and 114.3 ± 5 mm Hg and 833 ± 47 msec after digitalis. The p values refer to differences in the responses before and after digitalis. MAP = mean arterial pressure.
glycerin was 4.02, which did not differ significantly from the average value before digitalis.

**Neck Chamber**

The effects of digitalis on basal blood pressure and basal RR interval were similar to those previously described (no significant pressure change and a significant RR interval lengthening).

In the control condition, reducing the tissue pressure outside the carotid sinuses (i.e., increasing carotid transmural pressure and stimulating carotid sinus baroreceptors) caused a clear-cut reduction in arterial blood pressure (fig. 3), whereas increasing the tissue pressure outside the carotid sinuses (i.e., reducing carotid transmural pressure and deactivating the carotid sinus baroreceptors) caused a clear-cut increase in arterial pressure. The early and the steady-state responses to these maneuvers (see Methods) were similar. After digitalis, the hypotensive responses to carotid baroreceptor stimulation were significantly greater, whereas the pressor responses to carotid baroreceptor deactivation were not significantly altered.

The effects of carotid baroreceptor stimulation and deactivation on RR interval are shown in figure 3. Confirming previous findings, these responses were modest and variable. On average, RR interval was reduced slightly in response to carotid baroreceptor deactivation, while no significant change was observed when the carotid baroreceptors were stimulated. The only effect of digitalis was on the early response to baroreceptor stimulation, which consisted of a significant increase in RR interval.

**Discussion**

The bradycardic response to stimulation of arterial baroreceptors by phenylephrine and the hypotensive response to stimulation of carotid sinus baroreceptors by neck suction were greater after than before injection of 0.8 mg of Lanatoside C, which is within the therapeutic range adopted in man. Therefore, administration of clinical doses of digitalis in man augments the reflex effects of arterial baroreceptor stimulation, and the augmentation is evident with regard both to the heart rate and to the blood pressure. This potentiation may have beneficial effects. For example, enhancement of the inhibitory influence of baroreceptors on the sinoatrial and atrioventricular node may reduce the ventricular rate,
thus improving cardiac filling, stroke volume and coronary flow in conditions such as heart failure and atrial fibrillation if baroreflex potentiation occurs in these pathologic conditions as it does in normal subjects.

Our results also show that in man, only one side of the baroreflex is enhanced. When the opposite side of the reflex was studied, i.e., when the baroreceptors were deactivated below the existing level of stimulus by nitroglycerin and positive neck pressure, the reflex tachycardic and pressor responses were not significantly different before and after administration of digitalis. Thus, in man, the augmentation of the arterial baroreceptor function by this drug is limited to the effects of the baroreceptor stimulation and cannot be demonstrated for the effects of a baroreceptor deactivation below the level set tonically by the existing arterial pressure. This indicates a difference with animal studies using large doses of digitalis, in which the hemodynamic responses to deactivation of carotid baroreceptors by common carotid occlusion is also enhanced.5

We do not know why digitalis only potentiates the effects of baroreceptor stimulation and not those of baroreceptor deactivation. However, data from experimental animals suggest at least two explanations. The first is that digitalis stimulates vagal efferent fibers by an action at the central level and possibly at the nerve terminals.17 The second is that besides augmenting baroreceptor responses to increase in blood pressure (a "sensitization," which may account for the potentiation of the reflex that we observed), digitalis causes a direct pharmacologic stimulation of the receptors independent of any pressure stimulus.5, 18 These factors might oppose the tachycardic and pressor responses either by supporting cardiac vagal influence and by limiting the degree of baroreceptor deactivation that can be obtained by a fall in blood pressure or carotid transmural pressure. Whatever the mechanism involved, that digitalis does not potentiate the response to baroreceptor deactivation may be therapeutically beneficial because excessive tachycardia is avoided during reductions in blood pressure.

Several other aspects of our study should be discussed. First, our subjects showed widely different degrees of baroreceptor control of heart rate in the basal condition, consistent with their wide range of age and blood pressure.14, 20, 21 Yet digitalis enhanced the heart rate response to baroreceptor stimulation to the same degree in the subjects with lesser and in those with greater baroreflex sensitivity. One of the conditions in which the baroreflex has a reduced sensitivity is heart failure,15, 21 which is often preceded and caused by hypertension.22 Therefore, the effect of digitalis on the baroreflex may operate in the clinical conditions in which digitalis is used.

Second, we found a lack of correlation between the extent of the bradycardia induced by digitalis and the increase in baroreflex sensitivity caused by the drug. This finding suggests that arterial baroreflex potentiation by digitalis is just one of the many factors responsible for the effect of digitalis on heart rate, the others being the well-known influence of digitalis on cardio-vagal centers and vagal nerve terminals7 and possibly also the effect of this drug on reflexes originating in the heart.23

Third, we noted greater blood pressure responses to carotid baroreceptor stimulation after digitalis. Heart rate effects of baroreceptor manipulation are entirely mediated via the vagus,18, 24 but blood pressure effects depend mainly on the baroreceptor modulation of noradrenergic sympathetic tone.25, 26 Thus, our observations indicate that the baroreflex potentiation caused by digitalis in man is not limited to the cardiovascular component of the reflex, but involves its sympathetic efferent pathways.

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References

Coronary Artery Atherosclerosis: Severity of the Disease, Severity of Angina Pectoris and Compromised Left Ventricular Function

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SUMMARY To determine if the severity of angina pectoris and the degree of altered left ventricular function correlated with the severity and extent of the underlying coronary artery disease, a coronary scoring system was derived. The system was based on the severity of luminal diameter narrowing and weighted according to the usual flow to the left ventricle in each coronary vessel. Thus, the most weight was given to the left main coronary artery, followed by the left anterior descending, circumflex, and right coronary arteries. The resultant number was an indicator of the overall severity of the obstructive coronary artery disease. A coronary arterial system with no obstructive disease was scored as zero and the greater the degree of obstructive disease present, the higher the coronary score. From 202 subjects, four groups were evaluated: group 1 — coronary score = 0.5–4.5 (n = 10); group 2 — coronary score = 10.5–12.5 (n = 11); group 3 — coronary score = 17.5–20.5 (n = 11); and group 4 — coronary score = 25.0–36.0 (n = 11). All subjects had coronary artery bypass surgery and had preoperative and 1-year postoperative cardiac catheterization, including atrial pacing to maximal heart rate. The groups could not be separated on the basis of angina frequency, resting heart rate, cardiac index, left ventricular end-diastolic pressure, peak paced left ventricular end-diastolic pressure, dp/dt, V max, left ventricular end-diastolic volume index, left ventricular end-systolic volume index, stroke volume index, ejection fraction or mean circumferential fiber shortening velocity. Thus, based on this study, the severity of coronary artery disease does not statistically correlate with the frequency of angina pectoris or produce a predictable degree of altered left ventricular function. The frequency of angina pectoris cannot be used to predict prognosis or the adequacy of myocardial revascularization.

IF THE SEVERITY of angina pectoris correlated with the severity of the underlying coronary artery atherosclerosis, one could better judge the appropriate time for invasive diagnostic and therapeutic interventions. One could also ascertain the prognosis of the disease, as it has been adequately shown that prognosis is in part dependent on the severity of coronary artery disease (CAD). It would also be helpful if the severity of the CAD correlated with the degree of abnormal left ventricular function. This would be especially helpful in the postoperative state, when one could very simply ascertain the adequacy of the operation and judge the state of left ventricular function. To evaluate these possibilities, a coronary score was derived to assess the degree of CAD. The coronary score was then related to the frequency of angina pectoris to determine if the extent of CAD could be predicted based on the clinical presentation of angina pectoris. It was also compared with resting and paced left ventricular function measurements to determine if the severity of CAD had a predictably deleterious effect on left ventricular function. The coronary score was also determined at 1 year after coronary bypass surgery and was again compared with the frequency of

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