The Effect of Digitoxin on Sodium Excretion, Creatinine Clearance and Apparent Cardiac Output

By M. J. Greve, M.D., E. E. Eddleman, Jr., M.D., K. Willis, S. Eisenberg, M.D., and T. R. Harrison, M.D.

During the initial phase of decline in cardiac output following the administration of digitoxin to normal subjects, sodium excretion did not decline. Several days later, as cardiac output rose toward the normal level, sodium output decreased in most subjects. The possible implication of these results in relation to the regulation of sodium excretion is discussed.

In recent years there has been an increasing interest in the possible relationship between alterations in hemodynamics and in sodium excretion. The suggestion has been made\(^1\)\(^-\)\(^3\) that absolute or relative decline in cardiac output, consequent to peripheral circulatory failure or to heart failure, evokes an homeostatic mechanism which causes retention of sodium. The resulting increase in the volume of extracellular fluid and of blood would tend to increase venous return and to restore cardiac output, unless myocardial function were too gravely impaired.

The decline in sodium excretion during the states of circulatory failure has been thought by some observers to be mainly a consequence of diminished glomerular filtration\(^4\)\(^-\)\(^6\) associated with decline in renal blood flow. Other investigators have failed to substantiate this concept. Thus normal glomerular filtration rates have been noted in a patient with congestive failure,\(^7\) while failure of filtration rate to rise despite improvement of heart failure has also been reported.\(^8\)\(^-\)\(^10\) The available evidence points toward increased reabsorption of sodium by the renal tubules as a more important factor than decline in filtration rate.

The unanswered question is whether the increase in tubular reabsorption of sodium is brought about by decline in cardiac output or by some other factor present in patients with circulatory failure. One possible approach to this problem would be to eliminate the complexities of circulatory failure, and study normal subjects in an attempt to elucidate the relationship between various hemodynamic factors and sodium excretion.

In previous reports\(^11\)\(^-\)\(^13\) from this laboratory, it has been shown that sodium excretion is affected by hemodynamic factors other than cardiac output or glomerular filtration. Thus compression of the neck of sitting subjects caused increase in sodium excretion but had no detectable effect on cardiac output or creatinine clearance. Venesection of a degree too small to produce consistent changes in these functions, likewise, caused well marked decline in sodium excretion. On the other hand, changes in posture produced similar directional changes in cardiac output and in urinary sodium, with little or no change in filtration.

In order to complete the study of the relationship between these several functions in normal subjects, it would be desirable to reduce deliberately the cardiac output and observe the changes in sodium excretion.

In dogs and in normal men, digitalis has been shown to cause reduction in cardiac output\(^15\)\(^-\)\(^16\) and in blood volume.\(^17\)\(^-\)\(^19\) More recently the drug has been found to cause increase in thiocyanate space.\(^20\)\(^,\)\(^21\) It was thought, therefore, that an investigation of normal subjects receiving this drug might be of value in elucidating the relationship between sodium excretion and these hemodynamic factors.

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PROCEDURE

Nine healthy male medical students were placed on a diet calculated to contain 1.0 Gm. of sodium daily, and to the food was added 2.0 Gm. of sodium chloride at breakfast and 2.5 Gm. sodium chloride at each of the other two meals. No attempt was made to control potassium intake. After the subjects had been on the diet for one week, or longer, control studies were made. Ventricular excursion and apparent cardiac output were estimated by the electrokymographic method, in the sitting position, before meals, at 7:00 a.m., 12:00 noon, and 5:00 p.m. Plasma creatinine clearances were measured, using a blood sample drawn before breakfast or lunch, and three eight-hour urine periods (7:00 a.m. to 3:00 p.m., 3:00 p.m. to 11:00 p.m., and 11:00 p.m. to 7:00 a.m.). On the following day, after an additional electrokymogram, 2.0 mg. of digitoxin were taken orally by each subject, in divided doses; 1.0 mg. at 8:00 a.m., 0.6 mg. at 12:00 noon, and 0.4 mg. at 5:00 p.m. No other digitoxin was given. Cardiac excursion and creatinine clearances were measured as on the control day. For the following three days, cardiac studies were made at 7:00 a.m., daily; and creatinine clearances were done from 7:00 a.m. to 3:00 p.m., daily. Sodium and potassium excretion in the urine were measured for three or four days prior to the administration of digitalis, and for four days thereafter. Serum potassium was determined on the day following digitalis administration. During these studies the subjects engaged in no strenuous exercise but carried on normal sedentary activities, including attending classes and studying. The experiments were conducted during the months of January, February, and March when sweating was at a minimum. It should be noted that digitalis was administered on one day only.

Electrocardiographic tracings were made just prior to the first and last doses of digitoxin. The second electrocardiogram showed minimal lowering of T waves. The subjects were weighed daily throughout the experiment, and blood pressure was measured each time an electrokymographic tracing for cardiac output was taken.

METHODS

Cardiac outputs were calculated from the heart rates and the apparent stroke volumes as measured by the electrokymographic method, the original technic of Ring and associates having been slightly modified.23 The hemodynamic studies are being published in detail elsewhere,24 and the data reported here are only the percentage variations from the average of control values. The quantitative accuracy of the electrokymographic method of measuring cardiac output has not yet been established, and there may be errors in the figures presented here for percentage change. On the other hand, the method appears to be reliable for detection of directional alterations and for obtaining a general guide as to their magnitude.

Endogenous creatinine clearances were measured by the method of Bonsnes and Taussky22 as modified by Brod and Sirota.26 Clearances are given over 24 hour periods based on plasma creatinines drawn once during that period. It has been reported since this work was done that, for greater accuracy of 24 hour clearance, plasma levels of creatinine should be determined at four to six hour intervals.27 Hence the values for the first period of each day (7:00 a.m. to 3:00 p.m.) are probably more accurate than those for the subsequent periods. The latter are included in the data because they are probably significant where striking variations occurred. The creatinine clearance rather than the inulin clearance was measured, because it was believed preferable to have measurements over a period of several hours.

Urine sodiums were determined by the method of Hoffman and Osgood,28 with the slight technical modifications which have previously been reported.

Urine and serum potassiums were measured colorimetrically by the method of Shohl and Bennett,29 using the precipitation and washing procedures described by Consolazio and Dill.30

The observations on 3 additional subjects were discarded because their sodium excretions varied widely during the control period. In 2 instances in the reported subjects, single 24 hour sodium excretions were discarded in averaging the control days, but all of the data following digitalis administration are included.

RESULTS

Alterations in apparent cardiac output, endogenous creatinine clearance, and urinary sodium are presented in table 1. The data are arranged according to the number of hours following the beginning of digitoxin ingestion. In all subjects the apparent cardiac output fell below the lowest control value at some time during the experiment. The degree and time of maximum decline varied. When the output was lowest most of the subjects had mild symptoms of lethargy, drowsiness, and anorexia. In all but 1 subject the apparent output had returned to within the control range at 72 hours.

The endogenous creatinine clearances were used as a measure of glomerular filtration rate. There was no parallel variation in cardiac output and creatinine clearance. From the average results shown in figure 1, it can be seen that filtration rate declined slightly throughout the experiment, though to a lesser degree than
did cardiac output. From the complete data in table 1 it is observed that in only 1 subject, J. M., did creatinine clearance fail to fall. In 2 subjects, C. C. and R. C., creatinine clearance subjects, however, filtration rate was still low after output had returned to control levels.

The sodium excretion for 24 hour periods and for the 7:00 a.m. to 3:00 p.m. period of each

<table>
<thead>
<tr>
<th>Table 1.—Effect of Digitoxin on Cardiac Output, Endogenous Creatinine Clearance and Urinary Sodium.</th>
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<tbody>
<tr>
<td><strong>Subject</strong></td>
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<td></td>
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<tr>
<td><strong>M. G.</strong></td>
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<tr>
<td><strong>J. B.</strong></td>
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<tr>
<td><strong>J. M.</strong></td>
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<tr>
<td><strong>C. C.</strong></td>
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<tr>
<td><strong>T. E.</strong></td>
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<tr>
<td><strong>R. C.</strong></td>
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<tr>
<td><strong>H. W.</strong></td>
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<td><strong>J. K.</strong></td>
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<td><strong>D. V.</strong></td>
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</tbody>
</table>

| **Subject** | **7 AM-3 PM Control Average Range** | **24 Hour Control Average and Range** | **Urine Sodium, Gm.** | **Hours after Beginning of Digitoxin Administration** |
| | | | | **0-8** | **0-24** | **24-32** | **24-48** | **48-56** | **48-72** | **72-80** | **72-96** |
| **M. G.** | 1.41 (.9 to 1.7) | 3.38 (3.28 to 3.35) | 1.25 | 3.80 | 1.44 | 3.21 | 1.07 | 3.44 — | — |
| **J. B.** | 1.31 (1.1 to 1.5) | 3.24 (2.94 to 3.64) | 0.94 | 3.68 | 1.50 | 3.40 | 1.05 | 2.80 — — |
| **J. M.** | 1.24 (.5 to 1.9) | 3.96 (2.59 to 5.52) | 1.13 | 2.79 | .80 | 3.86 | 1.22 | 2.77 .80 2.44 |
| **C. C.** | 1.11 (.6 to 2.0) | 3.31 (2.25 to 4.45) | .47 | 3.15 | 1.78 | 5.12 | 1.06 | 2.42 1.63 3.58 |
| **T. E.** | 1.45 (.7 to 2.1) | 3.71 (3.24 to 4.18) | 1.41 | 4.13 | 1.53 | 4.01 | 1.00 | 2.73 1.06 2.68 |
| **R. C.** | 1.12 (.8 to 1.3) | 3.45 (3.15 to 3.86) | 1.40 | 3.27 | .75 | 3.25 | .65 | 2.06 .99 2.42 |
| **H. W.** | 1.17 (.5 to 1.7) | 3.19 (3.00 to 3.39) | 1.44 | 3.49 | 1.29 | 3.79 | 1.39 | 3.62 .68 2.02 |
| **J. K.** | 1.14 (.9 to 1.4) | 3.38 (3.10 to 3.94) | .75 | 3.19 | .58 | 2.27 | .90 | 3.51 .40 2.05 |
| **D. V.** | 1.33 (.8 to 1.4) | 3.30 (2.98 to 3.53) | 2.59 | 4.73 | 1.84 | 3.76 | 1.13 | 3.18 .53 2.53 |

In the first column (top) are shown the percentage variation of the extremes from the mean of 4 control cardiac output measurements, and individual measurements of cardiac output follow, according to the time elapsed from the beginning of digitoxin administration. Endogenous creatinine clearances are depicted in the second group of columns. The clearance figures not included in parentheses are considered more accurate than those in parentheses, which are based on plasma creatinines drawn during the earlier periods of each day. The first column of clearance data are for the three eight-hour periods in the control day, and the remainder are arranged according to the time following the first dose of digitoxin. In the last group of columns are the values for urinary sodium. The italicized numbers represent 24 hour sodium excretion, and the remainder cover 8 hour periods corresponding to the more accurate filtration rate measurements. The first column of sodium data depicts the mean of 3 or 4 control days, with the highest and lowest values given to indicate the range of control variation. The remainder of the sodium data are given according to the time period following the beginning of digitoxin administration. Digitoxin was given orally to all subjects on a single day only, the dosage schedule being 1.0 mg. at 8:00 a.m., 0.6 mg. at 12:00 noon, and 0.4 mg. at 5:00 p.m.

rose to control levels as apparent cardiac output rose at the end of the experiment; and, in 1 individual, T. E., both functions were significantly below control values when the experiment was ended. In the 5 remaining 24 hour interval are included in table 1. The eight hour results have been included because these time intervals correspond to the timing of the more accurate filtration rate measurements, and because the electrolymographic
observations were made at the beginning of this period. Since the eight hour sodium excretions were more variable than were the 24 hour, the latter are also presented.

In figure 1 it can be seen that there was an average rise in 24 hour urine sodium of 3 per cent and 5 per cent, respectively, in the first two 24 hour periods after the beginning of digitoxin ingestion. In only 2 of the 9 subjects was sodium excretion in the first two 24 hour periods of the experiment significantly (more than 10 per cent) less than the average of the controls, and in every subject the sodium excretion during the first two days after digitoxin was greater than on the day immediately preceding the administration of the drug. The findings in subject H. W. (fig. 1) illustrate a striking rise in sodium excretion in the presence of a marked fall in cardiac output during the first 48 hours.

![Figure 1: The Effect of Digitoxin on Cardiac Output, Urinary Sodium, and Endogenous Creatinine Clearance.](http://circ.ahajournals.org/)

In 1 instance (M. G., in the period 16 to 24 hours after beginning digitoxin) a very low sodium excretion (0.37 Gm.) was associated with a very low filtration rate (54 cc. per minute), and with a well marked decline in cardiac output. This was the only occasion in which a striking parallel decline was observed in the three functions. There were numerous
instances in which sodium excretion was unchanged or increased in the presence of reduction of cardiac output.

In 6 of 7 subjects, sodium excretion was decreased on the fourth day after digitalization and in 5 of these 6, cardiac outputs had returned to within or above the control range. The filtration rate often remained low during the third and fourth day after digitalis. The tendency for sodium excretion to fall as the cardiac output returned to normal, and while filtration rate remained low, is illustrated in figure 1 by subject J. K. This subject exhibited a trend toward a reciprocal relationship between cardiac output and sodium excretion.

There was no change in blood pressure except for a slight widening of the pulse pressure in the first 24 to 36 hours. In another study24 data concerning the effects of digitalis on peripheral resistance and on other hemodynamic functions will be presented. Here, it is sufficient to note that when cardiac output was low, peripheral resistance was increased. If it is assumed that the renal circulation participated in the general increase in peripheral resistance, then renal blood flow was probably diminished to a greater degree than was filtration rate.

Potassium excretion in the urine measured over 24 hour periods was not significantly altered, and there was no correlation between sodium and potassium (table 2). Serum potassium levels measured on the day following digitalis administration were within normal limits.

No significant changes in weight were noted during the experiments.

**DISCUSSION**

During the first two days after digitalization, the apparent cardiac output declined markedly, and the filtration rate was slightly diminished. At the same time there was either no change or an increase in sodium excretion. Thus it would appear that there is no necessary parallelism between these functions in normal subjects. However, in the only instance in which an extreme decline in filtration rate occurred there was a well marked decrease in sodium excretion.

During the second 48 hour period, as cardiac output returned to normal, sodium excretion

### Table 2.—Comparison between Sodium and Potassium Excretion following Oral Digitoxin.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Control Average and Range</th>
<th>Hours after Beginning of Digitoxin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0.24</td>
</tr>
<tr>
<td>M. G.</td>
<td>Na 3.33 (3.28-3.25)</td>
<td>3.30</td>
</tr>
<tr>
<td></td>
<td>K 3.24 (2.58-3.71)</td>
<td>3.54</td>
</tr>
<tr>
<td>J. B.</td>
<td>Na 3.24 (2.94-3.64)</td>
<td>3.68</td>
</tr>
<tr>
<td></td>
<td>K 3.86 (3.39-4.43)</td>
<td>3.83</td>
</tr>
<tr>
<td>J. M.</td>
<td>Na 3.96 (25.9-5.52)</td>
<td>2.79</td>
</tr>
<tr>
<td></td>
<td>K 2.59 (2.15-2.86)</td>
<td>3.08</td>
</tr>
<tr>
<td>C. C.</td>
<td>Na 3.31 (2.25-4.45)</td>
<td>3.15</td>
</tr>
<tr>
<td></td>
<td>K 3.04 (1.04-1.17)</td>
<td>3.71</td>
</tr>
<tr>
<td>T. E.</td>
<td>Na 3.71 (3.24-4.18)</td>
<td>4.13</td>
</tr>
<tr>
<td></td>
<td>K 3.34 (2.88-3.77)</td>
<td>3.05</td>
</tr>
<tr>
<td>R. C.</td>
<td>Na 3.45 (3.15-3.81)</td>
<td>3.27</td>
</tr>
<tr>
<td></td>
<td>K 3.24 (2.95-3.40)</td>
<td>3.20</td>
</tr>
<tr>
<td>H. W.</td>
<td>Na 3.19 (3.00-3.39)</td>
<td>3.49</td>
</tr>
<tr>
<td></td>
<td>K 1.99 (1.74-2.23)</td>
<td>3.10</td>
</tr>
<tr>
<td>J. K.</td>
<td>Na 3.38 (3.10-3.94)</td>
<td>3.19</td>
</tr>
<tr>
<td></td>
<td>K 1.99 (1.51-2.28)</td>
<td>2.44</td>
</tr>
<tr>
<td>D. V.</td>
<td>Na 3.38 (3.10-3.94)</td>
<td>4.73</td>
</tr>
<tr>
<td></td>
<td>K 2.83 (2.55-3.08)</td>
<td>3.45</td>
</tr>
</tbody>
</table>

The average 24 hour control excretion and range of control variation for both sodium and potassium are given, one above the other, for each subject. There follow the 24 hour excretions according to the time after the beginning of digitoxin administration. There was no significant consistent change in potassium excretion, nor any correlation between sodium and potassium excretion. The subjects were on a constant sodium diet, but no attempt was made to keep potassium intake constant.
declined, while glomerular filtration rate tended to remain low. From the average changes shown in figure 1, it is apparent that the increase in sodium excretion in the first 48 hours was of smaller magnitude than the decline in the second 48 hours. It is not likely, therefore, that the later decline was entirely the result of sodium depletion consequent to the initial increase in excretion.

One possible explanation of the late decline in sodium excretion is that a lowering of cardiac output caused such a decrease but only after a lag of 24 to 48 hours. Another possible explanation is as follows:

There is general agreement that digitalis causes decline in circulating blood volume. The mechanism responsible for this is unknown. There is evidence, which will be reviewed in another publication, that the drug causes venoconstriction. If this occurs, the immediate effect would be increased cardiac filling and output, while the persistent effect would be redistribution of blood away from the heart and great veins to the capillaries, and possibly to storage reservoirs. Such a peripheral plethora might lead to increase in blood destruction, such as occurs in normal subjects after transfusion.

If other factors remained equal, venous constriction would tend to elevate capillary surface area and pressure, and to cause increased transudation. Recent studies indicating that digitalis causes increase in extracellular fluid volume and concomitant decline in blood volume in normal subjects, are in accord with such an interpretation.

It seems likely, therefore, that in normal subjects digitalis causes redistribution of blood with increased volume in certain peripheral areas, and at the same time causes increase in extravascular extracellular fluid volume. If, as is uncertain, these changes affect the intracranial tissues, the directional effects would be similar to those produced by compression of the neck or by changing from the sitting to the recumbent posture. These procedures cause well marked increment in sodium excretion. Five of our 9 subjects studied with digitalis, likewise showed a tendency toward an initial rise in sodium excretion. The inconsistency of this increase would suggest that other, unknown, factors were also concerned.

As the effects of the drug began to wane cardiac output increased, and at the same time sodium excretion declined. Possibly this can be ascribed to a reversal of the previous sequence, with disappearance of venous constriction and movement of extracellular fluid from the extravascular to the intravascular compartment. The findings previously reported are readily interpreted by the assumption that alterations in intracranial extracellular fluid volume affect sodium excretion. The same assumption would account for the initial rise and the subsequent decline in sodium output, as observed in the present study.

The failure of potassium to vary in a reciprocal manner with sodium could be interpreted as suggesting that the adrenal cortex does not play a major role in these mechanisms. The lack of consistent changes in urinary potassium excretion seems to indicate that digitalis causes little or no alteration in the volume of the intracellular fluid.

In the attempt to elucidate the relationship between sodium output and alterations in hemodynamics, a number of procedures have been employed in the present and preceding studies. The findings are summarized in table 3. They reveal no tendency toward a consistent relationship between sodium excretion, glomerular filtration, and apparent cardiac output as measured by the electrokymographic method. It is, therefore, unlikely that in normal subjects either cardiac output or glomerular filtration is of major significance in the regulation of sodium excretion.

Such a conclusion is not contrary to the concept of a homeostatic mechanism, set into play by hemodynamic factors and serving to conserve sodium. On the contrary, the data appear to support such a concept but to point toward alterations in the volume and distribution of body fluids rather than changes in cardiac output as the initiating mechanism. All of the findings can be explained by the assumption of a volume regulating mechanism brought into play by deficit of extracellular fluid within the cranial cavity, and serving to restore extracellular fluid volume by causing renal conserva-
tion of sodium. In the absence of methods of measuring cerebral fluid volumes, the hypothesis cannot be subjected to direct test. In any case, it is clear that this postulated mechanism is only one of several factors concerned in are compatible with the idea that a homeostatic mechanism serving to conserve sodium exists, and that this mechanism is initiated by alterations in the volume and/or distribution of body fluids.

**Table 3.** Summary of Effects of Various Procedures on Sodium Excretion, Cardiac Output and Glomerular Filtration of Normal Subjects.

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Directional Change</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change from recumbent to sitting position</td>
<td>- - 0 - -</td>
<td>Compression of neck of recumbent subjects had little effect</td>
</tr>
<tr>
<td>Compression of neck of sitting subjects</td>
<td>0 0 ++</td>
<td></td>
</tr>
<tr>
<td>Venesection (2.5 cc. per Kg.) Sitting Neck not compressed</td>
<td>0 0 - -</td>
<td></td>
</tr>
<tr>
<td>Venesection (9 cc. per Kg.) Recumbent Neck not compressed</td>
<td>0 - - -</td>
<td></td>
</tr>
<tr>
<td>Recumbent Neck compressed</td>
<td>0 - - -</td>
<td></td>
</tr>
<tr>
<td>Digitoxin (2.0 mg. in 9 hours) Initial 2 days</td>
<td>- - - + or +</td>
<td>Period of maximal action</td>
</tr>
<tr>
<td>Subsequent period</td>
<td>+++ - -</td>
<td>Cardiac output returning to initial level</td>
</tr>
</tbody>
</table>

the regulation of sodium excretion. Whether it is of any significance in disease is as yet uncertain, and will be the subject of future investigation.

**Summary**

Healthy young men were given 0.2 mg. digitoxin in divided doses over a nine hour period.

During the initial 48 hours after the drug, the excretion of sodium increased or remained unchanged. At the same time creatinine clearance was slightly decreased and the apparent cardiac output (electrokymographic method) diminished markedly. This was followed by a period during which the cardiac output returned to the control level, and as this occurred sodium excretion declined. Creatinine clearance was usually still decreased at this time.

The results are considered to constitute evidence against the concept that decline in cardiac output leads to sodium retention. They

**References**

1. **Borst, J. G. G.:** The restoration of the circulation of blood after gross hemorrhage into the intestinal tract: A comparison of the failure of the circulation in heart failure and in bleeding from peptic ulcer. Nederl. tijdschr. v. geneesk. 45: 1523, 1941.

2. **Dock, W.:** Congestive heart failure considered as the body's adaptation to inadequate cardiac output. Roger S. Morris Lecture, Cincinnati, 1949.


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