Further Studies on the Effects of Changes in the Distribution of Extracellular Fluid on Sodium Excretion

Observations Following Compression of the Legs

By John A. Lusk, M.D., William N. Viar, M.D., and Tinsley R. Harrison, M.D.

Bandaging of the legs of sitting subjects resulted in an increase in the renal excretion of sodium which declined after the bandages were removed. Consistent results were not obtained in recumbent subjects. The findings appear to constitute further evidence that the distribution, rather than the total volume of extracellular fluids, has a regulatory action on sodium excretion.

Within the past few years it has been repeatedly suggested that the sodium retention occurring in patients with circulatory failure (both cardiac and peripheral) was the result of inadequacy of cardiac output. Such inadequacy has been thought by some to cause sodium retention as the result of decline in glomerular filtration.1, 2, 9, 10 Others have assumed that the retention was due to increased tubular reabsorption brought about in some manner by defective cardiac output.3, 4, 11 Both concepts are attractive because they offer simple and reasonable explanations for decline in sodium excretion in such clinically diverse states as bleeding peptic ulcer, intestinal obstruction, and congestive heart failure. However, the previously reported studies of the present series6-8 have offered what appears to us to be convincing evidence against the ideas of inadequate cardiac output, and of decline in glomerular filtration, as physiologic mechanisms responsible for sodium retention in normal subjects. It has been shown in healthy young males that the three functions (cardiac output, glomerular filtration, and sodium excretion) undergo independent alterations. Thus the change from recumbency to sitting caused marked decline in sodium excretion, slight decline in cardiac output, and no consistent change in glomerular filtration.7, 8

Compression of the neck of sitting subjects caused elevation of sodium output, the other two functions remaining unaffected.5, 7 Removal of small amounts of blood from sitting subjects produced decline in sodium excretion without alterations in glomerular filtration or cardiac output. When larger amounts of blood were removed, marked decrease in sodium excretion and slight decline in glomerular filtration were encountered without significant alterations in cardiac output.6 On the other hand, the administration of digitalis to normal subjects caused early decline in cardiac output, the sodium excretion remaining constant or increasing slightly. As cardiac output returned to the normal level, decline in sodium excretion and in glomerular filtration usually occurred.5 Thus studies on normal subjects lend no support to the concept that cardiac edema is the result of sodium retention consequent to forward failure. However, the possibility that these various findings in normal subjects may bear no relationship to the problem of heart failure cannot be excluded. The final answers to the question of the mechanism responsible for cardiac edema can only come from studying patients with heart failure. On the other hand most of the mechanisms of disease are exaggerations of normal mechanisms. Hence it seems probable that such studies will be more fruitful if conducted in the light of clear knowledge of the mechanisms.
regulating sodium and water balance in normal subjects.

There are a number of observations which suggest that alterations in the volume of body fluids may have an important regulatory effect on the renal output of sodium. Thus Peters has suggested that disturbances in the Starling equilibrium between oncotic and capillary pressures lead to increased transudation into the tissues, and that the consequent decline in blood volume initiates sodium retention by means of unknown mechanisms. However, this concept is difficult to reconcile with the findings in patients with congestive heart failure, who may retain sodium in spite of well marked evidence of hypervolemia. Similar objections apply to the suggestion of Welt and Seldin that increased oncotic pressure of the plasma consequent to escape of fluid from the blood stream into the tissues may be the stimulus responsible for sodium retention. Patients with nephrosis retain sodium in spite of marked decrease in oncotic pressure.

Further evidence against the idea that decline in blood volume is an important stimulus to sodium retention is furnished by the observations of Goodyer and co-workers and of Welt and Orloff. These observers found that sodium excretion of normal subjects declined following the administration of hypertonic albumin solution, a procedure which would be expected to increase the blood volume at the expense of the interstitial fluid.

The possibility that decline in the total volume of interstitial fluid (rather than the plasma volume) constitutes a normal stimulus to sodium retention merits consideration. This concept is compatible with the decline in sodium output occurring after the administration of hypertonic albumin solutions. However, it is not compatible with the tendency of markedly edematous patients to retain sodium.

The foregoing considerations are susceptible of several alternative interpretations: (1) Deficit of the total volume of extracellular fluid causes sodium retention in healthy subjects, but this mechanism is not operative in edematous patients. (2) The stimulus to sodium retention is not decline in the volume of extracellular fluid but some closely related function. The first assumption seems unlikely on a priori grounds. The second assumption is favored by a considerable body of recent evidence, which may now be reviewed briefly.

It has been shown that experimental venous congestion of the legs of normal subjects causes a pronounced decline in sodium output. These observations plus the effects of posture, bleeding, and digitalis, as considered in our previous communications, can all be explained by a single hypothesis: that decline in the intracranial extracellular fluid volume (or some closely related function) leads to sodium retention. If such a regulating mechanism exists, it may possibly be of importance in relation to sodium retention in edematous states. These can only be proved by studies on patients with various types of edema. However, such studies are more likely to be fruitful if conducted in the light of a thorough knowledge of the normal physiology of the mechanisms concerned. Hence we have preferred to continue our investigations of healthy persons before studying patients.

It is well known that the intravenous injection of solutions containing sodium is soon followed by an increase in the urinary output of sodium. Such an effect has naturally been assumed to be the result of an increase in the total volume of extracellular fluid. However, it might equally well be the result of a local increase in extracellular fluid volume in some regulatory area. Likewise, experimental congestion of the legs decreases sodium output, while experimental congestion of the head (carried out under appropriate conditions) has the reverse effect. These findings can, likewise, be explained by the assumption of alterations in extracellular fluid volume in an intracranial center. They raise the question whether alterations induced by redistribution of extracellular fluid from the legs to the remainder of the body might not tend to increase sodium excretion. The experiments to be reported in this communication were conducted in order to test this idea.
**Method of Study**

The procedure was similar to that previously reported. The subjects were healthy male medical students. They ingested their usual diets to which 2 Gm. of sodium chloride were added daily. For at least two days prior to the experiment they avoided activities which would tend to disturb their usual fluid and electrolyte balance. On the day of the experiment breakfast was omitted. Subjects were allowed 30 Gm. of milk chocolate every hour, so of nine hours. In other observations the feet, legs, and thighs were snugly compressed by an elastic bandage at the end of the third hour after the onset of loading. The bandages were kept in place for four hours and then quickly removed, urine being collected for two additional hours.

**Results**

One subject developed migraine on two different occasions and exhibited different re-

<table>
<thead>
<tr>
<th>Subject</th>
<th>Control Hour</th>
<th>Experimental Period Legs Compressed</th>
<th>Postexperimental Control Period Legs Not Compressed</th>
<th>Serum Sodium mEq./liter</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3rd Hr.</td>
<td>4th Hr.</td>
<td>5th Hr.</td>
<td>6th Hr.</td>
</tr>
<tr>
<td>J.A.L. (1)</td>
<td>2.21</td>
<td>3.99</td>
<td>17.11</td>
<td>12.30</td>
</tr>
<tr>
<td>J.A.L. (2)</td>
<td>2.81</td>
<td>6.50</td>
<td>6.75</td>
<td>3.88</td>
</tr>
<tr>
<td>K.L.Y.</td>
<td>18.70</td>
<td>19.41</td>
<td>24.42*</td>
<td>25.95</td>
</tr>
<tr>
<td>M.C.</td>
<td>13.80</td>
<td>17.11</td>
<td>18.60</td>
<td>13.33</td>
</tr>
<tr>
<td>C.P.C.</td>
<td>14.60</td>
<td>12.82</td>
<td>15.84</td>
<td>15.17</td>
</tr>
<tr>
<td>D.P.</td>
<td>12.15</td>
<td>16.06</td>
<td>15.03</td>
<td>19.00</td>
</tr>
<tr>
<td>L.L.S.</td>
<td>8.50</td>
<td>16.78</td>
<td>17.73</td>
<td>18.73</td>
</tr>
<tr>
<td><strong>Average</strong></td>
<td>10.39</td>
<td>13.24</td>
<td>16.49</td>
<td>15.48</td>
</tr>
</tbody>
</table>

**Urine Volume (ml./hr.)**

<table>
<thead>
<tr>
<th>Subject</th>
<th>3rd Hr.</th>
<th>4th Hr.</th>
<th>5th Hr.</th>
<th>6th Hr.</th>
<th>7th Hr.</th>
<th>8th Hr.</th>
<th>9th Hr.</th>
</tr>
</thead>
<tbody>
<tr>
<td>J.A.L.</td>
<td>425</td>
<td>384</td>
<td>398</td>
<td>300</td>
<td>260</td>
<td>348</td>
<td>291</td>
</tr>
<tr>
<td>J.A.L.</td>
<td>419</td>
<td>197</td>
<td>270</td>
<td>323</td>
<td>341</td>
<td>223</td>
<td>215</td>
</tr>
<tr>
<td>K.L.Y.</td>
<td>390</td>
<td>461</td>
<td>520</td>
<td>617</td>
<td>448</td>
<td>368</td>
<td>442</td>
</tr>
<tr>
<td>M.C.</td>
<td>445</td>
<td>398</td>
<td>620</td>
<td>325</td>
<td>419</td>
<td>318</td>
<td>592</td>
</tr>
<tr>
<td>C.P.C.</td>
<td>433</td>
<td>427</td>
<td>511</td>
<td>410</td>
<td>399</td>
<td>457</td>
<td>495</td>
</tr>
<tr>
<td>D.P.</td>
<td>434</td>
<td>462</td>
<td>401</td>
<td>481</td>
<td>350</td>
<td>323</td>
<td>315</td>
</tr>
<tr>
<td>L.L.S.</td>
<td>607</td>
<td>408</td>
<td>572</td>
<td>446</td>
<td>512</td>
<td>270</td>
<td>294</td>
</tr>
<tr>
<td><strong>Average</strong></td>
<td>452</td>
<td>391</td>
<td>471</td>
<td>415</td>
<td>390</td>
<td>329</td>
<td>378</td>
</tr>
</tbody>
</table>

* Bandages readjusted and tightened at end of 5th hour.

as to prevent hunger from becoming a disturbing factor. One cigarette per hour was smoked by those subjects who so desired.

The subjects ingested 200 ml. of 0.14 per cent sodium chloride solution at hourly (recumbent) or half-hourly (sitting) intervals. Urinary output was measured hourly. The specimens for the first two hours were discarded, because it has been shown that equilibrium is not usually obtained until the third hour. Urinary and serum sodium concentrations were determined with the flame photometer, by the method of Mosher and co-workers. In control experiments the subject continued to ingest the solution and to void at hourly intervals for a period sponses from those obtained in the other individuals. The data from this individual will be considered separately.

During the control experiment in which the legs were not wrapped, the sodium output exhibited relatively small changes after the third hour of ingesting the loading solution. Since these data are similar to those previously reported, they need not be considered further.

The effects of bandaging the legs of sitting subjects were studied in seven experiments (table
1, fig. 1). In one instance (subject C.P.C.) the results were inconclusive, while in the remaining six instances a slight to marked rise in sodium excretion occurred. The increment was least during the first hour, greatest during the second, and somewhat reduced during the third and fourth hours (fig. 1). Following removal of the bandages the sodium output declined, and sometimes to levels lower than those found prior to the application of the bandages. The average sodium output, which was approximately equal to the intake during the control hour, exceeded the intake by about 65 per cent while the legs were wrapped.

The similarity of the hourly changes in sodium excretion produced by wrapping the legs and by compression of the neck—as observed in a previous study—was striking, and is illustrated in figure 2.

In the three subjects in which serum sodium was determined, both before and after compression of the legs, the values showed no consistent change (table 1). In two of the subjects there was a decrease of 3 and 5 mEq. per liter. In the third subject the serum sodium rose 6 mEq. per liter.

The effects of wrapping the legs of recumbent subjects were observed in three experiments (table 2). No consistent changes were observed in urine volume. The sodium excretion was greater than the intake (5.76 mEq. per hour),
TABLE 2.—Sodium Excretion and Urine Volume of Normal Subjects in Recumbent Position with Legs Compressed

<table>
<thead>
<tr>
<th>Subject</th>
<th>Control Hour</th>
<th>Experimental Period Legs Compressed</th>
<th>Postexperimental Control Period Legs not Compressed</th>
<th>Serum Sodium mEq./liter</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3rd Hr.</td>
<td>4th Hr.</td>
<td>5th Hr.</td>
<td>6th Hr.</td>
</tr>
<tr>
<td>D.P.</td>
<td>14.5</td>
<td>9.4</td>
<td>21.1</td>
<td>13.8</td>
</tr>
<tr>
<td>M.C.</td>
<td>22.4</td>
<td>19.1</td>
<td>21.1</td>
<td>16.9</td>
</tr>
<tr>
<td>Average</td>
<td>14.21</td>
<td>17.05</td>
<td>20.70</td>
<td>16.58</td>
</tr>
</tbody>
</table>

Sodium Excretion (mEq./hr.)

<table>
<thead>
<tr>
<th>Subject</th>
<th>Control Hour</th>
<th>Experimental Period</th>
<th>Postexperimental Control Period</th>
<th>Serum Sodium mEq./liter</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3rd Hr.</td>
<td>4th Hr.</td>
<td>5th Hr.</td>
<td>6th Hr.</td>
</tr>
<tr>
<td>J.A.L.</td>
<td>141</td>
<td>136</td>
<td>127</td>
<td>119</td>
</tr>
<tr>
<td>D.P.</td>
<td>283</td>
<td>278</td>
<td>272</td>
<td>268</td>
</tr>
<tr>
<td>M.C.</td>
<td>295</td>
<td>293</td>
<td>288</td>
<td>284</td>
</tr>
<tr>
<td>Average</td>
<td>278</td>
<td>271</td>
<td>269</td>
<td>267</td>
</tr>
</tbody>
</table>

Urine Volume (ml./hr.)

**Fig. 3.** Effect of pain on sodium excretion and urine volume of subject in sitting position with legs compressed. Just prior to the application of the bandages, venepuncture was performed for determination of serum sodium (A). Within 10 to 15 minutes after the application of bandages subject developed a severe throbbing headache in the left temporal area, which could be relieved by pressure over the left temporal artery. The headache spread to the right temporal area, and decreased somewhat in intensity, but persisted throughout the experiment. The hourly sodium output (solid line) decreased consistently during the experiment. Unlike the changes shown in figure 1, there was no rise in sodium output after compression of the legs, indicating that the antinatriuretic effect of pain outweighs the naturetic effect of compression of the legs in the absence of headache (fig. 1). After an initial drop in urine volume the hourly output rose moderately but fell again after a second venepuncture at B. This illustrates the antidiuretic effect of a painful procedure.

As is usual with recumbent subjects, no consistent changes in sodium excretion were noted. Here again, there is a similarity of hourly changes in sodium excretion observed after wrapping the legs, and congestion of the head. Noteworthy changes in serum sodium values were not observed.

**The effects of pain on sodium excretion.** The findings are illustrated in figure 3. The subject developed a spontaneous attack of migraine shortly after the bandages were applied to the legs. The severe headache persisted throughout the experimental period, and was accompanied by a striking progressive decline in sodium excretion and a somewhat less pronounced decrease in urine volume (fig. 3). On another occasion the needle became plugged during an attempted venepuncture on the same subject. The resulting hematoma caused considerable discomfort and was followed by a milder attack of migraine. The sodium output declined in this experiment, the degree of decline being less than during the more severe attack of migraine.

**Discussion**

The data indicate that bandaging of the legs causes increased output of sodium in the urine. In view of the other observations which have been mentioned, it appears probable that the effect is analogous to that produced by an in-
travenous infusion of saline solution, and is due to an increase in the volume of extracellular fluid in some regulatory area.

The observations are in accord with numerous other findings in pointing toward a lack of correspondence between the renal excretion of sodium and of water.

The similarity in sitting subjects between the effects on sodium excretion of wrapping the legs and of compressing the neck (fig. 2) has already been mentioned. In each instance sodium excretion increased for two to three hours, and then gradually declined during the last of the procedure. The resemblance between the two curves may be fortuitous, but it is also possible that in both instances the effects were mediated by an increase in the extracellular fluid volume in the brain induced by distributional changes in the interstitial fluid. In this connection, it is of interest that in recumbent subjects neither compression of the neck nor bandaging the legs had any consistent effect on sodium excretion (table 2). The reasons for the differences between the effects of these procedures in the sitting and the recumbent posture are not clear at this time.

Further information is, likewise, needed in order to interpret the time curves of sodium excretion. The various procedures which are believed to alter sodium excretion by affecting intracranial fluid volumes have usually exhibited a definite lag of more than one hour before the maximal effect is apparent. This makes both a direct neurogenic mechanism and an adrenal cortical mechanism seem unlikely, the peak effect being too slow for the former and too rapid for the latter. The reasons for the failure of sodium excretion to remain at the maximal level during the third and fourth hours (figs. 1 and 2), despite the continued presence of the procedure which led to the increase, are, likewise, not clear. Presumably, the displacement of extracellular fluid from the legs was more rapid in the first two hours than subsequently, and the autoinfusion of saline solution proceeded more slowly in the subsequent period. If, however, the increase in sodium excretion was the result of an increment in interstitial fluid in the cranial cavity, it is difficult to understand why such increment should be of lesser magnitude during the third and fourth than during the second hour of leg compression. Here again, additional evidence is needed.

The starting point of these experiments was the desire to study the effect of alterations in the distribution of body fluids on sodium excretion. The demonstration of a pronounced increment when the legs were compressed constitutes further evidence, in addition to that already cited in the introduction, that alterations in distribution of body fluids without alterations in total volume may exert pronounced effects on sodium excretion.

If, as seems likely from the present and the preceding observations,6-8 changes in the distribution of body fluids are capable of exerting a regulatory effect on sodium excretion, the question naturally arises as to which fluid compartment is concerned. Evidence against the volume or distribution of blood plasma as a stimulus to the regulation of sodium excretion has already been cited.13 It seems unlikely that compression of the legs would result in a significant displacement of intracellular fluid. Furthermore, if increase in intracellular fluid in some regulatory area were more important than increase in extracellular fluid in causing augmentation of sodium excretion, one would expect that the administration of water (which diffuses freely into the intracellular compartment) would be a more effective natriuretic measure than the administration of solutions of sodium chloride. Such is not the case. On the contrary, ingestion of large amounts of water may actually lead to depression of sodium excretion.20

Most of the data in the literature, as well as our own previous observations, appear to be compatible with the concept that alterations in the volume of the intracranial interstitial fluid lead to similar directional changes in sodium excretion. However, the demonstration that tilting the head downward does not increase sodium excretion, and that compression of the neck or legs (which augments sodium output of sitting subjects) has no consistent effect on recumbent subjects,6,7 would appear to be opposed to this concept. The problem is
complex because the cranial cavity is a rigid box containing four fluid compartments instead of the usual three. Methods for measurement of the intracranial content of intracellular, interstitial, intravascular, and cerebro spinal fluid are not available. It is possible that in the sitting subject compression of the neck increases the interstitial fluid, while in the recumbent subject one of the other fluids is increased. More knowledge is, therefore, necessary before final conclusions can be drawn concerning the precise relationship between the volume of these several intracranial fluids and the control of sodium output.

In order that this discussion should not be misinterpreted, two points mentioned in previous reports merit re-emphasis. The first is that the intracranial mechanism under discussion is certainly not the only one, and is probably not the most potent mechanism regulating the renal excretion of sodium. Such factors as the endocrine balance of the subject, the presence or absence of discomfort or emotional stress, the degree of consciousness, the level of plasma sodium, and (probably most important) the state of the sodium stores of the body (that is, the balance between intake and loss during the several preceding days) are probably of great importance in determining sodium output. Further investigations are needed before the complexities of the interplay of these and other unknown variables can be understood.

A second point which merits re-emphasis is that the investigations thus far made on the relationship between the distribution of body fluids and the excretion of sodium have been limited to normal subjects. There is as yet no proof that the mechanisms under discussion play a role in edematous states, or in other diseases connected with alterations of sodium excretion.

**Summary**

Compression of the legs of healthy young males in the sitting position, by means of an elastic bandage, causes well marked increment in urinary sodium output. No consistent effect was found in the recumbent position. Urine volume was not significantly altered.

Pain, due to migraine or to unsuccessful venepuncture with the formation of a local hematoma, was attended by a pronounced decline in the output of sodium and a less marked decrease in urine volume.

The possible mechanism of these results has been discussed. It is believed that the augmentation of sodium excretion is due to redistribution of extracellular fluid from the legs to certain regulatory areas. Compression of the legs is, therefore, considered to be analogous to the intravenous administration of saline solution. The data are considered as being compatible with the previously suggested concept of an intracranial center, sensitive to alterations in the local volume of interstitial fluid, and exerting a regulating influence on extracellular fluid volume by altering sodium excretion.

**REFERENCES**


Further Studies on the Effects of Changes in the Distribution of Extracellular Fluid on Sodium Excretion: Observations Following Compression of the Legs

JOHN A. LUSK, WILLIAM N. VIAR and TINSLEY R. HARRISON

Circulation. 1952;6:911-918
doi: 10.1161/01.CIR.6.6.911

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1952 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/6/6/911

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/