THE EFFECT OF EXPERIMENTAL VENOUS OBSTRUCTION ON SALT AND WATER DISTRIBUTION AND EXCRETION IN MAN

BY MARVIN F. LEVITT,1 LOUIS B. TURNER,2 AND AVRON Y. SWEET WITH THE TECHNICAL ASSISTANCE OF CHARLOTTE SPANIÉR AND HERBERT HABER

(From the Departments of Medicine and Pediatrics, Mount Sinai Hospital, New York, N. Y.)

(Submitted for publication May 19, 1952; accepted August 1, 1952)

An acute increase in local venous pressure produces a pooling of blood in the congested area and an alteration of fluid exchange at the capillary wall (1). This pooling occurs quickly and when produced experimentally by tourniquets applied to three extremities, has been shown to trap a volume equivalent to about 15 to 20 per cent of the total circulating volume within 10 minutes (2, 3). Elevation of venous pressure, according to Starling’s fundamental hypothesis, will, in addition, initiate a filtration of fluid out of the capillaries into the local tissues (1, 2). This peripheral loss of fluid produces a decreased plasma volume and a rise in plasma protein concentration and hematocrit. The diminution in effective blood volume results in decreased venous return, a decreased cardiac output, a fall in blood pressure and a compensatory reflex vasoconstriction (4, 5). The increased plasma protein concentration combined with the fall in blood pressure will evoke a diffusion of interstitial fluid into those areas of the capillary bed not exposed to increased pressures. The ultimate stabilization of blood pressure will depend upon the extent to which these mechanisms compensate for the reduced circulating volume. The chain of events precipitated by the reduction in effective circulating volume is similar to that observed in dehydration and in hemorrhagic or traumatic shock (4–8).

The available evidence does not indicate whether or not, under the above circumstances, stores of electrolytes and water located outside of the fluid phase of the extracellular compartment contribute to the maintenance of plasma volume. Lands and Johnson suggested that hemorrhagic shock evoked a movement of intracellular water into the extracellular compartment (9). Stewart and Rourke concluded that blood loss was compensated, in part at least, by a movement of fluid from within the cells outward (10). In infants convalescing from dehydration due to diarrhea, a shift of water from the cells to the extracellular compartment has been noted (11). In conflict with these reports, Ashworth and Kregel found that cellular water increased at the expense of the extracellular volume after hemorrhage (12).

The use of recently described methods for measuring the distribution of water and electrolytes has suggested that significant stores of sodium and chloride are located outside of the fluid phase of the extracellular compartment (13–16). Such stores are labile and under appropriate stimuli may, in part, be transferred into this fluid phase (17–21). Using these techniques, an attempt has been made here to determine whether the systemic effects produced by local interference with venous flow include such an endogenous shift of electrolytes and water.

METHODS

The volume of the fluid phase of the extracellular compartment before and after the application of tourniquets was measured as the volume of distribution of inulin. Because the post-infusion method (13–16) for determining the inulin space permits only a single measurement in any 24-hour period, we have employed the difference method (20, 22, 23). The amount of inulin retained at any one instant is calculated as the difference between the total infused and the cumulative excretion. The latter technique permits serial space measurements over relatively brief periods of time so that acute changes may be detected. Both the post-infusion and difference methods afford identical volumes of distribution when urinary recovery of inulin is complete (20, 22–24).

Ten fasting adults were used in this study. Urine and plasma were collected for proper control determinations. An intravenous infusion containing 3.6 grams per cent of inulin and 100 mEq. per liter of sodium chloride was then administered from a calibrated burette accurate to 0.5 cc. In lieu of a priming injection, the infusion was started at

1 Sara Welt and Rosenstock Fellow in Medicine; Research Assistant in Medicine.
2 Dazian Fellow in Medicine; Research Assistant in Medicine.
a rate of 8 to 10 cc. per minute and then during the first
15 minutes gradually reduced stepwise to 0.8 cc. per
minute.\footnote{Technique, for attaining equilibrium distribution of
inulin more quickly, suggested by Dr. Domingo Gomez.} This rate, maintained constant to within ± 1
per cent with a Bowman infusion pump, provided plasma
levels of inulin between 30 and 50 mg. per cent. After
four to four and a half hours of infusion, a period of time
adequate to provide equilibrium distribution (13, 15, 16,
20), the bladder was catheterized and rinsed with distilled
water and air. Directly before emptying the bladder,
plasma was drawn for inulin and electrolyte analyses, and
the volume of solution infused was read from the burette.
A second control space was similarly measured five and a
half to six hours after the start of the infusion.

After two control determinations of extracellular space
were obtained, blood pressure cuffs were applied to both
upper thighs in eight of 10 patients and inflated to pres-
sures 5–10 mm. Hg below diastolic pressure so that venous
flow was markedly obstructed. Systemic blood pressure
was followed at frequent intervals and the pressure in
the obstructing cuffs constantly adjusted to subdiastolic
levels. The cuffs were kept in place for about three hours
throughout which time no change was made in the rate
of the inulin infusion. During this period additional
measurements of extracellular space were made one to
two hours and two to three hours after application of the
tourniquets. The fluid level in the burette was read fre-
cently to determine the constancy of the infusion rate.
Plasma for inulin and electrolyte analyses was drawn
from the non-involved arm before each bladder washout
and at intervals of 30 minutes. In three patients several
blood samples were drawn from the congested veins be-
low the tourniquets simultaneously with the blood from
the arm vein. After the final bladder washout the infu-
sion was discontinued, the tourniquets removed and urine
was collected for 18 to 24 hours to determine the complete-
ness of recovery of the administered inulin. In two con-
trol patients serial space measurements were made at
identical intervals without the application of tourniquets.

Each infusion and plasma and urine sample was ana-
lyzed for inulin four to 10 times by the resorcinol method
of Schreiner (25). Spaces were calculated as the amount
of inulin retained divided by the simultaneous plasma
concentration in the non-congested upper extremity. In-
ulin clearances (GFR) were determined by the usual
method (26), but the long intervals between bladder
emptying provided only three to four periods (each of
one to one and a half hours) in each patient.

Sodium and potassium concentrations were measured in
an internally compensated Perkin-Elmer flame photometer.
Chloride concentrations were determined by the Van
Slyke and Hille modification of the Sendroy method
(27), plasma protein concentrations by the biuret tech-
nique (28), and venous hematocrit with the standard
Wintrobe tube.

The electrolyte contained in the fluid phase of the
extracellular compartment was calculated as the product
of the inulin space and the plasma electrolyte concen-
tration without corrections for Donnan's equilibrium.
Throughout the experimental period, which lasted eight
hours, each patient ingested two glasses of water, one
during the control period and one about an hour after
the application of tourniquets. During the tourniquet pe-
riod a total of 12 to 14 mEq. of sodium chloride was in-
fused, a variable proportion of which was retained.

RESULTS

Within minutes after the inflation of the tourni-
quets, marked rubor and congestion of the legs de-
veloped and persisted throughout the tourniquet-
period. In three of the patients slight but definite
pitting edema became apparent after one to two
hours. Where pitting edema was not eluted, a
thickening and induration of the subcutaneous tis-
sue appeared. All subjects noted a sense of con-
striction and numbness but none complained of
pain.

Of the eight patients so studied, three manifested
moderate to marked reductions in blood pressure
(Table 1). Maximum falls in blood pressure oc-
curred 60 to 90 minutes after inflation of the tour-
niquets and were accompanied by other signs of
shock (salivation, nausea, vomiting in one patient,
diaphoresis, pallor). In these patients the cuffs
were temporarily partially deflated in order to
maintain subdiastolic pressures. The shock-like
reaction persisted for only three to 10 minutes
despite the continued application of the tourni-
quets. During the last one and a half hours of
the tourniquet period, the blood pressures gradu-
ally reverted toward control values. These three
patients were the only subjects in the series whose
control diastolic pressure exceeded 90 mm. of
mercury. In five subjects little or no reduction of
blood pressure occurred and no other untoward
effects were noted.

The two control pre-tourniquet inulin spaces
differed by less than 3 per cent. The control space
listed in Table I is the second of these two pre-
tourniquet determinations.\footnote{In one patient (Pan) only a single control space
was measured after 4 hours of inulin infusion, but a
similar control study performed subsequently demonstrated
that equilibrium had been attained within 4 hours.} Following inflation
of the tourniquets, each of the eight patients showed
an increase in the volume of inulin. The increases recorded in Table I
and Figure 1 averaged 16 per cent (1,400 cc.) with a range

...
### TABLE I

The effect of experimental venous obstruction on blood pressure, plasma protein concentration, inulin space, plasma electrolyte concentration, glomerular filtration rate and electrolyte excretion

<table>
<thead>
<tr>
<th>Subject</th>
<th>Time* (min.)</th>
<th>Blood pressure (mm Hg)</th>
<th>Total protein (mg. per cent)</th>
<th>Inulin space (cc.)</th>
<th>Serum electrolyte concentrations</th>
<th>Total electrolyte in ECF</th>
<th>Inulin clearance (cc./ min.)</th>
<th>Urine flow (cc./ min.)</th>
<th>Electrolyte excretion</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wee</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>165/95</td>
<td>7.8</td>
<td>8,570</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>22</td>
<td>148/96</td>
<td>7.5</td>
<td>140</td>
<td>4.5</td>
<td>107</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>82</td>
<td>115/70</td>
<td>8.3</td>
<td>148</td>
<td>4.7</td>
<td>111</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>119</td>
<td>125/80</td>
<td>7.8</td>
<td>9,320</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>188</td>
<td>144/90</td>
<td>7.5</td>
<td>10,200</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total increase</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1,630</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>110/70</td>
<td>6.9</td>
<td>7,500</td>
<td></td>
<td>1,020</td>
<td>840</td>
<td>61</td>
<td>0.49</td>
<td>361</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>106/70</td>
<td>7.5</td>
<td>133</td>
<td>4.4</td>
<td>112</td>
<td></td>
<td></td>
<td></td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>115</td>
<td>110/80</td>
<td>8.0</td>
<td>132</td>
<td>4.2</td>
<td>108</td>
<td></td>
<td></td>
<td></td>
<td>120</td>
</tr>
<tr>
<td></td>
<td>147</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total increase</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>230</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>110/80</td>
<td>6.7</td>
<td>7,420</td>
<td></td>
<td>980</td>
<td>839</td>
<td>85</td>
<td>2.78</td>
<td>321</td>
</tr>
<tr>
<td></td>
<td>62</td>
<td>110/84</td>
<td>7.3</td>
<td>7,740</td>
<td></td>
<td>1,040</td>
<td>859</td>
<td>65</td>
<td>0.76</td>
<td>124</td>
</tr>
<tr>
<td></td>
<td>123</td>
<td>104/76</td>
<td>7.4</td>
<td>8,700</td>
<td></td>
<td>1,210</td>
<td>957</td>
<td>50</td>
<td>1.27</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>Total increase</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>230</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>190/110</td>
<td>7.3</td>
<td>9,210</td>
<td></td>
<td>1,350</td>
<td>1,000</td>
<td>49</td>
<td>2.3</td>
<td>366</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>190/130</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>64</td>
<td>164/126</td>
<td>7.5</td>
<td>145</td>
<td>3.3</td>
<td>106</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>96</td>
<td>60/45</td>
<td>7.5</td>
<td>142</td>
<td>3.8</td>
<td>108</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>110</td>
<td>100/90</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>134</td>
<td>110/90</td>
<td>7.1</td>
<td>10,700</td>
<td></td>
<td>1,570</td>
<td>1,160</td>
<td>32</td>
<td>0.60</td>
<td>58</td>
</tr>
<tr>
<td></td>
<td>Total increase</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2,300</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>140/90</td>
<td>6.8</td>
<td>3,970</td>
<td></td>
<td>1,280</td>
<td>994</td>
<td>85</td>
<td>1.01</td>
<td>216</td>
</tr>
<tr>
<td></td>
<td>43</td>
<td>138/80</td>
<td>7.5</td>
<td>138</td>
<td>3.6</td>
<td>104</td>
<td></td>
<td></td>
<td></td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>65</td>
<td>110/78</td>
<td>7.2</td>
<td>151</td>
<td>5.0</td>
<td>104</td>
<td></td>
<td></td>
<td></td>
<td>120</td>
</tr>
<tr>
<td></td>
<td>82</td>
<td>88/68</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>102</td>
<td>114/75</td>
<td>7.5</td>
<td>140</td>
<td>3.9</td>
<td>107</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>120</td>
<td>130/80</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>141</td>
<td>150/90</td>
<td>7.5</td>
<td>9,950</td>
<td></td>
<td>1,320</td>
<td>1,040</td>
<td>71</td>
<td>0.45</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Total increase</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>480</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>130/76</td>
<td>7.4</td>
<td>12,200</td>
<td></td>
<td>1,710</td>
<td>1,310</td>
<td>83</td>
<td>0.91</td>
<td></td>
</tr>
<tr>
<td></td>
<td>56</td>
<td>122/70</td>
<td>7.1</td>
<td>138</td>
<td>3.6</td>
<td>110</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>118</td>
<td>114/75</td>
<td>7.4</td>
<td>138</td>
<td>3.9</td>
<td>111</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>156</td>
<td>116/76</td>
<td>7.2</td>
<td>14,800</td>
<td></td>
<td>2,100</td>
<td>1,600</td>
<td>82</td>
<td>0.47</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total increase</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2,600</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>110/76</td>
<td>8.6</td>
<td>12,000</td>
<td></td>
<td>1,630</td>
<td>1,260</td>
<td>106</td>
<td>0.56</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td>44</td>
<td>106/70</td>
<td>8.1</td>
<td>135</td>
<td>3.1</td>
<td>105</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>81</td>
<td>100/78</td>
<td>8.6</td>
<td>132</td>
<td>3.9</td>
<td>106</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>119</td>
<td>110/80</td>
<td>8.4</td>
<td>130</td>
<td>2.9</td>
<td>104</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>153</td>
<td>110/80</td>
<td>8.3</td>
<td>13,100</td>
<td></td>
<td>1,740</td>
<td>1,350</td>
<td>111</td>
<td>0.36</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Total increase</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1,100</td>
</tr>
<tr>
<td></td>
<td>Control patients—no tourniquets applied</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hall</td>
<td>95/60</td>
<td>6.7</td>
<td>8,850</td>
<td></td>
<td>1,270</td>
<td>995</td>
<td>103</td>
<td>1.3</td>
<td>277</td>
</tr>
<tr>
<td></td>
<td>63</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>115</td>
<td>87/50</td>
<td>6.3</td>
<td>8,750</td>
<td></td>
<td>1,240</td>
<td>950</td>
<td>100</td>
<td>0.30</td>
<td>233</td>
</tr>
<tr>
<td></td>
<td>Total change</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-50</td>
</tr>
<tr>
<td></td>
<td>Bro</td>
<td>190/110</td>
<td>6.7</td>
<td>11,300</td>
<td></td>
<td>1,560</td>
<td>1,220</td>
<td>56</td>
<td>2.1</td>
<td>248</td>
</tr>
<tr>
<td></td>
<td>62</td>
<td>110/80</td>
<td>6.7</td>
<td>11,300</td>
<td></td>
<td>1,560</td>
<td>1,230</td>
<td>56</td>
<td>1.8</td>
<td>249</td>
</tr>
<tr>
<td></td>
<td>131</td>
<td>110/80</td>
<td>7.3</td>
<td>11,200</td>
<td></td>
<td>1,520</td>
<td>1,220</td>
<td>51</td>
<td>1.5</td>
<td>222</td>
</tr>
<tr>
<td></td>
<td>Total change</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-100</td>
</tr>
</tbody>
</table>

* Time represents that number of minutes after the application of tourniquets.
† In this patient 65 minutes of venous congestion induced an expansion of the inulin space of 830 cc. and an increment of total extracellular sodium and chloride of 280 mEq. and 76 mEq., respectively. The subsequent fall accompanied a period of repeated and copious vomiting.

EFFECT OF VENOUS OBSTRUCTION ON FLUID DISTRIBUTION

887
from 9 to 21 per cent. The maximum increase in the inulin space occurred two to three hours after tourniquet application. In one patient (Oss) the maximum increase occurred after one hour of venous obstruction; this patient, however, vomited profusely during the latter part of the tourniquet period.

Between 30 and 60 minutes after inflation of the tourniquets, the plasma inulin concentration increased in five of the eight patients to levels of 5 to 15 mg per cent above control values. Thereafter the inulin concentration remained fairly constant or decreased slightly. Three patients showed no significant change in the plasma inulin concentration. In the three subjects in whom simultaneous plasma inulin concentrations were measured above and below the tourniquets, the latter concentration rose more slowly but finally approached

**TABLE II**

*Detailed data including the plasma inulin concentrations, the quantity of inulin infused, excreted and retained, and the calculated inulin spaces from two typical experiments*

<table>
<thead>
<tr>
<th>Subject</th>
<th>Time from onset of infusion (hr.-min.)</th>
<th>Inulin plasma concentration (mg. per cent)</th>
<th>Inulin infused during period (gm.)</th>
<th>Inulin excreted during period (gm.)</th>
<th>Inulin retained during period (gm.)</th>
<th>Inulin retained — cumulative (gm.)</th>
<th>Inulin space (cc.) Σ(b-c)/a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Col</td>
<td>4–6</td>
<td>38.1</td>
<td>10.23</td>
<td>7.37</td>
<td>2.86</td>
<td>2.86</td>
<td>7,510</td>
</tr>
<tr>
<td></td>
<td>5–6</td>
<td>38.7</td>
<td>2.05</td>
<td>2.04</td>
<td>.01</td>
<td>2.87</td>
<td>7,420</td>
</tr>
<tr>
<td></td>
<td>5–17</td>
<td>44.0</td>
<td>2.53</td>
<td>1.99</td>
<td>.54</td>
<td>.56</td>
<td>3.41</td>
</tr>
<tr>
<td></td>
<td>6–19</td>
<td>45.6</td>
<td>1.93</td>
<td>1.37</td>
<td>.56</td>
<td>.56</td>
<td>3.97</td>
</tr>
<tr>
<td></td>
<td>7–20</td>
<td>45.6</td>
<td>1.93</td>
<td>1.37</td>
<td>.56</td>
<td>.56</td>
<td>3.97</td>
</tr>
<tr>
<td>Hal (Control subject—cuffs not applied)</td>
<td>5–21</td>
<td>32.0</td>
<td>13.55</td>
<td>10.73</td>
<td>2.82</td>
<td>2.82</td>
<td>8,800</td>
</tr>
<tr>
<td></td>
<td>6–34</td>
<td>33.8</td>
<td>2.15</td>
<td>2.05</td>
<td>.10</td>
<td>2.92</td>
<td>8,640</td>
</tr>
<tr>
<td></td>
<td>7–26</td>
<td>33.8</td>
<td>1.79</td>
<td>1.75</td>
<td>.04</td>
<td>2.96</td>
<td>8,750</td>
</tr>
</tbody>
</table>
within 1 to 5 mg. per cent of the systemic plasma concentrations. The amount of inulin retained during the tourniquet period was proportionately greater than the coincident increase in systemic plasma concentration and, therefore, each patient evinced an expansion of the inulin space (Table I). In two patients in whom tourniquets were not applied no change in inulin space was detected during comparable time periods (Figure 1 and Table I—control patients). Table II records the detailed inulin data from two typical experiments.

Post-infusion urinary collections were complete in eight of the 10 patients studied. The inulin recoveries in these eight cases averaged 99.6 per cent with a range from 96.8 to 104 per cent.

Serial measurements of plasma protein concentration during the tourniquet period revealed increases in six of the eight patients (Table I). These changes were maximal after one to two hours of reduced venous flow and thereafter in four of these six subjects the protein concentration tended to return toward normal (Table I, Figure 2).

In five of the eight patients, no significant changes in plasma sodium or chloride concentrations were evident during the tourniquet period.

![Diagram](image-url)

**Fig. 2. Simultaneous Changes in Plasma Electrolyte Concentrations, Plasma Protein, Inulin Space, Blood Pressure, GFR and Salt Excretion in one Typical Experimental Subject**
In three patients (Wee, Pan, Oss), however, the plasma sodium concentrations increased one hour after the application of the tourniquets and then gradually returned to control or subcontrol levels (Table I, Figure 2). Similar, but smaller changes in chloride concentrations were noted in two of these patients. The increase in sodium and chloride contained in the inulin space averaged 190 and 140 mEq., respectively (Table I, Figure 3).

A decrease in glomerular filtration rate (GFR), of more than 15 per cent, was noted during the tourniquet period in five of the eight patients (Table I). This decrement was most marked in the first hour of venous obstruction and was associated with a reduction in blood pressure in three patients. In two of these five subjects the GFR approached control values during the latter phase of the tourniquet period.

Five of seven patients evinced a marked decrease in sodium excretion following the application of tourniquets (Table I). Generally, this reduction was associated with a simultaneous decrease in GFR. However, in three patients in whom the filtration rate remained unchanged or increased during the latter phase of the tourniquet period, the rate of sodium excretion continued to decrease (Table I, Figure 2). The changes in chloride excretion were generally similar to those noted in sodium excretion. No consistent alterations were detected in the rate of potassium excretion. The rate of urine flow remained essentially unchanged in four subjects (Wee, Par, Pan, Ben), fell transiently in one (Col), and showed a sustained fall in three (Bro, Oss, Ban) (Table I).

**DISCUSSION**

In evaluating the inulin space expansions noted during the tourniquet period, four possible sources of methodological error must be considered: 1) a failure to attain the maximum volume of distribution of inulin (equilibrium distribution) prior to the application of the tourniquets; 2) errors in the analyses of the urine, plasma or infusion samples; 3) an increase in renal dead space during venous congestion; 4) a state of disequilibrium produced by the experimental conditions and characterized by a concentration of inulin in the interstitial fluid higher than that of plasma.

Figure 1 and the examples shown in Table II reveal that the maximum volume of distribution of inulin was achieved after four to four and a half hours of infusion. Two control space determinations before the application of tourniquets and three consecutive space measurements in the control patients in whom venous flow was not obstructed agreed within 3 per cent. These findings indicate that uniform distribution had been achieved before the inflation of the tourniquets.

The multiple analyses of the urine, plasma and infusion provided a mean concentration with a standard deviation of ± 2 per cent. In the first prolonged equilibrating period in which large amounts of inulin were infused and excreted, a 2 per cent error in both quantities may produce a significant error in the calculated control space. Since subsequent changes in space depend upon the amount of inulin retained during the specific period in question, the absolute change in the inulin space will not be significantly influenced by any error in the calculated volume of the control space. In the interval periods about 2 gm. of inulin were infused and excreted; 2 per cent errors in determining these quantities could produce a maximal
EFFECT OF VENOUS OBSTRUCTION ON FLUID DISTRIBUTION 891

expansion of about 200 cc. To account for the average expansion of 1,400 cc., an error of 20 to 25 per cent in overestimating the amount infused or in underestimating the amount excreted in any specific post-tourniquet period would be required. Such consistent discrepancies hardly appear plausible.

In the three subjects in whom venous congestion induced a sustained fall in urine flow, it is conceivable that a significant increase in the amount of inulin contained within the renal dead space occurred, thereby artificially augmenting the calculated space. However, two control studies have revealed that comparable falls in urine flow induced by pitressin may artificially expand the inulin space by only 100 to 300 cc. The dead space error may, therefore, account for only a small fraction of the space increase in these three subjects.

In the five subjects who showed a fall in glomerular filtration rate, increases in plasma inulin concentration occurred about 30 to 60 minutes after inflation of the tourniquets. That this rise in plasma concentration was not immediately distributed throughout the inulin space is suggested by the slower rise in inulin concentration in the venous blood drawn from the congested extremities. This discrepancy between the plasma concentration in the non-congested and congested areas probably resulted from the fact that considerable quantities of plasma ultrafiltrate were accumulated in the congested legs before the rise in inulin concentration occurred. However, since all space calculations were based on the higher plasma concentration in the non-congested area, any delay in the even distribution of this increment in concentration could only obscure an expansion in the inulin space. The stabilization of the inulin concentration during the last one and a half hours of the tourniquet-period in these five subjects and the absence of any significant change in inulin concentration in three subjects suggests that virtual equilibrium distribution was again achieved before the final space measurements.

The conceivable sources of error do not explain the consistent expansion in the volume of distribution of inulin after two to three hours of venous congestion in the lower extremities. That this increase was not a result of inulin metabolism is confirmed by the completeness of urinary recovery.

The arguments which imply that the volume of distribution of inulin affords a reliable estimate of the extracellular fluid volume have been previously presented (13-16, 20, 22, 23, 29). The concept of a homogeneous, entirely fluid, extracellular compartment with precise, sharply defined boundaries undoubtedly represents an oversimplification. It has been contended that certain extracellular areas are rendered inaccessible to the inulin molecule by a difference in the architecture of the underlying medium (30, 31). Relatively solid phases as contained in bone and connective tissue (tendon) are probably not included in such space measurements (32). The recent demonstration of the identity of the volume of distribution of inulin with that of sucrose (23), mannitol (33), ferricyanide (22), and radiosulfate (34) suggests, however, that a finite and measurable fluid phase of the extracellular compartment probably exists. It is in this sense—that of a fluid phase in rapid exchange with the plasma and with the chemical composition of an ultrafiltrate of plasma (13)—that the terms extracellular fluid and interstitial fluid are used in this paper.

During the two to three hour period of reduced venous return, the total amount of salt administered in the inulin infusion equaled 12 to 14 mEq. Although the majority of these patients showed a reduction in salt excretion and thereby retained much of this amount, the positive exogenous balance can account for at most 5 to 10 per cent of the total increase in electrolyte contained in the inulin space. Accordingly, averages of about 180 mEq. of sodium, 130 mEq. of chloride and 1,300 cc. of water appear to have been transferred into the fluid phase of the extracellular compartment from endogenous sources during this period (Figure 3). The precise source of this salt and water is not clear. Significant quantities of salt (predominantly chloride) and water may be associated with the solid phase of connective tissue (35, 36). Large stores of sodium are located in the crystal structure of bone; salt and water are contained in the gastrointestinal tract. The salt and water may derive, in part at least, from any one of these sources. In addition, an unknown fraction may be furnished by cells.

It is unlikely that venous obstruction so alters tissues in the congested area as to induce a local outpouring of salt and water. Most observers have concluded that muscle anoxia and injury in-
duce a loss of intracellular potassium and a reciprocal gain of sodium (37, 38). The absence of an increase in plasma potassium or of a potassium diuresis suggests that no such cellular change occurred. Furthermore, the amount of salt available in the congested extremities (muscle cells are singularly free of sodium chloride [35]) appears inadequate to augment the extracellular fluid electrolyte by as much as 16 per cent. It is suggested, therefore, that the body tissue above the tourniquets may have supplied the bulk of endogenous salt and water. The amount of sodium chloride demonstrated to be contained outside of the insulin space is entirely adequate to supply 180 mEq of sodium and 130 mEq of chloride. Recent studies indicate that this degree of depletion would exhaust about one-fourth of the sodium and onethird of the chloride located outside of the insulin space (14, 15, 20, 39).

The increases in plasma protein concentration and hematocrit observed in the early stage of the tourniquet period are in accord with previous observations that tourniquets applied on the extremities at subdiastolic pressure produce a rapid reduction in plasma volume (1, 3). Whether any decrease in circulating volume, regardless of etiology, will initiate a movement of salt and water into the fluid phase of the extracellular compartment remains to be determined. Previous observations have suggested that DCA, cortisone, ACTH, and whole adrenal cortical extract produce similar shifts (17-19, 21, 40). The possibility, therefore, exists that this acute redistribution is similarly mediated through adrenal activity.

The tendency for the blood pressure to rise toward normal and for the serum protein concentration to fall in several subjects during the latter phase of the tourniquet period implies that some reconstitution of plasma volume was being accomplished. This reconstitution was abetted by a decreasing rate of plasma loss as local tissue pressure increased in the congested extremities (41). In addition, the endogenous expansion of the extracellular fluid volume may have enhanced the compensatory transfer of interstitial fluid into the depleted plasma in those areas of the capillary bed not exposed to increased pressure. Other investigators have demonstrated that the volume of the extracellular compartment in part determines the resistance of experimental animals to acute reductions in blood volume. Prior dehydration exaggerates the lethal effect of bleeding in dogs whereas prior saline infusions protect the animals (6, 42, 43).

Reductions of GFR have been noted following interference with local venous return (44, 45). These changes have been attributed to the fall in blood pressure and to the generalized vasoconstriction in which the renal parenchyma is involved (4, 5, 43). Because only two prolonged periods were obtained after tourniquet application, it is possible that in several subjects acute falls in GFR were obscured. The reduction in sodium excretion correlated only partly with the GFR as exemplified in those subjects where late in the tourniquet period sodium excretion continued to fall despite unchanged or increasing filtration rates (Table I, Figure 2). This phase of enhanced tubular reabsorption of salt coincided with the period of maximum redistribution of salt. Thus, these mechanisms, redistribution and retention, may be interdependent and complementary in retaining or augmenting extracellular fluid salt.

CONCLUSIONS AND SUMMARY

1. The volume of distribution of inulin, plasma electrolyte concentrations, plasma protein concentration, glomerular filtration rate, rate of electrolyte excretion, and blood pressure were measured serially before and during a two to three hour period in which tourniquets were applied at subdiastolic pressures to the thighs of eight human subjects. Comparable measurements were made at similar time intervals in two control subjects on whom tourniquets were not applied.

2. In each of the eight experimental subjects, two to three hours of venous congestion induced an expansion of the inulin space. The increase averaged 16 per cent with a range from 9 to 21 per cent. No consistent changes in plasma electrolyte concentrations were detected.

3. In five of the eight subjects, a reduction in glomerular filtration rate occurred. This reduction was most marked in the early phase of venous congestion. In five of seven subjects, a reduction in the rate of sodium excretion occurred. This reduction correlated only in part with the fall in glomerular filtration rate.

4. Transient falls in blood pressure were apparent in three of the eight subjects. Six sub-
jects showed a slight to moderate increase in plasma protein concentration which reached maximal values after one to one and a half hours of venous congestion. Subsequently, in four subjects, these concentrations tended to return toward normal.

5. Two control subjects showed no change in GFR, inulin space, blood pressure, plasma electrolyte concentrations, or electrolyte excretion.

REFERENCES


44. Smith, H. W., Lectures on the Kidney, University Extension Division, University of Kansas, Lawrence, Kansas, 1939.