Circulatory Studies in Wernicke’s Encephalopathy

With Special Reference to the Occurrence of a State of High Cardiac Output and Postural Hypotension

By Michael A. Gravallese, Jr., M.D., and Maurice Victor, M.D.

Although Wernicke’s disease is clearly related to thiamine deficiency, it is rarely accompanied by the overt signs of congestive failure. There are symptoms of disordered cardiovascular function in many patients with this disease, but the relation of these symptoms to thiamine deficiency has remained undefined. In the present study, an attempt is made to define these symptoms, particularly in relation to specific treatment with thiamine. Part 1 of this study is concerned mainly with the determination of the cardiac output in 7 patients, as determined by the Evans blue dye-dilution technic; part 2 describes the postural response to tilting in 12 patients.

WERNICKE’S encephalopathy is an acute neurologic disorder characterized by ocular paralyses, nystagmus, ataxia, and mental disorder. In this country the syndrome is encountered almost exclusively in patients with chronic alcoholism; however, it is generally agreed that the role of alcohol is secondary and that the primary cause is a nutritional deficiency, specifically of thiamine.¹

Despite the fact that the Wernicke syndrome is so clearly related to thiamine deficiency, it is rarely accompanied by overt signs of congestive heart failure. In a series of 86 patients with Wernicke’s encephalopathy, only 1 manifested the advanced signs of beriberi heart disease.² Nevertheless, there were indications of disordered cardiovascular function in many of these patients. The history may have disclosed complaints such as postural “dizziness” or fainting, and on examination, tachycardia and minor electrocardiographic abnormalities were frequent findings. Some patients showed dyspnea on slight exertion, and a few died suddenly, the mode of death suggesting “cardiovascular collapse.”

Little attention has been paid to the cardiac abnormalities of Wernicke’s disease, and the relation of these abnormalities to thiamine deficiency has remained undefined. It was thought worthwhile, therefore, to study some aspects of cardiovascular function in such patients, particularly in relation to specific treatment with thiamine.

MATERIALS AND METHODS

For the sake of convenience this paper is divided into 2 parts. Part 1 is concerned mainly with the determination of cardiac output (table 1) and part 2 with the postural response to tilting (table 2).

Part 1. Seven patients with acute Wernicke’s encephalopathy, ranging in age from 33 to 65 years, were studied. Six of these were men. None of the patients studied had fever or signs of congestive failure. Only patients who had definite ophthalmoplegia and had received no food after admission to the hospital were included in the study. With 1 exception (AN), all the patients had the characteristic mental symptoms. Chronic alcoholism, dietary deficiency, and loss of weight and of muscle bulk were common to the entire group. One patient (JC) had Laennec’s cirrhosis with edema and ascites, and 5 others had an enlarged liver or abnormal “liver function” tests. In 4 patients the tongue was red and atrophic. In 6 patients the knee and ankle jerks were depressed or absent, but there were no other signs of peripheral neuropathy. All the patients showed an ataxia of stance and gait, however, probably on a cerebellar basis. At the time the patients came under observation none showed signs of inebriation or the psychomotor signs of abstinence from alcohol.

An evaluation of the cardiovascular state was made before each study in all patients by clinical examination, fluoroscopy, estimation of venous pressure, and serial electrocardiographic tracings. X-rays of the chest were obtained periodically.
Cardiac output was determined by the Evans blue dye-dilution technic utilizing a photoelectric densimeter, as described elsewhere. Oxygen consumption was measured by a 3-minute collection of expired air in a Douglas bag, the partial pressure of oxygen being measured in a Pauling Oxygen Analyzer. Standard R. Q. corrections were used in calculation. Phasic and mean arterial pressures were measured directly by means of a Sanborn electromanometer. All these determinations were performed in duplicate in most instances. Peripheral vascular resistance was calculated according to the following formula:

\[
\text{Mean arterial pressure mm. Hg} \times \frac{1332}{\text{Cardiac output ml/sec}}
\]

\[=\text{Resistance in dynes seconds cm}^{-5}
\]

Blood pyruvic acid in cases 2 to 5 (table 1) was measured by the method of Friedemann and Haugen, and blood lactic acid by the method of Barker and Summerson. Normal values for fasting blood pyruvic acid concentrations ranged from 0.8 to 1.6 mg. per 100 ml. (average 1.3); for fasting lactic acid concentrations the normal values ranged from 4.7 to 12 mg. per 100 ml. of blood, (average 6.4). Cases 6 and 7 (table 1) were studied jointly with Dr. Mark D. Altschule, McLean Hospital, Waverley, Mass. Blood pyruvate and lactate in these 2 patients were determined in his laboratory by the methods of Seligson and Shapiro and of Barker and Summerson respectively. Normal values for pyruvic acid ranged from 0.52 to 1.32 mg. per 100 ml. (average 0.92); values for lactic acid ranged from 2.75 to 11.6 mg. per 100 ml. (average 7.4).

The original studies in each case were made after a control period of 1 to 3 days, during which time the patient was at rest in bed and had received an unfortified rice diet as the only source of nutrition. This diet supplied the patient with about 2,000 calories daily, but was deficient in all the B vitamins. All tests, including the estimation of blood pyruvate and lactate, were done in the morning with the patients at rest and in a fasting state for at least 12 hours. Two patients were restudied 1 to 11/2 hours after they had received thiamine intravenously in a dose of 100 mg. Six patients were restudied 4 to 6 days after the rice diet had been supplemented by 50 mg. of intramuscular thiamine daily.

Part 2. Postural studies were performed on 12 patients with Wernicke's encephalopathy at varying intervals in relation to treatment with thiamine (table 2). The criteria for selection of patients were the same as in part 1 of this study. The subjects consisted of 9 men and 3 women, ranging in age from 31 to 70 years; 10 of these were between 42 and 65 years. Six of the patients also served as subjects for part 1 of this study. Cardiac output studies were attempted but were unsuccessful in 4 of the remaining 6 patients.

Each subject was tested according to the following routine: At zero time the patient was placed in a supine position on a manually operated fluoroscopic table provided with a footboard and a loose leather restraining belt placed at chest level. Blood pressure was measured at approximately heart level with a standard cuff sphygmomanometer; the reading at which there was complete disappearance of sounds was taken as the diastolic pressure. Pulse rate was determined by palpation or auscultation. Control readings were made at 5-minute intervals during the first 15 minutes, and thereafter at 1-minute intervals. At 20 minutes the subject was tilted rapidly to 70° and the tilted position maintained for 5 minutes (occasionally from 10 to 30 min.). One-minute readings were continued throughout tilting and after return to the horizontal position until control levels were reestablished. Control readings of the systolic and diastolic pressures and of pulse rate were the average of the 3 stable readings just prior to tilting. During the tilt the patient was observed for evidence of pallor, sweating, and hyperactivity, and he was asked to report sensations of nausea, dizziness, faintness, or weakness.

Arbitrarily, a fall from control levels of 40 mm. Hg in systolic pressure, 30 mm. Hg diastolic, or a reduction in pulse pressure to 10 mm. Hg or less was considered to constitute an abnormal cardiovascular response to tilting.

Subjects who were tested in this way before the administration of thiamine had been kept strictly in bed; mobilization was variable during the subsequent course of treatment and testing.

Results

Clinically, none of our patients showed signs of congestive failure and in none was there an elevation of the venous pressure. One patient (JC) with advanced cirrhosis and ascites had x-ray evidence of right hydrothorax and "possible cardiac enlargement." No other case showed cardiomegaly and in most cases the heart was described as normal or small in size. The electrocardiograms were either normal or showed minor nonspecific changes (table 1).
### Table 1.—Circulatory Studies in Seven Patients with Wernicke’s Disease

<table>
<thead>
<tr>
<th>Patient, age, and sex</th>
<th>State</th>
<th>BSA MP</th>
<th>Pulse/min</th>
<th>CI</th>
<th>Mean CI</th>
<th>SI</th>
<th>BP (mean)</th>
<th>PVR</th>
<th>O₂ cons.</th>
<th>Pyruv.</th>
<th>Lact</th>
<th>Hct.</th>
<th>Appliance</th>
<th>ECG</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. JC, 33, F</td>
<td>Untreated</td>
<td>1.64</td>
<td>102</td>
<td>5.4</td>
<td>5.7</td>
<td>34</td>
<td>125/75 (97)</td>
<td>830</td>
<td>154</td>
<td>—</td>
<td>—</td>
<td>33</td>
<td>11</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>1 hr. after B₁</td>
<td>1.64</td>
<td>100</td>
<td>4.8</td>
<td>4.8</td>
<td>29</td>
<td>130/75 (95)</td>
<td>964</td>
<td>154</td>
<td>—</td>
<td>—</td>
<td>33</td>
<td>13</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>1½ hr. after B₁</td>
<td>1.67</td>
<td>63</td>
<td>1.4</td>
<td>1.4</td>
<td>13</td>
<td>125/65 (80)</td>
<td>3073</td>
<td>142</td>
<td>2.1</td>
<td>9.3</td>
<td>40</td>
<td>22</td>
<td>Borderline Q-T</td>
</tr>
<tr>
<td></td>
<td>6 days B₁</td>
<td>1.70</td>
<td>62</td>
<td>1.9</td>
<td>2.1</td>
<td>20</td>
<td>130/60 (78)</td>
<td>1746</td>
<td>126</td>
<td>0.8</td>
<td>6.9</td>
<td>38</td>
<td>21</td>
<td>—</td>
</tr>
<tr>
<td>2. MS, 57, M</td>
<td>Untreated</td>
<td>1.94</td>
<td>110</td>
<td>6.4</td>
<td>6.5</td>
<td>30</td>
<td>130/65 (80)</td>
<td>507</td>
<td>—</td>
<td>2.7</td>
<td>8.3</td>
<td>39</td>
<td>9</td>
<td>?Wolff-Parkinson-White syndrome</td>
</tr>
<tr>
<td></td>
<td>5 days B₁</td>
<td>1.94</td>
<td>69</td>
<td>3.3</td>
<td>3.0</td>
<td>22</td>
<td>130/70 (85)</td>
<td>1167</td>
<td>150</td>
<td>1.5</td>
<td>5.2</td>
<td>38</td>
<td>16</td>
<td>S-T improvement</td>
</tr>
<tr>
<td>3. JK, 65, M</td>
<td>Untreated</td>
<td>1.60</td>
<td>115</td>
<td>6.4</td>
<td>6.5</td>
<td>35</td>
<td>140/75 (95)</td>
<td>730</td>
<td>167</td>
<td>3.0</td>
<td>8.1</td>
<td>35</td>
<td>10.5</td>
<td>Borderline S-T's</td>
</tr>
<tr>
<td></td>
<td>5 days B₁</td>
<td>1.51</td>
<td>107</td>
<td>4.0</td>
<td>4.2</td>
<td>26</td>
<td>165/95 (130)</td>
<td>1638</td>
<td>172</td>
<td>1.6</td>
<td>8.8</td>
<td>38</td>
<td>11</td>
<td>No change</td>
</tr>
<tr>
<td></td>
<td>36 days B₁</td>
<td>1.48</td>
<td>125</td>
<td>5.0</td>
<td>5.3</td>
<td>29</td>
<td>180/115 (135)</td>
<td>1376</td>
<td>176</td>
<td>—</td>
<td>—</td>
<td>43</td>
<td>13</td>
<td>Minor changes</td>
</tr>
<tr>
<td></td>
<td>Same, exercise</td>
<td>1.48</td>
<td>148 — 6.9</td>
<td>47</td>
<td>290/130 (150)</td>
<td>1174</td>
<td>505 — 8.5</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>8.5</td>
</tr>
<tr>
<td>4. EK, 42, M</td>
<td>Untreated</td>
<td>1.60</td>
<td>115</td>
<td>6.4</td>
<td>6.5</td>
<td>35</td>
<td>140/75 (95)</td>
<td>730</td>
<td>167</td>
<td>3.0</td>
<td>8.1</td>
<td>35</td>
<td>10.5</td>
<td>Borderline S-T's</td>
</tr>
<tr>
<td></td>
<td>7 days B₁</td>
<td>1.65</td>
<td>93</td>
<td>4.4</td>
<td>4.4</td>
<td>29</td>
<td>155/105 (125)</td>
<td>1376</td>
<td>147</td>
<td>—</td>
<td>—</td>
<td>30</td>
<td>16</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Same, exercise</td>
<td>1.80</td>
<td>122</td>
<td>4.8</td>
<td>4.8</td>
<td>24</td>
<td>95/60 (73)</td>
<td>675</td>
<td>134</td>
<td>2.8</td>
<td>16.0</td>
<td>41</td>
<td>6.5</td>
<td>Borderline Q-T</td>
</tr>
<tr>
<td></td>
<td>5 days B₁</td>
<td>1.77</td>
<td>59</td>
<td>3.0</td>
<td>3.0</td>
<td>29</td>
<td>155/70 (98)</td>
<td>1475</td>
<td>115</td>
<td>1.9</td>
<td>10.2</td>
<td>35</td>
<td>18</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>29 days B₁</td>
<td>1.79</td>
<td>86</td>
<td>3.0</td>
<td>3.0</td>
<td>19</td>
<td>130/70 (90)</td>
<td>1339</td>
<td>142</td>
<td>—</td>
<td>—</td>
<td>39</td>
<td>8.5</td>
<td>Normal</td>
</tr>
<tr>
<td>5. AN, 43, M</td>
<td>Untreated</td>
<td>1.66</td>
<td>89</td>
<td>1.6</td>
<td>1.8</td>
<td>12</td>
<td>125/68 (80)</td>
<td>2138</td>
<td>128</td>
<td>3.4</td>
<td>19.0</td>
<td>46</td>
<td>15</td>
<td>Borderline Q-T, nonspecific abnormality</td>
</tr>
<tr>
<td></td>
<td>5 days B₁</td>
<td>1.66</td>
<td>52</td>
<td>1.9</td>
<td>1.9</td>
<td>22</td>
<td>110/55 (70)</td>
<td>1777</td>
<td>—</td>
<td>3.0</td>
<td>17.5</td>
<td>36</td>
<td>15</td>
<td>Ischemia pattern</td>
</tr>
</tbody>
</table>

All determinations done at rest except where specified "exercise." BSA = body surface area in square meters. CI = cardiac index in L./min./M.² SI = stroke output in ml./beat/M.² O₂ cons. = oxygen consumption in ml./min./M.² at standard temperature and pressure. Pyruvate and lactate values given in mg./100 ml. Hct. = hematocrit in per cent. Appearance time = time in seconds from injection of dye into antecubital vein until initial deflection of dye curve as recorded on densimeter. PVR = peripheral vascular resistance in dynes seconds cm⁻⁵.

None of our patients was a high output state suspected on clinical grounds.

### Part 1. Circulatory Studies in 7 Patients with Wernicke’s Disease (table 1).

Cardiac Index and Peripheral Vascular Resistance Prior to Treatment. Cardiac index was measured in 7 subjects prior to treatment with thiamine. The mean value was $4.37 \pm 2.11$ L./min./M.², with a wide range of 1.4 to 6.5 L. Normal values in this laboratory in a series of 7 convalescent hospital patients were $3.53 \pm 0.88$ L./min./M.². The difference in this small series is not statistically significant. However, of the Wernicke's encephalopathy patients, 4 were above and 2 below the "normal" mean ±
1 standard deviation (fig. 1). All the patients with an elevated cardiac index exhibited a low calculated peripheral vascular resistance and, in general, both a resting tachycardia and an augmented stroke index (fig. 2). In these cases the resting pulse rate ranged from 102 to 115 per minute. However, in 2 of the 3 patients studied after treatment with thiamine there was a decline in stroke index associated with a fall in cardiac index; the third showed a slight rise in stroke index accompanied by a considerable drop in heart rate. Arteriovenous oxygen difference, as calculated from the Fick equation, was relatively low for all subjects who exhibited an increased cardiac index, indicating that the elevation of blood flow was not due to an increased oxygen requirement.

**Immediate Response to Thiamine Administration** (fig. 1). Two subjects received thiamine intravenously in a dose of 100 mg. immediately on completion of the control studies. In the first subject (JC), the control cardiac index of 5.7 L./min./M.² fell to 4.8 L. 1 hour after thiamine, with minor changes in pulse rate and blood pressure. In the second (MS), the control value of 1.4 L./min./M.² rose to 2.8 L. in 1 and 1½ hours, associated with increasing pulse rate and blood pressure, and progressive restlessness.

**Response to More Prolonged Thiamine Administration** (fig. 1). Six subjects were studied on a second occasion after they had received thiamine as the only vitamin supplement for 4 to 6 days. Of the 4 patients with elevated control cardiac indices (table 1, cases 1, 3, 4, and 6), all showed a decrease to the normal range with a corresponding rise in peripheral resistance. One patient (case 5) who originally had a normal cardiac index showed no change. Each of the remaining 2 patients (cases 2 and 7) with initially low values, remained low after treatment. Three patients were studied on a third occasion 7 to 36 days after the administration of a full diet and multiple vitamins. There was no further change except for a slight increase of cardiac index in 1 case.

**Changes in Oxygen Consumption.** Oxygen consumption was measured in 7 subjects before

![Fig. 1. Top. Cardiac index related to treatment in 7 patients. Shaded portion represents the “normal” mean cardiac index ± 1 standard deviation.](image1)

![Fig. 2. Cardiac index related to heart rate (middle) and stroke index (bottom). •—values prior to therapy; △—values 1-1½ hours after IV thiamine; ○—values after 4-36 days of therapy.](image2)
treatment with thiamine and in 6 subjects 4 or more days after treatment. Excluding a questionable figure of 215 in one (JK), pretreatment values averaged 149 ml./min./M.2 (range 128–167) and post-treatment values averaged 141 ml./min./M.2 (range 115–172). The apparent similarity of the pretreatment and post-treatment values for the entire group obscures the fact that of the 5 subjects with adequate determinations in both periods, 4 exhibited a decrease in oxygen consumption ranging from 16 to 22 ml., and the fifth an insignificant increase of 5 ml. Oxygen consumption correlated roughly with the cardiac index, but in the subjects having the highest pretreatment cardiac minute volume, the cardiac index was elevated out of proportion to oxygen consumption, as indicated by low values for calculated arteriovenous oxygen difference. Again, increase in blood flow was disproportionate to oxygen requirement.

Changes in Arterial Pressure and Pulse Rate. Mean arterial pressure averaged 88 mm. Hg before and 101 mm. Hg after treatment with thiamine in 7 subjects. Much of this minor rise in average pressure was due to an increase in mean pressure exhibited by 2 patients (EK and AN) who became hypertensive following specific therapy. The previous hospital record of AN disclosed hypertension of similar degree at intervals in the past.

Heart rate averaged 98/min. before and 80/min. after treatment with thiamine in 7 patients. This appears to be a significant decrease.

Changes in Blood Pyruvate and Lactate Levels. Elevation of fasting blood pyruvate to abnormal levels was found in all 6 patients in whom it was measured (table 1). A comparable increase in blood lactate was less consistently found. After administration of parenteral thiamine for 4 or more days, fasting pyruvate and lactate values declined to normal or nearly normal levels. Prior to therapy there was no obvious correlation between blood lactate or pyruvate values and cardiac index.

Part 2. Postural Responses in 12 Patients with Wernicke's Disease (table 2)

The cardiovascular response to tilting was grossly abnormal at some time during the study in 7 of the 12 patients tested. In 3 patients the blood pressure was completely unobtainable for varying periods of time during multiple tilts; in 2 of these (JK and AN) it was unobtainable throughout most of the 5 minutes of tilting on one occasion in each patient. It was of interest that despite such profound alterations in cardiovascular response, none of our patients complained of “dizziness” or “light-headedness” during tilting, and syncope occurred on only one occasion during the entire study. However, postural “faintness” was a complaint in the histories of 3 of our more rational patients; 2 of these (EK and AN) demonstrated marked and prolonged postural hypotension on tilting.

In every case in which the blood pressure or pulse pressure fell abnormally there was ample evidence of reflex cardioacceleratory activity in terms of a rise in pulse rate of moderate to marked degree, but less consistent evidence of peripheral sympathetic activity (sweating, pallor).

Of the 6 patients studied before treatment, only 2 demonstrated an abnormality (MG and LH). Four patients were studied both before and after thiamine administration (EK, AN, LH, and WB). Of these, an abnormality was evident in only 1 patient (LH) before treatment. Two of these patients (EK and AN) showed inadequate compensation to tilting only after treatment with thiamine. Postural responses in these patients became markedly abnormal and remained so for relatively long periods following therapy. The fourth patient (WB) whose pressure readings were difficult to define on one occasion after treatment, exhibited at that time a response to tilting that was probably abnormal, in that his pulse pressure fell to about 20 per cent of control values. Marked and prolonged systolic “overshoot” of blood pressure occurred after return to the horizontal position in 2 subjects (MS and JK) on one occasion each.

The most marked abnormalities in this series were not restricted to the older nor to the most seriously incapacitated patients. EK and AN, aged 42 and 43, were 2 of the younger patients in the group. AN was in a relatively early phase of the disease and appeared well nourished.
GRAVALLESE AND VICTOR

TABLE 2.—Postural Responses of Twelve Patients with Wernicke’s Disease

<table>
<thead>
<tr>
<th>Patient, age, and sex</th>
<th>Days of treatment</th>
<th>Systolic pressure (mm. Hg)</th>
<th>Diastolic pressure (mm. Hg)</th>
<th>Pulse</th>
<th>Lowest pulse pressure (mm. Hg)</th>
<th>Duration of tilt (min.)</th>
<th>Normal or abnormal</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control Max. change</td>
<td>Control Max. change</td>
<td>Control Max. change</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. EK,42, M</td>
<td>0 130 +8 82 +6</td>
<td>108 +12</td>
<td>44</td>
<td>5</td>
<td>N</td>
<td>Marked dyspnea on slight exertion prior to therapy; history of postural “dizziness”</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 145 -45* 100 -22</td>
<td>116 +36</td>
<td>22</td>
<td>5</td>
<td>Abn.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>37 160 -90* 102 -42*</td>
<td>116 +24</td>
<td>12</td>
<td>5</td>
<td>Abn.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>44 153 -43* 106 -18</td>
<td>104 +36</td>
<td>12</td>
<td>30</td>
<td>Abn.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>44 158 -56* 93 -19</td>
<td>124 +16</td>
<td>22</td>
<td>30</td>
<td>Abn.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. AN,43, M</td>
<td>0 124 -8 89 +9</td>
<td>80 +36</td>
<td>16</td>
<td>5</td>
<td>N</td>
<td>History of postural “dizziness”; unobtainable B.P. readings throughout entire tilt on day 7; inconstantly unobtainable, day 10</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>7 120 x 100 x</td>
<td>88 +44</td>
<td>x</td>
<td>5</td>
<td>Abn.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>10 112 x 92 x</td>
<td>88 +40</td>
<td>x</td>
<td>10</td>
<td>Abn.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>14 154 -16 115 +17</td>
<td>92 +28</td>
<td>10*</td>
<td>10</td>
<td>Abn.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. MS,57, M</td>
<td>5 117 -29 70 +10</td>
<td>64 +24</td>
<td>12</td>
<td>5</td>
<td>N</td>
<td>Marked post-tilt “systolic overshoot” day 5 (73 mm. Hg over control level); history of postural “dizziness”</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>20 138 -36 75 +3</td>
<td>64 +24</td>
<td>24</td>
<td>5</td>
<td>N</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. JK,65, M</td>
<td>6 104 x 69 x</td>
<td>76 x</td>
<td>x</td>
<td>5</td>
<td>Abn.</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>6 144 x 79 x</td>
<td>68 +20</td>
<td>x</td>
<td>5</td>
<td>Abn.</td>
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<tr>
<td></td>
<td>13 102 x 58 x</td>
<td>68 +24</td>
<td>x</td>
<td>5</td>
<td>Abn.</td>
<td></td>
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<tr>
<td></td>
<td>13 110 -60* 63 +23</td>
<td>73 +19</td>
<td>±10*</td>
<td>5</td>
<td>Abn.</td>
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<tr>
<td></td>
<td>13 88 x 50 x</td>
<td>72 +24</td>
<td>x</td>
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<td>Abn.</td>
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<tr>
<td>5. LH,68, M</td>
<td>0 105 x 73 x</td>
<td>96 +16</td>
<td>x</td>
<td>5</td>
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<tr>
<td></td>
<td>0 111 -49* 76 x</td>
<td>88 x</td>
<td>x</td>
<td>15</td>
<td>Abn.</td>
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<tr>
<td></td>
<td>12 112 +10 61 +11</td>
<td>68 +20</td>
<td>36</td>
<td>20</td>
<td>N</td>
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<tr>
<td>6. WB,52, M</td>
<td>0 134 -36 72 -20</td>
<td>104 +16</td>
<td>28</td>
<td>5</td>
<td>— Pulse pressure fell to 20 per cent of control, day 5; syncope, day 0</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>5 111 -15 64 +26</td>
<td>68 +24</td>
<td>±10</td>
<td>10</td>
<td>?N</td>
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<tr>
<td></td>
<td>29 132 +12 75 +15</td>
<td>84 +20</td>
<td>36</td>
<td>10</td>
<td>N</td>
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<td></td>
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<tr>
<td>7. ES,31,F</td>
<td>0 136 -14 93 +11</td>
<td>96 +28</td>
<td>26</td>
<td>5</td>
<td>N</td>
<td></td>
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<tr>
<td>8. MG,63, F</td>
<td>0 100 -24 73 -11</td>
<td>98 +30</td>
<td>10*</td>
<td>5</td>
<td>Abn.</td>
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<tr>
<td>9. FM,44, F</td>
<td>65 111 -13 79 +13</td>
<td>84 +36</td>
<td>12</td>
<td>5</td>
<td>N</td>
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<tr>
<td></td>
<td>75 110 +12 81 +19</td>
<td>84 +36</td>
<td>8*</td>
<td>5</td>
<td>Abn.</td>
<td></td>
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<tr>
<td>10. JC,33,F</td>
<td>1 139 -12 84 +8</td>
<td>96 -4</td>
<td>40</td>
<td>5</td>
<td>N</td>
<td></td>
<td></td>
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<tr>
<td>11. JE,45,M</td>
<td>6 102 -18 76 +12</td>
<td>60 +24</td>
<td>8*</td>
<td>5</td>
<td>Abn.</td>
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<tr>
<td>12. TB,70, M</td>
<td>16 125 -11 63 +9</td>
<td>80 -4</td>
<td>42</td>
<td>5</td>
<td>N</td>
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</tbody>
</table>

* Abnormal Change: Arbitrarily, a fall from the baseline of 40 mm. Hg systolic, 30 mm. Hg diastolic or a drop in pulse pressure to 10 mm. Hg or less was considered abnormal.

x = Reading unobtainable one or more times during tilt.

**DISCUSSION**

The main abnormalities found in this study were the alterations in cardiac output and the high incidence of postural hypotension. Tachycardia, elevated cardiac output, and low peripheral resistance were found in 4 of 7 patients. Of 6 patients subjected to cardiac output and postural studies, 3 showed both tachycardia and postural hypotension.

A number of factors might be implicated in the high output state encountered in our patients. Laennec’s cirrhosis (and possibly “fatty liver”) is known to be accompanied by an elevation of resting cardiac output in certain instances.9 Of the 4 patients with an elevated cardiac output, 1 (JC) undoubtedly had cirrhosis and 3 were examples of “fatty liver.” However, when the cardiac output is elevated in cirrhosis alone, it has not been shown to decline to normal levels in a few days, or in response to treatment with thiamine alone.

Two of the 4 patients with an elevated cardiac output were anemic, with hematocrit readings of 33 and 35 per cent. In 1 of these patients the cardiac output returned to normal 5 days after the original studies, but the he-
matocrit did not increase significantly. Moreover, an elevated cardiac output has not been found with anemia of this degree.10

A state of apprehension may elevate the cardiac output,11-12 but this factor seems unlikely in our patients, who were generally indifferent and apathetic. The possibility that an abnormal accumulation of blood pyruvate or lactate may affect the peripheral vascular system has been adequately excluded by other investigators; the intravenous administration of these substances and a large variety of other metabolites in both animals and man has not resulted in significant alterations of cardiovascular function.13-14

A high cardiac output is characteristic of beriberi heart disease.15-20 The high cardiac output seen in our patients may represent the same abnormality. Our cases showed no signs of congestive failure, but the cardiovascular manifestations of beriberi need not take this form alone. Keefer21 studied 12 patients with neuritic beriberi who had no symptoms referable to the heart; yet 3 patients showed cardiomegaly and 10 had electrocardiographic abnormalities. It should be pointed out that electrocardiographic changes of the type seen in our patients have been reported in Wernicke's disease,22 beriberi,14 other types of nutritional deficiency,23 experimental thiamine deficiency in man24 and in animals,25-31 all without congestive failure.

One can only speculate on the infrequent occurrence of congestive failure in our patients. In patients with neuritic beriberi the infrequency of congestive failure has been attributed to the paralysis and generally decreased physical activity that reduced the burden on the myocardium.21-22 Neuropathy was minimal in our patients, but the immobility necessitated by ataxia may have prevented the development of clinical myocardial insufficiency.

We can offer no satisfactory explanation for the low cardiac indices seen in 2 patients (MS and HC). Neither showed evidence of congestive failure. Both these patients were malnourished to the point of emaciation, a state that may be associated with slightly lowered cardiac output.32 One patient (HC) was dehydrated and had arteriosclerotic heart disease; he died several days after his final study and postmortem examination disclosed an old apical myocardial infarction.

In attempting to explain the postural hypotension in our patients several pertinent factors should be considered. Undernutrition, present to some degree in all the patients, is commonly thought to be associated with poor vasomotor control. Postural hypotension, however, was not a prominent feature in a study on undernourished subjects.24 The altered vasomotor response to tilting in the older age group24 seems to be an inadequate explanation of the profound abnormalities found in the present series. Immobilization, however, in otherwise normal subjects, has been shown to predispose to orthostatic fainting in as short a period of time as 1 week.24 It is possible that the immobilization imposed on our patients by ataxia may explain the high incidence of postural hypotension.

The concurrence of tachycardia, elevated cardiac output, low peripheral resistance, and postural hypotension can best be explained by a state of peripheral vasodilatation. One patient (EK) was known to have essential hypertension (increased peripheral resistance) before the onset of Wernicke's disease. During the acute phase of the illness his blood pressure became normal and peripheral vascular resistance was lowered. After treatment, he again became hypertensive with elevation of the peripheral vascular resistance. The presence, before treatment, of a low arteriovenous oxygen difference with an elevation of cardiac index disproportionate to the oxygen consumption also favors a state of peripheral vasodilatation.

It is interesting to speculate on the rapid reversal of tachycardia, elevated cardiac output, and low peripheral resistance following the administration of thiamine. This sequence of events suggests that a deficiency of this vitamin is in some way responsible for the production of these abnormalities. The fact that postural hypotension, or altered vascular response to tilting, appeared most commonly after specific therapy was instituted does not negate the role of thiamine deficiency in its production. Other cardiovascular symptoms such as cyanosis and electrocardiographic abnormalities may be-
come more prominent or may appear for the first time after the institution of specific therapy. The cause of this phenomenon is unknown; possibly the increased metabolism accentuates the deficiency of other B vitamins or even of vitamin B₁.

Thiamine deficiency may have both a central and peripheral effect on the cardiovascular system. There is definitive evidence that the myocardium is affected in beriberi and in experimentally induced thiamine deficiency states. More recent studies on myocardial metabolism in thiamine-deficient animals have demonstrated an abnormal utilization of pyruvate and lactate. From our observations it would also appear that acute thiamine deficiency, as manifested by Wernicke's encephalopathy, is accompanied by a state of peripheral vasodilatation, qualitatively similar to that found in beriberi.

Summary

Cardiovascular studies were performed on 7 patients with acute Wernicke's encephalopathy. Four of these showed a cardiac output elevated out of proportion to oxygen consumption and associated with low peripheral vascular resistance. These abnormalities reverted to normal after treatment with thiamine and bed rest. Resting tachycardia was a frequent occurrence. In 2 patients the cardiac output was low and remained low with treatment; in another it was normal.

Postural hypotension was found in 7 of 12 patients. The most profound abnormalities in the cardiovascular response to tilting occurred after treatment with thiamine.

It is suggested that these changes reflect an abnormal state of peripheral vasodilatation which, in turn, may be related specifically to thiamine deficiency.

Summary in Interlingua

Studios cardiovascular esseva executate in septe patientes con acute encephalopathia de Wernicke. In quatro de iste casos le rendimento cardiac esseva elevate foras de proportion con le consumption de oxygeno. Isto esseva associate con bassa resistentia periphero-vascular. Tractamento con thiamina e allectamento resultava in le reversion del anormalitates mentionate. In duo patientes le rendimento cardiac esseva basse e remaneva basse post le tractamento. In un patiente le rendimento cardiac esseva normal.

Hypotension postural esseva constata in septe ex 12 patientes. Le plus pronunciate anormalitates del responsa cardiovascular effectuare per inclination occurreva post tractamento con thiamina.

Es sugerite que iste alteraciones reflecte un anormal stato de vasodilatation peripheric le qual, de su parte, es forsan relateate specificame a carentia de thiamina.

Acknowledgment

The authors are grateful to the medical services of the Boston City Hospital for making the patients available for study, and to Drs. W. H. Abelmann, L. B. Ellis, and R. D. Adams for their generous help in preparing this paper.

References


Circulatory Studies in Wernicke's Encephalopathy: With Special Reference to the Occurrence of a State of High Cardiac Output and Postural Hypotension

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