Cerebral Hemodynamic and Metabolic Studies in Patients with Congestive Heart Failure

II. Observations in Confused Subjects

By Seymour Eisenberg, M.D., Leonard Madison, M.D., and Willis Sensenbach, M.D.

The superlevation of mental aberrations in persons with advanced congestive heart failure often heralds the onset of rapid deterioration and death. The prognostic implications of such manifestations were appreciated more than 50 years ago, but their pathogenesis has remained an enigma. It has been suggested that edema, ischemia, or anoxia of the brain is responsible for these symptoms; digitalis, mercurial diuretics, hypertension, and cerebral arteriosclerosis have also been implicated. Previous studies of cerebral flow and metabolism in persons with congestive heart failure have not yielded information germane to this problem, as they apparently included only lucid patients. Moreover, the actual effect of the congestive process on cerebral hemodynamics and metabolism, regardless of mental state, has been the subject of considerable controversy.

Recently published data from this laboratory indicate that cerebral blood flow is indeed moderately diminished in alert persons with severe congestive failure. The present study was undertaken to determine whether cerebral perfusion and metabolism were further altered in those cardiac subjects with severe cerebral symptoms.

Materials and Methods

Twenty-four persons with severe, intractable congestive heart failure were studied; this diagnosis was established by the usual clinical criteria of breathlessness, cardiac enlargement, venous distention, and hepatomegaly, and was quite evident in every instance. In addition, these subjects displayed particular features that served to distinguish them from the usual decompensated cardiac patient. First, mental aberrations were prominent in all patients; this varied from simple confusion and somnolence to actual coma. Many of the subjects were slightly icteric and many displayed modest azotemia; however, at postmortem examination little histologic evidence of intrinsic renal or hepatic disease was encountered. Although dyspnea was prominent if the slightest exertion were undertaken, weakness and fatigability had become the dominant symptoms. Twenty-two of the 24 subjects died within several weeks following the onset of this constellation of clinical manifestations. Care was taken to exclude from the study patients with evident cerebral arteriosclerosis and individuals with preexisting renal, hepatic, or mental disease. The possibility of cerebral arteriosclerosis could not be completely excluded on clinical grounds, but none of the subjects had had previous cerebral infarctions; moreover, significant oblitative disease of the cerebral vessels was later excluded in all of the subjects on whom a postmortem examination was performed. Therapy included the usual regimen of digitalis, sodium restriction, and diuretics as required. Electrolyte derangements, particularly hyponatremia, were encountered in several of these patients. In most instances, however, the mental symptoms were present despite a normal serum sodium concentration, and when symptomatic hyponatremia was thought to be present, its correction did not significantly alter the patient’s mental state.

Cerebral blood flow was measured by the nitrous oxide method of Kety and Schmidt as modified by Scheinberg and Stead. The analytic methods employed were described in a previous communication. Mean arterial blood pressure was measured directly from a convenient artery by a damped mercury manometer. Cerebral vascular resistance was calculated from the cerebral blood flow and the mean arterial blood pressure and the cerebral met-
abolic rate of oxygen and glucose from the cerebral blood flow and arteriocerebral venous oxygen and glucose differences. The pH was determined by means of a Cambridge Research Model pH meter, and the carbon dioxide tension was calculated from the monogram of Singer and Hastings.9

Six patients were studied during both confused and lucid intervals. Four subjects had been studied prior to the development of mental aberrations, and 2 improved to the point of complete lucidity, at which time they were restudied.

The results in these confused persons with terminal congestive heart failure have been compared with the findings in lucid patients with "mild to moderate" and "severe" congestive heart failure. The results of the cerebral hemodynamic and metabolic studies in these lucid individuals were the subject of a previous report,5 and the criteria for classifying the congestive state as "mild to moderate" or "severe" were presented in detail. In brief, patients with "mild to moderate" failure responded promptly to digitalis administration and rarely required diuretic measures. Subjects classified as "severe" cardiac subjects had more marked cardiac enlargement, responded slowly to therapy, and usually required intermittent diuretic agents to remain edema-free.

Results

The results of the hemodynamic and metabolic studies in the 24 confused cardiac patients are presented in tables 1 and 2. Mean values for the previously published5 studies in lucid patients with congestive heart failure are included for purposes of comparison; in 21 of these lucid subjects the congestive state was classified as mild to moderate and in 13 as severe. Six patients were studied during both lucid and confused periods, and the differences were analyzed by the method of paired observations.

The mean cerebral blood flow for the confused patients was 26 ml. per minute per 100 Gm., which represents a profound reduction in cerebral perfusion. This differs significantly (p < .001) from the values obtained in mild to moderate (51 ml. per minute per 100 Gm.) and severe but lucid (39 ml. per minute per 100 Gm.) subjects with congestive heart failure. The cerebral vascular resistance was 3.61 mm. Hg per ml. per minute per 100 Gm., which significantly (p < .01) exceeded the values in cardiac subjects without mental symptoms.

The mean arterial blood pressure was 98 mm. Hg in the confused patients; this did not differ from the mean value in the severe but lucid group but was significantly (p < .01) less than the mean pressure of the group with mild to moderate congestive failure. The arteriovenous oxygen difference was 10.36 volumes per cent in the confused patients, which significantly (p < .001) exceeded the values obtained in lucid cardiacs. The value for cerebral oxygen consumption of 2.71 ml. per minute per 100 Gm. in the confused subjects was significantly (p < .01) less than that obtained in alert individuals with mild to moderate failure but did not differ significantly from the value in lucid patients with severe congestive heart failure. The arterial carbon dioxide content was significantly (p < .05) decreased in the confused group as compared with the results in alert subjects; there was, however, no significant difference in the partial pressure of carbon dioxide.

In 6 instances there was an opportunity to study the same individuals during alternating states of mental confusion and alertness. During periods of mental confusion significant changes were encountered. The cerebral blood flow decreased significantly (p < .01), and this was associated with an increase in both cerebral vascular resistance (p < .05) and mean arterial blood pressure (p < .05). The arteriovenous oxygen difference was significantly increased (p < .001) during the confused interval, but there was, nevertheless, a significant (p < .05) decrease in cerebral oxygen consumption. Arterial carbon dioxide was significantly (p < .01) decreased during the "confused" interval.

Discussion

The results of this study indicate that the blood supply to the brain may be profoundly decreased in persons in the terminal stages of congestive heart failure. This is commonly associated with mental aberrations of varying severity, although occasional patients will remain lucid despite this perfusion defect. The clinical impression that the supervision of mental symptoms in chronic congestive heart
failure constitutes a poor prognostic sign is amply supported by the extremely high mortality among the patients comprising this study.

The clinical manifestations of passive congestion in the patients with mental symptoms were qualitatively and quantitatively similar to those in lucid persons with severe congestive heart failure.
### Table 2

**Blood Constituents in Confused Subjects with Congestive Heart Failure**

<table>
<thead>
<tr>
<th>Name</th>
<th>Arterial O₂ content vol. % C</th>
<th>Arteriocerebral venous O₂ diff., vol. % C</th>
<th>Arterial CO₂ content, vol. % L</th>
<th>Arterial pH L</th>
<th>Arterial pCO₂ C L</th>
</tr>
</thead>
<tbody>
<tr>
<td>E.R.K.</td>
<td>17.27</td>
<td>8.90</td>
<td>45.39</td>
<td>7.37</td>
<td>43</td>
</tr>
<tr>
<td>F.K.K.</td>
<td>13.98</td>
<td>9.84</td>
<td>47.76</td>
<td>7.40</td>
<td>43</td>
</tr>
<tr>
<td>B.R.B.</td>
<td>16.54</td>
<td>9.08</td>
<td>45.49</td>
<td>7.45</td>
<td>37</td>
</tr>
<tr>
<td>G.D.</td>
<td>16.28</td>
<td>12.48</td>
<td>30.11</td>
<td>7.46</td>
<td>24</td>
</tr>
<tr>
<td>W.D.</td>
<td>15.92</td>
<td>13.25</td>
<td>38.70</td>
<td>42.58</td>
<td>33</td>
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<tr>
<td>J.D.</td>
<td>17.90</td>
<td>11.14</td>
<td>46.01</td>
<td>7.41</td>
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<tr>
<td>J.A.B.</td>
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<td>13.43</td>
<td>38.33</td>
<td>7.44</td>
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<tr>
<td>W.S.R.</td>
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<td>8.88</td>
<td>43.25</td>
<td>7.43</td>
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</tr>
<tr>
<td>T.P.H.</td>
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<td>14.63</td>
<td>46.04</td>
<td>55.93</td>
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<tr>
<td>W.E.J.</td>
<td>17.02</td>
<td>12.64</td>
<td>46.40</td>
<td>54.14</td>
<td></td>
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<tr>
<td>R.M.</td>
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<td>4.42</td>
<td>38.54</td>
<td>7.45</td>
<td>30</td>
</tr>
<tr>
<td>J.L.</td>
<td>18.00</td>
<td>12.83</td>
<td>46.23</td>
<td>52.01</td>
<td></td>
</tr>
<tr>
<td>G.P.M.</td>
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<td>7.82</td>
<td>21.82</td>
<td>7.35</td>
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</tr>
<tr>
<td>J.T.W.</td>
<td>17.97</td>
<td>15.37</td>
<td>46.28</td>
<td>57.50</td>
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</tr>
<tr>
<td>R.C.</td>
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<td>12.06</td>
<td>33.52</td>
<td>7.47</td>
<td>25</td>
</tr>
<tr>
<td>R.C.Z.</td>
<td>14.82</td>
<td>18.07</td>
<td>27.83</td>
<td>43.67</td>
<td></td>
</tr>
<tr>
<td>G.B.</td>
<td>17.16</td>
<td>11.37</td>
<td>41.19</td>
<td>7.44</td>
<td>35</td>
</tr>
<tr>
<td>M.W.</td>
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<td>11.31</td>
<td>49.38</td>
<td>7.42</td>
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</tr>
<tr>
<td>H.H.K.</td>
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<td>10.70</td>
<td>31.52</td>
<td>7.51</td>
<td>28</td>
</tr>
<tr>
<td>B.H.J.</td>
<td>14.96</td>
<td>10.16</td>
<td>37.25</td>
<td>7.47</td>
<td>25</td>
</tr>
<tr>
<td>M.D.R.</td>
<td>16.17</td>
<td>10.94</td>
<td>41.03</td>
<td>7.50</td>
<td>30</td>
</tr>
<tr>
<td>Mean</td>
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<td>10.36</td>
<td>40.10</td>
<td>7.44</td>
<td>7.38</td>
</tr>
<tr>
<td>S.E.</td>
<td>0.30</td>
<td>0.42</td>
<td>1.63</td>
<td>0.146</td>
<td>1.70</td>
</tr>
</tbody>
</table>

Comparison of values in 6 persons during alternating states of confusion and lucidity (paired observations)

Mean—lucid

Mean—confused

Difference

*p* < .05

Comparison of values in confused subjects with values in lucid patients with severe congestive heart failure

Mean—severe

Mean—confused

Difference

*p* > .05

Comparison of values in confused subjects with the values in lucid patients with mild to moderate congestive heart failure

Mean—mild to moderate

Mean—confused

Difference

*p* > .05

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* C, confused.

† L, lucid.

tive heart failure, and it is extremely doubtful that the reduction in cerebral blood flow was related to impedance imposed by an increase in the severity of cerebral congestion. It is more likely that the sharp decline in cerebral perfusion associated with the development of mental symptoms in these subjects resulted from hemodynamic alterations in the arterial segment of the vascular tree. It was suggested in a previous publication that the

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decline in cerebral blood flow in alert persons with severe cardiac decompensation was related to a decrease in cardiac output, which is consonant with the established relationship of renal and hepatic blood flow to cardiac output in persons with chronic congestive heart failure. It is therefore suggested that in the confused cardiac patients herein reported cardiac output had declined to critical levels and that as a result cerebral perfusion was impaired to the point that functional abnormalities supervened. There was no reduction in mean arterial blood pressure to support such a formulation; all of these patients, however, ultimately developed severe hypotension with clinical evidence of circulatory collapse. This was thought to represent a further fall in cardiac output or true "cardiac shock."

The failure of the brain to function adequately in these persons with "end-stage" congestive failure could have been due to abnormalities other than the poor blood supply to the brain. Alterations in electrolyte concentration, oxygen content, or pH of the arterial blood of sufficient magnitude to account for the mental symptoms, however, were not encountered. Therefore, it is likely that the failure of cerebral function under these circumstances was the result of a severe metabolic abnormality intimately linked with the critical reduction in the blood supply to the brain. These data, however, do not define precisely the nature of this abnormality. Although cerebral metabolic rate for oxygen was decreased in most of these confused cardiac patients, the results do not clearly establish that the mental symptoms resulted from inadequate utilization of oxygen. It is conceivable, however, that the estimation of total cerebral metabolic rate for oxygen fails to reflect abnormalities in individual cells or areas of the brain and that distributional changes could occur that might not be perceived by the method employed; under circumstances where perfusion is inadequate and oxygen is in critical supply, those centers concerned with consciousness could deteriorate while the remainder of the brain is functioning adequately.

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This study supports the concept that cerebral ischemia is chiefly responsible for the mental symptoms encountered in patients with far-advanced congestive heart failure. There was little evidence in these 24 cardiac patients that factors such as electrolyte abnormalities, digitalis therapy, anoxemia, or cerebral arteriosclerosis contributed significantly to the development of their altered mental state.

Conclusions
Cerebral blood flow was profoundly diminished (26 ml per minute per 100 Gm.) in 24 mentally confused persons with advanced congestive heart failure.

Cerebral utilization of oxygen was decreased in the majority of these confused individuals.

The supervention of mental symptoms in patients with advanced congestive heart failure has grave prognostic implications.

Acknowledgment
This work was done with the technical assistance of Miss Mary Frances Camp and Miss Mildred T. Brennan.

Summario in Interlingua
Le fluxo de sanguine cerebral eseva mareatemente reducteite (26 ml per minuta per 100 g) in 24 mentalmente confuse subjectos con avantiate formas de congestive disfallimento cardiae.

Le utilisation cerebral de oxyigeno eseva reducita in le majoritate de iste confuse individuos.

Le supervention de symptomas mental in patientes con avantiate disfallimento congestive del corde ha un grave signification ab le puncto de vista del progno.

References

Circulation, Volume XXI, May 1960
I believe it was Samuel Butler who said that one of the arts of living consists in the ability to come to adequate conclusions from inadequate evidence. In any event, much of our practical living involves action on the basis of assumptions of varying degrees of probability. We often forget, only to recall at leisure later, that the most improbable events are not impossible. They are only extremely improbable. In just this sense, I would think it highly improbable that medical students can wisely be expected to acquire for the first time at so late a stage in their preparation, basic intellectual honesty, industrious habits, dependable morality, or freedom from the shackles of tradition and authoritarianism if in neither home nor secondary school they have met examples of or training in honesty, responsibility, hard work, and freedom of mind and spirit. I do not think we often stop to realize how much of these qualities we assume to be present in medical students, nor how much we rely, unconsciously, on these qualities that are essential to the effectiveness of our institutions of higher learning.—ALAN GREGG, M.D. Challenges to Contemporary Medicine. New York, Columbia University Press, 1956, p. 114.
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