Cardiac and Cerebral Hemodynamics in Drug Induced Postural Collapse

By FRANK A. FINNERTY, JR., ROBERT L. GUILLAIDEU AND JOSEPH F. FAZEKAS

When signs of cerebral ischemia were induced by the administration of hexamethonium or head-up tilting, the cardiac output was reduced in all patients. Although the level of arterial pressure during cerebral ischemia varied between 34 and 100 mm. Hg, cerebral blood flow at this time was reduced to 30.8 ± 4.6 ml./100 Gm. brain/min. Despite a reduction in cardiac output averaging 47 per cent, approximately the same percentage was diverted to the brain during cerebral ischemia.

Because of inherent technical difficulties, previous hemodynamic data on postural hypotension have been collected either during the presyncopal, moderately hypotensive phase or during the recovery phase, but not during the period of cerebral ischemia. Since syncope occurs as a sudden and dramatic episode there is reason to suspect that it may be accompanied by hemodynamic changes equally sudden and profound which may not be present during the presyncopal or postsyncopal periods.

In a previous study, acute hypotension followed by cerebral ischemia was induced by administering hexamethonium intravenously to patients tilted in the head-up position. Under these conditions a considerably greater reduction in cerebral blood flow occurred in patients who developed syncope than in those who exhibited postural hypotension without syncope. Because of the significant difference in changes in cerebral blood flow in syncope patients compared with patients with postural hypotension without syncope it seemed important to restudy the hemodynamic alterations during cerebral ischemia and, in particular, to study the relationship between cardiac output and cerebral blood flow during syncope.

METHODS AND MATERIALS

The subjects were hospitalized patients from the Medical Wards of the District of Columbia General Hospital. Cardiac catheterization with Fick cardiac output determinations were performed on 12 patients and radiolabeled albumen cardiac output determinations were performed on 9 patients. Cerebral blood flow and cerebral metabolic determinations were performed in the latter group. For clarity these data will be presented separately.

Fick Cardiac Output Determinations. This group included 2 patients with malignant hypertension, 9 with essential hypertension and 1 patient with spontaneous postural hypotension. Control determinations were obtained after the patient had been tilted (head-up) 40° for a period of at least 30 min., except in the patient with spontaneous postural hypotension when control determinations were performed in the supine position. At least two control direct Fick cardiac outputs were performed. The oxygen content of expired air and oxygen consumption were measured as previously described. Oxygen content was measured by the method of Hickam and Frayser.

Following control observations, the subjects (who remained in the 40° head-up tilt position) were given a solution of hexamethonium intravenously at a rate of 1 mg. of the ion/min. The mean arterial pressure was rapidly 1-2 min.) reduced and the subjects carefully observed for signs of cerebral insufficiency or peripheral vascular collapse. The patient’s alertness, particularly his ability to follow simple command, i.e., close one eye, look at the ceiling, etc., was used as the best criterion for judging the adequacy of the cerebral circulation. At the appearance of the first sign of cerebral ischemia, i.e., confusion, yawning, staring, or convulsion (2 patients), the hexamethonium injection was promptly discontinued and the experimental procedure begun. The angle of head-up tilt was not altered during the first 2 minutes. Electrocardiograms were taken before, intermittently during, and after the procedures in all cases.

Combined Cardiac Output (RISA) and Cerebral Blood Flow Determinations. Ten patients were studied. Nine patients were hypertensive, 8 with essential hypertension and 1 secondary to glomerulonephritis. One of these hypertensive patients...
exhibited spontaneous postural hypotension. A normotensive patient who exhibited postural hypotension also was studied. Control studies were performed after the patient had been in the 40° head-up position for 30 min. except in the patients with spontaneous postural hypotension where control studies were performed in the supine position.

Scheinberg and Stead's modification of Kety and Schmidt's procedure for the determination of cerebral blood flow was utilized. The mean arterial pressure was obtained directly from the femoral artery by means of a damped aneroid manometer and also from the arm by the usual auscultatory method. Blood oxygen, CO₂ content, blood pH and cerebral oxygen consumption and the calculations of cerebral vascular resistance were performed as discussed previously.³

The femoral arterial needle used in the cerebral blood flow procedure served for the arterial sampling for cardiac output determination. Fifteen microcuries of radioiodinated serum albumen (RISA) were given rapidly and quantitatively into the ante-cubital vein or the internal jugular vein. The rapid injection (less than 2 sec.) and immediate elevation of the arm following injection insured adequate mixing of the isotope even where slowing of the circulation was evident. The radioactivity in 2 sec. arterial samples enabled the construction of a curve suitable for obtaining the cardiac output according to the Hamilton technic.⁷

The central blood volume and mean circulation times were calculated according to the method of Hamilton.⁸ Cardiac work was calculated from the formula of Starling and Visscher, i.e., cardiac work (Kg./M./min. equals cardiac output (ml./min.) X mean aortic pressure (mm. Hg) X 13.6).⁹ The mean femoral arterial pressure was substituted for the mean aortic pressure.

Using a mean brain weight of 1400 Gm. the total cerebral blood flow was estimated and this was divided by the cardiac output to give the estimated cardiac output diverted to the brain. (Total brain blood flow equals 51 ml./100 Gm. brain/min. X 14 = 714 ml./1400 Gm. brain/min. and, therefore, cardiac output going to the brain equals 714 + 4800 = 14 per cent.)

As with the patients in whom Fick cardiac output determinations were performed, the subjects in this group were given a 1 per cent solution of hexamethonium intravenously using as an "end point" a "sluggish response" to simple commands. At the first sign of impending cerebral insufficiency, the hexamethonium injection was promptly discontinued and measurement of cerebral blood flow was repeated. Immediately thereafter, 15 mc. of RISA were injected into the antecubital or internal jugular vein and the cardiac output was determined.

**RESULTS**

**Fick Cardiac Output Determinations.** Six patients developed symptoms of cerebral ischemia and 6 did not. In the patients who exhibited signs of cerebral ischemia, an acute reduction in arterial pressure from a mean of 139 ± 42 mm. Hg to 66 ± 36.4 mm. Hg (a 54 per cent reduction) was accompanied in 4 patients by a fall in cardiac index from a mean of 5.1 ± 1.3 L./min./M.² body surface to 2.6 ± .11 L./min./M.² body surface (an average reduction of 45 ± 17 per cent). In two remaining cases (E.K. and M.H.), the measured oxygen consumptions in collapse were extremely low, i.e., 62 cc. and 18 cc./min. in E.K. and 66 cc./min. in M.H. In these patients, brief periods of apnea were noted during the air sampling period and the inspiratory volume, in contrast to the others, was diminished approximately by one-half. Because of the markedly unsteady state in these patients, no attempt was made to calculate cardiac output.

Oxygen consumption increased in 3 patients and decreased in 3 patients. The arteriovenous oxygen difference increased in all patients from a mean of 4.3 ± 1.2 volumes per cent to 6.5 ± .9 volumes per cent.

Once signs of cerebral ischemia developed no significant change was evident in the total peripheral resistance. At least a 65 per cent reduction in cardiac work evident in each patient when collapse developed with an average reduction of 79 ± 9 per cent.

In all cases studied the pressures in the lesser circulation (right ventricular 3 and pulmonary artery 3) were reduced when signs of cerebral ischemia developed. In the right ventricle the pressures were reduced from a mean of 42/3 to 20/0.5 mm. Hg and in the pulmonary artery from a mean of 20/7 to 16/3 mm. Hg. Broadening and flattening of the intracardiac waves similar to changes described by Wiggers¹⁰ in animals in shock were seen in all patients studied when signs of cerebral ischemia were present (fig. 1).

The fall in the femoral artery pressure preceded the fall in the right heart pressures. The broadening of the intracardiac waves preceded by a few seconds the development of syncope in all patients studied. At this time also, the femoral artery pressure wave was characterized by a markedly reduced pulse pressure with lack of the usual continuous fall in pressure during the diastolic run off period (fig. 1).
Electrocardiographic abnormalities were not observed in any patient. Likewise, there was complete absence of angina despite the marked reductions in arterial pressure necessary to produce signs of cerebral ischemia. The development of bradycardia (average reduction in pulse rate was 9 beats/min.) and the reduction of cardiac work (more than 60 per cent) may explain in part the lack of objective data for coronary insufficiency.

In the 6 patients whose arterial pressures were lowered but signs of cerebral ischemia did not develop, the cardiac index was reduced from a mean of 4.7 ± 1.3 L./min./M.² body surface to 3.6 ± .9 L./min./M.² body surface. A 42 ± 17 per cent reduction in mean arterial pressure was accompanied by no significant change in oxygen consumption, arteriovenous oxygen difference, or total peripheral resistance. The average reduction in cardiac work in this group was 50 ± 22 per cent.

Combined Cardiac Output (RISA) and Cerebral Blood Flow Determinations. All of these patients manifested signs of cerebral ischemia. The results of the combined cardiac output and cerebral blood flow determinations are presented in table 1. When the mean arterial pressure was reduced from an average of 162 ± 10 mm. Hg to an average of 78.3 ± 24.1 mm. Hg (an average reduction of 45 ± 7.5 per cent) the cardiac index fell from a mean of 2.7 ± .6 L./min. to an average of 1.4 ± .3 L./min. and the cerebral blood flow fell from an average of 50.2 ± 9.6 ml./100 Gm. brain/min. to 30.8 ± 4.6 ml./100 Gm. brain/min. (an average reduction of 37 ± 8.8 per cent).

The fall in mean arterial pressure was associated with a reduction in the cerebral vascular resistance in all patients from an average of 3.2 ± 0.8 to 2.3 ± 0.8 mm. Hg/ml. of blood/min./100 Gm. brain (p = .3). No constant change was seen in the total peripheral resistance, however, for it was decreased in 6 patients and increased in 3 patients.

In the 40° head-up position an average of 15 ± 4.5 per cent of the cardiac output was diverted to the brain. During cerebral ischemia, despite a 46 per cent reduction of mean arterial pressure and a 48 per cent reduction in cardiac output, it was estimated that 19 ± 5.7 per cent of the cardiac output was diverted to the brain. The cardiac work was reduced more than 55 per cent in all patients with an average reduction of 77 per cent.

Although the mean circulation time did not change significantly, the “central blood volume” decreased by 3 to 64 per cent an average of 44 ± 17.5 per cent.

Without realization of the severe anemia present, patient W.H. was studied. The marked anemia (hematocrit 13) so altered the cardiac output and cerebral blood flow determinations that, although interesting in itself, it was thought not representative of the other cases studied so these data are not included in the calculations of the averages. It is of interest (a) that syncope developed at a mean arterial pressure of 112 mm. Hg; (b) the control cardiac...
output was approximately 3 times normal 14.3 L/min.; and (c) the total cerebral blood flow was 2.5 times normal (125 ml./100 Gm. brain/min.). When collapse was induced in this patient, although the cardiac output was reduced 43 per cent, an actual increase in cerebral blood flow (154 ml./100 Gm. brain/min.) was noted.

**Discussion**

Objections to the validity of determinations made during cardiovascular collapse have centered around inability to produce a steady state. Admittedly, only general trends can be interpreted from the Fick cardiac outputs. When an unsteady state was seen, as in patients E.K. and H.M., the data on cardiac output were meaningless and were, therefore, not used.

In the calculation of the cardiac output by the indicator dilution method using the Hamilton technic, all that is necessary is a constant flow of blood from the heart to the lungs during the collection period. If this flow is not constant, it would be reflected by distortion of the down slope of the isotope curve. When such distortion was found in curves, the data were not used. It is noteworthy that, despite different patients and the utilization of different methods, the two groups of the cardiac output data are fairly similar.

Reports of cardiac output determinations by Stead and Ebert,1 Ellis and Haynes,2 Hickam3 and more recently by Weissler4 have shown variable changes in the cardiac output in postural hypotension. It seems possible that if these investigators had permitted their subjects to be tilted longer, i.e., until the compensatory vasoconstrictor mechanisms "were broken through," a much greater reduction in cardiac output might have been witnessed. In this regard the youth and vigor of the subject used (young medical students) by Weissler, and the fact that experimental studies in some of these patients were performed in the presyncopeal state may account for the differences between their data and those here reported.

During the cerebral blood flow determinations an attempt was made to maintain a steady state at least during the first 2 min. of

**Table 1.**—Combined Cardiac Output (RISA) and Cerebral Blood Flow Studies, Changes in Cardiac Index, Mean Arterial Pressure and Cerebral Blood Flow During Head-up Tilt Before and After Hexamethonium*

<table>
<thead>
<tr>
<th>Subject, sex, age and comment</th>
<th>Cardiac index L./M.Vmin.</th>
<th>CBF</th>
<th>CVR</th>
<th>MAP</th>
<th>Per cent CO to brain</th>
<th>MCT sec</th>
<th>CBV ml.</th>
</tr>
</thead>
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<tr>
<td></td>
<td>C E</td>
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<td>C E</td>
<td>C E</td>
</tr>
<tr>
<td>J.B.: M, 53; Postural hypotension</td>
<td>3.4 1.5</td>
<td>39.3 26.3</td>
<td>2.2 1.3</td>
<td>85 34</td>
<td>9 14</td>
<td>32.5 26.7</td>
<td>3178 1148</td>
</tr>
<tr>
<td>E.E.: F, 56; HCVD</td>
<td>2.8 1.6</td>
<td>56.8 34.7</td>
<td>2.9 2.6</td>
<td>163 92</td>
<td>14 15</td>
<td>31.5 35.8</td>
<td>2857 1847</td>
</tr>
<tr>
<td>M.J.: F, 46; HCVD</td>
<td>1.7 1.0</td>
<td>52.8 32.6</td>
<td>3.1 2.6</td>
<td>165 86</td>
<td>22 23</td>
<td>25.5 41.0</td>
<td>2323 1235</td>
</tr>
<tr>
<td>R.M.: M, 59; HCVD</td>
<td>3.3 1.5</td>
<td>60.2 35.0</td>
<td>2.8 2.0</td>
<td>170 80</td>
<td>13 16</td>
<td>32.5 40.0</td>
<td>3500 1926</td>
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<tr>
<td>D.M.: F, 44; HCVD</td>
<td>3.0 1.6</td>
<td>43.0 25.3</td>
<td>4.0 3.6</td>
<td>173 76</td>
<td>11 12</td>
<td>33.2 36.0</td>
<td>2831 1709</td>
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<tr>
<td>C.R.: M, 25; HVD</td>
<td>2.5 0.9</td>
<td>64.5 54.0</td>
<td>2.9 2.1</td>
<td>155 100</td>
<td>19 29</td>
<td>33.5 35.9</td>
<td>2650 944</td>
</tr>
<tr>
<td>W.T.: M, 59; HCVD</td>
<td>2.2 1.2</td>
<td>41.1 23.0</td>
<td>4.2 3.4</td>
<td>172 78</td>
<td>15 16</td>
<td>46.0 40.0</td>
<td>2790 1293</td>
</tr>
<tr>
<td>M.U.: F, 50; HCVD†</td>
<td>2.2 1.5</td>
<td>55.1 32.4</td>
<td>2.7 1.9</td>
<td>149 100</td>
<td>19 26</td>
<td>30.0 42.7</td>
<td>2025 1064</td>
</tr>
<tr>
<td>Mean</td>
<td>2.7 1.4</td>
<td>50.2 39.8</td>
<td>3.2 2.3</td>
<td>162 87.3</td>
<td>15 19</td>
<td>30.4 31.5</td>
<td>2971 1641</td>
</tr>
<tr>
<td>Standard deviation</td>
<td>±0.6±0.3±6.4±6.5±0.8±0.8</td>
<td>±10±24.1±4.5±5.7±2.9±3.3</td>
<td>±270±42.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>W.H.: M, 22; G-nephritis</td>
<td>6.7 3.8</td>
<td>125.7 135.8</td>
<td>1.2 0.7</td>
<td>146 112</td>
<td>12.4 26.2</td>
<td>1992 3456</td>
<td></td>
</tr>
</tbody>
</table>

* In CBF signifies cerebral blood flow in ml./min./100 Gm. of brain; CVR, cerebral vascular resistance in mm. Hg/ml. blood/min./100 Gm. of brain; CO signifies cardiac output; MCT, mean circulation time; and CBV, central blood volume; HCVD, hypertensive cardiovascular disease; HVD, hypertensive vascular disease.

† Flow with legs wrapped.
the collection period. Flow was probably changing during the measurement, but for purposes of calculation, it was assumed that any change (if it existed) was at an approximately constant rate over a 10 min. period and were assumed to represent the average constant for that period. The close agreement of the cerebral blood flow data with the data reported previously from this laboratory would seem to lend support to the reliability of the method even during cerebral ischemia.

Since, at the time of the development of signs of cerebral ischemia the mean arterial pressure varied between 34 and 100 mm. Hg there appeared to be no critical level of arterial pressure at which cerebral ischemia occurred. Similarly no consistent relationship was evident between the per cent reduction of mean arterial pressure and the per cent fall in cardiac output nor between the per cent reduction of mean arterial pressure and the decrease in cerebral blood flow. The average level of cerebral blood flow during cerebral ischemia (30.8 ± 4.6 ml./100 Gm. brain/min. was quite similar to that reported for this state from this laboratory previously (31.5 ± 1.2 ml./100 Gm. brain/min.) It would seem that in contrast to the wide variation in arterial pressure, a fairly critical level of cerebral blood flow exists for the maintenance of consciousness. This level has a mean value close to 31 ml./100 Gm. brain/min.

The decrease in cerebral vascular resistance accompanying cerebral ischemia was greater than the decrease in peripheral vascular resistance. Such a decrease in the cerebral vascular resistance however, was not sufficient to compensate for the lack of blood supply delivered to the brain from the heart. The reduced cerebral blood flow during cerebral ischemia, therefore, would seem to be a direct consequence of the reduced cardiac output.

When the total brain blood flow was calculated, 15 per cent of the cardiac output was diverted to the brain in the 40° head-up position. This value agrees well with the data of Stead and Warren. During cerebral ischemia despite a 47 per cent reduction in cardiac output, 19 per cent of the cardiac output was diverted to the brain. Although this increase is not significant statistically, it is of interest that despite the marked absolute reductions of cardiac output and mean arterial pressure the per cent cerebral component of the cardiac output was maintained. Thus, the development of cerebral ischemia was not accompanied by any shunting of cardiac output away from the brain; rather the cerebrovascular bed shared equally in the reduction of the total body blood flow.

These data suggest that the initial change in hexamethonium induced cerebral ischemia is a reduction of venous return. This probably is secondary to a failure of compensatory vasoconstrictor reflexes resulting in either a redistribution of blood volume or "peripheral pooling." The catheterization data during cerebral ischemia reported herein have shown a marked decrease in right heart pressures and Fick cardiac outputs. These data, plus the consistent decrease in central blood volume would imply, therefore, that the blockade of vasoconstrictor impulses causes failure of venous return which in turn produces a decrease in right ventricular filling pressure and a decrease in cardiac output. The fact that the total peripheral resistance showed no significant change in collapse further supports this interpretation. These latter studies are in agreement with those of Fries.

**Summary**

When signs of cerebral ischemia were induced by the administration of hexamethonium and/or by head-up tilting, it was found that:

1. The cardiac output (Fick and RISA) was significantly reduced in all patients; those patients who developed signs of cerebral insufficiency exhibited a greater reduction in cardiac output than those whose state of consciousness was not altered.
2. Although the level of arterial pressure during cerebral ischemia varied between 34 to 100 mm. Hg, the level of cerebral blood flow at this time was reduced to 30.8 ± 4.6 ml./100 Gm. brain/min.
3. Despite a reduction in cardiac output averaging 47 per cent, approximately the same percentage of its output was diverted to the brain during cerebral ischemia.
4. Evidence is presented which indicates that the cause of cerebral ischemia in these experiments resulted from failure of the cardiac output.

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SUMMARIO IN INTERLINGUA

Quando signos de ischemia cerebral esseva inducite per le administration de hexamethonium e/o postura inclinate con le capite in alto, le sequente factos esseva constatate:

1. Le rendimento cardiac (Fick e RISA) esseva significativemente reducite in omne le patientes. Le patientes qui disveloppava signos de insufficicntia cerebral exhibiva un plus grande reduction del rendimento cardiac que le patientes sin alteration del stato de conscientia.

2. Ben que le nivello del pression arterial durante le ischemia cerebral variava inter 34 e 100 mm Hg, le nivello del fluxo cerebral de sanguine a iste tempore esseva reducite a 30,8 ± 4,6 ml/100 g de cerebro/min.

3. In despecto de un rendimento cardiac reducito per le valor medie de 47 pro cento, approximativemente le mesme procentage del sanguine esseva divertite al cerebro durante ischemia cerebral.

Es presentate datos que indica que le causa del ischemia cerebral in iste experimentos esseva le disfallimento del rendimento cardiac.

REFERENCES


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