THE EFFECT ON CEREBRAL CIRCULATION AND METABOLISM IN MAN OF ACUTE REDUCTION IN BLOOD PRESSURE BY MEANS OF INTRAVENOUS HEXAMETHONIUM BROMIDE AND HEAD-UP TILT •†‡

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The intentional reduction in arterial blood pressure during operation as a method of controlling blood loss has received wide clinical application (1–4). This has occurred in spite of the lack of objective evidence to verify the safety of induced hypotension (1). With any maintained acute reduction in mean arterial blood pressure, the blood flow to certain critical organs such as the brain, heart, liver and kidneys assumes great importance. Since cerebral complications such as thrombosis and anoxia have been reported with the use of hexamethonium-induced hypotension (5), and since the study of hypotension itself, whatever its mode of production, has physiological significance, it was thought that investigation of the effects of hypotension produced by hexamethonium and head-up tilt on cerebral hemodynamics in the human being would be of interest.

Methods

Ten hospitalized patients, without obvious cerebral symptoms, were chosen at random. Their ages ranged from 26 to 61 years. A control cerebral blood flow (C) was determined by means of the nitrous oxide method of Kety and Schmidt (6). Following this initial determination, divided doses of hexamethonium bromide were injected intravenously at a rapid rate, the total dose ranging from 50 to 225 mg., depending upon the blood pressure response obtained. Large doses of hexamethonium were employed because a maximal reduction in arterial blood pressure was desired. In 5 of the patients, the blood pressure did not fall sufficiently in spite of repeated injections of the drug and therefore the head of the table was elevated up to 15 degrees

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until a significant reduction of blood pressure was obtained. With
the blood pressure maintained and stabilized at this hypotensive level,
a second cerebral blood flow (E) was determined at least twenty
minutes after the first flow. The completeness of the block of the
sympathetic nervous system produced by the hexamethonium was
determined in each patient by the absence of the overshoot phase of
the Valsalva maneuver as advocated by various investigators (7, 8).

Blood pressure and pulse rates were recorded directly from the
femoral artery by means of a strain gauge manometer recording
through a Sanborn Polyviso galvanometer. Respiratory rates were
recorded before and during each study. Venous pressure was meas-
ured by a spinal fluid manometer. Cerebral oxygen consumption
(CMR O₂), cerebrovascular resistance (CVR) and cerebral respira-
tory quotients (RQ) were calculated as previously described (6).

Blood gas analyses were made by the manometric method of Van
Slyke and Neill (9). The hydrogen ion concentration of the blood was
measured anaerobically at room temperature by means of a glass elec-
trode and a potentiometer and was corrected to 37 C. according to the
factors of Rosenthal (10). Values for carbon dioxide tension were
calculated by the nomograms of Van Slyke and Sendroy (11). Oxygen
capacity was determined by the tenometer method of Van Slyke and
Neill (9).

**Results**

The data obtained in this study are presented in tables 1 and 2.
Following the intravenous injection of hexamethonium bromide, there
was a significant fall in perfusion pressure (arterial blood pressure
minus internal jugular pressure) from a mean of 117 to 62 mm. of
mercury (p < 0.001). This represents a reduction of 44 per cent in
the mean arterial blood pressure (127 to 71 mm. of mercury). Pulse
and respiratory rates were unchanged. The decrease in blood pressure
was accompanied by a reduction in cerebrovascular resistance from
2.4 to 1.3 mm. of mercury per cubic centimeter per 100 Gm. per minute
(p < 0.001). This lowering of cerebrovascular resistance maintained
the cerebral blood flow (53 to 47 cc. per 100 gm. per minute — p < 0.3).
There was a significant fall in the arterial oxygen content from 15.8 to
14.7 volumes per cent (p < 0.01). Similarly, a significant decrease in
internal jugular oxygen content was obtained (9.5 to 7.4 volumes per
cent — p < 0.001). Cerebral metabolism was not affected by the drug
(3.3 to 3.4 cc. of oxygen per 100 gm. per minute — p < 0.6). There
were no significant changes in the arteriovenous oxygen difference, the
arterial and jugular carbon dioxide tension (pCO₂) or hydrogen ion
concentration. The carbon dioxide content of the internal jugular
rose from 55.4 to 57.3 volumes per cent (p < 0.01) but the arterial
content did not change.

Stabilization of the systemic blood pressure at hypotensive levels
<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Total I.V. dose (mg)</th>
<th>CO₂ content (vol %)</th>
<th>A-V difference</th>
<th>O₂ content (vol %)</th>
<th>A-V difference</th>
<th>O₂ capacity (ml/dl)</th>
<th>pH</th>
<th>Pulse rate (per min)</th>
<th>Resp. rate (per min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F. H.</td>
<td>39</td>
<td>F</td>
<td>125</td>
<td>47.5</td>
<td>52.9</td>
<td>5.4</td>
<td>15.6</td>
<td>15.0</td>
<td>0.6</td>
<td>6.3</td>
<td>5.1</td>
</tr>
<tr>
<td>L. M.</td>
<td>39</td>
<td>F</td>
<td>97</td>
<td>48.4</td>
<td>52.8</td>
<td>4.4</td>
<td>15.6</td>
<td>15.1</td>
<td>0.3</td>
<td>6.3</td>
<td>5.5</td>
</tr>
<tr>
<td>D. H.</td>
<td>42</td>
<td>F</td>
<td>223</td>
<td>42.3</td>
<td>60.5</td>
<td>18.2</td>
<td>7.3</td>
<td>7.8</td>
<td>4.4</td>
<td>7.3</td>
<td>7.8</td>
</tr>
<tr>
<td>R. R.</td>
<td>41</td>
<td>F</td>
<td>50</td>
<td>51.8</td>
<td>51.3</td>
<td>0.5</td>
<td>15.6</td>
<td>15.1</td>
<td>0.5</td>
<td>6.3</td>
<td>5.5</td>
</tr>
<tr>
<td>A. K.</td>
<td>80</td>
<td>F</td>
<td>150</td>
<td>52.9</td>
<td>51.8</td>
<td>10.0</td>
<td>6.1</td>
<td>7.2</td>
<td>4.4</td>
<td>7.3</td>
<td>7.3</td>
</tr>
<tr>
<td>E. C.</td>
<td>42</td>
<td>F</td>
<td>75</td>
<td>54.0</td>
<td>54.9</td>
<td>0.9</td>
<td>15.7</td>
<td>15.3</td>
<td>0.3</td>
<td>6.2</td>
<td>5.4</td>
</tr>
<tr>
<td>M. W.</td>
<td>43</td>
<td>F</td>
<td>100</td>
<td>55.2</td>
<td>60.3</td>
<td>5.1</td>
<td>15.6</td>
<td>15.5</td>
<td>0.8</td>
<td>6.1</td>
<td>7.2</td>
</tr>
<tr>
<td>R. R.</td>
<td>49</td>
<td>M</td>
<td>173</td>
<td>48.4</td>
<td>53.9</td>
<td>5.5</td>
<td>15.7</td>
<td>15.8</td>
<td>0.8</td>
<td>6.1</td>
<td>7.2</td>
</tr>
<tr>
<td>J. D.</td>
<td>33</td>
<td>M</td>
<td>150</td>
<td>54.7</td>
<td>52.7</td>
<td>10.0</td>
<td>15.7</td>
<td>15.3</td>
<td>0.3</td>
<td>6.1</td>
<td>7.2</td>
</tr>
<tr>
<td>E. B.</td>
<td>43</td>
<td>F</td>
<td>75</td>
<td>42.0</td>
<td>55.1</td>
<td>13.1</td>
<td>15.7</td>
<td>15.3</td>
<td>0.3</td>
<td>6.1</td>
<td>7.2</td>
</tr>
<tr>
<td>Mean</td>
<td>45</td>
<td></td>
<td>121</td>
<td>49.6</td>
<td>50.0</td>
<td>0.4</td>
<td>15.0</td>
<td>15.0</td>
<td>0.0</td>
<td>6.0</td>
<td>7.0</td>
</tr>
</tbody>
</table>

* Patients listed up to 11° head-up tilt in addition to Hemocarson.
+ O₂ capacity performed on control samples only.
A = arterial; I.V. = intravenous; P = control; E = during hemocarson.
$\uparrow$ Significant or statistically significant change (p < 0.01).
**Acute Reduction in Blood Pressure**

Table II

<table>
<thead>
<tr>
<th>Patient</th>
<th>MABP-VP mm Hg</th>
<th>CBF cc/100 Gm/min.</th>
<th>CVR mm Hg</th>
<th>CMR O₂ cc/100 Gm/min.</th>
<th>R.Q.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C</td>
<td>E</td>
<td>C</td>
<td>E</td>
<td>C</td>
</tr>
<tr>
<td>F. B.</td>
<td>98</td>
<td>59</td>
<td>47</td>
<td>49</td>
<td>2.1</td>
</tr>
<tr>
<td>L. M.</td>
<td>85</td>
<td>66</td>
<td>94</td>
<td>67</td>
<td>0.9</td>
</tr>
<tr>
<td>D. N.</td>
<td>139</td>
<td>81</td>
<td>51</td>
<td>54</td>
<td>2.7</td>
</tr>
<tr>
<td>H. R.</td>
<td>124</td>
<td>31</td>
<td>41</td>
<td>37</td>
<td>3.0</td>
</tr>
<tr>
<td>A. S.</td>
<td>99</td>
<td>44</td>
<td>46</td>
<td>49</td>
<td>2.2</td>
</tr>
<tr>
<td>E. C.</td>
<td>136</td>
<td>80</td>
<td>45</td>
<td>48</td>
<td>3.0</td>
</tr>
<tr>
<td>M. Y.</td>
<td>141</td>
<td>53</td>
<td>84</td>
<td>50</td>
<td>1.7</td>
</tr>
<tr>
<td>N. R.</td>
<td>138</td>
<td>88</td>
<td>36</td>
<td>43</td>
<td>3.8</td>
</tr>
<tr>
<td>J. D.</td>
<td>79</td>
<td>44</td>
<td>48</td>
<td>43</td>
<td>1.7</td>
</tr>
<tr>
<td>T. B.</td>
<td>128</td>
<td>76</td>
<td>38</td>
<td>33</td>
<td>3.4</td>
</tr>
</tbody>
</table>

Mean 117 62\* 53 47 2.4 1.5\* 3.3 3.4 0.94 0.99

S. E. ±7.6 ±6.0 ±6.2 ±3.0 ±0.3 ±0.2 ±0.37 ±0.29 ±0.04 ±0.03

P. < 0.001 <0.3>0.2 < 0.001 <0.6>0.5 <0.7>0.6

C = control  E = during hypotension

\* Signifies a statistically significant change (p < 0.01)

occurred following the injection of hexamethonium and change in posture. Additional doses of hexamethonium failed to produce further reductions in blood pressure. This is in accordance with the experience and reports of other investigators (1, 2).

**Discussion**

This study was undertaken to determine whether or not the clinical method of inducing hypotension by hexamethonium, combined with head-up tilt, in a group of patients impaired the average cerebral circulation and metabolism. In an attempt to simulate as nearly as possible the clinical application of hypotension during operation, patients were studied at random without regard for age, previous cardiovascular status or blood pressure levels. An average reduction of 44 per cent in mean arterial blood pressure failed to produce a significant change in cerebral blood flow or metabolism. Maintenance of cerebral blood flow was accomplished by a 46 per cent reduction in cerebrovascular resistance. These results demonstrate that the
minimal blood pressure necessary to maintenance of cerebral blood flow was not exceeded.

The influence of other hypotensive agents such as histamine (12), dihydroergocornine (13), hydrazinophthalazine (14), tetraethyl ammonium bromide (15), and protoveratrine (16) upon cerebral hemodynamics and metabolism has been studied. The results of these investigations demonstrate that reductions in mean arterial blood pressure ranging from 24 to 35 per cent did not produce a significant change in cerebral circulation. The maintenance of cerebral blood flow in spite of a significant reduction in mean arterial blood pressure occurred because of a significant relaxation of cerebral vascular tone ranging from 25 to 31 per cent.

Others have studied the influence of hypotension induced by hexamethonium on the cerebral circulation and metabolism of man (17, 18). The results obtained by Crumpton (18) are essentially the same as those included in this study and demonstrated a 30 per cent decrease in cerebrovascular resistance following a 29 per cent reduction in mean arterial blood pressure without significant change in cerebral blood flow even when greater reductions in mean arterial blood pressure were produced. The 44 per cent reduction in mean arterial blood pressure reported in this investigation is frequently encountered during the clinical use of induced hypotension. The results obtained by Morris et al. (17) using hexamethonium differ from those reported by Crumpton (18) and those contained in this study. Morris et al. demonstrated a decrease in cerebral blood flow of 30 per cent following a reduction in mean arterial blood pressure of 39 per cent. The inability to maintain the cerebral circulation was attributed to an inadequate decrease (11 per cent) in cerebrovascular resistance. The lack of statistical analysis of Morris's data, however, prevents the formulation of any definite conclusions concerning the significance of the changes noted.

From the results reported by most investigators employing hypotension, it might appear that relaxation of cerebrovascular tone is a nonspecific response to the lower blood pressure by any hypotensive means rather than a specific response to the hypotensive agent itself. This has been previously suggested by Shenkin et al. (19).

The ability of the cerebral vasculature to dilate during periods of hypotension induced by various agents, with a maintenance of cerebral blood flow, demonstrates the complete compensation of which the cerebral vessels are capable. From the results of the present study it is not possible to predict at which level of mean arterial blood pressure this compensation fails. Whether or not cerebral vascular dilatation continues to parallel progressive acute reductions in systemic blood pressure to extremely low levels is still open to question. From the results of case 4 in which a 75 per cent reduction in mean perfusion pressure from 124 to 31 mm. of mercury was accompanied by a 73 per
cent reduction in cerebrovascular resistance without significant change in cerebral blood flow, it might be concluded that such a parallelism does exist at extremely low levels. The results obtained by Kety and his group (20), however, differ from those presented here. Kety demonstrated that when the mean arterial blood pressure of a group of hypertensive patients was reduced 26 per cent by the use of differential spinal anesthesia, a significant reduction in cerebral blood flow resulted. The failure in the maintenance of the cerebral circulation was attributed to an inadequate degree of cerebral vascular dilatation (16 per cent reduction in cerebrovascular resistance). Hypotension induced by differential spinal block may not activate compensatory mechanisms to the same degree as drug-induced hypotension. Two other factors may account for the discrepancy. A significant decrease of carbon dioxide tension (pCO₂) followed the use of differential spinal block. Although it was recognized that this factor may have contributed to the restriction of cerebrovascular relaxation, its importance was considered minimal on the basis of partial correlation analysis. Second, since all of the patients in Kety’s series were being evaluated as possible candidates for thoracolumbar sympathectomy, it is probable that they represented patients who, as a group, had failed to respond beneficially to the usual medical measures employed for the treatment of hypertensive cardiovascular disease. It is possible that these patients possessed a more advanced degree of sclerotic change in their vessels than would be present in normotensive patients or in hypertensive patients successfully responding to medical therapy. Since the ability of the cerebral vasculature to dilate is dependent upon the degree of organic change and fixation present in the vessels (10), the inadequate compensation as vasodilatation reported by Kety might be logically explained.

Various mechanisms might be postulated to explain the adjustments in cerebrovascular resistance which accompany alterations, in mean arterial blood pressure. The existence of an intrinsic mechanism, perhaps mediated through the pressor receptors of the carotid sinus, has been suggested previously (19, 22). Relaxation of cerebrovascular tone following the use of any hypotensive agent, such as hexamethonium, could be mediated reflexly through pressor receptors, situated in the walls of the cerebral vessels, sensitive to changes in intraluminal pressure. Although experimental evidence has failed to substantiate the existence of a tonically effective vasoconstricting reflex to the cerebral vessels (23), the ganglionic blocking effect of hexamethonium could interrupt the sympathetic efferent vasoconstrictor pathways and produce relaxation of cerebrovascular tone. Whether hexamethonium interrupts cerebral sympathetic impulses has not been established. The absence of the overshoot following the Valsalva maneuver, however, has been suggested as evidence of abolition of generalized sympathetic vasoconstrictor activity, and was
applied to each patient in this series. A direct dilating effect of hexamethonium on the cerebral blood vessels might explain the decreased vascular resistance associated with its use. Although unlikely, such an effect could explain the more complete vasodilatation obtained by hexamethonium compared with that of differential spinal anesthesia.

The absence of symptoms such as nausea, vomiting, weakness and syncope in this study during the hypotensive period, previously noted to be associated with cerebral anoxia on the basis of an inadequate cerebral circulation (20), was to be expected since cerebral circulation was not significantly reduced. In 9 out of 10 patients, the onset of hypotension produced a quieting and sedative effect without a measurable change in cerebral metabolism. This effect was especially marked in those patients who were most apprehensive at the onset of the study. This observation is of interest for it has frequently been noted clinically that, during periods of acute hypotension, patients receiving general anesthesia require less anesthesia to maintain a constant level of narcosis.

The significant decrease in arterial and internal jugular oxygen content without a significant change in cerebral metabolism probably reflects an increase in total blood volume. This hemodilution has been demonstrated by direct determinations of plasma volume (17). The exact mechanism responsible for the increase in plasma volume is not known. It may be associated with a decreased filtration pressure in the capillaries, with a net retention of fluid in the vascular bed. The increase in plasma volume is a rapidly occurring compensation requiring as little as thirty minutes for its development as evidence of it was seen in every case studied. The average lapse of time between the injection of the hexamethonium and the collection of the blood samples was thirty minutes.

Although this study demonstrates the completeness with which cerebrovascular tone may adjust to an acute decrease in mean arterial blood pressure of 44 per cent, it does not lend itself to generalizations prognosticating comparable compensation in every patient, especially those receiving general anesthesia. Additional factors may influence the adequacy of cerebral compensation and must be evaluated. The duration of the hypotension and the degree of arteriosclerosis and inelasticity present in the cerebral vessels are of primary significance. The cerebral circulatory effects of premedicating drugs, anesthetic agents, anoxia and alterations in carbon dioxide tension and hydrogen ion concentration, which occur during general anesthesia, could influence the development of adequate compensation. Their significance has not been fully determined. The safety of deliberately induced hypotension, as it affects the brain, depends upon the maintenance of cerebral nutrition during the period of reduced blood pressure. Although clinical practice has demonstrated how well young adults
tolerate hypotension, this has not been the experience with the aged, sclerotic patient. Even though Bessman et al. (15) have demonstrated that in some aged patients with advanced arteriosclerosis an adequate cerebral circulation can be maintained when mean arterial blood pressure is reduced 35 per cent, it is dangerous to conclude that all arteriosclerotic patients with cerebral insufficiency are capable of a similar degree of compensation.

SUMMARY

Studies are reported of arterial and internal jugular blood gases, cerebral blood flow, oxygen consumption and vascular resistance in 10 patients before and after systemic hypotension was produced by intravenous injections of hexamethonium bromide and a 15 degree head-up tilt.

Cerebral blood flow and oxygen consumption did not change significantly with acute reductions in mean arterial blood pressure. The cerebral circulation was maintained by a significant and adequate reduction in cerebrovascular resistance.

The decrease in arterial and internal jugular oxygen content without an increase in cerebral metabolism probably reflects hemodilution.

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