PHYSIOLOGIC ALTERATIONS ASSOCIATED WITH HEXAMETHONIUM-INDUCED HYPOTENSION • †

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INTRODUCTION

Since 1946, when Gardner (1) first employed arteriotomy to reduce the blood pressure in a surgical patient, the principle of induced hypotension has evoked increasing interest among surgeons and anesthesiologists. A recent survey of British clinicians ascertained that more than 21,000 such procedures had been carried out by 1952 (2).

The papers of Gardner (3), Hale (4), Gillies (5) and Enderby (6, 7) have elucidated fully the technical details involved in the various methods devised to attain a reduction of surgical hemorrhage. The indications for employment of the hypotensive method likewise have been examined critically.

Although credited with facilitating surgical procedures and reducing the need for extensive blood replacement, the technique has been found to carry considerable risk, as evidenced by numerous reports of serious sequelae. With the exception of several studies upon isolated bodily functions, no comprehensive assay of the alterations in physiologic processes occurring in the anesthetized human subject under the influence of induced hypotension has appeared.

It is the purpose of this paper to report the results of such a study and to interpret the findings as they relate to the clinical application of hypotensive anesthesia.

SUBJECTS, MATERIALS AND METHODS

Studies were carried out on 14 patients either before or during surgical intervention. There were 8 males and 6 females, and the ages ranged from 7 to 67 years.

Investigations were conducted in the recovery room on 5 patients before operation, because certain data were difficult to obtain during a surgical procedure. The other 9 patients were studied throughout the operative period.

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All patients were premedicated with morphine or codeine and atropine or hyoscine prior to anesthesia. Anesthesia was induced with a pentothal-curare mixture (pentothal 25 mg. and d-tubocurarine 0.75 mg. per cubic centimeter of solution) (8). The patients were intubated and then connected to a semiclosed circle absorption system. Anesthesia was maintained by additional increments of pentothal-curare mixture and a flow rate of 1,000 cc. each of nitrous oxide and oxygen per minute. Respiration was controlled and augmented by manual bag compression throughout the entire anesthetic period.

Hypotension was induced with hexamethonium (C6) which was given intravenously in doses of 25 mg. of the ion. Following the induction of hypotension in the operative cases, the nitrous oxide was discontinued so that 100 per cent oxygen could be supplied. The cases studied preoperatively were left on the original mixture of nitrous oxide and oxygen.

Arterial pressure studies were recorded by means of a Statham strain gauge (model P23A) attached to a Sanborn polyviso recorder. A 15 gauge needle in the brachial artery was connected directly to the strain gauge. The accuracy of this system, with a frequency response of 100 per cent to 17 c.p.s., has been found to be more than adequate for the recording of intra-arterial blood pressures (9).

Venous pressure studies consisted of recording relative changes in the external jugular or right atrial pressures. A catheter was inserted into the external jugular vein and the tip was either directed toward the heart or advanced into the right atrium. The catheter was connected to a Statham strain gauge (Model P23B) and pressures were recorded on a Sanborn polyviso recorder.

Circulation times were determined according to the method of Knotson et al. (10). The aid of the oximeter is employed with this method. Methylene blue (0.8 mg. per kilogram) is injected rapidly into the antecubital vein. The time required for the dye to reach the ear, as indicated by a fall in the oximeter reading, is referred to as the arm to ear circulation time. The normal arm to ear circulation time by this method is 13.4 seconds. Maximal dye concentration appears at the ear in 28.6 seconds.

Arteriovenous oxygen difference of the brain was determined in 4 cases in the following manner: with the brain exposed, heparinized samples were collected under anaerobic conditions from the middle cerebral artery and the superior sagittal sinus before, during and following hexamethonium-induced hypotension. Total blood oxygen contents were determined by the manometric method of Van Slyke and Neill.

Relative arterial oxygen saturations of the ear were measured by means of a model 17A Coleman anoxia photometer equipped with an Esterline-Angus recorder. This instrument measures arterial oxygen saturation with an accuracy of 3 to 5 per cent at the top of its range.
and within 8 per cent at the bottom. The time required for a full scale sweep of the recorder lies between five and six seconds.

Electrocardiograms were recorded on a single channel direct writing Cambridge electrocardiograph equipped with a relay-controlled remote marker, thereby furnishing a signal mark on the pressure tracing at the time each electrocardiogram was taken.

Electroencephalograms were recorded by a Grass model 3C console electroencephalograph, equipped with an ink writing recorder. The kymograph speed was 3 cm. per second and the machine was calibrated at 100 microvolts per centimeter.

Findings Related to the Primary Effects of Hexamethonium

I. Effect of Hexamethonium on the Arterial Blood Pressure

The average onset of action following a single intravenous injection of hexamethonium was twenty-nine seconds. The peak of action was attained within three to five minutes (fig. 1). The duration of hypoten-

![Graph](image-url)

Fig. 1. The upper tracing shows the effect of a single 25 mg. dose of hexamethonium on the arterial and right atrial pressures. The kymographic speed was changed from 0.25 mm. per second to 1 mm. per second about one minute after the injection of hexamethonium. The time of injection is indicated by a signal mark on the time line. The lower tracing shows the effect of a 50 mg. dose of hexamethonium. Timing pips are at one second intervals; arterial pressures are recorded in millimeters of mercury and right atrial pressures in centimeters of water.
sion obtained by a 25 mg. dose varied from fifteen to fifty minutes. A single intravenous dose of 25 mg. produced an average fall in systolic pressure of 48.8 per cent and a fall in diastolic pressure of 44.2 per cent.

Several factors directly influenced the level of hypotension attained, namely, the dose of the drug, the depth of anesthesia, the position of the patient, the level of the blood pressure before administration of hexamethonium and the presence of normovolemic or oligemic shock.

A. Dosage. Usually an initial dose of 25 mg. was employed and additional increments of 25 mg. were injected intravenously as indicated. The total dosage varied from 25 mg. to 225 mg. In some cases (graph 8) precipitous falls in pressure to dangerously low levels occurred with single 25 mg. doses. On the other hand, one patient (graph 5) received a total dose of 225 mg. of hexamethonium, yet failed to attain a satisfactory hypotensive level. Maximal pressure falls occurred usually with the first 25 mg. dose of hexamethonium (graphs 6 and 7). Subsequent doses failed to produce the low level attained by the initial dose. There was a tendency for the blood pressure to remain at a slightly higher level than that reached following the initial dose (graphs 1, 5, 6, 7, 9, 11 and 12).

**Graph 1.** Arterial pressure graph, Case 1. X represents 25 mg. of hexamethonium, V, 4 mg. of vasoxy®.
Early in the series it became evident that there was a point beyond which the pressure could not be reduced regardless of the dose employed. In general, this level was attained with 25 to 50 mg., and additional dosage only served to prolong the effect.

B. Depth of Anesthesia. An adequate plane of anesthesia appeared to complement the hexamethonium in maintaining hypotension. The fact that all of the patients were under anesthesia may account for the relatively large percentage falls in blood pressure accompanying a single 25 mg. dose of hexamethonium. Graph 7 illustrates a rising blood pressure despite administration of a second 25 mg. dose of this agent. At that time the anesthesia was very light as evidenced by the patient moving, straining and coughing on the endotracheal tube. When the anesthesia was deepened, the pressure again fell to a hypotensive level.

C. Position of the Patient. The majority of the patients undergoing surgery during hexamethonium-induced hypotension were in a
10 degree Fowler’s position before the administration of hexamethonium. For this reason, it was not possible to determine to what extent the postural pooling of blood in the lower extremities contributed to the over-all fall in pressure. Therefore, experimental studies were carried out on 6 anesthetized patients with hexamethonium-induced hypotension to determine the role posture played in producing a further pressure fall. Graph 13 depicts the effect of changing the patient’s position from supine to 10 degree and 15 degree Fowler’s position and then back to supine. Seven observations were made while tilting the

![Graph 3. Arterial pressure graph, Case 3. D represents the time at which cerebral decompression was accomplished; X, 25 mg. of hexamethonium; C, time at which cerebral cyanosis was detected; V, 4 mg. of vasoxylin.](image)

table from level to 10 degree Fowler’s position. This maneuver resulted in a further fall in systolic pressure, averaging 22.6 per cent, and in diastolic pressure, averaging 15.3 per cent. Five observations were made tilting the table from level to 15 degree Fowler’s position, revealing a further average fall of 39.7 per cent in systolic and 31.9 per cent in diastolic pressures.

D. State of Blood Pressure before Administration of Hexamethonium. Three patients (graphs 5, 9 and 11) could be classed as normotensives. In these subjects the average fall in systolic pressure was
36.2 per cent and in diastolic pressure 37 per cent. Six patients (graphs 1, 2, 4, 6, 7 and 12) were classed as hypertensives. In these, the average systolic fall was 46.4 per cent and diastolic fall 42.6 per cent. Six patients (graphs 1, 2, 3, 4, 8 and 10) had increased intracranial pressure before operation. This group underwent an average systolic drop of 48.9 per cent and diastolic drop of 47.6 per cent.

E. Normovolemic and Oligemic Shock. One patient (graph 3) was in severe normovolemic shock at the onset of the surgical procedure. Cerebral decompression restored the blood pressure, and hemorrhage started. Hexamethonium, 25 mg., produced a fall of 68.1 per cent in systolic pressure and a fall of 66.1 per cent in diastolic pressure.

Compensated oligemic shock at the time of administration of hexamethonium was present in another case and a fall of 61 per cent occurred in the systolic and 55.5 per cent in the diastolic pressures.

II. Effect of Hexamethonium on the Venous Pressure

The initial effect of Hexamethonium on the venous pressure varied. Some patients experienced a transitory fall (graphs 2 and 10), others
had an increase (graph 9) and still others, no change at all (graph 6). Figure 1 illustrates a transitory fall commencing twenty seconds after the injection of hexamethonium, reaching the lowest point within 1 minute and 15 seconds and returning to the initial level in 3 minutes. This variability in initial response was dependent principally upon the position of the subject at the onset of action of the drug. Fowler's position favored a fall in venous pressure while the level and Trendelenburg positions favored a rise.

GRAPH 5. Arterial pressure graph, Case 5. X represents 25 mg. hexamethonium; V, 2 mg. of vasoxy18.

Once the full effect of C6 was attained, a close parallelism between the venous and arterial pressures followed (graphs 6, 7 and 9). Alterations in the patients' positions, fluctuations of the anesthetic levels, subsequent doses of C6 and the administrations of pressor agents produced similar alterations in both venous and arterial pressure.

III. Effect of Hexamethonium on Certain Cardiorespiratory Reflexes

A. Positive Pressure Respiration and Valsalva's Maneuver. Ordinary intermittent positive pressure respiration has very little effect
upon the arterial pressure of patients under hexamethonium blockade. It may be noted in figure 2 that augmented respiration varies the systolic pressure about 5 mm. of mercury. The diastolic pressure shows even less variation. Apnea simply eliminates the respiratory waves in the arterial tracing.

When a constant positive intrapulmonary pressure of 8 cm. of water is applied to an apneic patient, there is practically no change in arterial pressure (fig. 3). However, application of a high intrapulmonary pressure (15 mm. of mercury) results in a marked decline in arterial pressure with complete disappearance of the pulse pressure (fig. 4). Release of the pressure results in a gradual return to the starting level without a tendency to overshoot (fig. 4).

B. Postural Changes. A complete absence of the vasopressor overshoot reflex was noted during the tilting experiments. Figure 5 and graph 13 illustrate the arterial pressure responses of patients when tilted from the supine to Fowler’s and back to supine positions. Again
it was obvious that there was no tendency of the arterial pressure to overshoot.

C. Hypoxia and Hypercarbia. Normal individuals and patients under moderate pentothal-curare anesthesia show a rise in arterial blood pressure when subjected to moderate hypoxia or hypercarbia. The question arose as to whether this pressure response would still obtain in the presence of a hexamethonium blockade.

![Graph 7](image)

**Graph 7.** Venous, arterial and oximeter graphs, Case 7. F represents Fowler's position; L, level; X, 25 mg. of hexamethonium; A, deepening of anesthesia; Val., application of high intrapulmonary pressure. Broken line on the oximeter graph indicates time when light source was shut off.

Figure 6 is representative of the effect of hypoxia on the blood pressure of a patient under the influence of hexamethonium. In this case, the oxygen tension was reduced to 80 mm. of mercury (10 volumes per cent) for a period of four minutes. During this time the arterial pressure gradually fell from 85 to 74 mm. systolic and from 65 to 57 mm. diastolic. After the fourth minute 100 per cent oxygen was administered and the pressure returned to the starting level.
Figure 7 shows the blood pressure response to hypercarbia in a patient who was given 10 per cent carbon dioxide (with the soda lime absorber off) for five minutes. Although the alveolar carbon dioxide attained a level of 18 to 20 per cent (as measured by means of the Nier mass gas spectrometer), no change in blood pressure occurred.

During the period of hypoxia, the heart rate increased from 94 to 104. Under the influence of hypercarbia, the heart rate fell from 110 to 92.

Graph 8. Venous and arterial pressure graphs, Case 8. S-S represents withdrawal of the arterial and venous blood samples for oxygen content; X, 25 mg. of hexamethionium; F, Fowler's position; W, 5 mg. of wyamine® sulfate; L, l-arterenol 4 micrograms; B, blood infusion started.

D. Altered Response to Peripherally Acting Vasopressors. The increased sensitivity to adrenergic agents of patients under hexamethionium blockade likens them to the sympathectomized subject. Graph 1 illustrates the exaggerated vasopressor response seen in ganglionic blockade. Methoxamine hydrochloride (vasoxyl®) 4 mg., was administered intravenously and within twenty seconds, a violent pressor response occurred; the pressure rose from 110 to 340 mm.
systolic and from 90 to 270 mm. diastolic. The reaction to vasopressors is so exaggerated that these agents should be diluted and administered in increments of about one fourth of the usual therapeutic dose until the desired level of pressure is achieved.

That the pressor effect of 1-arterenol, epinephrine and even methoxamine may subside, and the arterial pressure then revert to the hypotensive level, if the ganglionic blockade is still in effect, is illustrated in figure 8. In this case the pressure was varied from minute to minute by intermittent intravenous administration of 1-arterenol.

**DISCUSSION OF PRIMARY EFFECTS OF HEXAMETHONIUM**

Consideration of the site and mode of action of hexamethonium renders the foregoing findings readily understandable. Patan and Zaimis (11) demonstrated on cats that hexamethonium acts at the
GRAPH 10. Venous and arterial pressures, Case 10. X represents 25 mg. of hexamethonium; F, Fowler's position; W, 15 mg. of wyamine® sulfate; L, l-arterenol drip.

GRAPH 11. Arterial pressure graph, Case 11. X represents 25 mg. of hexamethonium; E, electrocardiogram taken; F, Fowler's position; L, level; CO₂, carbon dioxide accumulation; N, l-arterenol drip; V, 2 mg. of vasoxyl®. Numbers above the pressure graph indicate the arm to ear circulation times.
synapses of the preganglionic and postganglionic neurons and that the mechanism of action must be through an elevation of the response threshold of the postganglionic neuron to acetylcholine. Hexamethonium has its greatest effect upon the synapses of the autonomic nervous system. Therefore, a maximal effective dose will block completely all structures under autonomic nervous control. Not only is the nervous innervation of the heart and blood vessels interrupted, but in addition many of the reflex compensating mechanisms involved in circulatory homeostasis are abolished.

Graph 12. Arterial pressure graph. Case 12. X represents 25 mg. of hexamethonium; E, electrocardiogram recorded; F, Fowler's position; L, level; T, Trendelenburg; O, 100 per cent oxygen; Y, blood sample drawn for carbon dioxide analysis, proved to contain 8 volumes per cent; O—O (10 per cent), period during which the oxygen tension of the atmosphere was reduced to 10 per cent; C—C, carbon dioxide administration, alveolar concentration reached 18 per cent; A, 1-arterenol drip begun.

The arterial and venous pressure tracings clearly indicate that the anesthetized patient's response to hexamethonium is dramatic. Within less than a minute, the systemic circulation is converted from a high pressure system to a low pressure system. Low pressure systems are not considered harmful when they are the result of a decreased peripheral resistance (12). The complete sympathetic paralysis produced by hexamethonium dilates all the vessels under autonomic control, producing a markedly decreased peripheral resistance. Under these conditions it is presumed that tissue blood flow is increased. When the oxygen tension of the inhaled atmosphere is elevated, it

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would seem logical to assume that tissue oxygenation is adequate (13). This situation does not always obtain, however, since patients in the dilated vascular state have better tissue circulation in the dependent portions of their bodies than they do in the elevated portions. This was demonstrated clinically on several occasions. Hypotensive patients, undergoing neurosurgical procedures, were frequently placed in a 15 degree Fowler’s position. On several occasions severe cerebral cyanosis developed although the toenail beds remained pink. This constitutes striking evidence of unequal tissue blood flow in the various segments of the body. When vital organs are among the elevated port-

![Graph 13. Arterial pressure graphs illustrating the effect of 10 and 15 degree Fowler's position on the blood pressure. F represents Fowler's position; L, level.](image)

tions, it is imperative that an accurate knowledge of the intra-arterial pressure of the vessels supplying the organs be known. Enderby (6) recognized the danger of cerebral hypoxia and stressed keeping the head dependent.

Several factors contributed to the large reductions in arterial pressures encountered in this series. All of the patients were anesthetized with pentothal-curare anesthesia before hexamethonium was administered. There can be little doubt that the anesthesia potentiated the effect of hexamethonium. The continuous direct recordings of the intra-arterial pressures might account for the greater falls because of the increased accuracy of the direct method (14). The majority of
the patients were not normal; some were hypertensive; others had increased intracranial pressures; still others were in impending shock. All of these abnormal physiologic states rendered the patients more susceptible to hexamethonium.

Contrary to the findings of others (15–18), relatively normal patients in the supine position experienced large reductions in arterial pressure following the administration of hexamethonium. Pentothal-curare anesthesia may be the significant variable in this instance.

The maximal fall in arterial pressure was usually achieved with the initial dose, providing it was large enough. Immediately after the

![Graph showing effect of augmented respiration and apnea on arterial and right atrial pressures.](image)

**Fig. 2.** Effect of augmented respiration and apnea on the arterial and right atrial pressures. Note the drop in venous pressure with the disappearance of respiratory waves in the upper tracing. The arterial pressure tracing shows little change except for the disappearance of the respiratory waves during apnea. Arterial pressures are recorded in millimeters of mercury and right atrial pressures in centimeters of water.

initial drop, the pressure rose to a slightly higher level where it remained stabilized, even though additional hexamethonium was administered. This initial maximal fall is related to the suddenness of the change in circulatory dynamics. The acute peripheral vasodilatation and venodilatation allow blood to pool momentarily, with a resultant reduction in its return to the right side of the heart. Cardiac output will be markedly reduced at this point because of diminished cardiac filling. The circulatory system then accommodates to the
lowered pressures as arterial blood gradually pushes through the capillary beds, increasing the venous blood volume and pressure. As the venous pressure is restored, the volume of the blood entering the right heart increases and the cardiac output rises. Once the cardiac output becomes stabilized to the reduced peripheral resistance, additional hexamethonium will not alter the pressure. (This statement assumes that the initial dose of hexamethonium was large enough to effect maximal vascular dilatation. Under this condition, the peripheral resistance will remain constant.)

Fig. 3. Effect of positive intrapulmonary pressure of 8 cm. of water on the arterial and venous pressures. There is very little change in arterial pressure except for the disappearance of the respiratory waves (lower tracing). The venous pressure tracing shows a disappearance of the respiratory waves. The venous pressure increases by 8 cm. of water. Arterial pressure in millimeters of mercury and venous pressure in centimeters of water.

Positive pressure respiration has been advocated to reduce the arterial pressure to levels lower than those attained with hexamethonium alone (19). Experimentally, these results could not be confirmed when reasonable pressure was employed (manual bag compression ranged from 4 to 10 mm. of mercury). Very strong positive pressure respiration is necessary to produce a venous stasis which is sufficient to reduce cardiac output and lower the pressure. The advisability of this
maneuver is questionable because the circulation time of the brain would be increased by the obstruction of the cerebral venous return. Relative maintenance of the diastolic pressure has been reported by others (18). They attributed this to the increased heart rate which preceded the drop in pressure. Stroke volume was reduced, thereby conserving the diastolic level. In this series, the percentage falls in systolic and diastolic levels were about equal. Several explanations may account for this discrepancy in results. First, most of the patients had rapid heart rates because of atropine premedication before administration of hexamethonium and second, a more accurate method of recording arterial pressure was employed.

The variations in behavior of the venous pressure, following the initial injection of this agent, probably have several explanations. When hexamethonium is administered to a patient in Fowler's position, the jugular venous pressure will promptly fall since the sudden peripheral venodilatation permits a momentary mass pooling of blood in the dependent veins. At this time, the blood returning to the right heart will be mainly from the segments that are elevated above the heart.

Fig. 4. Effect of positive intrapulmonary pressure of 15 mm. of mercury on the arterial and jugular venous pressures of a patient under hexamethonium. The arterial pressure fell rapidly and the pulse pressure disappeared completely. On release of the intrapulmonary pressure, the arterial pressure climbed to normal without tendency to overshoot. The venous pressure rose approximately 20 cm. of water. The accuracy of the venous pressure tracing is questionable because of the high attenuation used. Arterial pressure in millimeters of mercury and venous pressure in centimeters of water.
Consequently, a fall in jugular venous pressure results. Patients in the supine or slight Trendelenburg position did not experience an initial fall in the jugular venous pressure.

The findings indicate that certain cardiorespiratory reflexes affecting circulatory homeostasis are abolished with hexamethonium. These data corroborate those of Finnerty and Freis (17) with respect to the usual vasopressor overshoot following both Valsalva's experiment and postural changes. The abolition of the vasopressor overshoot may be explained, at least in part, by blockade of the effector limb of the carotid sinus pressoreceptor regulatory mechanism.

It has been established that the existence of either hypoxia or hypercarbia or both before the injection of hexamethonium exaggerates the depressor response because of the presence of an increase in sympathectic tonus (11). Conversely, our results show that once a patient is subjected to hexamethonium blockade neither hypoxia nor hypercarbia is capable of producing their usual pressor reaction since the sympathetics are blocked at their synapses.

The adrenergic agents act directly upon the muscle fibers of the vessels themselves. In the normal subject these agents produce a primary pressor response through peripheral vasoconstriction. The magnitude of this response is tempered by the various homeostatic reflexes. Since these reflexes cannot function in the presence of hexamethonium blockade, no damping mechanism is present and the response to an adrenergic agent thus will be totally uninhibited, resulting in an accentuation of the normal pressor response.
Findings Related to Secondary Effects of Hexamethonium

I. Circulation Times

Arm to ear circulation times were correlated with the arterial pressures. Graph 12 illustrates the circulation times above the pressure plottings. In each case, the circulation time varied inversely with the pressure level. The circulation time before administration of hexamethonium, seen in graph 12, is fourteen seconds. (This is very close to the normal 13.4 seconds established by Knutson et al. [10].) Following an initial fall in systolic pressure from 174 to 66 mm. of mercury, the circulation time nearly doubled.

![Graph showing circulation times](image)

**Fig. 6.** Arterial pressure tracing with serial electrocardiograms showing the effect of hypoxia. At the first signal mark, the administration of 10 per cent oxygen was begun. The 4 succeeding signal marks follow at one minute intervals and indicate the recording of the electrocardiograms. Those taken at the end of the first and second minutes are comparatively normal. By the end of the third minute, depression of the ST segment occurred. At the end of the fourth minute, flattening of the T waves and depression of the ST segments were present. Arterial pressure in millimeters of mercury.

II. Anoxia Photometer Readings

Graphs 6 and 7 indicate the relative ear oxygen saturation levels. It should be borne in mind that the oxygen saturations are not absolute and are indicative of relative changes only.

Variations in arterial pressure did not significantly alter the ear oxygen saturations while the patients were in the supine position.
Fig. 7. Arterial pressure, in millimeters of mercury, and electrocardiographic tracings showing the effect of hypercarbia on the blood pressure and heart of a patient under hexamethonium. The first signal mark indicates the onset of administration of 10 per cent carbon dioxide. The second signal mark was made at the recording of the electrocardiogram five minutes later. Virtually no change occurred in either tracing except for a fall in heart rate from 110 to 92.

**TABLE I**

**Cerebral Arteriovenous Oxygen Differences**

<table>
<thead>
<tr>
<th>Case</th>
<th>Time</th>
<th>Blood Pressure in mm Hg</th>
<th>Pulse rate/minute</th>
<th>C(ΔV)O₂ in Vol. %</th>
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<td>132/88</td>
<td>104</td>
<td>6.5</td>
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<tr>
<td></td>
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<td>62/50</td>
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<td>128/84</td>
<td>96</td>
<td>7.3</td>
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<td>168/108</td>
<td>96</td>
<td>8.9</td>
</tr>
<tr>
<td></td>
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<td>120</td>
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<td></td>
<td>After C6</td>
<td>120/84.5</td>
<td>91</td>
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</table>
When the patients were tilted to Fowler's position, however, the oximeter readings fell significantly. The tilting experiments were repeated several times in each case to determine the constancy of the results. Graph 7 shows a severe drop in the oximeter reading when strong positive intrapulmonary pressure was applied continuously for three minutes.

**Fig. 8.** Arterial pressure tracing showing how quickly and easily the pressure can be varied by altering the flow rate of 1-arterenol. Arterial pressure in millimeters of mercury.

III. Cerebral Arteriovenous Oxygen Differences

The cerebral arteriovenous oxygen difference [C(A-V)O2] increased significantly in each of the 4 patients studied (table 1). The average arterial blood pressure of the anesthetized patients was 141.5 mm.
systolic and 99.5 mm. diastolic, the pulse rate per minute 97 and the C(A-V)02 6.85 volumes per cent before hexamethonium was injected. Following the induction of hypotension the average arterial pressure fell to 63.5 mm. systolic and 46.6 mm. diastolic, the pulse rate rose to

115.5 and the C(A-V)02 rose to 8.55 volumes per cent. After abolishing the hypotension with vasoxyll, the average pressure rose to 120 mm. systolic and 84.5 mm. diastolic, the pulse rate fell to 91 and the C(A-V)02 returned to 6.67 volumes per cent.
IV. Electrocardiographic Tracings

Electrocardiographic studies were done on several cases in the manner described under Materials and Methods. Several patients showed changes indicating myocardial hypoxia. Figure 9 illustrates the changes occurring in lead II of the electrocardiogram as the blood pressure is progressively reduced. The uppermost tracing shows that the ST segment takes off from the iso-electric line and the T wave is of normal shape and voltage. When the tracing was made, the blood pressure was 127 mm. systolic and 86 mm. diastolic. The middle tracing, taken at a pressure of 85 mm. systolic and 62 mm. diastolic, indicates slight depression of the ST segment with some flattening of the T wave. The lowermost tracing was made with the patient in a 15 degree Fowler's position. The arterial pressure was 65 mm. systolic and 55 mm. diastolic. Definite ST depression and flattened T waves are present. Figure 10 shows an enlargement of the electrocardiographic tracings before and after the induction of hypotension.

With the pressure still reduced (85 mm. systolic and 65 mm. diastolic), the oxygen was increased from 50 per cent to 100 per cent. A tracing was made after two minutes of 100 per cent oxygenation. The electrocardiogram again reverted to normal (fig. 11).

In the same patient, an attempt was made to prove this point. The inspired oxygen was reduced to 10 volumes per cent and tracings were
made at one, two, three and four minutes (fig. 6). The blood pressure was approximately 80 mm. systolic and 60 mm. diastolic during the test. Tracings made after the first and second minutes appear normal. The tracing at the end of the third minute shows a slight depression of the ST segment in the last two complexes. After the fourth minute, the ST take off is definitely depressed and the T waves flattened. It is interesting to note that the tracing made following four minutes of hypoxia is not as abnormal as the tracing made when the pressure was 65 mm. systolic and 55 mm. diastolic.

Fig. 11. Arterial pressure tracing, in millimeters of mercury, and electrocardiogram, showing reversion of the electrocardiogram to normal when the patient was given 100 per cent oxygen for two minutes. First marker: administration of 100 per cent oxygen was begun. Second marker: point at which electrocardiogram, shown below, was recorded.

V. Electro-encephalographic Tracings

Electrocorticograms and simultaneous arterial pressure tracings were run in an attempt to determine, indirectly, the extent of cerebral hypoxia during the hypotensive state.

Figure 12 is a graphic example of the depression of cortical activity as the arterial pressure is reduced progressively. The gradual depression in the high voltage, fast activity in all leads was striking. In this instance when the arterial pressure reached 55 mm. systolic and 45 mm. diastolic, virtually all activity had ceased. At this point the pressure was elevated with a vasopressor agent and the cortical activity immediately increased.
FIG. 12. Serial electrocorticograms showing the effect of lowering the pressure with hexamethonium from 110 to 55 mm. systolic and from 70 to 45 mm. diastolic and then raising the pressure to 70 mm. systolic and 45 mm. diastolic with vasopressor. Virtually all cortical activity ceased when the pressure reached 55 mm. systolic and 45 mm. diastolic.

DISCUSSION OF SECONDARY EFFECTS OF HEXAMETHONIUM

The circulation times, C(A-V)02, oximeter studies, electrocardiograms and electrocorticograms carried out on anesthetized patients with hexamethonium-induced hypotension, indicate that the circulation within vital organs may be reduced to such an extent that severe hypoxia can result. This is particularly true of the elevated portions when postural drainage in combination with hypotension is employed to secure a bloodless field. The maintenance of a normal circulation time during hexamethonium-induced hypotension has been reported
by others (7). In this instance, however, circulation times were merely estimated by the onset of action of drugs injected into a vein of the foot.

The anoxia photometer findings are difficult to interpret when one considers the purpose for which this instrument was intended. Theoretically, the oximeter measures "arterialized" capillary blood. Under normal conditions the oxygen saturation of the blood in the ear capillaries should remain constant as long as no alteration in pulmonary ventilation occurs. Neither pulmonary ventilation nor inhaled oxygen tension was allowed to vary during the tilting experiments, yet the oximeter readings fell. This might be interpreted as a variation in blood thickness; however, the model 17A anoxia photometer has a compensating circuit which largely nullifies this error in the normal range of adult ears. One interpretation of the depression in oximeter readings resulting from placing the hypotensive patient in Fowler's position could be stagnation of the ear capillary blood, caused by extremely low arterial pressures and slow circulation times. This interpretation would be consistent with the circulation times and the cerebral arteriovenous oxygen differences found. Strong positive intrapulmonary pressure reduced the oximeter reading markedly. In this instance, venous obstruction and a reduced cardiac output are both present. Stagnant anoxia must be the explanation of the fall in ear oxygen saturation during this maneuver.

That the cerebral arteriovenous oxygen difference was increased significantly in each of the four anesthetized patients studied, can be accounted for by their operative positions (Fowler's 10 to 15 degrees), general anesthesia, and probably complete ganglionic blockade. Under these conditions it was believed that cerebral blood flow would be reduced. Certainly, the circulation times and ear anoxia photometer studies indicated this. Assuming that cerebral oxygen utilization is not influenced by hexamethonium and that the arterial oxygen saturation remains constant, a change in cerebral blood flow may be roughly estimated from the change in the cerebral arteriovenous oxygen. During hexamethonium-induced hypotension our patients showed an increase of 1.7 volumes per cent in the cerebral arteriovenous oxygen. Since this represents a 24 per cent increase, it may be assumed that there has been a 24 per cent decrease in cerebral blood flow.

Crumpton and Murphy (20) studied cerebral circulatory and metabolic changes in hypertensive supine patients who were under treatment with hexamethonium. They found a reduction of 29 per cent in the mean arterial pressure and a 30 per cent decrease in cerebrovascular resistance. The cerebral flow, oxygen uptake and cerebral arteriovenous oxygen difference were not altered significantly.

Both Katz (21) and Wiggers (22) have advocated the use of serial electrocardiograms for the detection of myocardial hypoxia. Alterations in the shape of the T wave or depression of the ST take off, or
both, are considered indicative of myocardial ischemia. In several instances these electrocardiographic alterations appeared during hypotensive anesthesia. The fact that identical changes could be produced on the tracing of the same patient when subjected to an hypoxic atmosphere further substantiates the idea that hypotension, if profound enough, may produce myocardial hypoxia. Normal coronary blood flow has been reported in dogs subjected to hexamethonium hypotension. However, when it is considered that these determinations were made thirty minutes after the intravenous injection of hexamethonium and that the average mean reduction in blood pressure was from 178 to 119 mm. of mercury, it is understandable that adequate coronary flow was maintained since cardiac output and cardiac work were found to be decreased.

The modifications in cortical activity, produced by hexamethonium-induced hypotension, were severe in 4 of the 12 cases studied. It has been well documented that severe deprivation of cerebral oxygen will result in a gradual reduction in the amplitude of the slow waves until the tracing becomes flat (23–27). Some significance may be attached to the similarity of electro-encephalographic patterns resulting from severe hypoxia, profound hypotension, and very deep anesthesia. Conceivably, the metabolism of the cortical cells of the cerebrum virtually has ceased as a result of anoxic anoxia, stagnant anoxia or histotoxic anoxia, as the case may be.

**Summary**

The primary effects of hexamethonium-induced hypotension upon the anesthetized patient were investigated. In the 14 cases studied, the average fall in direct systolic and diastolic pressures was found to be 48.8 and 44.2 per cent, respectively.

Factors influencing the magnitude of the depressor response were investigated. Fowler's position and increased vascular tonus were predisposing conditions to the more precipitous falls in arterial pressure.

Abolition of the vasopressor overshoot reflex following Valsalva's maneuver and postural changes was demonstrated. The normal reflex cardiovascular responses to hypercarbia and hypoxia were absent following use of hexamethonium in anesthetized patients.

Certain secondary effects of hexamethonium upon the anesthetized patient were investigated. These findings revealed an increase in circulation time, decrease in the ear capillary oxygen saturation, and an increase in the cerebral arteriovenous oxygen difference accompanying moderate to severe hypotension.

Electrocardiograms and electrocorticograms revealed changes consistent with hypoxia of the hearts and brains of patients in Fowler's position with marked hypotension.
The findings suggest that cerebral and coronary blood flow may be reduced and that cardiac output is decreased. (Studies in progress show an average reduction in cardiac output of 23.5 per cent.)

The physiologic findings indicate that the production and maintenance of hypotensive anesthesia can be hazardous, since the capacity of the blood reservoir may exceed the blood volume. In such an instance it would be possible to render the brain completely ischemic by placing the patient in a steep Fowler’s position.

REFERENCES


