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EFFECTS OF DEPTH OF ANESTHESIA ON BEHAVIOR OF PERIPHERAL VASCULAR BED

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Evidence from both clinical and laboratory investigations has established that anesthetic drugs, of themselves, exert variable effects on the functional capacity of peripheral circulatory mechanisms (1, 2, 3). By utilizing the behavior of specific vascular mechanisms in the capillary bed as criteria of functional integrity, it was possible to demonstrate that, depending upon the particular anesthetic used, vascular reactivity was altered in a predictable fashion. In these experiments, however, the primary circumstance under investigation was the progressive circulatory stress induced by hemorrhage or trauma, the anesthetic being administered primarily to maintain a uniform light plane of narcosis. No systematic attempt was made to analyze the effects of anesthesia itself on an otherwise normal, intact animal.

During the course of these and other experiments in which experimental studies were made, it was a frequently related observation that vascular behavior was significantly influenced by varying the depth of anesthesia. Since the administration of anesthetic agents is often required to complete laboratory studies relative to the factors regulating the activity of the peripheral circulation, it seemed worth while to investigate the influence of varying depths of anesthesia, per se, on the circulatory criteria of the capillary bed.

MATERIAL AND METHODS

A. Conduct of Anesthesia. Each of three groups of 5 normal dogs was anesthetized with cyclopropane, ether or pentothal® sodium. The inhalation agents were administered, using a closed carbon dioxide absorption to-and-fro endotracheal technic. Pentothal was given as a continuous intravenous infusion in 1 per cent concentration in conjunction with oxygen. No other drugs were used. Respiration was assisted as required to obviate the effects of anesthesia on spontaneous respiratory movements. No analyses of blood samples for drug or gas concentrations were performed. Depth of anesthesia was estimated clinically.

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As far as could be determined by clinical signs and by the absence of characteristic vascular response in the omentum, which asphyxia uniformly produces, the latter was not a factor in these experiments.

Three clinical ranges of anesthesia were studied: light, moderate and deep. Light anesthesia was arbitrarily determined by the presence of an active blink reflex. Anesthesia was considered moderately deep in the range in which the blink was abolished to the point at which an obvious diminution of intercostal respiratory activity developed. The animal was considered to be in deep anesthesia when spontaneous respiratory movements began to be shallow up to the point at which they became irregular. Complete respiratory arrest was avoided.

In each experiment the initial observations were made during light narcosis. The range of anesthesia was deepened from light to moderate to deep, maintaining the animal in each range for five minutes. The anesthesia was then allowed to return to the light range spontaneously by opening the anesthetic system and administering oxygen only. When the circulatory observations indicated a return to the initial control status, the previous anesthetic procedure was repeated a second and third time.

B. Preparation of Peripheral Circulation. Blood pressure was recorded throughout from a femoral artery by a conventional mercury manometer. The circulation was prepared for direct microscopic observation according to a method previously described (4) by exteriorizing a portion of the omentum into a special moist chamber. This allowed continuous observation of the blood vessels in the omentum which were photographed at intervals.

C. Circulatory Criteria. The following peripheral vascular mechanisms were utilized as criteria of the influence of depth of anesthesia:

1—Reactivity to Epinephrine Applied Topically. The capacity of the terminal arterioles and precapillaries to react to epinephrine applied topically has been found to be a relative measure of the ability of these cells to react to a physiologic stimulus (5).

2—Vasomotion of the Metarterioles and Precapillaries. This refers to a periodic spontaneous muscular activity in these smallest arterial channels which, in effect, regulate the volume of blood entering the true capillary network. For each capillary unit this is not an all or none phenomenon but a graded activity conditioned by the relative frequency and duration of the muscular contraction-relaxation phases that constitute the mechanism of vasomotion.

3—Caliber of Terminal Arterioles. Relative variations in the caliber of the small arteries and arterioles, just proximal to the vessels of the capillary bed, provide an index of the activity of their vasoconstrictor-vasodilator mechanisms.

4—Capillary-Venous Outflow. The rapidity of outflow from the capillary bed into the collecting venules determines, in great measure,
the rate at which the blood returns from the tissues to the larger vessels of the active circulation.

5—Rate of Recovery. This implies, in terms of time interval, the return of the mechanisms of epinephrine reactivity, vasomotion, vasoconstriction and venous outflow to the initial control state observed during light anesthesia. These time intervals were determined to start not from the point of cessation of the administration of anesthesia but from the point of clinical determination of light anesthesia as indicated by the return of pharyngeal reflexes and spontaneous movements of the extremities.

6—Blood Pressure. Slight variations in blood pressure levels during each phase of anesthesia are of little critical importance in regard to the activity of the previously mentioned circulatory criteria. Capillary blood flow, however, would be significantly influenced by extreme fluctuations in blood pressure, particularly by marked hypotensive levels.

Observations and Results

The observations are summarized in table 1. It was noted that the patterns of activity in the peripheral circulation not only were characteristic for each of the three anesthetics but also, in the absence of induced circulatory stress, were significantly influenced by the depth of anesthesia produced by each narcotic. Previous comparative studies in the peripheral vascular bed were made either in dogs in which the omentum was exteriorized under local anesthesia, or in dogs subjected to general anesthesia (2). The vascular criteria in the omentum of locally anesthetized dogs, therefore, represent the closest approximation to the status of the circulation in the unanesthetized animal.

Ether Anesthesia.—On the whole, during light surgical anesthesia with all three agents, the capillary circulation, as measured by the selected criteria for peripheral circulatory efficiency, remained relatively unaffected when compared with that in dogs not receiving general anesthesia. Vasomotion of the muscular metarterioles and precapillaries was present and of good character. Venous return by way of the collecting venules was rapid and of good efficiency. The caliber of the small arterioles was normal, with no appreciable vasodilatation indicating good vasconstrictor tone.

Epinephrine reactivity, in the range 1:8 million, was not significantly different from the 1:4 million value obtained during local anesthesia. As anesthesia was deepened to a moderate level, only slight over-all change in vascular reactions was noted. There was no significant change in systolic blood pressure. Vasomotion was most affected, with the contraction phase of its cyclic activity being considerably shortened. Epinephrine reactivity, venous return and arteriolar caliber remained relatively unaffected. As the deep phase of anesthesia was instituted, considerable impairment in the capillary circulation was
seen. The response of the precapillary sphincters to epinephrine was depressed, a concentration of 1:2 million being required to elicit a control reaction. Vasomotion was rapidly suppressed and disappeared within one to two minutes. Circulation through the capillary bed was plethoric throughout. Blood flow in the collecting venules was seriously slowed so that individual blood cells in the venules could readily be seen. Marked arteriolar dilatation was noted. Systolic blood pressure then fell to 90 mm. of mercury. At this point the animal was returned to the light-plane of clinical anesthesia. The vascular alterations observed during deep anesthesia showed a considerable lag in their return to the

<table>
<thead>
<tr>
<th>TABLE 1</th>
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<tbody>
<tr>
<td>EFFECT OF GRADED DEPTH OF ANESTHESIA ON CIRCULATION IN OMEN'TUM OF DOG</td>
</tr>
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<table>
<thead>
<tr>
<th>Depth of Anesthesia</th>
<th>B.P. (mm. Hg)</th>
<th>Epinephrine</th>
<th>Vasomotion*</th>
<th>Venular Flow</th>
<th>Vasodilatation</th>
<th>Recovery from Deep Anesthesia†</th>
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</thead>
<tbody>
<tr>
<td>Ether</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Light</td>
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<td>1:8M‡</td>
<td>3+</td>
<td>Good</td>
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<td>None</td>
</tr>
<tr>
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<td>108</td>
<td>1:8</td>
<td>2+</td>
<td>Good</td>
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<td>None</td>
</tr>
<tr>
<td>Deep</td>
<td>90</td>
<td>1:2</td>
<td>0</td>
<td>Very slow</td>
<td>Marked</td>
<td></td>
</tr>
<tr>
<td>Cyclopropane</td>
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<td></td>
</tr>
<tr>
<td>Light</td>
<td>118</td>
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</tr>
<tr>
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<td>None</td>
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<tr>
<td>Deep</td>
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<td>1:30</td>
<td>0</td>
<td>Slow</td>
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<td></td>
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<tr>
<td>Pentothal</td>
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</tr>
<tr>
<td>Light</td>
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<td>1:10</td>
<td>4+</td>
<td>Excellent</td>
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<tr>
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<td>Good</td>
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<tr>
<td>Deep</td>
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<td>1:4</td>
<td>0</td>
<td>Very slow</td>
<td>Marked</td>
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* Spontaneous change in precapillaries and metarterioles.
† Time for complete restoration of peripheral vascular behavior to control status after return to light clinical anesthesia.
‡ Minimal effective dose of topically applied epinephrine expressed as 1:2 Million.

initial control status. Response to epinephrine returned to initial levels earliest at the end of ten minutes. Vasomotion reverted to its original cyclic pattern in approximately fifteen minutes. After twenty minutes, venous return and arteriolar caliber reverted to their original status. Repetition a second and third time of the above course of anesthesia yielded virtually identical observations except for a progressive increase in the interval needed for these mechanisms to revert to their initial state.

*Cyclopropane Anesthesia.—* There were no apparent alterations in the observed criteria during light and moderate depths of cyclopropane
narcosis, except for an increase in epinephrine reactivity from 1:25 million to 1:50 million. The high initial response to epinephrine during administration of cyclopropane (1:25 million) as compared with local anesthesia (1:4 million) was a constant feature. Vasomotion was of excellent character, as was venous return and arteriolar tone. In general, the efficiency of these peripheral vascular mechanisms seemed unaffected by light or moderate phases of cyclopropane anesthesia. Significant changes were noted, however, during deep anesthesia. Response to epinephrine which was elevated during the previous moderate range of anesthesia, fell but, unlike ether, did not become suppressed below its original level. During deep anesthesia, spontaneous vasomotion diminished rapidly and disappeared with dilatation of the metarterioles and pre-capillary sphincters. An unrestricted over-all capillary resulted. Outflow from the capillary bed by way of the collecting venules was considerably slowed but less than that observed during deep ether anesthesia. The arterioles at first remained unchanged, but after three of four minutes of deep anesthesia underwent slight vasodilatation.

After the return of the animal to the light phase of narcosis, the restoration of these mechanisms to their initial character was rapid, being complete within two minutes. Arteriolar vasodilatation disappeared earliest. Control levels of vasomotion, venous return and epinephrine response were re-established within two to three minutes. As with ether, repetition a second and third time of the foregoing anesthesia procedure yielded entirely comparable effects on the capillary circulatory mechanisms. The rate of recovery of these mechanisms showed no progressive lag with repeated anesthetic administration, in contrast with the poor recovery following the use of ether.

**Pentothal Anesthesia.**—As with ether and cyclopropane, light pentothal narcosis did not appreciably interfere with the activity of the peripheral vascular mechanisms. Systolic blood pressure averaged 120 mm. of mercury. Epinephrine reactivity was recorded at 1:10 million. Vasomotion was of normal periodicity. Venous outflow through the collecting venules was of excellent character. Arteriolar tone was maintained. As the rate of pentothal administration was increased to achieve a moderate depth of anesthesia in which spontaneous respiration was adequate, there developed, with the exception of the response to epinephrine, an appreciable depression of the different peripheral circulatory end points under observation. The blood pressure decreased slightly below 100 mm. of mercury. Vasomotion, capillary venous outflow and arteriolar tone were somewhat depressed. Further increase of pentothal dosage produced deep narcosis in approximately three minutes, after which administration of the drug was discontinued (average total dose of 0.25 Gm. for an average 10 kg. dog). Blood pressure fell abruptly to an average of 65 mm. and spontaneous respiration ceased. A profound depression of the circulatory mecha-
Fig. 1. Effect of graded depth of anesthesia on vessels of dog omentum. Capillary bed (times 90) during light and deep anesthesia. A = artery, V = vein. 1A and 1B during cyclopropane, 2A and 2B during pentothal, and 3A and 3B during ether administration. Note, with deep anesthesia, increased diameter of arteries and increased prominence of arterioles and capillaries (indicating diminution of vasoconstrictor tone and vasmotion).
nisms was observed. Response to epinephrine was depressed immediately to 1:6 million and then fell during the next five minutes to 1:4 million. Complete suppression of vasomotion developed rapidly thereafter. Venous return by way of the collecting venules was sluggish. Moderate dilatation of the arterioles occurred quickly and became extreme within five minutes. Leukocytic sticking was noted even in the arterioles.

The reversion to a light phase of clinical anesthesia was delayed as compared with either of the preceding agents, requiring approximately twenty-five minutes. In this interval, each of the circulatory criteria reverted gradually toward initial control values. Blood pressure rebounded to an average of 90 mm. of mercury within ten minutes and reached 116 mm. in twenty minutes. Vasomotion was absent and the response to epinephrine continued refractory through the twenty-five minute period of return to light anesthesia. Subsequent to this, vasomotion reappeared within five to eight minutes and epinephrine reactivity reached control level several minutes later. Venous return although sluggish during deep anesthesia, had been restored to a relatively effective outflow by the time the clinical level of anesthesia was light. It seemed entirely normal several minutes later. The arterioles did not regain their original tonic state of contraction until more than ten minutes after beginning of the recovery period. As noted in table 1, complete recovery of the peripheral circulation did not occur until thirty minutes had elapsed after the onset of light clinical anesthesia.

The experimental findings indicate that light or moderate levels of clinical anesthesia interfere but little with the efficiency of peripheral vascular mechanisms. On the other hand, deep anesthesia results in an undesirable depression in the functional capacity of the capillary bed. Fundamental differences which can usually be observed in animals subjected to light and deep anesthesia are evident in figure 1, which is composed of representative photomicrographs during ether, cyclopropane and pentothal anesthesia. The essential changes consist in a dilatation of the vessels feeding the capillary bed and a failure to restrict the circulation through the capillary bed proper.

**Discussion**

The foregoing observations and others reported elsewhere (2, 6) indicate that the functional efficiency of the peripheral circulation can be interfered with in varying degree by different anesthetics. The deleterious action of anesthetic agents on circulatory homeostasis within the capillary bed proper is strikingly accentuated during circulatory stress. The present experiments clearly demonstrate the influence of the depth of anesthesia per se in impairing the effectiveness of peripheral readjustment mechanisms. In all instances, anesthetic drugs, when used to induce surgical anesthesia, served to decrease the effec-
tiveness of the individual mechanisms which condition the over-all activity of the capillary vasculature. Interference with these mechanisms was most pronounced with ether, least with cyclopropane, and intermediate between these with pentothal (2). During light surgical anesthesia with the three agents employed, no significant differences could be seen in the functional response of the terminal vascular bed. However, when the effects of circulatory stress were superimposed, differences of considerable magnitude became apparent. During deep anesthesia, all of the anesthetic agents used in the present study produced a profound depression of peripheral homeostatic mechanisms.

It is a well established clinical thesis that functional impairment of the circulation develops more readily during deep anesthesia, particularly during prolonged procedures (7). The present experimental observations reinforce this thesis. The apparent advantages of one or another anesthetic agent in the presence of hemorrhage or trauma have been discussed elsewhere (1). These advantages, although still somewhat in evidence with cyclopropane, are in effect almost eliminated by profound narcosis.

The favorable or unfavorable influence of anesthetic drugs on the peripheral circulation is reflected, in last analysis, by the survival of the organism. Survival following hemorrhagic shock (8) was greatest in experiments in which the animals were desensitized locally by the infiltration of procaine, without subjecting them to general anesthesia. Under these conditions, individual homeostatic mechanisms in the capillary bed retained a high order of functional integrity. The capacity of anesthetized animals to withstand hemorrhagic hypotension without fatal outcome is affected in direct relation to the decrement in the functional integrity of these peripheral mechanisms. Profound narcosis, of itself, by impairing these mechanisms, thus also contributes an untoward circulatory influence.

Emphasis thus far has been placed on the contribution of positive decompensatory influences on vascular behavior during periods of circulatory stress. The other facet, that of exaggerated compensation, can likewise predispose the organism to peripheral circulatory collapse. For example, the deleterious effects of prolonged vasoconstriction are typical of such observations. As evidence of the undesirable effects of vasoconstriction is the protective action of sympatholytic drugs, such as dibenamine®, which interfere with the vasoconstrictor activity during shock (9). On the basis of the finding that ether anesthesia also interferes with vasoconstrictor activity, Beecher et al. (10) have suggested that this agent exerts a protective action on the circulation as compared with cyclopropane, which interferes less with vasoconstriction. Furthermore, since ether also depresses peripheral vasmotion to allow an unrestricted filling of the capillary bed, they have suggested that it may permit better tissue nutrition than cyclopropane. In terms of survival, the evidence indicates, however, that none of the anesthetics
examined has a real protective action. Actually, the reverse seems to exist in that anesthetic agents definitely predispose the organism to the development of irreversibility in direct relation to the degree of interference which they introduce in peripheral circulatory activities.

It is apparent that critical differences exist between the effects of autonomic blocking agents and anesthetic agents on homeostatic mechanisms within the capillary bed proper. In this regard, autonomic blockade from dibenamine (11) results in a decrease in muscle tone in those blood vessels whose activity is conditioned primarily by neurogenic control by way of the sympathetic nervous system (12). The caliber of the terminal arterioles, metarterioles and precapillaries, whose activities are predominantly conditioned by humoral factors (13), is not significantly affected, nor is there a reduction in the capacity of the muscular components in the terminal vascular bed to respond to physiologic stimuli.

Observations of these circulatory mechanisms indicate that anesthetic agents have a different influence from that of autonomic blockade. During anesthesia the larger blood vessels, under neurogenic control, become widely dilated to a degree in excess of that attributable to the diminution in vasoconstrictor tone imparted by sympathetic regulatory mechanisms. Vasomotion, due to muscular activity of the capillary blood vessels under humoral control, is depressed and frequently absent. The peripheral vasculature, in general, responds poorly to homeostatic regulatory influences. Since the muscular vessels show a decreased responsiveness to epinephrine, it can be assumed that this lack of response is primarily the result of an intrinsic inability of vascular smooth muscle to react to a normal physiologic stimulus. Thus, although autonomic blockade with dibenamine and anesthesia with ether are superficially similar, differences become apparent in their capacity to protect against the deleterious consequences of circulatory stress.

Conclusions

The three anesthetic agents employed in this study—ether, cyclopropane and pentothal—exert a deleterious effect of peripheral readjustment mechanisms within the capillary bed proper, which becomes increasingly evident with increasing depth of anesthesia. Anesthesia invariably predisposes toward the development of irreversibility following prolonged hemorrhagic hypotension. The circulatory effects of anesthetic agents and autonomic blocking drugs are basically different.

References

8. Shorr, Ephra"