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PERIPHERAL VASCULAR HOMEOSTASIS IN RELATION TO ANESTHETIC AGENTS * †

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ANESTHETIC agents, when administered to allow surgical intervention are invariably given to subjects during a period of circulatory stress. The influence of these drugs on the peripheral circulatory system is, therefore, of particular significance. For this reason it is worthwhile to consider the effects of anesthetic drugs on specific functions of the peripheral circulation being mindful that such functions are sustained, in large measure, by homeostatic mechanisms.

The peripheral circulation of the normal individual possesses a variety of means which serve to maintain its efficiency in circumstances of stress. These homeostatic mechanisms continually adjust the capacity of the circulatory bed and the volume of the circulating blood to each other. When this hemodynamic equilibrium is threatened, as from hemorrhage, certain well defined patterns of compensatory responses are activated to restore and maintain this balance (1). In the healthy organism these mechanisms serve to prevent circulatory insufficiency and remain remarkably intact, even when the blood loss is fatal. However, the efficiency of many homeostatic mechanisms may be impaired by age, by disease or by the administration of drugs; the result being that they cannot compensate effectively in stress situations. In such organisms, circulatory collapse occurs largely as a result of the impairment or failure of these peripheral homeostatic mechanisms (2).

Some of the anesthetic drugs in common use have been found to modify these homeostatic compensatory patterns unfavorably in the

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peripheral circulation (3). The anesthetized organism, insofar as these responses are concerned, therefore, reacts differently from the unanesthetized organism. The unanesthetized subject, in most instances, exhibits a purely compensatory pattern of response in the peripheral circulation. Anesthetized subjects, however, depending upon the agent used, exhibit a compensatory pattern of response only transiently. This is then succeeded by a decompensatory response in which the peripheral circulation shows progressive deterioration. Thus, other factors being equal, the anesthetic agent, of itself, can interfere with the normal optimum responses of the homeostatic mechanisms of the peripheral circulation. It is the purpose of the present report to illustrate this thesis by indicating the extent and direction of some of these alterations.

MATERIAL AND METHODS

Thirty dogs were anesthetized, each with one of three agents; ten with cyclopropane, ten with pentothal and ten with ether. Cyclopropane and ether were administered using the absorption to-and-fro endotracheal technic. Pentothal was given by intravenous drip as a 1 per cent solution together with oxygen by endotracheal catheter. In all instances the first plane of anesthesia with active blink reflex was maintained throughout. No other medication was used.

For visualization of the circulation a small portion of the omentum was exteriorized and draped over a glass horseshoe in a special moist chamber which served as the stage of a microscope (4). The blood vessels in the omentum were kept under continuous observation and photographed at frequent intervals during the experiments. A series of photomicrographs of Dog No. 12 (cyclopropane), Dog No. 20 (pentothal) and Dog No. 64 (ether) are presented as representative protocols of the three anesthetic groups.

Graded hemorrhage was utilized as the stress factor to activate circulatory homeostatic responses. The bleeding procedure consisted of an initial blood loss of 2 per cent (body weight) which was followed by successive small bleedings (0.5–0.2 per cent) at 15 to 20 minute intervals until maximum blood loss was reached. Maximum blood loss was identified by the complete cessation of blood flow during any bleeding in the larger omental arteries (100–150 μ) kept under microscopic observation. No sustaining infusions were given.

Peripheral Circulation—Description and Terminology

The present data are part of those derived from a protracted study of many aspects of the peripheral circulation. However, only those criteria employed for evaluating the functional state of the peripheral circulation as can be seen in the ensuing photographs are considered. These are: (1) degree of vasoconstriction; (2) degree of vasomotion; (3) evidence of capillary stasis and/or increased permeability; each

of these visible criteria being a measure of homeostatic or compensatory activity.

The peripheral vascular apparatus can be subdivided into two major divisions; (a) the larger blood vessels which act as conduits for distributing blood to the various organs and (b) the small blood vessels which penetrate the tissues and supply blood to them in accord with their varying needs. Accordingly, the reactions of the peripheral vessels fall into two main categories; those concerned with maintenance of blood pressure and those with local regulation of blood flow in tissues. The former is accomplished by the homeostatic activity of *vasoconstriction* of the small arteries and arterioles particularly of the terminal arterioles just proximal to the vessels of the capillary bed. Vasoconstriction is centrally integrated by means of the autonomic nervous system. This neurogenic control, however, does not extend to the distal ramifications of the arterial vessels which become endothelial tubes surrounded by a single discontinuous layer of muscle cells and are known as *Metarterioles,* in essence "muscular capillaries" (5). Beyond these are the final subdivisions of the peripheral vascular apparatus, as off-shoots of the metarteriole. These vessels are denuded of muscle cells except at their point of origin from the metarteriole and are the non-muscular or "true capillaries." The term *pre-capillary sphincter* has been applied to this strategic junctional muscular portion of the capillary bed since it directly controls blood flow into the capillary network.

A distinguishing feature of this division of the extreme peripheral vascular apparatus beyond the terminal arterioles and including the metarterioles and precapillary sphincters, is its marked responsiveness to circulating humors both blood-borne and of local tissue origin. The homeostatic entity that regulates the spontaneous periodic activity of the metarterioles and precapillary sphincters has been termed *vasomotion* (6). This mechanism determines the amount of blood entering the true capillaries by controlling the number of capillaries to be "active" according to wide variations in tissue needs.

Homeostatic Efficiency—Visual Evidence

The difference between favorable and unfavorable homeostatic compensatory patterns as described by Chambers, Zweifach et al. (7) may be briefly outlined. When compensatory activity is intact, vasoconstriction of the small arteries and arterioles is progressive and sustained. Vasomotion increases serving to direct blood through the capillary bed via preferential channels permitting only enough blood to enter a limited number of true capillaries to satisfy basic tissue needs. Active vasomotion, therefore, prevents large volumes of blood from being diverted into the extensive capillary bed where pooling and stasis will occur. In this way it provides for better capillary outflow and venous return.

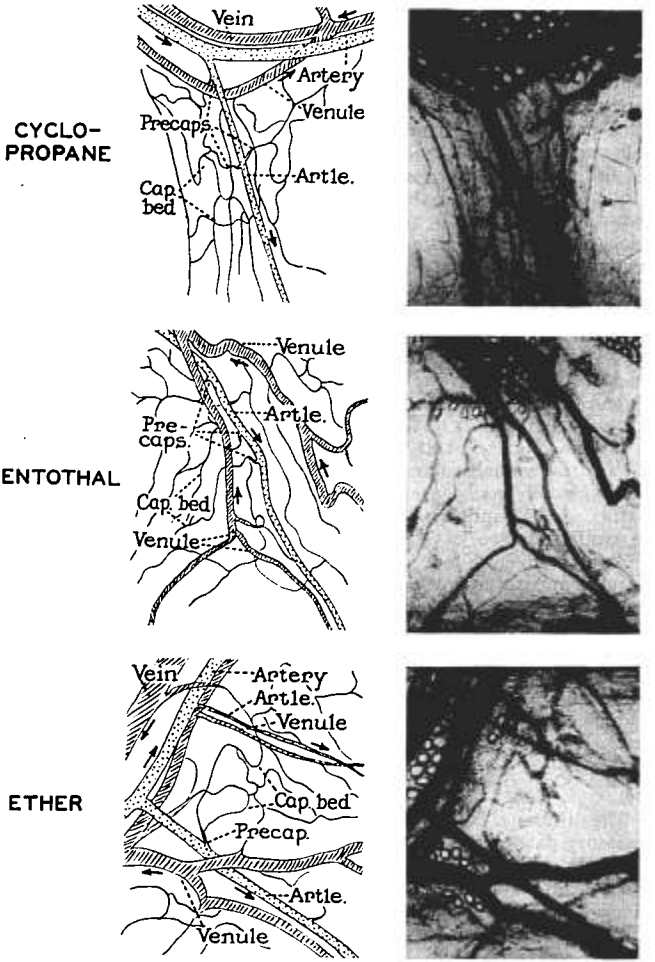

PLATE I

Vascular Response to Hemorrhage During Cyclopropane, Pentothal and Ether Anesthesia

Column 1: Schematized tracing of capillary bed is placed at the left, arteriole-Artle, precapillary sphincter-Precaps, capillary bed-Cap. bed, collecting venule-Venule.

Column 2: Photographs of capillary bed during anesthesia before hemorrhage (120 ×).

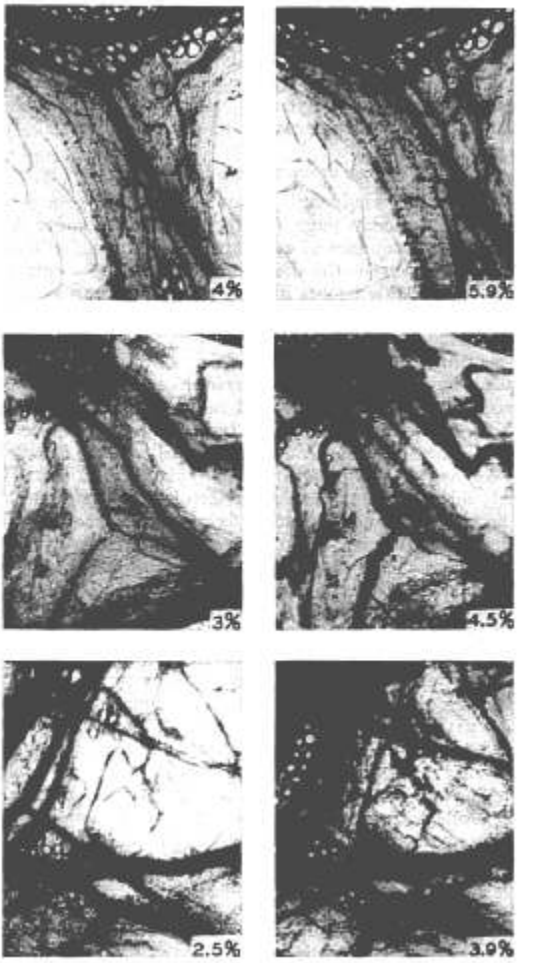

PLATE I

Columns 3 and 4: Photographs of capillary bed (120 ×) following hemorrhage (indicated on each photograph). Column 3 represents blood loss at optimum compensatory response. Column 4 represents maximum blood loss just prior to death.

Decompensatory patterns imply the opposite. Vasoconstriction is not as marked and is ultimately lost resulting in dilatation. Vasomotion is not as active and eventually becomes depressed or absent. As a result, the entire capillary bed contains blood, stasis is present, capillary outflow is poor and venous return impaired. Vascular permeability changes may also occur.

OBSERVATIONS AND RESULTS

The data for this study are presented as three groups of photomicrographs on a double page (Plate I). The photographs are arranged so that the sequence of events with each anesthetic can be followed horizontally across the double page and can be compared with the other two anesthetic agents in each vertical column.

Cyclopropane.—The *arteriole* becomes progressively constricted till at maximum blood loss it is a fine line (diagonally across the photograph). At this stage, when blood loss is fatal, the artery is also markedly narrowed. Several *precapillaries* readily visible before hemorrhage, are less prominent at 4 per cent blood loss and are no longer visible at maximal blood loss, indicating the presence of active vasomotion. This sustained and augmented vasomotion is reflected also in a decrease in the number of visible true capillaries. The *venule* immediately adjacent to the central arteriole contains little blood at 4 per cent hemorrhage and is practically empty at maximal blood loss. Venules, having little muscle, do not constrict effectively and participate little in these compensatory patterns. However, the venules here clearly demonstrate the absence of congestion and red cell packing indicating good venous flow even though the circulating blood volume is severely curtailed.

Pentothal.—Early in the period of circulatory stress (3 per cent blood loss) this animal shows good compensatory behavior, but later (4.5 per cent blood loss) the homeostatic mechanisms begin to deteriorate. The arteriole seen diagonally across the photograph becomes constricted early and remains so constricted until death. The degree of constriction, however, is not as pronounced as in the cyclopropane experiment. Since the arteriolar vasoconstriction is primarily under the influence of the autonomic nervous system, the persistence of this effect indicates there is little, if any, depression of the neurogenic homeostatic mechanism. Two prominent capillaries seen at the left of the photograph before hemorrhage are not visible at 3 per cent blood loss indicating good vasomotion and restriction in capillary filling. Later at 4.5 per cent blood loss these capillaries again become prominent demonstrating the subsequent failure of vasomotion. Closer inspection of these capillaries reveals stasis, congestion and actual extravasation, perhaps an indication of permeability alterations with a loss of circulating fluids into the tissues.

Ether.—During the control period it can be seen that most of the

capillaries are visible and the tissue appears moderately hyperemic, indicating a decrease in *vasomotion*. The (almost vertical) capillary loop between the two small (almost horizontal) arterioles is particularly noteworthy. At 2.5 per cent blood loss (maximum compensation) the artery and arterioles are partially constricted but not as completely as in the cyclopropane or pentothal experiments. Many of the true capillaries remain clearly visible in the field indicating poor vasomotion and a relatively unrestricted blood flow. The last photograph at 3.9 per cent blood loss (maximal) is especially striking when compared with the comparable scene in the cyclopropane experiment. The vascular reactions are almost purely decompensatory in nature. The arterioles by actual measurement are beginning to dilate although it can be seen that they are incompletely filled with portions of their lumina completely devoid of blood cells. This may indicate a partial failure of the neurogenic vasoconstrictor mechanism resulting in the inability of the vascular bed to accommodate itself to the decreased circulating blood volume. The capillary bed is congested and shows some extravasation of red cells indicating either capillary endothelial damage or permeability alterations of the capillary walls. Venous blood flow is virtually stagnant as indicated by the distended venules in which the red cells are closely packed.

DISCUSSION

An evaluation of some of the individual mechanisms that additively constitute peripheral circulatory homeostasis has demonstrated striking differences not only between anesthetized and unanesthetized animals but also in the effects of different anesthetic agents. While the photographic evidence is limited to the mechanisms of vasoconstriction and vasomotion and their direct implications, a number of additional mechanisms have also been studied, namely: rate of blood flow, reactivity of arterioles and precapillaries to epinephrine applied topically, presence in the blood of vasoactive substances, tolerance to blood loss, response to blood replacement, arterio-venous oxygen and CO_2 differences, and the accumulation in the blood of various end-products of metabolism (8). These are fully discussed elsewhere and only those bearing on the direct visual evidence presented will be considered.

The reactivity to epinephrine and the presence of vasoactive principles, as separable single homeostatic entities have a direct relationship to the visual data presented. Reactivity to epinephrine topically applied to the smooth muscle cells of the terminal arterioles and precapillaries is a measure of the intrinsic ability of these cells to respond to a physiological stimulus. In the cyclopropane experiments, as bleeding progressed, this response was greatly increased over the control level, the heightened response being maintained throughout. This would appear to indicate a relative lack of interference with this homeostatic mechanism by cyclopropane. During the pentothal experiments, the reactivity to epinephrine is also markedly increased at

first but later falls rapidly, eventually to become subnormal. In the ether series the response to epinephrine, which is subnormal even before bleeding, is increased moderately and transiently very early in the course of bleeding and virtually disappears toward the end of the experiment. Here again is another visual and measurable entity indicating that this homeostatic response in the presence of cyclopropane remains almost purely compensatory, while with pentothal an intermediate type of response is obtained and with ether the vascular response is almost purely decompensatory in nature.

The presence in the blood of vasoactive principles is also determined by direct visual means utilizing that rat mesoappendix assay previously described (4). While not a measure of the homeostatic integrity of a single visible structure it is determinable by a single clear-cut observation. Actually it is a measure of a complex homeostatic pattern directly related to renal and hepatic function (8). During normal conditions, as described by Zweifach et al., the blood contains extremely small amounts of two vasoactive principles in equilibrium with one another, as oppositely acting components of a homeostatic mechanism. These are vasoexcitor material (VEM) of renal origin and vasodepressor material (VDM) principally of hepatic origin (9). During circulatory stress this equilibrium is shifted either in one or another direction. In the compensatory phase of favorable homeostatic response, in which blood flow through the tissues is adequate, the blood contains large amounts of VEM. As the decompensatory phase of unfavorable homeostatic response sets in and a markedly reduced blood flow to the tissues persists, VEM gradually disappears being replaced by VDM which accumulates progressively. During the stage when VEM predominates the response to epinephrine is enhanced, and as VDM progressively accumulates the terminal vessels become increasingly refractory to epinephrine. When correlated with the experimental data presented here, it was found that in the cyclopropane series only VEM was present and VDM was never demonstrated in the blood. This is similar to the situation found in unanesthetized dogs (8). In the pentothal group VEM was present at first, but was gradually replaced by increasing amounts of VDM as the experiment progressed. For the ether experiments VEM was demonstrated transiently in small quantity and was early replaced by VDM which accumulated in the blood in large amounts. Actually it was possible to secure the highest titers of VDM by bleeding dogs anesthetized with ether.

The influence of anesthetic agents on the patterns of vascular response was therefore found to be characteristic and predictable. In fact the specific vascular effects in so far as each mechanism is concerned, were of sufficient magnitude to produce favorable, intermediate or poor homeostatic reactions in otherwise identical experimental procedures (10). For example procaine (regional), cyclopropane and

morphine (therapeutic dose) seemed to produce little, if any, impairment in the compensatory responses (8). Other agents such as pentothal and pentobarbital produced considerable depression of these compensatory activities (11). Ether administration resulted in extensive depression of these responses with sufficient vascular dilatation and endothelial damage leading to an early drastic limitation of these homeostatic phenomena.

In the last analysis the most satisfactory criterion of favorable homeostatic response to stress is the survival of the subject. Survival or reversibility, however, is an overall homeostatic pattern made up of a multiplicity of component individual mechanisms. Those directly related to the peripheral circulation are of critical importance and have been the subject of extensive investigation since Claude Bernard introduced the concept of the "milieu interne." Among the specific homeostatic mechanisms which enable the peripheral vascular system to protect the tissues and maintain unimpaired activity of the cells are, vasoconstriction, vasomotion, epinephrine reactivity (i.e., physiological integrity of the smooth muscle effector unit) and VEM-VDM equilibrium which have been correlated in these experiments as visual evidence of homeostatic efficiency. Doubtless, to these will be added many other mechanisms and measurements of neurogenic, metabolic and humoral nature.

From these visual, as well as other reported data, many inferences are possible both in relation to laboratory studies requiring the use of anesthesia and to the clinical administration of anesthesia for the completion of surgery. It would serve little purpose here to infer broad implications concerning the relative margins of safety of the different anesthetic agents. In essence, the data indicate that anesthetic agents, of themselves, have the capacity to alter the efficiency of some of the homeostatic or compensatory mechanisms of the peripheral circulation.

SUMMARY AND CONCLUSIONS

By means of visual (photographic) methods, the effects of cyclopropane, pentothal and ether on several homeostatic mechanisms regulating the peripheral vascular bed were compared. On the specific vasomotor mechanisms concerned, cyclopropane exerted little influence, pentothal an intermediate effect and ether a drastic, unfavorable effect.

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NOTICE CONCERNING ABA EXAMINATIONS

The Secretary of the American Board of Anesthesiologists has announced that the rule requiring six months notice before written examinations will be administered has been relaxed during this first period of the employment of the rule. Members desiring to take written examinations at the next period will be permitted to file their applications not later than April 21, 1950. This leniency is given because of the fact that the new rule was announced of late date.