Review

Anesthesia and the Systemic Venous Circulation

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This review has been prepared with two aims in mind: (1) to bring together data on the systemic venous circulation that may be of particular interest and concern to the anesthesiologist, and (2) to focus on the venous system as a hitherto neglected area that may be of even more concern in the physiology of the anesthetized patient than in the normal. Wiggers' recent suggestion that venous physiology presents a fertile field for investigation would seem to justify these aims, while at the same time conveying the additional hope of stimulating further studies as they relate to anesthesia.

Emphasis shall be placed on the physiology of the venous system and its role in maintaining circulatory stability. Responses of the venous system to the multiplicity of pharmacologic agents available may only be surmised by reviewing total circulatory responses or by comparison with similarly acting agents whose specific effects have been defined. There has been no systematic study of the effects of drugs on veins. Purchot has, however, reviewed the pharmacology of vascular smooth muscle. Other pertinent review articles and monographs cover many aspects of venous physiology that cannot be detailed here.

Cardiac Output and the Capacity System

The venous system contains more than 60 per cent of the blood volume and thus is an important reservoir in addition to functioning as a conduit to return blood to the heart at a sufficient filling pressure to maintain cardiac output. Despite changing concepts as to the significance of the several parameters influencing cardiac output, the venous return and right atrial filling pressure continue to be important, although they are by no means determine cardiac output.

As Patterson and Starling concluded, "The output of the heart is equal to and determined by the amount of blood flowing into the heart, and may be increased or diminished within very wide limits according to the inflow." This "inflow," it appears, is markedly influenced by venous activity.

More recently, Wiggers stated, "It is axiomatic that the heart can pump as much blood as it receives. Indeed, the volume of blood returned to the heart is the basic determinant of cardiac output. Since the latter varies tremendously under ordinary conditions of daily activity, the mechanisms that facilitate venous return have been the subject of discussion for centuries."

The factors considered to be of most importance in governing venous return have been (1) systemic arterial blood pressure, or vis a tergo, which supplies the distal pressure to effect a downward gradient back to the heart, and (2) factors on the venous side of the circulation, including the "thoracic pump" mechanism and the heart itself, which produce a low pressure area to which blood may flow. Both factors include the heart as a controlling influence, yet the heart is in many ways governed by the venous system. It would thus seem better to give up the concepts of vis a tergo and vis a fronte and to admit to an interdependent system where cardiac output cannot be considered independently of venous return. In discussing venous factors themselves one must be constantly aware that the separation can be made only for purposes of discussion and experimentation. As has been emphasized by Gauer and Guyton adequate cardiac filling is dependent not only upon a pressure gradient to permit flow to the heart but upon an adequate central blood volume. Thus, right atrial pressure is not so much a determinant of cardiac output as it is a parameter determined along with cardiac output.
output. Its value is governed in part by the capacity and volume of the entire circulatory system. The equilibrium pressure present at time of no flow has been measured by Guyton and identified as "mean circulatory filling pressure" (MCFP). This was found to be 6.3 mm. of mercury in the dog and fell 25 per cent with spinal anesthesia, but could be increased with fluid infusion or epinephrine. This static value provides a baseline upon which dynamic changes can be superimposed.

Since the largest part of the blood volume is contained in the veins, and the venous system is much more distensible than is the arterial, changes in mean circulatory filling pressure must be a function of the physical state of the venous system and its contained volume. It has been estimated, for example, that 40 ml. of blood added to the arteries could increase pressure by 40 mm. of mercury, but a similar quantity added to the venous side would increase pressure only 0.2 mm. of mercury. Since moderate hemorrhage or transfusion produces little change in pressure in either system, the altered volume must be accommodated by the more distensible area, where small pressure changes, varying linearly with volume, do, in fact, occur.

Many circumstances attest to the limited importance of right atrial pressure per se in influencing total flow. Under some circumstances, epinephrine can cause a reduction in right atrial pressure, but an increase in cardiac output; the cardiac output at rest is elevated in patients with anemia, A-V shunts, anxiety and thyrotoxicosis but there is no elevation of right atrial pressure unless congestive failure is present. Atropine and isoproterenol can increase cardiac output in the presence of decreased filling pressure and infusions of saline or albumin have been shown to effect no consistent change in cardiac output despite a regular rise in right atrial pressure. Similarly, stroke volume cannot be predicted from right atrial pressure in intact preparations.

Fowler correlated the increased cardiac output produced by hypervolemia with anemia rather than with volume itself, but could not relate change in output to cardiac filling pressure. Some of these changes may be due to viscosity alterations affecting the venous return primarily, with a secondary effect on cardiac output. Furthermore, the fall in right atrial pressure resulting from arterial bleeding cannot be correlated with cardiac output or stroke volume in man.

Having accepted arteriolar pressure distally and right heart filling pressure centrally as factors in maintaining flow, several others remain to be considered. The "thoracic pump" mechanism has been emphasized by Brecher as being important in that it helps to maintain a low downstream pressure and so to promote cardiac filling. In other words, right atrial pressure must be lower than peripheral venous pressure if blood is to flow toward the heart, and thoracic suction contributes to the maintenance of this low pressure. There is much to support this contention in that positive pressure breathing can decrease cardiac output, particularly in the patient with "circulatory inadequacy." Conversely, negative pressure breathing can increase cardiac output by increasing the amount of blood available to the heart.

Although there is evidence to the contrary, the reduction in output with positive pressure breathing probably arises not from increased pulmonary vascular resistance but from decreased cardiac filling due to the elevated intrathoracic pressure. The "pump mechanism" seems of less importance, however, when one considers the many situations, as with controlled respiration or prolonged periods of apnea during anesthesia, in which the venous return and cardiac output are not decreased significantly. It appears that with limited periods of apnea or well managed controlled respiration, loss of the normal thoracic pump mechanism may have only minimal circulatory effects.

In addition to thoracic "suction," right atrial pulsation has been considered a possible factor promoting venous return, but it now appears that pulsations of themselves are detrimental to cardiac filling, although a maintained fall in right atrial pressure of 1.0 mm. of mercury may increase return 14 per cent. The significance of ventricular diastolic suction is also problematical.

More peripherally, venous valves play a role, particularly in the erect position, and skeletal muscular activity promotes return by
externally compressing the veins during exercise. Although the roles played by these two factors have not been quantitated, the "muscle pump" venopressor mechanism as described by Yandell Henderson has assumed much less significance since it has been demonstrated that differential spinal anesthesia with sympathectomy block alone can produce the same circulatory changes as those occurring when the muscles are also paralyzed. This does not deny the fact, however, that with exercise the skeletal "muscle pump" is of significance in accelerating venous return, increasing the central blood volume and permitting an increase of cardiac output. This has been shown to occur instantaneously, although reflex autonomic stimulation of the heart has been prevented. The concept of a primary increase in venous return is not shared, however, by Franklin et al., who observed a simultaneous change in right and left ventricular output with onset of exercise and thought that venous return, therefore, cannot be a dominant mechanism in inducing the changes.

In this regard, the failure of leg exercise to elevate the cardiac output in the sitting position to levels attained with similar exercise when supine might give support to the latter viewpoint. Since the lower output when erect is presumed to be related to venous pooling, one might expect higher values of cardiac output than those observed when this is corrected by the "muscle pump."

**Venous Reactivity**

A further important factor governing venous inflow to the heart is the venous system itself and the dynamic changes which it undergoes in relation to the volume of blood it contains. Henderson was long an advocate of some venoressor mechanism regulating venous return to the heart, and laid much emphasis on depression of this mechanism with anesthesia, surgery, shock and trauma after noting decreased peripheral venous pressure in these situations. Although peripheral venous pressure itself is a relatively easy parameter to measure, it must be done with reference to a standard reference plane if values are to have any significance and to be comparable with those in other studies. The line chosen is usually the intersection of a frontal plane passing midway between the base of the xiphoid and the back with a transverse plane passing through the fourth interspace at the sternum. This locates the position of the right atrium. More crudely, it is a point lying in a frontal plane 10 cm from the back. This point is not to be confused with the "hydrostatic indifference point," which is defined as the locus of no pressure change when posture is altered and is determined physiologically by the elastic properties of the vascular bed. The latter point normally lies 9 cm below the diaphragm but its position may alter significantly. Thus, with application of negative g (acceleration with head as leading part) it comes to lie cephalad of the atrium.

The absolute reference point is useful for pressure measurements of both central and peripheral pressures and permits the two to be compared. They cannot be equated, however, because cardiac, respiratory, venomotor, pharmacologic and other variables affect the two differently. One particular postural situation in which peripheral venous pressure is a measure of central venous pressure has been described, but not extensively. In congestive heart failure the two pressures are closely related and parallel one another. In this situation the central venous pressure may rise to become equal to the peripheral venous pressure.

Intraluminal venous pressure measurement of itself can give little information as to the state of the veins because of the numerous variables (of which "venous tone" is one) which affect the pressure readings. Pressure readings (preferably transmural pressure) combined with volume measurements can give an expression of distensibility, or increment of volume change per unit of transmural pressure. Numerous studies of this type, as well as in vitro studies on isolated vein strips, have been the basis for most of the studies showing the systemic venous system to be a highly reactive one. It can alter its total and regional capacitances to a significant extent and thereby have a marked influence on overall circulatory dynamics. Evaluation of the characteristics of the total capacity system is made simpler because the arterial system is so much more rigid
than the rest of the circulation.\textsuperscript{119} Determinations of pressure-volume relationships in the total vascular bed therefore express the mechanical properties of the low pressure segment, of which the veins form the major fraction.\textsuperscript{120}

By means of moderate hemorrhage or transfusion such determinations have been made,\textsuperscript{20, 154, 276} and linear pressure-volume relations established,\textsuperscript{119} indicating a volume elasticity of 7 cm. of water per liter of blood in an average male subject. In these studies there was usually no interference from veno-motor activity nor evidence of any homeostatic regulation of venous pressure. Two subjects, however, who had the lowest central venous pressures, gave evidence of active venous constriction when stressed. It has been suggested that the low central venous pressures in these subjects may represent lowered central blood volume and that there is thus a greater need for a peripheral venoressor mechanism to operate if adequate circulation is to be maintained. On the other hand, the basis for the great variation in central venous pressures (25–130 mm. of water) among different "normal" individuals has not been defined and may represent differences in reactivity of venous smooth muscle.\textsuperscript{120}

Studies on isolated vein strips\textsuperscript{185} as well as those done on intact vascular beds\textsuperscript{4, 5} in animals have also shown veins to have a much greater distensibility than arteries. They exhibit, as do arteries, the phenomenon of "stress relaxation" with constant stretch of their walls, whereby distension results in relaxation and blood pooling.\textsuperscript{4} This phenomenon of "delayed compliance" could play a significant role in pooling in areas subjected to increased venous pressure from obstruction or other causes and may be a factor in sequestration of blood in the presence of a normal or only moderately elevated peripheral venous pressure.

Calculations of distensibility must include not only a $\Delta P/\Delta V$ relationship but must specify the time over which the change occurred. In addition, the starting point from which measurements are made should be specified, as distensibility curves are not linear (often presenting a sigmoid shape) and will depend on initial volume.\textsuperscript{5, 51, 241} The phenomenon of "hysteresis" has also been demonstrated to be present and results in different curves during the increasing and decreasing volume phases of measurement.\textsuperscript{4, 5, 165} While the physiological significance of this phenomenon is not clear, it has received much attention in relation to studies on vascular mechanics.\textsuperscript{214, 215}

Older evidence for neural control of the venous system has been reviewed by McDowall\textsuperscript{204} and Gollwitzer-Meier.\textsuperscript{126} More recently, further indications of the marked degree of venous smooth muscle reactivity is provided by studies analyzing changes in sequential segments of the circulation simultaneously\textsuperscript{201} in a preparation in which arterial inflow and venous outflow can be measured or fixed or both. Not only is a marked responsiveness of capacity vessels to sympathetic nerve stimulation demonstrable, but, most interestingly, maximal responses occur at a lower discharge frequency in the capacitance than in the resistance vessels. The presence of differential susceptibility or reactivity strongly suggests that vasoconstrictor responses must be further defined as to arterial or venous site and that use of the term "general vasoconstriction" gives an incomplete picture and can be very misleading. A dramatic example of this is Mellander's finding that sympathetic stimulation in the presence of constant inflow and outflow pressures can lead to a mobilization of 35 per cent of the regional blood volume in the capacitance vessels under conditions of "basal tone."

On the other hand, circumstances also arise whereby response to sympathetic stimulation appears to be strictly on the arterial side. Thus, in a study of changes in forearm blood flow in response to rapid alterations of intrathoracic pressure\textsuperscript{237} there was no change in forearm volume (capacity vessels) associated with reflex increase in flow. This suggests that neurogenic arterial vasoconstriction exists at a time when the capacity system is unaffected by such stimuli. A similar circumstance prevails in the dog foreleg, where studies of sequential vascular segments undergoing changes in pH demonstrate the ability of artery and "small vessel" resistance to change in opposite directions, while venous resistance remains unchanged.\textsuperscript{100}

A larger segment of the "reactive venous reservoir" has been studied in dogs using a
major vessel occlusion technique to isolate a large part of the venous system.20 A marked venous constriction in response to the increase in sympathetic activity resulting from carotid sinus hypotension augmented venous return independently of any elevation in arterial blood pressure. Thus, at least part of the arterial pressure response to carotid occlusion appeared to result secondarily from the augmented cardiac inflow following peripheral venous constriction. This would agree with Heymans' suggestion245 that "the most important change during reflex systemic hypertension of sino-aortic origin is probably that of venoconstriction." Although venous constriction appears not to occur in the central conduit, localized differential venomotor responses to both carotid occlusion and central vagal stimulation in dogs have been demonstrated in intestinal loops6 and in the lesser saphenous vein.245 Other areas also presumably participate in the response. This has been demonstrated by a technique utilizing extracorporeal circulation to permit constant arterial inflow and calculation of circulating blood volume from volume of blood remaining in the oxygenator.241

Modification of the major vessel occlusion technique has also lent support to this concept of individuality, particularly by providing further evidence that arterial hypertension is not the cause of the venous response to carotid occlusion.115 It therefore may be safely concluded that, in dogs, venous constriction and its associated redistribution of blood is an important primary component of the pressor response to carotid occlusion.

Other mechanisms of venous control are not so clearly established, nor is the role of the venous system as an initiator of reflexes very well defined.27,155 Even the venerable Bainbridge reflex 18 whereby increased central venous and right atrial pressure leads to cardioacceleration cannot be demonstrated with any consistency, and other reflexes (McDowall, Harrison) may in fact be mediated by chemoreceptors rather than by pressure changes in the great veins or atrium.13 Recently, however, there has been additional support for the idea that right atrial and other cardiac receptors have a profound effect on total venous capacity, thus to provide an important bulwark against circulatory overload.207,240 A similar reflex whereby elevations of caval venous pressure produce sympathetic inhibition and venous dilatation has also been demonstrated.7

Although a local limb reflex has been postulated in the dog whereby elevations of venous pressure leads to arteriolar constriction 144 the response may be a purely local one with no central nervous system mediation. In man, although small degrees of venous distention produced by cuff congestion result in no increase in extremity blood flow,57 raising or lowering the peripheral venous pressure by altering the position of the extremities results in diminished arterial inflow with any significant deviation of the limb from the horizontal. This has been confirmed in the dog with both normal and stenotic vessels 209 and suggests the presence of some yet ill-defined venous control over arterial blood flow.24,117 Support for a reflex effect is present in the finding 207 that although finger blood flow decreases with elevations of tissue pressure, maximal flow occurs at slightly positive pressures, a phenomenon that might not be expected were purely direct mechanical effects involved.

In addition, a local reflex response not dependent on innervation has been suggested to explain the increased resistance occurring in the dog's mesenteric bed when portal venous pressure is raised,252 but this may be a purely myogenic response.166 Although not considered a reflex phenomenon, most smooth muscles respond to distention with an increase in active tension and thus may contribute to vascular tone.101 This has been demonstrated in the resistance vessels of the human forearm, where there is an active vascular response to any increase in transmural pressure.29 The same does not appear to obtain in the dog's hind limb 210 or in the totally perfused dog.258 In the latter, there is actually a decrease in total peripheral resistance as venous pressure is elevated. The problem of peripheral venous reflexes thus remains an unsettled one.

While peripheral factors are of demonstrated significance in circulatory control, mechanisms of central control are just now coming under observation 192,242,243 and their relationship to peripheral controls being established. Thus, reflex response (with a known venous com-
ponent) to baroreceptor stimulation may be able to break through a strong central sympathectic drive. However, venous control \textit{per se} by central mechanisms is as yet an unexplored area. This may be of special concern to the anesthesiologist who is daily working with central depressants and yet has limited understanding of the mechanisms underlying many circulatory reflexes seen in practice. The changes seen with intra-abdominal manipulation \cite{222, 225} are a case in point: here, sympathetic inhibition and venous pooling may be a significant item in the production of lowered cardiac output and hypotension, \cite{278} although the myocardium itself may also be an important site of depression \cite{212} under these circumstances. Contrariwise, the reflex venoconstriction induced by instillation of fluid into the urinary bladder could be a source of \textit{hypertension} under certain circumstances.\cite{44}

The studies of venous distensibility in man alluded to above in relation to reflex activity form but a small segment of numerous investigations in patients and subjects relating venous volume, contractility and distensibility to a vast array of stimuli.

In 1933, Clark \cite{34} applied the plethysmographic technique to the extremities of man and described certain factors affecting the mechanics of veins and their alterations with age—older patients were found to have a more distensible system. Further use of plethysmography, \cite{10, 52, 58, 79, 80, 90, 120, 125, 128, 134, 152, 176, 198, 259, 277, 294} and measurement of pressure changes in isolated vein segments in man \cite{73, 108, 208, 255} have not only provided the majority of the evidence for venous reactivity in the extremities, but combined with other techniques (\textit{vide infra}) they have also permitted an evaluation of the role played by extremity veins in overall hemodynamics.

**Temperature**

Although forearm (primarily muscle) \cite{25} blood flow and oxygen uptake are significantly reduced with hypothermia and skin flow increased with elevated temperature, \cite{229} the capacity of forearm or calf vessels is changed but little by local or general heating above a comfortable temperature.\cite{134} Exercise produces little change \cite{176} or a vasoconstriction.\cite{296} In the hand (mostly skin) or entire extremity heating does not alter capacity although blood flow is increased. Cooling effects a reduction in capacity and distensibility as well as decreased blood flow in both skin and muscle \cite{52, 152, 153, 176, 294} and appears to shift blood centrally.\cite{154} In the finger, capacity vessels constrict and become less distensible with cold, while resistance vessels constrict initially and then undergo a period of dilatation.\cite{138, 164} Sequential segment studies in the dog also indicate different responses in various segments, with "small vessel" (partly "capacity") resistance increasing as the extremity is cooled.\cite{146}

In general, the response of capacity vessels to cooling (either general or local) is one of constriction and reduction of distensibility to as little as 70 per cent of the control value.\cite{58, 294} The release of catecholamines with cooling may play some role in effecting these changes.\cite{274} Heating, on the other hand, usually produces little change in capacity although increase in venous distensibility induced by nitrates results in more pooling at a 37.5° C. surface temperature than at 32° C.\cite{287} Furthermore, the limited circulatory response to stress during pyrexia\cite{163} may be related to a higher than normal venous capacity with peripheral pooling at elevated venous pressures.\cite{249}

It has not been established whether or not the findings quoted above may have clinical application during surgical hypothermia. Heretofore, investigations of circulatory problems during hypothermia have directed most attention toward the heart \cite{272} and essentially ignored the capacity system. Since the latter may undergo significant changes, particularly in the direction of \textit{increased} volume when \textit{rewarming} from a cool state, it seems possible that peripheral veins may play an important role in pooling blood in the rewarming period.\cite{30} This phenomenon might be aggravated by acidosis and contribute to the decreased cardiac output that is sometimes seen \cite{50, 95} during "rewarming shock."

On the other hand, depression of reflex response and the possibility of decreased venous tone \cite{31, 116} \textit{during} hypothermia, with recovery on rewarming suggests cooling itself as a possible source of difficulties. Hypothermia may also effect changes only indirectly; e.g.
decrease of plasma volume because of altered capillary exchange due to elevation of small vein pressures. Volume deficit, in turn, can be an important cause of hypotension and might contribute to some of the difficulties following inadvertent hypothermia in infants. On the other hand, small vein constriction may play an important and useful role by contributing the well-known reduction in brain volume that occurs with hypothermia. Thus, at present, the multiplicity of factors involved make it difficult to assign a specific role to the venous system as a factor in problems occurring during and after hypothermia.

In a more practical vein, the practice of applying local heat in order to make veins available for venipuncture has been shown to have a rational basis up to the point of comfortable warmth. This applies to total body heating as well, an item often forgotten in our cool operating suites. Light tapping can also produce venous dilation but pinprick, pinching and emotional stress cause only constriction.

Respiration and Carbon Dioxide

Alterations in ventilation may affect the systemic veins either mechanically, reflexly, or by varying pH, P CO2, or P O2.

The subject of intermittent positive pressure breathing has been reviewed recently and some of its effects have been alluded to here. With removal of the “thoracic pump” mechanism in apnea, one aid to cardiac filling is removed. Various degrees of positive pressure breathing, although producing fluctuations in intrathoracic pressure, result in further limitation of venous return and cardiac output by producing a less favorable pressure gradient for venous flow. An alternative explanation for the reduced output places emphasis on mechanical limitation of ventricular diastolic volume and force of ventricular contraction. In any event, cardiac output and central blood volume are both reduced in proportion to the mean positive pressure applied; peripheral venous pressure is increased and peripheral venous pooling occurs but can be reduced by counterpressure on the legs. Hemoconcentration follows as plasma volume decreases, probably because of elevated peripheral venous pressures. Systemic venous distensibility is decreased in the hand but not in the forearm. Venoconstriction as a compensatory mechanism appears to have little experimental basis and requires quantitation in terms of volume of blood not pooled as a result of a reduction in distensibility. This might be one approach to the analysis of the “compensatory mechanisms” which, if lacking, make the patient vulnerable to positive pressure ventilation. The instability due to hemorrhage, ganglionic blockade and general anesthesia, all of which may produce a relative volume deficit in relation to capacity, and the favorable response to drugs with known vennpressor activity is suggestive evidence that venomotor activity should be an area of primary concern.

The marked venous constriction occurring with the Valsalva maneuver is evidence of a similar nature. When repeated, the Valsalva maneuver, by leading to a reduction of plasma volume, may lead to further difficulty simply on the basis of volume deficiency. This, too, bears some similarities to conditions where a decreased plasma volume and elevated venous pressure may be related to controlled respiration.

The various alterations in hemodynamics produced by positive pressure ventilation may be produced indirectly during anesthesia and surgery, and in some situations result more from the surgery than from positive pressure itself. Thus, in the thoracotomized dog the changes observed have been ascribed to the open chest rather than to positive pressure. Anesthetized man, as well, when subjected to thoracotomy, suffers a reduction in stroke volume and central blood volume over and above any changes induced by controlled respiration. The reduction in cardiac output that appears as hypercapnia is corrected with controlled respiration during cyclopropane anesthesia may result partly from a reduction of abnormally elevated catecholamine levels and their vennpressor effect that had previously moved blood centrally. This mechanism, if operative, would complement the postulated “venpressor” effect of cyclopropane itself as a factor in maintaining a high venous pres-
sue and a normal or elevated cardiac output.\textsuperscript{169} Whatever the etiology of the elevated venous pressure during deep cyclopropane anesthesia, there is a greater tolerance to positive pressure breathing than during thiopental anesthesia\textsuperscript{220} or during light cyclopropane anesthesia with a proportionately lower central venous pressure.\textsuperscript{219}

The fact that hyperventilation with air or 5 per cent carbon dioxide compensates for the effects of positive pressure breathing\textsuperscript{177} suggests the presence of other respiratory reflexes altering hemodynamics. The venoconstriction of hyperventilation\textsuperscript{73, 80, 81, 268} with a centripetal shift of blood from the extremities may play a role here. The effect is not due entirely to hypocapnia since it occurs with 5 per cent carbon dioxide breathing as well, though to a less marked degree. Since pressure alterations in the respiratory tract are apparently not the cause of the response, a volume receptor has been postulated as the mediator.\textsuperscript{196}

The subject of alterations in hemodynamics consequent to changes in carbon dioxide tension has been recently reviewed.\textsuperscript{224} As in the case of arterioles, the direct effect of carbon dioxide on capacity vessels is one of dilatation. The reduction in $pH$ may, in fact, produce more complete relaxation here than in the resistance vessels.\textsuperscript{109} Since large vein resistance is not altered, it would seem likely that the hypotension occurring with carbon dioxide administration during spinal anesthesia\textsuperscript{193} may depend in part on venular relaxation. Capacity vessel dilatation in response to carbon dioxide has not been measured, however, in isolated denervated preparations.

In the intact preparation carbon dioxide has numerous effects dependent on autonomic stimulation, and the venous system is affected insofar as it responds to such stimuli. These may arrive in the form of increased concentrations of circulating catecholamines\textsuperscript{250} as well as from direct innervation.

Although cardiac output is increased with carbon dioxide breathing in conscious man\textsuperscript{224} this is accompanied by a small reduction in intrathoracic blood volume\textsuperscript{159} that may be caused by splanchnic pooling. During anesthesia, however, hypercapnia reduces the calculated splanchnic blood volume\textsuperscript{40} and in the dog reduces peripheral venous volume and distensibility.\textsuperscript{172} Increased venous return rather than increased peripheral resistance has therefore been suggested as the primary cause of the observed increase in cardiac output and elevation of blood pressure. The obtundation of circulatory responses to hypercapnia during anesthesia,\textsuperscript{225} studied primarily with reference to arterial blood pressure and heart rate, has not been examined with respect to venous responses.

Hypoxia as well as hypercapnia produce many responses via autonomic mediation, but these generally do not appear until inspired concentrations as low as 7 per cent are attained.\textsuperscript{83} At this point there is significant forearm venous constriction with little venous pressure change.\textsuperscript{83} This, if representative of a wider venous constriction, could shift considerable quantities of blood centrally and so increase cardiac output and blood pressure. Carotid chemoreceptor activation is the probable exciting influence since the use of perfusion techniques\textsuperscript{68} has demonstrated increased sympathetic discharge to the periphery with carotid body hypoxia, with venoconstriction being a characteristic response.

Post-hypercapnic hypotension,\textsuperscript{224} while having many theories propounded as to its etiology, remains an unsolved problem. The absence of any difference in response when seated or supine\textsuperscript{250} suggests that venous relaxation and pooling is not a significant factor. Nevertheless, activation of the sympathoadrenal system by carbon dioxide and the responsiveness of the venous system to sympathetic stimuli provide a basis for suspicion that this area might be involved when the stimulus is withdrawn.

**Posture**

Much impetus has been given to the study of physiological responses to postural change as a result of the greatly magnified accelerating forces encountered with man's exploration of space.\textsuperscript{121} Many of the problems encountered revolve about altered blood distribution and elevated venous pressures as the limiting factors in tolerance to gravitational forces. Thus, venous pooling is an important factor in the production of "blackout" with footward acceleration (positive g) and the probable
decrease in cardiac output and loss of blood from the thorax. The body responds with peripheral venous constriction. Similar changes, to a less marked degree, occur in man when arising from the supine to the erect position. Here, as much as 1,000 ml. of blood and fluid pools extra- and intravascularly in the extremities, plasma volume decreases, central venous pressure falls, and cardiac output is decreased. Accompanying these changes, heart and lung blood volume decrease as lower extremity volume increases.

Compensatory mechanisms are then brought into play to counteract these changes, and involve an increased output of catecholamines. The absence of catecholamine release is an indication of reduced sympathetic activity with venomotor instability that plays a large role in cases of postural hypotension. The compensatory tachycardia that appears is even greater when the blood volume is reduced. Total calculated peripheral resistance is increased, blood flow is decreased in many areas, and forearm arteriolar constriction (dependent on intact sympathetic innervation) also occurs as does veno-constriction. Entirely similar responses occur with volume depletion by other means, such as hemorrhage or venous congestion of the extremities.

In vasodepressor syncope and posthemorrhagic fainting reflex forearm dilatation accompanies the faint and is a distinguishing feature of these syndromes. However, peripheral venous pooling and decrease or lack of a compensatory increase in cardiac output are also factors leading to or perpetuating the syncope.

There is thus considerable evidence to suggest that both postural hypotension and vasodepressor syncope result at least in part from venous pooling in the lower extremities with a resulting fall in cardiac output, while tolerance to the erect posture is dependent upon sympathetic reactivity as it influences peripheral veins. This concept is bolstered by the ability to block the hypotensive response to tilt by "g" suits, extremity "massage" units, and water immersion, which effectively shift blood centrally; additional evidence is derived from the difficulty of producing syncope in the patient with congestive heart failure in whom there is an elevated blood volume and active venous constriction along with elevated venous pressures. Increased liability to postural hypotension produced by the application of negative pressure to the extremities, by sequestration of blood with application of cuffs to the thighs and by exercise prior to tilt all suggest central volume deficit as the limiting factor. These incriminate the extremity vessels as the storehouse of this volume, with a capacity that may be determined independently of the state of resistance vessels. Thus extremity flow is decreased with any deviation from the horizontal while volume is increased with dependency and reduced with elevation. This can be demonstrated further in the case of ganglionic and adrenergic blocking drugs (vide infra) wherein postural hypotension is due either to venous relaxation and a reduction in cardiac output while total peripheral resistance is largely unchanged, or at least to an inability to compensate elsewhere for a reduction in circulating volume in the face of extremity congestion.

The head-down or Trendelenburg position has not been as intensively studied as has head-up tilt. Far from innocuous when carried to extremes, even small degrees (20 degrees) of head-down tilt result in a reduction of plasma volume that may be missed later when a patient is returned to the horizontal position. Elevated cerebral venous pressure and cerebral edema are also distinct possibilities, although not as yet quantitated. Increased thoracic blood volume, though usually not deleterious, can be so if carried to extremes and may actually reduce cardiac output. The central shift of blood in the patient in congestive failure can indeed be catastrophic.

It has been documented that postural change during anesthesia is hazardous, as is any position that obstructs venous return. As long ago as 1895, Hill and later Henderson suggested insufficient venous return and blood pooling as the primary cause of circulatory depression with anesthesia. Since then, it has become accepted that depression of normal vasomotor responses with anesthesia increasingly limits tolerance to postural change with increasing depth of anesthesia. That the
depression markedly affects capacity vessels is suggested by the often recommended procedure of raising the extremities to correct a hypotension in situations where venoconstriction could have moved blood centrally had reflexes been functioning normally.

**Spinal Anesthesia**

The physiologic consequences of spinal anesthesia have been thoroughly reviewed by Greene. Clinically, hemodynamic alterations are commonly signified by arterial hypotension and, at times, bradycardia. A major cause of the arterial hypotension has been shown to be a reduction in cardiac output with a decrease in stroke volume and heart rate. Right atrial and pulmonary artery pressures are reduced as is blood flow in unblocked extremities. Calculated total peripheral resistance has been reported as either increased or decreased. The validity of the method of calculating total peripheral resistance in the presence of very low blood pressures was questioned by one investigator. Attempts to use a reduction in calculated peripheral resistance as an indication of arteriolar relaxation are, indeed, fraught with danger in the presence of altered flow rates and pressures. The variability of reported values together with the hazards in interpretation would suggest that changes in arteriolar resistance are of little importance compared to the reduction in cardiac output, despite the fact that blocked extremities do have an increased flow equivalent to that obtained with ganglionic blocking agents.

Extremity veins are dilated, total extremity volume is increased and pulmonary blood volume decreased. This would agree with the therapeutic value of spinal anesthesia in pulmonary edema. Peripheral venous pressure may be reduced although the veins be dilated, thus signifying a marked increase in distensibility. With loss of venomotor tone, the capacity system becomes inert and dilated and mean circulatory filling pressure is reduced. Volume then shifts strictly in relation to gravitational forces. Adequate cardiac filling becomes difficult when the head-down (Trendelenburg) position so vehemently advocated by Labat and Koster is not used, and the reduction in cardiac output and stroke volume can be ascribed in large part to insufficient venous inflow. Relative myocardial incompetence as a result of sympathetic block is undoubtedly a contributing factor since cardiac output at a given heart rate and given atrial pressure is lowered when activity of the cardiac sympathetic nerves is reduced. Under these circumstances the heart responds more clearly to an increase in filling pressure. This is readily seen clinically in the form of an increase in pulse rate when a patient hypotensive from spinal anesthesia is tilted to the head-down position.

This same position is described as a necessity for the safe management of total spinal anesthesia in the production of purposeful hypotension. The immediate implication here is that the maintenance of cardiac output is vital although it may not restore blood pressure. Under these circumstances there must certainly be a reduction in total peripheral resistance to account for the therapeutic hypotension. Any attempt to obtain it by head-up tilt is hazardous, though necessary on occasion.

Elimination of hypotension, on the other hand, frequently involves the prophylactic or therapeutic use of vasoconstrictor and cardiac stimulating drugs. Their rational use is dependent upon knowledge of their sites of action and on the pathophysiology of the syndrome being treated. A vasoconstrictor also having positive inotropic and chronotropic effects on the heart would seem to be most desirable. Few of the pressor drugs have been studied with respect to their ability to constrict veins although a large number are in common use. At present, mephenetermine, on the basis of its indicated ability to reduce forearm venous distensibility and at the same time stimulate the heart, would seem to meet the prerequisites. Metaraminol functions in a similar fashion. Both require further study with respect to their venous activity in man.

**Obstetric Hypotensive Syndrome**

In 1935 it was observed that a large number of women in the last trimester of pregnancy experienced relative hypotension, tachycardia, and respiratory difficulty when lying in the dorsal recumbent position. These diffi-
iculties, obviated by a change of posture, were ascribed to the uterus lying on the right posterior peritoneum and obstructing inferior vena caval flow. Heart volume was noted by roentgen-ray examination to be decreased. The syndrome has since been compared to that of fainting with the lordotic posture and to vasodepressor syncope; later it was identified as "postural shock in pregnancy," with the recommendation that the patient be turned on her side if she became hypotensive. A lateral or semilateral position, raising the uterus off the inferior vena cava, is generally effective in producing relief. The greater than normal incidence and degree of hypotension occurring in such patients either with spinal anesthesia or with tetraethylammonium ganglionic block has been ascribed to pre-existing excessive neurogenic tone which, when blocked, leaves the patient without needed support to propel venous blood past the obstructed vena cava. Here, emptying of the extremities followed by application of thigh cuffs was effective in preventing hypotension. Further descriptions of the "supine hypotensive syndrome" have appeared with some confirmation of the mechanism in dogs, where caval occlusion below the renal vessels was effective in producing hypotension only in pregnant animals. The femoral venous pressure in patients was further noted to be maximally elevated only in the supine position.

A reported 17 per cent incidence of hypotension after spinal anesthesia in such patients makes it a not uncommon problem. Uterine displacement is again effective therapy in restoring venous return. Skeletal muscular contribution to venous return is apparently not an important factor in this situation even though there is a mechanical obstruction to blood flow. Sensory anesthesia alone produced with 0.2 per cent procaine intrathecally results in a similar degree of hypotension.

Cardiovascular Disease

Two of the many disease entities presenting special pharmacological problems to the anesthesiologist are hypertension and congestive heart failure. In each, the systemic veins present special characteristics that may modify management of the patient during anesthesia and surgery.

Congestive Failure. Patients with congestive heart failure frequently have an elevated blood volume with an abnormally large fraction in the viscera and elevated central and peripheral venous pressures. Although volume increase in a system of limited distensibility could cause an increase in transmural pressure, there is reason to believe that the elevated pressures in congestive failure may result from active venoconstriction that can be blocked with hexamethonium and other blocking agents. These produce a reduction in central venous pressure (absent or less marked in normals) and central blood volume while not altering total circulating blood volume. Such treatment has been useful in the treatment of pulmonary edema, and the same can be accomplished with spinal anesthesia. Following cuff congestion in cases of heart failure the greater elevation of peripheral venous pressure than in controls can also be prevented with ganglionic blockers or stellate ganglion block and has been ascribed to peripheral venous constriction. Although spontaneous fluctuations in tone appear to be no greater than in normals, venous distensibility is decreased by 30 per cent in forearm segments of those in failure with elevated venous pressures and the reflex constrictor response to bladder distension is significantly increased. These changes can be reversed by successful therapy of congestive failure. The physiological significance of this abnormality, its probable central neurogenic mediation and ease of elimination by ganglionic, regional, or spinal block make it a vulnerable point in the patient receiving either general or spinal anesthesia as well as ancillary drugs, many of which can depress vasomotor reactivity (vide infra). The question of whether the resulting reduction in venous tone is helpful or deleterious remains to be answered. Clinically, however, it can result in a distention of peripheral veins that does not signify the onset or aggravation of heart failure. The venoconstriction may also be of distinct advantage in contributing to the flat response to the Valsalva maneuver (neither a fall nor a succeeding rise in arterial blood pressure) and in improving tolerance to situations inducing vasodepressor syncope in normals. Its
significance in promoting venous return and cardiac filling requires further clarification.

**Hypertension.** Although the mechanisms underlying essential hypertension are far from conclusively established, a substantial factor in the maintenance of the hypertension in many is an increased vascular reactivity. If stimuli are blocked, a larger fall of blood pressure results in hypertensives than in normals. Evidence provided by the intra-arterial injection of pressor drugs and by intravenous administration in the presence or absence of ganglionic blockers indicates greater responsiveness to such agents in the hypertensive than in the normal patient and suggests increased reactivity to be due to some property of the vessel itself rather than to excessive sympathetic discharge. The latter may, in fact, be diminished as evidenced by the absence of a normal plasma norepinephrine increase with head-up tilt. It has also been suggested that a primary increased tone of veins (capacity vessels) may be the primary change in the disease. At present, however, there is only suggestive evidence that capacity vessels are contracted or overactive, and also some evidence to the contrary. Forearm venous distensibility is not abnormal despite the presence of a marked increase in forearm peripheral resistance. It appears that, for the time being, there is little to incriminate the venous system in the pathogenesis and maintenance of hypertension in man. However, the abnormal catecholamine response to head-up tilt would lead indirectly to poor circulatory compensation in these patients, partly on the basis of inadequate vеноconstriction.

**Atropine**

A comprehensive review on the belladonna drugs has recently appeared in this Journal and considerable attention given to effects on the circulation. Some of this activity is directed at the venous system.

In recumbent man, atropine causes an elevation of cardiac output despite the presence of a decreased cardiac filling pressure and stroke volume. However, the ability of atropine in adequate doses (1–3 mg. i.m.) to produce postural hypotension has been well substantiated. Considerable evidence suggests that this is brought about by peripheral venous pooling leading to a reduction in cardiac output, despite an elevation in heart rate, but the mechanism causing venous relaxation has not been defined. Sympathetic ganglionic, central, and peripheral block are possibilities. In the anesthetized patient, where circulatory compensation for postural change is already inadequate, it seems likely that the belladonna drugs might produce further circulatory instability by their effect on veins. This is suggested by the ability of atropine to cause a diminution of the elevated central venous pressure that occurs during cyclopropane anesthesia in man. However, since it has been demonstrated in experimental preparations that vagal stimulation elevates mean atrial pressure at any given level of ventricular stroke work and that this effect is blocked by atropine, it may well be that the effect of atropine on the heart may be sufficient to explain changes in filling pressure.

On the other hand, the fall in central venous pressure with atropine has also been ascribed to either a change in pressure-volume characteristics of the venous system or a redistribution of blood within the vascular system, or to a combination of the two. Whatever the mechanism bringing about changes in filling pressure, the elevation of cardiac output in the intact subject receiving atropine could be considered advantageous, but no studies have come to our attention wherein anesthetized, atropinized patients have been subjected to postural stress. When this is done in the presence of nitrates, atropine does not block the syncopal response despite its ability to increase heart rate. If this type of pooling is similar to that which may occur during anesthesia, atropine would appear to be of little use in countering the resultant hypotension.

Since rate response is an important factor in altering cardiac output, the greater response of heart rate to atropine in younger subjects would, if considered as a compensation for peripheral pooling, make for greater circulatory stability in the young than in the old if liability to pooling is similar. Variation in rate responses with age has not been described for anesthetized patients, however, and may well not be as great as that in conscious sub-
jects. Rate increases are a general finding during anesthesia and appear to be related to the sympathetic and parasympathetic effects of the particular anesthetic being used.

Peripheral, the mechanism of the active cutaneous dilatation in the blush areas sometimes seen with atropine or scopolamine has not been defined. At least part of the response may be a primary or secondary venular dilatation, as skin color is partially dependent upon the state of venules. Since intra-arterial injections of atropine produce no increase in blood flow in the hand or forearm there is no basis for postulating secondary venous pooling from delayed compliance following increased flow. An effect on venules alone is still a possibility.

In search of a site of peripheral pooling, Horsley studied forearm venous distensibility and volume with the administration of atropine but found a decrease in both despite a fall in peripheral venous pressure. Thus, volume was shifted out of the extremity due to both active venous constriction and a fall in pressure. However, the same experiment has not been done under conditions of postural stress, where different findings might obtain. Since emotional stress can activate cholinergic vasodilator fibers to resistance vessels, atropine, under the conditions of the experiment, might have induced a relative constriction. However, evidence is conflicting on whether capacity vessels are able to increase their capacity from a normal resting state by further relaxation, and any increase in volume may be determined solely by the local transmural pressure. The general problem of cholinergic sympathetic vasodilator control has been discussed by Uvnäs. At present it is known to assume some importance only in skeletal muscle where it plays an important role in vasodepressor syncope. Little is known of its role, if any, in regard to capacity vessels.

**Narcotics**

Although arterial hypotension is a frequently occurring response to all narcotics the mechanisms underlying its appearance have not been elucidated. Tilt-table studies suggest vascular pooling as a likely cause but have produced no conclusive evidence explaining how the pooling occurs. Leg bandaging or anti-gravity suits are effective preventives. Histamine vasodilation may be one mode of action and has been shown to occur with meperidine in dogs in which a reduction in cardiac output appeared before any change in myocardial contractility, suggesting peripheral pooling as the basis of the hypotensive response. Antihistamine drugs can block the hypotensive response. Histamine has been shown to increase the extremity volume in man when infused intra-arterially but does not alter distensibility in the resting state. Although the exact site of action in causing pooling has not been identified, the fact that histamine may trap blood under certain circumstances suggests a possible role in opiate-induced hypotension.

Another possible mechanism of depression could be a direct action on the vasomotor center leading to a decrease in sympathetic impulses to capacity vessels or to a reduction in catecholamine liberation. Evidence for or against such a mechanism is not available. While correction of narcotic hypotension can be obtained, in part, with the opiate antagonists, one situation in which the vascular effect of the opiates is useful is that of pulmonary edema. Here the therapeutic efficacy is probably dependent upon vascular pooling.

**Local Anesthetics**

The effect of most local anesthetic agents other than cocaine on the peripheral circulation is believed to be one of vasodilatation. The mechanisms bringing this about as well as the exact loci of activity and dose-response relationships have yet to be determined. What appears to be inhibition of sympathetic vasoconstrictor activity can be readily seen clinically when a local anesthetic agent is injected intravenously to speed the administration of an infusion into constricted vessels. A direct effect on smooth muscle cannot, however, be excluded as the cause of the venodilatation. Although these peripheral effects may be of some clinical significance, emphasis on toxicity has been directed primarily at the heart and central nervous system and depressor circulatory responses ascribed to depression in these areas. Even with use as intravenous analgesics and anesthetics circulatory problems ap-
appear to have been minimal. In situations of uncontrolled absorption, however, peripheral venodilator effects may assume greater significance, but good evidence for this is lacking.

Digitalis

It is generally accepted that the most important site of action of the digitalis glycosides is the heart, although other areas are also affected. Arterioles are constricted, as measured by calculated peripheral vascular resistance and venous distensibility and forearm volume are reduced in man. In the dog as well there appears to be a generalized venoconstriction which increases venous return if pooling is prevented. Whether the venoconstriction produced by digitalis in man is useful in promoting cardiac filling and indirectly aiding ventricular function is, as yet, a moot question. It has been suggested, in fact, that the drug may foster pooling of blood and thus improve function.

Thrombosis

Thromboembolic disease is said to occur in 0.5–2 per cent of operative cases. Factors considered to be important in its etiology include trauma, hypercoagulability, and venous stasis. Radiographic evidence suggests that the last can be reduced by a 15 degree elevation of the lower extremities, and this position has been advocated for operating room use. Although total extremity flow is not increased in this position, indicators injected at the ankle appear to move centrally at twice the normal rate. This may signify more rapid flow through vessels liable to thrombosis. Another approach to the problem has been the development of various pneumatic circulators that apply intermittent pressure to various sites on the extremity. As yet, neither of these techniques appears to have been generally accepted.

It has been suggested that venous spasm from pressor stimuli may be an important factor in producing stasis. This thought should give pause to the anesthetist when observing a patient whose veins are obviously constricted, usually as a compensation for hypovolemia. It may also be an added reason for thinking twice before vasopressors are used to "support the blood pressure." At the present time, however, there is little reason to believe that venous constriction should result in stasis.

Pressor Substances

There is available a multiplicity of pressor substances of both exogenous and endogenous origin which produce venoconstriction and/or a reduction in venous distensibility, depending on the status of the vessel at the time of administration. An already constricted vessel will usually become more rigid (less distensible) while a dilated vessel will also become narrower. Distensibility may even be changed in opposite directions under different conditions. Looked on as a group, two major items stand out: (1) Responses of veins are not necessarily the same as those of arteries, either in direction or in degree. For example, epinephrine dilates forearm muscle resistance vessels while constricting capacity vessels. (2) Responses of different segments of the venous system vary with respect to direction, degree, duration and sensitivity depending upon vessel size and location. Similar differences occur in arteries, but may differ in degree and direction from the changes in veins.

Aviado has summarized the actions of many of the pressors and made a beginning at classification on the basis of pharmacological effects. Burn has presented an additional classification based on whether a given substance acts directly or via the release of norepinephrine. This has received some confirmation. Many drugs may act on veins in the latter fashion since venous innervation is similar to that of arteries and norepinephrine has been isolated from venous walls as it has been from the heart, arteries, and other tissues.

That norepinephrine can be discharged locally from venous walls by sympathetic stimuli has not yet been demonstrated, but administration into a vessel can produce intense constriction, as is frequently seen clinically (often with untoward results) and distant systemic administration produces effective responses. The same is true of the entire group of so-called "pressor drugs" which elevate arterial blood pressure, and to our knowledge there is none to which the venous response has
been studied which does not produce venoconstriction in some area. This, alone should suggest what has frequently been demonstrated: that the effectiveness in elevating blood pressure is often highly dependent on venoconstriction. This is shown most strikingly with norepinephrine, which can produce an increase in blood volume in the heart and lungs equivalent to 20 percent of the total blood volume before there is any elevation of arterial pressure. Both epinephrine and norepinephrine diminish the systemic vascular volume of the dog as they reduce venous distensibility and shift blood centrally. As might be expected, the pressor response is still dependent on intravascular volume. The multiplicity of evidence for the venoconstrictor activity of norepinephrine includes the following: increased rigidity of dog vena cava; human forearm venoconstriction with shift of blood centrally; human digital venous constriction; venous constriction with topical application in the dog; elevation of venous resistance in the dog foreleg; increase in small-vein pressures and constriction in the splanchnic circulation of the dog; elevation of venous pressure in the rabbit ear; weight loss of the dog’s hindlimb perfused at a constant flow rate.

In general, the following may be stated: norepinephrine (levarterenol) is a venoconstrictor in nearly all circumstances and locations. Of the other sympathomimetic amines, epinephrine (adrenalin) acts similarly but less effectively and at certain times and locations is a venodilator. Phenylephrine, metaraminol (Aramine) and mephenetermine (Wyamine) seem to be uniformly constrictors with the ability to shift blood toward the heart and counteract vascular pooling, while isoprotrenol (Isoprenaline) has more variable effects though still effectively moving blood centrally. Paredrinol (Pholedrine), ephedrine, and methamphetamine (Methedrine) likewise have been shown to be venoconstrictors where studied.

Some drugs of the ergot group have been used effectively to counteract the hypotension of spinal anesthesia and have been incriminated in producing excessive hypertension in the postpartum patient, especially when used in combination with pressor amines. Others appear to act only as blocking agents. Oxytocin may also have a pressor effect and vasopressin certainly is a venoconstrictor having direct action on vascular muscle.

5-Hydroxytryptamine (serotonin) is, as always, a difficult agent to classify and may have physiological venoconstrictor activity. Its effect may depend on a significant extent on the pre-existing condition of the vessels.

Methoxamine (Vasoxyl) has excited considerable comment of a negative nature and is said to be a pure peripheral vasoconstrictor (arterial) that reduces cardiac output primarily by effecting a reflex slowing. One piece of evidence suggests that it may cause pooling by trapping blood peripherally, an effect that would, indeed, be a new one for a drug of the pressor amine group. It continues to be used effectively to elevate blood pressure during both spinal and general anesthesia.

Angiotensin is a relatively new pressor principle that has been both isolated in man and synthesized. It appears to be a potent vasoconstrictor with venoconstric tor activity less than that of norepinephrine when used in doses producing an equal pressor effect.

The problem of postinfusional hypotension following the administration of epinephrine or norepinephrine remains unsolved. Local vascular insensitivity with excessive storage, ganglionic block and release of a dilator substance have been suggested as possible factors in its etiology. Although the capacity system is affected, the extent to which it is, and its significance in producing hypotension have not been determined.

Drugs Inducing Hypotension

Any drug interfering with sympathetic nervous system activity is apt to produce venodilatation or diminished responsiveness when the body must respond to circulatory stress, as with head-up tilt or the Valsalva maneuver. The major drugs in this group, all able to produce vascular pooling, are the ganglionic blocking agents such as hexamethonium, pendimidine, mecamylamine, pentamethonium, pentolinium (Anoslysen), chlorisondamine.
and trimetaphan (Arfonad).\textsuperscript{212, 232, 241, 280}

All of these drugs elicit vascular pooling, which is probably the primary cause of the associated postural hypotension and reduction in cardiac output. Calculated total peripheral resistance is minimally altered.

Adrenergic blocking agents such as bretyllium,\textsuperscript{50, 115} phentolamine (Regitine)\textsuperscript{51} and guanethidine,\textsuperscript{1, 50, 114, 115} although having different mechanisms of action from the ganglionic blocking drugs, also induce venous relaxation.

Drugs acting directly to induce venodilatation with significant pooling of blood include the nitrates and nitrates,\textsuperscript{109, 250, 287} histamine,\textsuperscript{63, 125, 147} and cobra venom.\textsuperscript{26}

Diuretic hypotensive agents of the chlorothiazide\textsuperscript{6, 175} group may effect vascular pooling or reduction of venous responses by producing ionic changes that alter smooth muscle reactivity.

The phenothiazine derivatives\textsuperscript{72, 77} with several sympatholytic sites of action, reduce venous reactivity as a result. Chlorpromazine, the best studied of the group, can produce marked postural hypotension, but its less well-studied congeners may be much safer in this respect.

Sodium nitroprusside\textsuperscript{202} has been described as a potent hypotensive agent and may exert its effects via systemic venous pooling.

Reserpine and its congeners act at least in part through the release of tissue catecholamines and probably exert their major vascular effects through depletion of these substances at the effector site. Implications of their use\textsuperscript{47, 48, 50, 53, 56, 61, 115, 203, 281, 299} in the anesthetized patient are discussed in the section on general anesthesia.

In summary, it is interesting to note that most of the hypotensive agents studied with respect to their relative arterial and venous effects appear to exert their major therapeutic or toxic effect through their influence on the venous system. This does not include, of course, drugs that have a primary action on the heart.

**General Anesthesia**

The general problem of hemodynamics during anesthesia has been reviewed recently.\textsuperscript{226}

Only certain aspects pertaining to venous function in particular shall be mentioned here.

Alterations in the venous system produced by general anesthesia result from a multiplicity of both direct and indirect effects of anesthesia and operation. As in the case of the heart and arterial system, analysis of mechanism becomes complex because of the many variables involved. Even the clinical evaluation of the status of the vein has lagged, in that usually no routine measurements comparable to the taking of pulse and arterial blood pressure are made.

Central and peripheral venous pressure monitoring has been done on occasion during routine anesthesia to aid in determining the need for blood replacement\textsuperscript{290} and to help evaluate cardiac status; but such information is of assistance only in the light of knowledge of other changes\textsuperscript{218} (e.g., some knowledge of quantity of blood lost, use of vasopressors) and must be interpreted carefully. Thus, an elevation of venous pressure is usually not due to congestive heart failure and a falling venous pressure need not signify hypovolemia. Venous pressure measurements are, nevertheless, of value and should probably be used more frequently.

The peripheral venous dilatation usually seen after induction of anesthesia signifies a reduction in venous "tone" (increase in distensibility) if the transmural venous pressure is not elevated. At times, however, it is. Venous relaxation appears to occur in the case of thiopental\textsuperscript{84, 279}; forearm venous distensibility\textsuperscript{84} is increased with large doses while venous pressure falls. Here, then, venous relaxation provides sufficient explanation for the occurrence of venodilatation. Transient increases in hand distensibility were also observed with induction doses of the drug.\textsuperscript{279} Although direct evidence for relaxation of capacity vessels in man is limited to the above, ancillary evidence makes it appear likely that the immediate effect of anesthetic agents on venules, postarteriolar or capacity vessels is one of depression.\textsuperscript{194, 800} though several have been shown to cause contractile responses in rabbit aortic strips\textsuperscript{228} and to increase the response to catecholamines.\textsuperscript{131, 228} It should be noted, moreover, that it is impossible to trans-
fer data from tissue to tissue, or species to species in studies of this nature.67

There is general agreement that cardiac output is reduced during thiopental anesthesia in man.92, 107 This is associated with a calculated reduction in central blood volume and no elevation of central or peripheral venous pressure.220 These findings, together with the presence of increased forearm venous distensibility, strongly suggest capacity vessel pooling as a major factor leading to the reduction in cardiac output. Decrease in hemoglobin concentration211 may be ascribed to an increased plasma volume consequent to a reduction in small vein pressure.185 The indifferent sympathetic response to thiopental anesthesia223 and consequent lack of venoconstriction would appear to be of fundamental importance in explaining the total hemodynamic change consequent to its administration.

Unlike thiopental, cyclopropane and ether anesthesia evoke marked sympathetic responses.58, 223 While there is incomplete agreement on changes in cardiac output, it would appear that it is increased during cyclopropane anesthesia in the unpremedicated patient169 and that ventricular function is not depressed.227 The associated consistent elevation of central venous pressure,187, 221 tolerance to hemorrhage,96 reduction in plasma volume222 or little change after thirty minutes150 are all findings consonant with an increase in venous constrictor activity that plays an effective role in maintaining venous return and, therefore, cardiac output. The similarity of responses to cyclopropane in the dog to those of carotid occlusion 229 further suggest important venous effects since a highly significant part of the response to carotid occlusion is venoconstriction (vide supra). Venous dilatation with induction of anesthesia is not inconsistent with an overall constrictor effect, since sleep itself is associated with an increase in venous distensibility which is probably related to release of sympathetic tone.

Introduced in 1956, halothane has in the past seven years come to be a commonly used anesthetic agent.168 Its effects on the circulation have been reviewed.64, 74 The sympathetic adrenal response seen with cyclopropane anesthesia is not present with halothane.223, 225 With other than very light anesthesia the myocardium is depressed in both intact and denervated preparations,52, 107, 257, 264 Cardiac output is reduced and central venous pressure increases initially but decreases with time.65, 182, 197, 253 While central blood volume is reduced,182 plasma volume is increased.130, 264 Peripheral dilatation occurs in muscle resistance vessels 27 and has been ascribed to both central and peripheral actions of the drug.46 Although capacity vessel dilatation has not been measured, increased venous distensibility and blood pooling have been suggested as a partial cause of the reduction in cardiac output.65

Given in sufficient doses, the relaxant drugs may alter hemodynamics by histamine release or ganglionic blockade209 in the case of curare and by the production of arrhythmias and hypertension with succinylcholine.289 The latter may appear because of ganglionic stimulation. There is, at present, no reliable evidence to confirm any important effect on the venous system, although succinylcholine has been reported to produce conjunctival vasodilatation and increased mesenteric and femoral arterial blood flow in the cat. Histamine in sufficient quantities or adequate ganglionic blockade by curare could, of course, result in capacity vessel dilatation, but this appears to occur rarely, if at all.

Much caution has been urged on the anesthetist managing patients receiving antihypertensive therapy.56, 61, 299 It has been suggested that those patients being treated with reserpine or its congeners have the drug withheld for ten days prior to anesthesia and operation, as this approximates the time required for restoration of norepinephrine stores that had been depleted by the drug.281 Many points in the circulation are made vulnerable by norepinephrine depletion and depression of venoconstrictor reflex responses in the dog receiving reserpine has been demonstrated.115 This could play an important role in producing hypotension during anesthesia. Guanethidine has similar effects, but its mechanism of action differs from that of reserpine. Although patients receiving such therapy have altered responses to some vasopressors their circulatory instability may respond well to careful management203 and need not warrant delay of operation. This has been our own experi-

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ence. Failure of reserpine therapy to alter the increased cardiac output of hypoxemia in man further suggests that the anesthetic hazards may not be as great as was supposed.58

Two other problems involving venous responses occurring during anesthesia must be mentioned. The release of arterial clamps and reinstitution of distal blood flow after aortic surgery is often accompanied by a temporary hypotension as the distal vascular bed is filled. This is associated with pooling of blood and a reduction in right atrial pressure and cardiac output.174, 210 Introduction of acid metabolites into the systemic circulation may contribute to the depression. Therapy with a drug having vasoconstrictor activity would appear to be indicated.

Pooling has also been reported to be a problem during cardiopulmonary bypass,128 with the splanchnic area or spleen,268 as a likely site for its occurrence in the dog. The problem would appear to be more common than published reports suggest and is currently undergoing further investigation.

Summary and Conclusions

The venous system, containing two-thirds of the circulating blood volume, has been shown to be a highly reactive one subject to a variety of stimuli which can readily alter its distensibility characteristics and capacity. Regulation of cardiac output is partly dependent upon such changes, which may arise through a variety of reflex phenomena, of which the carotid sinus mechanism is of outstanding importance. Major capacity changes and translocation of blood also occur with a variety of respiratory phenomena, variations in carbon dioxide tension, temperature change and alterations of posture. Venous reactivity or its inhibition plays an important role in many circulatory responses to both spinal and general anesthesia and shows deviations from the normal in the obstetrical patient and those with hypertension or congestive heart failure. Responses of the venous system to opiates, atropine, local anesthetics, digitalis and a variety of pressor and depressor drugs are considered and evidence presented which indicates the venous system to be an important site of action of such drugs. Pressor and depressor agents, in particular, may have this as their major important site of activity.

No attempt has been made here at a precise definition of the “capacity” system. It comprises those areas which can alter their volume significantly, including the pulmonary bed. The latter, however, has been omitted in this discussion. It is thought that veins and venules form the major segment of the capacity system and that it undergoes marked dynamic changes with a variety of stimuli. As a result, it has a profound influence on total circulatory dynamics.

If the reader upon finishing this review believes it to be in the nature of a plea for a place in the sun on behalf of the venous circulation, let no misunderstanding exist: it is.

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Surgical Teams for South Vietnam

Surgical teams are being recruited by the United States Public Health Service to provide emergency surgical care to the civilian population of South Vietnam. Four teams are now on duty in the cities of Can Tho, Nha Trang, Da Nang, and Pleiku.

Dr. Luther L. Terry, Public Health Service Surgeon General, said, "The Government of South Vietnam has requested additional surgical personnel. The teams now on duty are making an important contribution to the health program for the care of civilians in that country."

The staff of each team includes a chief surgeon, assistant surgeon, anesthesiologist or nurse anesthetist, operating room nurse, surgical ward nurse, and medical technologist. Only United States citizens are eligible for assignment. Teams are serving in regional hospitals where new surgical facilities have been completed. Assignments are for two years. Experienced surgeons and surgeons completing residency by July, as well as other team members, are being recruited.

Salaries correspond to the current scale for foreign duty, with allowances for quarters and dependents. Families may accompany team members to South Vietnam.

Details may be obtained from Dr. Leo J. Gehrig, United States Public Health Service, Washington 25, D. C.