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STERN - ROLE OF THE CNS IN HEMORRHAGIC HYPOTENSION

THE ROLE OF THE CENTRAL NERVOUS SYSTEM IN HEMORRHAGIC HYPOTENSION.

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ABSTRACT

The effect of head elevation during 150 min. of hemorrhagic hypotension was examined in unanesthetized dogs, as compared with animals in which the head was placed at the level of the aortic origin. Head elevation caused a more rapid onset of severe neurologic impairment to supervene during hypotension, together with significant lowering of mean pH and greater mortality. This may suggest that severe cerebral ischemia during shock augments reflex peripheral alpha adrenergic activation. Bradycardia occurred in 7 of 16 animals during the hypotensive interval. Six of the 7 affected animals were from the head-elevated group, while all had signs of marked neurologic deterioration; 100% of these animals died during post-shock monitoring. Concomitant observations of accelerated blood uptake after prior disappearance of phasic vasomotor activity, and of reduced total peripheral resistance following retransfusion, suggests that prolonged cerebral ischemia incurred during hemorrhagic shock may give rise to an eventual decline in both alpha and beta adrenergic activities.

TO CHERYL

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"The human mind is . . . . a most imperfect apparatus for the elaboration of general ideas . . . . General impressions are never to be trusted. Unfortunately, when they are of long standing, they become fixed rules of life, and assume a prescriptive right not to be questioned . . . . But it is the triumph of scientific men to rise superior to such superstitions, to devise tests by which the values of beliefs may be ascertained, and feel sufficiently masters of themselves to discard contemptuously whatever may be found untrue . . . . the frequent incorrectness of notions derived from general impressions may be assumed . . . ."(86)

The Role of the Central Nervous System in Hemorrhagic Hypotension

Chapter I:

PREFACE

The term "shock", with its several connotations, classifications, and modes of treatment, has been one which remains singularly difficult to characterize within an all-inclusive definition. In trying to encompass the major etiological schools of thought in this regard, Pierce[203] recently has offered a most comprehensive description of this entity: "The shock syndrome seems best defined as: A state of prolonged circulatory deterioration, initiated by damage to one or more of the components of the circulation, perpetuated by multiple endogenous factors and resulting in inadequate tissue perfusion and death of cells." The notion that the consequences of the shock state largely may be influenced or perhaps even engendered by a specific component of the circulatory system has been championed by several investigators, each propounding as being of overriding importance the particular "shock organ" in question.[46,100,162,234] A more sweeping viewpoint, emphasizing the importance during shock of generalized cellular dysfunction, recently also has become prominent, and Schumer has summarized this concept by labelling shock a "molecular disease".[232]

Regardless of one's theoretical preferences, however, it may be stated that the relevance of the central nervous system in the evolution of the shock syndrome has continued to be in question. Although considerable knowledge has accumulated concerning the secondary effects of shock on the brain, in addition to the impact of both destruction and protection of central nervous structures on the course of the shock state, this information has yet to be incorporated into a frame of reference from which a more cogent analysis of pertinent central nervous influences may be deduced.

In the approach to this problem, the present work utilizes as the method of choice that form of shock eventually precipitated by volume-depleting hemorrhage. The model chosen is one based on the Wiggers technique[261] as modified by Lamson and DeTurk[151]. Here, animals are bled into a reservoir until a predetermined arterial pressure level is attained, and are held at this level for a set period of time; alterations in arterial pressure are accommodated by an open communication between the reservoir and the bleeding artery, which allows continuous equilibration of pressure changes. If arterial pressure falls, blood is "taken up" from the reservoir, and conversely enters the reservoir when the pressure rises. At the end of the designated hypotensive period the blood remaining in the reservoir is reinfused; the animal may then either survive, or over a period of several hours succumb to "irreversible shock".

Certain aspects of this experimental model may be justly criticized. Apart from varied reactions to severe hemorrhage which are accountable to species differences alone[268], it remains open to question whether events in the latoratory can usefully be related to the clinical shock situation as it exists in man. The concept of irreversible shock, for example, has been emphasized by Moore[180] as applicable only to "certain laboratory phenomena; it is a term which should not be used in clinical surgery because it connotes an attitude of hopelessness which may cost the patient's life". Weil[258] later confirmed this viewpoint by stating: "Irreversibility is properly regarded as a statistical term, indicating likelihood of fatal progression of shock and failure to revive the experimental animal . . . The concept is only meaningful in the experimental laboratory in which a well-defined experimental technique is used to

produce shock with a statistically predictable mortality". Other complicating factors are those introduced by anesthesia[61,267] and traumatic preparative procedures,[73] both of which are known to affect the results of experimental studies to a significant degree; in addition, the inevitable exposure of reservoir blood to air and glass may alter plasma proteins and generate vasoactive substances which are capable of causing later undesirable effects[158].

In tending to bring the experimental procedure closer to the clinical circumstances under which hemorrhagic shock occurs in man, the present model nevertheless has certain definite advantages. Studies were performed in unanesthetized animals which had been subjected to minimal preparative surgical intervention. Hemorrhage was induced with dogs in the standing position; recent work by Desai et al[54] has demonstrated that this unanesthetized animal is able to withstand hypotension in this position for several consecutive hours. Assuming therefore that in making the control and experimental comparison the above-mentioned encumbering factors are equalized, significant differences elicited in relation to manipulation of a single variable are not necessarily invalid. Thus, while the course of hemorrhagic hypotension is manifested somewhat differently in the canine species as compared to man, within certain definable limits, the basic pathophysiological reactions to a hypotensive stress remain universal. Whether the conclusions of an experimental study have pertinent implications in the search for improved methods of treatment must await their painstaking evaluation both through further experimental documentation and in applied clinical research.

The purpose of the present investigation, then, was to observe the clinical neurologic and hemodynamic consequences of the cerebral ischemia

which inevitably occur during the course of hemorrhagic hypotension and shock. Cerebral ischemia during hypotension was augmented physiologically by the use of head elevation, and the effects compared to the results of cephalic dependency under similar circumstances. By applying the clinical neurologic picture as an index of the severity of cerebral blood deprivation during hemorrhagic shock, the significance of central nervous ischemia as a contributor to concurrent hemodynamic alterations was hopefully to be appreciated.

Chapter II

HISTORICAL REVIEW

Implication of the central nervous system as a prepotent influence on the syndrome known generally as shock has had, at best, a sporadic history. Even early records disclose a conflict of opinion as to whether the brain should retain a primary or secondary role in this regard, a controversy which in some respects persists to the present day. The following is a brief historical review outlining the sway held by these basic opposing viewpoints in the shaping of modern shock concepts, with the emphasis placed on that type of hypotensive shock due specifically to hemorrhage.

A. Effects of hemorrhagic hypotension directly on the central nervous system.

In his treatise on "constitutional irritation" and other related subjects, Travers[248] described shock and prostration as being due primarily to the impact of untoward events directly on the brain, with subsequent effects being exerted on the function of other body systems; this concept was propounded by later authors as well[112,135]. In an exhaustive historical review, Wiggers[261] cited the evolution of ideas leading to development of the first comprehensive theory of shock etiology: that of exhaustion of the medullary vasomotor mechanism with resultant vasomotor paralysis. Thus, despite a lack of definitive evidence until the turn of the century, circulatory failure with pooling of blood in the intra-abdominal vessels and subsequent hypotension were regarded as the salient features constituting the shock syndrome. Although some argued that shock, with its attendent signs such as hypotension and general insensibility, was due principally to inhibition of body systems[105,177], the concept of vasomotor failure was further strengthened by Crile[45], who established the experimental method as an essential avenue toward progress in this area. Using the dog as his basic laboratory preparation, Crile became convinced that a low blood pressure was the sine qua non of shock symptomatology. His conclusions gave scientific respectability to the conjectures of earlier investigators: "If the stimuli are so intense that the brain cells become so damaged as to be unable to perform their work, the condition is commonly designated shock . . . . in (vasomotor) exhaustion, the function of the brain cells was impaired before the blood pressure fell".

Crile's theory, however, was destined to be disproved on both of

its basic assumptions. Porter and Quinby[207], in a summary of experiments relating to excessive stimulation of afferent nerves as a cause of low blood pressure and shock, concluded that such afferent nerve activity could at no time be shown to produce hypotension; additionally, in finding that stimulation of the central end of the vagus nerve could raise the blood pressure at any level of hypotension, Seelig and Lyon[233] disproved the exhaustion theory decisively. In his monograph on traumatic shock, Cannon's[29] viewpoint reflected the gradual trend away from consideration of the brain as a prime factor in the development of shock; thus, while he concurred with accumulating evidence that vasomotor exhaustion was not responsible for hypotension[134], he did feel that its prolonged presence might eventually be detrimental to the brain.

Nevertheless, the theory of excessive afferent nerve stimulation as a cause of central nervous depression and subsequent shock had become prominent in the years surrounding the turn of the century, although having especial applicability to traumatic vs. hemorrhagic shock. Worth mentioning in this regard was the detrimental influence of superadded hemorrhage noted in experiments where afferent stimulation either preceded or was combined with the bleeding episode. Thus, Phemister[201,202] found that either situation shortened the survival period, while Overman and Wang[196] also concluded that strong sciatic stimulation in the dog during sublethal hemorrhage resulted in a higher mortality rate than with simple hemorrhage alone. That these undesirable effects might have been due to a cumulative sympathetic vasoconstrictor response precipitated by both hemorrhage and afferent nerve stimulation was not appreciated at that time.

More recently, numerous pathological studies have added to a growing body of knowledge concerning the direct effects of hypotension and shock on the central nervous system. In contrast to Mott's[184] early description of medullary chromatolysis due to hypotension of diverse cause, it has since been recognized that, in general, the more rostral parts of the neuraxis are most susceptible to ischemic or anoxic insult, whereas in proceeding caudally to the level of the medulla oblongata, relative resistance to such stress increases[165]. Using drug-induced hypotension in dogs combined with head-up tilt, Lewis and Zingg[157] have demonstrated cellular and myelin degeneration most commonly in cortical and subcortical tissue, including the centrum semiovale, basal ganglia, and hypothalamus; notably, the cerebellum and brain stem were never affected. In his series of experiments on the pathological sequelae of cerebrovascular hypotension, Brierley has further established both in monkey[23,24] and in man[3] that those cortical areas most vulnerable to ischemic-anoxic change are watershed zones where regions supplied by two major vessels overlap. Brierley concluded that these boundary zones are particularly vulnerable since they are most remote from parent arterial resources and thus may be affected especially by severe, precipitate reductions in cerebral blood flow. These findings appear to coincide with the distribution of cerebral blood flow during shock; in a study of differential capillary circulation under these conditions, Kovách[147] found the most pronounced changes to be ischemia of the cerebral cortex associated with a breaking up of capillaries, while the vascular pattern was better maintained in the diencephalon, cerebellum, and brain stem.

In concert with structural changes occasioned by hypotension, one might reasonably expect that both measured cerebral blood supply and

neuronal metabolism would be adversely affected. Thus, several studies have demonstrated that cerebral blood flow falls during severe hypotension, in experimental animals,[146,178,215,216], as well as in man[69,75,185,246]. In this connection, although the arteriovenous oxygen difference across the brain increases[69,246], so that cerebral oxygen utilization may remain constant[69,75,220] with prolonged hypotension both variables, including cortical tissue oxygen tension, may decrease[69,146,149,185,250]; since this derangement occurs despite a greater oxygen extraction theoretically being possible[69], it has been suggested that impaired cerebral metabolism at such times may contribute to irreversible cerebro-cellular deterioration[69,70]. Reflecting the onset of altered oxygen metabolism during hypotension, Kovách and Fonyo[147] have reported that cerebral glucose uptake and energy-rich phosphate content diminish in the terminal stages of shock. Furthermore, using isolated cerebral slices which were subjected to pH decrements as might be encountered in clinical shock, acidosis was found associated with impaired ability of these slices to preserve their normal ATP content, and since lactate production had also declined, it was postulated that the low tissue ATP values could have been secondary to its decreased synthesis[247]; that nervous tissue acidification probably occurs during hemorrhagic hypotension has been borne out by findings of decreased cerebrospinal fluid pH under these circumstances[239,245]. Of additional importance are reports of increased cerebrospinal fluid potassium and pseudocholinesterase levels incurred during hemorrhagic shock, which may be suggestive of concomitant neuronal injury[239]; because the cerebrospinal fluid pressure is elevated after reinfusion of blood, despite low terminal blood pressures, one manifestation of such injury may be cerebral edema[240].

Considerable neurophysiological evidence has also accumulated which implies that cerebral function is impaired during hemorrhagic hypotension. The amplitude of spontaneous electrocortical activity becomes reduced with

a decline in blood pressure[147], often progressing to relative electrocerebral silence as systemic arterial pressure reaches 30 - 40 mm Hg[176,259]. Return of activity correlated reasonably well with the duration of hypotension; a short latency period to restoration of function was directly related to a good prognosis for full recovery[147,176]. Others have demonstrated that if treatment is not instituted soon after the electroencephalographic appearance of continuous high-voltage, low frequency delta waves during hypotensive hemorrhage, subsequent mortality becomes prohibitive[74]. However, some workers consider that evoked cortical potentials are a more sensitive indicator of cerebral nervous impairment than is the electroencephalogram under these circumstances[173,176]. Full recovery of evoked potentials preceded return of spontaneous activity; conversely, failure of evoked potentials to reappear reflected cortical neuronal damage, which was substantiated by demonstrable morphological deterioration. There also appears to be a relatively early detrimental effect on mono- and polysynaptic reflex activity which occurs during hemorrhagic hypotension; multisynaptic pathways have been found more sensitive to the effects of blood loss and consequently are rendered non-functional more quickly than are monosynaptic reflex arcs[181,182]. When the latter do disappear after prolonged hypotension, they are also the first to recover, while the more complex reflexes may not reappear at all[182]. Peterson and Haugen[199] have determined this failure of recovery to be a reliable guide to the onset of the "irreversibly shocked state".

B. Peripheral effects of compensatory sympathetic alterations in hemorrhagic hypotension.

While the prevailing view at the turn of the century centered around the brain as the primary culprit in the genesis of shock, at the same time the rudiments of a more modern school of thought were gradually being forged. Both Savory[231] and LeGros Clark[37] maintained that shock from hemorrhage first depressed the cardiovascular system while other body organs, including the brain, were adversely affected in a purely passive way. Cannon[29] summarized the thoughts of succeeding pundits[65,105,170] in concluding that hypotension affected only secondarily the bulbar nerve centers, which were assumed not able to recover should the shock state persist for a prolonged period.

The association of increased autonomic nervous activity with clinical hemorrhagic shock was probably first observed by Marshall Hall[116]. He pointed out that loss of blood led to "increased power and energy of the system, and of increased action in some of its organs . . .". Horsley[127] noted that hemorrhage resulted in constriction of vessels, and concluded further that the eventual end result was vascular paralysis due to bulbar nerve center insufficiency. Others[20,168], in speculating on shock theory, also made reference to the occurrence of vasoconstriction during shock. However, it was not until the perfusion experiments of Cope[43] and Pilcher[204] that definitive experimental evidence of vasoconstriction during controlled hemorrhage was documented. Subsequent experimental work was in accord with this observation[19,28,92,260], and in a lengthy review of the then available data on shock, Harkins[117] deduced that "Adrenal medullary overaction with (secondary) overaction of the sympathetic nervous system and peripheral vasoconstriction definitely is

a factor in shock."

As knowledge of autonomic mechanisms expanded, therefore, sympathetic activation during hemorrhagic hypotension was generally recognized as more than simply a physiological curiosity. The beneficial nature of initial sympathetic activation in providing a normalizing cardiovascular compensation for a hypovolemic episode is now a well accepted fact[35,36,133]. This early autonomic response to hemorrhage is instrumental particularly in shifting a larger proportion of blood flow in favor of vital areas. Thus, coronary vascular resistance is known to decrease after blood loss[110,128,137], although Corday and Williams[44], using flowmeters in anesthetized dogs, found the opposite to occur. These latter measurements were, however, taken very soon after bleeding; in this regard, Granata[104] also noted an initial increase in coronary resistance, but further monitoring revealed a subsequent fall below control levels which continued throughout most of the hypotensive period.

Under hypovolemic conditions, the brain also receives a proportionately greater share of the reduced cardiac output as compared to its pre-hemorrhage allotment[137,178,216,241]. This at first appears to conflict with findings demonstrating decreased blood flow in the common and internal carotid arteries of the dog after hemorrhage[44,72,122]; however, Rittman and Smith[215] have noted that blood flow decreased considerably more in the carotids than in the vertebral vessels under these circumstances, and have rightly emphasized that this fact must be considered since the dog receives approximately 70% of its total cerebral blood flow via the vertebrobasilar system. Of importance in protecting intracranial tissues after blood loss is cerebrovascular autoregulation, which serves to promote blood redistribution favourable to the brain and thereby prevent a drastic fall in absolute cerebral blood flow[63]; however, autoregulatory

processes apparently become unable to cope with blood pressures less than 60-70 mm Hg[120,154] and as previously mentioned, this more severe hypotension results finally in a diminished cerebral blood supply. Also noteworthy in affording the brain protection during hypotension may be the limited nature of cerebrovascular sympathetic innervation. In an extensive review of current concepts regarding the intracranial autonomic vascular apparatus, Nelson and Rennels[188], in noting the conflicting results from studies of cerebrovascular responses to altered sympathetic activity, concluded: "Intimate nerve-muscle relationships have been observed only near the peripheral margin of the outermost layer of the media. Nerves have not been reported to have penetrated the media; therefore, the majority of smooth muscle cells must be without direct innervation".

Redistribution of blood flow to the heart and brain after blood loss is due not only to decreased vascular resistance and autoregulation in these organs, but also to marked vasoconstriction in vascular beds less immediately vital to survival. This is particularly true concerning the regional circulations of the skin[36,68,133], mesentery[2,218], and skeletal muscle[1,167,198,222]. As well, most flowmeter studies have shown that renal blood flow is reduced after hemorrhage[1,44,72,110,241], although vascular autoregulation may result in a considerable attempt to preserve blood flow in the initial stages of hypotension[122,137]. In general then, at least in the experimental animal, most have found that overall peripheral resistance rises during hemorrhagic hypotension[27,54,128,221,256]; while it was known that this relates to a cardiac output which decreases out of proportion to the fall in blood pressure[35,122], recent work comparing the response of intact and sympathectomized dogs has confirmed that with

severe hemorrhage, this generalized increase in vascular resistance must be due mainly to intensified sympathetic activity[34]. On the other hand, some have demonstrated inconstant measurements of total peripheral resistance with blood loss[115,212,262]. In this connection, Folkow[79] has observed that various vasoconstrictor neuron pools supplying functionally different vascular beds have both different levels of excitability and varying thresholds to excitation. These inconstant vascular resistance findings may therefore relate to the consequences of dissimilar experimental protocols[221] with subsequent effects on differential patterns of vasoconstrictor fiber discharge.

Augmented sympathetic activity also influences both the inotropic and chronotropic cardiac responses to hemorrhage. The heart rate is known to accelerate under these conditions[36,54,115,212,221,261]; in the unanesthetized dog, controlled bleeding results in an initial tachycardia which, after a transient fall to control levels, increases progressively[227]. That the positive chronotropic reaction of the heart may be accountable to sympathetic activation has been confirmed by the recording of similar responses to direct stimulation of the cardiac efferent sympathetic nerves[6,208,224]. In a comparable manner, such stimulation also produces both an elevated intraventricular[224] and pulse pressure, the latter due primarily to increase in its systolic component[6,208]. Since surgical elimination of systemic vasoconstriction did not significantly alter these parameters, Rohse[219] concluded that the source of these responses must be an augmented force of myocardial contraction. During hemorrhagic shock, inferred findings of increased ventricular contractibility are consonant with a similar prominent sympathetic participation[252].

In conjunction with changes in the efferent limb of the systemic circulation, the compensatory nature of sympathetic activation with hemorrhage is also particularly evident in consequent alterations of vascular capacity. In his monograph on the venous system, Franklin[82] summarized the work of earlier investigators, as well as his own observations, which affirm that direct sympathetic nerve stimulation results in constriction of large veins. More recently, it has been demonstrated that the smaller veins are also capable of active constriction during lumbar sympathetic stimulation[62,140], with similar neurogenic control extending down even to the level of the pre-capillary sphincter, itself actively closing down during low flow states[40,124]. Blood loss has been shown to simulate the effects of such direct sympathetic activation in promoting venoconstriction[27,56,175,236]. It has been estimated that as little as a 1-2% decrease in venous capacity would double venous return to the heart, whereas similar constriction of arterioles would have negligible effects[120]; because the venous system, including all channels beyond the capillaries, contains approximately two-thirds of the total blood volume[106], the potential of a decreasing venous capacitance for mobilization of blood reserves during hemorrhage must indeed be considerable[200].

Homeostatic compensation in the face of blood loss is also influenced by the effects of adrenal medullary catecholamine secretion. Epinephrine concentrations have been found to increase many-fold in the circulating blood under these circumstances[15,109,229], while concomitant norepinephrine release was distinctly more limited[169,254,255]. These catechols have been measured in similar proportions in adrenal vein blood during hemorrhagic hypotension[96,251], which suggests that their major source

of liberation is the adrenal medulla[254]. There is still some dispute as to the degree of influence which circulating catecholamines exert on relevant target organs as compared with their direct sympathetic innervation. On the one hand, Chalmer's experiments[33] in the unanesthetized rabbit have demonstrated that reflex increase in sympathetic nerve activity and in adrenal medullary secretion may be of almost equal importance in cardiovascular control after hemorrhage. However, using the normally innervated or sympathectomized pupil and nictitating membrane of the cat as indices of sympathetic neuronal and adrenal discharge respectively, Gellhorn[89] could not corroborate the idea that adreno-medullary secretion was supportive to direct neurogenic discharge under these circumstances. Lending support to this conclusion was Folkow's finding[78] that stimulation of the cardiac sympathetic nerves in the same animal had a much stronger effect on heart rate than did adrenal medullary catecholamine release at similar levels of sympathoadrenal activation. The extensive investigations of Celander[31], assessing the relative contribution of each of these aspects of sympathetic regional blood flow control have also led him to conclude that direct vascular sympathetic innervation exerts a much wider control over relevant blood vessels compared to adrenal medullary secretions.

C. Compensatory reflex and central sympathetic mechanisms in hemorrhagic hypotension.

In the event of blood loss therefore, the sympathetic nervous system becomes intimately associated with compensatory buffering of any subsequent adverse effects. Under these circumstances, sympathetic participation results from the combined activation of both reflex and central autonomic mechanisms which presumably operate in an integrated fashion in sustaining circulatory homeostasis.

Mechanoreceptors reflexly responsive to changes in arterial blood pressure are located in definitive areas of the circulatory system[120,187]. Even before blood loss is sufficient to produce alterations in blood pressure, the afferent input from intracardiac pressoreceptors decreases[113]; this has been found responsible for an early rise in heart rate and peripheral vascular resistance, and for reinforcement of similar responses from other reflexogenic areas elicited after more severe hemorrhage[191]. In the latter instance, reduced baroreceptor afferent impulses, primarily from the carotid sinus and aortic arch regions, are known to be particularly effective in initiating positive chronotropic and inotropic cardiac reactions with hypotension, in addition to peripheral vascular constriction[7,193,206]. That these cardiovascular alterations are due to increased sympathetic activity has been confirmed by observations of increased discharges in efferent sympathetic nerves under these conditions[13], as well as by elimination of relevant responses both by surgical[17,94] and pharmacological sympathectomy[55,131]. Reflex mechanisms activated by hemorrhage also reduce the size of the venous reservoir by inducing venoconstriction[4,22,230]; recent findings demonstrating alpha and beta

adrenergic receptors in the venous bed, both of which produce venoconstriction[138], strongly suggest that this constrictor effect is sympathetic in origin.

The peripheral chemoreceptor system constitutes another reflex mechanism which supports the circulation in the event of hemorrhage. Since McDowall's[174] discovery that vagal transection further lowered a blood pressure previously decreased by blood loss, experimental perfusion of the carotid and aortic bodies with hypoxic blood has shown that the primary reflex responsible for this early finding is peripheral vasoconstriction[18,49,50]. That the peripheral vasoconstrictor response partially could be due to a relative chemoreceptor hypoxia induced by a sympathetically mediated reduction in its blood supply has been shown by findings of a direct correlation between chemoreceptor activity and sympathetic discharges monitored in postganglionic branches supplying the carotid bifurcation[77], as well as by an inverse relationship between the level of the prevailing blood pressure and chemoreceptor discharge throughout a wide range of arterial blood oxygen concentrations[155].

In his studies on the compensatory reactions to hemorrhage, Rushmer[226] observed considerable variability in the nature of these responses. Using anesthetized dogs, he found that tachycardia was not an inevitable response to bleeding, and that in some animals cardiac output remained unchanged. In reference to the brainstem control of baroreceptor activity, he commented that reflex integration at this level must consist of more than a simple servomechanism. While Rushmer's opinions on this matter have been vindicated by more recent work, the primary location of the central autonomic substrate which occasions reflex sympathetic augmentation is at this time still in dispute. On

the one hand, Chai and Wang[32] have shown in anesthetized cats that a lesion either of the midline medullary periventricular grey matter, or one involving the entire caudal fourth ventricular floor and dorsal ventricular grey but sparing midline and dorsal reticular structures, leads to a reduced pressor response to carotid occlusion. Directly opposite in result is Manning's[171] similar experiment which showed not only that medullary lesions did not affect the carotid occlusion response, but also that the latter was abolished after inferior collicular decerebration; this implied baroreceptor integration at levels above the medulla oblongata. While there is much additional evidence to support Chai's conviction that the medullary centers are predominantly concerned with reflex hypotensive sympathetic activation[130,136,211], there is at the same time little doubt that higher functional levels also exert considerable influence on autonomic reflex mechanisms. In this connection, Reis and Cuénod[211] observed that in vagotomized cats with a single functioning carotid sinus baroreceptor, the pressor response to carotid occlusion is potentiated by hypothalamic stimulation, even though the latter failed of itself to raise the blood pressure. Using the pressor response to hypothalamic stimulation as a baseline, Gebber and Snyder[87] found that the obverse situation also applied: in a similar cat preparation, this pressor effect was magnified if the carotid sinus baroreceptor influence was subsequently eliminated, suggesting that the baroreceptors in some way interacted with the induced hypothalamic sympathetic drive. This interassociation has been studied extensively by Gellhorn[91], who established that sympathetic reactions characteristic of the hypothalamus are directly associated with the relationship between the circulatory status and baroreceptor activity at any particular

point in time. Thus, he was able to show that a decreasing blood pressure from any cause allowed a standard hypothalamic stimulus to produce a much stronger sympathetic effect than if the same stimulus had been applied at normal blood pressures; this finding was dependent on a functioning baroreceptor system since the sympathetic response to hypothalamic stimulation remained constant at any blood pressure when the baroreceptor reflex had been excluded. In this regard Kahn and Mills[136], while monitoring sympathetic splanchnic nerve activity in vagotomized decerebrate cats, noted that nerve discharges were enhanced far more by a moderate histamine-induced hypotension than by carotid occlusion alone, which theoretically should have reduced the intrasinus pressure to a much greater degree. They concluded that "some mechanisms other than carotid sinus baro- and chemoreceptors must play a role in response to systemic hypotension in vagotomized animals". Peiss[197], in reviewing previous studies on central cardiovascular control, concurred with this viewpoint and emphasized both the tonic and dynamic modulation of sympathetic efferent outflow exerted by higher centers; he as well put forth the reminder that autonomic pathways exist derived from the cortex and hypothalamus which are not directly linked with the medullary vasomotor area[64].

It has long been recognized that hypothalamic[121,171,205,243] and cortical[53,244] activation can alter sympathetic cardiovascular reactivity. Gellhorn[88] demonstrated that such sympathetic activation is not an all or none phenomenon, so that under physiological conditions, hypothalamic or brain stem stimulation may lead only to a partial discharge of the sympathetic system. In this context, increasing hypothalamic excitation may gradually convert a pure sympathetic neuronal to a sympathetico-adrenal discharge, or conversely invoke activity in a specific sympathetic

neuro-effector while simultaneously leaving the pulse rate and blood pressure unaffected[90]. Thus, aside from whether basic reflex cardiovascular integration resides in the medulla oblongata or higher in the brainstem[95], Keller's[139] observations are significant in pointing out the fundamental difference between supra- and infratentorial control mechanisms: he found that brainstem transection did not result in a generalized vasodilatation, and deduced that vasoconstrictor tone per se was independent of the hypothalamus. In agreeing with this interpretation, Oberholzer[192] summed up probably the essence of present concepts by according maintenance of general vasomotor tone to the brainstem centers, while affirming that more sophisticated cardiovascular manipulations, such as adaptation of differential organ blood flow to varying states of activity, is likely coordinated at high central neuronal levels.

The relevance of the above-mentioned reflex and central autonomic interactions to the situation of hemorrhagic hypotension perhaps is brought more into focus by the results of studies concerning the physiological consequences of primary cephalic ischemia. Using an isolated cerebral circulation in the dog, Sagawa[228] could not record a significant pressor response until the cranial perfusion pressure had fallen below 60 mm Hg, whereupon he observed that at similar blood pressure reductions, cerebral ischemia was four times more potent in generating a pressor reaction than was pure baroreceptor hypotension. Cephalic ischemia induced by brachiocephalic vascular occlusion has been shown to result in positive chronotropic and inotropic cardiac responses, as well as in increased systemic vascular resistance[57,58]; these responses were not influenced by carotid sinus baroreceptor denervation. Downing's[58] use of parasympathetic blockade, and Levy's [159] stellate ganglion ablation experiment under similar conditions, have strongly implicated increased central sympathetic discharges as the basis for the augmented cardiac

activity [60,160]. Cushing[47] was the first to document the pressor response to increased intracranial pressure; it has since been shown that cerebral ischemia elicited in this fashion causes blood pressure elevation largely via an evoked systemic peripheral vasoconstriction[25,111]. In fact, it appears that the latter supercedes the cardiac contribution to the generation of hypertension under these circumstances[25,57]. Increased intracranial pressure has also been associated with focal myocardial lesions[41] and with pulmonary edema[14]; that this edema is likely related to augmentation of central sympathetic activity under these conditions is evidenced by the effectiveness of antiadrenergic agents in preventing such pathology[11].

In general, then, central autonomic mechanisms are probably indispensable for the preservation of cardiovascular homeostasis, both under normal physiological conditions, and during the stress of hypotensive hemorrhage. Interruption of the cephalic blood supply for three hours has been shown to result in a progressively declining systemic arterial pressure [195] and cardiac output [26]. Conversely, during experiments in which cerebral blood flow was maintained during otherwise generalized hemorrhagic hypotension, it has been demonstrated conclusively that both survival time [145,163] and mortality rates [9,100] are reduced.

D. Deleterious effects of sympathetic alterations in hemorrhagic hypotension.

The adaptive response to hemorrhage, as manifested especially by vasoconstriction, has gradually come to be recognized as a double-edged sword. That prolonged vasoconstriction could itself be harmful was pointed out by Erlanger and Gasser[66] who demonstrated that repeated large injections of adrenalin led eventually to a declining blood pressure and death of the animal; vasoconstriction was maintained until the end of the experiment, and it was concluded that the adverse effects were due to a concurrent reduction in blood volume. Freeman[83,85] confirmed this finding, and further observed that abrogation of sympathetic activity prevented this circulatory fluid loss. In testing the consequences of sympathectomy on the course of hemorrhagic hypotension, Freeman[84] also found he was unable to produce shock after this procedure; thus, concerning the vasoconstrictor response to blood loss, he affirmed that ". . . the very mechanism by which the organism strives to survive, brings about its ultimate dissolution". Wiggers[263] attributed impairment of blood flow through the gut, liver, and kidney during hemorrhagic hypotension to sympathetically-mediated vasoconstriction, and after showing that sympathetic blockade improved the survival of bled dogs, also concluded that ". . . though initial vasoconstriction offers temporary benefits . . . the prolonged continuance of sympathetic vasoconstriction is deleterious in that it accelerates the onset of the irreversible state (of shock)."

More recent studies have employed norepinephrine as the basic vasoconstrictor prototype in the investigation and treatment of hypotensive hemorrhage. Although some have maintained that norepinephrine

infusion during hemorrhagic shock is beneficial[153], owing especially to a subsequently improved cardiac output and blood pressure[80,93,194], most workers now believe that this sympathomimetic agent is useful only as a temporizing measure, until blood volume depletion can be rectified[38,237]. As with epinephrine therefore, severe vasoconstriction due to continuous norepinephrine infusion results in a gradually decreasing blood pressure, fall in pH, and reduction in blood volume[62]; in addition, exogenous norepinephrine-mediated vasoconstriction during hemorrhagic hypotension is now regarded to be not only ineffective in improving survival rates[81,93], but also instrumental in provoking both accelerated and increased mortality[39,125,162,237]. Conversely, with elimination of sympathetic vasoconstrictor impulses before or soon after bleeding, there is evidence both of decreased spontaneous uptake from the bleeding reservoir[119,125] and of diminished cellular anaerobic metabolism[235] during hypotension, as well as of increased survival rates thereafter[12,16,132,213,214]; these findings attest to the rendering of a less severe insult under these circumstances. The potential liability of prolonged vasoconstriction during hemorrhagic hypotension is dramatically illustrated by Nickerson's st[illegible]n the chicken[189]. Because this species develops minimal vascular constriction after blood loss, the volume of fluid subsequently transferred into the vascular compartment can equal or exceed the total initial blood volume; thus, the compensatory phase of transcapillary refilling does not give way to decompensation with fluid loss, so that almost all chickens survive if the shed blood is reinfused at any time prior to onset of terminal respiratory failure.

E. Failure of sympathetic mechanisms in hemorrhagic hypotension

The concept of augmented sympathetic activity is now generally accepted as being concerned with the evolutionary course of hemorrhagic shock. However, there is a coincident reluctance to consider, aside from the secondary detrimental effects of prolonged vasoconstriction, that faltering of stressed neuronal mechanisms might contribute to onset of the terminal shock state. In discussing the possible causes for spontaneous autoinfusion of blood during the decompensatory phase of experimental hemorrhagic hypotension, Nickerson[190] dismisses a possible role for declining sympathetic activity: ". . . (this) require(s) that the vasoconstrictor and cardiac stimulant effects of the sympathetic nervous system decrease at some critical stage in the development of shock, but it has been impossible to demonstrate such an event".

The impression that cardiovascular collapse during shock might be associated with loss of vascular constrictor capability is a long-standing one, having been voiced by Horsley[127] in the later 19th century, and again incorporated by Crile[45] in the interpretation of his experiments on surgical shock. Pilcher and Sollman[204] noted that vasoconstriction consequent to blood loss in anesthetized dogs was followed by vasodilatation as the blood pressure approached 30 mm Hg. and that once this occurred, the pressor response to sciatic nerve stimulation was greatly diminished. According to Bayliss[10], maintenance of systemic arterial pressure at 58 mm Hg for one hour in cats stopped the appearance of vasomotor reflexes; as did Crile, he ascribed this finding to bulbar vasomotor failure. Using hindlimb perfusion methods in anesthetized dogs and cats respectively, both Penfield[198] and Cattell[30] were able to demonstrate an eventual loss of peripheral resistance after prolonged hypotension.

Similar findings were reported by Erlanger[65] and Gesell[92]. More recently, Wiggers[262] has shown in anesthetized dogs that some loss of peripheral vascular resistance may occur in late hemorrhagic shock; he felt that this may have been due partly to lessened reactivity of nervous control. Remington[212] concurred with these results, and further observed that this fall in vascular resistance was often precipitous. After an initial increase shortly after hemorrhage, Rothe[221] subsequently recorded in anesthetized dogs a progressive decline in total peripheral resistance as hypotension progressed; a number of animals did not regain control levels immediately after reinfusion, and although several of these showed a second compensatory increase in resistance during the phase of so-called normovolemic shock, a few again manifested a decrease in the terminal state. Employing arterial and venous segments as an index of peripheral vascular constrictor capability, Familiar[68] noted that small artery resistance gradually fell during maintained hemorrhagic hypotension. He also found that animals regained constrictor tone after reinfusion, but in reporting two dogs having the shortest survival times of the entire series, he observed that both animals continued with a low peripheral resistance from the end of reinfusion until death. The inverse finding that initial coronary vasodilatation after bleeding eventually gave way to a relative vasoconstriction during prolonged hypotension, led Granata and his co-workers[104] to conclude that coronary sympathetic beta-receptor reactivity had diminished; whether this was due to decreased generation of nerve impulses, declining transmitter release at the nerve terminals, or impaired receptor function was not determined.

Inferences that decreasing peripheral vascular resistance in late

hemorrhagic shock might be associated with diminished sympathetic efferent discharges have received strong support from studies in which sympathetic nerve activity has been monitored directly. Beck and Dontas[13], recording from sympathetic preganglionic splanchnic efferents during protracted hemorrhagic hypotension in cats, found that activity gradually abated with time; in dogs also, there was a marked diminution in discharges during spontaneous blood uptake from the reservoir, as well as with the post-reinfusion terminal decline in blood pressure. In anesthetized cats, Gootman and Cohen[103] have observed that with continuing blood loss, splanchnic nerve discharges at first are inversely proportional to the decreasing systemic arterial pressure; however, at critical mean pressures, usually between 20-40 mm Hg, there occurred a relatively sudden and drastic reduction of sympathetic activity, which frequently preceded cardiac arrest. This decline in splanchnic reactivity was attributed to lower brainstem ischemia. This same sequence had previously been reported by Lundgren[167] while recording from sympathetic vasoconstrictor nerves to skeletal muscle in anesthetized cats. Using a similar preparation in dogs, Rothe[222] found that the initial increase in vasoconstrictor nerve impulses following hemorrhage tended to give way after prolonged hypotension; retransfusion occasioned a temporary return of sympathetic discharges, followed by a secondary diminution during the terminal blood pressure decline.

The post-capillary venous system has long been considered another possible site where failing sympathetic reactivity might initiate circulatory failure after extended hypotension. Although definitive experimental evidence was lacking at that time, even early investigators hypothesized that shock must be associated with venous dilatation and subsequent venous pooling[118,126,183]. In anesthetized dogs, Rashkind[209] controlled

cardiac output so that changes in blood pressure could be ascribed solely to alterations in total peripheral resistance. He found that decreasing blood pressure was associated with a simultaneous drop in both peripheral resistance and venous return. In this connection, Rothe[221] concluded from his study of peripheral resistance during hemorrhagic hypotension that "the variable . . . decline of total peripheral resistance during severe hypotension suggests a reduced tone of the capacitance vessels and so might account for the autoinfusion (from the bleeding reservoir)". Gregg[110] also felt that the site of vascular collapse during hemorrhagic shock in conscious dogs must be post-arteriolar in location. One of the few studies which directly confirms that venous dilatation might be a factor in precipitating circulatory collapse after prolonged hemorrhage has been performed by Alexander[5] in anesthetized dogs. As hypotensive hemorrhage progressed, he noted a gradual waning of venoconstriction, with a further abrupt fall occurring in late hypotension; although retransfusion usually restored venomotor tone, the hypotensive levels reached during the terminal period did not provoke venoconstriction to nearly the same degree as did similar low blood pressures shortly after bleeding began.

The locus of presumed sympathetic functional deterioration has not yet been defined. However, certain aspects of this problem have been examined. Noradrenaline stores in the spleen[48] and heart[102] become depleted after prolonged hemorrhagic hypotension; it is pertinent here that Glaviano[97] found the myocardium almost completely refractory to stellate ganglion stimulation after hemorrhagic shock had ensued. Von Euler[67] has shown, however, that increased sympathetic activity alone cannot account for local norepinephrine dissipation. In this regard, waning cardiac responsiveness may be partially related to the metabolic acidosis which invariably accompanies low flow states, since it can be

demonstrated that this acidemia contributes to suppression of both spontaneous myocardial contractility, and that induced by injections of pressor catecholamines[51,252,266]. Another possible mechanism for reduced myocardial reactivity to catecholamines in hemorrhage may be decreased sensitivity of its beta-adrenergic receptors after prolonged exposure to high concentrations of these vasoactive agents[35]. Adrenomedullary secretion has also been found to decrease after prolonged hemorrhagic hypotension[109], and this appeared to coincide with uptake from the bleeding reservoir[253].

Disintegration of higher central nervous control as well as been postulated as a likely requisite for cardiovascular decompensation in hemorrhagic shock. Both Kovách[144] and Glaviano[98] have found that reflexly induced pressor responses to carotid occlusion or peripheral nerve stimulation are markedly reduced after protracted hemorrhagic hypotension; the pressor reaction to hypothalamic stimulation is also impaired at this time[225].

Chapter III:

EXPERIMENTAL STUDY

A. Introduction

The relevance of impaired central nervous function to the response of the experimental animal subjected to hemorrhagic hypotension and shock has remained controversial. In laying the foundation for the experimental approach to shock, Crile[45] placed great emphasis of impairment of the bulbar vasomotor mechanism as the major cause of the clinical syndrome. Although Cannon[29] concurred with accumulating evidence that vasomotor exhaustion was not responsible for the low blood pressure, he did feel that the prolonged presence of the hypotensive state might eventually be detrimental to the brain.

A considerable body of knowledge has since accumulated documenting the influence of hypotensive hemorrhage on central nervous physiology. Total cerebral blood flow is known to fall during hypotension, both in the experimental animal[178,216,242] and in man[69,185,246], despite preferential redistribution of cardiac output in favor of the brain[107,137]. Subsequent cerebral ischemia may well be responsible for observations of reduced[259] or abnormal[74,148,176] spontaneous cortical electrical activity under these circumstances, as well as for depression of electrical potentials evoked from spinal cord and cortical neurons by peripheral nerve or brain stem stimulation[173,176,199]. In addition, deleterious effects on reflexes subserved especially by multisynaptic and therefore higher suprasegmental pathways have been noted very soon after the onset of hypotensive hemorrhage[181,182]. In this regard, the possibility that hypothalamic cardiovascular regulatory mechanisms might be impaired during

the later stages of hemorrhagic shock has recently been put forward[225], and this finding has been supported by further evidence demonstrating increased susceptibility to traumatic shock after previous hypothalamic lesions[148]. The significance of the above mentioned physiological disturbances is accentuated by recent findings of impaired cerebral oxygen metabolism in advanced shock[69,149,250], associated with declining glucose consumption[146] and reduced ATP content[148,179]. Subsequent cerebral anaerobic glycolysis may supervene[71] accompanied by cerebrospinal fluid acidosis[245]; a concomitant rise in cerebrospinal fluid potassium concentration implies that tissue injury eventually occurs[239].

Just as pertinent to the understanding of central nervous influences on the course of hemorrhagic hypotension are studies emphasizing the reactions of remote body systems to preplanned alterations in the cerebrospinal tissue blood supply. Thus, prolonged severe cerebral ischemia may itself lead to eventual cardiovascular decompensation, as manifested by a gradually decreasing blood pressure and cardiac output[26,195]. In addition, while some have shown that perfusion of the brain during hemorrhagic hypotension may prolong only survival time[163], others have demonstrated a definite decrease in mortality[100,145].

However, despite efforts to establish a more precise mechanism through which the nervous system might modify the response to hemorrhagic shock, an avenue to a comprehensive understanding of this interaction remains elusive. Both the confusing element of general anesthesia[61,267] and the traumatic procedures[73] required to assess a seemingly inaccessible organ system, have made interpretation of subsequent experimental results extremely difficult.

The present study, relatively unencumbered by these disadvantages,

offers a fresh approach to this problem. The effects of head elevation on clinical neurologic parameters and cardiovascular hemodynamics during profound hemorrhagic hypotension were assessed in unanesthetized dogs. In providing an additional increment of physiologically induced cerebral ischemia during hypotension, the use of head elevation allowed a more meaningful evaluation of the relationship between subsequent neurologic dysfunction and associated hemodynamic alterations.

B. Methods

Sixteen successful experiments were performed on 21 adult mongrel dogs ranging in weight from 15 - 22 Kg. Animals with obvious signs of disease, a hematocrit less than 40%, or BUN greater than 20 mg.% were not accepted. The dogs were maintained on normal diets, but fasted for 12 hours prior to the procedure.

Anesthesia was induced by intravenous infusion of sodium methohexital (Brietal Sodium - Lilly), intubation carried out, and the methohexital discontinued. For maintenance anesthesia, 1.5% halothane (Fluothane - Ayerst) in an equal mixture of 100% O_2 and N_2O was employed. This was delivered to the endotracheal tube by a Harvard variable-volume animal respirator with an attached intermittent hyperinflation valve. The respiratory rate was maintained at 15/min., this value having been determined during preliminary experiments as that which assured both adequate oxygenation and arterial PCO_2 levels between 35-45 mm Hg during the period of assisted ventilation. Tidal volume according to weight of the animal could then be selected directly from a nomogram specific for the Harvard respirator. Both femoral arteries and the left femoral vein were cannulated with vinyl catheters (I.D.0.082 in.) 28.5 cm. in length, filled with heparinized saline, and the arterial catheters advanced to the level of the upper abdominal aorta. The right femoral artery was connected to a Statham P32A pressure transducer and electronically integrated mean aortic pressure (MAP) monitored on a Grass Model 5 polygraph. Tracheostomy was performed, and inhalation anesthesia sustained via this route. The dog was then placed on a Pavlov stand and the head secured on a specially designed head rest; with the animal supported in the normal standing position, lateral movement of the head was only moderately restricted, while a predetermined degree of

elevation could be kept constant. Standard electrocardiographic limb leads were inserted, as well as one central precordial lead. The animal was then heparinized (3 mg/Kg) and the left femoral artery connected to a siliconized, graduated, closed glass reservoir. Variations in body temperature were minimized by use of a heating blanket, rectal temperature being monitored by an indwelling probe (Yellow Springs Instrument Co.). Inhalation anesthesia was then discontinued and ventilation on room air prolonged until consciousness was regained, usually within 15 min.; from this point, the animals breathed spontaneously for the remainder of the experiment.

The fully conscious state was defined arbitrarily by comparing each dog's response to clinical neurologic examination before hemorrhage to similar testing during and after the hypotensive period. Preliminary experiments had shown that a 30 min. post-anesthesia, pre-hemorrhage interval was adequate for animals to regain a level of consciousness corresponding to the unanesthetized state. That which comprised consciousness for present purposes was depicted in terms of four broad response categories based on the clinical neurologic examination. Animals designated as "alert" were awake, appeared interested in their surroundings, responded quickly to a call or loud noise with searching movements of the eyes and head, withdrew the foreleg quickly to a mild toe web pinch, and demonstrated brisk corneal, blink and pupilary light reflexes. Animals that appeared listless were termed "drowsy", but these would still wake sufficiently to respond to environmental sounds either by opening the eyes or by searching movements. This latter characteristic distinguished this category from the third or "stuporous" group, in which animals appeared not only spontaneously unaware of their surroundings,

but also would not respond to sound or movements in the environment. Dogs in a "drowsy" or "stuporous" state (i.e.) the transitional categories, had impaired pain avoidance and reflex responses to varying degrees; because of this variability, assessment of these parameters did not contribute to distinguishing between these latter two groups. Finally, animals categorized as "comatose" had no awareness as with the "stuporous" group, but in addition showed no responses to painful stimuli, and had absent corneal, blink and pupillary reflexes.

Each dog was bled rapidly to a MAP of 40 mm Hg and held at this level for 150 min. by adjusting the height of the reservoir as necessary. The reservoir was connected to a mercury manometer which could be utilized to reinfuse blood rapidly if required. At the end of the hypotensive period, the animals were positioned lying on their left sides; since the volume of blood remaining in the reservoir varied from one animal to another, to maintain uniformity the rate of intra-arterial reinfusion was arbitrarily set at 12 cc/min. The post-hemorrhagic phase was observed for an additional 4 hrs; those animals which remained alive at the end of this time were arbitrarily considered survivors. The 4-hr. post-shock observation period was utilized on the basis of preliminary trials which had demonstrated that animals surviving this length of time remained in stable condition for a minimum of 12 hrs. after retransfusion; these dogs were therefore considered as having endured the acute sequelae of hemorrhagic shock. Conversely, those which did not survive 12 hrs. invariably had died within four hours of reinfusion. At either the time of death or after the 4 hr. post-shock period, all dogs were necropsied and specimens placed in 10% formal-saline for subsequent histological processing.

Hemodynamic, electrocardiographic and clinical neurologic parameters were measured prior to bleeding, and at 10 min. intervals during hypotension. Bleeding volume was similarly recorded: the volume of blood in the reservoir at the onset of hypotension, when the falling MAP first touched 40 mm Hg was designated as the initial bleeding volume (IBV), the largest volume at any time during the experiment as the maximal bleeding volume(MBV), the volume at any other time as the residual bleeding volume (RBV), and the volume at the end of the hypotensive period as the final bleeding volume (FBV).

Consecutive animals were alternately placed in one of two groups based on position of the head during hypotension. Control or head-down (HD) dogs were positioned with the cranium at the level of the aortic origin, estimated on the chest wall from the midpoint between sternum and spinous processes; in experimental or head-up (HU) animals, the head was raised such that the degree of elevation from aortic origin to the hard palate, taken as the base of the brain, measured $> 15 < 20$ cm. (Fig. 1).

Arterial blood samples for hematocrit, pH, and blood gas determinations as well as serum potassium, pyruvate and lactate concentrations, were drawn prior to hemorrhage, at 30 min. intervals during hypotension, and immediately after reinfusion was completed. Cardiac output determinations followed a similar schedule; these were measured via the indicator-dilution method using a Gilford densitometer and indocyanine green (Cardiogreen-Hynson, Westcott and Dunning Inc.). Dye dilution curves were analyzed by the Stewart-Hamilton method; calculated total peripheral resistance (T.P.R.) was expressed in mm Hg/L/min. Blood gases and pH were determined on an Instrumentation Laboratories blood gas analyzer, and hematocrit by the microhematocrit tube method. Serum lactates and pyruvates were analyzed with Boehringer test kits, and read on a

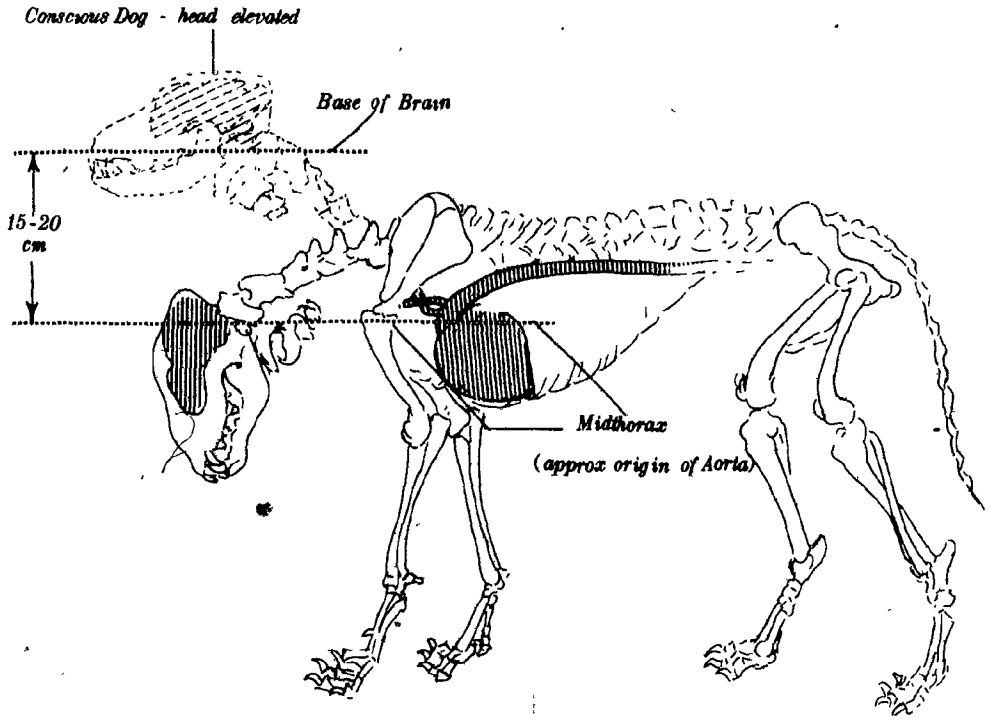


FIG. 1: The relationship of head position to the level of the aortic origin is shown. The distance from midthorax to hard palate, taken as the base of the brain, was adjusted to be >15 cm<20 cm in the HU animals.

Coleman 46 spectrophotometer (Perkin-Elmer Corp.); results were denoted as the lactate/pyruvate ratio (L/P). Serum potassium levels were recorded directly from an Instrumentation Laboratories flame photometer.

Group means are presented with their standard deviations. By use of Student's T-test, populations were regarded as differing significantly when the probability that their means came from the same population was less than 5%.

C. Results

1. Clinical:

Certain aspects of the clinical neurologic response to hemorrhagic hypotension are noteworthy. The clinical state appeared to reflect quite clearly the severity of cerebral ischemia; unmistakably, 7 of 8 HU animals were more seriously impaired than controls both during and at the end of the hypotensive period. One exception to this was the withdrawal response to a painful stimulus: this was abolished in all HU and HD animals within 1 hr. after the onset of bleeding, making this parameter generally the most sensitive of those measured to the adverse effects of hypotension. On the other hand, after a similar time interval, corneal reflexes were absent in 87.5% of HU animals as compared to only 12.5% of HD dogs; at 150 min. of hypotension, this reflex could be elicited in none of the HU dogs, but still was present in 3 of the 8 HD animals. In addition, the pupils were fixed to light in 87.5% of the HU group after 90 min. of hypotension, whereas fixation occurred in none of the HD animals even after the entire predetermined period of hypotension, although at this point the pupils generally reacted sluggishly or at times were unequal. As compared to the effect of hypotension on pain avoidance responses and on corneal and pupillary reflexes, the blink reflex was last to disappear in any particular animal during the course of the hypotensive interval. However, this reflex as well was abolished in 87.5% of HU animals at 150 min. of hypotension; in contrast, it could still be elicited at this time in all HD dogs. Finally, while 1 HU dog was classified as "drowsy" just prior to reinfusion of shed blood, the 7 animals remaining in this group were uniformly "comatose". Conversely, none of the HD animals was rendered "comatose" by the hypotensive

hemorrhage; only 2 HD dogs deteriorated sufficiently to be classified as "stuporous", while the remainder stabilized in the "drowsy" category.

The severity of cerebral ischemia, as manifested by the clinical state during shock, was also reflected in group mortality rates. There were no fatalities during the hypotensive period itself; however, 87.5% of HU animals succumbed within the predesignated post-shock observation period. Each of these animals had been rendered comatose during the course of hypotension, the only survivor being one animal which remained in the "drowsy" category through the shock interval. On the other hand, the HD mortality rate was 50% at the end of post reinfusion observation; two of these 4 dogs were classified as "stuporous" at the end of the hypotensive period, while two were "drowsy".

It is noteworthy that in the combined HU - HD series, 9 of the 11 animals that subsequently died had temporarily improved following retransfusion of shed blood. In fact, 4 of these latter 9 dogs recovered sufficiently to become actively aware of their surroundings in a fashion similar to the pre-hypotensive state, although 3 of these had some degree of clinically impaired pain avoidance or reflex responses which evidenced the neuronal insult incurred during hypotension. The clinical improvement afforded by reinfusion was maintained until shortly before death; only as the systolic blood pressure fell below 100 mm Hg did increasing stupor and terminal coma supervene.

2. Physiological and Pathological:

In Fig. 2, the mean arterial pH values are plotted against time. The pH was significantly lower in the HU group at 60, 90, and 120 min.

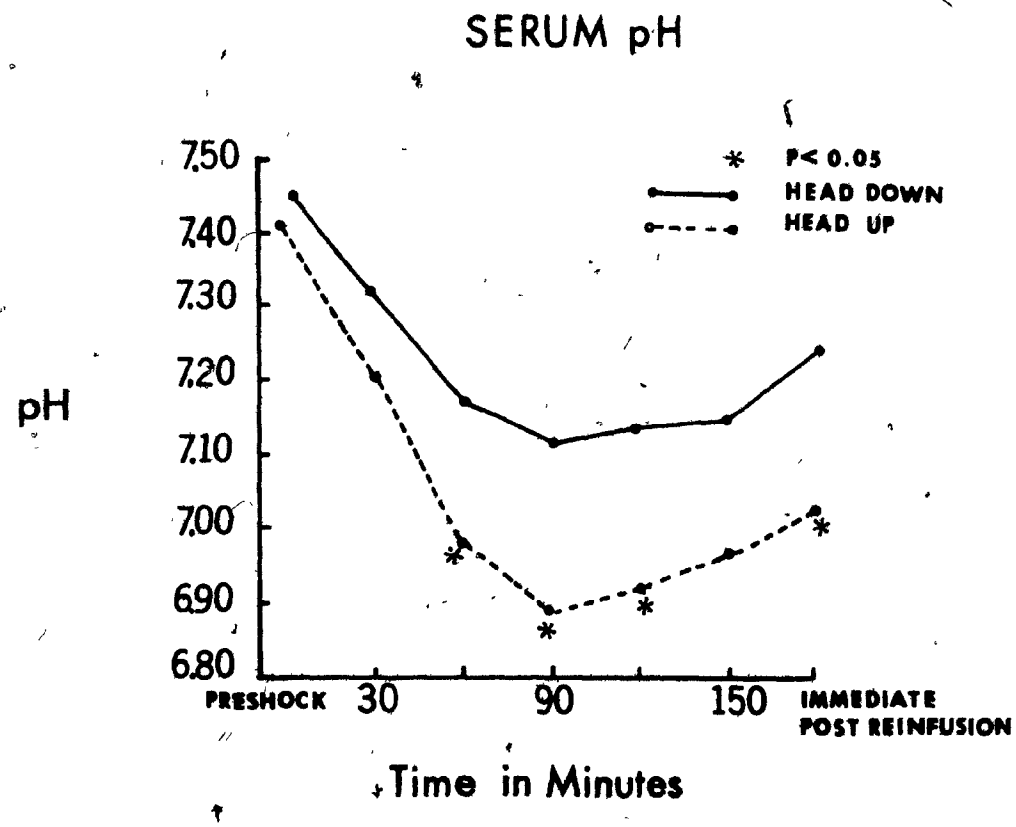


FIG. 2: Graph showing absolute mean serum pH values as plotted against time.

of hypotension, as well as after reinfusion ($P < 0.05$) (Table 1). Differences between other measured parameters did not reach statistical significance. Both groups demonstrated initial hemodilution followed by hemoconcentration (Table II) as well as similar overall patterns of bleeding and volume uptake from the reservoir during the hypotensive period[125] (Table III). HU dogs did show a trend toward higher serum potassium levels (Table IV) but differences from HD animals were not significant. The L/P ratio (Table V) and TPR (Table VI) were elevated in both groups during hypotension, in agreement with results from other studies[142,249]. Oxygenation was well maintained both during anesthesia, and throughout the hypotensive interval; as well, compensatory hypocapnia was observed which was consistent with the previously described pulmonary response to hemorrhagic hypotension[42].

Gross and microscopic examination of the heart, lungs, liver, kidneys, duodenum and terminal ileum confirmed that all animals in the combined HU-HD series manifested unequivocal evidence of tissue injury consonant with the known pathological sequelae of hemorrhagic shock[21,164,257] (Figs. 3-8). There were neither qualitative nor quantitative differences between HU and HD animals with regard to tissue damage incurred during hypotension.

3. The bradycardia phenomenon:

Within the combined HU - HD series, a peculiar variation in heart rate was observed in 7 animals: 6 of these were HU and 1 HD. A representative example (HU Dog #9258) is illustrated in Fig. 9.

After an initial 25 min. at the predesignated hypotensive level, this animal had the onset of intermittent sinus bradycardia associated

FIGS. 3-8: Are representative examples of the microscopic lesions sustained by animals which succumbed within 4 hrs. after retransfusion.

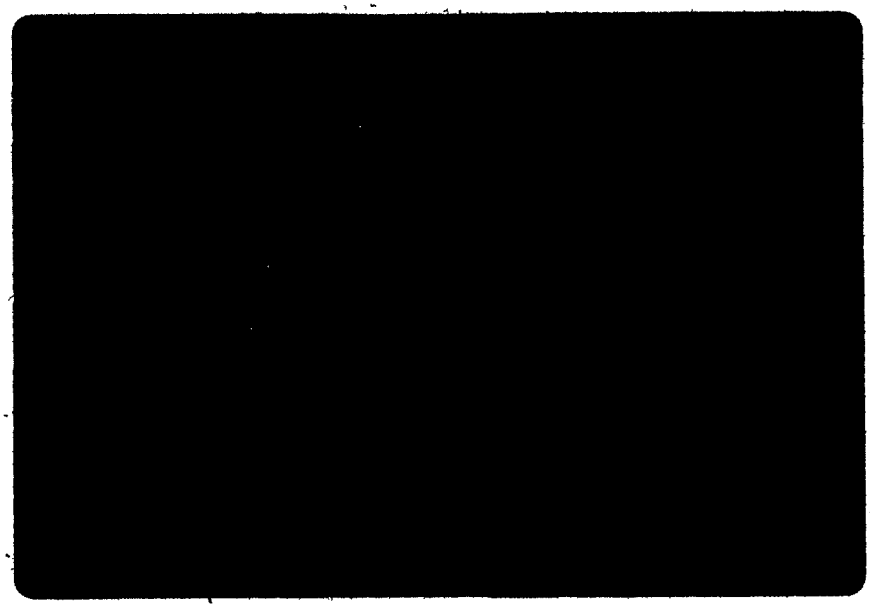


FIG 3: Shows a section through the left ventricular endocardium. Scattered small subendocardial hemorrhages are present.

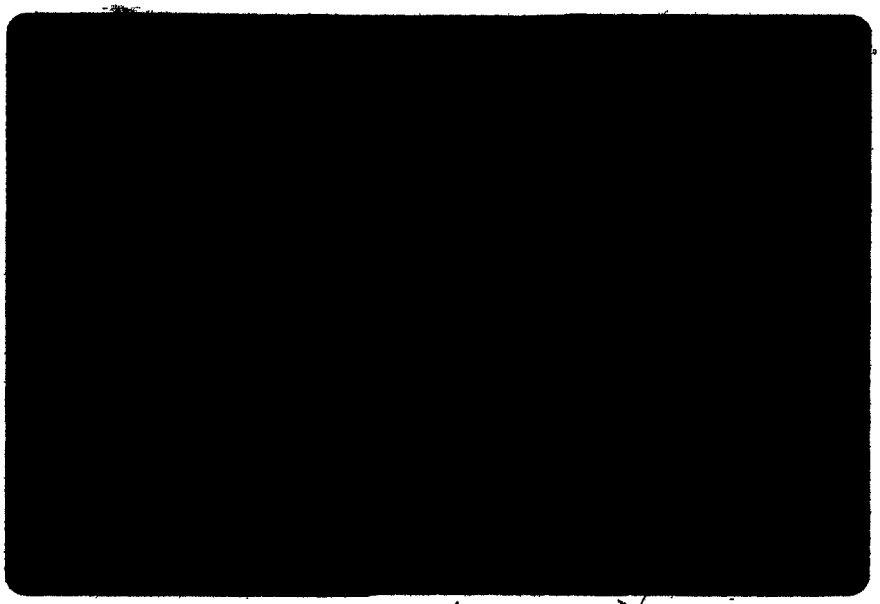


FIG 4: Shows a section through the left upper lobe of the lung. There is marked interstitial edema, patchy atelectasis, and sporadic interstitial and alveolar hemorrhages.

FIG 5: Shows a section through the liver where pericentrolobular congestion and early necrotic changes are visible.

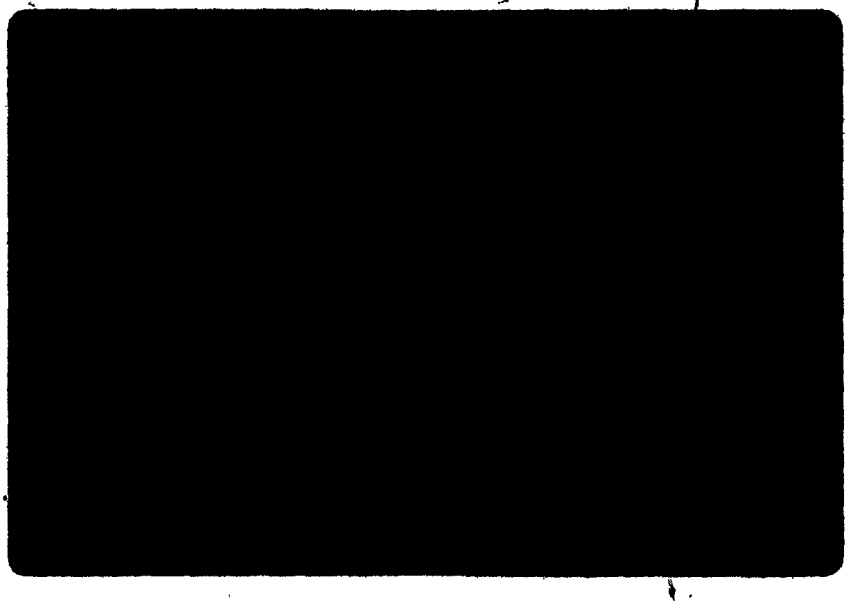
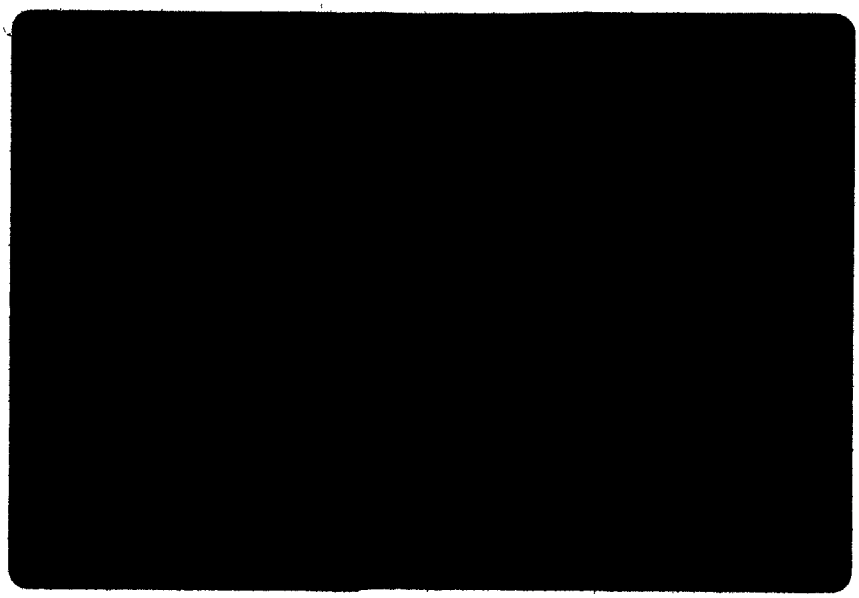


FIG 6: Shows a section through the corticomedullary junction of the left kidney. Interstitial hemorrhage is evident, and there is early tubular necrosis.

FIG 7: See overleaf for Legend



FIGS. 7 AND 8: Show sections through duodenal (Fig. 7) and terminal ileal mucosae (Fig. 8) respectively, demonstrating sloughing of epithelium from the tips of the villi.

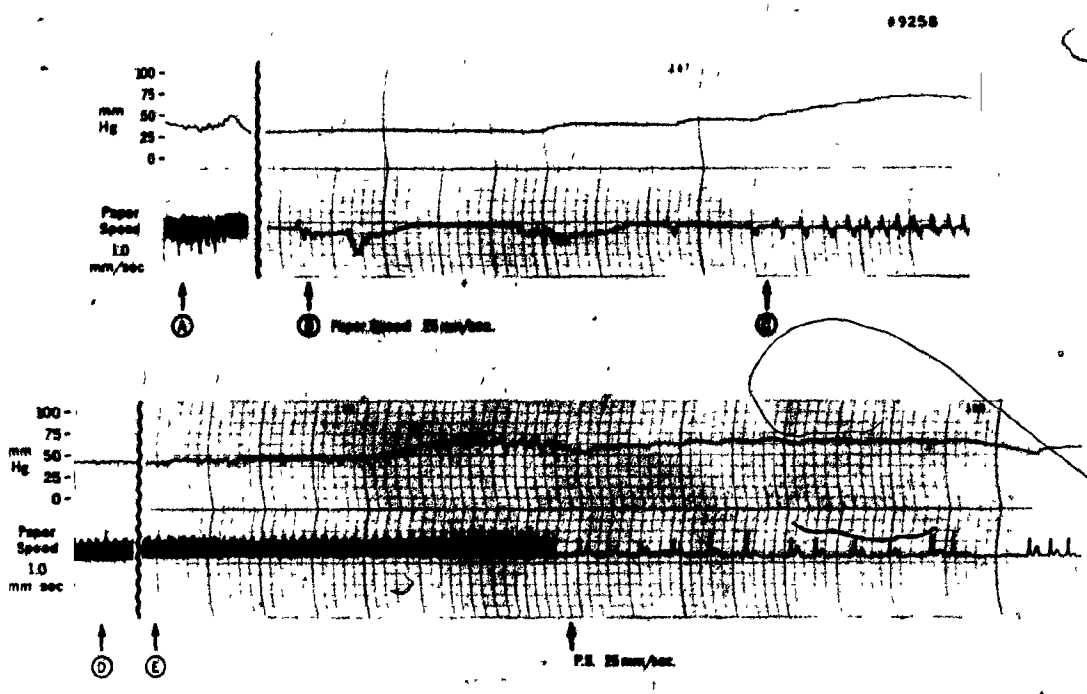


FIG. 9: Polygraph recording showing concurrent tracings of mean arterial pressure and electrocardiogram during portions of the hypotensive interval of HU dog #9258. Paper speed is increased where indicated to illustrate the nature of the bradycardia.

with large MAP fluctuations, which appeared in the form of Mayer waves 15-25 mm Hg in amplitude and up to 30 sec. in duration[81,120]. Mayer wave activity then ceased, and a more persistent sinus bradycardia then developed at 30 min. (A), the heart rate falling from 225/min. to less than 50/min. coincident with a drop in MAP below 40 mm Hg. Here, rapid elevation of the MAP by blood reinfusion under pressure was required to avert cardiac arrest and subsequent ventricular fibrillation, which had been seen previously with several HU animals during preliminary experiments. As MAP rose, the heart rate increased, with MAP rapidly falling back to 40 mm Hg as the infusion was discontinued. These infusions were delivered only until MAP began to respond, after which they were halted abruptly; the MAP might rise to 75 mm Hg nevertheless, but invariably fell back to the predetermined level within several sec., consequent to additional bleeding. Another similar episode occurred a few moments later (B) and again responded to pressure infusion (C). In this particular experiment, a MBV of 945 cc had been reached at 20 min.; 40 cc of blood was taken up spontaneously over the next 10 min. at which point bradycardia occurred. However, over the subsequent 20 min. interval, three similar episodes had precipitated rapid infusion of fully 300 cc of blood needed to prevent cardiovascular collapse. After this time, a less severe sinus bradycardia occurred intermittently in association with accelerated spontaneous blood uptake, such that at 120 min. of hypotension, 61.3% of the MBV had been returned; this episodic heart rate deceleration was punctuated by intervals in which a sinus tachycardia predominated (D). Bradycardia, now associated however with an atrioventricular junctional rhythm, was observed at

130 min. (E); elevation of MAP in this circumstance was no longer effective in alleviating the slow heart rate, which persisted to the time of reinfusion. Noteworthy immediately after retransfusion in this dog was both an increase in cardiac output to 130% of control, and a fall in TPR to 67% of control. The correlation between bleeding volume and heart rate for this experiment is summarized in Fig. 10.

The course of another animal (HU Dog #9317) is depicted in Fig. 11, and shows even more dramatically the association between bradycardia and blood requirement. A MBV of 785 cc had been reached at 20 min. after the onset of hypotension, and spontaneous uptake of blood to 80 min. had resulted in an RBV of 525 cc; during this interval, a progressive sinus bradycardia had developed, the heart rate having decreased from a peak of 156/min. at 40 min. to 126/min. This deceleration had not been preceded by or associated with Mayer wave activity. Onset of an intermittent bradycardic arrhythmia, now on the basis of atrial fibrillation, then appeared (A), and in spite of rapid blood infusion and subsequent increase in MAP, it became more pronounced, the rate varying from 78 - 90/min. (B). The end of pressure infusion 5 min. later (C) left a RBV of less than 100 cc, with a sinus tachycardia gradually supervening as MAP rose above 75 mm Hg. Notwithstanding a momentary relapse (D), the tachycardia which had ensued (E) was maintained even as the animal was again allowed to begin bleeding into the reservoir (F). The MAP gradually fell (G), so that at 100 min. (H) the RBV had increased to 545 cc; although the MAP was 45 mm Hg at this time, bradycardia had not recurred. This comparatively stable state continued for the next 35 min. during which time spontaneous uptake of blood had reduced the RBV to 485 cc. At this point, sinus bradycardia again recurred (Fig. 12A) and despite pressure reinfusion of the entire

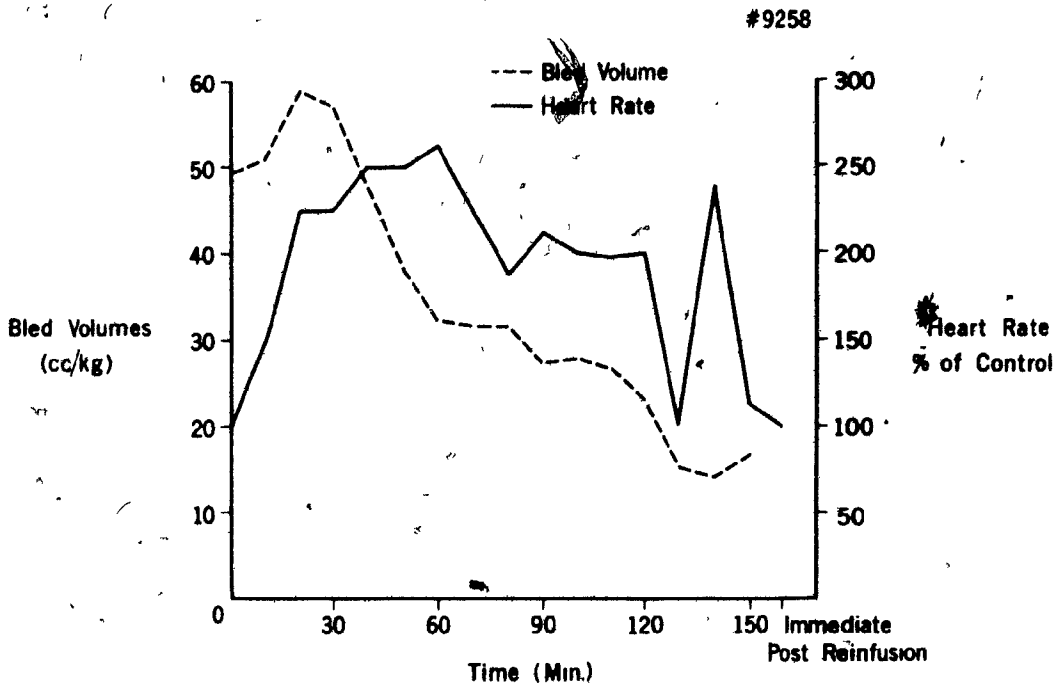


FIG. 10: A line graph demonstrating the correlation between changes in bled volume (RBV at any time during hypotension) and heart rate during the hypotensive period in HU dog #9258.

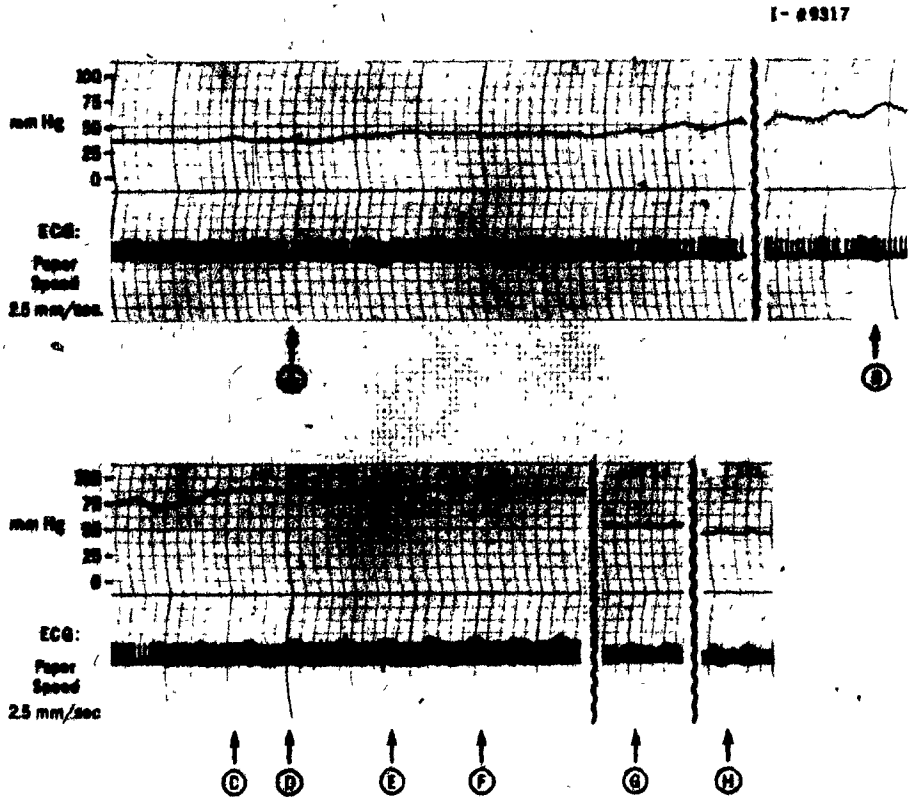


FIG: 11: Polygraph recording showing concurrent tracings of mean arterial pressure and electrocardiogram during portions of the hypotensive interval of HU dog #9317.

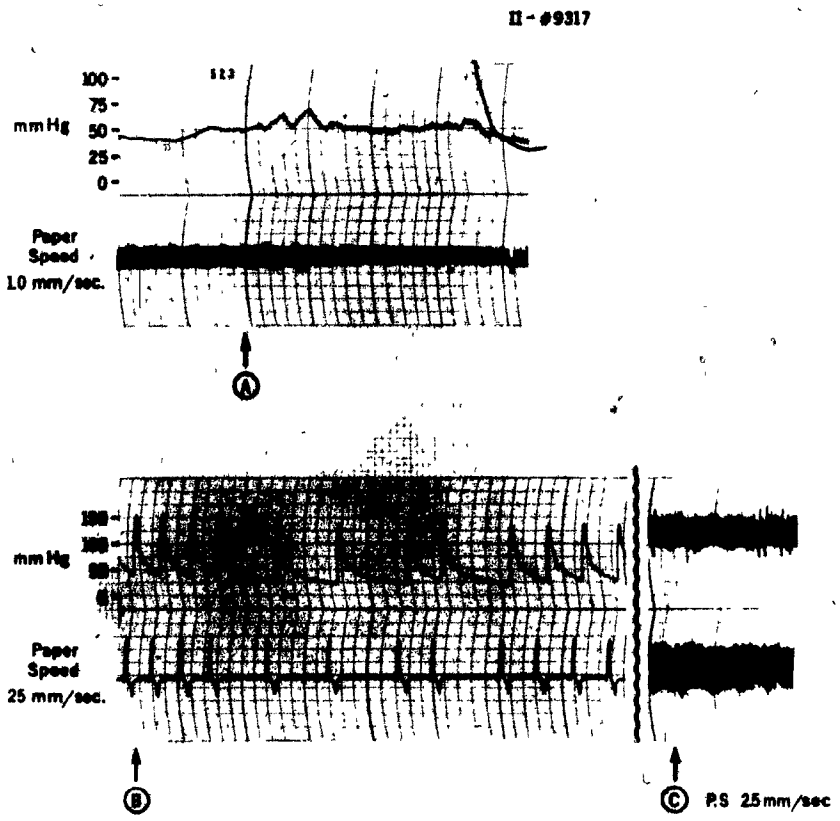


FIG. 12: Continuation of polygraph recording showing concurrent tracings of mean arterial pressure and electrocardiogram in HU dog #9317. (A) shows events which occurred just prior to the end of the hypotensive interval. (B) records events immediately after completion of reinfusion, using an increased paper speed to illustrate the wide pulse pressure with low diastolic component, and the bradycardia. (C) records events 20 min. after completion of reinfusion.

RBV over the succeeding few minutes, the deceleration increased in severity, while the MAP, rather than responding, began to fall. At approximately 140 min. therefore, (i.e.) 10 min. before the predesignated termination of hypotension, the dog was placed lying on its left side, and the full excursion of the aortic pressure curve was recorded (B). The extremely wide pulse pressure with a low diastolic component, and the marked bradycardia now apparently originating from the atrioventricular junction, were quite remarkable; these were associated with an increase in cardiac output to 191% of control, and a concomitant drop in TPR to 30% of control. Even more dramatic was both the rise in diastolic pressure and increase in heart rate which occurred over the next 20 min., such that the pulse pressure decreased considerably, while an atrioventricular junctional tachycardia greater than 200/min. replaced the previous bradycardia (C). In addition, this animal regained consciousness after reinfusion, dying subsequently in progressive "normovolemic" shock, as did 10 other dogs in this study[261]. The close correlation between bleeding volume and heart rate for this experiment is summarized in Fig. 13.

Because the appearance of bradycardia, with its attendant hemodynamic alterations, was deemed significant in terms of the physiological mechanism it might represent, closer scrutiny of the 7 affected animals seemed warranted. "Initial" heart rate deceleration observed in 3 animals (HU dogs # 9313, 9271, 9258) was usually of intermittent onset, and consisted always of a sinus bradycardia; its occurrence was not observed with the initial attainment of hypotension, but instead from 20-90 min. after the predetermined MAP had been reached. Four of the 7 dogs (HU dogs # 9313, 9271, 9258 and HD dog # 9298) exhibited large fluctuations in MAP early in the hypotensive period, appearing in the form of Mayer waves previously described (Fig. 14 A & B). While in one of these dogs

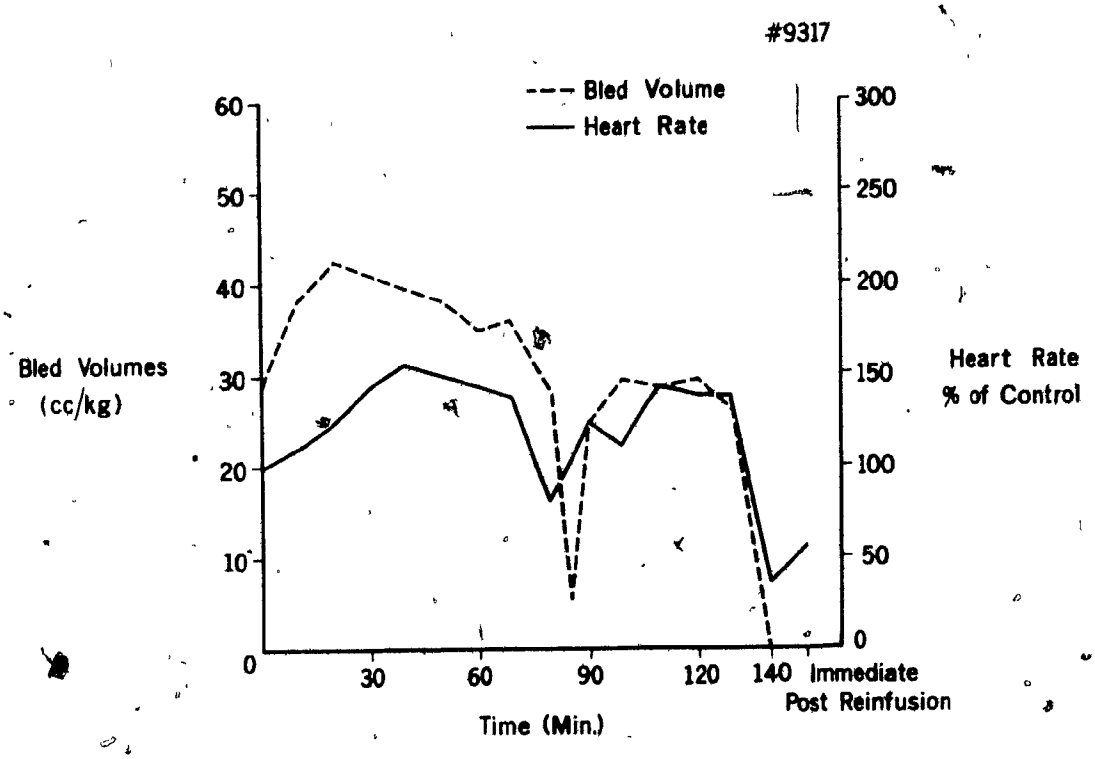


FIG. 13: A line graph demonstrating the correlation between changes in bled volume (RBV at any time during hypotension) and heart rate during the hypotensive period in HU dog #9317.

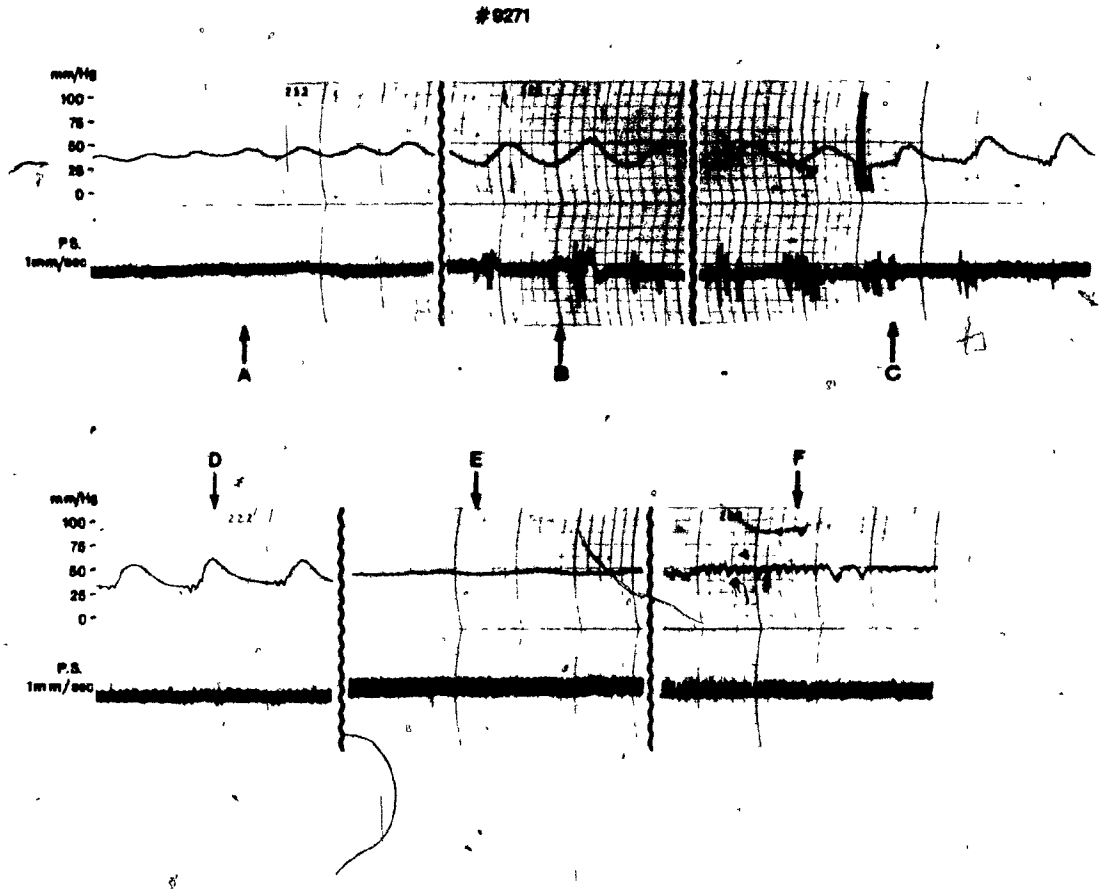


FIG. 14: A polygraph recording showing concurrent tracings of mean arterial pressure and electrocardiogram during portions of the hypotensive interval in HU dog #9271. Gradual intensification of Mayer wave activity in early hypotension (A and B) was eventually associated with sinus bradycardia occurring at the nadir of the wave (C and D); deceleration reversed either spontaneously or with the reinfusion of a small amount of blood. Mayer wave activity then disappeared (E) and was later succeeded by more severe sinus bradycardia together with accelerated blood uptake (F).

this rhythmic activity had ceased well before onset of sinus bradycardia (HD dog #9298), in the 3 dogs manifesting "initial' bradycardia the deceleration would be evident only at the nadir of a wave, which might be as low as 30 mm Hg. The bradycardia would then reverse as MAP began to rise, the latter either spontaneously or with infusion of a small amount of blood (Fig. 14 C & D). "Initial" bradycardia was therefore arbitrarily defined as deceleration occurring in association with Mayer wave activity and/or unaccompanied by accelerated blood uptake. In one animal (HU dog #9313) this "initial" bradycardia subsequently disappeared, and a normal sinus rhythm continued until reinfusion.

However, though these "initial" heart rate decreases rarely demanded blood uptake to prevent a fall in MAP, later onset of more severe "symptomatic" bradycardia in 6 of the 7 affected animals often necessitated an accelerated blood return; this latter type of deceleration as well was almost always sinus in origin. It was especially notable that bradycardia occasioning uptake of relatively large increments of blood invariably was preceded by disappearance of Mayer wave activity (Fig. 14 E & F). "Symptomatic" bradycardia, therefore, was arbitrarily defined as deceleration unassociated with Mayer wave activity, and/or accompanied by accelerated blood uptake. Two dogs (HU dog #9306 and HD dog #9298) may be said to have manifested "symptomatic" bradycardia of a less severe nature, as evidenced by lack of need for blood pressure support other than that provided by spontaneous RBV uptake. Reference to Table IX however will make readily apparent the trend towards increased blood uptake generally evinced by these 7 animals during the hypotensive period.

As opposed to the sinus types of bradycardia, 2 dogs (HU Dog #9258 and HD dog #9298) late in hemorrhagic hypotension developed "terminal"

heart rate deceleration associated with atrioventricular junctional rhythms; this arrhythmia was preceded in one by a variable degree of heart block. "Terminal" bradycardia was arbitrarily defined, therefore, as deceleration associated with varying degrees of heart block and/or atrioventricular junctional arrhythmias. At this point, not only was elevation of MAP unsuccessful in alleviating the bradycardia, but also generally higher blood pressures became necessary to avert cardiac arrest and subsequent cardiovascular collapse. Fig. 15 depicts the course of one such animal (HD dog # 9298) in which onset (A) and dissipation (B) of Mayer waves, as well as "symptomatic" deceleration similar to that seen with other dogs (Fig. 14) was followed by the appearance of "terminal" bradycardia (Fig. 15 C & D); temporary support of the MAP via intermittent blood infusions was required as the bradycardia evolved. After reinfusion, moreover, deceleration here too associated with an atrioventricular junctional arrhythmia, invariably punctuated the terminal blood pressure decline; this stage also was often accompanied by bizarre electrocardiographic configurations[143].

Of particular interest was the relationship between the occurrence of bradycardia and the concurrent neurologic status. Of the 7 dogs concerned, 3 were stuporous and 3 were comatose with the onset of heart rate deceleration of any type; 1 dog (HD dog #9298) which was "drowsy" with the initial appearance of a moderate "symptomatic" bradycardia subsequently became "stuporous" before a more severe similar deceleration necessitated a copious infusion of blood. Conversely, of the 9 non-affected animals, only 2 were markedly obtunded, 1 having become "stuporous" and the other "comatose" by the end of the hypotensive period. Relevant to this observation was the position of the head in relation to the

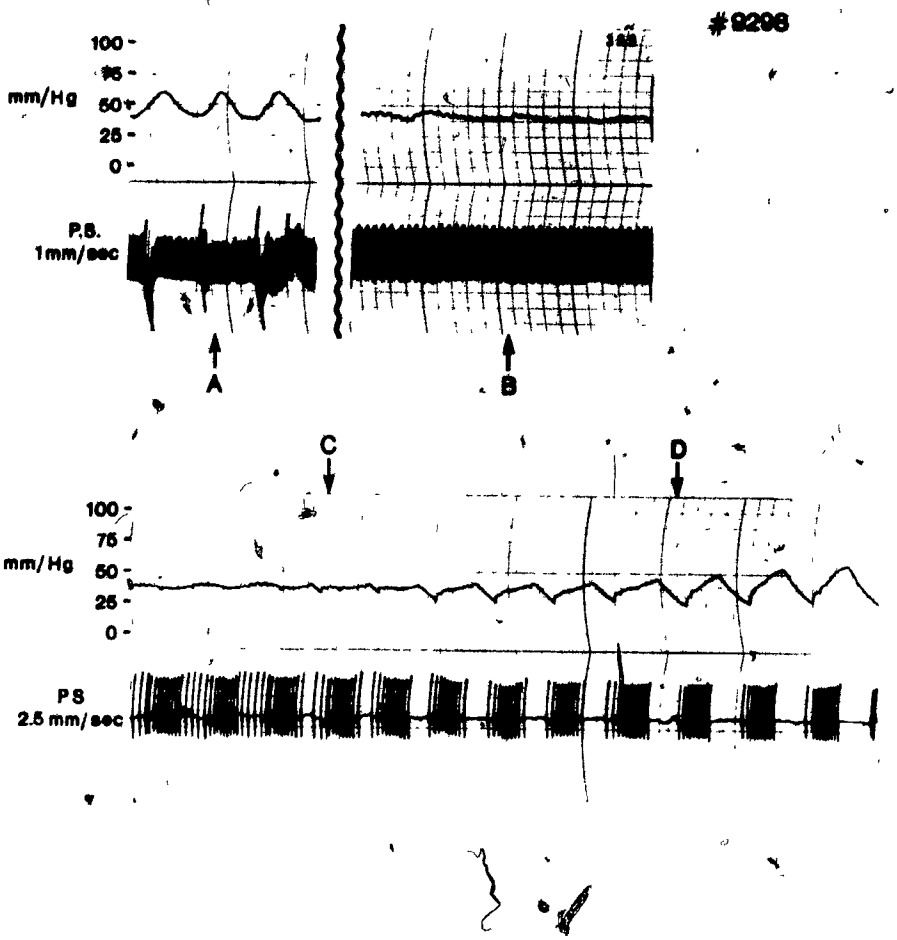
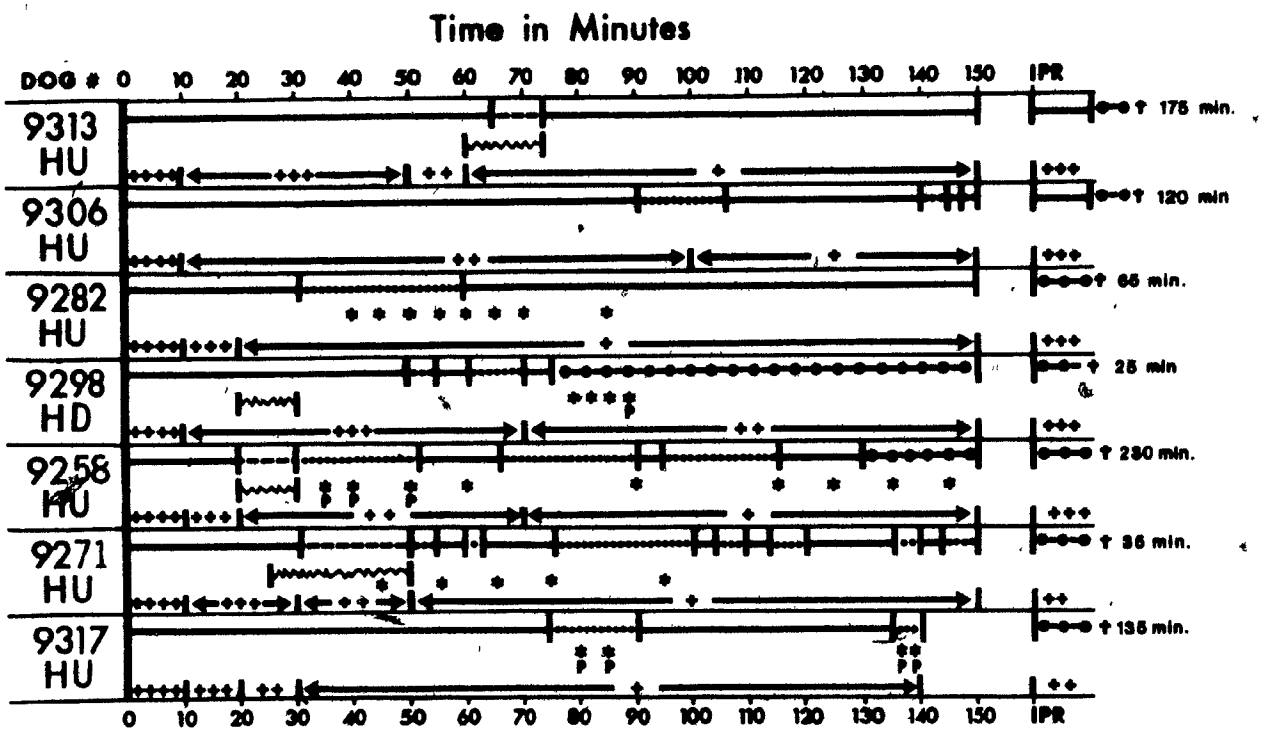


FIG. 15: A polygraph recording showing concurrent tracings of mean arterial pressure and electrocardiogram during portions of the hypotensive interval in HD dog #9298. Mayer wave activity, here unassociated with sinus bradycardia (A) gradually abated, and was followed by more severe sinus bradycardia (not shown); this led directly to onset of decreased heart rate associated with an atrioventricular junctional rhythm (C and D). Although initially requiring MAP support via blood infusion as it developed, this arrhythmia otherwise remained self-sustaining until the end of the hypotensive period.

FIG. 16: A composite diagram showing the relationship between the appearance of the various forms of bradycardia, the requirements for accelerated blood uptake, and the concurrent clinical neurologic status in the 7 animals which manifested heart rate deceleration during the hypotensive period.



sinus rhythm
initial bradycardia
symptomatic bradycardia
terminal bradycardia
Mayer waves

* spontaneous accelerated blood uptake
*P mandatory blood uptake via infusion under pressure
† death
IPR immediately post reinfusion

CLINICAL NEUROLOGIC STATUS

Alert
Drowsy
Stuporous
Comatose

development of bradycardia: of the 7 affected animals, 6 were from the HU group. Despite the often higher MAP afforded dogs which incurred bradycardia, the more severe insult rendered them was also expressed by their mortality rate: 100% of these animals succumbed within 4 hrs. of reinfusion, versus 55.6% of those not so affected. Figure 16 summarizes briefly the clinical and hemodynamic course followed by animals in which the various types of bradycardia were observed.

D. Discussion

Though a significant central nervous element is indisputably mingled with the organism's response to hemorrhage, a framework for inclusion of relevant neural mechanisms in a working hypothesis has not yet been formulated. Perhaps best established is the profound influence of sympathetic activity on the course of hemorrhagic hypotension; although it is generally recognized that sympathetic activation provides a beneficial hemodynamic compensation to initial blood loss, the deleterious consequences particularly of prolonged alpha adrenergic activity are also well known[35,261].

The present experiment, if viewed from a clinical neurologic standpoint, indicates that an elevated head position during hypotension undoubtedly has given rise to a more severe cerebral ischemic insult as compared to HD animals. Head position appears to have little influence on cerebral blood flow under normotensive conditions[172], due both to reflex compensatory mechanisms[166] and to cerebrovascular autoregulation[63]. During hypotension, however, these mechanisms become impaired[120,154]; in this regard, superadded cerebral ischemia is the most likely cause for diminished cortical electrical activity[176] and neural damage[157] occasioned by head-up tilt. Using a hydrostatic correction factor[99], the perfusion pressure at the base of the brain in HU dogs was calculated to be 11.6 - 15.5 mm Hg less than that recorded at the level of the aortic origin. Thus, the present experimental model furnishes a unique physiological means whereby central nervous influences on the course of hemorrhagic hypotension may be studied, by utilizing the additional increment of cerebral ischemia provided by head elevation.

Cushing[47] was the first to emphasize the importance of the hemodynamic response to cerebral ischemia. With this impetus, cardiac and peripheral vascular sympathetic activation are now known to be derived not only from baro- and chemoreceptor reflex mechanisms[4,49,57,131,141,152,230], but especially from the ischemic central nervous system itself[25,58,160,228,236]. Both Grimson[111] and more recently Brown[25] have demonstrated that the major consequence of the centrally mediated sympathetic reaction is marked peripheral vasoconstriction. The possibility that the HU animals had suffered greater deleterious effects from excessive vasoconstriction, here accorded to experimentally augmented cerebral ischemia, is suggested not only by the significantly lower pH ($P < .05$) but also by the higher mortality evinced by this group.

Of considerable interest was the further finding that in the combined HU - HD series, retransfusion of shed blood at the end of the hypotension produced transient clinical neurologic improvement in 9 of the 11 animals that later succumbed under post-shock observation. Generally, more severe degrees of neurologic impairment after reinfusion precluded a good prognosis[238]; however, the present work revealed that 4 of these latter 9 non-survivors actually became alert with minimal deficits at this time. It may be of significance that 3 of these 4 were more impaired clinically during the hypotensive period than were any of the survivors; this finding would then remain consistent with the concept that incremental cerebral ischemia, in precipitating a destructive alpha adrenergic augmentation <u>during</u> hemorrhagic hypotension, could itself be a major determinant in the predisposition to later death.

The appearance of bradycardia at some point during hemorrhagic hypotension, here observed in 8 (43.8%) animals, has also been noted by previous investigators. Both Roth[223] and Wiggers[261] believed its onset to be an ominous sign during severe hypotensive hemorrhage, the latter finding additionally that vagotomy did not prevent its occurrence. Rushmer[225] frequently observed severe bradycardia in later hemorrhagic shock; though he did not discover its cause, he did note it commonly to be associated with marked clinical neurologic deterioration. More recently, agonal bradycardia following an initial tachycardia has been reported in exsanguinating dogs, together with bizarre electrocardiographic patterns which preceded asystole or ventricular fibrillation[143].

The present study demonstrates for the first time the close association between clinical neurologic impairment and the occurrence of bradycardia: six of the 7 animals which exhibited this phenomenon were from the HU group, while all 7 summarily developed signs of severe cerebral ischemia. In addition, the mortality rate for these affected animals was 100%.

The precise mechanism underlying the bradycardia itself is not revealed in the present study. In considering the available data, however, the relevance of certain findings may be discerned.

"Initial" sinus bradycardia

Intensification of chemoreceptor-modulated vasomotor activity during hemorrhagic hypotension is known to be the basis of the Mayer

waves observed in the current investigation[186]; since one of the principal responses of chemoreceptor activation is bradycardia[49], this reflex mechanism likely accounts for the initial episodes of heart rate deceleration which occurred at the nadir of Mayer waves in the early stages of hypotension. Concordant with this interpretation was the rhythmic intermittent nature of the sinus bradycardia, and its quick reversal with slight elevation of MAP, the latter taking place either spontaneously, or with a minimal infusion of the RBV. The effects of traction on the cervical vessels have been demonstrated not to be a significant factor in the reflex response of blood pressure to changes in head position[150].

"Symptomatic" sinus bradycardia

The sinus bradycardia observed after the prior disappearance of Mayer wave activity appeared to represent one facet of an entirely different physiological process, one which may suggest that declining sympathetic activity plays a significant role in the cardiovascular deterioration often witnessed after prolonged hemorrhagic hypotension. During prolonged cerebral ischemia, Brown[26] felt that a falling cardiac output unaccompanied by a compensatory tachycardia might be indicative of a loss of sympathetic effectiveness. Measurements of regional arterial blood flow in late hemorrhagic shock have also implied that some degree of resistance vessel dilatation may occur[225]. More recently, a progressive loss of coronary vasodilatation was noted to occur as the heart decelerated during prolonged hemorrhagic shock, and this was regarded as possibly due to waning beta adrenergic discharge[104]. Interestingly enough, though these workers commented on this rapid fall

in heart rate as being significant in irreversible shock, this sign was considered to be unreliable in predicting its occurrence. Pertinent here may be findings that despite unvarying tissue norepinephrine levels under ordinary circumstances[67], both splenic[48] and myocardial[102] catecholamine content have been shown to decrease after long periods of hemorrhagic hypotension. The capacitance aspect of the vascular system has also been implicated as a possible site where an even less than dramatic loss of neurogenic venoconstriction might be of major significance. Notwithstanding the fact that fluid loss from the vascular compartment may account largely for gradual autoinfusion of blood during protracted hypotension[125], the impression that circulatory capacity may increase in late shock has been supported by positive evidence of both decreased venous tone and return under these circumstances[5, 209]. Especially relevant are Glaviano's observations that carotid occlusion would not elicit a cardiovascular pressor response after prolonged hemorrhagic shock; occlusion during the terminal normovolemic phase also resulted in a diminished arterial pressure elevation which was attributed to waning sympathetic reflex activity[98]. In addition, both pre- and post-ganglionic sympathetic discharge have been found to decrease after extended hypotension, as well as with the post-reinfusion decline in blood pressure[13,167,222]. Particularly significant were Gootman's[103] observations during progressive hypotensive hemorrhage in vagotomized cats: an initial compensatory increase in efferent sympathetic splanchnic discharge eventually gave way to rapidly declining neuronal activity which might then recover in shed blood were reinfused, or otherwise lead to cardiac arrest.

As associated with the phenomenon of "symptomatic" bradycardia,

hemodynamic alterations observed during the current investigation may also indicate the onset of a similar relative sympathetic incapacitation. Because reflex sympathetic activity[114] as influenced by higher nervous levels[8] is largely responsible for phasic vasomotor activity, gradual disappearance of Mayer waves during hemorrhagic hypotension may be a manifestation of impaired sympathetic circulatory control. The close relationship between bradycardia and accelerated blood uptake, the latter required to offset an often drastic fall in blood pressure, may again be suggestive of failing cardiovascular neurogenic compensation under these circumstances. Because the venous system contains approximately 65% of the total blood volume[106], while conversely the resistance arterioles are not very distensible and hold quantitatively little blood, the venous bed would seem the area most likely receptive to rapid massive blood reinfusion in the event of declining sympathetic venoconstrictor capability. In addition, although increased fluid loss from the microcirculation may well be concerned in the trend towards a generally increased blood uptake during hypotension, conceivably this finding could be partially based on a relative conjoint increase in venous capacity. Thus, the coexistence of severe sinus bradycardia, unimproved by mandatory infusion of a large volume of blood, and a subsequent drastic reduction in TPR, especially if manifested by a wide pulse pressure with a low diastolic component constitutes compelling evidence for a marked decrease in both alpha and beta adrenergic responsiveness. In one animal described in detail above (HU dog #9317), a gradual rise in diastolic pressure soon after reinfusion suggests that some degree of sympathetic tone may have been regained to offset what at first appeared to be imminent cardiovascular collapse. That re-establishment of an

effective circulation may lead to at least temporary restoration of neuronal function after prior severe blood deprivation has been demonstrated by previous investigators[103,129,222]. It seems plausible, therefore, that the increased cerebral blood flow occasioned by reinfusion may have, in this instance, unmasked a somewhat reversible neural deficit. This would be consistent with the temporary improvement in the animal's neurologic status at this time. Indeed, the gradual alleviation of bradycardia seen in some dogs after a moderate increase in cerebral perfusion pressure may also indicate this type of functional deficiency. Conversely, should any particular episode of severe bradycardia engendered by the hypotensive state have been allowed to persist, it is conceivable that neural deterioration incurred at such times might be instrumental in the genesis of acute circulatory failure. Because severe cerebral ischemia was universal in animals which developed the bradycardia phenomenon during hypotension, the possibility remains that at some critical point, the resulting intense sympathetic activity may have precipitated a state of relative neural exhaustion.

Recent physiological studies on the autonomic control of heart rate also lend credence to the concept of sympathetic decline as a possible cause of "symptomatic" sinus bradycardia. Sympathetically mediated sinus tachycardia has been established as one of the classical hemodynamic compensations to volune-depleting hemorrhage [35,261]; however, cerebral ischemia is known to activate both divisions of the autonomic nervous system [160], and in fact vagal influences on the sino-auricular node are considered predominant [160,161]. In addition, while impaired responsiveness of the heart to sympathetic stimulation has been demonstrated during

hemorrhagic shock, vagal function at such times appears to be unaffected[97]; of interest is recent work showing that elevated serum potassium levels, a trend to which has occurred here, may enhance this vagal activity[123]. With these points in mind it does not seem unreasonable to visualize "symptomatic" sinus bradycardia as due to a relative vagal preponderance consequent to declining beta adrenergic reactivity.

"Terminal" bradycardia

The appearance of bradycardia associated with atrioventricular junctional rhythms or with varying degrees of heart block witnessed in the present study during late hypotension or after reinfusion, may constitute yet another type of heart deceleration. At this late stage, several severe metabolic derangements coexist which no doubt contribute to primary depression of the myocardium. Although metabolic acidosis[59,252], elevated serum potassium levels[76,265], or circulating cardiotoxins[156] are of less likely concern in causation of "symptomatic" sinus bradycardia, as evidenced by its alleviation with temporary MAP elevation, these factors, as well as that of myocardial failure[101,210], may well be implicated in the onset of "terminal" bradycardia. This interpretation would be consistent with failure to reverse the deceleration by means of the higher, more persistent elevations of MAP provided at these times. As well, declining sympathetic activity may enhance myocardial depression induced by metabolic acidosis[217,264]; since high rates of vagal stimulation are known to result in complete heart block[224], which in turn may be accentuated by increased serum potassium levels[108], autonomic instability due to decreasing sympathetic responsiveness may itself be a contributor to the production of "terminal" bradycardia.

E. Summary

The effect of head elevation on the course of hemorrhagic hypotension was examined in unanesthetized dogs, as compared with animals in which the head was placed at the level of the aortic origin. Head elevation caused a more rapid onset of severe neurologic impairment to supervene during hypotension, in association with a significant lowering of mean pH and a higher mortality rate. Seven of 16 animals developed bradycardia at some point during the hypotensive interval, accompanied by hemodynamic alterations; six of these animals belonged to the head-elevated group, while all 7 had signs of severe neurologic deterioration and subsequently succumbed. Three types of heart deceleration were observed. "Initial" sinus bradycardia noted in 3 animals was related to phasic vasomotor activity early during hypotension and reversed quickly with minimal elevation of MAP. "Symptomatic" sinus bradycardia was observed in 6 dogs, and occurred after prior disappearance of phasic vasomotor activity. It often resulted in a rapid drop in MAP which if not supported by massive reinfusion of blood, would lead to cardiovascular collapse; it could gradually be reversed with a temporary MAP elevation, after retransfusion was accompanied in 2 dogs by a decreased TPR, and in one of these also by a wide pulse pressure with a low diastolic component which rose spontaneously after the animal was made recumbent. "Terminal" bradycardia was observed in 2 animals consequent to prolonged hypotension and invariably after reinfusion, was related to atrioventricular junctional arrythmias or atrioventricular block, and did not respond to MAP elevation. Animals exhibiting bradycardia showed a trend towards higher percent uptake of the MBV during the hypotensive interval. It is proposed that during

hemorrhagic hypotension, increasing central sympathetic augmentation due to progressive cephalic ischemia may serve to reinforce reflex alpha adrenergic activation, thereby promoting accelerated deterioration with a prolonged hypotensive interval. Under these conditions, persistent cerebral ischemia eventually may result in waning alpha and beta adrenergic activity; this might then either contribute to the organism's terminal decline, or in certain instances of critical cerebral blood deprivation, actually precipitate acute circulatory failure.

Chapter IV

A. Conclusions

I. Elevation of the canine head during prolonged hemorrhagic hypotension produced progressively severe clinical neurologic impairment. This indicates that head elevation during a hypotensive stress leads to augmented cerebral ischemia.

II. Head elevation during hemorrhagic hypotension resulted in a significant reduction in serum pH; and a high mortality of 87.5%. It is suggested that these findings are due to the detrimental effects of excessive peripheral alpha adrenergic activation, consequent to reinforcement of reflex sympathetic responses by marked central autonomic activity, itself the result of severe cerebral ischemia.

III. The appearance of bradycardia, observed in 7 animals during the hypotensive interval, accompanied a trend towards increased blood uptake, was related in 6 dogs to the head-elevated position, and in all animals was associated with signs of severe cerebral ischemia and subsequent death. It is concluded that the bradycardia observed during profound hemorrhagic hypotension at least partially relates to the co-existence of intense cerebral blood deprivation, and that its appearance portends a grave prognosis.

IV. During hypotension, bradycardia observed after prior dissipation of phasic vasomotor activity and associated with mandatory blood reinfusion for support of blood pressure and avoidance of cardiovascular collapse, was accompanied in 2 dogs by a markedly reduced total peripheral resistance, and in one of these by a wide pulse pressure with a low diastolic component; this suggests that prolonged cerebral ischemia

incurred during shock may give rise to declining alpha and beta adrenergic activity which could well be of significance in determining the clinical course of hemorrhagic hypotension. Both the frequent alleviation of bradycardia with moderate blood pressure elevation and the spontaneous rise in the low diastolic component of a wide pulse pressure shown after reinfusion imply that this presumed waning of sympathetic responsiveness may temporarily be reversed by an increased cerebral blood flow.

B. Claims for original work

Although several investigators have studied the central nervous system during hemorrhagic hypotension, the information accumulated has not yet given rise to a mechanistic hypothesis from which central neuronal influences during shock might be better understood. In the present study, a new model has been introduced which has allowed a clearer conception of these influences to emerge. Through the unequivocal observation that HU animals had suffered more severe clinical neurologic deterioration with a prolonged hypotensive stress, head elevation has been demonstrated to be an effective physiological method whereby the cerebral ischemia incurred during hemorrhagic hypotension may be augmented. This concept is supported also by previous studies which have shown that head-up tilt after previously induced hypotension is both physiologically and histologically detrimental to the brain[157,176]. Moreover, in addition to adverse effects on the clinical neurologic status, use of this model has indicated that head elevation during hemorrhagic hypotension accelerates metabolic decompensation, and as well results in a higher mortality. From this constellation of findings, the arguments for a tenable hypothesis concerning significant central nervous influences operative during hemorrhagic shock have been set forth. It has been previously documented that the alpha adrenergic response evoked by cerebral ischemia is much more powerful than that due to reflex sympathetic activation alone[228] and that this augmented autonomic pressor reaction is primarily vasoconstrictive in nature[25]; these findings support the contention that an ischemic brain may act to accelerate the known detrimental effects of prolonged vascular constriction during shock. The present observation that eventual death invariably is associated with severe neurologic impairment during hypotension, in spite of temporary clinical improvement after reinfusion

remains entirely consistent with this concept.

This study has also shown for the first time a link between the occurrence of bradycardia during profound hemorrhagic hypotension, and the presence of severe concurrent neurologic impairment. Several investigators have noted the appearance of heart rate deceleration during terminal shock, but its definitive relationship to marked neurologic deterioration at this time had not been previously established. Three forms of bradycardia have been characterized, each with somewhat different accompanying hemodynamic parameters; what here is considered particularly significant is that type of bradycardia preceded by disappearance of phasic vasomotor activity and necessitating rapid copious uptake of reservoir blood to deter a falling systemic arterial pressure and subsequent cardiovascular collapse. Since in addition two of these animals were observed to have a decreased total peripheral resistance closely associated with events of this nature, one as well manifesting a wide pulse pressure with a low diastolic component, it is suggested that this study provides compelling evidence for the expression of declining alpha and beta adrenergic activity during prolonged hemorrhagic hypotension. Although Gootman[103] has demonstrated that the sudden fall in blood pressure coincides with diminished sympathetic neuronal discharges under these conditions, the current work specifically relates this form of hemodynamic alteration to the presence of severe cerebral ischemia.

INDEX OF TABLES

TABLE 1: Shows absolute values for serum pH. Means ± standard deviations are calculated for each time interval. Head up animals had significantly lower values at 60, 90 and 120 minutes of hypotension, as well as after reinfusion ($P < 0.05$).

TABLE I B

SERUM pH
ABSOLUTE VALUES
HEAD UP

Time in Minutes

DOG #	9258	9264	9271	9282	9293	9306	9313	9317	MEAN	± SD	
PRE-* SHOCK	7.362	7.292	7.470	7.355	7.390	7.375	7.482	7.410	7.392	0.062	
30	7.210	7.320	7.020	7.230	7.304	7.218	7.330	7.012	7.206	0.126	
60	< 6.800	7.250	< 6.800	6.905	7.005	7.082	7.183	< 6.800	6.978	0.180	●
90	< 6.800	7.210	< 6.800	6.810	6.860	6.925	6.885	< 6.800	6.886	0.139	●
120	< 6.800	7.265	< 6.800	6.821	6.972	< 6.800	6.992	6.916	6.921	0.160	●
150	< 6.800	7.220	< 6.800	< 6.800	7.057	< 6.800	7.110	-	6.941	0.182	●
POST REINFU-SION	6.888	7.284	6.828	7.000	7.100	7.080	7.210	< 6.800	7.024	0.177	

*Preshock= Control

● P< 0.05

TABLE I A

SERUM pH
ABSOLUTE VALUES
HEAD DOWN

Time in Minutes	DOG#	9261	9269	9273	9291	9298	9311	9316	9322	MEAN	±SD
	PRE-SHOCK *	7.528	7.420	7.420	7.470	7.410	7.490	7.395	7.478	7.451	0.046
	30	7.410	7.315	7.221	7.410	7.175	7.340	7.345	7.280	7.312	0.084
	60	7.345	7.218	7.140	7.333	6.948	7.140	7.193	7.010	7.166	0.139
	90	7.305	7.250	7.083	7.325	< 6.800	6.996	7.189	6.960	7.114	0.186
	120	7.312	7.335	7.090	7.320	< 6.800	7.000	7.250	6.955	7.135	0.199
	150	7.418	7.344	7.095	7.210	< 6.800	7.085	7.192	7.022	7.146	0.193
	POST REINFUSION	7.395	7.360	7.130	7.280	6.988	7.238	7.260	7.232	7.235	0.128

* Preshock = Control

● $P < 0.05$

Table II: Shows hematocrit values expressed as percent of control (i.e) preshock values. Means ± standard deviations are calculated for each time interval.

TABLE II B

HEMATOCRIT
% of CONTROL
HEAD UP

Time in Minutes

DOG #	9258	9264	9271	9282	9293	9306	9313	9317	MEAN	± SD
PRE-SHOCK*	36.0	40.0	45.0	48.5	43.0	49.0	41.0	48.0	43.8	4.7
30	104	82	77	82	100	108	75	75	88	14
60	133	77	86	92	111	102	73	72	93	21
90	136	72	91	102	127	96	68	81	97	25
120	141	75	111	118	125	104	65	81	103	27
150	136	67	117	126	127	110	67	-	107	29
POST REINFU-SION	141	117	117	119	127	122	95	102	118	14

*Preshock = Control = 100 %

TABLE II A

HEMATOCRIT
% of CONTROL
HEAD DOWN

Time in Minutes

DOG#	9261	9269	9273	9291	9298	9311	9316	9322	MEAN	± SD
PRE-SHOCK*	36.0	38.0	42.0	51.0	44.5	47.0	51.0	41.0	43.8	5.6
30	100	84	82	104	98	101	78	121	95	15
60	83	73	71	106	98	97	80	107	89	14
90	77	78	82	107	116	97	74	136	96	22
120	91	81	92	109	126	125	72	132	104	23
150	102	84	103	118	130	106	76	131	106	20
POST REINFU-SION	105	107	117	123	132	127	111	143	121	13

*Preshock = Control = 100%

Table III: Shows absolute values for bleeding volumes expressed in cc/Kg. of animal weight. Both groups demonstrated similar trends in bleeding volume and later blood uptake from the reservoir during hypotension. Episodes of rapid blood infusion and re-bleeding are not necessarily reflected in the values shown, since rapid changes may have occurred between predesignated recording intervals.

TABLE III B

BLEEDING VOLUME in cc / kg
HEAD UP

Time in Minutes

DOG #	9258	9264	9271	9282	9293	9306	9313	9317	MEAN	± SD
0•	49.7	39.5	27.6	59.5	40.0	29.2	27.2	28.4	37.6	11.9
10	50.9	40.3	33.4	57.1	45.0	29.2	28.5	38.1	40.3	10.2
20	59.0 *	46.3	39.2 *	56.6	47.4	48.9	29.8	42.4 *	46.2	9.4
30	56.7	48.3	37.6	61.8 *	52.1 *	45.6	34.9	40.8	47.2	9.4
40	47.8	54.3	37.1	61.2	51.2	51.0	35.5	39.7	47.2	9.0
50	37.8	54.3	33.9	58.3	48.1	52.7 *	42.6	38.1	45.7	8.9
60	32.2	54.3	30.3	54.2	39.7	48.9	42.6	34.8	42.1	9.5
70	31.6	55.3	28.1	52.5	35.0	51.0	40.0	35.9	41.2	10.4
80	31.3	56.3 *	25.5	49.6	33.8	50.0	43.8 *	28.4	39.8	11.5
90	27.2	55.0	25.0	44.4	32.6	49.4	40.0	25.1	37.3	11.6
100	27.8	54.3	22.4	44.4	31.3	46.7	40.6	29.4	37.1	11.0
110	26.6	54.3	21.3	42.6	31.3	43.5	39.4	28.4	35.9	10.9
120	22.8	55.3	19.7	39.7	29.5	42.3	40.0	29.4	34.8	11.7
130	15.3	55.3	17.1	38.6	28.2	39.2	38.7	26.2	32.3	13.3
140	19.1	55.3	16.0	34.8	26.4	39.2	37.4	0	32.6	13.4
150••	16.6	51.3	15.0	28.1	26.0	37.0	36.2	-	30.0	12.7
%Uptake of MBV	71.9	8.9	61.7	54.5	50.1	29.8	17.4	100.0	49.3	30.0

T= 0• = IBV (Initial Bleeding Volume) | T=150•• FBV (Final Bleeding Volume) | * = MBV (Maximum Bleeding Volume)

TABLE III A

BLEEDING VOLUME in cc / kg
HEAD DOWN

DOG #	9261	9269	9273	9291	9298	9311	9316	9322	MEAN	± SD
0°	24.3	31.6	33.7	33.9	43.2	41.9	36.6	38.0	35.4	6.0
10	28.3	35.3	31.0	36.3	44.3	41.9	41.0	43.7	37.7	6.0
20	31.7	37.8	38.3	39.7	51.4	43.0	43.2	48.3	41.7	6.2
30	33.7	40.6	38.3	43.2	52.0	44.8	45.4	49.5 *	43.4	5.9
40	37.7	42.8	42.3	44.4	54.2 *	46.2*	49.5*	49.0	45.8	5.1
50	39.0	43.8	46.7 *	47.9 *	53.1	44.8	48.7	47.2	46.4	4.1
60	39.0	43.8	45.0	46.7	42.1	44.2	48.7	44.4	44.2	2.9
70	41.7 *	44.1 *	44.3	47.9	39.3	43.0	48.1	43.5	44.0	2.9
80	41.0	42.8	43.0	46.7	36.0	41.3	47.6	39.8	42.3	3.7
90	40.4	41.6	40.3	45.5	31.1	38.5	46.0	38.0	40.2	4.7
100	40.0	41.6	40.0	46.7	31.1	37.9	46.5	34.5	39.8	5.4
110	39.0	41.3	37.7	47.3	27.8	35.6	47.6	36.7	39.1	6.5
120	36.4	40.3	37.0	46.7	28.9	35.6	45.9	33.8	38.1	4.5
130	35.0	40.0	33.7	45.0	25.6	34.5	45.4	33.4	36.6	6.6
140	33.7	40.0	33.3	43.2	25.6	33.4	45.4	31.5	35.8	5.4
150°	31.0	36.6	33.3	40.9	21.2	32.8	45.4	30.6	34.0	6.6
%Uptake of MBV	25.7	17.0	28.7	14.6	60.1	29.0	8.3	38.2	27.8	16.4

Time in Minutes

T= 0°= IBV T=150=FBV *=MBV

Table IV: Shows absolute values for serum potassium concentrations, in mg percent. Means ± standard deviations are calculated for each time interval.

TABLE IV B

SERUM POTASSIUM CONCENTRTION in mg %
ABSOLUTE VALUES
HEAD UP

Time in Minutes

DOG #	9258	9264	9271	9282	9293	9306	9313	9317	MEAN	± SD
PRE * SHOCK	3.3	3.2	3.7	3.1	4.0	3.8	3.0	3.5	3.5	0.3
30	8.7	4.0	5.9	6.5	5.6	4.6	4.0	7.2	5.8	1.6
60	9.8	4.0	9.1	8.8	8.5	5.1	4.6	9.0	7.4	2.4
90	7.8	4.8	9.0	7.7	6.5	7.4	5.0	9.2	7.1	1.6
120	9.2	4.0	8.3	8.1	7.0	8.8	5.9	8.9	7.5	1.8
150	9.4	5.6	8.0	8.8	7.9	8.4	6.8	-	7.8	1.3
POST REINFU-SION	9.8	4.5	9.8	8.4	7.6	8.8	6.2	9.5	8.0	1.9

*Preshock = Control

TABLE IV A

SERUM POTASSIUM CONCENTRATION in mg %
ABSOLUTE VALUES
HEAD DOWN

Time in Minutes

DOG #	9261	9269	9273	9291	9298	9311	9316	9322	MEAN	±SD
PRE-* SHOCK	3.1	3.3	3.6	3.8	4.2	4.0	3.6	3.5	3.6	0.3
30	3.8	4.2	5.1	3.5	5.7	4.9	4.3	5.4	4.6	0.8
60	3.7	4.8	6.5	4.7	10.7	5.2	4.9	5.8	5.8	2.1
90	3.7	4.1	6.3	4.6	9.2	6.3	5.4	5.7	5.7	1.7
120	3.7	4.5	6.2	6.5	9.3	6.1	5.5	6.9	6.1	1.7
150	3.7	4.8	6.3	6.5	9.4	7.5	5.8	7.3	6.4	1.7
POST REINFU-SION	3.4	4.4	5.9	6.4	10.3	6.3	6.1	6.1	6.1	2.0

* Preshock=Control

TABLE V: Shows the lactate/pyruvate ratios expressed as percent of control (i.e) preshock values. Means ± standard deviations are calculated for each time interval.

TABLE V B

LACTATE / PYRUVATE RATIO
% of CONTROL
HEAD UP

Time in Minutes

DOG#	9258	9264	9271	9282	9293	9306	9313	9317	MEAN	± SD
PRE-* SHOCK	19.10	9.24	14.45	8.37	7.77	8.85	7.68	5.64	10.14	4.41
30	261	485	475	384	172	148	248	381	319	131
60	258	490	1099	505	299	304	517	631	513	270
90	156	353	913	326	418	241	431	812	456	268
120	238	282	796	277	353	394	- -	550	413	198
150	167	351	417	361	521	302	312	-	347	109
POST REINFU-SION	201	247	477	359	428	310	363	313	337	90

*Preshock = Control = 100%

TABLE V A

LACTATE/PYRUVATE RATIO
%of CONROL
HEAD DOWN

Time in Minutes

DOG #	9261	9269	9273	9291	9298	9311	9316	9322	MEAN	± SD
PRE-SHOCK*	7.58	11.61	11.20	6.35	13.08	4.25	4.39	4.06	7.82	3.67
30	293	494	344	212	534	377	251	547	382	130
60	318	496	451	262	429	381	252	459	381	94
90	413	314	399	210	317	369	270	354	331	68
120	531	361	462	376	239	401	323	545	405	104
150	577	478	528	374	236	434	391	552	446	113
POST REINFU-SION	1741	482	440	383	242	757	365	934	668	489

*Preshock=Control=100 %

Table VI: Total peripheral resistance in mm Hg/liter/minute, expressed as percent of control (i.e.) preshock values. Means ± standard deviations are calculated for each time interval.

TABLE VI B

TOTAL PERIPHERAL RESISTANCE in mm Hg/liter/minute
% of CONTROL
HEAD UP

Time in Minutes

DOG #	9258	9264	9271	9282	9293	9306	9313	9317	MEAN	± SD
PRE-* SHOCK	50.66	46.05	36.34	32.86	52.04	50.00	41.81	39.04	43.60	7.17
30	165	87	246	320	170	92	128	197	176	79
60	162	60	240	196	88	88	158	171	145	61
90	101	58	124	196	85	108	111	66	106	43
120	108	57	188	228	79	92	98	72	115	60
150	118	59	163	133	110	84	89	-	108	34
POST-REINFU-SION	67	141	156	242	125	191	79	30	129	69

* Preshock = Control = 100%

TABLE VI A

TOTAL PERIPHERAL RESISTANCE in mm Hg/liter/min.
% of CONTROL
HEAD DOWN

Time in Minutes	DOG#	9261	9269	9273	9291	9298	9311	9316	9322	MEAN	± SD
	PRE-SHOCK*	47.33	59.28	38.87	40.98	81.17	29.41	21.66	45.28	45.50	18.35
30		85	70	143	121	82	236	284	224	156	82
60		94	56	145	155	63	235	250	99	137	74
90		72	60	164	138	75	196	192	115	126	55
120		89	68	137	174	65	140	152	140	121	41
150		90	67	146	155	62	129	155	127	116	38
	POST REINFUSION	154	164	181	340	81	317	361	138	217	106

* Preshock = Control = 100%

Table VII: Shows cardiac output in liters/minute expressed as percent of control (i.e.) preshock values. Means ± standard deviations are calculated for each time interval. During hypotension, both groups demonstrated severe decreases in cardiac output; low outputs also pertained after reinfusion, such that with two exceptions as described in the text, no animal regained its pre-shock value at this time.

TABLE VII B

CARDIAC OUTPUT in litres/minute
% of control
HEAD UP

Time in Minutes	DOG#	9258	9264	9271	9282	9293	9306	9313	9317	MEAN	± SD
	PRE * SHOCK	2.27	3.04	3.44	3.50	2.21	2.50	2.99	3.33	2.91	0.52
	30	21	33	16	11	22	33	25	16	23	3
	60	24	48	13	18	37	34	18	25	26	11
	90	37	50	27	18	41	30	27	47	32	12
	120	36	47	22	14	44	33	31	43	32	11
	150	42	45	22	25	32	36	34	-	34	8
	POST REINFUSION	130	78	37	31	66	50	38	191	78	30

*Preshock=Control=100%

TABLE VII A

CARDAIC OUTPUT in litres / minute
% of control
HEAD DOWN

Time in Minutes	DOG #	9261	9269	9273	9291	9298	9311	9316	9322	MEAN	± SD
	PRE * SHOCK	2.43	1.94	2.83	2.44	1.54	3.91	5.77	2.54	2.93	1.34
30		46	50	25	37	39	14	11	15	30	15
60		37	59	25	23	47	15	13	33	32	16
90		45	58	21	29	48	17	16	28	33	16
120		37	52	27	23	49	23	20	23	32	13
150		36	52	23	26	65	25	19	26	34	16
	POST REINFU-SION	74	69	45	25	64	37	36	85	54	22

*Preshock = Control = 100 %

Table VIII: Shows heart rates/minute expressed as percent of control (i.e.) preshock values. Means ± standard deviations are calculated for each time interval. Both groups demonstrated a compensatory tachycardia during the hypotensive period. Transient episodes of bradycardia are not necessarily revealed since the values shown were recorded at the predefined time intervals only.

TABLE VIII B

HEART RATE / MINUTE
% of CONTROL
HEAD UP

Time in Minutes

DOG #	9258	9264	9271	9282	9293	9306	9313	9317	MEAN	±SD
PRE SHOCK	80	180	150	150	110	160	200	160	149	38
10	150	72	73	107	173	94	65	113	127	43
20	225	78	87	120	200	125	75	125	129	56
30	225	89	93	120	218	138	90	144	115	55
40	250	106	73	100	245	150	85	156	146	69
50	250	111	87	100	236	156	85	150	147	65
60	263	106	93	107	218	150	95	144	147	63
70	225	122	80	100	191	163	100	138	140	50
80	188	122	67	100	173	156	105	81	124	44
90	213	111	73	113	191	156	95	125	135	48
100	200	117	67	113	182	113	90	113	124	45
110	188	122	73	113	191	119	90	144	130	42
120	200	122	93	107	191	131	90	138	134	42
130	100	128	93	107	191	119	90	138	121	33
140	238	122	80	100	200	119	90	35	123	66
150	113	111	80	93	191	125	85	-	114	38
POST-REINFUSION	100	83	67	100	209	119	95	56	104	47

Preshock=Control=100%

TABLE VIII A

HEART RATE / MINUTE
% of CONTROL
HEAD DOWN

Time in Minutes

DOG #	9261	9269	9273	9291	9298	9311	9316	9322	MEAN	± SD
PRE SHOCK	250	160	150	170	70	180	170	130	160	50
10	76	94	93	71	229	72	88	92	102	52
20	76	113	100	76	257	94	88	108	114	59
30	80	131	93	98	257	111	94	108	120	58
40	88	138	100	94	286	133	112	131	135	64
50	88	138	107	100	271	150	112	138	138	58
60	84	144	113	100	271	156	118	146	142	58
70	92	150	113	112	229	161	118	146	140	43
80	92	144	120	118	171	156	118	154	134	26
90	92	150	120	129	171	150	118	154	136	25
100	96	144	127	129	143	150	124	154	133	19
110	96	144	133	135	129	150	124	154	133	18
120	96	150	127	135	186	144	124	154	140	26
130	100	150	133	129	114	122	124	146	127	16
140	100	150	133	129	114	144	118	146	129	18
150	100	150	133	135	114	144	118	138	129	18
POST-REINFUSION	76	106	113	106	157	111	94	108	109	23

Preshock = Control = 100 %

Table IX: Compares during hypotension the percent uptake of the maximal bleeding volume in animals manifesting bradycardia vs. those which did not. This was calculated as

$$\frac{MBV - FBV}{MBV} \times 100$$

The trend towards higher percent uptake in animals which demonstrated bradycardia is evident.

TABLE IX
PERCENT UPTAKE OF MAXIMAL BLEEDING VOLUME

Non Bradycardia

DOG #	9316	9264	9291	9269	9261	9273	9311	9322	9293
% UPTAKE	8.3	8.9	14.6	17.0	25.7	28.7	29.0	38.2	50.1

Bradycardia

DOG #	9313	9306	9282	9298	9271	9258	9317
% UPTAKE	17.4	29.8	54.5	60.1	61.7	71.9	100.0

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