THE EFFECT OF HYDRALAZINE (APRESOLINE) ON SHOCK

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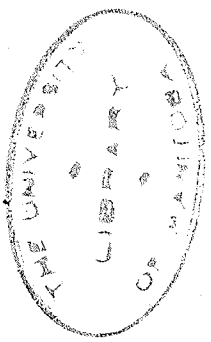

by

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Abstract

Review of the pertinent literature indicates that vasoconstriction and decreased cardiac output result in diminished blood flow to most organs during shock. Impairment of blood supply to vital viscera, especially the liver, may well be responsible for the development of irreversibility to transfusion. Drugs which increase blood flow by interfering with sympathoadrenal vasoconstriction decrease mortality of animals subjected to traumatic or hemorrhagic shock.

In the present study, hydralazine, an agent which increases cardiac output and causes dilatation in the splanchnic area in normal animals and man, decreased mortality of animals subjected to milder, but not those subjected to more severe hemorrhagic or traumatic procedures. In addition, it protected remarkably against acute traumatic deaths due to tumbling, the first demonstration of protection against this type of death by a pharmacological agent.

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CHAPTER I

Introduction *

Numerous definitions of shock have been proposed during the past century. None, however, is entirely satisfactory and their large number reflects the inadequacy of our knowledge and understanding of the problem. Shock remains a general concept or syndrome rather than a well defined entity. It can be precisely recognized only in its advanced stages which are characterized by some as yet incompletely understood event or events leading inexorably to death hours or even days after the end of the period of stress.

In most of its forms, shock may be considered to be a s u b a c u t e, g e n e r a l i z e d c a r d i o v a s c u l a r i n s u f f i c i e n c y. This term differentiates it from chronic conditions such as congestive heart failure, and from acute and subacute impairment of blood supply to localized areas, e.g., due to embolism or thrombosis. It differentiates it further from acute deaths which may result from the same causes which under different circumstances lead to the typical picture of shock. Deaths from acute exsanguination and acute traumatic deaths such as may result from trauma in the Noble-Collip drum (71) fall into this category.

In shock blood flow to most organs is reduced, although the extent of the reduction may differ widely in different vascular beds. The blood supply to some organs may become insufficient for their functional and/or

* The literature, on which the ideas outlined in this introduction are based, is reviewed in some detail in the following chapters. Therefore no references to specific articles are made, except in cases where no further discussion is presented.

metabolic demands and if this inadequacy persists too long, undefined irreversible changes in vital organs may develop. Once this has occurred, recovery will not take place in spite of all treatment presently available and the shock is said to be irreversible.

Although other primary factors may operate, a deficit in the effective circulating blood volume appears to be present early in most forms of clinical and experimental shock including shock due to hemorrhage, burns and various forms of trauma (13,14,15,17,32,59). Various mechanisms may be brought into play by the body in attempts to correct or compensate for this circulatory inadequacy. These may be divided into two main categories:

1) Those tending to increase the circulating blood volume.

2) Those associated with circulating the available blood volume in the most effective manner.

Mechanisms prominent in the first category are: a) discharge of blood from "reservoir areas" such as the spleen, at least in the dog (63), and perhaps other visceral or vascular spaces (42), and b) entrance of fluid from the extravascular spaces into the circulatory system.

The most effective circulation of the available blood volume would be such that each organ would receive just enough blood for its "survival" and for the minimum level of function necessary for survival of the organism as a whole. The requirements of various tissues and organs obviously will vary. In shock the extent of changes in blood flow to various vascular beds also varies, and in any particular area it will depend on:

1) The perfusion pressure or arterial pressure.

2) The resistance to flow offered by the vascular bed in question.

The blood pressure in turn depends on the cardiac output and the total peripheral resistance, the resultant of the resistances of all vascular beds in the body.

The degree to which the vasculature of any organ or tissue participates in the generalized vasoconstriction which occurs in shock will thus be the major factor determining the blood flow to that area, assuming that the blood pressure available to all parts of the body is the same or approximately the same. The great variations in the amount of vasoconstriction occurring in the blood vessels of various tissues in shock probably are due both to differences in the amount of vasomotor innervation and to differences in the responsiveness of the various vascular beds to humoral vasoactive agents. For example, in the skin, where the nerve supply to the blood vessels is rich and where wide fluctuations in the amount of vasoconstriction and vasodilatation occur under physiological conditions, vasoconstriction and reduction in blood flow in shock are marked. Severe vasoconstriction in shock also takes place in some abdominal viscera, e.g., in the kidney and the splanchnic area. In contrast, blood vessels of the heart and brain are supplied with few sympathetic vasoconstrictor nerve fibres, and their blood flow is governed largely by metabolic demands rather than by nervous or humoral constriction. Thus there is less vasoconstriction in the cerebral and coronary vessels and the blood flow is reduced to a lesser degree than in most other areas during shock. In other words, the body tends to maintain blood flow to some organs, such as the brain or the heart, at the expense of others where severe vasoconstriction takes place. This results in a

redistribution of the available cardiac output.

Although some of the organs in which severe vasoconstriction occurs can withstand long periods of low blood flow without irreparable damage, e.g., the skin, others are more sensitive to prolonged curtailment of blood supply and irreversible changes may occur. Several lines of indirect evidence suggest that the liver may be particularly sensitive, perhaps because of its unique position in the vascular system. Indeed, the marked reduction in the blood flow to the liver has been implicated as an important factor in the development of irreversibility in shock.

The idea that the severe vasoconstriction which occurs in response to various shock-inducing procedures, may itself be harmful is not new, and is supported by the following findings:

1) Infusion of adrenaline or noradrenaline can produce typical shock.

2) More favourable response to trauma, longer survival, and decreased mortality can be produced by spinal cord section, spinal anaesthesia, or section or local anesthetic blockade of peripheral nerves to the traumatized extremities; these beneficial effects probably resulting from the blockade of reflex sympathetic stimulation.

3) Selective interference with sympathetic pathways by means of sympathectomy or chemical blocking agents affords protection to groups of animals subjected to hemorrhagic and traumatic shock.

In the presence of hypovolemia, the cardiac output is limited primarily by the low venous return which may be accentuated by low velocity of the circulation. A reduction in peripheral resistance, e.g., by means of adrenergic blockade, if not associated with too much relaxation of veins,

may increase the velocity of the circulation and produce an overall increase in cardiac output in addition to the effects on regional blood flow. Although impaired myocardial function has not been implicated as a primary factor in the decreased cardiac output in various forms of shock, several groups of workers have suggested that some degree of myocardial insufficiency might occur during the course of the shock process and thus accentuate the inadequate output.

Two therapeutic approaches for counteracting the effects of this myocardial insufficiency are possible:

1) To decrease the total peripheral resistance by inhibition of "excessive" vasoconstriction and thus to reduce the work of the weakened heart (although a resulting decrease in blood pressure might have a detrimental effect on the myocardium by decreasing the coronary perfusion pressure) and

2) To stimulate the weakened myocardium by means of a suitable pharmacological agent.

The object of the present study was to investigate the effects on shock of hydralazine, an agent which has been used fairly extensively in the treatment of hypertension for a number of years. Although the pharmacology of this drug is not completely understood, it appears to have two main and independent actions: 1) it increases cardiac output through an indirect effect on the heart and 2) it produces vasodilatation, predominantly in visceral vascular beds. In addition it may produce some dilatation of the coronary and cerebral vessels. Hydralazine thus seemed to be a particularly suitable agent with which to attempt to modify the development of shock because it might be expected to exert a favourable influence by increasing

cardiac output and/or by preventing the development of irreversible changes in the viscera by selective vasodilatation without at the same time interfering extensively with adrenergic vasoconstriction in other organs better equipped to withstand extensive reduction in blood flow.

CHAPTER II

Blood Flow and Peripheral Resistance in Shock.

Pallor and coldness of the skin are among the most obvious features in patients in various forms of shock, and indicate vasoconstriction and decreased blood flow to this organ. Extensive vasoconstriction with decreased rates of flow to various organs in the course of hemorrhagic and other types of shock has been amply corroborated by experimental evidence.

In 1918 Gesell (40) in his classical study on the submaxillary gland demonstrated a pronounced decrease in blood flow to this organ when blood volume was decreased. The flow was decreased to a greater extent than the blood volume. A reduction in blood volume of only 10% was accompanied by a 60% fall in blood flow. In addition marked decreases of blood flow (down to 15%) were found to occur with little or no change in the head of pressure. These facts indicated that marked vasoconstriction took place.

Similarly Erlanger et al. (27) demonstrated diminished inflow rates of blood into the splanchnic and femoral vascular beds in shock induced in dogs by intestinal manipulation, while Gesell and Moyle (41) showed decrease in flow through the muscle of the dog's leg after graded hemorrhage, estimating the blood flow by counting drops from the femoral vein tied below the muscular tributaries. The decrease in flow was again greater than the decrease in blood volume. More recently Freeman et al. (35) and Eckstein et al. (23) using a plethysmographic method observed diminished blood flow and increased peripheral resistance in the unoperated limbs of dogs in hemorrhagic shock.

In 1936 Freeman et al. (36) measured changes in hand blood flow of

patients in surgical shock by means of a plethysmograph. They found a pronounced decrease in only a few patients. However, their group was very heterogenous and it seems likely that several of them might not have been in true shock which is corroborated by essentially normal blood pressure values.

The decrease in blood flow is not limited to the organs of the body wall but involves deeply seated viscera as well. Experimental and clinical studies show that the kidney is severely affected. In 1943, Corcoran et al. (19) demonstrated decreased renal blood flow and glomerular filtration rate by means of clearance studies in dogs subjected to tourniquet shock. A year later similar work was carried out on 39 patients in shock of various etiologies by Lawson et al. (61) who found pronounced vasoconstriction with increased renal resistance and a decrease in the proportion of cardiac output flowing through the kidney. Observations on dogs have been further extended to include hemorrhagic and traumatic shock by Phillips et al. (76) who noted markedly diminished renal blood flow values in the presence of almost normal blood pressures. Selkurt in 1946 (88) using simultaneously clearance and direct methods for measuring renal flow demonstrated that the clearance methods became unreliable at low levels of flow. However, his studies using the direct method confirmed the markedly diminished renal blood flow and increased renal resistance, especially in the later stages of hemorrhagic shock in the dog.

The pronounced vasoconstriction and curtailed blood flow found to exist in several organs in shock (including the hepato-splanchnic area, to be discussed separately) might not, however, be associated necessarily with an increase in total peripheral resistance (TPR). This is due to the

fact that the TPR does not equal the sum of peripheral resistances in various vascular beds, but because of their parallel rather than in series arrangement, the reciprocal of TPR equals the sum of reciprocals of all peripheral resistances (103). Therefore severe vasoconstriction in a particular vascular bed or beds does not increase the TPR as much as might be expected.

The time-course of TPR changes in shock has been studied by Wiggers and Werle (105), and Wiggers and Middleton (108). The latter authors used a saline dilution method to estimate cardiac output and this method is subject to the possible criticism of inadequate mixing at low levels of cardiac output. Nevertheless both groups agreed that the TPR was extremely variable during the course of hemorrhagic shock. Wiggers and Middleton found an increase in TPR in the early stages in only 50% of their dogs, the others showing either a decrease or a decrease followed by a return to the control values. The late stages of hemorrhagic, hypovolemic hypotension were usually accompanied by a decrease in TPR below control level. Following reinfusion of the withdrawn blood, there was a fall in TPR usually followed by an increase above control values, which was again superceded by a fall shortly before death. In some animals, however, no rise above control levels occurred throughout the experiment. The variability in the values of TPR in hemorrhagic shock has also been found by other authors in more recent studies (47,82).

In most of these studies, however, no correlation was made with the cardiovascular status of the animals at the time of measurements of TPR. Obviously if the dogs are already decompensating as indicated by falling

blood pressure or the bleeding volume decreasing at a constant pressure, lower values of TPR are likely to be obtained. On the other hand if they are still able to compensate as shown by rising blood pressure or increasing bleeding volume, higher values will usually be found. General elevation of TPR in hemorrhagic shock has recently been reported by Remington et al. (79) and by Beck (8). Similarly Reynell et al.(82) found increased TPR in acute hemorrhage, although no consistent changes were evident in protracted hemorrhagic hypotension. Furthermore, increased electrical activity in the preganglionic sympathetic fibres during hemorrhagic shock has been demonstrated by Beck and Bentas (9).

The reports dealing with TPR in shock are meaningless unless evaluated in relation to the cardiovascular status of the animals, and it seems that an increase in TPR does exist usually in the early stages before decompensation sets in, and in some cases again after reinfusion.

The considerations of the parallel arrangement of regional vascular beds in the body indicate, however, that the importance of vasoconstriction in maintaining blood pressure in shock might have been overestimated. On the other hand one should guard against a too drastic opinion in the opposite direction. The vasoconstriction in various organs and tissues, might be beneficial, not so much by maintaining blood pressure, but by redistribution of the available cardiac output from some of the vasoconstricted areas, to those in which vasoconstriction is less severe. Furthermore, it has not been postulated, that regional vasoconstriction is without any effect on blood pressure. The small effect which it must exert, might be of importance in the critical stages of hypotension in relation to the perfusion of the cerebral and coronary beds.

CHAPTER III

The Role of the Liver

This organ has been the subject of special attention in studies on experimental shock and has been implicated in the development of irreversibility to transfusion. Involvement of the liver might be related to the partial dependence on the portal venous system for its blood supply. Because changes in the vasculature of the liver affect the hemodynamic phenomena in the splanchnic region, and vice versa, they will be considered together in the following discussion.

A marked fall in blood flow through the hepato-splanchnic area during hemorrhage has been shown by several investigators. Selkurt et al. (89) using the method of periodically diverting blood from the portal vein, found that the mesenteric flow fell from 26 to 8 and even 4 ml/kgm/min. during severe hemorrhagic hypotension. Although this measurement excluded the liver and its resistance and thus resulted in artifically high values of flow, other authors (50,53,82) using the BSP clearance method found reductions in the effective splanchnic blood flow of 40 to 75% depending on the severity of the hemorrhage.

Reynell et al. (82) using an I^{131} dilution technique, further demonstrated a decrease in the circulating splanchnic blood volume during hemorrhage, a finding which supported the earlier observation of Friedman et al. (39) that the vascular x-ray shadows of the porto-hepatic system are decreased in shock. The reduction in splanchnic blood volume was proportionately greater than the total blood loss and consequently, a transfusion effect was ascribed to it (82).

Although a reduction in splanchnic blood volume occurs early during hemorrhage, few gross pathological changes are usually found at this stage (101). However, marked congestion and hemorrhage in the splanchnic viscera is a constant finding on pathological examination in animals dying of hemorrhagic shock after transfusion (25,89,101,102), as well as in other forms of shock (17,71). This congestion and the associated loss of circulating blood into the splanchnic area has frequently been held responsible for the ultimate circulatory failure following reinfusion. Selkurt et al. (89) found a marked increase in mesenteric resistance soon after the beginning of hemorrhage. This declined later but remained above control values. In the late stages there was again a sharp rise. Reinfusion resulted only in a temporary decrease of mesenteric resistance below normal. These authors also measured portal pressure and found an increase in $\frac{\text{portal pressure}}{\text{aortic pressure}}$ ratio during the hemorrhagic hypotension and after reinfusion. This study together with certain observations of aorto-portal, and porto-caval pressure gradients by Wiggers et al. (104) suggests that hemodynamic relations consistent with pooling exist in the splanchnic area. Such relations which seem to be due to the greater elevation of hepatic than of mesenteric resistance were found to exist in the later stages of oligemic hypotension, and to a greater extent following reinfusion.

On the other hand, Frank et al. (29) subjected Eck-fistula dogs to hemorrhagic shock and found no effect on survival and bleeding volumes, although there was no splanchnic congestion. They concluded that diversion of blood into the splanchnic bed is not a critical factor in the development of irreversibility. It is probable, therefore, that the development of irreversibility takes place before reinfusion and that congestion and hemorrhage in the splanchnic viscera is rather a sequel than a cause. However, it still might be a contributing factor in the terminal circulatory failure. In addition, the failure of agents to protect from fatal outcome in hemorrhagic shock when given after reinfusion, although significant protection is afforded after earlier administration, confirms the idea that irreversibility develops before blood is returned to the animal.

The importance of adequate blood supply to the liver has been brought out by experiments in which the animals were rendered hypotensive by means of hemorrhage, but the liver flow was maintained at normal levels by means of artificial perfusion. Frank et al. (31) and Seligman, Frank and Fine (87) found that vivi-perfusion of the liver from the donor dog reduced the mortality from 88% to about 11%. The control animals received donor blood into the jugular instead of the splenic vein. Similar protection was obtained by other workers whose treated animals were prepared by anastomosing aorta (18), right renal artery (5) or splenic artery (52) to the portal venous system.

The inadequate blood supply to the liver appears therefore to be an important if not the crucial factor in the occurrence of irreversible circulatory failure. However, the mechanism of its development is far from understood. Although some compensation for diminished blood flow takes

place, as indicated by an increased hepatic A-V oxygen difference, this compensation is not complete in protracted hemorrhage. Hamrick et al. (50) demonstrated that splanchnic oxygen consumption remains normal for a short time after acute hemorrhage, but declines when the blood pressure is kept at low levels for longer periods of time.

Observations of reduced prothrombin activity and prothrombin conversion factor during hemorrhagic shock by Frank et al. (28) suggest that liver function is impaired in hemorrhagic shock. The reduction was roughly related to the severity of hemorrhage.

Shorr et al. (90) demonstrated release from the liver of a vasodepressor material (VDM) which was later identified as ferritin. The release of VDM was noted in late stages of hemorrhagic and traumatic shock and was thought to be responsible for the decreased responsiveness of the small blood vessels observed in irreversible shock. It was demonstrated by these workers that whereas normal liver slices were capable of inactivating VDM under aerobic conditions, this was not true of livers from animals in irreversible shock. In addition, liver slices from rats made resistant to drum shock inactivated VDM for 2 hours in the absence of oxygen, whereas normal liver slices failed to inactivate the material under anaerobic conditions (113). However, the hypothesis that the release of VDM by the liver bears a causal relationship to the development of irreversibility is questioned by the fact that no increase in susceptibility to shock resulted when tissue VDM was artificially increased prior to the experiment (49). It is possible, therefore, that it may be only an associated phenomenon.

When Frank et al. (30) and others (57,86) reported protection of dogs subjected to hemorrhagic shock by premedication with antibiotics, the liver

was again incriminated as the anoxic tissue in which various bacteria, notably anaerobes, were multiplying. However, others (10,21,110) have been unable to repeat these experiments and in addition, demonstration of metabolic actions of aureomycin (3,96) has thrown a further doubt on the importance of the bacterial factor in the development of irreversibility. Rees et al. (3) showed that liver slices from rats premedicated with aureomycin did not release VOM under anaerobic conditions for significantly longer periods of time than slices from normal animals.

Impairment of the blood supply to the liver appears, therefore, to be intimately related to the development of irreversibility, but the mechanisms involved are not yet understood.

CHAPTER IV

Protective Action of Sympatho-Adrenal Blockade.

The idea that severe vasoconstriction, which occurs in response to various shock inducing procedures, may actually be harmful, has been referred to previously. Experiments demonstrating that a shock-like state can be produced by the injection of vasoconstricting drugs gave it early support.

In 1917 Bainbridge and Trevan (6) observed hypotension and shock following the slow intravenous infusion of adrenaline for 20 minutes. Associated with the rise in blood pressure during the injection was an elevation in portal venous pressure, which persisted after the infusion was discontinued. The latter was thought to be related to the splanchnic congestion associated with shock. Similar elevation of portal pressure after reinfusion of blood in experimental hemorrhagic shock was discussed in the previous section. These experiments were supported by similar results obtained by Erlanger and Gasser (26) who found also that the pathological changes in animals dying following adrenaline infusions were indistinguishable from those of animals dying as a result of traumatic shock.

More recently Freeman (33) showed that prolonged infusion of adrenaline resulted in a marked decrease in blood volume. This effect was blocked by ergotamine. The production of shock by prolonged infusion of adrenaline (34) or noradrenaline (111) has been reported to be associated with the same high mortality, hemoconcentration, decreased plasma volume, low peripheral blood flow, and pathological findings characteristic of shock produced by other procedures. These findings acquired additional importance when high

blood levels of adrenaline were demonstrated during hemorrhagic shock (100).

Procedures which interfere with vasoconstrictor pathways were applied quite early to the study of shock. In 1919 Erlanger et al. (37) observed that shock was induced more easily in two dogs after abdominal sympathectomy than in control animals. However, the condition of the animals was very poor and one actually began to slip into shock before the shocking procedure was initiated.

Investigating the importance of "noxious" stimuli from the injured areas in the etiology of shock, O'Shaughnessy and Slome (75), Swingle et al. (94) and Wang (99) observed a more favourable response to trauma, longer survival and decreased mortality, following cord section, spinal anaesthesia or local anaesthetic blockade or section of peripheral nerves to the traumatized extremities. The interruption of the afferent fibres, and the decrease in reflex sympathetic stimulation was probably the main factor responsible, but the direct section or inhibition of the sympathetic vasoconstrictor pathways was probably also of importance in some of these experiments.

Schlossberg and Sawyer (85) demonstrated that sympathectomized and ergotaminized cats, as might be expected, could be rendered hypotensive, by withdrawal of smaller volumes of blood than normal controls. On the other hand Freeman et al. (35) showed that 3 sympathectomized dogs resisted hemorrhage better and survived while 7 out of 9 controls died. The latter results, however, are difficult to evaluate because although in both groups the blood pressure was reduced to comparable levels, the blood loss was definitely smaller in the sympathectomized animals.

Chemical blocking agents also have been shown to exert a beneficial influence on the outcome of hemorrhagic and traumatic shock in various laboratories. H.C. Wiggers et al. (107) used dibenamine in dogs subjected to 40 to 43 mm Hg hemorrhagic hypotension for 90 minutes. Dogs pretreated with 10 to 15 mgm/kgm half an hour before hemorrhage had a higher mortality than the controls in spite of bleeding volumes less than 50% those of the controls. They ascribed the poorer response of the treated animals to the inability to compensate shortly after the administration of the rather large dose of the blocking agent. In a second series of experiments in which the stress was somewhat increased (35 to 38 mm Hg) dibenamine was administered 20 hours before the experiment. The mortality was 70% in 20 control dogs and 40% in the same number of treated animals. The difference although not striking ($p = 0.1$), suggested a beneficial influence of the drug. However, it is possible that the lower mortality may have been due to approximately 25% smaller maximal bleeding volumes in the treated group.

In similar experiments, the same authors (106) reported that administration of only 3 mgm/kgm of the drug half an hour after beginning of hemorrhage resulted in a decrease in mortality from 70% to 10%. This difference is highly significant. Although some differences in bleeding volumes between the treated and control animals were noted, they were most pronounced between the survivors of the two groups. The control fatalities and treated survivors appeared to be quite comparable in this respect.

Remington et al. (78) also obtained significant protection by the use of 5 mgm/kgm of dibenamine 30 minutes before graded hemorrhage whereas 15 mgm/kgm did not offer as much protection as the smaller dose. There was no difference between "total" bleeding volumes in the control and treated groups, although

the authors did not state whether this referred to maximal bleeding volume or bleeding volume at the time of reinfusion.

Protection against fatal outcome in hemorrhagic shock in dogs and rats by agents blocking sympathetic vasoconstrictor activity has been confirmed in other laboratories using dibenamine (4,8), dibenzyline, S.C. 2139, (55), tetraethylammonium (43) and chlorpromazine (54). In some of these experiments (8,43,54) the bleeding volumes were again smaller in the treated animals.

The administration of a dilating agent before or while an animal is connected to a blood reservoir can result in a smaller volume bled out or a greater volume of blood taken up, and this difference might be responsible for some of the good results mentioned above. However, the fact that the differences in bleeding volumes were relatively small and the differences in mortality were striking, suggests a beneficial influence of the drugs apart from any effect which they might exert on blood loss.

Beck (8) and Lotz et al. (64) who ran their control and treated animals in parallel, demonstrated that in dibenamine treated dogs there was a smaller increase in TPR, a smaller reduction in cardiac output, greater oxygen consumption, greater oxygen transport and lower levels of plasma amino-acid nitrogen in treated than in control animals. Smaller decreases in renal blood flow and smaller increases in renal resistance during hemorrhage following dibenamine have been found by Brandfonbrener and Geller (16).

Although dibenamine and related compounds seem to offer protection when given before or early in the course of hemorrhage, Beck (8) has shown that no significant protection could be obtained when the drug was given after 85 minutes of a 90 minute period of hypotension, although some improvement in hemodynamic indices was evident.

Numerous investigators have demonstrated the protective influence of various blocking agents in traumatic shock. Remington and his group (80) demonstrated a significant decrease in mortality in dibenamine pretreated dogs when they w ere put into shock by palpation of abdominal viscera or by multiple blows to the leg. Similar results were obtained in rats subjected to shock in a Noble-Collip drum, using dibenamine (4), and other blocking agents such as dibenzyline (55,62), dihydroergotamine, tolazoline, phentolamine, piperoxan, S.Y. 28 (62), and others (72).

Speerel (91) was able to protect from fatal outcome in tourniquet shock by hexamethonium administered at the time of release of the tourniquets, and to a lesser, but siguificant extent when the drug was given two hours later. Chloropromazine, together with saline therapy, was reported to be beneficial in tourniquet shock in mice (11).

As in the case of hemorrhagic shock, the drugs appear to be ineffective when administered in the later stages. Levy et al. (62) found no protection when dibenzyline or dihydroergotamine over a wide range of doses, was given intravenously or intraperitoneally after drumming and Speerel (91) found no effect in tourniquet shock when hexamethonium was administered 4 hours after the release of the tourniquets.

Another shortcoming of the blocking agents was indicated by the finding of Levy et al. (62), that although various blocking agents decreased significantly the overall mortality from drum trauma, the incidence of deaths during drumming was increased. They felt that these acute deaths were more frequent with larger doses of the drugs. The unfavourable effect of large doses of ergotamine on the response to acute hemorrhage has also been reported by Schlossberg and Sawyer (85) whereas Wiggers et al. (107) found increased

mortality in dogs subjected to hemorrhagic shock after premedication with large doses of dibenamine, although smaller doses afforded significant protection. These findings suggest, that although adrenergic blocking agents afford protection to groups of animals subjected to various forms of experimental shock they interfere, particularly in larger doses, with the animals' ability to cope with an acute stress. Furthermore, partial adrenergic blockade seems to be optimal for protection against shock.

Hershey et al. (55) after finding that atropine protected from drum trauma postulated that the protection afforded by various drugs is not due to an increase in blood flow, but might be related to some metabolic action. Protection by atropine and scopolamine had previously been reported by Zahl et al. (112) and North and Wells (72). However, these agents are capable of producing ganglionic blockade and thus an increase in blood flow in some areas. Hershey et al. employed 20 mgm/kgm of atropine and Zahl et al. administered even larger doses. It seems probable that with these very large doses ganglionic blockade was produced. It can be said, therefore, that protection against death from shock has not been achieved by drugs which are not capable of producing an increase in blood flow. Postulation of an additional metabolic factor seems to be superfluous at present.

Surgical or chemical interference with the effects of sympatho-adrenal activity has been shown to afford protection from fatal outcome in various forms of shock when used before or early during the shocking procedure. No protection, however, has been demonstrated when the therapy is given in the late stages.

CHAPTER V

The Heart and Cardiac Output in Shock.

A marked decrease in cardiac output during hemorrhagic shock has been reported by numerous investigators (1,8,24,47,79,105,108). H.C. Wiggers and Middleton (108) found cardiac outputs amounting to 29 to 45% of control values in the course of hemorrhagic hypotension, and values below 20% of "normal" have been found by Edwards et al. (24) and Beck (8). Following reinfusion there is always an increase, the values ranging from 45 to over 100% of the initial cardiac output, although they are usually below normal. There is subsequent decrease at a variable rate in cases of irreversible shock.

Although decreased blood volume and venous return is the primary factor responsible for the decreased cardiac output found in hemorrhagic hypotension, the possibility that it might be depressed further as a result of impaired myocardial function, was suspected by Wiggers and his school.

In 1942 Werle et al. (101) measured effective central venous pressure during hemorrhagic shock. They found in some dogs that after the initial drop with bleeding, it was restored to normal for about one hour after cessation of bleeding, although the arterial pressure continued to fall. Similarly normal effective central venous pressure was found to persist during deterioration of blood pressure after reinfusion. They postulated that depression of the myocardium was responsible for those findings. Observations of ventricular alternans during shock by those authors also suggested involvement of the heart muscle.

The finding of diminished cardiac output in spite of normal effective

central venous pressure after reinfusion in 30 out of 48 dogs (102) added strength to the hypothesis that myocardial inadequacy may be a factor in the development of shock. Observations of decreasing inferior vena cava flow in the presence of rising or high right atrial pressure before and after reinfusion were also consistent with myocardial depression (22), which was further inferred from the study of right ventricular and aortic pressure pulses by Opdyke and Wiggers (74).

Diminished coronary flow is a possible factor responsible for the impairment of myocardial function and this possibility has been explored by several authors. In 1947, Opdyke and Foreman (73) studied coronary flow and coronary resistance during hemorrhagic shock. They found that coronary flow during hemorrhage was decreased to 30 to 60% of the control rate. This was associated with a marked decrease in coronary resistance. Following reinfusion the flow rose to 120 to 430% of normal and persisted above normal until shortly before death. These high values rule out diminished coronary flow as the factor directly responsible for terminal circulatory failure. However, the low flow during hemorrhage might have resulted in decreased myocardial function. Decreased coronary flow in hemorrhagic shock was confirmed by Edwards et al. (24) and Allbaugh and Horvath (1) using different methods. Hackel and Goodale (47) found normal coronary flow during hemorrhage but this was probably due to the somewhat less severe hemorrhagic procedure they employed.

The reports of Sarnoff et al. (84) also suggest that insufficient coronary flow with resulting myocardial failure may be a complicating factor in hemorrhagic shock. They observed a rise in left atrial pressure in open chest dogs late in the course of hemorrhagic hypotension, which

could be consistently reversed by artificially increasing coronary perfusion. The significance of this report becomes somewhat questionable, however, in view of the fact that no rise in left atrial pressure occurred in 4 closed-chest dogs which they studied.

Impairment of myocardial metabolism in experimental hemorrhagic shock was found by Edwards et al. (24) and Hackel and Goodale (47). Myocardial oxygen consumption was found diminished by Edwards et al., but was normal during the less severe experiments of Hackel and Goodale. Both groups, however, reported diminished lactate and pyruvate utilization, and diminished (almost to zero) pyruvate extraction in the presence of elevated blood levels of both compounds.

Involvement of the heart in shock is further suggested by the finding of:

1) Increased heart size late in hemorrhagic hypotension (60).

2) Electrocardiographic changes, consistent with ischemia (56).

3) Pathological changes in the heart of some dogs dying of hemorrhagic shock (70).

In summary, impairment of myocardial function, perhaps due to insufficient coronary perfusion, exists in the late stages of hemorrhagic hypotension and after reinfusion, at least in some cases, and may be an important contributing, although probably not a primary factor determining the outcome of hemorrhagic shock.

CHAPTER VI

The Properties of Hydralazine*.

Gross et al. (46) noted the hypotensive effect of hydralazine in 1950. In the same year other reports describing its cardiovascular actions appeared (27,37,45,81,98), and numerous articles followed in the next five years. However, the pharmacology of the drug is not as yet completely understood.

A. The Effect on Blood Pressure.

A definite hypotensive effect has been obtained by all investigators in all species studied, including the guinea pig, rat, rabbit, cat, dog and man. The degree of blood pressure fall depends on the size of the dose, but consistent effects have been obtained with doses as small as 0.2 mgm/kgm. Doses above 1 mgm/kgm do not result in a greater decrease in blood pressure (21). As the hypotension sets in slowly (12,21,46), a metabolic alteration to an active compound or a slow accession to the susceptible structures has been suggested (21). The fall in diastolic is greater than in systolic pressure (2,37,97), suggesting a peripheral vasodilatation, which is confirmed by a marked decrease in TPR (2,38,65,83).

B. The Mechanism of Peripheral Dilatation.

The vasodilatation, which occurs following administration of hydralazine does not appear to be due to blockade of responses to sympatho-adrenal activity. Although modification of certain vascular reflexes or responses

* Although some work on the effects of hydralazine on patients with hypertension and some other conditions will be quoted, no attempt will be made to review the effect of the drug in the treatment of hypertension.

to sympathomimetic amines have been reported by some authors after intravenous doses of hydralazine (21,37,45,46,68,97), inhibition was usually either incomplete (45,46) or inconsistent (45), or required quite large doses of the drug (21,45,46,68,97). Some workers have been unable to obtain these effects (2,37,93), and Moyer et al., (68) reported the absence of blockade of the effects of adrenaline and noradrenaline when these drugs and hydralazine were given intra-arterially into the same vascular bed. The persistence of contraction of the nictitating membrane in response to preganglionic stimulation in the presence of hydralazine (12,20) rules out an effect of the drug on ganglia. It appears, therefore, that hydralazine has little, if any adrenergic or ganglionic blocking action. The limited blockade reported is probably largely nonspecific, as suggested by the demonstration of similar antagonism to other substances such as ergotamine (46), pituitrin (20), histamine, angiotonin, serotonin and barium chloride (12).

Although hydralazine had been thought by some workers to effect vasodilatation by means of central inhibition of vasomotor tone (12,20,37), no direct evidence of such an action has been presented. This supposition was based originally on experiments of Freis and Finnerty (37), who found inhibition of vasoconstriction in the fingers in response to various stimuli, while there was no blockade of the presser response to adrenaline. No definite conclusion regarding mechanism of action can be reached from these experiments, as evident from the previous discussion. Craver et al. (20) also suggested a central inhibitory action when they found no change in blood flow in the isolated rabbit's leg after hydralazine. These workers, however, apparently did not use any vasoconstricting agent to increase the

tone in the vessels of the rabbit's leg before administration of hydralazine. The vessels in this type of preparation are frequently fully dilated and therefore dilating effect of the drug cannot manifest itself. Furthermore, vasodilation in the same preparation was reported to be effected by hydralazine after a variety of vasoconstricting agents (12). More convincing evidence in favour of a central action has been presented by Bein et al. (12) who showed that hydralazine in small doses inhibited pressor response to stimulation of the central end of the cut sciatic and vagus nerves or to clamping of carotid arteries in the cat.

It seems to this author, however, that the available facts suggest that a direct action on the peripheral vessels is primarily responsible for the dilatation produced. The finding of persistence of normal pressor response to the stimulation of the central end of the cut vagus nerve in the dog by Grimson et al. (45) after very large doses of hydralazine, a result opposite to that found in the cat (12), seems to offer fairly strong evidence against central inhibition being a major factor, as the drug exerts comparable hypotensive effects in the two species. The diminished or absent hypotensive effect in spinal preparations whose pressure was raised by means of naphasoline reported by Crever et al. (20) again should not necessarily be accepted as evidence for a central action in view of the opposite results obtained by Gross et al. (46). The latter authors found that hydralazine had no effect in the spinal cat, the blood pressure of which had fallen to 50 to 60 mm Hg, but the usual hypotensive action was observed when the blood pressure of the spinal preparation was raised to 120 to 160 mm Hg by infusion of ephedrine or ergotamine. This

indicates that hydralazine does possess a peripheral dilator effect which cannot be manifested when the vessels are already dilated as in the spinal cat with low blood pressure. The fact that dilatation obtained with hydralazine is not complete, as indicated by a further drop in blood pressure obtained by administration of a nitrite, histamine or acetylcholine after hydralazine (20), adds to the difficulty of demonstrating its peripheral action in the presence of pre-existing dilatation.

Further evidence for a peripheral effect of hydralazine was provided by Stunkard et al. (93) and Redisch et al. (77) who found an increase in blood flow in denervated human extremities after hydralazine. The finding of a more consistent increase in the blood flow in the legs after intra-arterial than after intravenous administration (93,109), also favours a peripheral site of action, as does the fact that the increase in renal blood flow after hydralazine is not blocked by hexamethonium (67,92).

C. The Effects on Regional Vascular Beds.

1) Extremities.

Hydralazine appears to have a relatively weak dilating action on the blood vessels of the extremities, both in skin and muscle. Moyer et al. (68) found a slight decrease in the flow in the dog's leg at the height of the hypotensive action. Similarly a 15% decrease in calf blood flow was reported by Freis et al. in humans (38). On the other hand, some rise in the skin temperature of the fingers in normal man, and in hypertensive and toxemic patients was obtained by Assali et al. (2), and Vanderkolk (95), whereas Stunkard et al. (93) and Redisch et al. (77) were able to show an increase in the skin and muscle blood flow in denervated but not in innervated extremities. The latter authors also reported that the effect

of hydralazine on the flow in normal extremities may be better demonstrated in a warm room. The drug, therefore, has a relatively weak dilating effect on the vessels of the human extremity, which may not be manifested in the presence of a high sympathetic vasoconstrictor tone or more marked dilatation in other vascular beds.

2. Kidney.

Reubi (81) was the first to report an increase in renal blood flow (C_{PAH}) due to hydralazine in normal subjects, hypertensives and 2 patients with chronic nephritis. The increase averaged 38% with a range of 16% to 68%. It was associated with a decrease in filtration fraction, but no consistent change in glomerular filtration rate. Reubi's results have been confirmed by others (68,92,95,109). Moyer et al. (68) found that in the dog the effect on renal blood flow began about 10 minutes after intravenous injection, reached a peak in 1/2 to 1 hour and returned to control levels in 2 to 3 hours. The increase in renal blood flow can occur in hypertensive patients after a single oral dose of hydralazine, but repeated oral administration may have only a minimal effect (95). Stein and Hecht (92), found that the increase in renal blood flow due to hydralazine occurred only if the flow was near normal to start with. No increase, and often even a decrease was found in hypertensive patients with low initial flows. Although parenteral hydralazine causes a consistent and significant increase in renal blood flow in normal subjects, the vasodilatation in the kidney must be exceeded by vasodilatation in other vascular beds because the increase in flow is proportionally less than the accompanying increase in cardiac output (109).

3) Brain.

The effects of hydralazine on cerebral hymodynamics have been studied primarily in patients with toxemia (66) or hypertension (48) and in elderly patients with senile psychoses and associated primary systolic hypertension (58). Haffkenschiel et al. (48) found that the hypotension produced by hydralazine was associated with a significant decrease in cerebral vascular resistance in hypertensive patients, and therefore its hypotensive effect was not associated with a decrease in cerebral blood flow. Kleh and Fazekas (58) reported a decrease in cerebral vascular resistance and in cerebral arterio-venous oxygen difference, and either no change or an increase in cerebral blood flow in their group of elderly patients. In women with toxemia there was a rise in cerebral blood flow after hydralazine (66).

4) Heart.

The effects of hydralazine on coronary vessels have been studied only in the canine heart-lung preparation (7). Hydralazine was found to cause a slow progressive dilatation lasting about an hour. It was capable of antagonizing the constrictor effect of pitressin and of potentiating the dilator effect of adrenaline and noradrenaline. However, inversion of T-waves in the EKG (37), angina and even myocardial infarction (67) have been reported in hypertensive patients following the administration of the drug. Consequently, it is possible that in intact organisms with a marked decrease in blood pressure due to hydralazine, no increase in coronary flow may occur in spite of the dilator effect, or the dilatation may be inadequate to meet the oxygen requirement imposed by the increased cardiac activity, particularly if the vessels are affected by atherosclerosis.

5) Hepato-splanchnic area.

Freis et al. (38) found an increase of 75% (range 31% to 110%) in hepato-portal blood flow in 5 out of 6 hypertensive patients and in one normal subject after 0.25 mgm/kgm of hydralazine. The accompanying average maximal increase in cardiac output was 128%. Marks et al. (65) observed that in dogs given 0.5 to 1.0 mgm/kgm of hydralazine there was an average rise in hepatic blood flow (BSP clearance) from 524 to 830 ml/min. In dogs given 1.0 mgm/kgm the increase was no greater than in those given 0.5 mgm/kgm. With increased splanchnic blood flow there was an associated increase in the circulating splanchnic blood volume (from 17% to 29% of the total blood volume), which the authors invoked to explain the inability of the increased cardiac output to compensate for the peripheral vasodilatation and consequently the hypotension.

D. Effect on Cardiac Output.

A considerable rise in cardiac output associated with tachycardia has been reported to occur after administration of hydralazine by numerous investigators both in animals (65,68) and in normal and hypertensive man, (2,38,83,92,109). The exceptions which have been reported were patients in whom administration of the drug was followed by a severe hypotensive reaction (83,92), and patients with congestive heart failure in whom the increase amounted to only about 20% (109), the latter within the experimental error. The usual increase observed with doses of 0.25 to 1.0 mgm/kgm is about 100% in normals, but may be considerably less in patients with hypertension (83).

The stimulation of the heart is mediated through the nervous system, as it has been shown to be blocked by hexamethonium (67,69,92) and

sympathectomy (44). However, it may not be simply secondary to peripheral dilatation because it apparently precedes and outlasts the hypotension (68), although the evidence for the latter is far from convincing. Additional evidence against a direct action on the heart muscle is provided by the report of Craver et al. (20) that large doses of the drug had no effect on the perfused heart or the heart-lung preparation.

E. Effect on Respiration

Moyer et al. (68) reported an increase in rate and depth of respiration after intravenous hydralazine. This was later confirmed by Marks et al. (65) who also found an increase in oxygen consumption and in minute ventilation, and a decrease in arterio-venous oxygen difference. Similar findings have been reported by Rowe et al. (83). Although the decreased arterio-venous oxygen difference must be due to the increase in cardiac output, the increased ventilation may be produced by the same mechanism as the cardiac effect, that is, it may be secondary to the decrease in blood pressure or to a central excitatory action.

In summary, hydralazine seems to possess two independent effects: 1) It produces peripheral vasodilatation, probably primarily by a direct action on the vessel walls, which is much more pronounced in the visceral vascular beds such as the splanchnic and renal than in the skin and muscle, and 2) It increases cardiac output by means of reflex or central stimulation.

The reasons why hydralazine seems to merit trial as an agent to modify the shock pattern will be reemphasized in relation to the phenomena associated with shock discussed in previous chapters of this review.

1) Excessive vasoconstriction may be harmful, and may actually be responsible for the development of irreversible shock. The vasodilator effect of hydralazine might be beneficial in the same way that other drugs which increase blood flow afford protection in shock.

2) Because impairment of blood flow to the liver has been shown to be an important, if not crucial, factor in the development of irreversibility, the major vasodilating effect of hydralazine in the splanchnic and renal areas might be of particular value, especially because its weak dilating action on the muscle and skin vessels would not interfere with vasoconstriction and redistribution of blood from those areas to the more vital viscera.

3) The dilating effect of hydralazine on the cerebral and coronary vessels might guard against a further decrease in flow to these vascular beds, even if its administration should be associated with a fall in blood pressure.

4) The increase in cardiac output caused by hydralazine might tend to counteract the marked fall in cardiac output which occurs in shock.

Summary

The review of the literature relating to the pathogenesis of shock allows one to define shock of the more common traumatic and hemorrhagic varieties as a form of cardiovascular insufficiency, characterized by inadequate effective blood volume, decreased cardiac output and increased peripheral resistance, at least at some stages of its development.

The resulting decrease in blood flow to the vital viscera may lead to irreparable damage. Once this has occurred, recovery will not take place in spite of all treatment presently available and the shock is said to be irreversible. Indirect evidence suggests that impairment of blood supply to the liver may be intimately related to the development of irreversibility in shock.

Although a degree of myocardial insufficiency may exist in some cases, it is only a contributing factor in the developing circulatory failure in traumatic and hemorrhagic shock.

Numerous studies show that drugs which increase blood flow by interfering with responses to sympatho-adrenal activity afford significant protection to groups of animals subjected to trauma or hemorrhage when these are administered before or early in the course of the shock inducing stress. It remains for the clinical studies to prove whether these agents will become an important adjunct to the blood volume replacement in the treatment of shock.

Hydralazine produces marked vasodilatation in the visceral vascular beds, probably by a direct effect on the vessel walls, and increases cardiac activity by means of reflex or central stimulation. Because of these properties the drug merits a trial in the study of shock.

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PART II

THE EFFECT OF HYDRALAZINE (APRESOLINE) ON SHOCK

Introduction

Several reactions may occur in response to various shock-inducing procedures. Among these, the intense vasoconstriction in several vascular beds is perhaps the most striking. The resulting increase in regional vascular resistance and diminished blood flow have been demonstrated to occur in shock in such organs as the skin (6), muscle (4), salivary glands (8), kidneys (21), and hepato-splanchnic area (19).

The production of typical shock by infusions of adrenaline (5) and noradrenaline (24) supported the idea that the severe vasoconstriction itself can be harmful. Among the various organs, the liver may be particularly sensitive to the diminished blood supply. Indeed, the marked reduction in the blood flow to the liver (19) has been implicated as an important factor in the development of irreversibility in shock (20).

A number of drugs which cause a general increase in blood flow have been applied to the study of shock in the course of the past decade. Numerous reports, recently summarized by Nickerson (15), indicate that, when administered before or early in the course of shock inducing procedures, they reduce significantly the mortality of animals subjected to hemorrhagic or traumatic shock. The drugs which have been used so far fall, for the most part, into the category of ganglionic or adrenergic blocking agents.

The purpose of the present study is to report the effects on shock of hydralazine, an agent which has been used extensively in the treatment of hypertension for a number of years. Although the pharmacology of this drug is not completely understood, it appears to possess two main actions: 1) It increases cardiac activity and cardiac output by means of reflex or central

stimulation (3,12,14); and 2) it produces vasodilatation, predominantly in the visceral vascular beds. It has been shown to increase markedly the renal (18) and splanchnic blood flow (12). In addition, it may produce some dilatation of the coronary (1) and cerebral vessels (13). In contradistinction to other drugs applied to the study of shock hydralazine does not block ganglia (3) and has only a weak adrenergic blocking action (7). The vasodilatation it produces probably is due to a direct effect on the vessel walls (22).

The drug, therefore, seemed to be a particularly suitable agent with which to attempt to modify the development of shock because it might be expected to exert a favourable influence:

1) By preventing the development of irreversible changes in the viscera through selective dilatation, without at the same time interfering extensively with adrenergic vasoconstriction in other organs better equipped to withstand marked reduction in blood flow.

2) By increasing cardiac activity, particularly in view of evidence suggesting that myocardial depression may be a contributing factor in the development of circulatory failure in shock (23).

The report consists of two parts. The first deals with the effects of hydralazine on traumatic shock and on the response to acute trauma in the rat; the second describes the effects on hemorrhagic shock in the dog.

The Effect of Hydralazine on Traumatic Shock and on the Response to Acute Trauma in the Rat

Materials and Methods

Female albino rats of an inbred Wistar strain were used. Their weight ranged from 125 to 155 gm, but the average spread within groups run on the same day was only 12 gm (range 5 to 20 gm) and the weight within each run was randomized among the control and treated groups. The rats were fasted for about 15 hours prior to the experiments, but had access to water.

The animals were subjected to 400 or 450 turns of a standard Noble-Collip drum with two shelves (16) in the first part of this study. Because of the variability in the number of falls from animal to animal, when subjected to the same number of turns, a drum with one shelf was used in the latter part of this work. Nine hundred turns of the drum with one shelf were necessary to achieve a comparable mortality. The speed of the drum was 40 revolutions/minute when two shelves were used and 48 revolutions/minute for the drum with one shelf.

Various treatment groups of 12 to 21 animals were divided into subgroups of four to five, which were subjected to trauma on three to five separate days spread over two to four weeks, in order to make sure that any effects which might be observed were reproducible. Each control subgroup of four or five animals was run parallel to one to three treated subgroups, each subgroup having received a different treatment. The rats of all subgroups were alternated between the two drums used. The results described below include all runs except three in which, for unknown reasons, the usual number of revolutions resulted in only a mild stress as evidenced by a mortality of 25% or less in the control animals.

After tumbling, the animals were observed for several hours and those surviving this period were then returned to their cages. Rats alive 48 hours

after tumbling were considered survivors. Gross post mortem examinations were performed on all fatalities, and special note was taken of deaths associated with intraperitoneal hemorrhage due to ruptured liver or spleen.

The animals which died in the drum or within 15 minutes after termination of the trauma were not considered to have died of shock. The mechanisms operating in producing such early deaths are probably different from those leading to the typical picture of shock in animals dying later. Apart from the different time-course, it has been reported (16) that patho-physiological findings characteristic of shock are absent or minimal in such cases. They were classified as acute traumatic deaths in the present study and the effect of drugs on their incidence was assessed separately.

The effect of hydralazine was compared with that of the powerful adrenergic blocking agent dibenzyline, previously shown to afford protection from drum trauma (9,11). The drugs were administered intraperitoneally while control animals received equivalent volumes of saline (usually less than 0.5 ml). The details of dosage and time of administration are given with the results.

Results

The effects of drugs on the incidence of various types of death resulting from tumbling procedure are summarized in Table 1 and are considered under the following headings:

a) Overall Mortality (all animals included).

b) Overall Mortality excluding Deaths associated with Intraperitoneal Hemorrhage due to Ruptured Liver or Spleen.

c) Incidence of Acute Traumatic Death (hemorrhagic deaths excluded).

d) Incidence of Deaths due to Traumatic Shock (hemorrhagic and acute traumatic deaths excluded).

a) Overall Mortality.

Pre-medication with 2.0 mgm/kgm of hydralazine given intraperitoneally one hour before tumbling reduced mortality due to 400 turns of a Noble-Collip drum from 76% in the controls to 24% in the treated group. This difference is highly significant ($P < 0.01$)*. At a more severe level of trauma (450 turns), hydralazine in doses of 1.0 to 5.0 mgm/kgm did not protect ($P > 0.3$). Only the combined mortality is shown in the table because there appeared to be no significant difference in the effects of various doses in this range.

Dibenzyline 1.5 mgm/kgm given intraperitoneally one hour before the experiment decreased the mortality from 75% to 33% at 400 turns, and from 81% to 30% at 450 turns. These differences do not reach statistical

* The P values were obtained by the use of x^2 test.

Effects of Drugs on Tumbling Shock

No. Turns	Group	Overall Mortality		Excluding Hemorrhagic Deaths				
		No. Animals	Total Deaths %	No. Animals	Overall Mortality %	Acute Traumatic Deaths %	Mortality Due to Shock (Acute deaths excluded)	
							No. Animals	Shock Deaths %
400	Control	21	76	21	76	19	17	71
	Hydralazine (2.0 mgm/kgm)	21	24	21	24	0	21	24
	P		< 0.01		< 0.01	< 0.2		< 0.01
450	Control	20	90	18	89	50	9	77
	Hydralazine (1.0-5.0 mgm/kgm)	28	75	26	73	15	22	68
	P		> 0.3		> 0.3	< 0.05 (<0.01)*		> 0.5
400	Control	12	75	12	75	17	10	70
	Dibenzyline (1.5 mgm/kgm)	12	33	11	27	27	8	0
	P		< 0.2		< 0.1	> 0.5		< 0.02
450	Control	16	81	15	80	40	9	67
	Dibenzyline (1.5 mgm/kgm)	16	50	11	27	27	8	0
	P		< 0.2 (< 0.02)*		< 0.05 (< 0.01)*	> 0.5 (> 0.5)*		< 0.02 (< 0.001)*
900**	Control	16	69	13	62	31	9	44
	Hydralazine (3.0 mgm/kgm) and Dibenzyline (1.5 mgm/kgm)	15	47	12	33	33	8	0
	P		> 0.3		> 0.3	> 0.5		< 0.2

* P values in brackets represent significance when groups at 400 and 450 turns are combined.

** Drum with one shelf.

significance ($P < 0.2$) due, at least in part, to the relatively small number of animals in these groups. However, when all the dibenzyline-treated and control animals at 400 and 450 turns are combined, the overall difference in mortality is significant at the 2% level. The latter is a valid statistical procedure because the dibenzyline-treated and control groups at the two levels of trauma are homogenous with respect to their responses.

b) Overall Mortality excluding Hemorrhagic Deaths.

After exclusion of hemorrhagic deaths, hydralazine still protected at 400 turns (no hemorrhagic deaths in this series) and remained without protective influence on overall mortality due to 450 turns ($P > 0.3$).

The protective effect of dibenzyline became more pronounced when hemorrhagic deaths were not considered. At the lower levels of trauma the mortality was reduced from 75% to 27% (P slightly greater than 0.05), and at 450 turns from 30% to 27% ($P < 0.05$). Combination of the groups at 400 and 450 turns demonstrates a highly significant protection ($P < 0.01$).

c) Survival Time and Effect of Drugs on Incidence of Acute Traumatic Death.

The cumulative percentage of deaths at various time intervals is shown in Table 2. The survival time of animals which succumbed varied considerably. Some rats died in the drum while others lived for periods varying from one minute to 40 hours. However, about 80% of the deaths occurred within six hours of the end of the trauma.

There was a striking difference in the effects of hydralazine and dibenzyline on the occurrence of acute traumatic deaths (during or within 15 minutes after the end of drumming). All deaths due to intraperitoneal hemorrhage were excluded from the following statistical comparisons.

Table 1 shows that dibenzyline did not affect the incidence of acute traumatic death ($P > 0.5$) in contrast to hydralazine which reduced this incidence remarkably. No acute deaths occurred in the hydralazine-treated group at 400 turns and only 15% of animals subjected to 450 turns died an acute death compared to 19% and 50% respectively in the corresponding control groups. The 15% acute traumatic deaths in hydralazine-treated group at 450 turns all occurred in animals which were given doses of 2.0 mgm/kgm or less. Although the difference at 400 turns is not statistically significant ($P < 0.2$), probably due to low incidence of acute deaths among the controls, the differences at 450 turns and when groups at 400 and 450 turns are combined are significant at the 5% and 1% levels respectively.

The data shown in Table 2 indicate that most of the control animals not dead within the first 15 minutes survived over two hours. However, in the hydralazine-treated group a considerable number of animals died between 15 minutes and two hours after drumming. This suggests that protection by hydralazine against acute death is only transient, death being delayed 1 to 2 hours.

It is also obvious that acute traumatic deaths were more frequent in control animals subjected to the more severe trauma. Including preliminary experiments not shown in Table 1, 14% of all control rats subjected to 400 turns died an acute traumatic death compared to 46% of animals subjected to 450 turns ($P < 0.02$).

Table 2

Cumulative Percentage of Deaths*

Group	Total No. Deaths	Time after Drumming									
		In the drum	0–15 min.	16–30 min.	30–60 min.	1–2 hr.	2–4 hr.	4–6 hr.	6–12 hr.	12–24 hr.	24–48 hr.
Control											
400 turns	29	0	32	-	-	44	76	84	-	-	100
450 turns	27	7	63	70	-	-	85	89	93	96	100
Hydralazine											
400 turns	7	0	-	-	29	71	100	-	-	-	-
450 turns	21	9	19	24	43	62	71	76	86	91	100
Dibenzyline											
400 turns	4	75	100	-	-	-	-	-	-	-	-
450 turns	8	75	100	-	-	-	-	-	-	-	-

* This table includes the data on some preliminary experiments. All deaths including those associated with hemorrhage are considered.

d) Effect of Drugs on Incidence of Death due to Traumatic Shock.

The effect of any treatment on mortality from "true" traumatic shock resulting from tumbling can be properly assessed only after exclusion of all acute traumatic deaths and deaths due tohemorrhage. Table 1 demonstrates that dibenzyline provided protection against shock in animals subjected to both 400 and 450 turns, whereas hydralazine protected only those subjected to 400 turns. The reductions in mortality are all significant at least at the 2% level. The striking feature of the effect of dibenzyline was complete elimination of all late (shock) deaths at both levels of trauma. However, the results must be assessed in relation to changes in acute traumatic deaths in the case of hydralazine which protects against acute death. This factor might tend to move weaker animals into the late (shock) death group and would tend to put the drug at a disadvantage. The presence of a significant protection in spite of this factor makes it even more certain that hydralazine provides real protection against death from traumatic shock in animals subjected to 400 turns. The absence of protection at 450 turns, however, must also be real because there was no effect on overall mortality at this level of trauma.

e) Effect of Pretreatment with both Hydralazine and Dibenzyline.

Because hydralazine provided protection against acute deaths, whereas dibenzyline protected remarkably against shock deaths, it was thought that pretreatment with both drugs might prove more effective than with either one alone. However, premedication with 3.0 mgm/kgm of hydralazine and 1.5 mgm/kgm of dibenzyline one hour before tumbling (not illustrated in the table) resulted in more deaths in the treated than in the control

animals in a preliminary experiment and this combined treatment was not investigated further. The results of premedication with 3.0 mgm/kgm of hydralazine one hour before the experiment and with 1.5 mgm/kgm of dibenzyline just prior to drumming are presented in Table 1. This study was performed using 900 turns and one shelf only. The difference in the overall mortalities between the control and treated groups is not statistically significant ($P > 0.3$).

All deaths in the treated group were acute, indicating that hydralazine did not protect from acute traumatic death in the presence of dibenzyline. However, dibenzyline appeared still to exert its protection against shock deaths.

f) Incidence of Intraperitoneal Hemorrhage from Ruptured Liver or Spleen.

Table 3 illustrates the incidence of intraperitoneal hemorrhage due to ruptured liver or spleen. Rupture of the liver accounted for 60% or more of the ruptures in the control and treated groups. Ten percent or less of all control animals subjected to tumbling succumbed following rupture of one of the two organs.

Hydralazine had no effect on this incidence. In contrast, dibenzyline increased the overall incidence of intraperitoneal hemorrhage from 5% to 22%. The differences between dibenzyline-treated rats and their controls at 400 and 900 turns are not statistically significant, due in part at least to the smaller numbers of animals in these groups. The difference between the larger groups subjected to 450 turns is significant at the 5% level and the overall difference is significant at the 2% level.

Table 3

The Effect of Drugs on Incidence of Intraperitoneal Hemorrhage due to Ruptured Liver or Spleen*

Group	400 Turns			450 Turns			900 Turns			Total		
	No. Animals	% Hemorrhage	P	No. Animals	% Hemorrhage	P	No. Animals	% Hemorrhage	P	No. Animals	% Hemorrhage	P
Control	23	4	> 0.5	20	10	> 0.5	20	10	> 0.5	63	8	0.5
Hydralazine (1.0-3.0 mgm/kgm)	23	9		28	7		12	8		63	8	
Control	21	0	> 0.3	24	4	< 0.05	20	10	> 0.3	65	5	< 0.02
Dibenzyline (0.5-1.5 mgm/kgm)	21	10		36	28		10	30		67	22	

* Because of relatively small number of hemorrhagic deaths, the data from a number of preliminary experiments are included in this table.

g) Pathological Findings

Congested and/or hemorrhagic bowel on gross post mortem examination was a constant finding in the control and hydralazine-treated animals, but was practically absent in those treated with dibenzyline. This difference is somewhat difficult to evaluate because most of the deaths in the dibenzyline-treated group occurred in the drum, whereas in the control and hydralazine-treated groups even the early deaths occurred usually a few minutes after termination of the trauma. However, the lack of congestion and hemorrhage was probably due to the action of dibenzyline because a few control and hydralazine-treated animals which died during trauma exhibited definite congestion, although not hemorrhage, in the intestines. Furthermore, it has been reported (17) that other blocking agents are capable of preventing pathological changes in the intestinal tract of rats subjected to the Noble-Collip procedure.

Hemorrhagic areas in the lungs have been frequently observed in all groups. They appeared to be somewhat more marked in the animals dying acute traumatic death.

No evidence of intracranial hemorrhage was encountered.

The Effect of Hydralazine on Hemorrhagic Shock in the Dog.

Materials and Methods

Healthy mongrel dogs of both sexes weighing from 8.0 to 29.5 kgm were used. The animals were fasted overnight but had access to water. Light anaesthesia was induced by intravenous administration of sodium pentobarbital. The average initial dose was 27.7 mgm/kgm with the range of 20.7 to 37.9 mgm/kgm. Small supplements were given when necessary to maintain a smooth level of anaesthesia. The dogs were anticoagulated with heparin 5 mgm/kgm. Supplements of 1 mgm/kgm were given, if necessary, once or twice during the experiment.

One brachial artery was cannulated to permit withdrawal of arterial blood samples and to measure the blood pressure, and another polyethylene cannula was introduced through a femoral artery well up into the aorta for bleeding purposes. A self-guiding catheter, connected to a saline manometer, was introduced into the right ventricle or the pulmonary artery through the right external jugular vein (10). The entrance of the right ventricle was signalled by a sudden, pulsatile rise in pressure. The position of the catheter was checked post mortem in several experiments and the tip was always found to be in the right ventricle or pulmonary artery. The heart rate and respiratory rate were noted periodically. Blood pressure records were taken visually every 5 minutes until reinfusion and at 10 to 20 minute intervals for one to two hours thereafter. A mercury manomter was used until the blood pressure dropped to about 50 mm Hg. At that point a change was made to a saline manometer, zeroed 5 cm above the table, for greater accuracy. Bleeding volumes were also recorded every 5 minutes. Cardiac output was measured using the Fick

principle. The oxygen consumption was taken over a period of 4 minutes on a modified Benedict-Roth spirometer with a narrow bell (10 cm in diameter) connected to an endotracheal tube with an inflatable cuff. During the middle of that period the blood samples were withdrawn simultaneously into oiled syringes from the brachial artery and the right ventricle or pulmonary artery over a period of about 30 seconds. Oxygen saturation was estimated on a Warburg apparatus. Duplicate estimations were made on all the venous and on some of the arterial samples. The average error was 0.16 vol.% $\pm$S.D. 0.05 for the venous, and 0.11 vol.% $\pm$S.D. 0.04 for the arterial blood. The reliability of the cardiac output estimations was checked by calculating the average error of 25 pairs of measurements taken at 10-minute intervals during various preliminary experiments, and this amounted to 10.7 $\pm$S.E. 1.99%. Duplicate control determinations were made in 5 of the 9 experiments in which cardiac output was measured. The TPR was calculated in peripheral resistance units ($TPR = \frac{\text{blood pressure in mm Hg}}{\text{cardiac output in ml/min}}$) for each animal and expressed as percentage of the control estimation.

Hemorrhage was initiated by bleeding from the femoral artery into an inverted reservoir connected to a constant pressure oxygen system by means of which a desirable level of blood pressure could be maintained with only narrow fluctuations. The blood was mixed continuously by means of oxygen bubbling through it. The reservoir contained 1 mgm/kgm of the animal's weight of heparin. At the end of the experiment all the blood was reinfused intra-arterially. The volume of blood taken for samples and oozing losses was replaced by an equal volume of dextran.

Control and treated dogs, matched as well as possible as to weight and

sex, were run in parallel on the same day, the stress being induced and completed not more than an hour apart on the two animals. The treatment was randomized by means of a card system. It was not known which dog would receive the drug until the first dog bled was clamped off from the reservoir. Post mortem examinations were carried out on all dogs which died. Dogs alive 48 hours after completion of the reinfusion were considered survivors.

A series of preliminary experiments was performed in order to arrive at a bleeding procedure which would meet, as nearly as possible, the following requirements:

1) Drugs should not be administered before or during the period when the animals are connected to the reservoir because of possible effects on bleeding volumes.

2) Drugs should be acting during the critical period when irreversibility is developing.

3) The method should be suitable for the evaluation of both vasoconstrictor and vasodilator drugs.

The experiments on the effect of hydralazine were performed in two series. The animals of series A were bled down to the blood pressure of 45 mm Hg over a period of 10 minutes and then kept at this level for 30 minutes or until maximal bleeding volume* was reached. At this point the blood pressure of the animal was raised to 70 mm Hg by increasing the pressure in the reservoir-oxygen system. The pressure was kept at 70 mm Hg

* Maximal bleeding volume was considered to be reached when there was no increase in bleeding volume over three consecutive readings at 5 minute intervals, a criterion which had to be applied only once in each of the control and treated groups.

for 20 minutes and then the animals were clamped off from the reservoir for 75 minutes. At the time of clamping the treated animal received 0.5 mgm/kgm of hydralazine intravenously. At the end of the final 75-minute period all the blood was reinfused over a period of 15 minutes.

The animals of series B were subjected to a milder stress in that they were kept for only 20 minutes at 45 mm Hg and then for 30 minutes at 70 mm Hg before clamping. Otherwise the procedure was identical with that used in Series A.

If at any time during the clamped-off period the condition of the animal became precarious, portions of the withdrawn blood were reinfused in an attempt to carry the dog through the remainder of the 75 minutes. The condition was considered to be precarious when there was:

1) Marked fall in the rate and depth of respiration (invariably heralding onset of apnea and/or

2) Precipitous drop in blood pressure with or without sudden bradycardia.

Results

SERIES A

This series consisted of 6 pairs of dogs. The comparability of the treated and the control groups is illustrated in Table 4. There were no striking differences in sex, weight and amount of anaesthetic given to the two groups.

a) Mortality and Survival Time.

There was no apparent difference in mortality. All 6 control dogs died and there was only one survivor among the 6 treated animals. Two control and one treated dog died during the clamped-off period, in spite of reinfusion of 15% to 45% of their bleeding volumes in an effort to save them when their condition became precarious. On the basis of observations on other animals in this series and several preliminary experiments, we believe that these 3 dogs would have died even if they had been carried through the clamped-off period and they are considered to be fatalities. They are not included, however, in the calculation of the survival time. Although the mean survival time was 14.3 hours (range 18 minutes to 39 hours) in the control and 4.1 hours (range 3 hours 10 minutes to 5 hours) in the treated group, this difference is not significant because of the variability of the controls.

b) Cardiovascular Events

Bleeding volumes at various stages of the experiment are shown in Table 5. No significant differences between the two groups are apparent.

Table 6 summarizes the changes in various cardiovascular indices during the experiments. Hydralazine exerted a hypotensive effect during

Table 4

Comparability of the Control and Treated Groups

Group	No.	Males	Weight in kgm	Anaesthesia (mgm/kgm Na pentob)	
				Initial	Total
Series A					
Control	6	4	16.7 (13.8–20.0)	25.6 (20.7–30.0)	30.9 (24.5–35.6)
Treated	6	3	15.8 (11.6–24.0)	28.3 (22.3–34.1)	30.8 (23.6–35.1)
Series B					
Control	6	4	16.0 (8.0–28.5)	30.5 (23.0–37.5)	31.8 (26.2–37.5)
Treated	6	5	16.6 (9.2–29.5)	26.4 (23.5–32.6)	27.0 (23.7–32.6)

hemorrhagic shock as indicated by a fall in blood pressure within 10 minutes after administration of the drug at the time of clamping in all 6 treated dogs, and by the fact that the average highest blood pressure reached during the clamped-off period was significantly lower in the treated than in the control animals ($P < 0.05$)*. The fall in blood pressure caused by hydralazine was followed by a rise within 30 minutes after administration in 4 out of 6 animals.

Although the blood pressure of 4 of the 6 controls fell after clamping, the fall was obviously due to decompensation as evidenced by the necessity for the administration of blood because of threatened respiratory failure. There was no striking difference in the blood pressure of the two groups after reinfusion.

Table 6 also indicates that no striking differences between the two groups were apparent in other cardiovascular indices before, during or after the period of stress. There was a slightly greater fall in total peripheral resistance in the treated group during the clamped-off period. However, the fact that it was declining spontaneously in the controls at the same time makes it difficult to be sure that the effect was due to the drug.

SERIES B

This series consists of 6 pairs of dogs. Data comparing the animals in the control and treated groups are shown in Table 4. There are no striking differences in the sex and weight. The control group required

*P values in experiments on hemorrhagic shock were obtained by means of _t_ test.

Table 5

Bleeding Volumes

Group	Volumes in ml/kgm				
	Initial*	Maximal**	Net Change during 70 mm Hg Period	At Clamping	At Reinfusion
Series A					
Control	30 (23–44)	40 (34–52)	-3 (-9)–(+2)	37 (28–45)	32(4)+ (20–40)
Treated	33 (26–50)	44 (33–61)	-3 (-18)–(+6)	39 (15–61)	36(5)+ (15–45)
Series B					
Control	34 (24–46)	41 (27–54)	-2 (-12)–(+3)	38 (16–50)	32(4)+ (16–47)
Treated	35 (26–43)	42 (29–54)	0 (-7)–(+4)	40 (25–53)	38 (25–51)

* Bleeding volume when blood pressure declined to 45 mm Hg

** Maximal amount bled out during the experiment

\+ Numbers of animals on which the mean and range are based. Six animals if not otherwise indicated.

somewhat larger amounts of sodium pentobarbital.

a) Mortality and Survival Time

Four out of 6 treated animals survived, whereas there was only one survivor among 5 control dogs*. The difference, although not significant statistically, represents a reduction in mortality from 80% to 33%.

The two fatalities in the treated group died 1.75 hours and 32 hours after reinfusion, whereas among the control animals two died 25 and 33.5 hours after reinfusion, and the remaining two succumbed during the clamped-off period.

b) Cardiovascular Events

Bleeding volumes are shown in Table 5. No significant differences between the treated and control groups were found.

As in Series A, the blood pressure fell to levels ranging from 23 to 51 mm Hg in all 6 treated dogs, beginning within 10 minutes after administration of hydralazine at the time of clamping. This was followed by a spontaneous rise within 30 minutes after clamping in 5 of the 6 animals. The remaining dog required reinfusion of a total of 26% of the bleeding volume to avert respiratory arrest during the clamped-off period.

In the control group there was an initial fall after clamping in 3 of the 6 dogs. Two of them required blood and were given approximately 30% of their bleeding volumes over less than 10 minutes but succumbed nevertheless. In the remaining 3 control animals, the blood pressure

*Post mortem revealed pulmonary infection in one of the control dogs and it is not considered in regard to mortality and survival.

Group	Mean Blood Pressure (mm Hg)					Cardiac Output					Total Peripheral Resistance (% Initial)					Heart Rate (Beats/minute)				
	Initial	Clamped-Off			Post Infusion	Initial l/m²	% Initial				Initial					Initial				
		Low*	High**	At CO*			45mm	70mm	Clamped Off	Post Infusion		45mm	70mm	Clamped Off	Post Infusion		45mm	70mm	Clamped Off	Post Infusion
Series A																				
Control	157	38	84 (3)	55 (5)	108 (3)	5.42 (5)	13 (2)	21 (3)	22 (4)	81 (2)	100 (5)	308 (2)	241 (3)	174 (4)	111 (2)	189	185	220 (4)	224	196 (4)
	(136-184)	(33-49)	(72-90)	(40-90)	(90-125)	(3.11-8.82)	(6, 19)	(17-33)	(17-27)	(55, 107)	-	(159, 457)	(147-300)	(113-242)	(83, 139)	(160-225)	(145-220)	(185-260)	(195-260)	(160-240)
Treated	141	44	64 (4)	52 (5)	108	5.27 (5)	17 (2)	20 (4)	27 (4)	75 (3)	100 (5)	188 (2)	278 (4)	145 (4)	100 (3)	186 (5)	175 (5)	208 (5)	223 (5)	217 (5)
	(120-170)	(35-61)	(55-72)	(37-66)	(66-144)	(3.01-6.26)	(16, 17)	(13-36)	(16-42)	(62-86)	-	(181, 194)	(160-327)	(91-216)	(87-117)	(175-195)	(125-210)	(200-210)	(185-260)	(175-245)
P			<0.05																	
Series B																				
Control	140	56	92 (4)	72 (5)	121 (4)	4.13 (4)	-	30 (4)	31 (3)	64 (3)	100 (4)	-	199 (4)	230 (3)	149 (3)	168	155	191	204 (5)	165 (4)
	(90-173)	(35-70)	(70-112)	(40-84)	(105-146)	(3.88-4.37)		(19-55)	(20-49)	(43-91)	-		(134-236)	(164-300)	(98-188)	(155-180)	(120-205)	(160-220)	(185-230)	(120-210)
Treated	155	38	63 (5)	53	113	4.45 (4)	-	23 (4)	36 (4)	99 (4)	100 (4)	-	193 (4)	109 (4)	73 (4)	182	158	183	182	193
	(123-176)	(23-51)	(45-95)	(38-73)	(75-155)	(3.27 6.17)		(19-49)	(27-45)	(61-127)	-		(111-249)	(83-149)	(67-82)	(160-200)	(105-195)	(105-260)	(150-235)	(175-230)
P			<0.05											<0.05	<0.05					

The measurements were taken approximately in the middle of each period and 15 to 30 minutes after reinfusion.
Means and ranges are based on 6 animals, unless otherwise indicated by the numbers in brackets.
* Excluding readings shortly before death and after blood administration during the clamped-off period.
** Excluding animals whose blood pressure never rose spontaneously.
\# At the time of cardiac output estimation.

rose shortly after clamping and continued to climb throughout this period, reaching values between 90 and 110 mm Hg before reinfusion. Table 6 shows that the average lowest blood pressure during the clamped-off period was 56 mm Hg in the controls and 38 mm Hg in the treated animals. The highest blood pressure during clamped-off period averaged 92 mm Hg in the controls and 63 mm Hg in the treated group. The latter difference is statistically significant ($P < 0.05$).

It was also noted that hydralazine-treated animals seemed to be able to withstand lower blood pressures than control dogs without the occurrence of respiratory arrest. In one treated dog blood pressure fell to 30 mm Hg, which was followed by a spontaneous rise and ultimate recovery; and in another case the blood pressure fell to below 25 mm Hg before respiration began to fail. In contrast, apnea usually developed in control dogs soon after the blood pressure fell below 35 mm Hg.

Table 6 suggests other differences between the two groups in cardiovascular indices. Cardiac output was reduced to 19 to 55% during the 70 mm Hg period. The values during the clamped-off period did not show appreciable change in the control animals, but a rise of 7% to 24% of the control output occurred in 3 out 4 treated dogs on which estimations were made. This difference is not statistically significant.

TPR rose in the control group from 199% of the control values during the 70 mm Hg period to 230% during the clamped-off period, while in the treated animals it fell from 193% to 109%, a statistically significant difference ($P < 0.05$). Similarly, after reinfusion the average TPR was 149% of control values in the control, compared to 73% in the treated group; again a significant difference ($P < 0.05$).

Other Observations

In both series there were no striking differences between the control and the treated animals in oxygen consumption, respiratory rate and minute ventilation.

All animals of both series which died exhibited characteristic changes in the gastro-intestinal tract consisting of congestion and/or hemorrhage in the wall and frequently free blood in the lumen. These findings were also present, often to the same extent, in the animals which died before reinfusion. However, they were less pronounced in dogs which died more than 10 hours after the experiment. No differences between the control and treated animals were observed.

Discussion

The data presented indicate that hydralazine is capable of providing a measure of protection against both the traumatic and hemorrhagic shock. This is evidenced by a reduction in the mortality due to traumatic shock from 71% to 24% in rats subjected to 400 turns of a Noble-Collip drum, and by protection of 4 out of 6 dogs from death due to hemorrhagic stress which killed 4 out of 5 control animals. However, the inability of the drug to protect against more severe hemorrhagic and traumatic procedures indicates that its protective influence is limited. When the effect of hydralazine on traumatic shock was compared with that of the powerful adrenergic blocking agent, dibenzyline, the superiority of the latter drug became evident, as it provided comparable protection against both the milder and the more severe procedures whereas hydralazine was capable of exerting a protective influence only at the lower level of trauma.

The mechanism of protection afforded by hydralazine is not clear. The cardiac output in the treated animals in Series B was somewhat higher than in the control dogs before and after reinfusion although the difference was not statistically significant in this small group of animals. The available data do not rule out participation of an effect on cardiac output in the protection against shock afforded by the drug.

However, vasodilatation, perhaps in the splanchnic region, was more likely responsible for the effect observed. A significant decrease in TPR during the clamped-off period and after reinfusion was found in hydralazine-treated dogs subjected to the milder hemorrhagic procedure (Series B). The fact that the decrease in TPR was striking in the animals of Series B, which the drug protected, and only slight in Series A dogs, which did not benefit, adds strength to the supposition that peripheral dilatation was the factor responsible for the protection afforded against shock by hydralazine. The effect on TPR in Series A probably was masked by the spontaneous decrease in TPR due to decompensation at this stage of the more severe procedure.

Administration of hydralazine during hemorrhagic hypotension was associated with a fall in blood pressure in all the treated dogs, a finding obviously related to the peripheral dilatation. The fact that the initial drop in blood pressure was soon followed by a rise in most cases may be related to the fact that dilatation produced by hydralazine is unable to oppose a high sympathetic tone (22), or else it may reflect an improvement in the cardiovascular status of the animal effected by the drug.

The most striking effect of hydralazine in the present study was its ability to protect against acute traumatic death resulting from the tumbling

procedure. A large number of ganglionic and adrenergic blocking agents have been applied to the study of tumbling shock. Although capable of reducing overall mortality, they either increased (11) or did not affect (present study) the incidence of early acute traumatic death. Thus, hydralazine is the first agent to be shown to provide protection against early deaths due to the immediate effects of the trauma.

The presence of severe hypotension (30 to 40 mm Hg) on removal from the drum (2) suggests that cerebral hypoxia may be responsible for the early deaths from "acute trauma". The presence of extensive blockade of sympathetic vasoconstriction would impair the animals' ability to counteract an acute hypotension and maintain adequate cerebral blood flow. This impairment of compensation is probably responsible for the absent or unfavourable effect of the more powerful blocking agents on the response to acute trauma.

Hydralazine, on the other hand, has only a weak and inconsistent adrenergic blocking action (7) and therefore would not be expected to interfere with the compensatory reactions to acute stress. In addition, because of the ability of the drug to increase cardiac output (12,14) and possibly to increase cerebral blood flow (13) it may improve the cerebral oxygen supply during the period of acute trauma and thus protect from death. The inability of hydralazine to produce striking rise in cardiac output in the presence of the hypovolemia of hemorrhagic shock is not inconsistent with a large increase in the rats subjected to the Noble-Collip procedure with normal blood volumes at the time of tumbling. The fact that a few hydralazine-treated dogs were capable of withstanding lower blood pressures than controls without the occurrence of respiratory arrest during hemorrhagic shock supports the contention that hydralazine is capable of increasing cerebral perfusion during periods of

stress and that this is at least one of the factors responsible for the protection afforded by the drug against acute traumatic death.

In contrast to the protective influence of hydralazine against shock which was expressed only when relatively mild stress was employed, the protection against acute traumatic death was present both at the lower and higher levels of trauma.

When hydralazine and dibenzyline were both administered to the animals before tumbling, the protection against acute trauma was absent. This indicates that hydralazine is unable to protect against acute death in the presence of effective adrenergic blockade.

The present study also showed that premedication with dibenzyline resulted in an increased incidence of ruptured liver and spleen in rats subjected to tumbling, whereas no such effect was observed in hydralazine-treated animals. This effect of dibenzyline might be ascribed to blockade of vascular or capsular contraction, leaving the organs more engorged and therefore more susceptible to traumatic rupture.

Summary and Conclusions

1. Hydralazine decreased the mortality in groups of animals subjected to traumatic (tumbling in a Noble-Collip drum) or hemorrhagic shock.

2. The protective influence of the drug was limited; no protection against more severe hemorrhagic or traumatic procedures was observed. In contrast to hydralazine, the strong adrenergic blocking agent, dibenzyline, produced a comparable decrease in mortality at both lower and higher levels of trauma.

3. The drug significantly lowered the total peripheral resistance during hemorrhagic hypovolemic hypotension and after reinfusion in animals subjected to the milder hemorrhagic procedure. This suggests that peripheral vasodilatation was responsible for the observed protection against irreversible shock, although some increase in cardiac output cannot be ruled out as a contributing factor.

4. Hydralazine protected remarkably against acute traumatic death (during or within 15 minutes after drumming) both at lower and higher levels of trauma, in contrast to dibenzyline which had no effect on the incidence of acute traumatic death. Combined premedication with both drugs did not protect against acute traumatic death, indicating that hydralazine is unable to protect in the presence of adrenergic blockade.

5. Whereas dibenzyline significantly increased the incidence of intraperitoneal hemorrhage due to ruptured liver or spleen in rats subjected to the Noble-Collip procedure, hydralazine had no effect on the incidence of this complication.

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PART III

APPENDIX A

Assessment of the Noble-Collip Method for the Production of Traumatic Shock

1. Previous Observations.

The method of inducing traumatic shock by tumbling was first reported by Noble and Collip in 1942 (8). Animals are placed in rotating drums of standard dimensions with projections or shelves which raise the animals and allow them to fall one or more times per revolution. Noble and Collip originally used 2 or 3 shelves and various drum speeds, and obtained most consistent results with two shelves and a speed of 40 revolutions per minute. The animals used in the original study were rats and guinea pigs, but the method has since been applied almost exclusively to rats. As the animals are unanesthetized, most observers have found it necessary to tape their feet in order to prevent them from jumping over the shelves. Noble and Collip reported that mortality is a function of the number of revolutions to which the animals are subjected, and this has been confirmed by others (1,4,12). They also found that larger animals are somewhat more resistant than small, and that female rats are more resistant than males. Animals weighing about 150 gm have been used by most investigators.

This method appears to possess several desirable features:

1) It is convenient and can be applied to large groups of animals in a short period of time.
2) The experiments are uncomplicated by anesthesia.
3) The trauma administered can be accurately graded.
4) It can be applied to rats, which are the most uniform of the commonly available laboratory animals.

However, variability of results has been a major complication of shock studies in the past, and a careful assessment of the reliability and limitations of this method is in order before it can be used to test the effects of various drugs and treatment procedures.

a) Consistency of Results

The first characteristic of importance about any method is its consistency and factors which influence it. On careful scrutiny, it becomes obvious that although the mortality is largely a function of the number of revolutions to which the animals are subjected, some variation does occur even when animals of the same breed, age, sex and weight are apparently subjected to the same amount of trauma. For example, Levy et al. (4) found that the mortality induced by 650 turns varied from 67% to 100% on various days. The obvious implication of these observations is that the control and treated animals must be subjected to trauma at the same time, and this has been the practice of most workers in the field. However, even this precaution has not always insured reproducibility of drug effects. This is exemplified by recent studies of the protection afforded by dibenzyline. The drug was found to offer significant protection to rats subjected to drum trauma by Levy et al. (4) and Hershey et al. (3). Noble (7), however, was unable to repeat these results although he tested three different strains of animals. The reliability of any series of experiments may be increased by dividing the treated and control animals into several groups run at different times, preferably several days or weeks apart.

b) The Time-Course of Deaths.

Noble and Collip (8) reported that the average survival time varied inversely with the mortality e.g., it was less than one hour with trauma resulting in 80 to 100% mortality, but increased to 2½ hours following trauma resulting in 50% mortality. Deaths more than 6 hours after drumming were rare; deaths 5 to 15 minutes following trauma were frequent with the more severe procedures. Chambers et al. (1) who used 650 revolutions, found that most rats died 1 to 2 hours after the experiment, with a range of 20 minutes to 10 hours. These authors rejected all the deaths occurring in the drum or within 20 minutes after termination of tumbling (10% to 15% of the total). Levy et al. (4) observed that whereas most of the control animals died 15 minutes to 24 hours subsequent to the experiment, treatment with adrenergic blocking agents resulted in a striking increase in the incidence of deaths during trauma.

Separation of the early from the late deaths is essential when the Noble-Collip method is applied to the study of shock. Reasons for believing that animals which die during or shortly after the termination of trauma do not die of traumatic shock are as follows:

1) Pathological findings characteristic of shock (see next section) are absent or minimal (8).

2) Hemoconcentration is less than in animals dying later (8).

3) Intraperitoneal hemorrhage due to ruptured liver or spleen is not infrequent (1,8).

Separate consideration of the early deaths appears therefore, to be justified, but they may still provide useful information regarding cardiovascular events. Although intraperitoneal hemorrhage may at times

complicate early deaths, no evidence of intracranial injury (1,8) or obvious fractures (8) are found, and it appears likely that most of these animals die an acute traumatic death which may be analogous to acute hemorrhagic death as distinct from hemorrhagic shock (11). Whether the acute deaths are due to hypoxia of vital cerebral centres is not known, but the finding of severe hypotension (30 to 40 mm Hg) shortly after tumbling (1) makes this a distinct possibility.

The effect of any treatment on animals subjected to drum trauma should therefore be analyzed with respect to:

1) The effect on overall mortality.

2) The effect on overall mortality excluding hemorrhagic deaths.

3) The effect on acute traumatic deaths.

4) The effect on deaths due to traumatic shock.

5) The effect on incidence of intraperitoneal hemorrhage due to ruptured liver or spleen.

c) The Evidence for the Presence of Shock.

The general appearance of rats removed from the drum has the same characteristics as that of cases of clinical shock. The rats are conscious, but are pale, inactive and prostrate (1,8). Polydipsia occurs frequently, and diarrhea, often bloody, has also been observed (6). The urine is scanty and may be bloody (1). The animals are cold and there may be several degree fall in body temperature (1,8). As in shock produced by other procedures, marked hemoconcentration occurs (1,8). The hematocrit tends to return to normal in 1 to 3 hours in animals which recover, but remains high or increases further in those which ultimately die. This hemoconcentration is associated with a decrease in plasma volume (1).

Circulatory reactions in "drum shock" have been studied in detail by Chambers et al. (1). The mean arterial pressure is decreased to 30 to 40 mm Hg when the animals are removed from the drum. Within 20 minutes it rises to 60 to 70 mm Hg, but then falls slowly over the next 2 to 4 hours in cases which proceed to death. Increased sensitivity of the mesenteric vessels to adrenaline is found during the early phases, followed by decreased sensitivity, stagnation and decreased vasomotion. The elaboration of VDM and VDM has been reported to follow a pattern similar to that found in hemorrhagic shock (13).

Distortion of the normal blood biochemistry has also been reported. Neufeld et al. (5) found increased blood levels of nonprotein nitrogen, glucose, lactic and pyruvic acids, and phosphate, and Clarke and Cleghorn (2) noted marked elevation in serum K^+ in animals on the verge of death.

Pathological findings following "drum shock" are essentially the same as in animals dying from shock due to other causes and include congestion, engorgement, and bloody fluid in the gastrointestinal tract, congestion of the liver, spleen, kidney and adrenals, and in some cases of the lungs (1,8).

There appears to be little doubt that except for those dying during or shortly after the termination of the trauma, animals subjected to tumbling in the Noble-Collip drum die of shock with all the characteristic findings encountered in shock due to other procedures.

d) The "Motion Factors".

These will be mentioned only to be dismissed. In 1943, Zahl et al.(12) reported that similar course of events to that found after tumbling, exists after rats have been enclosed for about 1 hour in a sponge-lined box oscillating through a 6" distance 4 times/second, and that cross-resistance

to the two methods was found to develop in their animals. They suggested that motion effects might be important in the development of shock in animals subjected to trauma in a Noble-Collip drum. As an argument against this possibility, Toby and Noble (10) reported a year later that no effects were observed when rats enclosed in rigid tubes attached to the drum, were allowed to revolve at the usual speed.

However, it seems that in neither of these experiments were the animals subjected to the same motion effect as when they are taken up by the shelf and dropped repeatedly during the usual drumming. The answer to the problem is provided by the experiments of Chambers et al. (1), as well as of Noble and Collip (9) and Zahl et al. (12) themselves, which were performed with a different purpose in mind. All these authors found that padding of the abdomen protected rats from death even when they were subjected to the numbers of revolutions much higher than these necessary to cause a 100% mortality. The obvious conclusion was that shock induced by this method was due to the trauma to the abdominal viscera. However, the experiments also seem to indicate, that gross motion effects are at the most but a minor contributing factor, regarding that the animals with protected abdomen, were subjected to the same motion as that present during usual drumming, and yet they survived without obvious ill effects.

2. Present Experience.

Because of variability in the mortality in the different control groups, an attempt was made to detect possible sources of variation in the procedure itself. With two shelves per drum, the number of falls over a period of time could vary. Although it was claimed originally that one revolution was equivalent to two falls (10), Chambers et al. (1) remarked that the rats

more often fell twice than once per revolution. However, they gave no more detailed data. We found marked variations in the number of falls per revolution not only between drums, but to almost the same extent in the same drum on different occasions. The range of variation found is shown in the accompanying table.

Relation of the Number of Revolutions to the Number of Falls in Noble-Collip Drum with Two Shelves

No. of Turns	No. of Tests	No. of Falls (Range)
400	10	560-705
450	11	633-795
550	11	770-972
600	9	847-988

These variations were accentuated by such factors as:

1) Changes in the position of the drums on the table.

2) Change in the position of the table in the room.

3) Loosening or tightening the belt driving the drums, although the speed remained constant.

The first two of these factors were probably related to slight changes in the plane of rotation of the drum.

As a result of these observations, drums with only one shelf were used in the latter part of this study in order to eliminate the variability in the number of falls. With one shelf, each turn registered on the automatic counter was equivalent to one fall.

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APPENDIX B

Development of Bleeding Procedure for Production of Hemorrhagic Shock

Preliminary experiments were performed on some 30 dogs in an attempt to arrive at a procedure which would be suitable for the purpose of the present investigation and for other work being carried out in the laboratory.

The requirements to be met were as follows:

1) Drugs should not be administered before or during the period when the animals are connected to the reservoir, because of possible effects on bleeding volumes. (See Part I, Chapter IV).

2) Drugs should be acting during the critical period when irreversibility is probably developing.

3) The method should be suitable for the evaluation of both vasoconstrictor and vasodilator drugs.

In early experiments animals were bled down to the mean pressure of 45 mm Hg in 10 minutes and kept at this level until they began to take up blood from the reservoir. At that time all the blood was returned over a 10 to 15 minute period. All animals which began to reinfuse and took up from 3 to 10 ml/kgm died with the typical pathological picture of shock.

These experiments suggested that in our canine population irreversibility was reached at about the time of maximal bleeding.

A modification of the procedure was then tried in which the dogs were kept at 45 mm Hg until they ceased to bleed out further (maximal bleeding volume). At that time they were clamped off from the reservoir for 45 minutes. Maximal bleeding volume was considered to be reached, when there was no increase in bleeding volume over 3 consecutive readings at 5 minute intervals.

It was found, however, that all but one dog subjected to this procedure went into acute respiratory arrest within 20 minutes after clamping, and died unless blood was given. Even when all blood was returned at the time of apnea, all eventually died of shock. When pressures higher than 45 mm Hg were used (50,55 and 60 mm Hg), the animals still stopped breathing within 20 minutes after clamping. This procedure was unsuitable because acute respiratory deaths are not equivalent to shock deaths.

In an attempt to fortify the animals before clamping, the following experiments were performed. When the animals ceased to bleed out, one sixth to one third of the maximal bleeding volume was reinfused from the reservoir before clamping. It was found that although the partial reinfusion before clamping allowed the dogs to bring their blood pressure to over 100 mm Hg, they all died of shock a number of hours after the rest of the blood was reinfused at the end of a 60 minutes clamped-off period. This procedure was unsuitable, because the spontaneous blood pressure rise during the clamped-off period would not allow the study of vaso-constrictor drugs.

The same difficulty was encountered when animals were clamped off before reaching the point of maximal bleeding in a few experiments, although they all survived when blood was reinfused an hour after clamping.

It was then decided to follow the initial period of 45 mm Hg by a period of higher pressure (70 mm Hg) before clamping as outlined in the description of the method in Part II.

It was hoped that the period of increased pressure (70 mm Hg) would serve a dual purpose:

1) The stronger animals would keep bleeding out during this period, and consequently would be unable to overcompensate and bring their blood pressure up to normal during the clamped-off period.

2) The weak animals would take up enough blood to sustain them during the clamped off period.

Unfortunately, the second expectation was not fulfilled and about a third of the animals had to be given blood in an attempt to carry them over the clamped-off period of 75 minutes. Not infrequently these attempts were unsuccessful and the dog died in the clamped-off period. At times, reinfusion of up to a third of the blood in the reservoir over a few minutes was of no avail. However, the presence of pathological findings characteristic of shock in these animals and the usually rapid downhill course in cases which required blood but were carried over the remainder of clamped-off period and reinfused, indicates that the dogs which died before reinfusion were in irreversible shock.

APPENDIX C

Detailed Data from Hemorrhagic Shock Experiments

Table 1

Bleeding Volumes and Survival Time

Animal and Sex	Volumes in ml/kgm						Survival Time+
	Initial*	Maximal**	Net Change during 70 mm Hg	At Clamping	Reinfused during Clamped-Off Period	At Reinfusion	
Series A							
C1 - M	26	38	-9	28	10	-	(-45 min)
C2 - M	44	52	-6	45	22	-	(- 6 min)
C3 - F	27	34	-1	33	14	20	18 min
C4 - F	23	35	+2	35	-	35	16 hrs
C5 - M	32	41	-2	40	6	34	2 hrs
C6 - M	30	42	-2	40	-	40	39 hrs
	30	40	-3	37	13	32	14hrs 20 min
H1 - M	26	41	-1	40	-	40	4 hrs45 min
H2 - F	50	61	+3	61	17	45	3 hrs35 min
H3 - F	36	42	-6	38	-	38	Survivor
H4 - M	29	33	-18	15	-	15	3 hrs 10min
H5 - F	23	39	+6	39	6	-	(-45 min)
H6 - M	35	44	+1	43	-	43	5 hrs
	33	44	-3	39	12	36	4 hrs 7 min
Series B							
C1 - F	25	33	+2	33	-	33	33hrs 30min
C2 - M	35	48	+3	47	-	47	Survivor
C3 - M	45	54	-4	50	15	-	(-40 min)
C4 - M	48	53	-5	47	16	-	(-45 min)
C5 - M	26	32	+3	32	-	32	25 hrs
C6 - F	24	27	-12	16	-	16	25 hrs
	34	41	-2	38	-	32	28 hrs
H1 - M	33	34	-7	25	-	25	32 hrs
H2 - M	29	37	-1	36	-	36	Survivor
H3 - M	43	54	0	53	14	39	1 hr 43 min
H4 - M	43	51	+3	51	-	51	Survivor
H5 - M	38	45	+4	45	-	45	Survivor
H6 - F	26	29	+1	29	-	29	Survivor
	35	42	0	40		38	

* Volume when blood pressure declined to 45 mm Hg
** Maximal amount bled out during experiment
\+ From end of reinfusion; in brackets - before reinfusion
C Control animals
H Hydralazine-treated animals

Table 2

Series A. Cardiovascular Indices

Animal	Blood Pressure (mm Hg)					Cardiac Output					Total Peripheral Resistance (% Initial)					Heart Rate (Beats/min.)				
		Clamped-Off			Post-	Init.	% Initial													
	Init.	Low*	High**	At CO	Inf- usion	(l/m^2)	45 mm Hg	70 mm Hg	Cl. Off	Post-Inf- usion	Init.	45 mm Hg	70 mm Hg	Cl. Off	Post Inf- usion	Init.	45 mm Hg	70 mm Hg	Cl. Off	Post Inf- usion
C 1	155	38	-	-	-	7.12	6	-	-	-	100	457	-	-	-	175	145	185	210	-
C 2	184	33	72	49	-	8.82	-	14	17	-	100	-	277	153	-	200	190	225	210	-
C 3	160	34	-	40	-	-	-	-	-	-	-	-	-	-	-	225	220	260	260	240
C 4	158	37	90	53	125	3.28	-	17	19	107	100	-	300	189	83	205	180	210	260	180
C 5	150	37	-	44	90	3.11	19	33	27	-	100	159	147	113	-	160	170	-	195	205
C 6	136	49	90	90	110	4.79	-	-	26	55	100	-	-	242	139	170	205	-	210	160
	157	38	84	55	108	5.42		21	22		100		241	174		189	185	220	224	196
H 1	140	61	72	58	97	5.40	17	-	22	-	100	181	-	216	-	190	190	200	260	175
H 2	170	35	-	37	144	6.26	-	13	16	86	100	-	319	131	97	195	205	210	200	225
H 3	120	55	72	66	105	-	-	-	-	-	-	-	-	-	-	175	145	210	185	215
H 4	122	36	56	46	66	5.57	-	36	42	62	100	-	160	91	87	195	210	200	220	225
H 5	155	41	-	-	-	3.01	16	15	-	-	100	194	297	-	-	-	-	-	-	-
H 6	140	36	55	54	130	6.09	-	14	27	77	100	-	327	140	117	175	125	200	250	245
	141	44	64	52	108	5.27		20	27	75	100		278	145	100	186	175	204	223	217

The measurements were taken approximately in the middle of each period and 15-30 minutes after reinfusion unless otherwise indicated.

Abbreviations:
At CO - at the time of cardiac output
Cl. Off - clamped off

* excluding values shortly before death and after blood was administered during clamped-off period.

** excluding animals whose blood pressure never rose spontaneously during clamped - off period.

Table 3

Series B. Cardiovascular Indices

Animal	Blood Pressure (mm Hg)					Cardiac Output				Total Peripheral Resistance (% Initial)				Heart Rate (Beats/min.)				
		Clamped-Off			Post		% Initial											
	Init.	Low*	High**	At CO	Infusion	Init. (l/m²)	70 mm Hg	Cl. Off	Post Infusion	Init.	70 mm Hg	Cl. Off	Post Infusion	Init.	45 mm Hg	70 mm Hg	Cl. Off	Post Infusion
C 1	125	60	70	66	110	4.05	21	23	43	100	236	225	162	170	125	160	165	170
C 2	146	70	96	84	124	-	-	-	-	-	-	-	-	180	150	160	200	160
C 3	150	36	-	40	-	4.23	23	-	-	100	196	-	-	155	180	215	230	-
C 4	173	35	-	-	-	-	-	-	-	-	-	-	-	170	205	220	-	-
C 5	156	70	112	98	146	3.88	19	20	91	100	231	300	98	155	120	175	205	120
C 6	90	65	90	71	105	4.37	55	49	57	100	134	164	188	180	150	215	200	210
	140	56	92	72	121	4.13	30	31	64	100	199	230	149	168	155	191	204	165
H 1	123	36	51	45	88	3.27	49	40	101	100	111	83	67	160	130	130	150	175
H 2	170	30	45	38	115	-	-	-	-	-	-	-	-	180	175	200	150	230
H 3	158	23	-	41	75	6.17	21	27	61	100	208	98	72	195	195	260	235	210
H 4	176	46	57	56	130	-	-	-	-	-	-	-	-	160	175	225	190	185
H 5	155	39	95	73	155	5.05	19	31	127	100	205	149	72	195	170	180	215	175
H 6	146	51	66	65	115	3.30	21	45	106	100	249	106	82	200	105	105	150	180
	159	38	69	53	113	4.45	23	36	99	100	193	109	73	182	158	183	182	193

The measurements were taken approximately in the middle of each period and 15-30 minutes after reinfusion unless otherwise indicated.

Abbreviations:
At CO - at the time of cardiac output
Cl. Off - clamped-off
* excluding values shortly before death and after blood was administered during clamped-off period
** excluding animals whose blood pressure never rose spontaneously during clamped-off period

Table 4

Respiratory Indices

Group	Oxygen Consumption					Minute Ventilation (l/min.)				
	Initial ml/min.	% Initial				Initial				
		45 mm Hg	70 mm Hg	Clamped-Off	Post-Infusion		45 mm Hg	70 mm Hg	Clamped-Off	Post-Infusion
Series A										
Control	152(5) (110-229)	49(2) (42,55)	83(3) (67-96)	87(4) (76-103)	109(3) (72,135)	5.9(5) (3.3-10.7)	6.9(2) (3.8,9.9)	8.2(3) (6.6-9.6)	10.7(3) (6.9-13.8)	6.6(2) (3.6,9.7)
Treated	132(5) (107-178)	78(2) (64,92)	83(3) (67-89)	98(4) (74-128)	113(3) (42-131)	4.8(5) (4.0-5.9)	8.1(2) (5.6,10.7)	8.9(4) (7.5-10.3)	12.4(4) (9.6-15.4)	9.7(4) (8.3-11.9)
Series B										
Control	112(4) (74-185)	—	89(4) (85-92)	86(3) (77-100)	80(3) (62-98)	4.9(4) (3.7-6.7)	—	9.4(4) (7.0-13.6)	7.9(3) (7.0-8.4)	6.4(3) (4.8-7.7)
Treated	122(4) (64-202)	—	95(4) (82-123)	99(4) (88-122)	102(4) (97-108)	4.9(4) (2.3-5.9)	—	7.4(4) (2.9-11.5)	8.4(4) (5.1-11.3)	5.5 (3.8-6.9)

Conventions the same as in previous tables.