# THE EFFECT OF HYDRALAZINE (APRESOLINE) ON SHOCK

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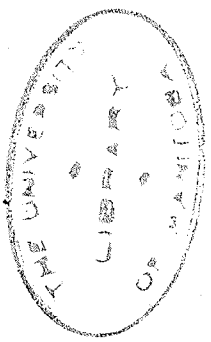


by

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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).