THESIS

THE MECHANISM OF CARDIAC OUTPUT CHANGES IN SHOCK

Ishaq Hussain Jaffar

Szent-Györgyi Albert Medical University
Institute of Experimental Surgery
Szeged

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I. Cardiac output (CO)

It is the amount of blood pumped by the heart per minute. It is about 5.0-5.5 L/min. The circulation of blood in man requires a pump and a circuit. The pump adds sufficient energy to the column of blood so that circulation occurs. The properties of the circuit determine the distribution of vascular volumes and pressures. Cardiac output is determined by HR, by contractility and afterload, and by diastolic compliance and preload.

II. Shock

Shock is an acute serious condition in which blood flow to peripheral tissues is inadequate to sustain life because of insufficient cardiac output or maldistribution of peripheral blood flow, usually associated with diminished peripheral circulation, hypotension, oliguria.

History

In the 35 years between 1945 and 1980 there has been a logarithmic increase in the study of hemorrhagic shock. In the beginning it was thought that trauma and blood loss result in a shock-like syndrome. However, it was not until the middle of 20th century that the concept that hemorrhage had nothing to do with traumatic shock was abandoned.

Before 1930, the relationship between trauma and shock rested on a hypothetical histamine-like substance that

produced generalized vasodilation.

Blalock in 1930 demonstrated that sufficient blood and plasma were sequestered in a traumatized extremity to cause hypovolemic shock. This led to the current volume replacement therapy in shock. Carl J. Wiggers in 1950 laid down the foundations of the science of shock, the years between 1941 and 1945 provided the data base on which Wiggers built his thesis. The Wiggers model for the study of hemorrhagic shock clearly established the concept of irreversible shock. Other important concepts also emerged such as that adrenalectomy reduces the resistance of animals to bleeding and increases lethality; there is no difference in the onset of the irreversible phase when either morphine or barbiturate anesthesia is employed; and the CO-existence of trauma increases lethality.

In 1943, Kohlstaedt and Page devised a canine model of hemorrhagic hypotension. They found that with profound hemorrhagic hypotension there was a blunted pressor response to both epinephrine and angiotensin.

In 1945, Lamson and De Turk utilized the 'pressure bottle' system and described a canine model of hemorrhagic shock.

The same year Frank et al. utilized a similar model and they observed that the reversible phase of shock could be treated with volume replacement. Further, the use of pressor agents (Pitressin with or without ergotamine) and the correction of acidosis with HCO_3^- did not alter the deterioration of animals in advanced hemorrhagic shock.

Wiggers and Ingraham defined three stages of hemorrhagic

hypotension: simple hemorrhagic hypotension resulting from the loss of 30 to 40% of total blood volume and the animal recovers; an impending shock state in which blood loss exceeds 40% and can be reversed by reinfusion, and an irreversible shock state occurs during the 90 min. hypotensive period (40 mm Hg), death ensues even after volume resuscitation.

Main types of shock

a) Hypovolemic shock
   - hemorrhagic shock
   - burn shock
   - exsiccation shock.

b) Septic shock - infections (endotoxin)

c) Cardiogenic shock - acute myocardiac infarction (20% of cases)
   pericardial tamponade, etc.

II.a. Pathophysiology of cardiac output changes and peripheral circulatory derangements in shock

A) Low cardiac output forms of shock

There are two basic mechanisms for the decrease of cardiac output in shock:

1) Diminished venous return
   a) Decreased blood volume (most important).
   b) Decreased vasomotor tone.

2) Decrease of efficiency of pump

Cardiogenic shock.

Compensatory mechanisms of the circulation in hypovolemic shock

After hemorrhage with significant blood loss, the body uses a variety of mechanism to maintain the blood flow to critical vital organs until volume restitution can occur through redistribution of extracellular fluid volume into the intracellular space. At the organ level, maintenance of perfusion during mild to moderate hypotension occurs through autoregulation of blood flow by local control of vasoconstriction to ensure tissue oxygen delivery, seen primarily in the brain, heart, and kidney.

At the integrated level, the central nervous system (CNS) response is organized by the pattern of medullary vasomotor sympathetic discharge carried over the cardiac sympathetic efferent nerves and the efferents to the peripheral arteries and the adrenals. These are mediated by the hypotensive reduction in the level of carotic and aortic baroreceptor afferent discharges that normally inhibit the vasomotor center and through the activation of carotid body chemoreceptors by changes in pH and $PaCO_2$ that stimulate the medullary vasomotor center, but does not enhance the sympathetic discharge to the heart. At the cardiac level, this sympathetic efferent activity results in an increase in the pumping activity of the heart and at the peripheral

vascular level in a general vasoconstriction seen in arteriolar resistance and venous constriction with consequent redistribution of blood volume away from the periphery into the central circulation.

The improved heart function results from direct catecholamine release at cardiac sympathetic nerve endings in proximity to myocardial beta-adrenergic receptors and by vasomotor center inhibition of vagal parasympathetic efferent outflow. The result of this sympathetic/parasympathetic balance is to increase sino atrial activity and reduce atrioventricular conduction time and to increase myocardial contractility directly.

The central redistribution of blood volume is caused by a selective vasoconstriction vessels at the expense of skin and skeletal muscles, followed late in the hypovolemia process by vasoconstriction in the abdominal organs. However, adrenergic stimuli cause coronary vasodilation and peripheral hypercapnia and acidosis produce cerebral vasodilation, thereby protecting these vital organs until the very last.

The immediate mechanism whereby circulating volume is restored invalues the movement of fluid from extravascular to intravascular space as a direct result of the decreased intracapillary hydrostatic pressure associated with blood loss. At the renal level, the efferent arteriolar vasoconstriction and low flow activates the juxtaglomerular apparatus with the release of renin and angiotensin-mediated aldosterone secretion by the adrenal cortex tends

to result in fluid retention.

All these mechanisms result in an increase in circulating blood volume from its hypovolemic low point toward normal levels.

In addition, at the metabolic response level, the adrenal-mediated acute increase in hepatic gluconeogenesis and the production of other osmotically active metabolic products assist in the restitution of extracellular and intravascular blood volumes at the expense of intracellular volume, through both catecholamine and glucocorticoid secretion-controlled processes. These interrelated and integrated mechanisms behind compensation are homeostatic attempt to ensure short term survival.

II.b. The progressive stage of shock

Shock can be divided into two separate stages representing different degrees of severity called compensated shock and progressive shock. The compensated shock can also be called recovering shock and progressive can be called degenerating shock.

On the other hand, if shock becomes more severe than a certain critical degree, the shock itself breeds more shock.

The critical point between recovering shock and progressive shock

In 1961 Guyton performed a series of experiments on

36 dogs, divided into six separate groups, with six animals in each group.

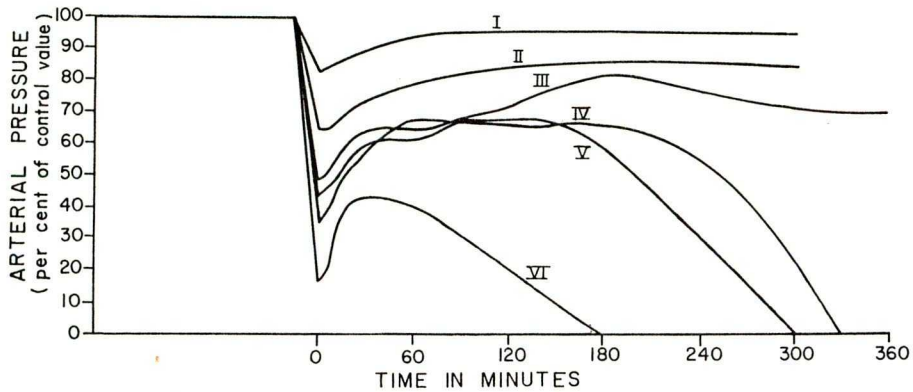

FIGURE 159. Effect of different degrees of bleeding on the subsequent course of the systemic arterial pressure. Each curve represents average effects from six different animals. All animals represented by the first three curves recovered while all animals represented by the last three curves died. (Reprinted from Guyton and Crowell, 1961c.)

He obtained the following results, all the animals lived if they were bled to arterial pressures above 47 mm Hg, whereas those bled to pressures below 47 mm Hg died. Though the cardiac outputs were not measured in the particular animals studied in these experiments, but this same general pattern occurs also for cardiac output (Stone and Guyton, unpublished observations). Therefore, it is obvious that a cardiac output difference of only a few millilitres or an arterial pressure difference of only a few millilitres of mercury can determine whether an animal in shock will proceed in a progressive downhill direction or in an uphill direction. Furthermore, an animal very near the critical balance point may go for many hrs. with arterial pressure or cardiac output changes so slight that one can't determine whether recovery will take place or whether the shock will progress to death.

Positive feedback as the cause of progression in shock

Severe shock breeds more shock; this type of effect is called positive feedback (Guyton, 1961). That is, severe shock affects the circulation itself in such a way to make the shock still more severe. Thus, each increase in the degree of shock causes another increase, and after many cycles of such feedback the shock becomes so intense that death ensues.

Circulatory deterioration resulting from the feedback during shock

At least four different types of the feedback can occur. These are the following:

1) As nutrition to the brain reduces, the vasomotor and respiratory centers begin to fail. Failure of vasomotor center reduces vascular tone, which leads to the reduction of the mean systemic pressure. This in turn causes cardiac output to fall to lower level. Respiratory failure results in decreased oxygenation of the tissues throughout the body. Respiratory failure occurs late in the shock.

2) Blood flow through some of the vascular beds becomes so sluggish during shock that blood begins to clot in the small vessels (Crowell, 1955). Crowell's studies have shown that anticoagulant therapy can protect to some extent against progression of shock.

3) In severe shock, even the blood vessels themselves will not receive adequate nutrition. As a result of this peripheral vasculature dilate, resulting in reduced mean

circulatory pressure and further reduction in cardiac output. Diminished vascular nutrition can also lead to increased capillary permeability (Landis, 1934), this resulting in loss of fluid from the blood, diminished blood volume, diminished cardiac output. However, these effects probably occur only in the terminal stages of shock rather than early in progressive shock.

4) Probably the most important of all factors that cause shock to progress is cardiac deterioration resulting from the feedback.

Cardiac deterioration in the progressive stage of shock

The ability of the heart to pump blood is highly dependent on the transport of oxygen and perhaps other nutrients, to the heart by the coronary vessels (Case, 1954, 1955). In other words if the coronary blood flow decreases, the pumping ability of the heart also decreases. Furthermore, the shock itself can decrease the blood flow through the coronary system sufficiently to cause the heart to fail. As the heart fails, the cardiac output falls still more, resulting in further nutritive deficiency in the myocardium. Consequently, the heart fails still more, the cardiac output falls more, and the cycle continues again and again, resulting in positive feedback that eventuates in death.

Negative feedback as a deterrent to the progression of shock

All the compensatory mechanisms that tend to return cardiac output toward normal are negative feedback processes (Guyton, 1961). The number of impulses transmitted by the pressoreceptor reflex, one of the most important of all compensatory mechanisms, becomes reduced, when the arterial pressure falls too low; this in turn reduces the inhibitory effect of these impulses on the sympathetic centres of the brain and thereby allows massive discharge of sympathetic impulses throughout the body. At the same time, the parasympathetic fibres to the heart are inhibited. As a result of both sympathetic and parasympathetic effects, the heart becomes a much stronger pump. Also, the sympathetic impulses to the peripheral circulation increase the mean systemic pressure and the total peripheral resistance. As a consequence, the cardiac output and arterial pressure rise back toward normal. In other words, the initiating effect, a decrease in pressure, results in an increase in pressure. That is, the response is negative to the initiating factor.

Two other negative feedback compensatory mechanisms which help to prevent the progression of shock are: 1) the stress relaxation recovery mechanism in which a decrease in mean circulatory pressure causes the blood vessel tone to increase. The increased tone, in turn, causes the mean circulatory pressure, to rise back toward normal. 2) the capillary fluid shift mechanism also provides a negative feedback compensatory mechanism. That is, if the blood

volume falls very low, the capillary pressure, eventually falls very low, and fluid is pulled osmotically into the blood through the capillaries, resulting in an increase in blood volume.

These negative feedback mechanisms all operate in opposition to the different positive feedback. If the negative feedback is greater than the positive feedback, one would expect recovery rather than deterioration of the circulation.

Cardiac output in the irreversible stage of shock

After shock has progressed long enough, transfusion or any other type of therapy becomes incapable of saving the life of the patient. Therefore, the subject is then said to be in the irreversible stage of shock.

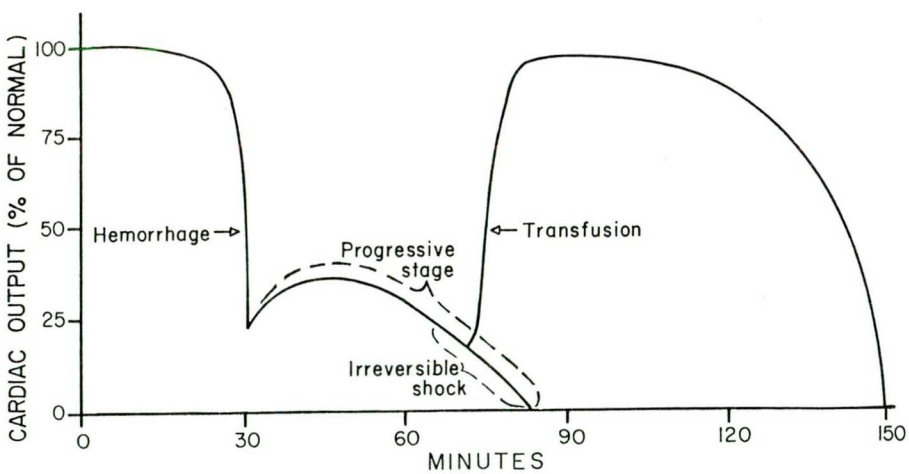

FIGURE 163. Progressive deterioration of cardiac output during the progressive stage of shock following severe hemorrhage, and failure of transfusion to effect permanent recovery once the irreversible stage of shock has been reached.

If a transfusion is given to the animal in the early phases of the progressive stage of shock, the arterial pressure rises very rapidly back toward normal, and the animal eventually recovers. However, once the circulatory system has deteriorated beyond a certain point, transfusion or any other type of therapy will not save the life of the animal even though for temporary periods of time transfusion can often return the cardiac output and arterial pressure all the way to normal (Wiggers 1945, Crowell 1962). That is, the heart is often still capable of pumping large quantities of blood if sufficient blood is made available to the input side of the heart. However, some of the intrinsic factors of the heart have already become so damaged that the heart continues to deteriorate until complete failure ensues.

The role of vascular failure in irreversible hemorrhagic shock

It has been agreed on that the myocardial failure is the sole contributor to the irreversible phase of shock, but Wiggers originally proposed a primary vascular defect - a failure of venous return. Later, Zweifach and Fronek postulated that peripheral organ dysfunction and a failure of venous return act together to trigger any post reinfusion cardiovascular collapse. This failure in venous return is thought to represent either an increase in venous capacitance or a decrease in circulating blood

volume. A decrease in circulating volume may be due to either a loss of ultrafiltrate or a loss of whole plasma resulting from changes in permeability at the microcirculatory level.

Rothe et al., using pentobarbital-anesthetized canine models also concluded that vascular failure plays a minor role in the pathogenesis of irreversible shock. Further insight into this matter was supplied by Bond et al. Using the pentobarbital-anesthetized dog with both the innervated and denervated hindlimb preparation, they concluded that an important feature in irreversible shock is a progressive increase in skeletal muscle vascular conductance. In the intact canine model, Bond et al. modified the concept of an increase in vascular conductance to include either an increase in capacitance or a progressive loss of intravascular fluid. Thus the concept of a defect in the vascular capacitance system during the irreversible phase of hemorrhagic shock emerges. This capacitance abnormality was found to be independent of perfusion pressure, arterial pH, blood flow, and the constituents present in arterial shock blood. This prompted the suggestion that this loss of vascular tone (increased capacitance and/or conductance) may be due to prejunctional inhibition of adrenergic transmission or to alpha-receptor fatigue. The mechanism of this vascular decompensation (vasodilatation) has been shown to be independent of reflex vasodilatation and may in fact be due to the local production of prostaglandin E_1 (PGE_1). However, a possible central mechanism contributing to the

vasodilatation can't be excluded. Both in the anesthetized rat model of hemorrhagic shock and the canine model of hemorrhagic shock, for example, the opiate receptor antagonist naloxone has been shown to improve cardiovascular function.

Association of the irreversible stage of shock with oxygen debt

Crowell and Smith have demonstrated that there is a high degree of correlation between the amount of oxygen debt that an animal builds up during shock and the onset of irreversible stage of shock. That is, because of the poor circulation of blood, the tissues of the body begin immediately to suffer an oxygen deficit in shock.

A decrease in oxygen consumption below the current demand for oxygen is compensated for by an increase in anaerobic glycolytic metabolism, with a concomitant rise in serum lactate and in the lactate/pyruvate ratio. If the shock is very severe, this oxygen debt builds up very rapidly, whereas if the shock is not so severe, the oxygen dept builds up very slowly. Regardless of how rapidly the oxygen debt build up, when it reaches an average value of approximately 120 ml of oxygen per kilogram of body weight, the animal will have reached the irreversible stage of shock (the value is higher than this when the heart is digitalized).

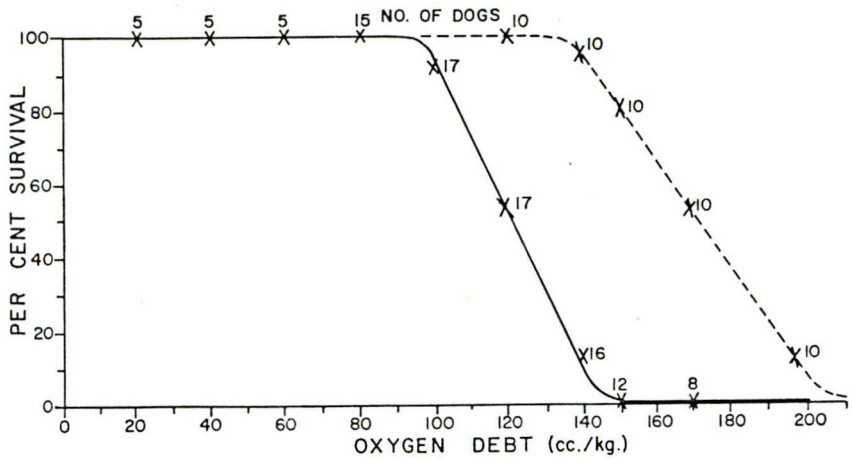

FIGURE 164. Survival rates of dogs following various degrees of oxygen debt in hemorrhagic shock (a) without digitalization (solid curve) and (b) after digitalization with strophanthin (dashed curve). The numbers represent the number of dogs in each group. (Courtesy of Dr. J. W. Crowell.)

The figure shows Crowell's results. All nondigitalized dogs in shock with oxygen debts less than 100 ml/kg will survive following adequate transfusion, and essentially all with oxygen debts above 150 ml/kg will die, with an average LD-50 of approximately 120 ml/kg oxygen debt.

When an animal has incurred a lethal amount of oxygen debt, treatment by transfusion may cause the heart to pump a normal output for as long as 30 minutes to an hour, and even part of oxygen debt may be repaid, but, unfortunately, by this time so much damage has resulted that the oxygen debt can't be repaid rapidly enough to prevent the downhill trend toward death.

Cornand's studies showed that oxygen consumption was maintained by an increased extraction of the arterial oxygen content from the arterial blood with a widening of the arteriovenous-oxygen content difference, so that there

was a tendency for total oxygen consumption to be maintained.

It can be seen that in patients in cardiogenic shock (as well as pulmonary embolus shock) pure hypovolemic shock, or nonseptic posttraumatic shock, an increase in cardiac index (CI) results in an increase in oxygen consumption until a critical level of flow is reached at which an increase in body perfusion produces no further rise in oxygen consumption. The physician caring for a critically ill patient should attempt to achieve this level by adjusting volume support, vasodilatation, and cardiac inotropic support, if necessary.

Delay of the irreversible stage of shock by digitalization

This effect has been demonstrated by Crowell (1961). If the heart is digitalized, the animal can withstand a considerably higher degree of oxygen debt and still survive than is the case without digitalization. These results substantiate the fact that cardiac failure is one of the most important occurrences in the irreversible stage that prevents recovery from shock.

Cardiac failure as the cause of the irreversible stage of shock

Other studies by Crowell have demonstrated that proper use of transfusion can correct any problem of venous

return even in the irreversible stage of shock (Crowell 1961, 1962). Despite this, all possible therapeutic measures cannot make the heart continue to pump adequate quantities of blood, once irreversible changes have begun, to cause recovery of the animal.

Toxic polypeptide hypothesis

The first clear suggestion that cardiac failure could be a significant factor in the hemorrhagic shock syndrome is generally ascribed to 'Wiggers and Werle'.

In 1950 Wiggers proposed that the plasma of hemorrhagic-shocked animal may contain a toxic factor capable of depressing myocardial function. This postulate was based on the assumption that profound and prolonged hypotension could result in the breakdown and release of tissue products that might potentially be cardiotoxic.

The controversy dates back to the late 1940 when the original proposed toxic factor, vasodepressor material, was discovered to be only 'ferritin'. In 1966 Brand and Lefer reported the finding of a circulating myocardial depressant factor (MDF). Utilizing the cat in a Wiggers model of hemorrhagic shock with barbiturate anesthesia, they reported that plasma from cats in irreversible postoligemic shock could depress an *in vitro* cat papillary muscle preparation. They demonstrated that this depressant action of shock plasma was not due to pentobarbital anesthesia, plasma K^+, decreased pH, or increased osmolarity.

Myocardial depressant factor is a low molecular weight, heat stable and dialyzable substance. It accumulates in concentrations proportional to the duration of the oligemic phase of hemorrhagic shock. The anatomical origin of myocardial depressant factor is thought to be the pancreas. The pathogenesis of myocardial depressant factor seems to involve a decreased splanchnic blood flow and a loss of pancreatic lysosomal stability, resulting in a release of hydrolytic enzymes (cathepsin, phospholipase A,C,D, etc.). With the acid pH of the ischemic episode, pancreatic zymogenic enzymes such as trypsin, kallikrein, and phospholipase A are activated, and together with the lysosomal enzymes result in the formation of myocardial depressant factor. It is postulated that myocardial depressant factor then enters the systemic circulation (via veins and lymphatics) and causes a direct negative inotropic effect. The critical test of the myocardial depressant factor hypothesis was performed by Glenn and Lefer when they infused a normal cat with approximately 1 000 U of myocardial depressant factor. They observed a significant depression of myocardial function.

It is interesting to mention that in the published studies there is a definite time lag between the infusion of myocardial depressant factor and the onset of myocardial depression. The reason for this time lag is unknown, it may be that myocardial depressant factor has an intracellular site of action and that the observed time lag is necessary for penetration.

Although the presence of myocardial depressant factor was questioned by Wangensteen et al., it has since been characterized as a containing four amino acids: glutamic acid, glycine, serine, and an unknown. Furthermore, the presence of myocardial depressant factor activity has been confirmed in the rat, baboon, pig and rabbit models of hemorrhagic shock.

Thus it appears that in multiple animal species, using a variety of anesthetic agents, the plasma of animal models exhibit a direct negative inotropic effect that is capable of contributing to the myocardial failure of the irreversible hemorrhagic shock syndrome.

Functional and structural evidence for cardiac involvement in hemorrhagic shock

Hackel and Goodale showed in 1956 that dogs bled to arterial pressure levels of 45 to 55 mm Hg for 3 hrs developed important changes in cardiac metabolism. These included increased oxygen extraction and reduction of pyruvate uptake. Regan et al. found a close association between progressive myocardial failure following hemorrhage, and rising concentrations of serum glutamic-oxaloacetic transaminase in coronary sinus blood.

A more detailed study was provided by Henson et al. who used dogs subjected to usually lethal episodes of hemorrhagic shock. In 12 survivors sacrified at intervals of 3 to 7 days, significant myocardial damage was identified,

and the morphological changes increased in frequency and severity with time. Intramyocardial hemorrhage with focal necrosis was present at 3 days after recovery from shock and fibre hyalinization, myocytolysis, and heavy leucocytic infiltrates were present at later stage. The ultrastructural findings included loss of myofibrils with translocation and swelling of mitochondria and sarcomeric disorganization.

A distinctive lesion has been recognized by electron microscopy that appears to be associated with hypovolemic shock. This has been termed the zonal lesion. Its features include hypercontraction with marked sarcomeric shortening occurring adjacent to an intercalated disc. There is also Z band fragmentation, distortion of myofilaments and displacement of mitochondria away from the disc. Moreover, in contrast with the myofibrillar degeneration lesion, which represents irreversible injury, the zonal lesions are thought to be reversible.

In contrast with the changes of myocardial hemorrhage and necrosis seen in late irreversible shock, the zonal lesions appear early.

Whether or not these structural changes can explain the progressive decline in cardiac performance before the stage of irreversible failure is reached is uncertain, but this provides tempting speculation.

Global ischemia hypothesis: role of coronary flow

The studies of Sarnoff et al. were probably the first

to demonstrate accurate measurements of coronary flow during hemorrhagic shock in the canine model using morphine-chloralose anesthesia. They measured base-line left coronary flow at 100 cc/min and observed a progressive decrease in flow during the hypotensive period. From this data, they proposed that myocardial failure plays a significant role in hemorrhagic shock, and that is failure is a direct consequence of insufficient coronary flow.

They also observed increased myocardial oxygen supply/consumption mismatching, a phenomenon that might explain the subendocardial hemorrhagic necrosis that they observed on pathological examination. Moreover, there is a progressive increase in sensitivity to hypoxia during shock. Data from the experiments indicate that subendocardial blood flow becomes sharply reduced as the duration of shock is extended. Studies using thioflavin-s fluorescent staining techniques have shown absence of blood flow to the papillary muscles in late shock.

Thus it seems that in the canine model of hemorrhagic shock, there exists a critical degree of hypotension below which coronary flow is not maintained. Prolonged hypotension below 50 mm Hg appears to be associated with a measurable decrease in coronary flow. Thus it is interesting to speculate that the transition from impending to irreversible shock may be related to a decrease in coronary flow.

As with declining coronary blood flow the myocardial wall tension also decreased and thus a decrease in contractility occurred.

Effects of metabolic acidosis on cardiac performance. Relationship to oxygen tension

A hallmark of oligemic shock is the appearance of progressive severe metabolic acidosis, ascribed in large part to a generalized increase in anaerobic glycolysis and reduced lactate and pyruvate metabolism, but also to reduced excretion of sulfate and phosphate radicals by kidneys. Whereas normal myocardium is quite resistant to systemic acidosis, this is not the case if hypoxia or adrenergic failure coexists.

The myocardial depression likely relates altered Ca^{2+} exchange and to competition by H^+ with Ca^{2+} at troponin binding sites. In the presence of acidosis there is enhanced sensitivity of the heart to hypoxia. Thus, in hemorrhagic shock accompanied by progressive metabolic acidosis, loss of adrenergic stimulation from neural or adrenal pathway would be of considerable importance, permitting the intrinsic negative inotropic action of H^+ to be fully expressed.

But probably of greatest importance is the recognition that acidosis reduces energy production from anaerobic pathways by inhibiting the phosphofructokinase (PFK) reaction in myocardial tissue.with increasingly severe metabolic acidosis, the capacity for ATP production from anaerobic pathways declines, and the myocardium becomes more completely dependent on aerobic metabolism. One can postulate that oxygen availability (flow x O_2 content) is a factor in determining the reversibility of myocardial

depression in acidotic animals during hemorrhagic shock.

It is clear that systemic acidosis, sympathetic nervous system (SNS) activity, coronary perfusion pressure, and oxygen availability are all potentially important factors in the impairement of myocardial function.

Autonomic regulation of the heart in shock

The shock syndrome in most instances is associated with the early appearance of hypotension and a substantial narrowing of the pulse pressure as LV output falls. After hemorrhage of 20% of the intravascular blood volume, reflex compensation is reflected by a 50 to 70% increase of total peripheral resistance, tachycardia, and modest recovery (20 to 25%) of cardiac output.

In the initial stages of circulatory shock, reduction in carotid sinus baroreceptor inhibition of sympathetic outflow to the cardiovascular system is a dominant compensatory mechanism. The aortic arch system is less effective because the threshold is higher (in the range of 100 mm Hg). The vagal afferent fibres contribute primarily to the tachycardia as well as the splanchnic and vasoconstrictor components.

In the event of massive blood loss, arterial pressure may fall to a level that causes ischemia of the central nervous system. This enhances sympathetic discharge to the heart and blood vessels, producing tachycardia, increased cardiac contractility. When blood loss is severe and

hypotension is prolonged, reflex compensatory mechanisms may fail.

Failure of baroreflex control after hemorrhage is related largely to loss of the efferent sympathetic limb of the reflex, while parasympathetic function remains and may be enhanced by acidosis. The latter effect may contribute to cardiac slowing and ultimate circulatory collapse.

Integrative hypothesis of the cardiovascular spectrum of hemorrhagic shock model

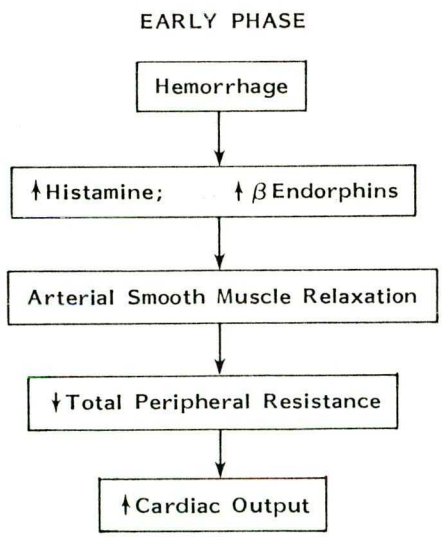

FIG. 1. Graphic analysis of the early postinfusion phase following a standard Wiggers protocol. Immediately with the return of the volume to the system, circulating histamine and centrally acting endorphins result in arterial smooth muscle relaxation, a decrease in TPR, and an increase in cardiac output. During this early phase, cardiac function, by hemodynamic parameters, would not be compromised.

HEMORRHAGIC SHOCK

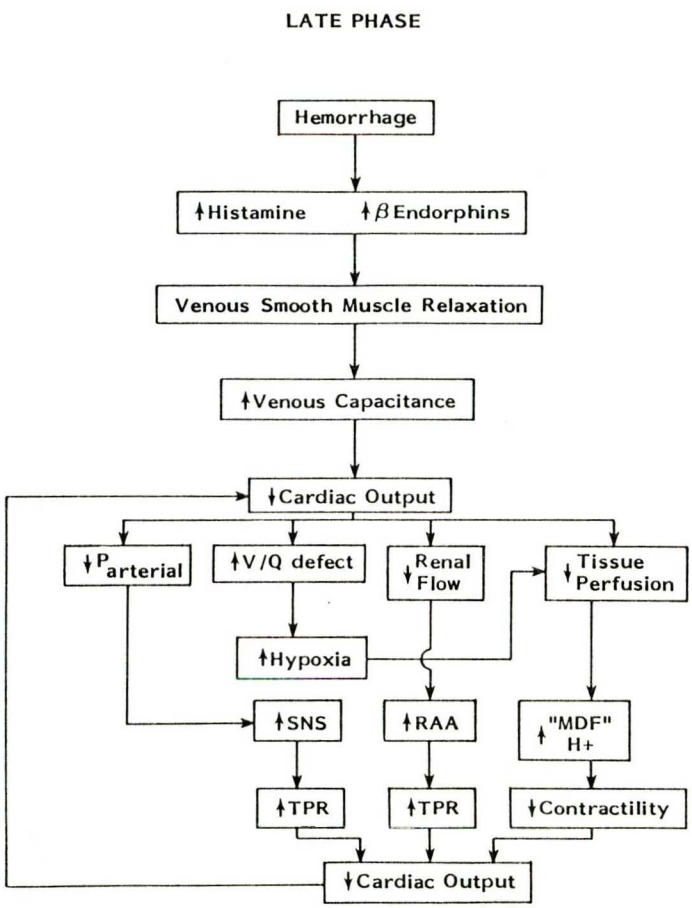

FIG. 2. More complex graphic analysis of the late postinfusion phase following a standard Wiggers protocol. During this phase, histamine and endorphins have an effect on venous capacitance, a decrease in venous return, and a decrease in cardiac output. This decrease in cardiac output sets into motion several different circles of positive feedback, all contributing to the decrease in cardiac output. There is a decrease in arterial pressure ($P_{arterial}$), which activates the SNS and increases TPR. This increase in TPR increases impedance to LV ejection and decreases cardiac output. The decrease in venous return could lead to ventilation/perfusion defects (V/Q defects) in the pulmonary bed, decreasing oxygenation and contributing to a decreased systemic tissue perfusion. The decrease in cardiac output leads directly to decreased tissue perfusion and the formation of MDF and systemic acidosis (H^+), which directly depress myocardial contractility and contribute to the decrease in cardiac output. The decrease in cardiac output is also seen as a decrease in renal blood flow and further activation of the renin-angiotensin-aldosterone system (RAA). This activated system further increases TPR, increases impedance to LV ejection, and decreases cardiac output. The decrease in cardiac output continues to feed the circuit and a positive feedback loop is initiated that terminates as the irreversible phase of hemorrhagic shock.

HEMORRHAGIC SHOCK

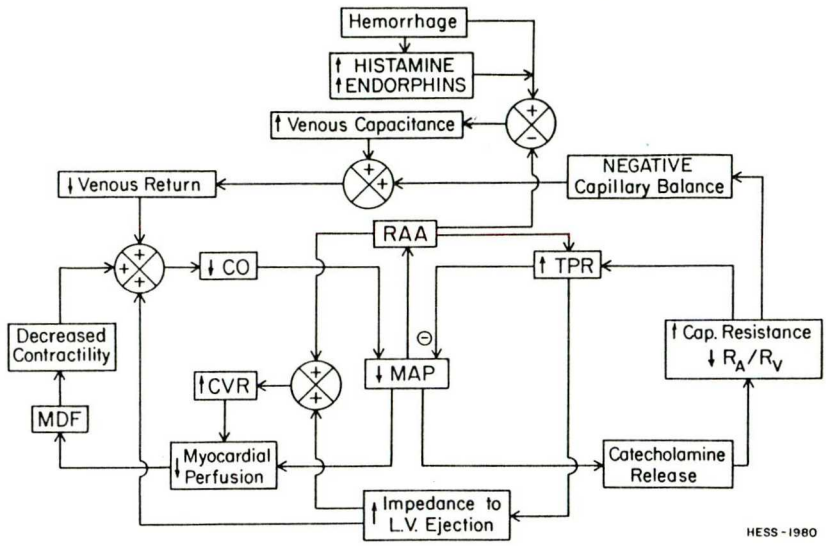

FIG. 3. Detailed systems diagram of the myocardial failure of hemorrhagic shock. The net result of hemorrhagic shock (Fig. 2) and its increase in venous capacitance summates (+) into a decreased venous return and a decrease in cardiac output (CO). The decrease in CO results in a decrease in mean arterial pressure (MAP) that in turn results in two positive feedback loops. (a) The decrease in MAP increases circulating catecholamine concentrations which increases the capillary resistance ratio (R_a/R_v), resulting in a net movement of fluid from the vascular compartment to the interstitial space (negative capillary balance), which in turn will summate (+) and contribute to the decrease in venous return. (b) The decrease in MAP will activate the renin-angiotensin-aldosterone system (RAA), increase TPR, increase impedance to LV ejection, and, summating with the decrease in venous return, result in a decrease in CO. Further, the activated RAA system will increase coronary vascular resistance (CVR), decreasing myocardial perfusion, leading to a relative state of myocardial ischemia. This myocardial ischemia acting in concert with the systemically produced MDF will directly depress myocardial contractility. This depression of myocardial contractility will further summate and contribute to the observed decrease in cardiac output, which will continue to fuel the circle of positive feedback. Thus the myocardium becomes the target of the multiple organ failure of hemorrhagic shock and involves an interaction with the venous capacitance system, the arterial resistance system, interstitial fluid dynamics at the capillary level, the splanchnic system, and the renal system.

Future areas of research in shock models

The irreversible phase of hemorrhagic shock is still an enigma to the investigator. It has clearly served us well as a model for study, but after 35 years of research in the field, there are still more questions than answers. Several important areas still await investigation. A more precise definition of the role of the central nervous system in shock would be helpful. It appears that the role of

opiate receptors has just begun to evolve. The regulation of the peripheral vasculature system with special emphasis on interstitial fluid dynamics still needs clarification. Mechanical augmentation of coronary flow has met with limited experimental success.

From pharmacological point of view, one is faced with a failure of past and present therapy to reverse the circles of positive feedback. Interesting work is emerging, including attempts at inhibition of angiotensin and the vasoconstrictor prostaglandins and therapeutic administration of the vasodilator prostaglandins. Free radical products of oxygen reduction may emerge as mediators of the ischemic process. Pharmacological therapy aimed at these free radicals has yet to be developed. It would appear that a single pharmacological agent will not be found for the multiorgan system dysfunctions, and an appropriate combination of drugs has yet to be.

One true concept does emerge: we must continue to work on both pathogenesis and therapy. Without a better understanding of what is happening, we will continue to flounder in the black box of therapeutics. Dr Wiggers' original challenge is still with us; namely, how to make the irreversible phase of shock reversible. The answer still awaits formulation.

B) High cardiac output shock (Sepsis-septic shock)

When bacteremia is associated with inadequate tissue

perfusion, especially with Gram-negative organisms, septic shock with hypotension, vascular collapse, renal failure and death may ensue. Sepsis can be initiated by a large number of microorganisms including bacteria (Gram-negative and Gram-positive), viruses and fungi. Of these the Gram-negative sepsises occur most frequently with E.coli being the predominant, in hopitalized patients with underlying disease, followed by Klebsiella, Pseudomonas and Proteus.

The circulatory defect of septic shock

Septic shock in man is generally characterized by a normal or mostly increased cardiac output (CO), a decreased systemic vascular resistance (SVR), a decreased arterio-mixed venous oxygen content difference ($Ca-\bar{v}O_2$) and elevated blood lactate levels. This hyperdynamic profile is usually observed in the earlier stages of this highly lethal disease but a significant number of patients show such a pattern throughout the course of their illness.

Decreased peripheral vascular resistance

The initiating hemodynamic change in sepsis is presumably a decline in peripheral vascular resistance. Prospective serial studies during genito-urinary instrumentation have demonstrated a decrease in systemic vascular resistance and central venous pressure (CVP) in those patients who developed

Gram-negative bacteremia or positive limulus test for endotoxemia. This fall in systemic vascular resistance is usually accompanied by a reflex mediated increase in cardiac output.

A decrease in systemic vascular resistance may be caused by loss of vascular tone and vasodilation or by opening of anatomic arterio-venous shunts. It has been suggested that the fall in systemic vascular resistance might be related to increased true peripheral anatomic shunting. In a study in human sepsis capillary muscle flow (Xe clearance studies) was greater in septic than in nonseptic patients and increased in direct proportion to the increase in cardiac output. This observation strongly argues against (but does not entirely rule out) the existence of peripheral anatomic shunts as an explanation for the hyperdynamic circulation in sepsis. Therefore, loss of vascular tone and vasodilation are now recognized as the most important mechanisms responsible for a decrease in systemic vascular resistance.

Clinical observation of septic shock patients suggests marked redistribution of flow: e.g. oliguria and altered mentation assumed to be caused by hypoperfusion together with signs of a well perfused skin. Flow to organs expressed as percentage of cardiac output changes significantly in shock. Apparently, changes in local vascular resistance may show wide differences. However, as systemic vascular resistance declines vasodilation must be the prevailing mechanism.

A number of mediators has been implicated in the pathogenesis of peripheral vasodilation including products of complement activation, histamine, vasodilator cyclooxygenase products, bradykinin and beta-endorphin. In sepsis both the classical and the alternative pathway of the complement system are activated, the latter probably in an earlier phase. Complement factors almost uniformly decrease when septic shock develops, while the lowest values are found during shock episodes that end fatally. These observations suggest that excessive activation of the complement system may have pathogenetic significance.

Excessive activation of the complement system may be the result of excessive amounts of activator or may be associated with insufficiency of functioning inhibitors. Also, markedly increased levels of proteolytically inactivated C1-esterase inhibitor have been found in a series of patients with sepsis and septic shock. These findings suggest loss of regulatory function of inhibitors of the complement system (and also of the contact system of coagulation - Hageman factor). A number of reports has confirmed the presence of decreased levels of Hageman factor, prekallikrein and high molecular weight kininogen during severe systemic infections. The contact system therefore presumably has an important pathogenetic role in septic shock.

The naturally occurring prostaglandins, thromboxanes and leukotrienes are involved in the complex pathophysiology and hemodynamic alterations of septic shock in man. Prostacyclin, PGE_1 and PGE_2 have vasodilatory properties.

However, their precise role remains to be established. The endogenous vasodilating beta-endorphin is released as part of the stress response (together with ACTH) and elevated levels have been demonstrated in experimental endotoxic shock. However, administration of naloxone fails to increase peripheral resistance in septic shock. Apparently they do not possess a major role. Undoubtedly other mediators, including effector substances from neutrophils and platelets, tumor necrosis factor (cachectin), interleukin 1 and others are involved either directly or indirectly in the extremely complex pathophysiology of septic shock clinically presenting as vasodilation.

Increased cardiac output

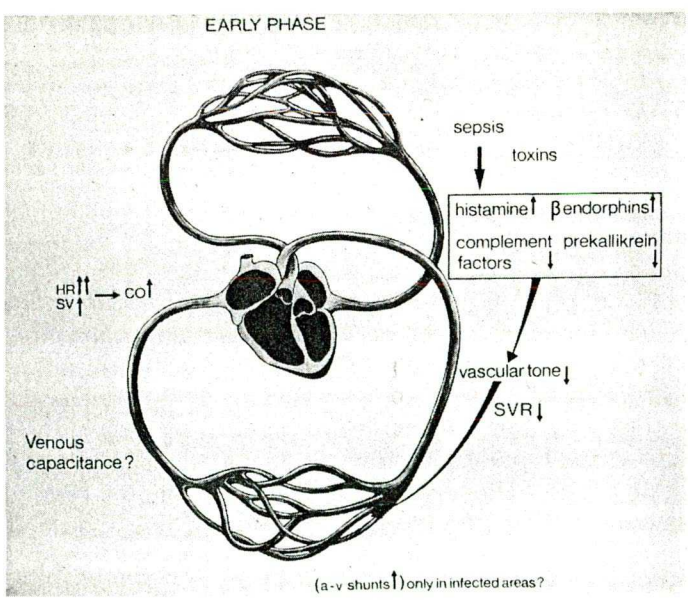

Fig. 1. Hemodynamic events during an early phase of septic shock

In response to peripheral vasodilation and mediated by the baroreflex cardiac output increases in order to maintain blood pressure. Both stroke volume and heart rate increase, the latter usually more pronounced. The magnitude of this increase is influenced by a number of factors: volume status, myocardial function prior to the septic episode and some pre-existing diseases (e.g. chronic liver disease). Following generalized vasodilation a state of relative hypovolemia is present. Therefore, the hyperdynamic state is often only apparent after correction of hypovolemia. On the other hand chronic liver disease as such is usually characterized by a high cardiac output and supervening septic shock may result in an extremely hyperdynamic syndrome. However, there seems to be a common sense in the theory that patients with a compromized cardiac function are less able to cope with the burden posed on the circulation by the septic insult and therefore have a less favourable outcome.

Both myocardial and peripheral vascular dysfunction may occur producing inadequate and maldistributed tissue flow, progressive organ dysfunction and multiple organ failure. Mechanisms involved in this pathogenesis are cardiac failure, intravascular pooling, peripheral vascular failure and increased microvascular permeability with loss of proteins and fluids from intravascular compartment.

Myocardial depression and failure

It was widely assumed up till recently that in non-

survivors (septic shock patients) the hyperdynamic state slowly evolves into a hypodynamic state. In other words some patients develop a decrease in cardiac output during their later clinical course, ultimately leading to death. Myocardial dysfunction was therefore assumed to occur late in human septic shock.

In fact, however, only a limited number of reports describe patients dying in a hypodynamic state i.e. CI$<$2.5 L/min/m^2, hypotension, increased peripheral resistance and progressive lactacidemia. Probably about one-third of non-survivors develop a low cardiac index prior to demise and the number of patients actually dying from overt myocardial failure is presumably small. Myocardial depression therefore does not seem to be the most common cause of death.

A new dimension was added to the study of cardiac behaviour in septic shock with the introduction of bedside nuclear medicine techniques permitting measurement of ejection fraction and approximation of end-diastolic and end-systolic volume of right and left ventricles. Studies in septic shock patients revealed that central venous pressure and wedge pressure did not correlate with RV and LV end-diastolic volume (EDV) respectively indicating a change in diastolic compliance.

In one of the first studies, at the onset of septic shock a subpopulation of these patients was revealed in which a decreased LVEF (left ventricle ejection fraction) and increased LVEDV indicating decreased LV function with dilatation of the left ventricle were demonstrated.

It has been observed that some non-survivors did not develop LV dilatation. An explanation for the absence of the LV dilatation might be the occurrence of myocardial edema with loss of myocardial compliance and inability of the LV to dilate.

Recently, LV performance curves have been constructed in patients with and without septic shock employing conventional hemodynamics and serial radionuclide blood pool scans in response to volume infusion. Two abnormalities were found in patients in sepsis and early septic shock. Some patients showed an increase in LV volume and wedge pressure without increase in stroke work. This was considered evidence of an abnormality in ventricular contractility. Another group of patients failed to develop ventricular dilatation despite a volume-induced elevation of wedge pressure pointing at a compliance abnormality.

In a similar study in critically ill patients it was suggested that a change in LV compliance could be caused by a change in RV loading conditions. It was suggested in 1970 that right heart failure secondary to pulmonary hypertension might be an important mechanism contributing to circulatory insufficiency and death. Although pulmonary artery pressure is usually normal in early septic shock a subgroup of patients may demonstrate a progressive increase in pulmonar vascular resistance with a decrease in cardiac output. It has been suggested that aggressive volume therapy in the presence of pulmonary hypertension may be responsible for RV dilatation and a left shift of the intraventricular

septum with decrease of LV volume and compliance and fall of cardiac output. Therefore, RV may in this way adversely influence LV performance.

Pathogenesis of myocardial depression

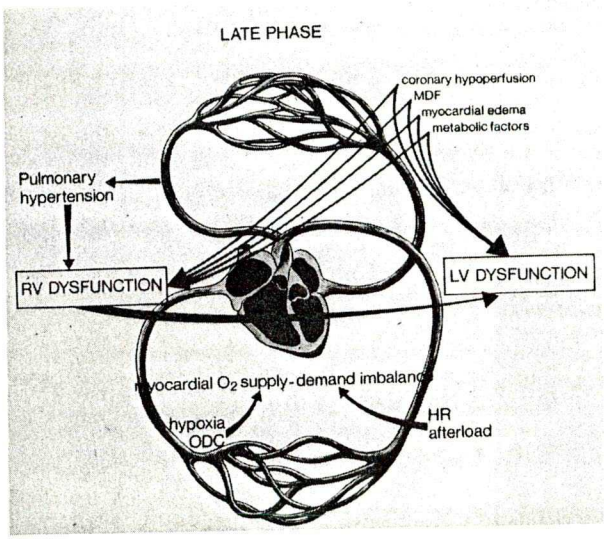

Fig. 2. Factors influencing myocardial function, especially during a later phase of septic shock

Coronary hypoperfusion and subsequent myocardial ischemia have been implicated as major factors. However, in human septic shock no correlation has been found between coronary artery perfusion pressure and LV stroke work, LVEF and the frequency of LV segmental wall dysfunction. However, they do not rule out the possibility that coronary hypoperfusion may contribute to myocardial depression at lower blood pressures than in that study, especially in combination with hypoxemia.

It has been suggested that local vasoconstriction induced by humoral factors such as serotonin, norepinephrine, thromboxane A_2 and angiotensin may be responsible for

segmental myocardial abnormalities. Arterial hypoxemia and reduced oxygen unloading capacity of the blood (left shifted oxygen dissociation curve) may be additional factors producing myocardial ischemia. Recently, myocardial depressing factor has been implicated as an additional cause of myocardial depression.

A number of factors can induce a decrease in compliance such as ischemia and inotropic drugs. An additional explanation for loss of compliance might be the occurrence of myocardial edema. Edema may not only affect compliance but also systolic contractile behavior. Several studies have implicated a variety of metabolic factors including low insulin levels in the pathogenesis of myocardial dysfunction in septic shock. Elevated afterload induced by factors such as catecholamines and angiotensin may contribute to depressed LV performance in some patients.

Increase in pulmonary vascular resistance poses an increased pressure load on the right ventricle. This makes the RV vulnerable to diminished coronary flow and then RV failure. Blockage of the pulmonary circulation with microthrombi composed of platelets and leukocytes has been implicated. Hypoxic vasoconstriction increases pulmonary vascular resistance but this is not likely to be the sole mediator. Direct effects of endotoxin and neurogenic factors acting through the autonomous nervous system may be invalued. Also, a number of humoral factors such as histamine, serotonin, catecholamine, angiotensin, bradykinin, thromboxane A_2 and prostaglandin F_2 may be invalued.

Intravascular pooling

Sequestration of blood in peripheral vascular compartment with loss of or with less effective participation in the circulating blood volume is referred to as pooling. The most likely site of intravascular pooling is the venous capacitance system, either generalized or restricted to some selected areas. Changes in the venous capacitance system which contains about 70% of the total blood volume may have important consequences for cardiovascular performance.

Recently, in a number of experiments with radiolabeled red cells and a noninvasive detection technique a marked redistribution of red cells in two septic shock models was found. This might indicate redistribution of blood volume and alterations in local blood volume. However, also local cell aggregation ("sludging") in postcapillary areas may (partly) explain or contribute to these results. Whatever mechanism is operative, red cells are apparently less available for active participation in the circulating (central) blood volume. In a subsequent study it was shown that neither volume loading nor dopamine infusion could reverse or even alter this redistribution phenomenon.

The mechanisms by which changes in the venous system are affected in human septic shock remain largely unsolved. Increase in capacitance may be caused by increased distending pressures either due to downstream venoconstriction or to extremely pronounced arteriolar vasodilation or "active" venodilation as a result of humoral factors.

Peripheral vascular failure

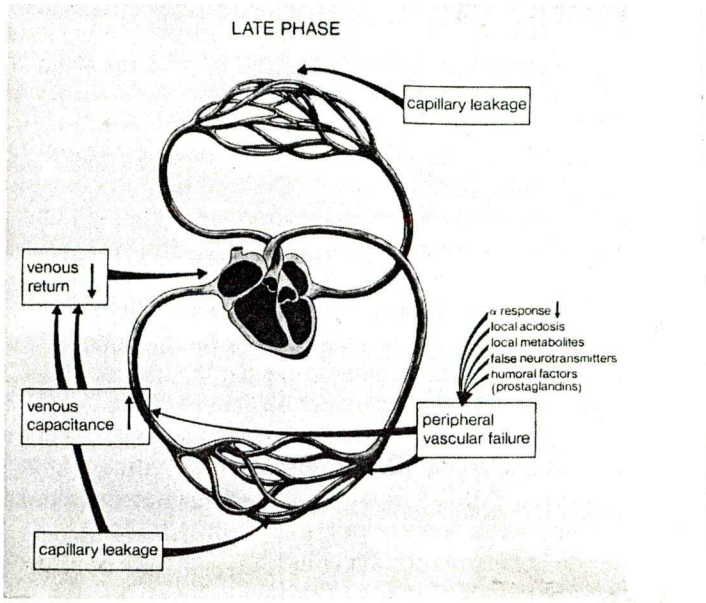

Fig. 3. Peripheral hemodynamic defects in a later phase of septic shock

Recently it has been reported that in nonsurviving patients with septic shock peripheral vasodilation may persist and contribute to mortality. In a series of 50 culture-proven patients with septic shock approximately two-third of the nonsurviving group had a very low systemic vascular resistance and a normal or high cardiac output to within a few hours prior to demise. The common denominator of the patients who died of septic shock seemed to be persistant vasodilation. These findings suggest that patients with septic shock are more likely to die of peripheral vascular failure than of cardiac failure. Clinically this phenomenon is characterized by unrelenting hypotension not or only temporarily responsive to vasoconstrictive catecholamines. Apparently, these patients in contrast to survivors lack the ability to regulate peripheral vascular tone in

response to a decrease in cardiac index.

The exact pathogenesis of this persisting vasodilation is unknown. Undoubtedly local metabolic and humoral factors are important. Tissue hypoxia and acidosis may induce vasodilation. Diminished responsiveness to catecholamines may signify down-regulation of adrenergic receptors or decreased vasomotion. In patients with liver cirrhosis and septic shock patients, impaired hepatic metabolism of aromatic aminoacids in both conditions might lead to the production of false neurotransmitters which may be responsible for a decrease in vascular tone.

Microcirculation and peripheral oxygen utilization

A major function of the cardiovascular system is to transport oxygen to the tissues and defects somewhere in the carefully regulated chain of oxygen transport are normally compensated for e.g. a decreased cardiac output and subsequent low oxygen delivery (DO_2) is compensated by increased peripheral oxygen extraction to maintain oxygen consumption (VO_2). Although DO_2 is usually normal or elevated in septic shock VO_2 is frequently subnormal notwithstanding increased systemic oxygen demands. There appears to be an imbalance between systemic oxygen utilization and systemic oxygen demands not related to an insufficient DO_2.

Lactacidemia is a common finding in septic shock and is generally considered a marker of oxygen debt. Alternatively, lactate production might reflect abnormalities of carbo-

hydrate metabolism rather than changes in tissue perfusion. However, a substantial number of clinical observations favors the concept of cellular hypoxia as a major source of lactate production. Thus, the dysbalance between oxygen utilization and systemic oxygen demands is largely reflected in blood lactate levels.

A decreased arterio-mixed venous oxygen content difference ($Ca-\bar{v}O_2$) may be caused by anatomic shunts, a left shifted oxygen dissociation curve (ODC), disturbed cellular function with impairment to utilize available oxygen and "physiological" shunting. Anatomic shunting may be of importance in areas of inflammation but does not appear to be a generalized phenomenon. A left shifted oxygen dissociation curve caused by alkalosis, hypothermia or low red cell 2,3 DPG levels with impaired unloading capacity for oxygen ("chemical shunting") may in some cases be contributing factor but is presumably only of limited significance. Inhibition of cellular oxygen utilization due to cellular damage has been implicated as a major mechanism.

At present so called "physiological shunting" appears to be the major mechanism of impaired peripheral oxygen extraction. At least three mechanisms seem to be operative in concert in reaching such microcirculatory derangements that oxygen uptake is impaired:

i) vasodilatation

ii) microembolization

iii) and endothelial cell injury.

i) Vasodilation

Vasodilation may interfere with normally fined timed autoregulation of tissues that adapt perfusion to oxygen demand. When such adaption is impaired tissue areas with relative low oxygen demands may be overperfused and extract little oxygen, while on the other hand relative hypoperfusion of tissues in need of high amounts of oxygen may occur especially when perfusion pressure (blood pressure) is low. This hypothesis is supported by the observation that systemic vascular resistance and oxygen extraction ratio were positively correlated in a series of septic shock patients, i.e. the lower the vascular resitance the lower the oxygen extraction. Also, a decrease in systemic vascular resistance during the course of septic shock was associated with an increase in lactate levels and vice versa.

Therefore, vasodilation as such may result in maldistribution of flow with ineffective oxygen extraction.

ii) Microembolization

The role of microembolization in the peripheral microcirculation in the pathogenesis of impairment of peripheral oxygen utilization has been investigated in experimental models using polysterene microspheres. These data suggest that microembolization leads to an oxygen utilization defect similar to that observed in sepsis and trauma. The possible effects of microembolization are: loss of autoregulatory function, decreased ability to recruit capillaries and inhomogeneity of flow.

In human septic shock aggregation of granulocytes and platelets may mimick this experimental microembolization process. It has been proposed that thromboxane A_2 is involved and amplifies the mechanical effects by intense vasoconstriction and (additional) platelet aggregation. Also, complement activation greatly enhances microembolization by inducing granulocyte aggregation with subsequent release of toxic products which in turn amplifies the whole process.

iii) Endothelial cell injury

Endothelial cell injury, either granulocyte dependent or independent, may be induced resulting in increased permeability, increased transvascular flux of macromolecules and tissue edema. Tissue edema further impairs oxygen diffusion by increasing diffusion distances and may compress capillaries thereby contributing to maldistribution of flow. Therefore, these changes may lead to severe cell dysfunction, increasing (local) acidosis, production of toxic factors and presumably form the basis of irreversibility of septic shock.

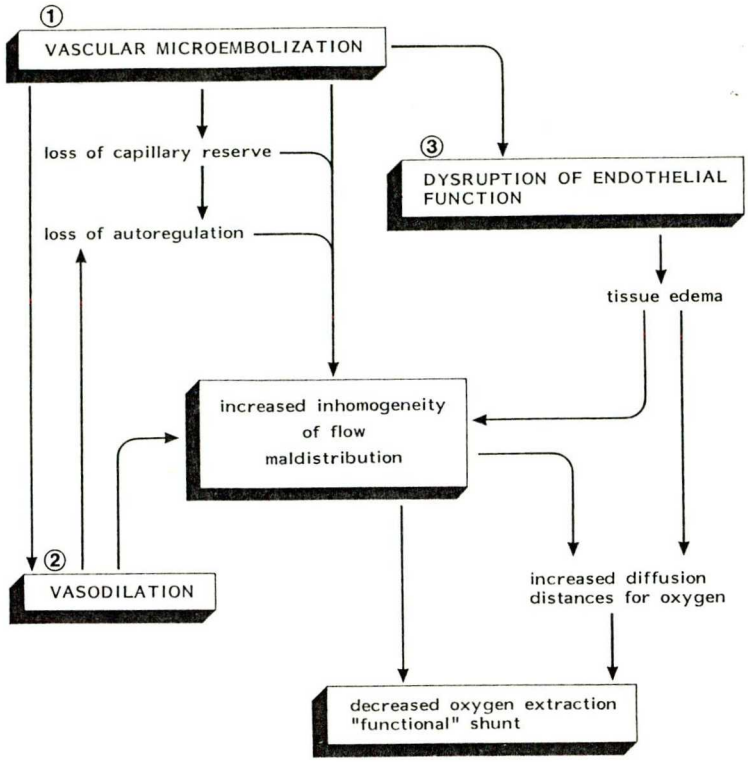

Fig. 4. Schematic representation of microcirculatory changes in septic shock resulting in maldistribution of flow and functional peripheral shunting

Several reports indicate that in septic shock (as in ARDS) VO_2 is dependent DO_2. Patients who exhibit such an abnormal supply dependency of VO_2 had elevated blood lactate levels, while corresponding increases in VO_2 to increases in DO_2 upon volume loading were not found in patients without lactic acidosis. Elevated lactate levels in septic patients may therefore predict whether further increases in cardiac output and DO_2 by volume therapy will result in increases in VO_2. This finding supports the view that blood lactate levels reflect oxygen debt. In contrast, when cardiac output and DO_2 were increased by catecholamine administration VO_2 also increased when blood lactate was

not elevated, which suggests a direct effect of catecholamines on oxidative metabolism. These observations have important therapeutic implications.

In figure 5 the concept of the main processes and their interrelations during septic shock has been summarized.

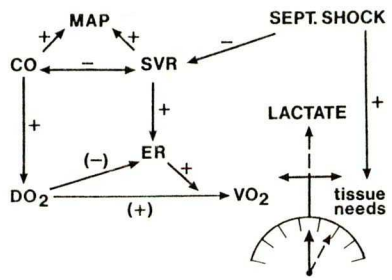

Fig. 5. Schematic representation of the main hemodynamic events in relation with oxygen transport and utilization in septic shock. ER = extraction ratio; + = positively correlated; – = negatively correlated

In a septic period tissue needs for oxygen increase while at the same time systemic vascular resistance declines with resulting decrease of peripheral oxygen extraction which has a bearing on VO_2. In order to maintain blood pressure (MAP) cardiac output increases and therefore DO_2 increases. Under physiological conditions peripheral oxygen extraction decreases above a critical level of DO_2 when DO_2 increases further. This negative relationship may be disturbed in septic shock.

Also, in septic shock DO_2 may be positively correlated with VO_2 (abnormal supply dependency of VO_2). Therefore, peripheral extraction of oxygen and oxygen delivery both determine the total available oxygen for utilization. Both a declining cardiac output and a persisting extremely

pronounced peripheral vasodilation may therefore result in a progressive oxygen deficit in tissues and ultimately in irreversible septic shock.

Acute adult respiratory distress syndrome in hyperdynamic septic shock

Development of septic process is associated with a sequence of events leading to altered permeability of the alveolar capillary membranes. The induction of immune complexes by trauma or sepsis has been demonstrated to initiate the complement activation response, which also may be initiated by a variety of leukocyte chemotaxins for bacteria. The elaboration of arachiodonic acid and the cyclooxygenase cascade results in the formation of thromboxane A_2. In association with this response there is platelet and neutrophil aggregation on the capillary and endothelial membranes with formation of microthrombi. The net result of these microthrombi in the pulmonary circulation is a diversion of blood flow from some alveolar segments to others. In addition, the white cell superoxides, neutral proteases, and leukotrienes alter the permeability characteristics of alveolar capillary intravascular space into the pulmonary interstitial area, with the formation of the ARDS of sepsis. These phenomena together produce abnormalities in the cardiopulmonary ventilation/perfusion relationships.

The initial pulmonary insufficiency of sepsis is a

'direct' consequence of the sympathetic cardiovascular compensation to the metabolically induced alterations in peripheral vascular tone and the immunologically induced changes in lung capillary permeability.

Classification of physiological states

We can distinguish four pathophysiological states of stress response: A, B, C, and D.

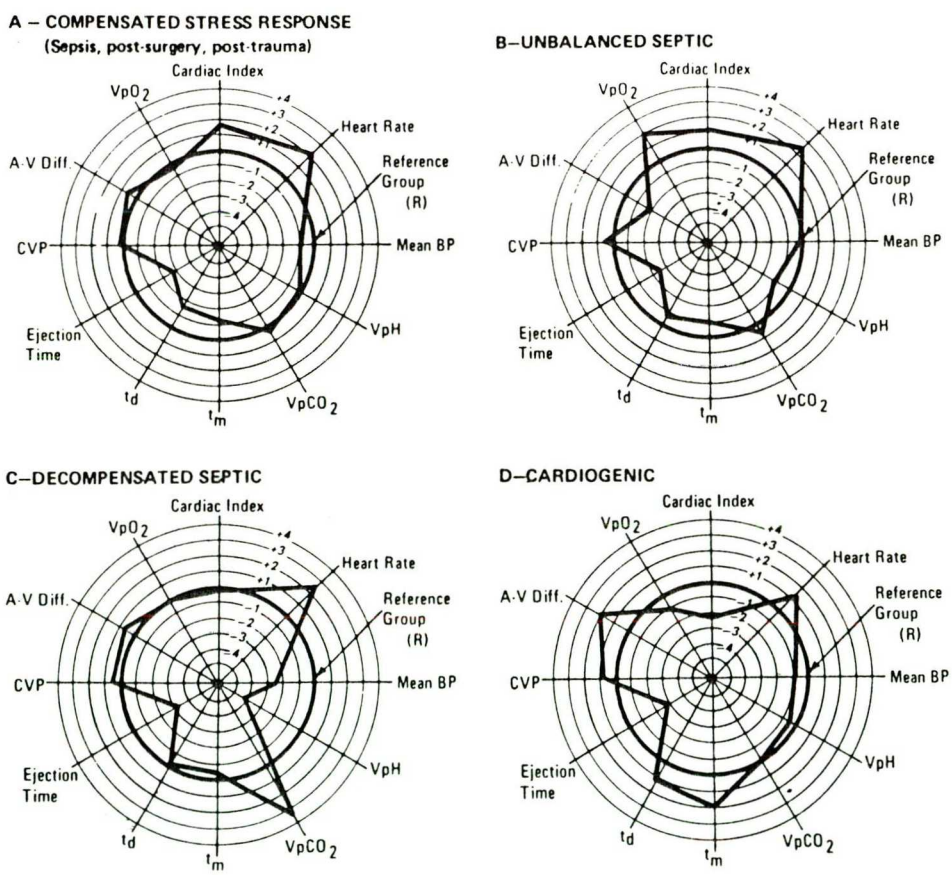

FIG. 15-2. Circle diagrams of physiologic states. Shown are the prototype mean patterns for the A, B, C, and D states. The perfect dark circle in the center of each pattern equals 0 standard deviations from the reference control (R) state. Each dotted line represents 1 standard deviation from R, either increased or decreased. The rays of the circle diagram represent respectively cardiac index, heart rate, mean blood pressure, mixed venous pH (VpH), mixed venous CO_2 tension ($VpCO_2$), cardiac washout time (t_m), pulmonary mean transit time (t_d), cardiac ejection time, right atrial pressure (CVP), arteriovenous oxygen content difference (A-V Diff) and mixed venous oxygen tension (VpO_2). (Siegel JH, Farrell EJ, Goldwyn RM, Friedman HP: The surgical implications of physiologic patterns in myocardial infarction shock. Surgery 72: 126, 1972.)

i) The A state

The A state is a normal stress response seen in compensated sepsis and after trauma or major intervention. It is characterized by:

increase in heart rate,

increase in cardiac output,

increase in contractility,

increase in ejection fraction,

increase in oxygen consumption,

decrease in BP

CVP is normal.

ii) The B state (unbalanced septic)

The B state is also a hyperdynamic cardiovascular state, but it represents a more severe stage of deterioration in the septic process. The increased cardiac index and other evidences of sympathetic response (reduced washed out time /tm/ and increased ejection fraction /EF_x/, increased heart-rate, decreased systolic ejection time /ET/) are insufficient or unable to supply peripheral needs. Consequently, the consumption of oxygen is normal or reduced when it should be increased, because of a disproportionately reduced arteriovenous oxygen extraction gradient compared to the increase in body flow (CI).

iii) The C state (decompensated septic)

In the C state, respiratory decompensation is superimposed on the unbalanced septic process and on the

metabolic acidosis seen in the B state, and retention of CO_2 with prefound respiratory acidosis occurs.

iv) The D state (cardiogenic)

This state represents a pattern of primary myocardial rather than peripheral failure. In this state there is a decrease in myocardial contractile function. This can occur as a result of biventricular septic myocardial depression but it is also characteristic of shock after acute myocardial infarction, after surgical intervention, and hypovolemic shock. There is a prolonged cardiac washout time (tm) reflecting a reduced ejection fraction (EF_x). The cardiac index falls, and the arterio-venous oxygen difference widens as the body's extraction of oxygen increases to compensate for the low flow state.

Thus, the D state is a delivery failure rather than an extraction failure (B state) of oxygen consumption.

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