Abnormal Vascular Tone, Defective Oxygen Transport and Myocardial Failure in Human Septic Shock

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IT HAS BECOME increasingly obvious to investigators in the field of shock that the nature of circulatory abnormalities in hypotension associated with bacterial sepsis may be different from that associated with shock produced by other causes.[6, 12, 25, 27] Recent studies [4, 19, 26] have shown that there appear to be two general groups of patients in septic shock who can be segregated by different hemodynamic responses. There is a group whose cardiac output is appreciably reduced, and a group in whom cardiac output is normal or increased. Clowes and his colleagues [2] in their studies of circulatory alterations associated with peritonitis have suggested that the ability to recover from the septic process is a function of the individual's capacity to maintain an elevated cardiac output. The purpose of this study is to examine in detail some of the physiologic abnormalities associated with the septic process in an attempt to ascertain ways of evaluating the patient's clinical course, and to determine which factors may be of greatest relevance in influencing the therapeutic approach to an individual patient.

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Materials and Methods

Cardiovascular dynamics, oxygen consumption, and acid base balance were determined in 30 patients in septic shock. Data were compared with those from nine patients whose shock processes were on the basis of hypovolemia, seven patients in pulmonary embolus shock, and 13 patients who were not in shock and who had no significant disease of the liver. Twenty-eight patients with hepatic cirrhosis and portal hypertension were also evaluated, and although the results for this group will be noted, they will be reported in detail in another publication. All patients considered to be in shock had a significant drop in blood pressure from preshock values and had one of the various clinical syndromes usually associated with shock. All patients considered to be in septic shock had the septic process demonstrated either at laparotomy or autopsy, or had pathogenic organisms cultured from their peripheral blood.

Clinical Procedure. A 36 polyvinyl intravenous catheter *** was introduced into the basilic or external jugular vein percutaneously and passed into the right atrium. In some instances a surgical exposure of the

*** Supplied by C. S. Bard, Inc.

vein was necessary. The catheter was flow directed into the right atrium and the intracardiac electrocardiogram was continuously recorded and observed during introduction, as previously described.[3] This catheter was used for the monitoring of central venous pressure using a Statham P23Db strain gauge. A Teflon catheter was passed percutaneously into the femoral artery, or placed into the radial artery when femoral catheterization was not possible. It was also connected to a Statham P23Db strain gauge for the measurement of dynamic and mean arterial pressures. Known quantities of cardio-green dye were injected via the central venous catheter and arterial samples were obtained using a constant speed withdrawal pump, and electronically evaluated using a Waters photoelectric densitometer. Calculation of cardiac output, mean transit time, and central blood volume were made by semilogarithmic replot and extrapolation by the technic of Hamilton *et al.*[9] Estimation of the body surface area used in the calculation of cardiac indices and stroke indices was obtained from the Dubois nomogram.[15] Mean blood pressure was measured electronically and total peripheral resistance was calculated in absolute units.[28] Arterial and mixed venous hemoglobin, pH, pCO_2, and pO_2 were determined, and arterial and venous oxygen saturations were calculated.[15] Blood buffer base was estimated by means of the Singer-Hastings nomogram.[24] Left ventricular stroke work was calculated as described by Sarnoff,[14]

An attempt was made to evaluate the vascular tone relationships as described by Green *et al.*,[8] in which a given patient's peripheral vascular resistance was evaluated as function of flow to provide a basis for comparison with values obtained from other individuals, and also to gain insight into the degree of net vasoconstriction of the vascular system considered as a whole. An attempt was made to evaluate the effectiveness of oxygen transport by determining milliliters of oxygen consumed per liter of total blood flow. This index of effective oxygen transport was examined as a function of total peripheral resistance to ascertain whether any group patterns of oxygen extraction existed which might suggest differences in the relative degree of peripheral arteriovenous shunting. The extent of pulmonary veno-arterial admixture was calculated by Berggren's equation[1] during inhalation of 100% oxygen. An approximation of cardiac ventricular function relationships[14] was provided by examining the relationship between left ventricular stroke work and central venous pressure (mean right atrial pressure). Finally, in a small number of patients an attempt was made to evaluate myocardial contractility directly from right ventricular dynamics by a modification of the Isometric Time-Tension Index.[22] Except when indicated, all points represent the initial values obtained in each patient.

Results

Vascular Tone. As has been described previously,[4, 25, 26] two groups of patients suffering from shock associated with sepsis were found. The first of these had considerable reduction in cardiac output associated with an increase in total peripheral resistance, and a prolongation of the mean circulation time. The second group, in whom the cardiac index was significantly higher than normal, had a decrease in both total peripheral resistance and in mean circulation time. It was of interest therefore to find that when the vascular tone relationships[8] were evaluated in all patients in septic shock (Fig. 1), and compared with patients whose hypotensive process was on a nonseptic basis, and with a group of older patients not in shock who had neither sepsis nor hepatic disease, that the Net Vascular Tone (total peripheral resistance as a function of flow) was sig-

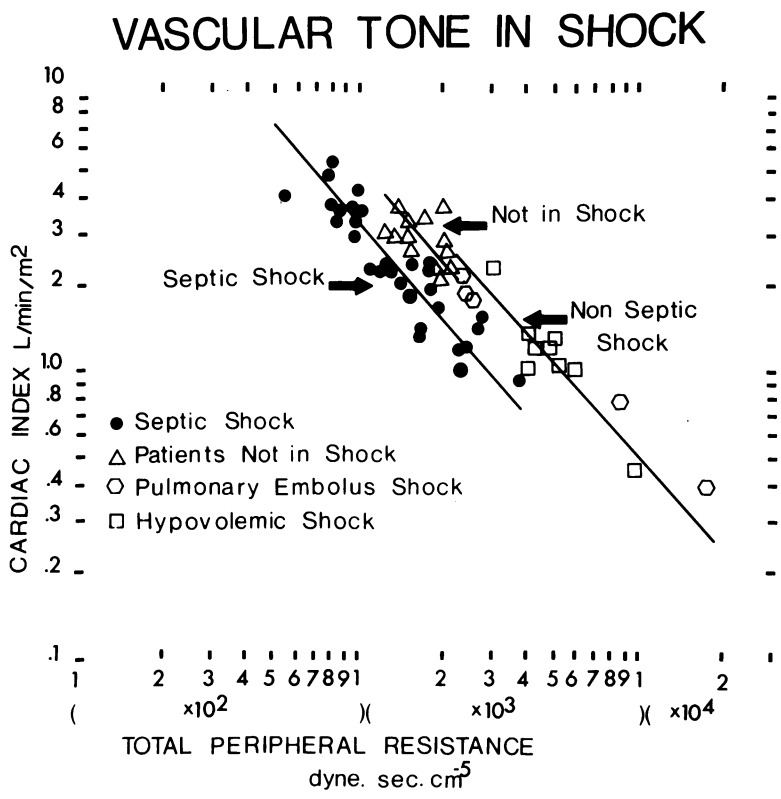

FIG. 1. Net Vascular Tone. Log-log plot of the cardiac index in liters/min./m.^{2} on the ordinate versus the total peripheral resistance in dyne · second · cm.$^{-5}$ on the abscissa.

nificantly decreased compared both to normal individuals and to patients in nonseptic shock. This decrease in Net Vascular Tone was comparable to that found in severe hepatic disease,[18] and was characteristic of all patients in septic shock, regardless of whether their cardiac indices were in excess of normal, normal, or decreased. In contrast, the 14 patients whose shock process was nonseptic, either on the basis of hypovolemia or pulmonary embolus, were noted to be on a vascular tone relationship which was significantly increased compared to the normal. This striking difference between *all* patients in septic shock compared with those in nonseptic shock would suggest that a fundamental difference exists in the pattern of vascular responses in these two groups.

Since the relationship between pressure and flow is nonlinear, it is apparent that differences in total peripheral resistance alone do not necessarily represent differences in the qualitative nature of the vascular response. If there is a fundamental difference between patients in septic shock with regard to cardiac output it is not to be found in their pattern of vascular tone relationships. Therefore, an attempt was made to examine other parameters in the physiologic response to the septic process. To ascertain whether the level of cardiac output had any special physiologic significance, 30 patients in septic shock were divided arbitrarily into three groups on the basis of the Cardiac Index. Hyperdynamic patients whose cardiac indices were 3 liters/min./m.^{2}, or greater, normodynamic patients whose cardiac indices were between 2 and 3 liters/min./m.^{2}, and hypodynamic patients whose cardiac indices lay below 2 liters/min./m.^{2}.

Oxygen Transport. Perhaps the most striking physiologic finding in patients in

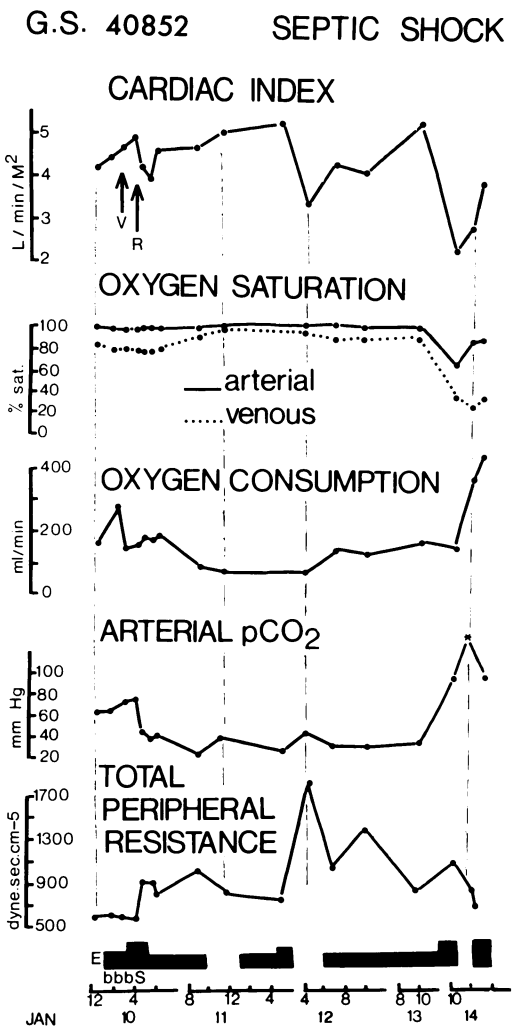

FIG. 2. Clinical course of patient in hyperdynamic shock. A 62-year-old white female with subdiaphragmatic abscess following anastomotic leak from esophagojejunostomy performed after total gastrectomy for carcinoma of the stomach. The patient suddenly became hypotensive on 1/11/65 and was maintained on a vasoconstrictor (Epinephrine-E) by intravenous drip for 12 hours prior to being referred for evaluation on the Shock Service. After the initial cardiac output determination the patient was switched to the inotropic vasodilator Isoproterenol (2γ/min. infusion) (black bars), received a volume infusion of 500 cc. of Lactated Ringer's (V) and was placed on an Air Shields volume-controlled respirator (R). In addition, the patient was begun on steroids (S) and was noted to improve clinically over the next two days, although her oxygen consumption remained poor. She was found to have a mixed infection including resistant Aerobacter organisms, and despite what was believed to be adequate drainage of her abscess cavity she began to show clinical evidence of deterioration on 1/13/65. This was associated with a fall in blood pressure and a progressive elevation of central venous pressure. At this time she was noted to have a rapidly increasing arterial pCO_2 and a further decline in peripheral vascular resistance, which was followed by a sudden and progressive increase in oxygen consumption. Despite an attempt to compensate for the deteriorating ventricular function relationship by an increase in the rate of the Isoproterenol infusion, the patient expired in high output failure on 1/14/65 accompanied by the striking increase in oxygen consumption.

hyperdynamic septic shock was that although their arterial oxygen saturations were normal, or in the near normal range, venous oxygen saturations were pathologically increased so that arteriovenous differences were abnormally narrow and oxygen consumption was decreased (Fig. 2). This patient was a 62-year-old woman in septic shock secondary to an inadequately drained subdiaphragmatic collection caused by a leak from an esophagojejunal anastomosis following total gastrectomy for carcinoma of the stomach. This defect in oxygen extraction was characteristic of the hyperdynamic patient and was either reversed slowly by resolution of the septic process, or, as in this patient, rapidly at the time of progressive and irreversible vascular collapse. This collapse was frequently associated with evidence of further peripheral vasodilatation.

When an attempt was made to evaluate Effective Oxygen Transport (oxygen consumption as a function of total blood flow) in patients in high output septic shock as compared to those whose shock was on a nonseptic basis, or to patients not in shock, a marked difference was found (Fig. 3). When oxygen consumption was evaluated as a function of total blood flow, it can be seen that patients in hyperdynamic shock were different from those in hypodynamic septic or nonseptic shock. This difference was manifested in two ways. Not only was a higher peripheral flow necessary at each level of oxygen consumption in the hyperdynamic group compared to all other patients studied (save those with

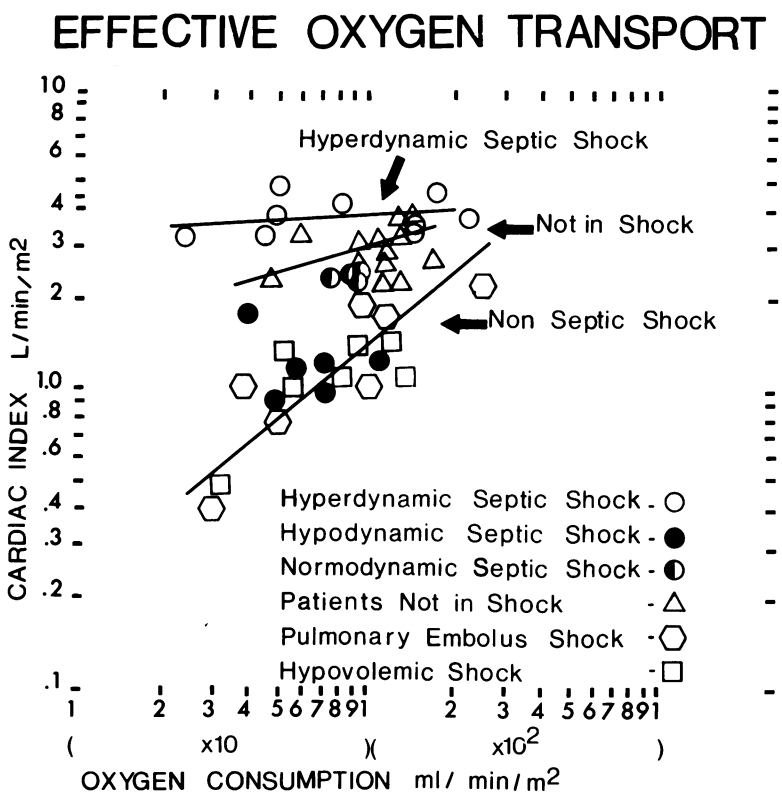

FIG. 3. Effective Oxygen Transport. Log-log plot of cardiac index liters/min./m.^{2} on the ordinate, versus oxygen consumption in ml./min./m.^{2} on the abscissa.

extensive hepatic disease),[18] but the relationship was much less flow-dependent than that seen in patients in shock with hypodynamic sepsis, hypovolemia, or pulmonary embolus. In the latter groups small increments in total flow were associated with relatively large increments in oxygen consumption. Those patients whose septic shock was normodynamic had an Effective Oxygen Transport similar to that found in normals, and these patients appeared clinically to have a less severe septic process.

Systemic and Pulmonary Arteriovenous Shunting. When Effective Oxygen Transport was evaluated as a function of total peripheral resistance to determine whether a diminished vascular tone was associated with inefficient oxygen extraction as an index of Relative Peripheral Shunting (Fig. 4), there was again a significant separation of patients in hyperdynamic septic shock from other groups studied. In the hyperdynamic septic group, any given level of oxygen transport occurred at a lower total peripheral resistance than in normal patients. In contrast, hypodynamic septic patients and nonseptic patients had a higher peripheral vascular resistance at any given level of oxygen transport than the normal group.

Since compared to other groups, Net Vascular Tone (Fig. 1) was decreased in *all* patients in septic shock regardless of cardiac output or effective peripheral flow, consequently these data suggest that in septic shock there may be anatomic arteriovenous shunts, perhaps at the prearteriolar level, in which shunt flow is a direct function of total aortic flow. The data also suggest that in contrast to normal shunting over which some degree of sympathetic control exists, there is a relative paralysis of regulatory control over these pathologic shunts, so that the degree of arteriovenous

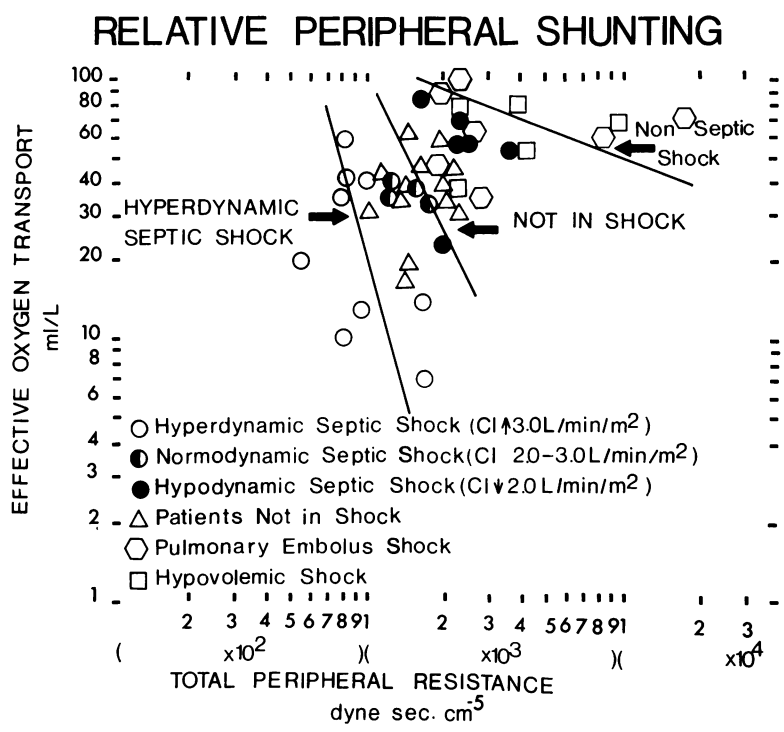

FIG. 4. Relative Peripheral Shunting. Log-log plot of effective oxygen transport in ml. of oxygen/liter of blood flow on the ordinate, versus total peripheral resistance in dyne · second · cm.$^{-5}$ on the abscissa.

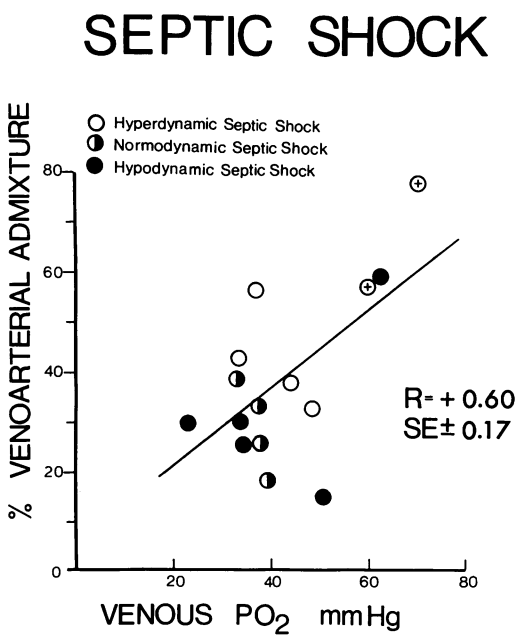

FIG. 5. Pulmonary Venoarterial Admixture evaluated as a function of the venous pO_2. Hypodynamic patients, closed circles. Normodynamic patients, half-closed circles. Hyperdynamic patients, open circles. Pearson's coefficient of correlation shown as R with its standard error (SE).

shunting is a passive consequence of the increase in flow.

That the evidence of increased peripheral shunting in the patients in septic shock may represent a more general phenomenon than systemic precapillary arteriovenous shunting is suggested by data shown in Figure 5. In this figure the percent of pulmonary veno-arterial admixture (calculated by Berggrens' equation [1, 4]) in patients in septic shock is related to venous pO_2 in the mixed venous blood. As was demonstrated in Figure 2, one characteristic feature of patients in hyperdynamic septic shock was a narrowing of the arteriovenous difference caused primarily by elevation of venous pO_2. While an occasional hypodynamic patient had high levels of pulmonary veno-arterial admixture (possibly due to associated pulmonary consolidation or atelectasis), no hyperdynamic patient had pulmonary veno-arterial admixture less than 30% (normal 6%). This figure demonstrates that the percent of

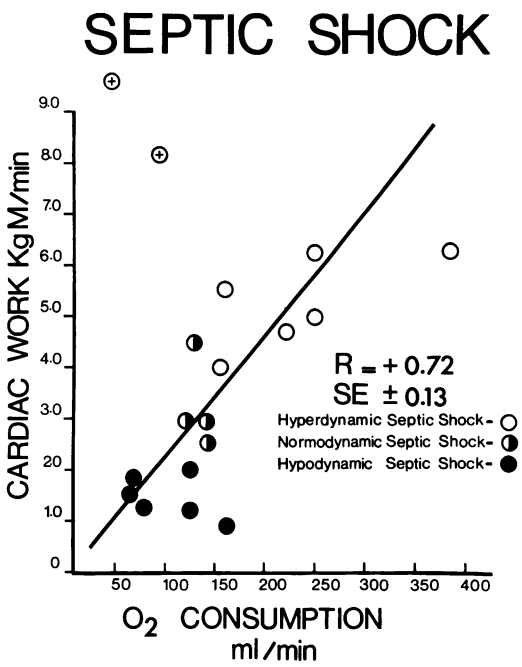

FIG. 6. Cardiac Work in Septic Shock evaluated as a function of the oxygen consumption per minute. Pearson's coefficient of correlation (R) calculated for all points except those marked with a cross. (See text for discussion.)

pulmonary veno-arterial admixture is correlated with the elevation in venous pO_2, suggesting that both pulmonary and systemic arteriovenous shunting are occurring together.

If the decreased vascular tone seen in septic shock does not represent true vasodilatation, but is rather a manifestation of parallel resistances of low value (arteriovenous shunts), then it may be that a significant degree of true precapillary arteriolar vasoconstriction exists. This is suggested by the data shown in Figure 6, in which oxygen consumption per minute is related to cardiac work per minute in patients in septic shock who were maintained on assisted respiration, so that the work of breathing was reduced. The observation that a direct relationship exists, between oxygen consumption and cardiac work in these patients suggests that arteriovenous shunting may impose such limits on peripheral oxygen consumption that a major fraction of measured oxygen consumption is a result of cardiac work. In this regard, it is of interest that the two hyperdynamic patients who failed to follow this general rule (circles with crosses) also had both the highest pulmonary veno-arterial admixture (76% and 55%, respectively) and the highest mixed venous pO_2 values (Fig. 5). The resultant arterial desaturation may have further limited their capacity for oxygen extraction.

The increase in oxygen consumption preceded by a sudden increase in acidosis and pCO_2 seen in some patients (Fig. 2) is suggestive of a rapid precapillary arteriolar vasodilatation with perfusion of previously inadequately oxygenated capillary beds in a patient in hyperdynamic septic shock. This observation supports the contention that there is a significant peripheral anaerobic metabolism with build-up of substrates which can be metabolized in the Krebs cycle once oxidative metabolism is possible. That perfusion in many peripheral beds is virtually absent would also explain the lack of an excessive rise in pCO_2, or of a major decrease in arterial pH which is frequently seen in the hyperdynamic patient when oxygen consumption is low.

Myocardial Function. The final aspect of the cardiovascular response to septic shock is shown in Figure 7 in which an attempt was made to examine ventricular function relationships occurring in patients in shock. In this figure, left ventricular stroke work is plotted against central venous pressure. Although this type of analysis assumes that there is no major disparity between the function of the two ventricles such that the central venous pressure does not reflect alterations in the left ventricular end diastolic pressure, this assmption seems to be reasonably valid if patients with pulmonary embolus shock are excluded. We did not find any instance in septic patients in which pulmonary edema

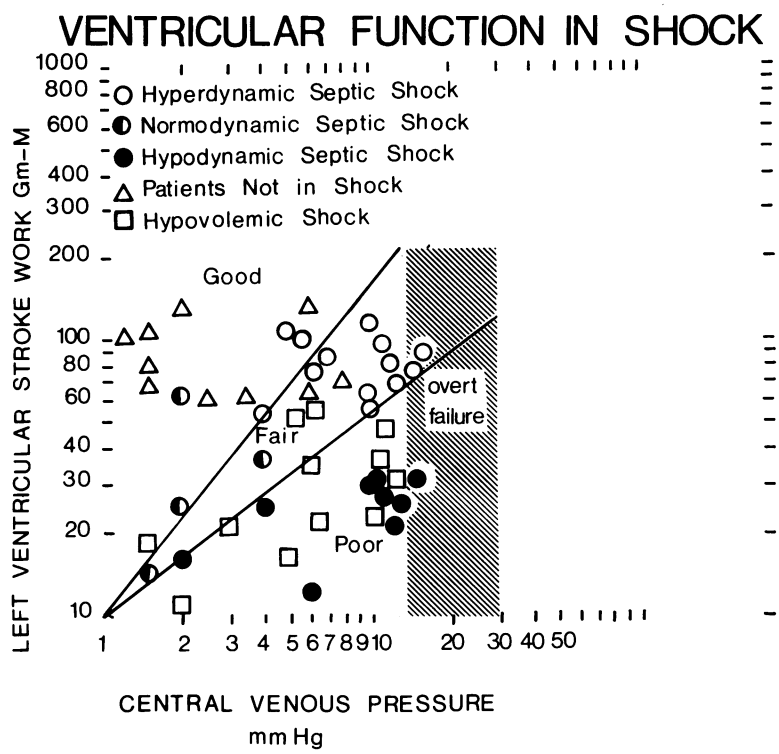

FIG. 7. Ventricular Function Relationships in Shock. Log-log plot of left ventricular stroke work in Gm. meters on the ordinate, versus central venous pressure in mm. Hg on the abscissa.

occurred without concomitant elevation in the central venous pressure. Further, in a series of experimental studies [17, 20] on myocardial effects of shock caused by purified endotoxin there was no evidence of a selective effect on one ventricle and not in the other.

Also the tendency of these patients to segregate into hyperdynamic and hypodynamic groups with regard to ventricular function suggests that this method of evaluation reflects a meaningful difference. As can be seen in Figure 7, normal patients appeared to have generally good ventricular function (VF) relationships, those patients with hyperdynamic septic shock appeared to fall in a fair VF range, and those with hypodynamic septic shock in a poor VF range. Only patients in normodynamic septic shock appeared to be distributed between the fair and good range rather evenly, and as noted previously, this group of patients appeared clinically to be in less severe septic shock. It was also found that many patients in hypovolemic shock appeared to have depressed ventricular function relationships. These data suggest that myocardial function is depressed in all patients in septic shock, but that the relative degree of depression is less in patients in hyperdynamic septic shock than in those with hypodynamic septic shock. That the depression in ventricular function curves in septic shock reflects a true depression in myocardial contractility is supported by observations in patients in whom Isometric Time-Tension relationships were measured in the right ventricle (Fig. 8). Right ventricular stroke work was correlated with right ventricular end diastolic pressure, and with the simultaneously determined changes in the time from the onset of contraction to maximum dp/dt. This index has been shown to be inversely proportionate to the myocardial contractility as quantified by the Isometric Time-Tension Index,

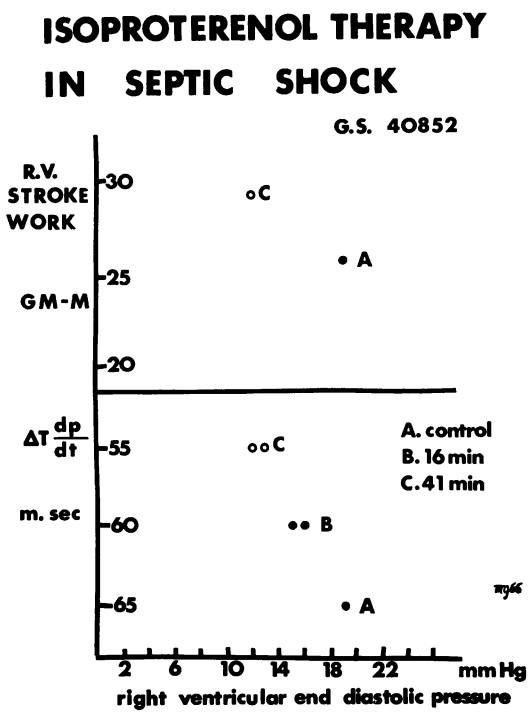

FIG. 8. Comparison of Ventricular Function Relationships and Isometric Time-Tension Relations in a patient in hyperdynamic septic shock. (Top) Right ventricular stroke work plotted as a function of right ventricular end-diastolic pressure in the patient before and after the administration of infusion of Isoproterenol (1γ/min. infusion). (Bottom) Isometric Time-Tension relations evaluated as a function of right ventricular end-diastolic pressure. Points are simultaneous with those used for calculation of right ventricular stroke work relations shown above.

in that the longer the interval Δt dp/dt the lower the contractility.[21, 22] In this patient in hyperdynamic septic shock, the right ventricular stroke work was approximately 26 gram meters and was performed at an end diastolic pressure of 19 mm. Hg. The Δt dp/dt determined at this time was 65 milliseconds which, in view of the patient's high heart rate of 110 per minute, represents a decreased myocardial contractility when compared to patients not in shock.[22] That a significant increase in contractility is possible over the baseline was demonstrated by the administration of Isoproterenol (1γ/min.), which has been shown to increase myocardial contractility in endotoxin shock.[20] Right ventricular stroke work increased slightly to 29 gram meters; however, this was performed at a right ventricular end diastolic pressure of 11 mg. Hg representing a significant shift to the left in the ventricular function curve. The infusion of Isoproterenol also resulted in a progressive decrease in the Δt dp/dt relationship to 60 milliseconds after 16 minutes of Isoproterenol infusion, and to 55 milliseconds after 41 minutes of Isoproterenol infusion, all without significant increase in heart rate. Nevertheless, despite an initial improvement in myocardial function produced by the use of an inotropic agent, this patient had a progressive increase in central venous pressure as her hyperdynamic

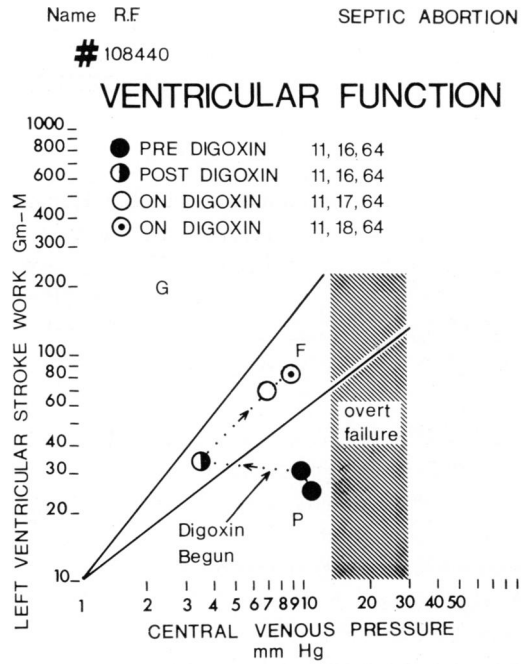

FIG. 9. Ventricular Function Relationship in shock following septic abortion. Response to Digoxin. Closed points represent hypodynamic state; half circles, normodynamic state; open circles, hyperdynamic state. In spite of the improvement both in clinical response and ventricular function relationship produced by Digoxin, the patient remained on a septic vascular tone curve until 11/18/64 (open point with black dot) when she returned to a normal vascular tone curve and was believed to be clinically not in shock. Legends as in Figure 7.

state persisted. At the time of her demise (Fig. 2) she was clearly in high output failure with a cardiac index of 3.8 liters/min./m.^{2} and a central venous pressure of 18 mm. Hg.

Improving the decreased myocardial contractility and combatting cardiac failure can play a significant role in reversing the pathophysiology of septic shock as is shown in Figure 9, in which the ventricular function relationships of a single patient were followed. This young woman was hypotensive secondary to a septic abortion and failed to respond to a variety of therapeutic measures including antibiotics, fluids, and steroids. Determination of her cardiovascular function showed a hypodynamic cardiac index and a decreased vascular tone. She continued to do poorly as evidenced by persistent hypotension and poor ventricular function relationships until digitalization was carried out. Within three hours, her ventricular function relation had improved and her cardiac index rose to the normodynamic level. Receiving Digoxin she remained on a better ventricular function curve and even became very mildly hyperdynamic by the following day. This improvement in ventricular function curve preceded by nearly 48 hours return of vascular tone relationship and blood pressure to normal levels. This demonstrates not only that the level of cardiac index can be a direct function of the myocardial contractility but also that some patients in septic shock may be greatly benefited by therapy directed specifically at the decrease in myocardial contractility.

Discussion

It has become painfully apparent to those attempting to quantify the physiologic derangements associated with hypotension that the clinical entity known as "shock" is in reality not one, but a multitude of pathophysiologic states. Physicians since Hunter and Koch have become used to thinking of illnesses in anatomic or etiologic terms. It is becoming clear, however, that some disease entities might be better described in terms of patterns by physiologic imbalances and the entity known as septic shock falls into this category. While it is clear from observations by a number of investigators [4, 19, 25, 26] that there is a valid basis for the separation of patients in septic shock into hyperdynamic and hypodynamic groups, it seems apparent from this study that the underlying defect in the hypotensive process associated with sepsis is an abnormality in vascular tonus. Vascular tone has been defined as a state of active contraction of the muscular walls of small blood vessels, and is generally considered to be subject to alteration by vasomotor nerves, hormonal substances and metabolic byproducts. When one thinks of net vascular tone, as being the summated state of the vascular tonus in all perfused vascular beds, one must also include anatomic precapillary arteriovenous anastomoses as small blood vessels. Although it is clear that there is no method for expressing change of vasomotor activity currently devised which rests on a completely logical basis, nevertheless, as Green and co-workers [8] have concluded, "The most satisfactory *practical* expression for change of vascular tonus due to vasomotor nerve activity, and for the appearance of constrictor or dilator substances in the blood stream, is the ratio of the peripheral resistance in the experimental period to the peripheral resistance measured in the control period *at the same rate of flow.*" The nature of this relationship has been demonstrated most closely to approximate a parabolic function and differing states of vascular tone ideally represent parabolic functions with different X-Y coordinates.[16] While it is virtually impossible to obtain a complete net vascular tone relationship in man, the data presented suggest that there is a general range of normal vascu-

lar tone relations, and that significant departures from this normal range occur in some pathophysiologic states. The most surprising information in this regard is the observation that all patients studied in septic shock lie in a general area of vascular tone relationships which is decreased compared to normal. This pattern is widely different from the vascular tonus of patients in hypovolemic or pulmonary embolus shock where the net vascular tone appears to be increased. This suggests that there may be a common physiologic denominator initiated by the septic process, and that the differences in cardiac output and peripheral resistance seen in individuals within the septic group may represent the degree of compensation which each individual is able to maintain in reacting to the basic vascular tone abnormality.

Perhaps the major physiologic abnormality separating patients within the septic shock group is the extent of the defect in oxygen transport. It is clear that there is a spectrum of oxygen extraction patterns with patients in the high output range at one end, and those in the low output range at the other. As the main function of the heart is to insure the delivery of oxygen to the peripheral tissues, it can reasonably be assumed that there is some advantage in having the ratio of oxygen extraction to body flow as high as possible. It is then apparent that in the hyperdynamic patient there is an enormous waste of energy on ineffective circulatory work as the Effective Oxygen Transport ratio is so low. Unfortunately, there are no data available from patients in septic shock on the relationship between oxygen utilized by the tissues and the metabolic requirements for oxygen of peripheral tissues. If there is an unrequited disparity between demand and supply this might explain the mechanism of progressive deterioration in these patients at a time when their cardiac output is higher than normal.

The mechanism of the defect in oxygen extraction is not entirely clear. However, that there appears to be a correlation between an abnormally low peripheral vascular resistance and defective or inefficient oxygen transport suggests that the mechanism may be precapillary arteriovenous shunting. That this does not represent cellular death or oxidative block is suggested by the observation that at times individuals with abnormally low oxygen consumption are capable of achieving major increases in oxygen extraction far in excess of normal which appear to represent the repayment of a peripheral oxygen "debt."

If precapillary arteriovenous shunting is the physiologic cause of vascular abnormalities seen in patients in septic shock, it would explain both the decreased Net Vascular Tone in these patients and also the fact that the degree of abnormality in Effective Oxygen Transport is a function of the level of the cardiac output. For if these arteriovenous shunts were unresponsive to ordinary regulators of arteriolar vasoconstriction, then the shunts would be expected to allow passage of arterial blood to the venous circulation merely as a function of the level of flow in the arteries, and this is what is observed. That arteriovenous shunting is a general vascular phenomenon is also suggested by the observation that patients with the most pronounced degree of mixed venous oxygen saturation are those who have the highest degree of pulmonary veno-arterial admixture because of arteriovenous shunting in the pulmonary vascular circulation as well.

A major degree of arteriovenous shunting and an absolute deficiency in ability to consume oxygen further suggests that true arteriolar vasoconstriction is occurring in these patients, and that this may be preventing adequate tissue perfusion. It is legitimate to speculate as to what pattern of vascular accommodation may be acting to account for these physiologic abnormali-

ties, and the key, perhaps, is in observations on myocardial function. In both hyperdynamic and hypodynamic patients in septic shock there appears to be some degree of depression in myocardial contractility, and this is compatible with the observation [20] that administration of purified endotoxin is associated with a specific depression in myocardial contractility. What is most striking, however, in regard to the abnormality in ventricular function in septic shock is not the general depression manifested by all patients, but the fact that almost without exception hyperdynamic patients lie on a better series of ventricular function curves than hypodynamic patients. This also correlates positively with a greater degree of abnormality in the Effective Oxygen Transport index and in the function which we arbitrarily call Relative Peripheral Shunting.

If the basic pathophysiologic defect in septic shock is the opening of many precapillary arteriovenous anastomoses with a circulatory impact comparable to the sudden opening of a large arteriovenous fistula, then the pattern of adaptation noted by Siegel [16] in response to the opening of an acute interventricular septal defect, and by Nakano and Fisher [13] in response to opening a large central arteriovenous fistula, explains the remaining abnormalities and the differences between hyperdynamic and hypodynamic patients. When a large arteriovenous fistula is opened there is a tendency for mean blood pressure to fall and this baroreceptor hypotension initiates a reflex increase in heart rate, an increase in true peripheral arteriolar vasoconstriction distal to the fistula (which in this instance would be hard to detect because the fistula instead of being in the central circulation is in the microcirculation), an increase in venous return, and a shift in the ventricular function relation to an improved Starling curve. This mechanism, as well as stimulation of chemoreceptors, has also been demonstrated to result in the release of significant quantities of catecholamines, from the adrenals [10] and from the myocardium.[7]

Similarly, the opening of a large central arteriovenous fistula results in an increase in pulmonary vascular resistance [16] despite the increase in pulmonary flow, and if precapillary arteriovenous shunts are also present in the lung in response to the septic process, one would expect that an increase in true peripheral pulmonary vascular resistance would result in a greater pulmonary arteriovenous shunt with resulting increase in veno-arterial admixture. If the defect in vascular tone caused by opening multiple precapillary arteriovenous fistulae is the primary lesion, then the pattern of oxygen transport in the hypodynamic patient could also be explained by inability to respond to the cardiac sympathetic barrage induced by septic hypotension. If the myocardium were so depressed by toxins released by the septic process that it was unable to respond to these compensatory stimuli, then the level of cardiac output which could be achieved would be decreased, the level of total flow would be decreased, and the passive arteriovenous shunting would be diminished both in the systemic circulation, and in the pulmonary circulation (except in the presence of massive atelectasis or pulmonary consolidation). This is what appears to happen in hypodynamic patients who have a poor ventricular function relationship. Similar severe myocardial depression which is largely unresponsive to sympathetic influences, occurring when there is other evidence of appreciable sympathetic efferent activity, has been noted in experimental animals after endotoxin administration.[20]

The entity of septic shock can therefore be considered the result not only of the primary insult, but also of the host's response. It is the physiologic analogue of inter-relationships between infection of the

host with mycobacterium tuberculosis and the degree of delayed hypersensitivity by the host in response to the tubercle baccilus which results in clinical differences between infantile and adult tuberculosis.

It is important to emphasize, however, that whether a patient falls into the hyperdynamic or hypodynamic category may be a function of time, and that there is a continuum between these two states, such that the patient with a normodynamic or a mildly hypodynamic septic course may become hyperdynamic as sepsis worsens. Conversely, hyperdynamic patients often become hypodynamic as progressive myocardial failure ensues, and hypodynamic patients in failure may be made normodynamic or mildly hyperdynamic by administration of an inotropic agent which decreases the degree of myocardial failure. While it is true in our experience that patients who could not maintain an adequate cardiac output in response to the septic process generally did poorly, it has not been necessarily true that patients who are hypodynamic have a poorer prognosis than those who are hyperdynamic. A more significant inverse correlation exists between the extent of the abnormalities of oxygen consumption and survival, than between the level of the cardiac output and a successful outcome. The poorest prognosis, in contrast to Clowes' observations [2] appears in those patients who have the highest cardiac output, the most extreme shift to the left in the index of Relative Peripheral Shunting, and the greatest degree of pulmonary veno-arterial admixture. Instances in which we intervened most successfully have been those in which there was a vascular tone defect, but the greatest degree of physiologic abnormality appeared to be myocardial failure, such as is seen in younger patients in shock from septic abortion. In these patients administration of a positive inotropic agent such as Digoxin has often initiated recovery.

Although the purpose of this paper is not to emphasize the therapeutic approach to septic shock, there are certain obvious correlations. It is clear that as nearly all patients with hypotensive processes initiated by sepsis have depressed myocardial function (and the patients with a high cardiac output are as susceptible to progressive cardiac failure as those with a low cardiac output), a cardiac inotropic agent is indicated more often than has been generally appreciated. The therapeutic advantages of a positive inotropic agent have also been demonstrated in experimental hypovolemia [23] and in endotoxin shock,[20] and appear to be confirmed clinically.[11, 12] We feel confident that a cardiac inotropic agent will significantly alleviate myocardial depression associated with septic shock. Our experience has not led us, however, to any revolutionary concept of how to treat the specific defect in vascular tone. One may buy time by therapeutic measures directed at improving myocardial contractility, but it remains mandatory to drain abscess cavities and otherwise to treat infection, as the abnormality in vascular tone responds only to adequate and complete resolution of the septic process.

Summary

Cardiovascular function and oxygen consumption were measured in 46 patients in shock from a variety of causes, and in 13 normal subjects. All hypotensive patients whose shock states were secondary to sepsis were shown to have abnormalities in vascular tone different from those whose shock was due to other causes. The patterns of oxygen extraction and myocardial function were demonstrated in septic shock and provided for separation of patients into hyperdynamic and hypodynamic groups. A hypothesis which may explain the abnormalities in septic shock is put forward, and a rationale for the use of cardiac inotropic agents is presented.

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