Part VIII: Shock

Chapter 58: Hypovolaemic Shock

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Shock is usually defined as a severe pathophysiological syndrome associated with inadequate or disordered tissue perfusion and abnormal cellular metabolism. The term actually encompasses a group of cardiovascular disorders with distinctive aetiologies and pathophysiological patterns. The most important subgroups are hypovolaemic, septic, anaphylactic and cardiogenic shock, but other types such as traumatic and toxic shock are also recognized.

Aetiology

Hypovolaemic shock is due to inadequate left ventricular preload, which usually requires a relative or absolute reduction in the circulating blood volume by 15-25%, leading to a major reduction in cardiac output. Haemorrhage is the commonest cause, but loss of plasma or protein-free extracellular fluid can also result in hypovolaemic shock. Commonly associated clinical conditions include trauma, burns, peritonitis, pancreatitis, severe vomiting, diarrhoea, fistulae and excessive diuresis.

Pathophysiology

Most of the cellular changes and compensatory mechanisms seen are common to all forms of shock. Ischaemia and impaired tissue perfusion lead to generalized cellular damage, although organs may vary considerably in their ability to withstand ischaemia. Anaerobic cellular metabolism leads to depletion of adenosine triphosphate and failure of the cell membrane sodium potassium pump, resulting in cell swelling due to sodium and water influx. Anaerobic metabolism also produces a progressively worsening metabolic (lactic) acidosis, and blood lactate levels may be used as a guide to the severity, prognosis and effectiveness of therapy in shock. Mitochondrial calcium loss further impairs the efficiency of oxidation and phosphorylation, and may interfere with other organ-specific functions such as myocardial contractility. Eventually, a large number of cytotoxic, vasodilator, vasoactive and other substances are released into the circulation, resulting in progressive vasodilation, myocardial depression, increased capillary permeability and, eventually, intravascular coagulation. These substances include histamine, kinins, lysosomal enzymes, various prostaglandings, serotonin and tumour necrosis factor (cachectin).

Compensatory mechanisms include autoregulation of tissue blood flow and increased sympathetic discharge. This results in arteriolar as well as venous vasoconstriction, and an increase in heart rate and myocardial contractility, thus tending to improve cardiac output, venous return, and blood pressure. Blood is diverted away from less important areas to vital organs, which initially include the brain, heart, kidneys, liver and respiratory muscles. Because of the alteration in Starling forces surrounding capillaries, interstitial fluid is mobilized into the vascular tree. However, as shock progresses, the vasoconstrictive effects of the sympathetic nervous system is overwhelmed by the accumulation of local tissue metabolites,

and capillary permeability increases, leading to extravasation of plasma into the interstitial space. These late changes compound the effects of intravascular hypovolaemia.

Clinical Features

Cardiovascular System

The terms "hypotension" and "shock" should not be regarded as interchangeable, as either can occur without the other being present. Classical features of hypovolaemic shock include, in addition to hypotension, tachycardia, pallor, sweating, cyanosis, hyperventilation, confusion and oliguria. As the blood pressure falls, the pulse pressure narrows and measurement by non-invasive methods mays become increasingly difficult and inaccurate.

Tachycardia usually precedes the development of hypotension, but may not be present if the patient has pre-existing heart disease or has been taking beta-adrenergic blocking drugs. Myocardial contractility may be impaired due to ischaemia, infarction, pre-existing heart disease, or possibly the presence of endotoxin or a myocardial depressant factor.

Respiratory System

Hyperventilation occurs early in shock due to peripheral chemoreceptor stimulation and later, metabolic acidosis. A reduced pulmonary blood flow results in an increased physiological dead space, which is however, more than compensated by the increase in respiratory rate and minute volume. PaO_2 is often well-maintained, but advanced shock may result in respiratory failure due to progressive atelectasis, the onset of the adult respiratory distress syndrome (ARDS), respiratory muscle fatigue due to inadequate respiratory muscle perfusion or more rarely, respiratory centre depression due to inadequate cerebral perfusion. Pre-existing lung disease, chest trauma and cardiac failure may all contribute.

Kidneys

In early shock, the glomerular filtration rate (GFR) is well preserved by autoregulation, but oliguria nevertheless occurs, due to antidiuretic hormone (ADH) and aldosterone secretion. As GFR falls, oliguria persists or worsens. These changes may be modified by renal trauma, pre-existing renal disease or infection, the presence of crush injuries, or the use of nephrotoxic drugs such as aminoglycosides. If shock is severe or prolonged, acute renal failure (ARF) may result. This is initiated by a temporary disorder of glomerular blood flow regulation, and mechanisms such as acute tubular necrosis (ATN) may be of less significance than was once believed.

Liver

Both hepatic arterial and portal venous blood flow are reduced in shock. The commonest clinical consequence is the development of a benign and reversible conjugated hyperbilirubinaemia following a shock episode. In addition, the liver's reticuloendothelial function is impaired following shock, though the clinical significance of this uncertain.

Gastrointestinal Tract

Shock produces profound mucosal vasoconstriction throughout the gastrointestinal tract. The most clinically important consequence of this is an increased susceptibility of the gastric mucosa to acid damage, and subclinical gastric bleeding is probably much more common than the well-recognized association of stress ulceration (gastric erosions) with shock would suggest.

Intermediary Metabolism

Hyperglycaemia is mainluy due to insulin resistance to which catecholamines, glucagon and glucocorticoid secretion all contribute. Catecholamines also inhibit insulin release. Catabolism of both fat and carbohydrate is inhibited in shock, and there is increasing reliance on skeletal muscle amino acids, especially branched chain amino acids, as a fuel source. Lactic acid production is increased due to both mitochondrial dysfunction and hypoxia.

Management

It is important to remember that shock is a dynamic disorder in which haemodynamic and metabolic variables are continually changing. An urgent and well organized approach is important, and frequent or even continuous reassessment will be required. As in other areas of Intensive Care, the diagnostic and therapeutic processes must proceed in parallel rathen than in series.

1. Ventilation and Oxygenation

As with other types of resuscitation, airway and breathing should receive the most immediate attention. It is well established that the combination of shock and respiratory failure has an extremely high mortality. Hence, all shocked patients should receive high flow supplemental oxygen by face-mask, and intubation and mechanical ventilation should be instituted early if there is evidence of respiratory inadequacy. The presence of pneumothorax should be specifically sought and treated in trauma cases.

2. Circulatory Resuscitation

The use of one or more large bore peripheral intravenous cannulae is usually more appropriate than the urgent placement of a central venous catheter, unless peripheral access is unavailable. Obvious external haemorrhage should be controlled by local pressure, but procedures such as urgent thoracotomy with aortic cross-clamping are probably of little value in the vast majority of cases. The use of a PASG suit (pneumatic anti-shock garment) remains controversial, but may help tamponade intra-abdominal bleeding in some circumstances. When the response to resuscitation suggests ongoing intra-abdominal or intra-thoracic bleeding, complex investigations should be kept to a minimum, and every effort should be made to organize definitive surgical management as soon as possible.

3. Choice of Intravenous Fluids

As a general rule, the fluid chosen should most closely match the fluid lost. There has been controversy over the relative merits of crystaloids and colloids as plasma expanders. Supporters of colloids contend that resuscitation with colloids is more rapid and with less adverse effects on the lungs. On the other hand, crystalloid users consider that crystalloids are more appropriate, as they equilibrate between intravascular and interstitial fluid space, overcoming the main problem in shock, i.e. shrinkage of the entire extracellular compartment. Crystalloids are also cheaper although 2-4 times the volume may be required to achieve a comparable degree of resuscitation. Colloids present a very small risk of allergic reactions. There is however, no clear evidence to favour either fluid type, especially as regards adverse influence on pulmonary function. A mixture of colloids (initially for rapid improvement) and crystalloids is commonly used in practice.

There is new interest in use of hypertonic saline solutions, i.e. 3% for plasma expansion and resuscitation. The mechanism of plasma volume expansion is thought to be due to an increased osmolality pulling intracellular fluid into the extracellular spaces. Smaller volumes are required to achieve the same physiological endpoints, and improvement may be more sustained if dextran is added. Hypertonic saline solutions may play an important role but further clinical studies are required.

Blood should be transfused where significant blood loss has occurred, with the aim of maximizing tissue oxygen delivery by maintaining a haematocrit of at least 0.3 (equivalent to a haemoglobin concentration of about 10 g/dL). The use of oxygen-carrying blood substitutes such as perfluorocarbons and stroma-free haemoglobin is not established.

4. Monitoring

Heart rate, blood pressure, respiratory rate, urine output, mental state and temperature should all be measured and recorded with a frequency appropriate to the clinical state of the patient. A central venous catheter may be useful to assess the right ventricular preload, particularly if trends rather than individual readings are observed. However, the central venous pressure (CVP) may be difficult to interpret in patients with lung disease or selective right or left ventricular dysfunction. In some of these cases, a pulmonary artery catheter may be helpful, but in uncomplicated hypovolaemia, this should only uncommonly be required. Neither the CVP nor the pulmonary capillary wedge pressure (PCWP) provide a meaningful measure of the circulating blood volume.

5. Acid-Base and Electrolyte Therapy

Hypokalaemia, hyponatraemia and metabolic acidosis are characteristic of most shock states, and should be managed in the usual ways. Hyponatraemia and acidosis will almost always respond to volume repletion using appropriate fluids. Bicarbonate administration carries a considerable concurrent sodium load, and may worsen intracellular acidosis, tissue oxygen delivery, and hypokalaemia. Hence, only severe and persistent acidosis should be treated in this way.

6. Inotropic Drugs

Failure of the patient to respond to fluid replacement should prompt a careful search for some other problem, i.e. tension pneumothorax, pericardial tamponade, or continuing bleeding. In a few cases, the use of an inotrope may be indicated, and the choice is best determined by haemodynamic measurements. However, differences among these agents are probably of minor clinical importance in this setting and adrenaline (1-10 microg/min), dopamine (1-20 microg/kg/min) and dobutamine (1-20 microg/kg/min) are all commonly used.

7. Diuretics

Frusemide (10-40 mg) or mannitol (10-20 g) are often given when oliguria persists despite apparently adequate fluid resuscitation. However, there is no clear evidence that this improves renal perfusion or can prevent or ameliorate the development of acute renal failure, and care must be taken to ensure that a brisk diuresis does not worsen hypovolaemia or hypokalaemia. There is some evidence to suggest that infusion of dopamine at low dosage (2-5 microg/kg/min) may be helpful.

8. Other Treatment

The use of corticosteroids in shock has been studied extensively for about 30 years with no firm conclusion. This in itself suggests they are unlikely to be of major benefit, despite theoretical and laboratory-based support for their use. They are almost certainly contraindicated if concurrent sepsis is present.

Naloxone has been used in shock, and anecdotal reports suggest it may temporarily reverse hypotension, possibly by antagonizing central delta receptors. Currently there is no good evidence that outcome from shock can be significantly improved by the use of naloxone.

A number of other agents have potential value in the therapy of shock. These include glucagon, fructose diphosphate, amrinone, thyrotropin-releasing hormone (TRH), tri-iodothyronine (T3), prostaglandin E1 and prostacyclin. All require considerably more study before they can be recommended for clinical use.

Chapter 59: Cardiogenic Shock

G. Dobb

Although myocardial function may be impaired in any shocked patient, the term "cardiogenic shock" is reserved for patients with shock caused by heart disease. It is a clinical syndrome which is defined as:

1. A systolic arterial pressure less than 90 mmHg (12 kPa);

2. Evidence of reduced blood flow as shown by:
(a) Urine output less than 20 mL/h;
(b) Impaired mental function; and
(c) Peripheral vasoconstriction with a cold, clammy skin.

Hypotension resulting from pain, vasovagal reaction, serious arrhythmias, drug reaction or hypovolaemia is excluded. In patients with known hypertension, a reduction in the blood pressure of 30 mmHg (4 kPa) is used to define hypotension. Occasionally, urine output or cerebral function is preserved in cardiogenic shock.

Other changes seen in cardiogenic shock include reduced coronary blood flow, myocardial lactate production, abnormally high myocardial oxygen extraction, and an intense neurohumoral stress response. There are big increases in plasma concentrations of adrenaline and noradrenaline, glucose, free fatty acids, cortisol, renin, angiotensin II and glucagon, and decreased concentrations of insulin.

Aetiology (Table 1)

The most common cause of cardiogenic shock is myocardial infarction (MI). It affects up to 15% of those admitted to hospital with an acute infarct and is the commonest cause of hospital death. Factors associated with an increased risk of cardiogenic shock are age, diabetes, previous MI and anterior (rather than inferior) infarction. Myocardial dysfunction after cardiac surgery is considered in Chapter 15, Postoperative Intensive Care. Patients with severe cardiomyopathy suitable for heart transplant may need admission to an ICU for assessment and support while awaiting a donor heart.

Table 1. Causes of Cardiogenic Shock

Myocardial infarction
Myocardial dysfunction after cardiac surgery
Myocardial contusion by direct chest trauma
Reduced systemic flow from left ventricular contraction
- rupture of the interventricular septum
- acute mitral regurgitation
- acute aortic regurgitation
- left ventricular aneurysm

Obstruction to flow
- myxoma
- hypertrophic obstructive cardiomyopathy

Cardiomyopathy
Myocarditis
Heart transplant rejection

Pathophysiology

Autopsy studies show that over 40% of functioning myocardium has been lost in patients who die of cardiogenic shock after MI. The effects of recent and old infarction are additive. Extension of the area of infarction during a single hospital admission is common in patients who develop cardiogenic shock. This may represent loss of viability of an ischaemic zone surrounding the initial infarct. The neurohumoral changes seen in cardiogenic shock, and to a lesser extent after aby infarct, cause an increase in heart rate, contractility and blood pressure.

The clinical findings of cardiogenic shock occur when the cardiac index is less than 1.8 L/min/m^2. Heart rate and systemic vascular resistance (SVR) increase to try and maintain arterial pressure. The neurohumoral responses and these reflex changes increase myocardial oxygen demand at a time when myocardial perfusion is reduced by hypotension. The result is to further jeopardize ishaemic but potentially viable tissue and further impair left ventricular function, completing a vicious circle which ends with the patient's death.

In cardiogenic shock caused by septal perforation, ventricular aneurysm, or acute valvular regurgitation, there is a reduction of flow through the systemic circulation because a proportion of the blood ejected from the left ventricle is directed into the right ventricle, the aneurysm, the left atrium or back into the left ventricle.

Clinical Presentation

The clinical features are in keeping with the definition of cardiogenic shock above. Arrhythmias and the extremes of heart rate, cardiac tamponade, pulmonary embolism and other causes of shock must be excluded. Most patients with cardiogenic shock also have pulmonary oedema with raised left ventricular end diastolic pressure (LVEDP) and pulmonary capillary wedge pressure (PCWP). Pulmonary oedema may cause severe dyspnoea, central cyanosis and crepitations. The diagnosis of pulmonary oedema can be confirmed by an erect chest X-ray.

Less often, cardiogenic shock occurs without the PCWP being elevated. This group includes:

1. Patients with clinical and radiological evidence of pulmonary oedema, but normal or low PCWP. This can be a result of diuretic therapy or plasma volume depletion by the fluid lost into the lungs.

2. Patients with relative hypovolaemia, i.e. below the risk level of pulmonary oedema (18-20 mmHg, 2.4-2.7 kPa).

3. Patients with significant right ventricular infarction. Hypotension in patients with inferior infarction and the clinical signs of right heart failure should alert to this possibility, although the signs are more specific than sensitive. Right ventricular infarction can also mimic pericardial tamponade or pericardial constriction.

Patients presenting with these three syndromes are a minority of those with cardiogenic shock, but it is important to identify them. They may improve dramatically with plasma volume expansion and deteriorate if diuretics are given inappropriately.

A systolic murmur appearing after MI suggests mitral regurgitation or septal perforation. Clinical distinction between the two is difficult. Patients with infarction who respond to volume expansion or who have a mechanical lesion amenable to surgery, have potentially reversible cardiogenic shock. When shock is due solely to extensive left ventricular infarction it is usually irreversible. If cardiogenic shock fails to respond to treatment, multiple organ failure, metabolic acidosis, hypothermia and coma may precede death.

Management

The treatment of cardiogenic shock is difficult and the results often disappointing. Efforts have therefore been made to reduce the incidence of cardiogenic shock by techniques that will preserve myocardium during cardiopulmonary bypass and limit the amount damaged by MI. Studies in acute MI suggest improvement in global left ventricular function in patients treated with angioplasty and decreased mortality in patients given 1.5 MU of IV streptokinase. However, a consensus on the best management plan and the timing of its components has still to be reached. What is clear, is that for patients to benefit from active management of acute coronary occlusion, treatment must occur within the first few hours from the onset of symptoms.

If cardiogenic shock becomes established, management consists of general supportive measures, characterization of haemodynamic problems, mesures to optimize the myocardial oxygen supply:demand ratio and improve the haemodynamic disturbance, and specific treatment when possible.

1. General Supportive Measures

These include relief of pain, correction of severe acid base or electrolyte disturbances, and treatment of cardiac arrhythmias. Patients with bradyarrhythmias causes by atrioventricular block or junctional bradycardia may respond dramatically to sequential atrioventricular or atrial pacing. Oxygen is given to correct hypoxaemia. If hypoxaemia persists in patients with potentially reversible shock, continuous positive airway pressure (CPAP) or tracheal intubation and mechanical ventilation with positive end expiratory pressure (PEEP) may be used. The copious frothy sputum of severe pulmonary oedema is controlled by increasing PEEP rather than repeated endotracheal suction. Patients with cardiogenic shock may, however, become profoundly hypotensive when given sedation for intubation, and this can be exacerbated by the effects of positive pressure ventilation on the circulation.

2. Monitoring

The principle and methods for monitoring any critically ill patients apply to cardiogenic shock. These should include:

(a) Measurement of intra-arterial blood pressure.

(b) Assessment of venous pressures: direct measurement of central venous pressure is more accurate than clinical assessment of the jugular venous pressure, but only reflects the right ventricular filling pressure. Pulmonary oedema may be diagnosed by hearing wide spread crepitations and confirmed by the chest radiograph, but the most accurate assessment of left ventricular filling pressure is gained by measuring the PCWP.

(c) Assessment of cardiac output: while skin perfusion, hourly urine output and mental state provide clinical guides to cardiac output, changes in cardiac output with time or treatment are best measured directly bu the haemodilution method.

(d) Other investigations:

(i) Electrocardiogram and cardiac enzymes to confirm a diagnosis of MI.

(ii) Blood gases, pH, and plasma lactate.

(iii) Haemoglobin, electrolytes, urea, and creatinine.

Insertion of a pulmonary artery balloon flotation (Swan-Ganz) catheter helps to characterize the haemodynamic problems. When cardiogenic shock is caused by septal perforation, blood sampling during insertion of the catheter will show an increase in oxygen saturation between the right atrium and the right ventricle. Patients with severe mitral regurgitation usually have a large V-wave on the wedge pressure trace, but this is nonspecific; large V-waves are also seen in the absence of mitral regurgitation.

Echocardiography provides information about lesions of the valves, septum and overall ventricular function, and also helps to exclude rarer causes of shock such as an obstructing atrial myxoma.

3. Improvement of Haemodynamic Disturbance

The same principles can be applied in cardiogenic shock from all causes. The overall prognosis should be carefully considered before starting invasive monitoring and aggressive support, especially in patients with large myocardial infarcts without a correctable lesion and patients with severe cardiomyopathy.

PAWP < 18 mmH (2.4 kPa)

Plasma volume expansion is the initial treatment. Although a left ventricular filling pressure of 18 mmHg (2.4 kPa) is greater than normal, this is usually the optimum for ventricular performance in patients with recent myocardial infarcts and anything less is consistent with hypovolaemia. Blood should be used to correct anaemia, otherwise repeated fluid challenges with 100-200 mL of colloid should be used.

In patients with predominant right ventricular infarction, fluid loading may produce a CVP of 30 mmHg (4 kPa) or more. Conversely, drugs conventionally used in the treatment of acute MI which reduce preload, exacerbate hypoperfusion in these patients.

PAWP > 18 mmHg (2.4 kPa)

This group contains most patients with cardiogenic shock, including those who initially have low PCWPs and are still hypotensive after fluid loading. The treatments available include drugs and mechanical circulatory assistance.

(a) *Drug Therapy*

(i) *Catecholamines,* including adrenaline, noradrenaline, isoprenaline, dopamine and dobutamine. The aim of these drugs is to increase arterial pressure and improve coronary

perfusion. They do this by varying degrees of increased cardiac contractility and rate (beta-adrenergic stimulation) and peripheral vasoconstriction (alpha-adrenergic effect). The increased arterial pressure is, however, at the expense of increased myocardial oxygen consumption which may endanger additional areas of myocardium. Other side effects include potentiation of arrhythmias by beta stimulation and a reduction in renal blood flow by alpha-mediated vasoconstriction.

Dopamine may have advantages over other catecholamines. At low infusion rates of 0.5-5 microg/kg/min the main effect is renal and mesenteric vasodilation mediated by dopaminergic receptors. Infusion rates of 5-20 microg/kg/min cause increased beta-adrenergic stimulation, and above 20 microg/kg/min alpha-adrenergic stimulation and vasoconstriction become increasingly prominent.

Dobutamine acts mainly on beta-1-adrenergic receptors. In the majority of patients, it has little effect on SVR or heart rate in lower doses. Reduction of venous pressures and SVR may, however, cause hypotension and tachycardia in some patients with shock. The range of infusion rates is 2-40 microg/kg/min. Comparisons in patients with a low cardiac output between dopamine and dobutamine have shown greater haemodynamic benefit from dobutamine, but there is considerable variation between patients. When low cardiac output complicates recovery from cardiac surgery, there can be considerable changes in the response to an inotropic drug with time.

(ii) *Digoxin* has been used to improve myocardial contractility but its relatively slow onset of action, long half-life and low therapeutic ratio make it less suitable as an inotropic in cardiogenic shock.

(iii) *Vasodilators* used in cardiogenic shock include sodium nitroprusside, nitroglycerin, isosorbide dinitrate, salbutamol and angiotensin converting enzyme (ACE) inhibitors. The potential benefits are: a reduction in myocardial work and oxygen demand; pooling of blood on the venous side of the circulation with a reduction in atrial pressures to promote clearing of pulmonary oedema; and possibly a redistribution of blood flow within organs and tissues to improve the supply of oxygen and metabolites at cellular level. The greatest danger is a precipitous fall in arterial pressure which reduces coronary perfusion. Invasive haemodynamic monitoring is therefore essential. Vasodilators also tend to increase hypoxaemia by increasing intrapulmonary shunting.

Sodium nitroprusside infusion consistently increases cardiac output in patients with left ventricular failure and shock after MI. An initial dose of 10 microg/min should be increased slowly to a maximum of 500 microg/min above which cyanide toxicity becomes a hazard of prolonged infusion. Patients with cardiogenic shock are usually quite sensitive to its effect.

Nitroglycerine is predominantly a venodilator when given by intravenous infusion. The rapid onset of action is useful in the management of pulmonary oedema. The acute haemodynamic effects of intravenous isosorbide dinitrate in MI are very similar.

Salbutamol is a relatively specific beta-2-adrenergic receptor agonist. Its main effect is arteriolar dilation. In patients with cardiogenic shock after infarction, infusions of 10-40 microg/min increased cardiac output without affecting PCWP.

Impressive results were reported in a small group of patients with cardiogenic shock given the ACE inhibitor captopril. More often, these drugs are used to treat residual cardiac failure in patients being weaned off intravenous drugs.

(iv) *Other drugs:* steroids, glucagon and glucose-insulin-potassium infusions have been used in patients with cardiogenic shock. They are generally considered ineffective. The role of newer vasoactive drugs such as amrinone, enoximone and dopexamine in cardiogenic shock has still to be defined.

A combination of catecholaminae and vasodilator is often found to produce the best haemodynamic response.

(b) *Mechanical Circulatory Assistance*

This should be considered for patients who remain hypotensive and shocked after a short trial of aggressive medical treatment. Factors favouring its use are a potentially reversible cause of cardiogenic shock and shock after cardiac surgery or chest trauma. Intra-aortic counterpulsation with a balloon pump (IABP) is the method of choice. The IABP is contra-indicated in patients with aortic regurgitation. Percutaneous insertion of the IABP has generally superseded surgical arteriotomy. Using the Seldinger technique to place the introducer in the femoral artery and inserting the balloon over a flexible tip J-wire guide under fluoroscopy, an IABP can be inserted quickly and comparatively atraumatically in nearly all patients.

Potential hazards include limb ischaemia from occlusion of the femoral artery by the balloon catheter or thrombus, aortic dissection, infection and embolization. The IABP is synchronized with the patient's ECG. Inflation and deflation are adjusted by inspection of the ECG and arterial pressure wave form. The balloon is inflated during early diastole (on the dicrotic notch of the arterial wave form), so increasing diastolic pressure and coronary perfusion. The balloon is deflated immediately before ventricular systole, decreasing aortic pressure and so reducing ventricular afterload. The net effect is to increase cardiac output and coronary perfusion, while decreasing myocardial work and oxygen demand.

Patients with cardiogenic shock after surgery or trauma frequently improve with time and can be weaned off IABP. In those with cardiogenic shock after MI, the IABP is usually a prelude to coronary angiography and ventriculography to demonstrate lesions correctable by surgery. The IABP is also used in patients suitable for cardiac transplant.

Various types of mechanical ventricular assist devices (VAD) have been used in patients with cardiogenic shock which is unresponsive to drugs and IABP. Most of the patients treated with VAD have had recent cardiac surgery but other indications have included shock after MI, myocarditis and support while awaiting cardiac transplantation.

4. Specific Treatment

In some centres, surgical revascularization has been used in patients with MI and cardiogenic shock. The results have been variable and uncontrolled reports make it difficult to assess the effect of patient selection on the results obtained. Systemic blood flow can be improved in patients with acute valvular regurgitation or a ventricular septal defect by afterload reduction with vasodilators and the IABP. Definitive treatment, however, is surgical repair. Early surgery improves the overal outcome. The definitive treatment of an obstructing atrial myxoma is also surgical.

Hypoperfusion in patients with hypertrophic obstructive cardiomyopathy will usually be exacerbated by the measures used to treat other forms of cardiogenic shock, i.e. inotropic drugs and afterload reduction. Plasma volume expansion and intravenous titration of beta-adrenergic blocking drugs reduce ventricular outflow obstruction and improve cardiac output.

Cardiogenic shock caused by poor compliance with immunosuppressive treatment in patients with a cardiac transplant can respond rapidly to high dose intravenous steroids.

Prognosis

The prognosis of cardiogenic shock associated with myocardial infarction is poor. In the absence of a surgically correctable lesion, only about one-third of the patients treated actively survive the initial episode, and many of the survivors have continuing angina, congestive heart failure and decreased exercise tolerance. Approximately half of the patients with a surgically correctable lesion should survive to leave hospital. Some of the best results, but from an uncontrolled study, of surgical revascularization in patients with cardiogenic shock but no other surgically correctable lesion, show a 70% thirty day survival and 48% survival at 2 years.

The mortality in patients who need maximal therapy and the IABP to separate from cardiopulmonary bypass, is about 50%. Survival in patients who have required VAD in addition to inotropic drugs and the IABP has been 35-45%. The functional prognosis for these survivors seems relatively good.

Patients remaining dependent on inotropic drugs or mechanical assistance may be considered for heart transplantation. Criteria for this vary between centres, but patients with dilated cardiomyopathy are particularly suitable candidates because they are usually young adults who are otherwise healthy and over 50% die within 2 years of diagnosis. It has been stated that contra-indications to heart transplantation are age over 55 years, widespread vascular disease, high pulmonary vascular resistance, diabetes mellitus, recent pulmonary infarction, active infection and neoplastic disease. The prognosis after cardiac transplantation is relatively good with 70-80% surviving 2-4 years.

Chapter 60: Anaphylaxis

M. M. Fisher

Anaphylaxis is the symptom complex accompanying the acute reaction to a foreign substance to which a patient has been previously sensitized (immediate hypersensitivity or Type 1 hypersensitivity). The term anaphylactoid reaction is used to describe reactions clinically indiscernible from anaphylaxis, in which the mechanism is non-immunological or has not been determined. Both conditions can be incorporated under the title "clinical anaphylaxis". The symptom complex may be produced by direct drug effects, physical factors, or exercise, and a causative agent cannot always be determined.

Aetiology and Pathophysiology

Clinical anaphylaxis commonly follows injection of drugs, blood products, plasma substitutes or contrast media; ingestion of foods or food additives; or insect stings.

In anaphylaxis, sensitization occurs following exposure to an allergenic substance, which either alone, or by combination with a hapten, stimulates the synthesis of immunoglobulin E (IgE) which binds to the surface of mast cells and basophils. Later, re-exposure to antigen produces an antigen-cell surface IgE antibody interaction, resulting in mast cell degranulation and the release of histamine and other mediators such as slow-reacting substance of anaphylaxis (SRS-A), eosinophil chemotactic factor (ECF-A) and platelet activating factor (PAF). The overall effects of the mediators are to produce vasodilation, smooth muscle contraction, increased glandular secretion and increased capillary permeability.

In an anaphylactoid reaction, the clinical picture is identical to anaphylaxis, but the mechanism of its initiation is uncertain. Intravenous hypnotic drugs and X-ray contrast media may activate complement C3. Plasma protein and human serum albumin reactions are thought to be induced by either albumin aggregates or stabilizing agent-modified albumin molecules. Other reactions, including those to dextrans and gelatin preparations, may be activated by antibody already present in the plasma.

The direct histamine releasing effects of some drugs may produce reactions due to the effect of histamine alone, and such reactions are related to volume, rate and amount of infusion. Anaphylactic reactions are largely seen in fit patients. It is likely that the adrenal response to stress "pretreats" sick patients and blocks the release and effects of anaphylactic mediators. The exception to this appears to be patients with asthma in whom reacions to additives in steroids and aminophylline may occur, and this may be related to the reduced catecholamine response reported in asthma.

Pathophysiology of Cardiovascular Changes

The traditional concept of the cardiovascular changes in anaphylaxis is that there is an initial vasodilation, followed by capillary leak of plasma which produces endogenous hypovolaemia, reduced venous return and lowered cardiac output. Whether or not cardiac function is impaired has been a controversial issue. Although most anaphylactic mediators adversely affect myocardial function in vitro, most case reports of analphylaxis in which

invasive cardiovascular monitoring was used, suggest a minimal impairment of cardiac function. Patients with premorbid normal cardiac function rarely showed evidence of cardiac failure or arrhythmias other than supraventricular tachycardia, but evidence of these cardiac complications increased in patients with pre-existing cardiac disease. Recently, prolonged global myocardial dysfunction was described in patients with no evidence of cardiac disease, and the use of a balloon counterpulsator was lifesaving.

Clinical Presentation

The latent period between exposure and development of symptoms is variable, but usually occurs within 30 min if the provoking agent is given parenterally. Reactions may be transient or protracted, lasting days, and may vary in severity from mild to fatal. Cutaneous, cardiovascular, respiratory or gastrointestinal manifestations may occur singly or in combination.

Cutaneous features include erythematous blush, generalized urticaria, angio-oedema, conjunctival injection, pallor and cyanosis.

Cardiovascular system involvement is evidenced by tachycardia, hypotension and the development of shock. It is the most common feature and may occur as a sole clinical manifestation.

Respiratory manifestations include rhinitis, bronchospasm and laryngeal obstruction.

Gastrointestinal symptoms of nausea, vomiting, abdominal cramps and diarrhoea may be present.

Other features include apprehension, metallic taste, choking sensation, coughing, paraesthesiae, arthralgia, convulsions, clotting abnormalities and loss of consciousness. In addition, pulmonary oedema is a common post-mortem finding, and rarely, a massive high protein pulmonary oedema may occur.

Management

1. *Oxygen* is given by facemask. Endotracheal intubation may be required to facilitate ventilation, especially if angio-oedema or laryngeal oedema is present. Mechanical ventilation may be indicated for bronchospasm, apnoea or cardiac arrest.

2. *Adrenaline* is the drug of choice for severe reactions. A dose of 0.3-1.0 mg is given intramuscularly (IM) and 0.5 mg is often sufficient. If muscle blood flow is thought to be compromised by shock, or as a chosen alternative, an intravenous infusion of 1-2 mg in 100 mL saline is started with electrocardiographic (ECG) monitoring. Adrenaline should be used with caution in patients who have received volatile anaesthetics and, in such patients, a trial of metaraminol may avoid ventricular arrhythmias. Adrenaline, by increasing intracellular levels of cyclic adenosine monophosphate (C-AMP) in leucocytes and mast cells, inhibits further release of histamine and SRS-A. It has beneficial effects on myocardial contractility, peripheral vascular tone and bronchial smooth muscle.

3. *Cardiopulmonary resuscitation* should be instituted irrespective of rhythm, if the patient is pulseless. A common error in management is not to institute external cardiac massage (ECM) as the arrhythmia is benign.

4. *Plasma or plasma expanders* are given rapidly to correct the hypovolaemia consequent to acute vasodilatation and leakage of fluid from the intravascular space. Plasma protein solution, dextran 70, and gelatin preparations are favoured above crystalloids as they remain longer within the vascular compartment. Very large volumes of fluid may be required and central venous pressure (CVP) monitoring and measurement of haematocrit are helpful.

5. *Aminophylline* 5.6 mg/kg IV is given slowly over 30 min if bronchospasm is unresponsivew to adrenaline alone. Aminophylline increases intracellular C-AMP by phosphodiesterase inhibition, and its effect on inhibiting histamine and SRS-A release is theoretically additive to that of adrenaline. In patients with refractory hypotension despite adequate volume, noradrenaline may be lifesaving. If refractory bronchospasm occurs other bronchodilators are therapeutic agents and procedures should be tried.

6. *Steroids* have no proven benefit and should be reserved for refractory bronchospasm.

7. *Antihistamines* are only indicated in protracted cases or those with angio-oedema.

Ideally, patients are managed in an Intensive Care Unit. Continuous ECg monitoring enables detection of arrhythmial secondary to hypoxia, hypotension, or exogenous adrenaline. Close monitoring of arterial blood pressure, CVP, and arterial blood gases are mandatory during the acute phase. Blood for measurement of complement levels may be helpful in determining the nature of the reaction.

Follow Up

Following successful management of the anaphylactic reaction, the drug or agent responsible should be determined by in vitro or in vivo testing if possible. Hyposensitization should be considered for food, pollen and bee sting allergies. A "medic allert" bracelet should be worn and the patient given a note stating the nature of the reaction to the particular causative agent.

If re-exposure to the allergen is likely at home, patients or their relatives should be instructed in the use of adrenaline, salbutamol inhalation and antihistamines. Clinical anaphylaxis may be modified by pretreatment with disodium cromoglycate, corticosteroids, antihistamines, salbutamol and isprenaline.

Chapter 61: Septic Shock

G. M. Clarke

This chapter and Chapter 63, Severe Sepsis, are related and should be read in sequence. Septic shock is a clinical syndrome characterized by a diversity of haemodynamic and metabolic abnormalities. The syndrome is associated with the presence in the blood of

micro-organisms, their toxic products or both. Nevertheless, it is common to diagnose septic shock in patients with negative blood cultures, i.e. the toxic shock syndrome, which is associated with isolation of *Staphylococcus aureus*, usually from the vagina.

While clinical features of septic shock may differ markedly from the classical hypovolaemic and cardiogenic varieties, one common feature is inadequate oxygen delivery to the tissues. In septic shock, total body O_2 delivery (DO_2) may be above normal, but any increase in O_2 demand by the tissues may not be met by the usual homeostatic mechanisms for O_2 delivery.

Microbiology

Gram-negative bacteria are the commonest causes of septic shock in the ICU. However, Gram-positive organisms, anaerobes and fungi (especially *Candida*) may also be responsible.

Pathogenesis

The clinical and physiological response to sepsis appears to be determined by the host, and is not peculiar to specific pathogenic micro-organisms. Patients with septicaemia caused by Gram-positive organisms, Gram-negative organisms, anaerobes and fungi, have shown similar fever, leucocyte, acid-base, and haemodynamic responses.

It seems that the host responds to the toxic products of these microorganisms (endo or exotoxins) by the release of mediators which produce the clinical syndrome. Currently, the monocyte macrophage system is under investigation as it appears to be the most important source of such mediators. Interleukin I and cachectin are just two such products of macrophage monocyte systems cited as playing central roles in this response. Indeed, synergism may exist between two cytokines. The response in humans to injected endotoxin is associated with a brief pulse of circulating cachectin (tumour necrosis factor) and the resultant responses are effected through the cyclooxygenase pathway. Tumour necrosis factor was detected in 10 of 11 patients who died with meningococcal infection but in only 8 of 68 who survived. Patients with the highest levels of tumour necrosis factor all died.

The septic patient usually exhibits a hyperdynamic response, when seen early. A hypodynamic response is usually due to pre-existing hypovolaemia, cardiac disease, or advanced septic response.

Vascular Effects

1. Peripheral Systemic Vascular Resistance (SVR)

Lowered SVR is a usual finding in septic shock and is independent of the type of invading organism. It is the dominant abnormality in patients dying of this condition. There is data to suggest that peripheral vascular failure, rather than cardiac failure, led to death in many patients with septic shock. Among postulated mechanisms of this response is incomplete catabolism of aromatic amino acids, leading to the production of vasoactive substances. Other

mediator theories implicate histamine, beta endorphins, decreased C3 component of complement, C3 proactivator, and decreased prekallikrein.

2. Venous Capacitance

An increase in venous capacitance in severe sepsis from a relative hypovolaemia, will cause a fall in preload, and may adversely affect cardiac output.

3. Pulmonary Vascular Resistance (PVR)

This may be abnormal in septic shock. If PVR is not elevated initially, it frequently rises at a later stage. In one series 32% of patients were found initially to have pulmonary hypertension, increased PVR, and a pullmonary artery diastolic to pulmonary capillary wedge pressure (PCWP) gradient of greater than 5 mmHg (0.67 kPa). These findings were associated with an 83% mortality within 48 hours. Again, the mechanisms of an increased PVR are ill understood. Hypoxaemia and metabolic acidosis are well known causes. However, in septic patients, pulmonary hypertension may still be seen without the presence of hypoxaemia or acidosis. Other postulated mechanisms include micro-thrombi, vasoactive amine, endotoxin and angiotensin.

4. Capillary Permeability

In sepsis, capillary permeability may increase rapidly so that fluid is lost from circulation. The clearance of radio-iodinated serum albumin may increase from a normal of 5-10%/h to 20-35%/h in severe sepsis. Cachectin (a cytokine which can lead to fibronectin depletion and decreased cell to cell adherence) may be one of the factors mediating such a capillary leak. Activated leukocytes which release toxic factors such as superoxides, protease and leukotrienes may also increase capillary permeability.

5. Myocardial Effect

Myocardial dysfunction is a common finding in patients with severe clinical sepsis. In most instances, mortality was highest in patients with such dysfunction. Two distinct ventricular abnormalities have been demonstrated in patients with severe sepsis. In response to a volume load sufficient to significantly elevate PCWP, some develop ventricular dilation, while others do not. The former demonstrate an abnormality of ventricular contraction and the latter an abnormality of venticular compliance. Radionuclide scans detected a large sub-group of septic shock patients who developed substantial falls in acute phase ejection fraction, associated with ventricular dilation and normal or high cardiac output. Most non-survivors in this study had normal ejection fractions but died of refractory hypotension due to low SVR.

It is important to remember that the myocardial dysfunction of sepsis is biventricular. Right ventricular (RV) afterload may increase as a consequence of elevated PVR. Increasing RV preload may maintain flow from right to left ventricle for mean pulmonary artery pressures up to 40 mmHg (5.3 kPa). Beyond this pressure, the increase in RV preload is insufficient to overcome the sequelae of depressed RV contractility, so that cardiac output and oxygen delivery will fall.

Possible causes of myocardial dysfunction in septic shock include a myocardial depressant factor (MDF) and diminished coronary blood flow. Systemic acidosis and hypoxaemia, if present, have added deleterious effects. Myocardial oedema will worsen cardiac compliance. There are circulating humoral factors in the plasma of septic patients which can depress myocardial function in vitro, but the concentration and ability to do so in vivo has yet to be elucidated. Abnormal calcium flux within myocardial cells and diminished alpha and beta adrenergic receptor response are also thought to be important.

6. Oxygen Transport and Consumption

Oxygen consumtion (VO_2) is frequently normal or decreased relative to metabolic demands and this situation occurs at or even prior to the initial hypotensive crisis. Other common findings in the hyperdynamic patient include "pathologically" increased mixed venous oxygen saturation and decreased arteriovenous (A-V) O_2 differences. Two major hypotheses have been proposed to explain this decreased O_2 extraction. The first is the existence of peripheral A-V shunts in severe sepsis and septic shock. This mechanism would explain the observation that at times, septic individuals with low VO_2 are capable of major increases in O_2 extraction. Such shunting and maldistribution of blood flow has recently been reviewed. Microemboli of platelets and white cells, oedema, localized intense vasoconstriction from Thromboxane release and other mediators, could all increase the diffusion distance from capillary to cell. The second view is that cellular and metabolic defects limit the cells' ability to utilize oxygen.

Although VO_2 in septic shock increases if DO_2 is increased, it is controversial whether this tissue demand for oxygen can always be satisfied. Studies in normal subjects in whom DO_2 was artificially manipulated, showed a biphasic response with respect to VO_2. As DO_2 was increased from low levels, a linear increase in VO_2 occurred until a plateau phase was reached where further increase in delivery did not result in increased consumption. However, in sick patients there is a linear relationship between those two variables over a wide range. Indeed, from mathematical analysis, this linear relationship was seen over the entire range of DO_2 recorded.

Clinical Presentation

Manifestations of septic shock cover a wide spectrum. In the classic presentation, the patient is febrile, vasodilated, tachypnoeic and has a hyperdynamic circulation despite a lowered blood pressure. Urine output may be normal, low or high. This is the classic picture of *"warm shock"*. As well as sepsis, other causes producing this picture include acute pancreatitis and hepatic failure. It is also sometimes seen following cardio-pulmonary bypass and following resuscitation for multiple trauma.

If the septic patient was previously hypovolaemic, had poor myocardial function or was referred late, the picture may be one of hypotension, vasoconstriction and peripheral cyanosis. This has been termed *"cold shock"*. It is not unusual for such patients to be normothermic (or even profoundly hypothermic) and be labelled as having cardiogenic shock, pulmonary embolism, hypovolaemic shock and profound hypothermia. Respiratory failure (associated with the adult respiratory distress syndrome, ARDS), coagulopathy, renal failure, and glucose intolerance are common features (see below).

Management

Septic shock has a high mortality rate and efforts should be made to recognize and treat sepsis before shock occurs. Recognition of sepsis requires both a high index of suspicion and an awareness of conditions which predispose to sepsis. Fever, tachypnoea, glucose intolerance, increasing serum creatinine and altered mental state must always be investigated. Toxic granulations and a shift to the left of the neutrophils are supportive evidence of sepsis regardless of the total white cell count.

As with any shocked patient, management is carried out along lines which encompass:

1. Initial combined assessment and resuscitation.

2. Attempts to ensure adequate oxygen delivery so that O_2 demands are met. This may be guided by clinical, haemodynamic and laboratory monitoring.

3. Methods of diagnosing the cause of the shock, and where possible, eradication of that cause.

A practical set of management guidelines are set out in Tables 1 and 3.

Table 1. *General Measures - Septic Shock*

Administer oxygen, ventilatory support if indicated.

Basic clinical monitoring

- Pulse, systemic arterial pressure
- Central venous pressure
- Pulmonary artery pressure
- Pulmonary capillary wedges pressure (PCWP)
- Cardiac output
- Oxygen delivery (DO_2)
- Temperature, urine output

Chest x-ray

Basic laboratory monitoring

- Arterial blood gas/acid base
- Lactate
- Electrolyte, creatinine
- Blood sugar, haemoglobin
- Platelet and white blood cell count
- Prothrombin ratio
- Liver function tests.

1. Adequate Oxygen and Ventilation

Hypoxaemia is common and in the early phase can usually be reversed by mask oxygen therapy. Should this be inadequate, then continuous positive airway pressure (CPAP) by mask may be employed. Where respiratory failure is severe, endotracheal intubation and either CPAP or mechanical ventilatory support is necessary. An adequate haemoglobin level must also be maintained.

2. Clinical Monitoring and Intervention

Basic monitoring involves repeated or continuous assessment of heart rate, rhythm, venous and arterial pressures. A central venous pressure (CVP) line and in selected cases, a balloon tipped thermodilution pulmonary artery (Swan-Ganz) catheter is inserted. The latter is especially useful if respiratory failure is evident or response to initial fluid loading is inadequate. Haemodynamic monitoring allows cardiac output as well as various pressure measurements to be obtained. Furthermore, the SVR, PVR and left and right ventricular stroke work can be derived. With additional data, DO_2 and VO_2 can be calculated.

Manipulation of the various determinants of cardiac output (Table 2) to attain or maintain the hyperdynamic state can then be made, as survival from septic shock can be directly related to cardiac output, DO_2 and VO_2.

Table 2. *Basic Determinants of Cardiac Output*

Heart rate
Stroke volume
1. preload
2. afterload
3. contractility.

(a) *Preload*

Preload is first manipulated by a colloid fluid "challenge" to a PCWP of 12 mmHg (1.6 kPa). The usual response is a prompt increase in cardiac output. This relatively low PCWP level of 10-12 mmHg (1.3-1.6 kPa) is associated with peak left ventricular stroke work and cardiac indices in patients with severe sepsis and septic shock. Further fluid loading beyond this level should only be used if improvement in cardiac output can be demonstrated and respiratory deterioration does not occur.

Table 3. *Specific Measures - Septic Shock*

Blood cultures
Gram stain and culture from possible sites of infection
Antibiotics
Surgical drainage
Other measures.

(b) *Contractility*

When fluid loading produces an unacceptable rise in PCWP without the desired increase in cardiac output, inotropic support or afterload reduction is then considered. As most of patients with septich shock have lowered SVR, afterload reduction is often inappropriate. An inotropic drug infusion (dopamine 5-10 microg/kg/min or adrenaline 1-15 microg/min) should be started. Often when systemic vascular resistance is profoundly depressed, noradrenaline by infusion is of benefit. A combination of noradrenaline and low dose dopamine is useful. Low dose dopamine prevents noradrenaline-induced renal hypoperfusion in dogs.

If no satisfactory response is obtained, a different inotrope or addition of other agents may be tried. Dobutamine may be used advantageous when one wishes to provide inotropic support whilst lowering both afterload and preload.

(c) *Afterload*

Afterload reducing therapy is conisdered in patients with "cold septic shock" who remain vasoconstricted despite volume loading and inotropic support. Topical nitroglycerine paste was used to treat 8 such patients of whom 5 survived. However, there was a coincident need for more volume expansion which implied an effect of venous capacitance also. Other agents which could be used in this setting include sodium nitroprusside (a vasodilator affecting both preload and afterload) or hydrallazine (affecting primarily afterload). Hydrallazine has also been used to lower PVR in patients with primary and secondary pulmonary hypertension. Pulmonary hypertension occurring in sepsis is associated with a high mortality.

(d) *Oxygen Delivery and Consumption*

DO_2 can be estimated from calculations utilizing the O_2 content of arterial blood (CaO_2) and cardiac output (CO). The measurement of VO_2 clinically is less reliable. VO_2 is most commonly calculated from the formula:

$$\mathbf{VO_2 = (CaO_2 - CvO_2) \times CO}$$

Apart from errors inherent in its calculation, the result reflects only overall VO_2 and not individual organ O_2 utilization. One is thus limited to optimizing DO_2 and VO_2 based upon probable inaccurate data.

It is suggested that optimal goals of therapy in critically ill postoperative patients should be: cardiac index (CI) 50% in excess of normal (ie, 4.5 L/min/m^2), a blood volume 500 mL greater than normal (provided PCWP , 20 mmHg, 20.1 kPa), DO_2 greater than 600 mL/min/m^2 and VO_2 greater than 170 mL/min/m^2. Severely traumatised and septic patients may require greater increases. However, one cautions against sustaining high levels of PCWP as respiratory problems will result.

(e) *Urine Output*

A urine output in excess of 0.7 mL/kg/h should be maintained. If severe oliguria persists despite appropriate fluid loading and adequate peripheral perfusion, a low dose dopamine infusion, IV bolus mannitol (25 g) and IV frusemide (250-500 mg) are commonly employed. There is evidence that all of these agents increase renal blood flow and promote diuresis. Frusemide by its venodilator effect can reduce preload and precipitate hypotension. It may also worsen toxic nephropathy.

3. Chest X-ray

An early erect chest X-ray may show evidence of raised pulmonary venous pressure. In severe sepsis (eg, in any patient with early ARDS) considerable tachypnoea and hypoxaemia may exist despite a deceptively normal-looking chest X-ray.

4. Laboratory Monitoring

This will detect biochemical and haematological abnormalities (Table 3, see also Chapter 63, Severe Sepsis).

Rises in blood lactate suggest severe tissue hypoxaemia and as such, may indicate an advanced stage of decompensation. However, in severe sepsis, lactate may be elevated by mechanisms other than hypoxaemia. Increased circulating catecholamine, by augmenting levels of glycogen phosphorylase (through stimulation of cyclic AMP), lead to increased glycolysis. The pyruvate produced may exceed its ability to enter the TCA cycle. Conversely, in malnourished patients with low glycogen stores, the rise in lactate for a given level of hypoxia may be less. As tissue pH falls, glycogen flux is inhibited. Hence lactate may be an insensitive marker of tissue hypoxia.

Complications and Other Treatment

1. Metabolic Acidosis

This is commonly present as a result of lactic acidaemia due to anaerobic metabolism. Measures to correct hypoxaemia and improve cardiac output will usually reverse this. However, severe metabolic acidosis may lead to further depression of myocardial function, increased PVR and venoconstriction. For these reasons, bicarbonate in aliquots of 50 mmol may be given with close monitoring, although its value in this setting is controversial.

2. Hyperglycaemia

Acute glucose intolerance is commonly precipitated by severe sepsis. Steroids, if employed, may also induce this state. Hypertonic glucose solutions will aggravate the problem. If severe, a low dose insulin infusion is started. Hypoglycaemia may occasionally be seen, especially in the very young and those with severe hepatic dysfunction.

3. Coagulopathy

Disseminated intravascular coagulation (DIC) may occur in septic shock, ranging from a mild, barely detectable disorder to the full-blow syndrome. Management is directed towards reversal of the shock and removal of the septic source. Platelets, fresh frozen plasma and other factors are given if necessary (see Chapter 88, Haemostatic Failure). Vitamin K and folate are routinely given if no contraindication exists.

4. Gastrointestinal Bleeding

This is common in severe uncontrolled sepsis. Antacids, H_2-receptor blockers and cytoprotective agents such as sucralfate are effective in reducing the incidence of this disorder. The aim is to maintain the intragastric pH above 4.0 when antacids and H_2-blockers are used. This necessitates 1-4 hourly monitoring of the pH of gastric fluid. Sucralfate has minimal effect on intragastric pH and has antimicrobial properties. Gastric colonization and nosocomial pneumonia in ventilated patients are less likely to occur when this agent is used.

5. Other Organ Failure

Septic shock can result in failure of virtually any body organ or system. Sepsis is one of the commonest causes of acute respiratory failure (including ARDS), acute renal failure and multiple organ failure seen in the ICU.

6. Adequate Nutrition

Severe sepsis is associated with a hypercatabolic state. Accelerated muscle wasting is frequently alarmingly obvious. Negative nitrogen balance can be minimized by providing nutritional support. This often necessitates intravenous feeding, while avoiding excessive glucose loads. (See Chapter 82, Parenteral Nutrition.)

7. Steroids

The use of high dose steroids (examples: methylprednisolone 30 mg/kg and dexamethasone 6 mg/kg) in septic shock cannot be recommended. Shumer in both retrospective and prospective trials reported lower mortality in those treated with high dose steroid. However, a later prospective study concluded that steroids do not improve the overall survival rate of patients with severe, late septic shock, but may be helpful early in the course and in certain subgroups of patients. More recent controlled clinical trials also demonstrated no benefits from high dose steroids in severe sepsis and septic shock. Moreover, of those treated with steroids, significantly more deaths were related to secondary infection.

8. Agents of Experimental Interest

(a) *Prostaglandins* are known to participate in the pathophysiology of endotoxic and septic shock in both animals and man. Prostaglandin cyclo-oxygenase inhibitors (eg, indomethacin, a non-steroidal antiinflammatory drug) improves survival in animal septic shock models, even when administered after the onset of shock. However, these cyclo-oxygenase inhibitors interfere not only with the formation of the stable prostaglandins, but also with

thromboxane A_2 and prostacyclin (PGI_2). Inhibition of prostacyclin synthesis in septic shock may be undesirable. Prostacyclin is a vasodilator, an antagonizer of Thromboxane A_2, an inhibitor of platelet aggregation and granulocyte adherence. It increases red cell deformability (thereby increasing blood flow through the microcirculation), inhibits gastric acid secretion and stimulates the rening-angiotensin-aldosterone system. Prostacyclin infusion has increased survival in dogs with endotoxaemia. In a recent study of prostacyclin administered to critically ill subjects, the majority who increased their VO_2 had increased the peripheral extraction rate.

(b) *Endogenous opioid peptides* derived from beta-lipotropin are released in septic shock as well as in many other stress states. Experiments in dogs with septic shock have shown that the opioid receptor blocker naloxone can raise blood pressure and improve survival. There are also reports of improvements following the administration of naloxone to humans suffering from septic shock, though more recent reports are not as encouraging.

(c) *Corticosteroids* inhibit beta-lipotropin and therefore endorphin release, and abolish the pressure response to naloxone in septic shock. This suppression of pituitary endorphin release may explain part of their apparent beneficial effect in shock. However, such theoretical benefits do not appear to improve mortality in clinical trials. Also, if interleukin I and cachectin do play a central role in the pathophysiological and clinical response to severe sepsis, then high dose steroids would be expected to be beneficial, as steroids suppress the production of these cytokines. However, circulating cachectin is only detected at the onset of clinical responses to endotoxin. In clinical practice, steroids have been given at the height rather than the beginning of the clinical response and this may explain their ineffectiveness.

(d) *Thyrotropin releasing hormone (TRH)* a tripeptide from the hypothalamus and other sites, has many physiological effects. It opposes many opioid-mediated actions and like naloxone, has been used to treat endotoxic shock in animals. Both TRH and naloxone improved cardiovascular function in experimental endotoxin shock, but TRH also increased the mean arterial pressure of control animals who were not in shock. Another important difference between TRH and naloxone is that TRH does not reverse opioid-induced analgesia.

(e) *Antibodies to lipopolysaccharide (LPS).* Two prospective, randomized clinical trials have demonstrated improved survival time after the administration of antibodies to LPS during sepsis.

(f) *Monoclonal antibody against cachectin.* The haemodynamic collapse, metabolic acidosis and tissue injury stimulated by infusion of recombinant cachectin can be inhibited by monoclonal antibody against cachectin. Pretreatment of baboons with similar antibodies prevented their death after injection with a lethal dose of *E. coli.* Such antibody administration, directed against either the circulating cachectin or peptide receptor binding, has been suggested as a possible new therapeutic modality in the management of clinical endotoxaemia. However, passive immunization against cachectin has a negative effect on survival in murine malarial infection.

Currently, cyclo-oxygenase inhibitors (eg, indomethacin), prostacyclin infusions, naloxone and TRH are not recommended in the management of septic shock at our present state of knowledge. Similarly, whilst cachectin has deleterious effects when produced in

excessive quantities, it has protective effects when produced on a smaller scale in the course of a limited infectious process.

Prognosis

Mortality rate generally remains about 50% in septic shock. Factors discussed in relation to prognosis in Chapter 63, Severe Sepsis, are equally applicable to septic shock. Mortality can be directly related to age and the severity of underlying illness. Origin of the sepsis is also important. Urological cases with septic shock have a better prognosis than sepsis in other organ systems. Haemodynamic findings associated with a favourable prognosis include the ability to maintain an elevated cardiac output and DO_2. Pulmonary hypertension is an averse factor.

When cardiac index decreases in septic shock, survivors are more able to augment SVR than non-survivors. Peripheral vascular failure may thus be a major haemodynamic determinant of mortality in septic shock.