achieving survivor values (or at maintaining \( S_{O_2} \)) is of no benefit (Alia et al., 1999; Gattinoni et al., 1995; Hayes et al., 1994) and might even be harmful (Alia et al., 1999; Hayes et al., 1994) in such patients. Although there is no doubt that the prognosis for those who do achieve survivor values in response to fluids alone or only moderate inotropic support is excellent, in a significant number (often the older or more severely ill patients) it proves impossible to achieve target values, even with high-dose inotropic support (Alia et al., 1999; Gattinoni et al., 1995; Hayes et al., 1994) and in such patients mortality rates are extremely high (Hayes et al., 1993, 1997). The failure of these non-survivors to respond to aggressive haemodynamic support is in part related to reduced responsiveness of the myocardium to inotropes but is particularly associated with peripheral vascular failure, resistance to vasopressors and an impaired ability of the tissues to extract or utilize the increased amounts of delivered oxygen and/or to metabolize aerobically (Hayes et al., 1997) – so-called ‘tissue dysoxia’ (see above).

Nevertheless, it remains possible that earlier institution of some form of ‘goal-directed’ treatment might prevent progression to refractory shock, tissue hypoxia and organ failure and thereby improve outcome. In patients admitted with severe sepsis or septic shock, for example, early goal-directed therapy in the emergency room aimed at maintaining central venous oxygen saturation at more than 70% significantly reduced in-hospital mortality (Rivers et al., 2001). On the other hand, institution of treatment aimed at achieving ‘supranormal’ values for \( CI \), \( DO_2 \) and \( VO_2 \) immediately after admission failed to improve outcome in critically injured patients (Velmahos et al., 2000). These authors concluded, as have others (Hayes et al., 1997), that the ability to achieve the recommended target values simply indicates an adequate physiological reserve, with preserved cellular function and therefore a good prognosis. This suggestion is supported by studies demonstrating the prognostic value of the responses of \( DO_2 \) and \( VO_2 \) to a short-term infusion of dobutamine in patients with sepsis syndrome and normal lactate levels (Vallet et al., 1993), and in patients with sepsis, severe sepsis or septic shock (Rhodes et al., 1999).

In conclusion, although The Surviving Sepsis Guidelines do not recommend aggressive targeting of ‘survivor values’ for \( CI \), \( DO_2 \) and \( VO_2 \) for critically ill patients after admission to intensive care (Dellinger et al., 2008), early resuscitation, aimed especially at achieving an adequate circulating volume (see above), combined with the rational use of inotropic and/or vasoactive agents to maintain blood pressure and an appropriate cardiac output, is essential. Resuscitation may be more effective when guided by monitoring of venous oxygen saturation, or cardiac output, e.g. by oesophageal Doppler, but the value of routine pulmonary artery catheterization is increasingly in doubt (see Chapter 4).

**Vasodilator therapy, afterload and preload reduction**

In selected patients, afterload reduction may be used to increase stroke volume and decrease myocardial oxygen requirements by reducing systolic wall tension. Vasodilatation also decreases heart size and diastolic ventricular wall tension so that coronary blood flow is improved. The relative magnitude of the falls in preload and afterload depends on the pre-existing haemodynamic disturbance, concurrent volume replacement, the agent selected and the dose used (see later). There is also reason to believe that, in some circumstances, specific vasodilators may improve microcirculatory flow (see later).

Vasodilator therapy can be particularly helpful in patients with cardiac failure in whom the ventricular function curve is flat, so that falls in preload have only a limited effect on stroke volume. This form of treatment, combined in selected cases with inotropic support, can therefore sometimes be useful in cardiogenic shock and in patients with cardiogenic pulmonary oedema, mitral regurgitation or an acute ventricular septal defect. In such cases, nitrate vasodilators are usually used. Furthermore, because of their ability to improve the myocardial oxygen supply:demand ratio, nitrates can be used to control angina and limit ischaemic damage following myocardial infarction. Vasodilators may also be valuable for controlling hypertension in post cardiac surgery patients, as well as for the treatment of hypertensive emergencies, dissecting aneurysm, accelerated hypertension of pregnancy and in pulmonary hypertension.

Vasodilator therapy is potentially dangerous and vasodilatation should be achieved cautiously, usually guided by invasive haemodynamic monitoring. The circulating volume must be adequate before treatment is started and, except in those with cardiac failure, falls in preload should be prevented to avoid serious reductions in cardiac output and blood pressure. If diastolic pressure is allowed to fall, coronary blood flow may be jeopardized and myocardial ischaemia may be precipitated, particularly if a reflex tachycardia develops in response to the hypotension. Provided myocardial performance is not impaired, it is therefore sometimes appropriate to control the tachycardia with a β-blocker. Other side-effects of vasodilators include:

- hypoxaemia;
- vertigo;
- flushing;
- nausea and vomiting;
- headache;
- rebound hypertension.

The selection of an appropriate agent in an individual patient depends on a careful assessment of the haemodynamic disturbance and on whether the effect required is predominantly a reduction in preload, afterload or both.

**NITRIC OXIDE DONORS**

Sodium nitroprusside (SNP). This agent dilates both arterioles and venous capacitance vessels, as well as the pulmonary vasculature. SNP therefore reduces the afterload and preload of both ventricles and can improve cardiac output and the myocardial oxygen supply:demand ratio. Some authorities...
have suggested, however, that SNP can exacerbate myocardial ischaemia by producing a ‘steal’ phenomenon in the coronary circulation. The increased cardiac output is preferentially distributed to musculoskeletal regions. If arterial pressure falls, hepatic and renal blood flow are unchanged, whereas if pressure is maintained, splanchnic flow increases slightly.

The effects of SNP are rapid in onset and spontaneously reversible within a few minutes of discontinuing the infusion. Moreover, tachyphylaxis is not a problem. SNP is most commonly used to control resistant hypertension after cardiac surgery and in malignant hypertension. SNP has been shown to improve cardiac function rapidly in patients with decompensated heart failure due to severe left ventricular systolic dysfunction and severe aortic stenosis (Khot et al., 2003).

An overdose of SNP can cause cyanide poisoning with histotoxic hypoxia caused by inhibition of cytochrome oxidase, the terminal enzyme of the respiratory chain. This is manifested as a metabolic acidosis and a fall in the arteriovenous \((C_{\text{a}}-C_{\text{v}})\) oxygen content difference. These effects should not inhibit the clinical use of SNP since they are only seen when a gross overdose has been administered and are easily avoided with care. In the short term (a few hours) infusions should be limited to a total dose of 1.5 mg/kg. There is only limited information concerning the safe dosage for long-term administration (several hours to days, or even weeks), although it has been suggested that maximum infusion rates of approximately 4 μg/kg per min (certainly less than 8 μg/kg per min) and a total dose of 70 mg SNP/kg over periods of up to 2 weeks are the maximum allowable without risking toxic effects (Vesey and Cole, 1985). Although thiocyanate accumulation is not a concern during hypotensive anaesthesia, high plasma levels may be achieved during long-term administration, with possible toxic consequences. Monitoring of thiocyanate levels has therefore been recommended during infusions lasting more than 3 days, particularly in the presence of renal insufficiency (Vesey and Cole, 1985). Treatment of cyanide toxicity is discussed in Chapter 19. SNP is broken down during prolonged exposure to light; this problem can be avoided by making up the solution in relatively small quantities or by protecting it with silver foil.

**Nitroglycerine (glyceryl trinitrate, GTN) and isosorbide dinitrate (ISDN).** At low doses these agents are predominantly venodilators but as the dose is increased they produce arterial dilatation, thereby decreasing both preload and afterload; cardiac output may increase, although most of the additional flow is distributed to musculoskeletal regions. Nitrates are particularly useful in the treatment of acute cardiac failure with pulmonary oedema and are conventionally used in combination with intravenous furosemide. In these circumstances the reduction in right ventricular volume and preload may lead to an increase in left ventricular volume and an improvement in stroke volume, with relief of pulmonary oedema. The reduction in preload may also reduce ventricular wall tension and improve coronary perfusion. With higher doses of nitrate the reduction in afterload might increase cardiac output and further reduce pulmonary congestion, whereas furosemide can activate both the sympathetic and renin-angiotensin systems, potentially increasing afterload and reducing stroke volume. Moreover, the majority of patients presenting in acute heart failure are hypovolaemic as a result of vomiting, sweating, reduced fluid intake and extracellular fluid shifts. This hypovolaemia will be exacerbated by the diuresis induced by furosemide, leading to vasoconstriction and further reductions in cardiac output. Indeed, many patients will benefit from judicious expansion of the circulating volume in conjunction with vasodilator therapy. There is evidence that the use of high-dose ISDN (given as a 3-mg intravenous bolus every 5 minutes after low-dose furosemide) is more effective than high-dose furosemide with low-dose ISDN (Cotter et al., 1998). In particular, the need for mechanical ventilation and the frequency of subsequent myocardial infarction were significantly reduced by high-dose ISDN.

Because nitrates can reverse myocardial ischaemia by increasing and redistributing coronary blood flow, as well as reducing ventricular wall tension, they can be used to control angina, prevent myocardial infarction and limit infarct size. GTN and ISDN are usually used in preference to SNP in patients with cardiac failure and/or myocardial ischaemia. Both GTN and ISDN reduce pulmonary vascular resistance, an effect that can occasionally be exploited in patients with a low cardiac output secondary to pulmonary hypertension. Finally, recent evidence suggests that in patients with septic shock who have been volume-resuscitated, cautious administration of GTN can improve microvascular flow (Spronk et al., 2002).

**ADRENERGIC BLOCKERS**

Adrenergic blockers predominantly dilate arterioles and therefore mainly influence afterload. Phenoxybenzamine is unsuitable for use in the critically ill because of its slow onset (1–2 hours to maximum effect) and prolonged duration of action (2–3 days). Phentolamine is very potent with a rapid onset and short duration of action (15–20 minutes). It can be used to control blood pressure acutely in hypertensive crises, but may produce a marked tachycardia and is expensive to administer as a continuous infusion. Labetalol is an \(\alpha\)- and \(\beta\)-blocking agent which can be given as a continuous infusion. It is particularly indicated for control of blood pressure in patients with dissecting thoracic aortic aneurysms in whom the reduction in shear stress consequent on \(\beta\)-blockade may be an advantage. Side-effects include bradycardia, heart block and bronchoconstriction. It is contraindicated in asthma and chronic obstructive pulmonary disease.

**HYDRAZINE**

This agent predominantly affects arterial resistance vessels. It therefore reduces afterload and blood pressure while cardiac output and heart rate increase. Renal and limb blood...
flow are also increased. Hydralazine can be administered orally to patients with chronic cardiac failure, but in intensive care practice it is usually given as an intravenous bolus (5–10 mg) to control acute increases in blood pressure, particularly after cardiac surgery.

**CALCIUM ANTAGONISTS**

The calcium channel blocker nifedipine can be administered orally or sublingually to control hypertension. It is a particularly potent peripheral smooth-muscle relaxant that causes a reduction in systemic vascular resistance and an increase in cardiac output. Most of the increased flow is distributed to musculoskeletal beds, with lesser increases in hepatic, splanchnic and renal flow.

**ANGIOTENSIN-CONVERTING ENZYME INHIBITORS**

ACE inhibitors such as captopril and enalapril reduce systemic vascular resistance and generally increase renal blood flow by reducing angiotensin-induced arteriolar tone. This effect is, however, more pronounced in the efferent vessels, and GFR may therefore remain unchanged or fall despite the increased flow. Nevertheless, sodium excretion usually increases, largely due to a reduction in aldosterone release. ACE inhibitors can be useful when weaning patients with cardiac failure from intravenous vasodilators.

**Note:** when used in patients with respiratory failure most inotropes and vasoactive agents increase venous admixture; this may be due simply to passive opening of pulmonary vessels by the increased flow and pressure or to a specific reversal of the hypoxic vasoconstrictor response.

**Mechanical circulatory assistance**

**INTRA-AORTIC BALLOON COUNTERPULSATION**

Various techniques for mechanically supporting the failing myocardium have been described; of these, intra-aortic balloon counterpulsation (IABCP) has proved most practical and is now widely used.

A catheter with an inflatable sausage-shaped balloon is inserted via a femoral artery using a percutaneous Seldinger technique and passed into the aorta until its tip lies just distal to the left subclavian artery (Fig. 5.17). If the Seldinger

![Fig. 5.17 Intra-aortic balloon counterpulsation (IABCP). (a) Rapid deflation of the balloon occurs at the onset of systole and causes a reduction in afterload. Early in diastole the balloon is rapidly inflated to increase the pressure in the aortic root and enhance coronary blood flow. (b) An intra-aortic balloon pump and console.](image-url)
When an intensive care technique fails, an open surgical approach can be used. Fluoroscopy makes insertion safer and allows accurate positioning of the catheter tip. In the absence of fluoroscopy, the position of the catheter must be verified by chest X-ray. Occasionally, the balloon is inserted via the ascending aorta in those undergoing cardiac surgery, whilst in other cases the axillary or subclavian arteries are used.

Early in diastole, the balloon is rapidly inflated so that the pressure in the aortic root rises and coronary blood flow is increased. Rapid deflation of the balloon is timed to occur at the onset of systole (usually triggered by the R wave on the ECG) and this leads to a reduction in afterload and left ventricular wall tension. Preload, pulmonary artery pressure and pulmonary vascular resistance may also be reduced. Heart rate is usually unchanged. The reduction in left ventricular work reduces myocardial oxygen requirements and this, combined with the increased coronary blood flow, may result in a reversal of ischaemic changes and limitation of infarct size. IABCP may not, however, increase coronary blood flow distal to significant stenoses. Improved myocardial performance, together with the reduction in afterload, can lead to an increased cardiac output. Inflation and deflation of the balloon must be precisely timed to achieve effective counterpulsation (Fig. 5.18).

The only absolute contraindications to IABCP are aortic aneurysms (or other severe disease of the descending aorta) and significant aortic regurgitation. Relative contraindications include arrhythmias and extreme tachycardias, both of which limit the ability of the device to trigger balloon deflation accurately, and severe peripheral vascular disease.

IABCP is associated with significant morbidity. Complications include:

- failure to pass the balloon (usually in those with severe atheromatous disease);
- arterial dissection;
- limb ischaemia;
- thrombosis;
- embolism;
- infection;
- a distally positioned balloon may intermittently occlude the renal vasculature;
- balloon rupture is rare.

In order to minimize the risk of thrombosis on the surface of the balloon, the patient should be heparinized to achieve a partial thromboplastin time of about 1 1/2 times normal and the balloon should be kept in motion. Because there is a tendency to develop thrombocytopenia, the platelet count should be carefully monitored.

IABCP has proved most useful for weaning patients from cardiopulmonary bypass and for those who develop myocardial ischaemia in the perioperative period. It may also be used to support patients in cardiogenic shock who have surgically correctable lesions, such as ischaemic ventricular septal defects or mitral regurgitation, while they are being prepared for surgery. In patients with severe ischaemia (e.g. those with unstable angina) IABCP may relieve pain and possibly prevent infarction while preparations are made for coronary artery bypass grafting or percutaneous transluminal coronary angioplasty (PTCA) (see Chapter 9). The use of IABCP for the treatment of cardiogenic shock complicating myocardial infarction without a surgically correctable lesion has been less successful, although some feel that this may be due partly to delay in instituting IABCP and extension of the infarct caused by the prior use of inotropes. Although there are no PRCT data to indicate that IABCP can improve outcome in cardiogenic shock, it has been suggested that the technique might be beneficial when used in conjunction with revascularization, either surgically or by coronary angioplasty (Hasdai et al., 2000).

IABCP may also be indicated in patients with a failing transplanted heart and in those with viral myocarditis. IABCP is occasionally used prophylactically in patients undergoing high-risk cardiac surgery or PTCA. There is only limited experience with the use of IABCP in myocardial failure complicating septic shock, but it seems that the technique may be life-saving in those with reversible global myo-

(a) Balloon initially inflating on alternate beats (1:2) then 1:1

(b) Balloon inflating on alternate beats (1:2)

(c) Balloon inflating immediately the aortic valve closes (i.e. on the dicrotic notch).

Fig. 5.18 (a) The effect of intra-aortic balloon counterpulsation (IABCP) on the arterial pressure trace. Note the increased diastolic pressure, the slight fall in systolic pressure (due to afterload reduction) and reduced end-diastolic pressure (due to rapid balloon deflation). (b) It is important that the balloon inflates immediately the aortic valve closes (i.e. on the dicrotic notch). In this case the balloon is inflating too early. This impedes left ventricular ejection. (c) In this case balloon inflation is delayed.
cardial dysfunction complicating anaphylaxis (Raper and Fisher, 1988).

**OTHER VENTRICULAR ASSIST DEVICES**

Centrifugal pumps can be used to bypass and ‘off-load’ the right or, more often, the left ventricle while maintaining adequate systemic blood flow. Such devices are usually used as a means of discontinuing cardiopulmonary bypass in the hope that ventricular function will improve significantly over the ensuing 48–72 hours. They may also be used as a ‘bridge’ to cardiac transplantation. Alternative devices include mechanical hearts, used to support potential cardiac transplant recipients and arteriovenous pumps.

**HAEMATOLOGICAL PROBLEMS**

The most commonly encountered haematological problem in shock is a coagulation defect, usually due to massive blood transfusion and/or consumption coagulopathy (DIC), the latter being particularly common in sepsis (see above). This can usually be corrected with transfusions of fresh frozen plasma, occasionally combined with platelets, or cryoprecipitate. DIC should be prevented or reversed by aggressive treatment of the underlying condition. Heparinization has been recommended, but this is potentially extremely dangerous, particularly in trauma victims and postoperative patients, and is rarely indicated. Later, coagulation may be impaired secondary to the development of renal and/or hepatic failure.

**RENAL FUNCTION**

Prevention of acute intrinsic renal failure is best achieved by restoring cardiac output, blood pressure and renal blood flow as rapidly as possible, combined with early and aggressive management of oliguria (see Chapter 13).

**MULTIPLE-ORGAN FAILURE**

Although it is now usually possible to support patients through the early stages of shock, trauma or other life-threatening illnesses, a disappointingly high proportion subsequently develop progressive failure of several vital organs (Barton and Cerra, 1989; DeCamp and Demling, 1988). Mortality is high and correlates with the number of organs which fail; those with prolonged three-system failure have a mortality rate exceeding 50%, whilst more than 90% of those with prolonged six-system failure die. Sequential MOF is now the commonest mode of death in intensive care patients, accounting for as many as 75% of all deaths in surgical ICUs (Barton and Cerra, 1989). Moreover, these patients spend long periods in intensive care and consume a large proportion of available resources.

**DEFINITION**

Currently there is no consensus on the definition of the MOF syndrome and criteria for failure of individual organs differ. Because the extent of organ dysfunction can vary both between patients and within the same patient over time, the term *multiple-organ dysfunction syndrome* (MODS) has been suggested to indicate the wide range of severity and dynamic nature of this disorder (Bone et al., 1992; Members of the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference, 1992). Organ dysfunction is defined as ‘the presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention’. Transient impairment of organ function rapidly responsive to short-term measures should probably be excluded from this definition.

**AETIOLOGY AND CAUSES** (see also pp. 96–99)

There are two distinct, but not mutually exclusive, pathways by which MODS may develop (Fig. 5.19).

- **In primary MODS** there is a direct insult to an individual organ (e.g. pulmonary aspiration, lung contusion or renal damage due to rhabdomyolysis), which fails early as the result of an inflammatory response that is confined, at least in the early stages, to the affected organ.
- **The aetiology of secondary MODS** is complex but, in general terms, organ damage is thought to be precipitated by systemic dissemination of a poorly controlled inflammatory/anti-inflammatory response associated with haemodynamic disturbance, microcirculatory abnormalities and defective oxygen utilization, as described earlier in this chapter. However, the precise mechanisms responsible for organ damage have yet to be determined. Secondary MODS can therefore be viewed as a complication of SIRS (see above) and can be considered as representing the more severe end of the spectrum of illness of patients with SIRS/sepsis/septic shock. Secondary MODS usually evolves after a latent period from the initiating event, which is most commonly infectious (usually bacterial, but sometimes viral, fungal or parasitic), but may be non-infectious (e.g. the presence of extensive wounds or necrotic tissue). Secondary MODS may therefore follow sepsis, trauma, shock, major surgery and many other serious illnesses (e.g. pancreatitis, perforation of the gastrointestinal tract, pneumonia), or may arise in response to SIRS precipitated by primary MODS.

![Fig. 5.19 Pathways for the development of multiple-organ dysfunction syndrome (MODS). SIRS, systemic inflammatory response syndrome.](image-url)


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