Cardiogenic shock and the ICU patient

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Cardiogenic shock is one of the most important complications of acute myocardial infarction (MI) and acute left ventricular failure (LVF). It threatens the life of 5-10% of patients with ST-segment elevation myocardial infarction (STEMI) particularly in the presence of inappropriately low peripheral vascular resistance. Cardiogenic shock results in poor tissue perfusion, end-organ damage and carries a high mortality risk. The goal of therapy is to prevent end-organ dysfunction and severe metabolic derangement by raising mean arterial blood pressure, which is achieved with the use of inotropes and vasopressors, often at the expense of tachycardia, elevated myocardial oxygen consumption and extended myocardial ischaemia. Current therapeutic approaches include early coronary artery revascularisation (which has significantly improved the survival rate), fluid resuscitation, inotropic support and mechanical circulatory support using intra-aortic balloon pumps or ventricular assist devices. In this article, we review the pathophysiology, diagnosis and management of cardiogenic shock.

Keywords: *cardiogenic shock; myocardial infarction; inotropes; ventricular assist devices*

Introduction

Cardiogenic shock (CS) is a complex, degenerating clinical spiral of multi-organ dysfunction that begins when the heart is no longer able to provide sufficient resting pressure and flow[1] (**Figure 1**). Without effective intervention, progression of shock is rapid and fatal.[2] The mortality rate approaches 70-80% if CS is managed only medically.[3,4] Since the publication of the SHOCK (Should we emergently revascularise occluded coronaries in cardiogenic shock) trial,[5] in which it was reported that early coronary revascularisation was more beneficial than medical therapy in patients with post-MI CS, hospital mortality has decreased steadily. This improvement is generally attributed to increased rates of primary percutaneous coronary intervention (PPCI) for acute coronary syndromes (ACS), which would be expected to prevent progression to CS in those at risk.[6] Nonetheless, despite these advances (including medical therapy and mechanical support), in-hospital case-fatality rates linked to CS remain above 50%. Intriguingly, the incidence rate of CS complicating ACS has remained stable over the past three decades, in the region of 7%.[7]

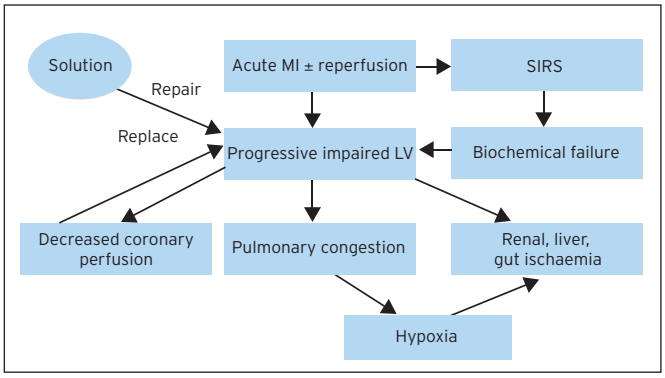

Figure 1 Self-perpetuating mechanisms of cardiogenic shock. Only restoration of cardiac index and coronary perfusion to physiological levels can stop the vicious cycle. Abbreviations: LV, left ventricular; MI, myocardial infarction; SIRS, systemic inflammatory response syndrome. Courtesy Westaby *et al*.[6]

Definition of cardiogenic shock

The clinical diagnosis of CS is made if all the following criteria are present:

- the systolic blood pressure (SBP) is persistently ≤90 mm Hg or vasopressors are required to maintain SBP ≥90 mm Hg
- evidence of end organ hypoperfusion (eg urine output <30 mL/hr or cold/diaphoretic extremities or altered mental status), and
- evidence of elevated left ventricular filling pressures, for example, pulmonary congestion on examination or on chest radiograph.[2]

There is however great variability in the degree of hypotension that defines CS. The usual boundary for SBP is less than 90 mm Hg, but some authors have used a cut-off of less than 80 mm Hg (**Table 1**).[3,8] Systemic signs of low blood pressure often manifest with altered mental state, cold and clammy skin, and oliguria. Regardless of this, a patient may still enter into a clinical condition (with tachycardia, dyspnoea, mild reduction in urine output) prior to CS in the presence of a SBP measurement greater than 90 mm Hg, in circumstances where medication is administered to avert the development of full-blown CS. Blood pressure measurement using a simple

Systolic blood pressure <90 mm Hg for ≥ one hour that is: • Not responsiveness to fluid administration alone • Secondary to cardiac dysfunction • Associated with signs of hypoperfusion, including cold clammy extremities, poor capillary refill, altered mental state, and urine output <30 mL/hr, together with cardiac index <2.2 L/min/m^2 and pulmonary capillary wedge pressure >18 mm Hg
Low cardiac output state, but with systolic blood pressure >90 mm Hg in response to inotropes with or without the use of an IABP
Profound shock: cardiac index <1.8 L/min/m^2 with mean blood pressure <65 mm Hg and unresponsive to inotropes with or without the use of an IABP

Table 1 Diagnostic criteria for cardiogenic shock.[6]

blood pressure cuff may not be reliable and invasive recording and measurement of blood pressure may be indicated.[1]

Similarly, haemodynamic data obtained from right heart catheterisation may be used to determine the presence of CS. For example, a cardiac index of 2.2 L/min/m^2 is supportive of the diagnosis in the presence of the aforementioned criteria.[1] The availability of non-invasive technology, such as echocardiography, to assess cardiac function, and the pitfalls of invasive determination (eg super-normal cardiac output measurements in patients with ventricular septal defects or elevated pulmonary capillary wedge pressure (PCWP) in those with right ventricular (RV) infarcts) have reduced the reliance on invasive methods to diagnose CS.[1] Furthermore, by the time invasive monitoring has been started, patients are usually already established on appropriate medical therapy. These may have already altered haemodynamics, for example, a diuretic may reduce PCWP while positive inotropic agents will improve cardiac output measurements.[1] In a sub-study of the SHOCK trial,[9] the echocardiographic features of CS and their relation to outcomes with either early coronary revascularisation or medical treatment revealed that the univariate echocardiographic predictors of 30-day survival were left ventricular ejection fraction (LVEF) and the severity of mitral regurgitation, whereas end-diastolic and -systolic left ventricular volumes were found to be univariate predictors of 1-year survival.[10]

Presenting symptoms

The presenting symptoms of CS are quite variable. Patients can present with either classical physical signs of heart failure such as pulmonary oedema, or can present with minimal lung signs, in which case the mortality rate is higher. In addition, based on the Acute Decompensated Heart Failure National Registry (ADHERE), almost 50% of patients admitted with acute heart failure had relatively preserved systolic function.[10] Some patients with anterior STEMI present with clinical signs and biochemical parameters of CS while maintaining systemic arterial pressure >90 mm Hg.[6] Urine production remains low in the face of fluid resuscitation, which can precipitate pulmonary oedema. A sinus tachycardia (>100 bpm) compensates for the reduction in stroke volume. Beta blockers given to reduce the heart rate can depress cardiac output further. Invasive monitoring of these patients shows the cardiac index to be <2.0 L/min/m^2, although cardiac output can temporarily increase with inotropic drugs or a fall in peripheral vascular resistance.[6] Peripheral vasoconstriction is the normal physiological response to hypotension and is an intentional result of vasopressor therapy.

Pathophysiology of cardiogenic shock

High levels of nitric oxide (NO) synthase expression are seen, due to the release of inflammatory mediators during MI, which is consistent with the high body temperature, raised white cell count, and elevated C reactive protein (CRP) levels among patients with extensive necrosis.[11] An interleukin 6 (IL6) level >200 pg/mL is associated with increased mortality irrespective of whether the patient has had successful PPCI.[12] Elevated IL6 exerts a negative inotropic effect and predisposes the patient to multiple organ failure. Patients with a high vasopressor requirement had an 86% mortality, consistent with the fact that cytokine-induced release of NO within vascular cells causes reduced catecholamine responsiveness.[13] Successful coronary revascularisation and IL6 levels <200 pg/ml were associated with only 24% mortality compared with the overall series mortality of 47%.[5] High levels of NO and per-oxynitrites cause inappropriate vasodilatation and negate the reflex vasoconstriction normally seen with hypotension.[5] Tilarginine acetate is an isoform non-selective NOS inhibitor. In the TRIUMPH trial (Tilarginine acetate in a randomised international study in unstable MI patients with cardiogenic shock),[13] patients with post-MI CS accrued no benefit with NO synthase inhibition by tilarginine.

IL-6 is only one of a range of cytokines that may be released during ischaemia. Tumour necrosis factor-α (TNF-α) has been shown to depress cardiac function in the context of post-sepsis CS.[14] This has been demonstrated in healthy volunteers using endotoxin administration to stimulate a septic response resulting in an elevation in TNF-α levels.[15] Several animal studies have also confirmed the cardio-depressant effects of TNF-α in rat cardiomyocytes.[16] Interferon-gamma (IFN-γ) has both immune-modulatory and immune-stimulatory effects and its administration in animal models (mice who are heterozygous for IFN-γ) has been associated with the development of fatal myocarditis and cardiomyopathy.[16] Macrophage inflammatory protein-1 beta (MIP-1β) causes inflammation through its effects on neutrophil function, by attracting monocytes to sites of tissue injury. MIP-1β has been acknowledged as an independent risk-stratifying biomarker but has also been discussed as a potential therapeutic target.[17-19] Another cytokine, granulocyte-colony stimulating factor (G-CSF) has been considered in acute MI, with numerous mechanisms being postulated, such as regeneration of the infarcted myocardium, and an enhanced healing process or protection from apoptosis.[20] To date, it has been shown to attenuate ventricular remodelling in patients with an anterior infarct with concomitant depressed left ventricular function following successful percutaneous coronary intervention. Intriguingly, in another study, G-CSF was shown to increase inflammatory markers such as TNF-α and CRP.[16]

In a sub-study of the intra-aortic balloon pump (IABP) SHOCK trial, the predictive value of the above cytokines was explored in patients with acute MI complicated by CS.[16] The IABP SHOCK trial, a prospective randomised controlled trial, was designed to test whether the haemodynamic effects and disease severity in AMI patients with CS were modified by the use of IABP, and found no significant difference between the group who had counter-pulsation therapy compared to those without.[21] The investigators were able to demonstrate an inverse correlation between survival and levels of cytokines.[16]

Finally, neopterin, a pteridine synthesised by macrophages upon stimulation by IFN-γ, is a novel marker for macrophage activation and its presence has been found to be a strong predictor of heart failure (HF).[22] Inflammation is involved in the pathogenesis of HF and neopterin is thought to exert its pro-inflammatory action via promotion of oxidative stress.[22]

Management

Intervention to treat the underlying cause

Primary PCI and rescue PCI are the gold standard treatment for patients with acute MI complicated by CS, as this therapeutic approach rapidly restores cardiac output and prevents end-organ dysfunction. This has improved the outcome of CS complicating acute coronary syndromes dramatically since the 1970s (GUSTO-I trial,[23,24] SHOCK trial[4]).

Medical management

The goal of medical management is to rapidly restore cardiac output and prevent end-organ dysfunction. This may be achieved by the use of inodilators, which are the treatment of choice for the medical management of cardiogenic shock.[6]

Mechanisms of action and effects of inodilators

The most commonly used inodilator agents work through a common pathway, increasing intracellular cyclic adenosine monophosphate (cAMP) and calcium concentrations. These include β-adrenergic agonists, endogenous catecholamines, and phosphodiesterase inhibitors.

High dose inotropes have potentially damaging effects when administered in the acute phase of shock, a time when LV unloading is preferable to reduce MI size.[6] Adrenergic inotropes elevate stroke work and wall tension, increase myocardial oxygen consumption and deplete energy reserves.[6] These changes can result in endocardial necrosis and impaired diastolic function, with an overall negative effect on myocardial recovery.[6] Nevertheless, because stunned myocardium remains partially responsive to inotropic support, these agents are first-line therapy during and after reperfusion.

Dobutamine – β-adrenergic agonist

For isolated LV failure, ACC/AHA guidelines recommend beginning therapy with dobutamine unless profound hypotension is already present.[25] Dobutamine is a racemic mixture that stimulates β1- and β2-receptors.[27] The negative enantiomer is also an agonist for β1-receptors, whereas the positive enantiomer is a very weak partial agonist. Through its action on β1-receptors, dobutamine activates a guanine nucleotide regulatory cascade (via G proteins). This leads to increased adenylate cyclase activity and increased conversion of adenosine triphosphate (ATP) to the intracellular second messenger cAMP. Intracellular cAMP causes release of calcium from the sarcoplasmic reticulum. The calcium is used by myofibrillar proteins to increase contractility, resulting in increased stroke volume.[14]

To increase cardiac output, a dose of 2.5 to 15 µg/kg/min of dobutamine is usually used. The onset of action is within one to two minutes, but it may take as long as 10 minutes to see the peak effect of a particular infusion rate. The plasma half-life of dobutamine is two minutes. In studies with infusion periods greater than 24 to 72 hours, cardiac output was noted to return toward baseline values in some study subjects, raising the concern of pharmacologic tolerance with prolonged infusion.[14]

Dobutamine augments diastolic coronary blood flow to the ischaemic area and boosts myocardial contractility, thereby increasing cardiac output and lowering LV filling pressures.[26] For more profound hypotension (mean blood pressure <60 mm Hg), dopamine or noradrenaline are employed early to rapidly restore cerebral and renal perfusion.[27] In acute pulmonary hypertension, low-dose dobutamine (2-5 µg/kg/min) increases cardiac output and reduces pulmonary vascular resistance.[26,27]

Dopamine and endogenous catecholamines

For patients with low systemic vascular resistance, the combination of dopamine and noradrenaline is usually effective. In the face of continued deterioration, other agents such as vasopressin, adrenaline and phenylephrine are used, pending insertion of a circulatory support system. High doses of α-adrenergic agents must be used with caution because of the risk of limb ischaemia.[6]

Dopamine is an endogenous substance with dose-dependent effects. Acting on both β-adrenergic and dopamine-1 receptors at low doses (1-4 µg/kg/min), the α-adrenergic effects escalate more rapidly than β-adrenergic effects as the dose increases.[26,27] Dopamine raises blood pressure and cardiac output together with renal and splanchnic blood flow. However, dopamine also increases myocardial oxygen demand and exerts arrhythmogenic effects. Increasing the dose of dopamine to >20 µg/kg/min does not usually improve haemodynamic parameters further; this drug is more arrhythmogenic than noradrenaline.[27] At doses of ≤2 µg/kg/min, based on estimated lean body weight, dopamine causes vasodilation by direct stimulation of dopamine post-synaptic type 1 and pre-synaptic type 2 receptors in the splanchnic and renal arterial beds. Dopamine also has direct effects on renal tubular epithelial cells, resulting in increased natriuresis. Intermediate infusion rates of 2-5 µg/kg/min cause direct stimulation of β-adrenergic receptors in the heart and induce noradrenaline release from vascular sympathetic neurons. This results in increased heart rate and cardiac output. Infusion rates of 5-15 µg/kg/min generally stimulate β- and α-adrenergic receptors, leading to increased heart rate and peripheral vasoconstriction.[27] Higher doses induce tachycardia and increase myocardial oxygen consumption without a further fall in pulmonary artery pressure.[10,11] A major side effect of dopamine is tachycardia.

Another concern when using dopamine is correct dosing. The dopamine dose is based on lean body weight, which can be difficult to estimate.[27] There are published data that demonstrate increased mortality associated with dopamine use in septic shock trials. The SOAP study[28] (Sepsis Occurrence in Acutely Ill Patients) was an observational study involving 3,147 patients with shock, from 198 European ICUs. Patients were followed up for 60 days, until death or hospital discharge; 14.7% had septic shock and 35.4% received dopamine. This study suggested that administration of dopamine may be associated with increased mortality in shock. Subsequently, in 2010, a comparison was made between dopamine and noradrenaline in a multi-centre trial where 1,679 patients were randomised to receive either dopamine (858) or noradrenaline (821) as first-line vasopressor therapy.[27] The primary outcome was the mortality rate at 28 days after randomisation, and secondary endpoints included occurrence of adverse events and the days without need for organ support. In this comparative study, the death rates were similar in both groups, however the dopamine group experienced increased adverse events including skin ischaemia, arrhythmias and required additional agents to maintain blood pressure and cardiac output. Furthermore, a subgroup analysis demonstrated that dopamine (compared with noradrenaline) was associated with an increased rate of death at 28 days among the 280 cardiogenic shock patients, but not among the 1,044 patients with septic shock or 263 with hypovolemic shock.[29] Similarly, in a subsequent meta-analysis comparing dopamine to noradrenaline, more deaths and arrhythmias were associated with dopamine.[29]

Milrinone – phosphodiesterase inhibitors

Phosphodiesterase is the enzyme that breaks down intracellular cAMP to its inactive metabolite (5'AMP).[27] Milrinone is a bipyridine derivative that selectively inhibits the phosphodiesterase III enzyme, leading to increased intracellular cAMP.[26] This results in increased intracellular calcium concentration and myocardial contractility as well as acceleration of myocardial relaxation. Increased cAMP peripherally produces vasodilation in both the arterial and venous circulation. The end result is decreased systemic and pulmonary vascular resistance, decreased left and right ventricular filling pressures and increased cardiac output

Milrinone may be initiated with a loading dose of 50 µg/kg/min followed by a continuous infusion of between 0.25 and 1.0 µg/kg/min, or as an infusion without the loading dose. Most patients show improvements in haemodynamic function 5 to 15 minutes after initiation of therapy. The elimination half-life is 30 to 60 minutes when tested in healthy individuals, but it is doubled in patients with severe HF.[26] Milrinone is actively secreted in urine, with 60% and 90% of the drug being recovered within two and eight hours respectively following dosing. It requires dose reduction in patients with significant renal impairment (renal clearance 0-30 mL/min) due to its increased terminal half-life elimination.[30,31] In a study by Hasei *et al*[32] that studied the correlation between plasma milrinone concentration and renal function in patients with cardiac disease, patients with renal impairment who received a continuous infusion at 0.2 µg/kg/min reached a steady state by six hours and 64.5±9.5% of the drug was recovered in urine during the first 24 hours.

A major side effect of milrinone is hypotension, and milrinone is often administered without a loading dose in an attempt to minimise the decrease in blood pressure.[27] Other side effects include increased atrial and ventricular ectopy. Although milrinone's potential arrythmogenic properties have been most evident with oral long term therapy, evidence suggests that arrhythmias may also occur during short-term administration.[33] Asymptomatic increases in the number of ventricular ectopics (couplet, non-sustained VTs) and more serious ventricular arrhythmias may occur during short-term use of intravenous milrinone.[34-36] Atrial and ventricular arrhythmias have been noted in relation to rate of administration in some studies in which large loading doses (50-75 µg/kg) have been administered over less than 10 minutes.[35,36] In these studies, the incidence of atrial and ventricular arrhythmias were 5% and 5-9%, respectively. During phase II and phase III trials of milrinone, ventricular arrhythmias were reported in 12.1%, ventricular ectopic activity in 8.5%, non-sustained VT in 2.8%, sustained VT in 1% and VF in 0.2% of cases.[37] Fortunately, life-threatening ventricular arrhythmias are rare and when present have been associated with pre-existing abnormalities such as electrolyte disturbances. In these trials, the incidence of supraventricular tachycardias was 3.8% and neither of the arrhythmias was related to the plasma concentration of the drug.[37]

Levosimendan – calcium sensitiser

Levosimendan has global vasodilatory and anti-ischaemic properties, mediated by the activation of ATP-sensitive potassium channels in the mitochondria of smooth muscle cells and by endothelial inhibition.[38] This drug sensitises cardiac troponin C to the effects of intracellular calcium, thereby increasing contractility without an increase in myocardial oxygen consumption. The pulmonary vasodilatory effects lower pulmonary vascular resistance and increase cardiac output in acute heart failure. Levosimendan is particularly effective in right ventricular failure.[39] Adequate right ventricular function is necessary to avoid central venous hypertension and end-organ venous congestion.[39]

It is initiated with a loading dose of 6-12 µg/kg infused over 10 minutes followed by a continuous infusion of 0.1 µg/kg/min (up to 0.2 µg/kg/min) for the recommended duration of 24 hours with the response of the patient being assessed following the loading dose or 30-60 minutes following dose adjustment. Following the 24-hour infusion, the haemodynamic effects may persist for at least 24 hours and may be seen for up to nine days. It must be used with caution in patients with mild to moderate renal impairment and it is contraindicated in patients with severe renal impairment (creatinine clearance <30 mL/min) as this may lead to increased concentration of the active metabolites, which may lead to enhanced and longer haemodynamic effects.[40] The most common undesirable effects include ventricular tachycardia, hypotension and headache, as experienced by 53% of patients

in placebo-controlled trials (REVIVE programme /REVIVE I[41] and II[42]). In the REVIVE trials, the results of the primary endpoint also demonstrated that a greater number of patients were labelled as 'improved' with a smaller portion of patients labelled as 'worsened' over several time points.[42] B-type naturetic peptide was significantly reduced in the levosimendan group compared to placebo. Although not statistically significant, the levosimendan group had a higher death rate (15% *vs* 12%) and *post hoc* analysis identified SBP <100 mm Hg or DBP <60 mm Hg as risk factors associated with the increased death rate in the intervention group.

In a recent meta-analysis[43] exploring the effect of levosimendan on hospitalisation and mortality, including 5,480 patients from 45 RCTs, the overall mortality was 17.4% in the levosimendan-treated group compared to the control group mortality of 23.3%. This reduction in mortality was confirmed in placebo and dobutamine controlled trials in cardiology and cardiac surgery. Length of stay was also reduced in the levosimendan-treated group. However a greater number of patients experienced hypotension in the levosimendan-treated group (risk ratio 1.39, p=0.053). Overall, the suggestion is that levosimendan may reduce mortality in adults in both settings of cardiology and cardiac surgery.[43]

By contrast prostacyclins are not used in cardiogenic shock because of their systemic vasodilatory effects.[11] Both inotropes and vasodilators are complemented by the use of an intra-aortic balloon pump (IABP). Through a reduction in pulmonary artery pressure, the IABP can improve systemic blood pressure, RV efficiency, and coronary blood flow.[11]

Intra-aortic balloon counter pulsation

The ACC/AHA guidelines recommend early consideration of intra-aortic balloon counter pulsation placement for patients with cardiogenic shock who are candidates for an aggressive treatment strategy. The IABP is valuable for stabilising patients with cardiogenic shock. Introduced in the 1960s, the IABP is inserted into the descending aorta between the arch vessels and renal arteries.[44] The balloon (34 mL or 40 mL) inflates immediately after left ventricular ejection and is deflated before the onset of the following systole.[45] Accurate timing is essential for optimum performance. It increases diastolic coronary arterial perfusion and decreases systemic afterload without increasing myocardial oxygen demand.[45]

It must be noted that in the randomised SHOCK trial, use of IABP was strongly recommended in both the early revascularisation and in the conservative treatment arms.[5] IABP utilisation was 87% in this trial and may have contributed to the improved outcomes observed in both groups compared to historical controls.[5] The observed rates of IABP utilisation in US sites increased from 35% in GUSTO-I to 47% in GUSTO-III (p=0.001).[46] IABP is currently under-utilised in the setting of shock, and community or outlying hospitals have been encouraged to develop IABP programmes so that this treatment may be initiated before transfer whenever possible.[47] IABP is beneficial in improving borderline haemodynamics (a good prognostic sign), but is of dubious value in established CS. Among patients with acute anterior STEMI without shock, IABP plus primary PCI compared with PCI alone did not result in reduced MI size.[48] Interestingly, the recently published IABP-SHOCK trial has questioned the routine use of IABP in patients presenting with post-MI CS, reporting no difference in 30-day mortality in patients in whom early revascularisation was planned.[49]

- LVF secondary to myocardial infarction
- Ventricular septal rupture post myocardial infarction
- Acute mitral regurgitation
- Isolated right ventricular failure
- Tamponade
- Prior severe valvular disease
- Dilated cardiomyopathy
- Excess beta-blockade/calcium channel blockade
- Aortic dissection
- Pulmonary embolism

Table 2 Aetiology of cardiogenic shock in the combined SHOCK trial registry and trial.[5]

Mechanical ventilation

Mechanical ventilation must be used carefully in patients with cardiogenic shock.[1] The lowest tidal volume and positive end expiratory pressure are used to achieve oxygen saturations >92%. Hypercapnia (or hypercarbia) can increase pulmonary artery pressure and worsen RV function through vasoconstriction.[50] By contrast, hyperventilation decreases CO_2 level and pulmonary artery pressure. Hyperventilation is achieved by increasing the frequency of ventilation not the tidal volume.

Mechanical circulatory support

Due to the dismal prognosis associated with CS, medical therapy is often inadequate in isolation and therefore requires mechanical circulatory support (MCS) to relieve the ventricles, thereby minimising further injury partly through decreasing myocardial demand.[51] As a result, the haemodynamic status is improved allowing adequate or improved end-organ perfusion before definitive intervention takes place, be it cardiac transplantation or simply allowing time for the heart to recover.

In 2006, NICE released guidance on MCS with left ventricular assist devices (LVADs) as a bridge to cardiac transplantation or recovery. The main indications for patients with end-stage heart failure are:

- those awaiting donor heart for transplantation
- patients with severe acute decompensated heart failure (ADHF) syndromes from which myocardial recovery is anticipated (eg myocarditis) and
- sometimes used if weaning from cardiopulmonary bypass following cardiac surgery fails.

A variety of surgically implanted continuous-flow and pulsatile blood pumps have proven to be effective post-infarction.[52,53] The advantage of these devices is that central cannulation of atria, ventricles, and great arteries can bypass and unload the failing ventricle and provide blood flow of up to 10 L/min.[54] For left ventricular support, the ventricular assist

- Cardiogenic shock (related to surgery or not)
- Difficulty weaning from cardio-pulmonary bypass following cardiac surgery
- Graft failure following heart/lung transplantation
- In-hospital cardiac arrest
- Acute myocardial infarction
- Massive pulmonary embolism
- Acute pulmonary oedema
- Fulminant myocarditis
- Post-partum cardiomyopathy
- Drug overdose and cold water immersion
- Procedural support such as lung transplantation or airway procedures

Table 3 Indications for ECMO, modified from mechanical circulatory support for cardiogenic shock.[43]

device (VAD) drains the left atrium or ventricle and pumps blood into the aorta.[54] For right ventricular bypass, the right atrium is normally used for VAD inflow with blood pumped into the main pulmonary artery, thereby avoiding peripheral vascular complications.[54] The outcome depends on myocardial viability following revascularisation, pre-existing left ventricular dysfunction, and potential for recovery in stunned or hibernating myocardium. In contrast to percutaneously inserted systems, all centrally implanted pumps can be kept *in situ* for periods ranging from weeks to several years.[54] In support of this strategy, Dang *et al* showed that patients with acute anterior wall myocardial infarction and shock had improved survival at six and 12 months when early salvage LVAD implantation was undertaken before attempted revascularisation by coronary artery bypass graft (CABG) surgery.[55]

Extra-corporeal life support is more commonly referred to as extracorporeal membrane oxygenation (ECMO) and is designed to provide temporary support for less than a month. Its use was primitive in operating rooms before being extended for respiratory support in newborns in the 1970s, followed by its use to address cardio-respiratory failure in adults. Veno-venous ECMO (V-V ECMO) is used for respiratory support whereas veno-arterial ECMO (V-A ECMO) is used for cardio-respiratory support. Indications for ECMO are summarised in the (**Table 3**).[43] Its use may be justified where expected survival is reasonable (>50%) but is contraindicated where survival is low or disability is high[56] (10% and 30% respectively) in addition to the presence of terminal illness, irreversible neurological damage and multi-organ failure. Anatomical contra-indications include aortic dissection and severe aortic regurgitation.[57] Numerous outcome studies have been performed in relation to ECMO. In a study by Chung *et al*, of 134 CS patients recruited for ECMO, 50% were weaned and 42.5% survived to discharge.[58] In another study by Hei *et al*, 76% were weaned off ECMO and 63% survived to discharge.[59] In the study by Loforte *et al*, there were 47 survivors of 73 CS patients and 45% survived to discharge.[60] It has also been reported that both early and long-term survival rates are better in non-cardiotomy groups *vs* cardiotomy groups (63% *vs* 45% and 63% *vs* 33% respectively).[61] With ECMO, systemic anticoagulation with heparin is usually required; however newer heparin-bound ECMO circuits are available allowing reduced or no anticoagulation. The main complications associated with ECMO include bleeding and thrombosis.[62]

The TandemHeart (TH) is a percutaneous LVAD with a circuit connecting the left atrium to the femoral arteries. A venous cannula is placed via the femoral vein into the left atrium by performing a septotomy and then blood is delivered to either one or both femoral arteries in a non-pulsatile fashion. It is indicated during acute CS as a bridge to recovery or as a bridge to achieve a stable haemodynamic status in patients with a significant ischaemic burden during surgical or percutaneous revascularisation procedures.[47] Severe peripheral vascular disease is a contraindication for the placement of TH due to the method employed during placement of the left atrial catheter.[47] Relative contraindications include bleeding diasthesis, right heart failure and large ventricular septal defects.[63,64] Common complications include bleeding, lower limb ischaemia, infection of the implanted foreign body as well as complications associated with transeptal puncture.[57] Thiele *et al* examined the effect of TH in 18 CS patients following an ischaemic event and found that, when compared to patients without LVAD support, the cardiac output and mean arterial pressure were higher and pulmonary capillary wedge and central venous pressures were lower, resulting in reduced myocardial oxygen demand with enhancement of tissue perfusion.[65] In studies comparing TH to IABP, no significant difference in 30-day mortality was observed.[66,67]

The Impella system is another percutaneous LVAD that is placed across the aortic valve in a retrograde fashion. The inflow portion placed in the left ventricle aspirates blood and ejects it directly into the ascending aorta, leading to direct offloading of the left ventricle. Indications for its use include high risk PCIs and CS complicating acute coronary events.[43] Contraindications include the presence of LV thrombus, mechanical aortic valve, moderate-severe aortic stenosis/incompetence and peripheral vascular disease.[51] The Academic Medical Center Mechanical support for Acute Congestive Heart Failure (AMC MACH) in ST-elevation MI (STEMI) examined the safety of the impella device as an adjunct to high-risk PCI and found only one patient of a total of 19 patients experienced a serious device-related complication, ie bleeding requiring blood transfusion.[68] In another safety study (PROTECT), no device-related deaths were reported in the 20 patients who were recruited.[69] Furthermore, the AMC MACH 2 investigators recruited 20 patients with anterior STEMI treated with PCI to IABP or impella and found no differences in the primary outcome measures, device-related complications or adverse cerebral or cardiac events.[70] There was however a significant improvement in the LV function in patients supported with the impella device. This is in keeping with two large multi-centre observational registries (Europella and USpella) where patients in both groups underwent high-risk PCI with impella support and statistically significant improvement in LVEF was noted. [70,71]

Prognosis of CS

For patients receiving medical therapy and an IABP, serum lactate level >11 mmol/L, base deficit of >12 mmol/L, mean arterial pressure <55 mm Hg, urine output <50 mL over two hours, and infusion of adrenaline or noradrenaline >0.4 mg/kg/min, herald impending death.[1,6,11] Left atrial pressure >17 mm Hg and mixed venous saturation <65% reinforce the likelihood of poor outcome.[6] These patients have reached the stage of profound shock with little chance of recovery without urgent mechanical restoration of systemic blood flow. In patients with shock, acute inflammation and stent insertion can cause platelet activation and propagation of thrombus.[72] As well as lowering lipid levels, statins are known to have favourable effects on platelet adhesion, endothelial function, inflammation, and thrombosis.[73]

Cardiac power as a prognostic indicator

The concept of power reserve in CS was explored more than 20 years ago by Tan and Littler.[74,75] Cardiac power is the product of simultaneously measured cardiac output and mean arterial blood pressure. Coupling of these parameters provides a measure of cardiac hydraulic pumping ability and represents the energy input that the arterial system receives from the heart at the level of the aortic root. One watt (W) is the normal resting cardiac power output of an average-sized adult. During stress or exercise, the normal heart can generate up to 6 W.[14] In shock, the basal resting cardiac performance is depressed, but can be improved by boosting heart rate, preload, and contractility from resting valves.

Conclusion

Unfortunately, with respect to CS, a substantial gap persists between evidence-based recommendations and clinical practice. In particular, around 25% of patients do not benefit from reperfusion therapy and as few as 15% receive PCI within two hours of the onset of pain.[6] As a result, CS still threatens life in 5-10% of patients with STEMI, particularly in the presence of inappropriately low peripheral vascular resistance.[6] An aggressive management plan is necessary to interrupt the vicious cycle and prevent metabolic derangement and end-organ dysfunction.

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