Medications in Cardiogenic Shock

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Mei-Tzu Wang, Cheng Chung Hung, and Wei-Chun Huang

18.1 Introduction

Shock is circulatory failure with inadequate cellular oxygen utilization. Four potential pathophysiological mechanisms result in shock, including hypovolemic, cardiogenic, obstructive, and distributive factors. Cardiogenic shock (CS) decreases myocardial contractility and is the most common cause of death in patients with acute myocardial infarction (AMI). To differentiate the type and cause of shock, medical history, physical examination, and clinical investigations are important. Focused echocardiography offers advanced information for differentiation and should be performed as soon as possible in any shock patient.

AMI with subsequent ventricular dysfunction is the most frequent cause of CS accounting for about half of cases, and other causes of CS include end-stage cardiomyopathy, advanced valvular heart disease, myocarditis, and cardiac arrhythmias. Around 5–15% AMI patients complicated with CS. For AMI patient, early revascularization is the most important strategy [1]. In addition to percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), intra-aortic balloon pumping (IABP), active assist devices, inotropes, and vasopressors are widely used

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for CS management. Resuscitation should be started early and adequately to prevent organ dysfunction worsening. The basic resuscitation principles for patients with CS are based on the "VIP rule," including ventilate (oxygen administration), infuse (fluid resuscitation), and pump (vasoactive agents). The chapter focused on inotropic support in cardiogenic shock patient.

18.2   Definition and Initial Assessment

CS is a lethal disease and a state of reduced cardiac output and critical end organ hypoperfusion. It ranges from mild hypoperfusion to profound shock and multi-organ system dysfunction. Established criteria for the diagnosis of CS are (1) systolic blood pressure (SBP) <90 mmHg for >30 min, vasopressors required to achieve SBP ≥90 mmHg, or a reduction of cardiac index (<1.8 L/min/m^2 without support and less than 2.2 L/min/m^2 with support); (2) pulmonary congestion or elevated left ventricular filling pressures (pulmonary capillary wedge pressure > 18 mmHg); and (3) impaired organ perfusion. Inadequate organ perfusion contains at least one of the following criteria: (a) altered mental status; (b) cold, clammy skin; (c) oliguria; and (d) increased serum lactate. Clinical signs of tissue hypoperfusion are apparent through three "windows" of the body: (1) skin (cold and clammy skin, with vaso-constriction and cyanosis), (2) kidney (urine output of <0.5 mL per kilogram of body weight per hour), (3) and brain (altered mental state, which typically includes obtundation, disorientation, and confusion). Hyperlactatemia is typically present, indicating abnormal cellular oxygen metabolism. The normal blood lactate level is approximately 1 mmol per liter, but the level is increased (>1.5 mmol per liter) in acute circulatory failure. A full clinical assessment contains skin color and tempera-ture, jugular venous distention, and peripheral edema. Point-of-care echocardio-gram offers advanced information for diagnosis via the evaluations of pericardial effusion, left and right ventricular size and function, and respiratory variations in vena cava dimensions, the calculation of the aortic velocity–time integral, and a measure of stroke volume [1–3].

18.3   Initial Approach to the Patient in Cardiogenic Shock (VIP)

Irrespective of early revascularization by PCI or CABG, the basic principle of treat-ment for CS is "VIP rules" to maintain ventilation, obtain euvolemia with volume expansion, and administer vasopressors or inotropes for the prevention or treatment of multi-organ dysfunction.

18.3.1 Ventilation

Oxygen should be administered immediately to increase oxygen delivery. Pulse oximetry is not reliable due to peripheral vasoconstriction, and blood gas

monitoring is required for precise determination of oxygen. For CS patients presenting with severe dyspnea, hypoxemia, persistent, or worsening acidemia (pH <7.30), symptoms could rapidly progress in respiratory failure and cardiac arrest, which prompted physicians to perform endotracheal intubation and invasive mechanical ventilation. Invasive mechanical ventilation also reduces the oxygen demand of respiratory muscles and decreases left ventricular afterload by increasing intrathoracic pressure. After the initiation of invasive mechanical ventilation, an abrupt decrease in arterial pressure implies hypovolemia, and sedative agents in minimum should be kept to avoid further decrease in arterial pressure and cardiac output.

18.3.2 Fluid Resuscitation and Objective Fluid Status Evaluation

The pragmatic endpoints for fluid resuscitation are to achieve the plateau portion of the Frank–Starling curve and become preload-independent status. In patients receiving mechanical ventilation, signs of fluid responsiveness could be identified directly from beat-by-beat stroke-volume measurements with the use of cardiac-output monitors or indirectly from observed variations in pulse pressure on the arterial-pressure tracing during the ventilator cycle. There are several limitations in such bedside inferences, including that patients must have no spontaneous breathing effort (usually requires the administration of sedatives or muscle relaxants), receive ventilation with relatively large tidal volumes, and be free of major arrhythmia and right ventricular dysfunction. A passive leg-raising test is an alternative method, but the effect is transient and requires a rapid response device.

Four elements are incorporated in fluid challenge, including (1) the type of fluid, (2) the rate of fluid administration, (3) the objective of fluid challenge, and (4) the safety limit. First, crystalloid solutions are the first choice, and the use of albumin to correct severe hypoalbuminemia may be reasonable in some patients. Second, fluids should be infused rapidly to achieve a quick response but not fast to develop an artificial stress response. (i.e., infuse 300–500 mL of fluid during a period of 20–30 min). Third, the objective of the fluid challenge contains an increase in SBP, a decrease in heart rate, or an increase in urine output. Finally, the safety limit is to avoid fluid infusion-associated pulmonary edema, and central venous pressure of a few millimeters of mercury above the baseline value is usually set to prevent fluid overload, although it is not a perfect guideline. Because hemodynamic management depends on optimal filling pressures, pulmonary artery catheters, Pulse Contour Cardiac Output (PiCCO), or other measure systems should be used in all complicated patients [4].

18.4   Vasoactive and Inotropic Agents

Catecholamines are used in near 90% CS patients, but there is limited evidence from randomized trials to compare different catecholamines. In SOAP II (Sepsis Occurrence in Acutely Ill Patients) trial, dopamine was shown to have higher rates of arrhythmias and mortality in CS subgroup [5]. Nevertheless, clinical and

methodological concerns have raised questions about the external validity and applicability of the findings because SOAP II trial did not have an operationalized definition of CS. The predefined CS subgroup had lower mortality with norepinephrine [5]. Therefore, norepinephrine should be the first choice as vasopressor in patients with CS. European STEMI guidelines recommend dopamine (IIa/C recommendation) over norepinephrine (IIb/B recommendation), which are partly confusing and are in contrast to current evidence, but it is also stated that norepinephrine is preferred over dopamine when the blood pressure is low.

There are no clear SBP or mean arterial pressure (MAP) recommendations for CS patients. MAP targets are often extrapolated from non-CS populations and 65–70 mm Hg has been considered a reasonable target. However, higher blood pressure is not associated with beneficial outcome [6]. CS is a hemodynamically heterogeneous disorder; thus despite improvements in hemodynamic variables, microcirculatory dysfunction may persist. Inotropic and vasopressor agents have been recommended and used in the treatment of patients with shock. Despite the benefit of myocardial contractility, the pharmacodynamics of different inotropic agents and associated side effects (arrhythmias and increased myocardial oxygen consumption) may increase mortality [7]. The use of catecholamine and vasoconstrictors should be restricted to the shortest duration and the lowest possible dose. The ideal inotrope would increase cardiac output and reduce ventricular filling pressures and mortality without adverse effects. Several studies still continue to develop ideal inotrope for the treatment of CS [8]. Omecamtiv mecarbil is a promising new drug for stable heart failure that exerts inotropic effects by activating cardiac myosin [9]. Gene therapy is another area and further results of these new approaches are awaited [10]. Medications and their characteristics prescribed in CS patients are listed in Table 18.1 [11]. Initial vasoactive management strategies in different types of CS are presented in Table 18.2.

18.5 Vasoactive Agents

18.5.1 Norepinephrine

Norepinephrine is a naturally occurring catecholamine and acts mainly on α-adrenergic receptor but has small effect on beta receptor. Norepinephrine can increase blood pressure by constricting small vessels. The increasing blood pressure will stimulate the parasympathetic tone, with little change in heart rate or cardiac output. The well-known adverse effects are reduced renal and splanchnic blood flow, especially in patients needing volume expansion. Norepinephrine is associated with fewer arrhythmias and may be the vasopressor of choice in many patients with CS. However, in light of SOAP II trial limitations, the optimal first-line vasoactive medication in CS remains unclear, but norepinephrine should be considered as the vasopressor of first choice.

Table 18.1 Medications used in cardiogenic shock patients

Medication	Class	Mechanism of action	Receptor binding	Half-life	Usual infusion dose	Hemodynamic effect
Vasopressor/inotropes						
Dopamine (0.5–2 μg/kg/min)	Catecholamine	β- and α-adrenergic and dopaminergic agonist	α_1 (−) β_1 (+) β_2 (−) D (+++)	2 min	0.5–2 μg/kg/min	↑CO
Dopamine (5–10 μg/kg/min)	Catecholamine	β- and α-adrenergic and dopaminergic agonist	α_1 (+) β_1 (+++) β_2 (+) D (++)	2 min	5–10 μg/kg/min	↑↑CO, ↑SVR
Dopamine (10–20 μg/kg/min)	Catecholamine	β- and α-adrenergic and dopaminergic agonist	α_1 (+++) β_1 (++) β_2 (−) D (++)	2 min	10–20 μg/kg/min	↑↑SVR, ↑CO
Norepinephrine	Catecholamine	α-adrenergic agonist	α_1 (++++) β_1 (++) β_2 (+) D (−)	2–2.5 min	0.05–0.4 μg/kg/min	↑↑SVR, ↑CO
Epinephrine	Catecholamine	α- and β-adrenergic blockade	α_1 (++++) β_1 (+++++) β_2 (++++) D (−)	2 min	0.01–0.5 μg/kg/min	↑↑CO, ↑↑SVR
Phenylephrine			α_1 (+++) β_1 (−) β_2 (−) D (−)	5 min	0.1–10 μg/kg/min	↑↑SVR

(continued)

Table 18.1 (continued)

Medication	Class	Mechanism of action	Receptor binding	Half-life	Usual infusion dose	Hemodynamic effect
Vasopressin	Vasopressor	Stimulate V_1 receptors in vascular smooth muscle	V_1 and V_2 vasopressin receptor agonist	10–20 min	0.02–0.04 U/min	↑↑SVR, ↔PVR
Inodilators						
Dobutamine	Catecholamine	β-adrenergic blockade	α_1 (+) β_1 (++++) β_2 (++) D (−)	2–3 min	2.5–20 µg/kg/min	↑↑CO, ↓SVR, ↓PVR
Isoproterenol			α_1 (−) β_1 (++++) β_2 (+++) D (−)	2.5–5 min	2.0–20 µg/min	↑↑CO, ↓SVR, ↓PVR
Milrinone	PDE inhibitor	Increases cAMP by inhibiting PDE3	PDE3	2 h	0.125–0.75 µg/kg/min	↑CO, ↓SVR, ↓PVR
Enoximone		PDE3 inhibitor	PDE3	3–6 h	2–10 µg/kg/min	↑CO, ↓SVR, ↓PVR
Levosimendan	Calcium sensitizer	Increases sensitivity of troponin C to intracellular Ca^{2+}	Myofilament Ca^{2+} sensitizer, PDE3 inhibitor	1 h (metabolites up to 80 h)	0.05–0.2 µg/kg/min	↑CO, ↓SVR, ↓PVR

cAMP cyclic adenosine monophosphate, *CO* cardiac output, *D* dopamine, *PDE* phosphodiesterase inhibitor, *PVR* pulmonary vascular resistance, *SVR* systemic vascular resistance

Table 18.2 Initial vasoactive management strategies in different types of cardiogenic shock

Cause or presentation	Vasoactive strategies	Hemodynamic rationale	Further management
Classic wet and cold (low CI and high SVR)	1. Norepinephrine or dopamine 2. Inotropic agent	1. Norepinephrine (↑HR or arrhythmias) 2. Dopamine (↓HR preferred but associated with higher risk of arrhythmias)	Inotropic agent when stabilized and after revascularization (MI only)
Euvolemic cold and dry (LVEDP may be low, and patients may tolerate fluid boluses)	1. Norepinephrine or dopamine 2. Inotropic agent 3. Small fluid boluses	1. Norepinephrine (preferred in ↑HR or arrhythmias) 2. Dopamine (↓HR preferred but associated with higher risk of arrhythmias)	Inotropic agent when stabilized and after revascularization (MI only)
Vasodilatory warm and wet or mixed cardiogenic and vasodilatory (low SVR)	Norepinephrine		Hemodynamics-guided therapy
RV shock	1. Fluid boluses 2. Norepinephrine, dopamine, or vasopressin 3. Inotropic agents 4. Inhaled pulmonary vasodilators	1. Maintaining preload 2. Lowering RV afterload 3. Treat absolute or relative bradycardias 4. Maintain atrioventricular synchrony	Inotropic agent after initial hemodynamic stabilization and revascularization
Normotensive shock (SBP >90 mm Hg and relatively high SVR)	Inotropic agent or vasopressor		
Aortic stenosis	1. Phenylephrine or vasopressin 2. In patients with reduced LVEF, echocardiography or PAC-guided dobutamine titration	1. An afterload-dependent state 2. Inotropy may not improve hemodynamics if LVEF is preserved	Surgical aortic valve replacement or balloon valvuloplasty and/or transcatheter aortic valve replacement
Aortic regurgitation	1. Dopamine 2. Temporary pacing	Maintaining an elevated HR may shorten diastolic filling time and reduce LVEDP	Surgical aortic valve replacement

Table 18.2 (continued)

Cause or presentation	Vasoactive strategies	Hemodynamic rationale	Further management
Mitral stenosis	1. Phenylephrine or vasopressin 2. Esmolol or amiodarone	1. A preload-dependent state 2. Slowing the HR to increase diastolic filling time 3. Maintain atrioventricular synchrony to improve preload	Surgical mitral valve replacement or balloon valvuloplasty
Mitral regurgitation	1. Norepinephrine or dopamine 2. Inotropic agents 3. Temporary MCS, including IABP	1. Afterload reduction may help reduce LVEDP 2. IABP may reduce regurgitation fraction by reducing afterload and increasing CI	Surgical mitral Valve replacement/repair and percutaneous edge-to-edge repair
Post-infarction ventricular septal defect	1. Classic wet and cold considerations 2. Temporary MCS, including IABP	IABP reduces shunt fraction by reducing afterload and increasing CI	Cardiac surgical referral for repair or percutaneous interventional umbrella closure
Dynamic LVOT Obstruction	1. Fluid boluses 2. Phenylephrine or vasopressin 3. Avoid inotropic agents 4. Avoid vasodilating agents 5. Esmolol or amiodarone 6. RV pacing	1. Increasing preload and afterload reduces dynamic gradients 2. Reduce inotropy and ectopy 3. Maintain atrioventricular synchrony 4. Induce ventricular dyssynchrony	
Bradycardia	1. Chronotropic agents: atropine, isoproterenol, dopamine, dobutamine, and epinephrine 2. Temporary pacing	Identifying and treating underlying cause of bradycardia	
Pericardial tamponade	1. Fluid bolus 2. Norepinephrine		Pericardiocentesis or surgical pericardial window

CI cardiac index, *CS* cardiogenic shock, *HR* heart rate, *IABP* intra-aortic balloon pump, *LVEDP* left ventricular end-diastolic pressure, *LVEF* left ventricular ejection fraction, *LVOT* left ventricular outflow tract, *MCS* mechanical circulatory support, *MI* myocardial infarction, *PAC* pulmonary artery catheter, *PVR* pulmonary vascular resistance, *RV* right ventricular, *SBP* systolic blood pressure, *SVR* systemic vascular resistance

18.5.2 Epinephrine

Epinephrine is a naturally occurring catecholamine which acts on both α- and β-receptor. Epinephrine has predominantly β-adrenergic effects in lower dosage, which increases myocardial contraction and heart rate. In higher dosage, it acts on α-adrenergic receptor and constricts peripheral small vessels which can increase blood pressure. Epinephrine is associated with arrhythmia and decreases splanchnic blood flow. It also increases blood lactate levels, probably by increasing cellular metabolism. Prospective, randomized studies have not shown any beneficial effects of epinephrine over norepinephrine in septic shock. Therefore, epinephrine was considered as a second-line agent for severe cardiogenic shock.

18.5.3 Vasopressin

Vasopressin is a hormone that binds to its own receptors. Binding to V1 receptors leads to vasoconstriction due to contraction of the vascular smooth muscle, while V2 stimulation increases renal free water reabsorption. Norepinephrine is effective and safe for treating patients in septic shock and enables tapering down other vasopressors. Vasopressin deficiency can generate in those patients with severe distributive shock. Administration of low-dose vasopressin may result in substantial increases in arterial pressure. Addition of low-dose vasopressin to norepinephrine in the treatment of patients with septic shock was safe and may have been associated with a survival benefit for patients with forms of shock that were not severe and for those who also received glucocorticoids. Vasopressin should not be used at doses higher than 0.04 U per minute and should be administered only in patients with a high level of cardiac output [12, 13].

18.6   Inotropic Agents

18.6.1 Dopamine

Dopamine is a natural precursor of norepinephrine and epinephrine. Its effects are dose-dependent: at low doses (1–2 µg/kg/min), it binds to dopaminergic receptors and has a vasodilatory effect, while at higher doses (5–10 µg/kg/min), it acts as a β1 receptor agonist and thus has inotropic effects. At even higher levels (>10 µg/kg/min), dopamine stimulates α-adrenergic receptors, leading to vasoconstriction and an increase in BP. Previously, dopaminergic effects at very low doses (<3 µg/kg/min) may selectively dilate the hepatosplanchnic and renal circulations, of which the protective effect on renal function was not supported by controlled trials, and its routine use for this purpose is no longer recommended [14]. Dopaminergic stimulation may be associated with undesired endocrine effects on the hypothalamic–pituitary system and reduction of the release of prolactin, resulting in immunosuppression.

18.6.2 Dobutamine

Dobutamine acts on the myocardium by stimulating β1-adrenergic receptors to increase heart rate and enhance myocardial contractility, and it also acts on smooth muscle via β2 receptors to induce system vasodilation and lower blood pressure. As a result, dobutamine can increase cardiac output and reduce LV filling pressures. Dobutamine may be given simultaneously with norepinephrine to improve cardiac contractility. It may improve capillary perfusion in patients with septic shock, independent of its systemic effects. For CS patients, dobutamine is less likely to induce tachycardia than isoproterenol. Intravenous doses in excess of 20 μg/kg/min could not provide additional benefit. Dobutamine has limited effects on arterial pressure, although pressure may increase slightly in patients with myocardial dysfunction or decrease slightly in patients with underlying hypovolemia.

18.6.3 Levosimendan

Levosimendan increases the myocardium sensitivity of troponin C to intracellular calcium and thus has inotropic and lusitropic properties. It also acts on ATP-dependent potassium channels, making the relaxation of vascular smooth muscle associated with coronary and peripheral vasodilation. Levosimendan induces vasodilation and improves myocardial contractility without increasing oxygen requirements and affecting blood pressure or heart rate. Compared to enoximone, levosimendan showed a borderline survival benefit in AMI complicated by cardiogenic shock or low cardiac output syndrome (hazard ratio 0.33; 95% confidence interval 0.11–0.97) and had only small differences in hemodynamics and length of hospital stay [15]. This study also showed that there was no difference between levosimendan and dobutamine in cardiogenic shock. Furthermore, levosimendan has a half-life of several days, which limits the practicality of its use in acute shock states.

18.6.4 Phosphodiesterase Inhibitors (Milrinone and Enoximone)

By inhibiting PDE3, milrinone prevents degradation of cyclic adenosine monophosphate (cAMP) and increases cAMP levels, which promotes calcium uptake by cardiomyocytes and increases myocardial contractility without affecting heart rate. In vascular smooth muscle, it reduces the degradation of cAMP and accelerates the removal of intracellular calcium, leading to relaxation and vasodilation. These agents reinforce the effects of dobutamine by decreasing the metabolism of cyclic AMP. Milrinone may also be useful in patients recently treated with beta-blockers or when β-adrenergic receptors are downregulated. However, phosphodiesterase type III (PDE III) inhibitors have long half-lives (4–6 h) and may complicate with unacceptable adverse

effects in patients with hypotension. Thus, intermittent and short-term infusions of small doses of PDE III inhibitors may be preferable to a continuous infusion in shock states.

18.7 Outcome

CS remains the leading cause of in-hospital mortality in the setting of an acute MI. Most longitudinal studies and registries have reported a decline in MI-associated CS mortality. The prevalence of CS from 6 to 10% in the overall population and from 7 to 12% among patients >75 years of age presenting with STEMI was reported in an analysis of the Nationwide Inpatient Sample Database between 2003 and 2010 [16]. In-hospital mortality decreased from 45 to 34% over the same time frame, although mortality rates remained high (55%) in patients >75 years of age. In the IABP-SHOCK II trial, despite inotropic and vasopressor therapy, in addition to the benefit of intra-aortic balloon counterpulsation, mortality in patients with CS complicating AMI was still around 40%. Mortality in CS patients occurs mainly in the first 3 days. Thus, besides medical therapy, mechanical circulatory support devices should be considered as soon as possible in CS patients [2].

18.8 Conclusion

CS decreases myocardial contractility and represents the majority causes of death in patients with AMI. It can result in both acute and subacute derangements to the entire circulatory system, including the peripheral vasculature. A full clinical assessment and point-of-care echocardiogram offer more information for differentiation of different mechanisms of shock. The initial approach and basic principle of treatment for CS are "VIP rules" to maintain ventilation, obtain euvolemia with volume expansion, and administer vasopressors or inotropes for the prevention or treatment of multi-organ dysfunction. Stimulation of each type of adrenergic receptor has potentially beneficial and harmful effects. For example, β-adrenergic stimulation increases blood flow but also increases heart rate and elevates the risk of myocardial ischemia; hence, the use of pure β-adrenergic agent (i.e., isoproterenol) is limited for patients with severe bradycardia. At the other extreme, α-adrenergic stimulation increases vascular tone but decreases cardiac output and impairs tissue blood flow, especially in the hepatosplanchnic region. For this reason, phenylephrine is rarely indicated. Adrenergic agonists characterize rapid onset of action, high potency, and short half-life and thus are the first-line vasopressors. In order to prevent tissue hypoperfusion and organ dysfunction, inotropes and vasopressors are essential in the management of patients in CS to maintain a mean arterial pressure of 65–70 mmHg. Physicians should keep in mind to administer vasopressor temporarily while fluid resuscitation is ongoing and discontinue it as soon as possible after hypovolemia has been corrected.

18.9   Case Example: Successful Medical Management of Cardiogenic Shock

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18.9.1 Case Example

A 58-year-old male suffered from inferior wall STEMI. His blood pressure was low before primary PCI, which was shown as 90/60 mmHg. Fluid challenge was provided. During primary PCI, his blood pressure dropped to 80/50 mmHg with junctional rhythm, while blood clot was aspirated (Figs. 18.1 and 18.2). Therefore, atropine 1 mg was injected immediately, but in vain. Norepinephrine 100 mcg were injected directly via the coronary artery (Fig. 18.3). After 10 s, sinus tachycardia regained, and his blood pressure increased to 120/80 mmHg. Norepinephrine 10 mcg/kg/min was used to infuse continuously via the peripheral vein, and his vital sign remained stable with inotropic agents support (Figs. 18.4 and 18.5).

Fig. 18.1 Coronary image before percutaneous coronary intervention
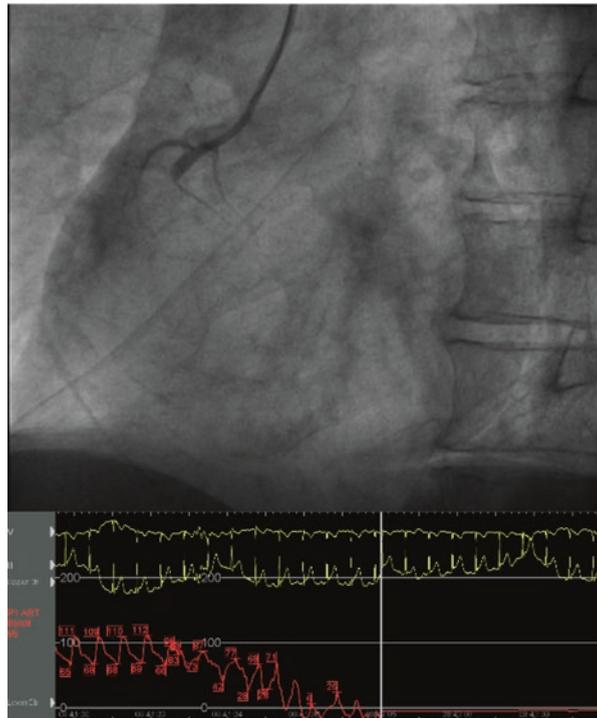
Fig. 18.2 Coronary image
after thrombus aspiration
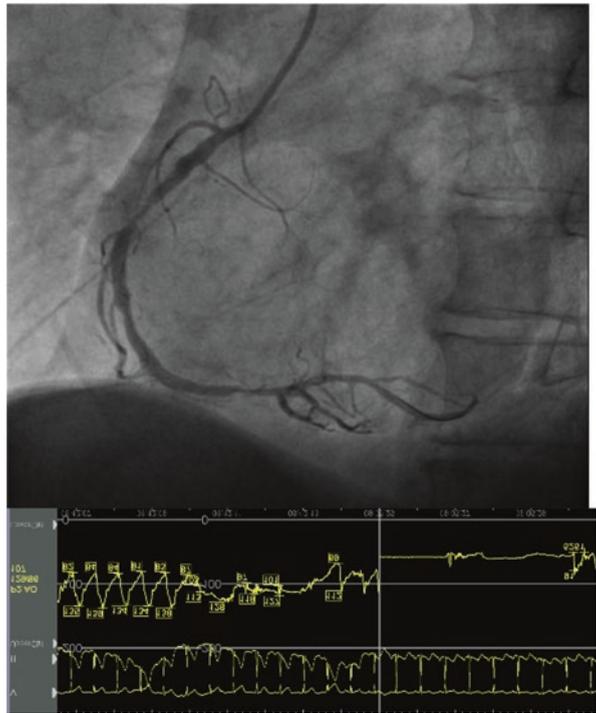
Fig. 18.3 Norepinephrine
was used due to low blood
pressure
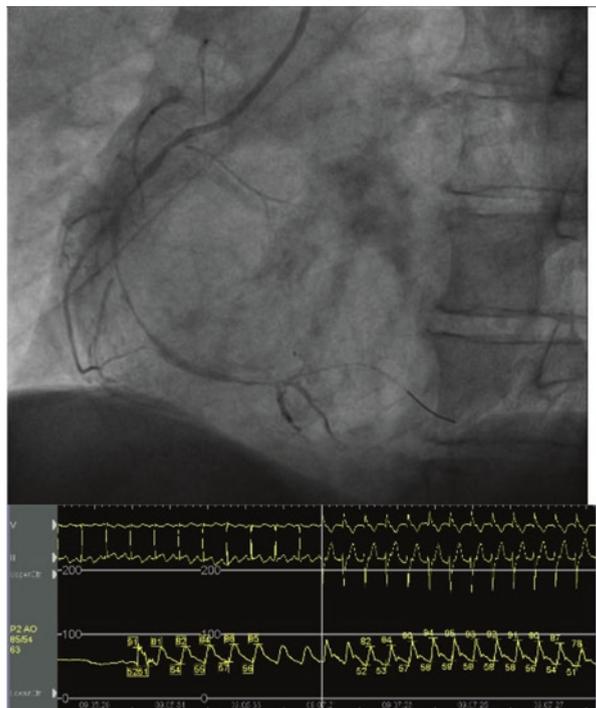
Fig. 18.4 After norepinephrine infusion, blood pressure increases rapidly
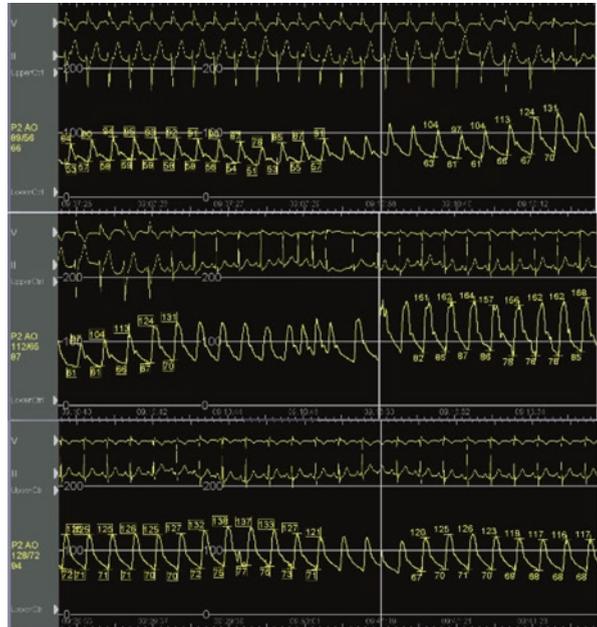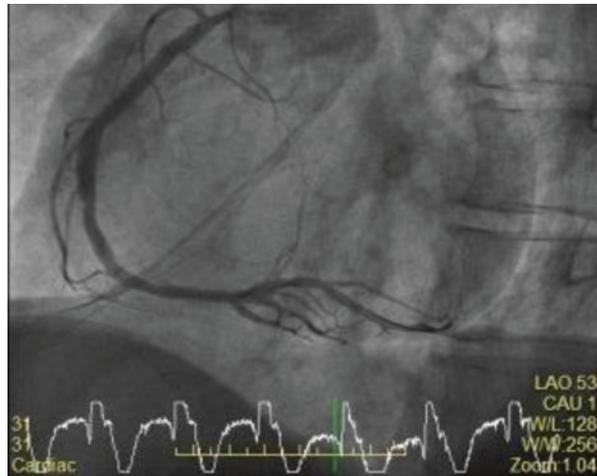

Fig. 18.5 Final images

References

1. Hochman JS, Sleeper LA, Webb JG, et al. Early revascularization in acute myocardial infarction complicated by cardiogenic SHOCK. SHOCK investigators. Should we emergently revascularize occluded coronaries for cardiogenic shock. N Engl J Med. 1999;341:625–34.
2. Thiele H, Zeymer U, Neumann FJ, Ferenc M, Olbrich HG, Hausleiter J, Richardt G, Hennersdorf M, Empen K, Fuernau G, Desch S, Eitel I, Hambrecht R, Fuhrmann J, BoÅNhm M, Ebelt H, Schneider S, Schuler G, Werdan K, IABPSHOCK II Trial Investigators. Intraaortic balloon support for myocardial infarction with cardiogenic shock. N Engl J Med. 2012;367:1287–96. https://doi.org/10.1056/NEJMoa1208410.

3. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, GonzaÅLlez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure of the European Society of Cardiology (ESC) [published correction appears in *Eur Heart J*. 2016;38:ehw383]. Eur Heart J. 2016;37:2129–200. https://doi.org/10.1093/eurheartj/ehw128.
4. Vincent JL, De Backer D. Circulatory shock. N Engl J Med. 2013;369(18):1726–34.
5. De Backer D, Biston P, Devriendt J, Madl C, Chochrad D, Aldecoa C, Brasseur A, Defrance P, Gottignies P, Vincent JL, SOAP II Investigators. Comparison of dopamine and norepinephrine in the treatment of shock. N Engl J Med. 2010;362:779–89. https://doi.org/10.1056/NEJMoa0907118.
6. Werdan K, Russ M, Buerke M, Delle-Karth G, Geppert A, SchoÅNndube FA, German Cardiac Society, German Society of Intensive Care and Emergency Medicine, German Society for Thoracic and Cardiovascular Surgery, Austrian Society of Internal and General Intensive Care Medicine; German Interdisciplinary Association of Intensive Care and Emergency Medicine, Austrian Society of Cardiology, German Society of Anaesthesiology and Intensive Care Medicine, German Society of Preventive Medicine and Rehabilitation. Cardiogenic shock due to myocardial infarction: diagnosis, monitoring and treatment: a German- Austrian S3 Guideline. Dtsch Arztebl Int. 2012;109:343–51. https://doi.org/10.3238/arztebl.2012.0343.
7. Amado J, Gago P, Santos W, Mimoso J, de Jesus I. Cardiogenic shock: inotropes and vasopressors. Rev Port Cardiol. 2016;35(12):681–95.
8. Arrigo M, Mebazaa A. Understanding the differences among inotropes. Intensive Care Med. 2015;41(5):912.
9. Francis GS, Bartos JA, Adatya S. Inotropes. J Am Coll Cardiol. 2014;63:2069–78.
10. Jessup M, Greenberg B, Mancini D, et al. Calcium upregulation by percutaneous administration of gene therapy in cardiac disease (CUPID): a phase 2 trial of intracoronary gene therapy of sarcoplasmic reticulum Ca2+-ATPase in patients with advanced heart failure. Circulation. 2011;124:304–13.
11. van Diepen S, Katz JN, Albert NM, Henry TD, Jacobs AK, Kapur NK, Kilic A, Menon V, Ohman EM, Sweitzer NK, Thiele H, Washam JB, Cohen MG. Contemporary management of cardiogenic shock: a scientific statement from the American Heart Association. Circulation. 2017;136(16):e232–68.
12. Russell JA, Walley KR, Singer J, et al. Vasopressin versus norepinephrine infusion in patients with septic shock. N Engl J Med. 2008;358:877–87.
13. Russell JA, Walley KR, Gordon AC, et al. Interaction of vasopressin infusion, corticosteroid treatment, and mortality of septic shock. Crit Care Med. 2009;37:811–8.
14. Bellomo R, Chapman M, Finfer S, Hickling K, Myburgh J. Low-dose dopamine in patients with early renal dysfunction: a placebo-controlled randomised trial. Lancet. 2000;356:2139–43.
15. Unverzagt S, Wachsmuth L, Hirsch K, Thiele H, Buerke M, Haerting J, Werdan K, Prondzinsky R. Inotropic agents and vasodilator strategies for acute myocardial infarction complicated by cardiogenic shock or low cardiac output syndrome. Cochrane Database Syst Rev. 2014;1:CD009669.
16. Kolte D, Khera S, Aronow WS, Mujib M, Palaniswamy C, Sule S, Jain D, Gotsis W, Ahmed A, Frishman WH, Fonarow GC. Trends in incidence, management, and outcomes of cardiogenic shock complicating ST-elevation myocardial infarction in the United States. J Am Heart Assoc. 2014;3:e000590. https://doi.org/10.1161/JAHA.113.000590.

Further Readings

Amado J, Gago P, Santos W, Mimoso J, de Jesus I. Cardiogenic shock: inotropes and vasopressors. Rev Port Cardiol. 2016;35(12):681–95.
van Diepen S, Katz JN, Albert NM, Henry TD, Jacobs AK, Kapur NK, Kilic A, Menon V, Ohman EM, Sweitzer NK, Thiele H, Washam JB, Cohen MG. Contemporary Management of

Cardiogenic Shock: a scientific statement from the American Heart Association. Circulation. 2017;136(16):e232-e268.

Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, GonzaÅLlez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure of the European Society of Cardiology (ESC) [published correction appears in Eur Heart J. 2016;38:ehw383]. Eur Heart J. 2016;37:2129–200. https://doi.org/10.1093/eurheartj/ehw128.

Thiele H, Ohman EM, Desch S, Eitel I, de Waha S. Management of cardiogenic shock. Eur Heart J. 2015;36(20):1223–30.

Vincent JL, De Backer D. Circulatory shock. N Engl J Med. 2013;369(18):1726–34.