A "bridge to decision" for patients with refractory acute cardiogenic shock

Extracorporeal membrane oxygenation for acute cardiogenic shock

Markus J. Wilhelm

Clinic for Cardiovascular Surgery, University Hospital, Zurich, Switzerland

Summary

Veno-arterial extracorporeal membrane oxygenation (ECMO) is utilised as a short-term mechanical circulatory assist device for treatment of refractory acute cardiogenic shock. After a period of support, called "bridge to decision", the options for ensuing therapy include weaning from ECMO, switch to a long-term ventricular assist device, or heart transplantation, depending on the occurrence of myocardial recovery and the presence of comorbidities. The femoral vessels are the standard access for implantation. The subclavian artery or central cannulation are the alternatives in peripheral artery disease. Early survival rates amount to approximately 40%. Patients who survived the early period have a good long-term survival. The poor outcome of ECMO therapy results from the high frequency of complications, including vascular, bleeding, neurological, infectious and renal adverse events, as well as from the particular circumstances of cardiogenic shock. The condition triggers a cascade of systemic inflammation, which is aggravated depending on the duration of the hypotensive period. The extent of the subsequent multiorgan dysfunction syndrome substantially affects outcome. As a consequence, early ECMO implantation is advocated. In unclear neurological conditions and severely compromised end-organ function, the anticipated poor outcome has to be weighed very carefully against ethical and economical aspects before ECMO is initiated.

Key words: bridge to decision; veno-arterial; inflammatory cascade; multiorgan dysfunction syndrome; survival

Introduction

Extracorporeal membrane oxygenation (ECMO) is established as veno-venous ECMO (vvECMO) for respiratory failure and as veno-arterial ECMO (vaECMO) for cardiogenic shock which may result from acute or acute-on-chronic heart failure and from postcardiotomy syndrome subsequent to cardiac surgery. Therapy with ECMO has been steadily increasing over the past few years. This is mainly due to its application as vvECMO in respiratory failure, particularly acute respiratory distress syndrome (ARDS). Since the CESAR trial documented a survival and quality-of-life benefit for ARDS patients treated with vvECMO as compared with those on ventilator therapy only [1], the use of ECMO for ARDS has grown tremendously. Also for cardiac failure, usage of vaECMO becomes more and more popular. The technical advancement of ECMO pumps and tubing, as well as the unfavourable results of the SHOCK II trial for the use of the intraaortic ballon pump in cardiogenic shock [2] have led to a broader application of vaECMO. In postcardiotomy syndrome, vaECMO therapy is associated with rather poor results due to the critical myocardial damage during cardiac surgery [3]. The management of ECMO is still challenging and should be reserved for experienced interdisciplinary teams, consisting of cardiac surgeons, intensivists and cardiologists. Nonphysician personnel, such as perfusionists and intensive care nurses, are also of crucial importance for the successful management of patients on ECMO. This report focuses on vaECMO for acute cardiogenic shock. It outlines the intention to treat of ECMO, technical aspects and outcome with respect to survival and complications, while it takes into consideration the particular circumstances of cardiogenic shock.

The state of cardiogenic shock

Cardiogenic shock is far more than loss of cardiac contractility with subsequent low output syndrome. It is a complex, degenerating clinical downward spiral of multiorgan dysfunction that begins when the heart is no longer able to provide sufficient flow to the peripheral organs [14]. Hypotension, systemic hypoperfusion and end-organ ischaemia follow. Compensatory vasoconstriction is insufficient, at least in part because of the developing systemic inflammatory response syndrome (SIRS). Proinflammatory cytokines such as interleukin (IL)-1β, IL-6, IL-8, tumour necrosis factor-α (TNF-α), as well as C-reactive protein, soluble adhesion molecules, leucocytes and the complement system are upregulated in cardiogenic shock following myocardial infarction [15, 16]. Intestinal hypoperfusion constitutes an important origin for the evolution of SIRS in cardiogenic shock, since it facilitates bacterial transmigration which, in turn, promotes systemic inflam-

A part of this review was presented at the Joint Annual Meeting of the Swiss Society of Cardiology and the Swiss Society of Cardiac and Thoracic Vascular Surgery, Zurich, Switzerland, June 10, 2015.

mation [15, 17]. The effects of proinflammatory cytokines are mediated, to a large extent, through upregulation of nitric oxide (NO) production. Excessive NO decreases myocardial contractility, suppresses mitochondrial respiration, reduces the responsiveness to catecholamines and, thus, inhibits the positive inotropic response and induces inappropriate systemic vasodilation, leading to generalised hypoperfusion of peripheral organs [14, 15]. High levels of NO are generated by induction of inducible nitric oxide synthase (iNOS), which is expressed in rather small amounts under physiological conditions and is upregulated in inflammatory states [15, 18]. Inhibition of the iNOS, however, could not be shown to improve outcome in cardiogenic shock. The randomised multicentre TRIUMPH trial, designed to test the effect of NOS inhibition on mortality in patients with persistent cardiogenic shock complicating myocardial infarction, did not detect a difference in 30-day and 6-month mortality between patients who received the nonselective NOS inhibitor tilarginine and those who received placebo [15, 19]. The main reason for the failure of NOS inhibition to improve outcome in cardiogenic shock might be that a nonselective NOS inhibition was applied, which also inhibited the two other NOS isoforms, endothelial (eNOS) and neuronal (nNOS) and, thereby, adversely affected the protective actions of constitutively generated NO [15]. In septic shock, nonselective NOS inhibition has been shown to even increase mortality [20]. Other trials examining the effects of various mediator-specific anti-inflammatory agents in septic shock, directed against TNF-α, IL-1, platelet activating factor, and others, were not able either to demonstrate an improvement in outcome [15, 21]. More general, nonspecific anti-inflammatory treatment of septic shock with low-dose steroids achieved, in contrast to high dosage, beneficial effects on survival, presumably since low steroid doses still attenuate the deleterious effects of systemic inflammation, while they do not eliminate the favourable actions of low-grade cytokine activation [15, 22]. This concept might be a way to improve outcome also in cardiogenic shock. The restoration of cardiac output via ECMO is intended to reverse this inflammatory cascade.

ECMO treatment strategies

Veno-arterial ECMO for cardiogenic shock is implanted in an emergency situation. There is not much time to make a decision about which therapeutic approach will follow ECMO. Potential comorbidities and the psychosocial environment cannot be evaluated, but this is a precondition before a therapeutic concept can be elaborated. Therefore, ECMO is implanted as a bridge to decision to make time for further evaluation. Once the investigations are completed, one of the following four options may be chosen for the ensuing treatment (fig. 1): (I) weaning the patient from ECMO in case of myocardial recovery; (II) bridge the patient to a ventricular assist device (VAD); (III) heart transplantation if the heart does not recover and investigations did not reveal contraindications; (IV) terminate ECMO therapy if myocardial failure persists and contraindications prohibit a bridge to VAD or heart transplantation. The most recent *Guidelines of the European Society for Cardiology for the diagnosis and treatment of acute and chronic heart failure*, published in 2012, outline that short-term mechanical circulatory support may be considered as a "bridge to decision" in patients deteriorating rapidly before a full diagnostic and clinical evaluation can be made [4]. It is regarded as a class IIb recommendation with a level of evidence C. If the underlying disease which leads to ECMO implantation is of a potentially reversible cause, such as viral myocarditis, or a surgically correctable condition (e.g. acute interventricular septal rupture), the guidelines upgrade ECMO therapy to a class IIa recommendation, still with a level of evidence C.

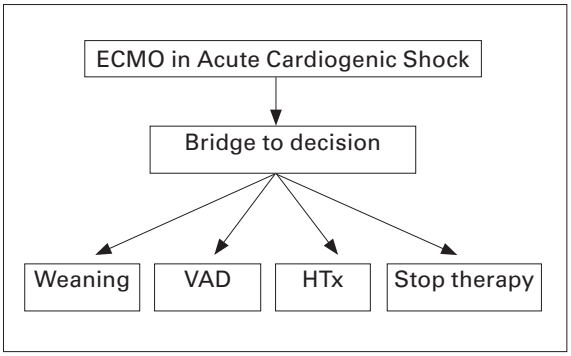

Figure 1: ECMO in acute cardiogenic shock: intention to treat. VAD = ventricular assist device; HTx = heart transplantation

Technical aspects: ECMO mode and configuration

The indication for ECMO determines the ECMO mode and configuration. While in respiratory failure, ECMO is implanted as a veno-venous circuit, cardiogenic shock requires ECMO in a veno-arterial configuration. For venous drainage, a cannula is inserted into the right atrium through puncture of the common femoral vein (CFV). The right CFV is preferred since advancement of the cannula might be easier on the right side than the left side as a result of the bent course of the

left iliac veins. The tip of the cannula is advanced to the right atrium and placed just into the entrance of the superior vena cava to obtain optimal drainage of the upper and lower body parts. This is guided by transoesophageal echocardiography or fluoroscopy for safe and proper placement. The standard access for arterial cannulation is the common femoral artery (CFA). Percutaneous puncture is preferred over surgical cut-down. Before insertion of the cannula, a percutaneous vascular closure device is used in order to facilitate later percutaneous removal. An introducer sheath is inserted into the CFA distally to the cannula and directed towards the superficial femoral artery (SFA) to maintain limb perfusion and prevent leg ischaemia, since the cannula in the CFA may be occlusive. It is preferrable not to place the arterial and venous cannulae on the same side to avoid a compartment syndrome, which might develop when arterial hypoperfusion caused by the arterial cannula and venous congestion provoked by the venous cannula act together. If severe peripheral artery disease prohibits cannulation of the femoral arteries, the right subclavian artery can be used, if implantation is not performed under resuscitation. A graft is anastomosed to the subclavian artery in which a cannula is inserted. To prevent hyperperfusion of the arm, a vessel loop is placed around the artery distally to the anastomosis, which can adjust the flow to the arm. A radial artery line is required on the side of subclavian cannulation to control the arm perfusion. In exceptional cases, central ECMO via sternotomy with cannulation of the right atrium and ascending aorta might be required, such as in case of refractory pulmonary oedema caused by a very low ejection fraction and the absence of left ventricular drainage, or postcardiotomy refractory cardiogenic shock. The technique described here is the preferred technique in our centre, it is based on available evidence and current practice, but some variations may be seen among implanting centres, including high-volume centres.

Outcome

Early survival

The outcome after ECMO therapy for cardiogenic shock is associated with low survival rates. But taking into account that, without ECMO, survival would be extremely poor, the outcome may be regarded as acceptable. Several notable studies reported early survival of approximately 40% (fig. 2). The group in La Pitié, Paris, which is one of the most experienced centres in ECMO therapy, retrospectively examined 81 patients who were put on ECMO for cardiogenic shock due to medical, postcardiotomy or posttransplantation heart failure [5]. The analysis showed a 42% survival to hospital discharge and a 38% survival at 3 months. Early independent predictors of death in the intensive care unit (ICU) included ECMO implantation under resuscitation, severe renal or liver failure at the time of ECMO institution and female gender whereas myocarditis as cause of cardiogenic shock was associated with better outcomes. Mortality in the ICU was as high as 79% in patients with pre-ECMO liver failure, 83% in patients with pre-ECMO renal failure, and 90% when both conditions were present. Cardiopulmonary resuscitation at the time of ECMO implantation was the strongest predictor for ICU mortality, being as high as 93%. The authors suggest that in such scenarios, the indication for ECMO should be highly selective, and reinforce the importance of early recognition of patients in need for ECMO before end-organ failure develops. The reason for the association of female gender with poorer outcome cannot definitely be explained by the authors, but they speculate that, owing to women's smaller femoral vessels, smaller calibres of cannulae are chosen which might be the cause for suboptimal cardiac unloading and insufficient flow delivery by the pump. The association of myocarditis with favourable outcome is explained by the frequently reversible cause of the condition which increases the potential for successful weaning from ECMO. A very recent, large analysis of the international Extracorporeal Life Support Organisation (ELSO) registry by Schmidt et al. focused on the establishment of a score to predict survival from refractory cardiogenic shock requiring ECMO [6]. The availability of a reliable score is a serious concern of each centre offering ECMO therapy. Because of the tremendous costs for specialised personnel, ICU

Source	Number of patients	Survival to hospital discharge	Citation
La Pitié, Paris (Combes et al. [5])	81	42.0%	Crit Care Med 2008;36:1404–11
ELSO registry 2003–2013 (Schmidt et al. [6])	3846	42.0%	Eur Heart J 2015;36:2246–56
Meta-Analysis of 7 electronic databases 2000–2013 (Xie et al. [7])	1199	40.2%	J Cardiothorac Vasc Anesth 2015;29:637–45

Figure 2: Early survival following ECMO for acute cardiogenic shock, as depicted by three representative studies.
ELSO = Extracorporeal Life Support Organisation

capacity and ECMO equipment, it is intended to offer ECMO therapy primarily to patients with a predicted potential survival benefit from ECMO. The study extracted data of 3 846 patients from the international Extracorporeal Life Support Organisation (ELSO) registry who were treated with ECMO for refractory cardiogenic shock between January 2003 and December 2013 [6]. Patients who received ECMO during cardiopulmonary resuscitation (CPR) were not included in the analysis. Forty-two percent of patients survived to hospital discharge. Pre-ECMO organ failures, pre-ECMO cardiac arrest, longer duration of mechanical ventilation before ECMO initiation and lower serum bicarbonate, among others, were identified to be associated with mortality. Acute myocarditis was found to be protective. Based on their findings, the authors developed the SAVE-score as a tool to predict survival for patients receiving ECMO for refractory cardiogenic shock and validated the score in an Australian population of 161 patients. A most recently published meta-analysis by Xie et al. reported on outcome after ECMO for cardiogenic shock and cardiac arrest [7]. Twenty-two observational studies from the year 2000 until January 2014 were included, each of which examined at least 10 adult patients who had received ECMO for refractory cardiogenic shock or cardiac arrest. The meta-analysis was performed on a total of 1199 patients. Overall survival to discharge was 40.2%. Patients with cardiogenic shock had a significantly higher 30-day survival than patients with cardiac arrest (42.1% vs 35.9%). The authors interpreted the findings as being similar to previously published meta-analyses, which reported 30-day survival rates of 47% [8] and 35% (20–65%) [9], respectively. However, the investigation of Nichol et al. [8] differed from the recently published meta-analysis by Xie et al. [7] inasmuch as it included studies from 2005 back to 1966 when ECMO therapy was still at its beginning and absolutely not comparable to current management. A large proportion (39%) of all included studies examined only up to four patients, and 19% of all studies were single case reports [8]. The study of Cheng et al. [9] included 20 more recent studies, dating from 2012 to 2000, comprising a total of 1866 patients. Prerequisite for inclusion of a study into the meta-analysis was that it investigated more than 10 patients and also reported on complication rates on ECMO. The rather low cumulative survival of 35% may be explained by the fact that 10 of the 20 studies included only patients with cardiogenic shock due to postcardiotomy syndrome, which is known to be associated with poor survival [3]. For all these reasons, the meta-analysis of Xie et al. [7] currently represents the best overview on early outcomes following ECMO for refractory cardiogenic shock, keeping in mind that large randomised studies have not been performed so far and, thus, at the moment pooled analysis represents the best available method for evaluating ECMO [7].

Long-term results

Long-term results following ECMO for refractory cardiogenic shock are reported scarcely in the literature. In the meta-analysis by Xie et al. [7], the estimated 3-year survival was 42.7%, which was rather comparable to the survival to discharge, indicating that mortality was low once patients survived the initial hospitalisation for cardiogenic shock with subsequent ECMO therapy [7]. This has also been described in two other studies by Wu et al. [10] and Lidén et al. [11]. They reported 88% 3-year and 100% 5-year survival, respectively, of those patients who survived until hospital discharge following ECMO for nonpostcardiotomy cardiogenic shock or cardiac arrest [10, 11]. This corresponded with an overall 47% 3-year and a 63% 5-year survival, respectively. The Cleveland Clinic group reported much lower 3-year and 5-year survival rates of 26% and 24%, respectively [12]. This is explained by the fact that 53% of the 202 patients examined received the ECMO for postcardiotomy cardiogenic shock which is, as mentioned above, associated with poor outcome [3, 12]. Patients who receive the ECMO for cardiogenic shock due to acute myocardial infarction seem to do better than patients in cardiogenic shock because of acute decompensating chronic cardiomyopathy [13]. Bermudez et al. found in their small cohort of 42 patients that at 2 years after ECMO therapy, 48% of infarct patients were alive, as compared with only 11% of patients with previous chronic heart failure [13]. The poorer outcomes of patients with acutely decompensated chronic heart failure might be explained by the higher frequency of systemic, hepatic and renal involvement at the time of ECMO initiation, indicating the lower reserve of such patients to withstand an acute decompensating event [13].

Complications

Vascular

Morbidity on ECMO is considerable and frequently has an unfavourable impact on outcome. More than half of all patients develop one or more major ECMO-related complication [5]. Peripheral cannulation of the femoral vessels can cause a severe perfusion issue. The cannula in the CFA compromises perfusion of the leg to a varying extent depending on the size of the vessel and the calibre of the cannula. If perfusion drops under a criti-

cal limit, leg ischaemia develops, which may require fasciotomy and, in some cases, amputation. Lower limb ischaemia has been reported to occur in 10–20% of patients [5, 7, 9, 12]. As a consequence, in 2–10% of patients a fasciotomy is needed, and in 2–5% of patients an amputation is performed [7, 9, 12]. To prevent such complications, which may be life-determining, the current state of the art is to place a distal perfusion limb into the SFA at the time of ECMO implantation.

Bleeding

Bleeding complications are triggered by the disseminated intravascular coagulation disorder, which is frequently associated with cardiogenic shock, insufficient production of coagulation factors resulting from liver failure, thrombocytopenia and the need for anticoagulation on ECMO. Major bleeding is reported to occur in 26–41% of patients [5, 7, 9]. Bleeding at the peripheral implantation site is described in 32% of patients [5].

Neurology

Neurological complications include ischaemic stroke, cerebral bleeding, diffuse anoxic and metabolic brain injury and brain death. They may result from insufficient cerebral perfusion in cardiogenic shock or cardiac arrest before ECMO implantation, or develop under ECMO therapy caused by the complex coagulation disorder following cardiogenic shock. Two large meta-analyses reported the cumulative rate of all neurological complications to be at 13% [7, 9], another single-centre study described neurological events in 33% of patients [12]. In particular, ischaemic or haemorrhagic stroke is experienced by 6–8% of patients [7, 9].

Infection

Infectious complications include infections locally at the cannula implantation site and systemic infections such as pneumonia and sepsis. The exit sites of the ECMO tubes constitute an entry pass for microorganisms. In addition, surgical scrubbing and draping may not reach the usual sterility standards if the ECMO is implanted in an emergency situation, thus favouring the incurrence of a local infection. Femoral exit site infections have been described in 17% of patients [5]. Pneumonia may develop as a consequence of pulmonary congestion during cardiogenic shock and following prolonged ventilation. Sepsis occurs on the basis of the compromised immune system associated with the scenario of cardiogenic shock. Taking all types of infections together, the frequency of such events amounts to 25–49% [7, 9, 12, 13].

Kidney

Renal failure occurs quite frequently in patients on ECMO as a consequence of cardiogenic shock, despite restoration of sufficient circulation. It develops as acute renal failure in patients with prior normal kidney function or as acute-on-chronic event in patients with a history of chronic cardiomyopathy which is frequently associated with chronic nephropathy. The cumulative rate of renal injury in ECMO patients is as high as 47–55% [7, 9]. Renal replacement therapy is required in 40–46% of all ECMO patients [9, 12, 13].

Concluding comment

The fact that cardiogenic shock is not just a compromised circulation, unable to maintain sufficient organ perfusion, but also causes a complex cascade of systemic inflammation, may explain the unsatisfactory outcome following ECMO therapy. Installation of ECMO can restore sufficient circulation, but it cannot stop the inflammatory insult, which has already occurred. The period of insufficient blood flow from the beginning of cardiogenic shock until initiation of ECMO triggers the extent of organ damage and systemic inflammation. It constitutes the crucial phase with decisive impact on outcome. The duration of this interval has been shown to be a risk factor for mortality [5, 11]. This was most clearly shown in the extreme case scenario of the cardiogenic shock spectrum, namely ongoing CPR treated with ECMO (ECPR) [23]. Rapid implantation of ECMO is required to keep the period of low output as short as possible and to break the vicious cycle of inflammation early in its evolution. This, however, implies organisational and structural challenges, including mobile ECMO teams. The significant complication rates of ECMO therapy have to be incorporated into the risk-benefit analysis before treatment is initiated [7]. In patients with unclear neurological status, e.g., following unwitnessed out-of-hospital arrest, or with advanced end-organ failure and metabolic derangement, ECMO therapy may be denied since ethical and economical aspects argue against application of ECMO in patients with anticipated poor outcome.

Correspondence:
Prof. Dr. med.
Markus J. Wilhelm
Clinic for Cardiovascular Surgery
University Hospital Zurich
Rämistrasse 100
CH-8091 Zurich
markus.wilhelm[at]usz.ch

Disclosure statement
No financial support and no other potential conflict of interest relevant to this article was reported.

References

– The full list of references is included in the online version of the article at www.cardiovascmed.ch.

References

1 Peek GJ, Mugford M, Tiruvoipati R, Wilson A, Allen E, Thalanany MM, et al. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. Lancet 2009;374:1351–63.
2 Thiele H, Zeymer U, Neumann FJ, Ferenc M, Olbrich HG, Hausleiter J, et al. Intra-aortic balloon counterpulsation in acute myocardial infarction complicated by cardiogenic shock (IABP-SHOCK II): final 12 month results of a randomised, open-label trial. Lancet 2013;382(9905):1638–45.
3 Rastan AJ, Dege A, Mohr M, Doll N, Falk V, Walther T, et al. Early and late outcomes of 517 consecutive adult patients treated with extracorporeal membrane oxygenation for refractory postcardiotomy cardiogenic shock. J Thorac Cardiovasc Surg 2010;139:302–11.
4 McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2012 Aug;14(8):803–69.
5 Combes A, Leprince P, Luyt CE, Bonnet N, Trouillet JL, Léger P, et al. Outcomes and long-term quality-of-life of patients supported by extracorporeal membrane oxygenation for refractory cardiogenic shock. Crit Care Med 2008;36:1404–11.
6 Schmidt M, Burrell A, Roberts L, Bailey M, Sheldrake J, Rycus PT, et al. Predicting survival after ECMO for refractory cardiogenic shock: the survival after veno-arterial-ECMO (SAVE)-score. Eur Heart J 2015;36:2246–56.
7 Xie A, Phan K, Tsai YC, Yan TD, Forrest P. Venoarterial extracorporeal membrane oxygenation for cardiogenic shock and cardiac arrest: A meta-analysis. J Cardiothorac Vasc Anesth 2015;29:637–45.
8 Nichol G, Karmy-Jones R, Salerno C, Cantore L, Becker L. Systematic review of percutaneous cardiopulmonary bypass for cardiac arrest or cardiogenic shock states. Resuscitation 2006;70:381–94.
9 Cheng R, Hachamovitch R, Kittleson M, Patel J, Arabia F, Moriguchi J, et al. Complications of extracorporeal membrane oxygenation for treatment of cardiogenic shock and cardiac arrest: a meta-analysis of 1,866 adult patients. Ann Thorac Surg 2014;97:610–6.
10 Wu MY, Lee MY, Lin CC, Chang YS, Tsai FC, Lin PJ. Resuscitation of non-postcardiotomy cardiogenic shock or cardiac arrest with extracorporeal life support: The role of bridging to intervention. Resuscitation 2012;83:976–81.
11 Lidén H, Wiklund L, Haraldsson Å, Berglin E, Hultman J, Dellgren G. Temporary circulatory support with extra corporeal membrane oxygenation in adults with refractory cardiogenic shock. Scand Cardiovasc J 2009;43:226–32.
12 Smedira NG, Moazami N, Golding CM, McCarthy PM, Apperson-Hansen C, Blackstone EH, et al. Clinical experience with 202 adults receiving extracorporeal membrane oxygenation for cardiac failure: Survival at five years. J Thorac Cardiovasc Surg 2001;122:92–102.
13 Bermudez CA, Rocha RV, Toyoda Y, Zaldonis D, Sappington PL, Mulukutla S, et al. Extracorporeal membrane oxygenation for advanced refractory shock in acute and chronic cardiomyopathy. Ann Thorac Surg 2011;92:2125–31.
14 Westaby S, Kharbanda R, Banning AP. Cardiogenic shock in ACS. Part 1: prediction, presentation and medical therapy. Nat Rev Cardiol 2012;9:158–71.
15 Shpektor A. Cardiogenic shock: the role of inflammation. Acute Cardiac Care 2010;12:115–8
16 Pudil R, Krejsek J, Pidrman V, Gregor J, Tichy M, Bures J, et al. Inflammatory response to acute myocardial infarction complicated by cardiogenic shock. Acta Medica 2001;44:149–51.
17 Brunckhorst FM, Clark AL, Forycki ZF, Anker SD. Pyrexia, procalcitonine, immune activation and survival in cardiogenic shock: the potential importance of bacterial translocation. Int J Cardiol 1999;72:3–10.
18 Moncada S, Palmer RM, Higgs EA. Nitric oxide: physiology, pathophysiology and pharmacology. Pharmacol Rev 1991;43:109–42.
19 The TRIUMPH investigators. Effect of tilarginine acetate in patients with acute myocardial infarction and cardiogenic shock: The TRIUMPH randomized controlled trial. JAMA 2007;297:1657–66.
20 Lopez A, Lorente JA, Steingrub J, Bakker J, McLuckie A, Willatts S, et al. Multiple-center, randomized, placebo-controlled, double-blind study of the nitric oxide synthase inhibitor 546C88: Effect on survival in patients with septic shock. Crit Care Med 2004;32:21–30.
21 Seam N, Suffredini AF. Mechanisms of sepsis and insights from clinical trials. Drug Discov Today Dis Mech 2007;4:83–93.
22 Annane D, Bellisant E, Bollart PE. Corticosteroids in the treatment of severe sepsis and septic shock in adults: a systematic review. JAMA 2009;301:2362–75.
23 Chen YS, Yu HY, Huang SC, Lin JW, Chi NH, Wang CH, et al. Extracorporeal membrane oxygenation support can extend the duration of cardiopulmonary resuscitation. Crit Care Med 2008;36:2529–35.