The Role and Efficacy of Peripheral Veno-arterial Extracorporeal Membrane Oxygenation in Treating Cardiogenic Shock and Cardiac Arrest

Takeshi Tada and Kazushige Kadota

Cardiogenic shock (CS) complicates acute myocardial infarction (AMI) with an incidence from 5% to 10%, and is a main cause of death in patients with acute cardiovascular disease including AMI. Short-term mortality associated with CS may approach nearly 30% to 45% in the contemporary era. Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) may represent the final option for severe CS that is refractory to medical therapy. Peripheral VA-ECMO can be initiated percutaneously and promptly via femoral artery and femoral vein access, and is widely used for CS and CA in emergency situations. In this review, we describe the role and efficacy of peripheral VA-ECMO in treating CS and CA.

KEY WORDS: cardiogenic arrest, cardiogenic shock, IABP, IMPELLA, VA-ECMO

I. Introduction

Cardiogenic shock (CS) complicates acute myocardial infarction (AMI) with an incidence from 5% to 10%\(^1\)\(^-\)\(^3\), and is a main cause of death in patients with acute cardiovascular disease including AMI. Short-term mortality associated with CS may approach nearly 30% to 45% in the contemporary era.\(^1\)\(^-\)\(^6\) Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) may represent the final option for severe CS that is refractory to medical therapy. Peripheral VA-ECMO can be initiated percutaneously and promptly via femoral artery and femoral vein access, and is widely used for CS and CA in emergency situations. In this review, we describe the role and efficacy of peripheral VA-ECMO in treating CS and CA.

II. The role and efficacy of VA-ECMO in treating CS

Major indications for VA-ECMO are thought to be refractory CS in the setting of acute coronary syndrome including ST elevated AMI (STEMI), acute heart failure, postcardiotomy patients who are unable to wean from bypass, myocarditis, and refractory ventricular arrhythmias.\(^10\) In a report, 55.4% of 144,425 CS patients were associated with AMI.\(^14\) In other reports, more than 75% of CS patients were associated with AMI.\(^15\)\(^-\)\(^16\) The incidence of CS complicating STEMI has increased during the past decade, and is reported to be 7.9%.\(^17\) In patients with acute coronary syndrome, CS usually results from extensive damage to left ventricular (LV) myocardium such as left main trunk disease or mechanical complications such as ventricular septal perforation, LV free wall rupture, and papillary muscle rupture. Intra-aortic balloon pump (IABP) has been widely used in patients with STEMI and CS, although it could not improve the outcomes in the IABP-shock II trial.\(^17\) Recently, Impella (Abiomed, Danvers, MA, USA) became available in such situations. However, in cases where the use of IABP or Impella seems to be insufficient for circulatory support, using VA-ECMO should be considered promptly. Sheu et al. compared 30-day outcomes of patients with STEMI and CS between the periods when VA-ECMO was unavailable (n = 115) and available (n = 219), reported that the usage rate of VA-ECMO in the latter was 21% (46 patients) and that 30-day mortality was significantly lower in the latter (41.7% vs. 30.1%, p = 0.034), and found significant improvement in mortality of STEMI patients with severe CS (sBP < 75 mmHg)
in the latter (72% vs. 39.1%, \( p = 0.008 \))\(^{10} \). Xie et al. examined 1,199 patients with CS or CA who received VA-ECMO in their meta-analysis and reported that survival to discharge was 40.2% (95% confidence interval [CI], 33.9 to 46.7), whereas the survival rates at 3, 6, and 12 months were 55.9% (95% CI, 41.5 to 69.8), 47.6% (95% CI, 25.4 to 70.2), and 54.4% (95% CI, 36.6 to 71.7), respectively\(^8 \). Schmidt et al. reported that of 3,846 CS patients who received VA-ECMO, 1,601 (42%) patients left hospital arrive, and that chronic renal failure, longer duration of ventilation prior to VA-ECMO initiation, pre-VA-ECMO organ failures, pre-VA-ECMO CA, congenital heart disease, lower pulse pressure, and lower serum bicarbonate were risk factors associated with mortality\(^9 \). Despite high mortality in patients with CS or CA who received VA-ECMO, VA-ECMO is a well-established life-saving strategy in emergency situations.

III. The role and efficacy of VA-ECMO in treating fulminant myocarditis

The usefulness of VA-ECMO in patients with CS due to fulminant myocarditis (FM) has been reported since late 1990s\(^{20-24} \). VA-ECMO can be used quickly and easily to prevent hemodynamic deterioration in FM patients with CS. Early VA-ECMO deployment prior to CA in FM patients may be associated with better outcomes\(^{25} \), and favorable prognosis can be expected if patients survive the acute decompensated phase, because FM is a self-limiting disease\(^{26} \). However, mortality in FM patients who receive VA-ECMO is still high. Matsumoto et al. studied 37 consecutive FM patients who had received VA-ECMO, examined clinical determinants of successful weaning from VA-ECMO, and reported that 22 patients (59%) were successfully weaned from VA-ECMO after a median of 6.5 days of support, suggesting that myocardial injury, as evidenced by CK-MB and LV wall thickness, and prolonged presence of cardiac rhythm disturbances were associated with successful weaning from VA-ECMO, whereas VA-ECMO duration, VA-ECMO cannula size, and maximal VA-ECMO flow were not\(^{27} \). Recently, Chong et al. reported that the in-hospital survival rate was 57.1% in their 35 FM patients who had received VA-ECMO, and that the time from shock to VA-ECMO and the duration of VA-ECMO use were not associated with survival from FM\(^{28} \). VA-ECMO support is consistently a tool to be used until LV function recovery and does not appear to directly promote LV function recovery in FM patients\(^{29} \), and transition from VA-ECMO to a LV assist device needs to be considered if myocardial recovery is inadequate within 3 to 5 days after the initiation of VA-ECMO\(^{30} \).

IV. The role and efficacy of VA-ECMO in ECPR

Recently, ECPR became popular, and its efficacy has been reported largely from Asia. Chen et al. reported that they had performed ECPR on 57 patients with in-hospital CA that was refractory to cardiac resuscitation more than 10 minutes, and that the success rate of weaning from VA-ECMO and the in-hospital mortality were 66.7% and 31.6%, respectively\(^{31} \). In another report using a propensity score matching analysis, they compared 59 patients who had received ECPR and 113 patients who had received conventional CPR, and reported that ECPR significantly improved in-hospital mortality (hazard ratio [HR], 0.51; 95% CI, 0.35 to 0.74; \( p < 0.0001 \)), 30-day mortality (HR, 0.47; 95% CI, 0.28 to 0.77; \( p = 0.003 \)), and 1-year mortality (HR, 0.53; 95% CI, 0.33 to 0.83; \( p = 0.006 \))\(^{32} \). Mackawa et al. used propensity score matching to compare 53 out-of-hospital CA patients who had received ECPR with 109 out-of-hospital CA patients who had received conventional CPR, and reported that ECPR improved neurologically preserved survival at 3 months (29.2% vs. 8.3%, log-rank \( p = 0.018 \))\(^{33} \). Sakamoto et al. compared 234 out-of-hospital CA patients with ventricular fibrillation or pulseless ventricular tachycardia detected in the first electrocardiogram who had received ECPR with 159 out-of-hospital CA patients who had received conventional CPR, and reported that ECPR significantly improved neurologically preserved survival at 1 month (13.7% vs. 1.9%, \( p < 0.001 \)) and 6 months (13.7% vs. 3.1%, \( p = 0.002 \))\(^{34} \). Although several single center studies supported the use of VA-ECMO for refractory CA, American Heart Association (AHA) guideline 2015 showed that ECPR may be considered for refractory CA in carefully selected patients (Class 2b) because of insufficient evidence and that ECPR may be considered for select CA patients for whom the suspected etiology of the CA is potentially reversible during a limited period of mechanical cardiorespiratory support\(^{35} \). In a short, ECPR should be performed in carefully selected patients.

V. Using a concomitant LV unloading device during VA-ECMO: IABP or Impella?

Although VA-ECMO support stabilizes CS and CA, it can cause further impairment or delay in LV function because retrograde aortic flow due to VA-ECMO increases LV afterload\(^{36} \). Increased LV afterload consequently causes LV dilatation, LA pressure elevation, and pulmonary edema. Furthermore, in a poor LV contractile situation, high retrograde flow due to VA-ECMO makes the aortic valve remain closed even during systole and LV thrombus formation\(^{5,35} \). The concomitant use of an LV unloading strategy is therefore highly recommended\(^{32} \). Major LV unloading strategies include IABP, surgical LV venting, and percutaneous LV venting with Impella\(^5,35 \). In the IABP-shock 2 trial, IABP could not improve the outcomes of patients with STEMI and CS, without mechanical complications\(^{37} \). Thereafter, the routine use of IABP in CS patients is not recommended\(^{34,38} \). Although the effectiveness of the
concomitant use of IABP with VA-ECMO is still controversial, two reports showed improved mortality of CS patients after the concomitant use of IABP with VA-ECMO. Li et al. performed a meta-analysis of 29 studies comprising 4,576 CS patients, and reported that VA-ECMO plus IABP was associated with decreased in-hospital mortality (58.4% vs. 63.1%; risk ratio, 0.90; 95% CI, 0.85 to 0.95; \( p < 0.0001 \)) and may not increase complications, and that IABP was related to decreased in-hospital deaths of patients receiving ECPR, postcardiotomy CS, and ischemic heart disease. On the other hand, Vallabhajosyula et al. performed a meta-analysis of 22 observational studies comprising 4,653 CS patients, and reported that short-term mortality was not significantly different in patients treated with and without IABP (42.1% vs. 57.8%; risk ratio, 0.80; 95% CI, 0.52 to 1.22; \( p = 0.30 \)); however, they also reported that the concomitant use of IABP was associated with lower mortality in CS patients with AMI (50.8% vs. 62.4%; risk ratio, 0.56; 95% CI, 0.46 to 0.67; \( p < 0.001 \)). Despite controversy, the concomitant use of IABP with VA-ECMO may improve mortality of CS patients, especially those due to AMI.

In a small pilot study, Impella 2.5 percutaneous LV venting device was able to provide superior hemodynamic support in the acute phase, but could not show superiority in 30-day mortality of patients with AMI and CS compared with IABP. Recently, an explorative randomized controlled trial using Impella CP could not show superiority in 30-day and 6-month mortality in the same setting compared with IABP. Two retrospective studies, however, reported the usefulness of the concomitant use of Impella with VA-ECMO. Schrage et al. evaluated 106 CS patients treated with Impella CP or Impella 2.5 in combination with VA-ECMO, and 30-day survival rate was 35.8%, which was higher than that predicted by established risk scores, and also reported a marked decrease in pulmonary capillary wedge pressure after addition of the device to VA-ECMO. Pappalardo et al. performed a propensity-matching analysis to compare 21 patients who had received VA-ECMO and Impella with 42 patients who had received VA-ECMO alone, and reported that the former had a significantly lower hospital mortality (47% vs. 80%, \( p < 0.001 \)) and a higher rate of successful bridging to either recovery or further therapy (68% vs. 28%, \( p < 0.001 \)). These results suggested that the concomitant use of Impella with VA-ECMO improves short-term mortality of CA patients in comparison with using VA-ECMO alone; a prospective, randomized study is needed to further investigate this approach, and the efficacy of the concomitant use of Impella with VA-ECMO compared with IABP with VA-ECMO is also needed to examine.

VI. Exit strategy of VA-ECMO

VA-ECMO is basically one of circulatory support devices used in the acute decompensated phase and may act as a bridge to myocardial recovery or durable mechanical circulatory support including external or implantable LV assist devices; it is unsuitable for long-term circulatory support due to short durability of membrane oxygenator. Although VA-ECMO circuits can be exchanged several times, it may lead to complications including bleeding and infection, and therefore an exit strategy of VA-ECMO should be considered at the initiation of VA-ECMO. Reversibility of impaired ventricular function, patient-specific risk factors, and anticipated duration of support should be assessed as soon as possible, and next strategies such as external or implantable LV assist devices need to be employed if indicated.

VII. Complications of VA-ECMO

The use of VA-ECMO sometimes causes various types of complications, some of which could be fatal without an appropriate therapy. Kreebler et al. summarized the prevalence of common complications in their review article. Vascular complications are reported to be 20% to 30%, in which limb ischemia was most common and its prevalence was as high as 40%. Distal perfusion strategies for the cannulation site should be considered at the initiation of VA-ECMO. Neurological complications include ischemic and hemorrhagic stroke, subclinical cognitive impairment, seizures, paraplegia, peripheral neuropathy, and the incidence of all neurological complications is reported to be 13.3%, whereas that of ischemic and/or hemorrhagic stroke is reported to be 5.9% to 7.8%. Infections associated with VA-ECMO include bloodstream infections, pneumonia, and urinary tract infections. The incidence of bloodstream infections is reported to be 3% to 18%, that of hemolysis 5% to 18%, and that of severe hemolysis or thrombosis requiring circuit change 8.9%. The incidence of renal failure is reported to be 33% to 55.6%; that of renal failure requiring hemodialysis 28% to 52%. The incidence of bleeding is reported to be 30% to 56%, and common bleeding sites were thorax, gastrointestinal, and cannulation site. The incidence of systemic inflammatory response syndrome is reported to be 30%. All these complications are reported to be associated with high mortality. The shorter duration of VA-ECMO support may reduce complications associated with VA-ECMO, and early weaning from VA-ECMO is recommended.

VIII. Conclusion

Peripheral VA-ECMO is clinically useful for refractory CS and CA, and is one of life-saving strategies because it quickly improves hemodynamics and can be started with speed and ease. Although VA-ECMO is associated with serious complications and high mortality, its use for CS and CA deserves consideration. The concomitant use of an LV unloading device and an
exit strategy should be considered at the initiation of VA-ECMO.

Acknowledgements
We appreciate Miho Kobayashi for her secretarial assistance.

Disclosure statement
The authors declare no conflicts of interest associated with this manuscript.

References
1) Goldberg RJ, Samad NA, Yarzebski J, et al: Temporal trends in cardiogenic shock complicating acute myocardial infarction. N Engl J Med 1999; 340: 1162–1168
2) Goldberg RJ, Gore JM, Thompson CA, et al: Recent magnitude of and temporal trends (1994–1997) in the incidence and hospital death rates of cardiogenic shock complicating acute myocardial infarction: the second national registry of myocardial infarction. Am Heart J 2001; 141: 65–72
3) Kolte D, Khera S, Aronow WS, et al: Trends in incidence, management, and outcomes of cardiogenic shock complicating ST-elevation myocardial infarction in the United States. J Am Heart Assoc 2014; 3: e00590
4) van Diepen S, Katz JN, Albert NM, et al: Contemporary management of cardiogenic shock: a scientific statement from the American Heart Association. Circulation 2017; 136: e232-e268
5) Vallabhajosyula S, O’Horo JC, Antharam P, et al: Concomitant intraventricular balloon pump use in cardiogenic shock requiring veno-arterial extracorporeal membrane oxygenation. Circ Cardiovasc Interv 2018; 11: e006930
6) Xie A, Phan K, Tsai YC, et al: Venoarterial extracorporeal membrane oxygenation for cardiogenic shock and cardiac arrest: a meta-analysis. J Cardiothorac Vasc Anesth 2015; 29: 637–645
7) Barra J, Toyoda N, Goldstone AB, et al: Extracorporeal membrane oxygenation in New York state: trends, outcomes, and implications for patient selection. Circ Heart Fail 2016; 9, pii: e003179
8) Gerke AK, Tang F, Cavanaugh JE, et al: Increased trend in extracorporeal membrane oxygenation use by adults in the United States since 2007. BMC Res Notes 2015; 8: 686
9) Rao P, Kralpey Z, Smith R, et al: Venoarterial extracorporeal membrane oxygenation for cardiogenic shock and cardiac arrest. Circ Heart Fail 2018; 11: e049095
10) Kekbler ME, Haddad EV, Choi CW, et al: Venoarterial extracorporeal membrane oxygenation in cardiogenic shock. JACC Heart Fail 2018; 6: 503–516
11) Phillips SJ, Ballentine B, Slonine D, et al: Percutaneous initiation of cardiopulmonary bypass. Ann Thorac Surg 1983; 36: 223–225
12) Chen YS, Chao A, Yu HY, et al: Analysis and results of prolonged resuscitation in cardiac arrest patients rescued by extracorporeal membrane oxygenation. J Am Coll Cardiol 2003; 41: 197–203
13) Chen YS, Lin JW, Yu HY, et al: Cardiopulmonary resuscitation with assisted extracorporeal life-support versus conventional cardiopulmonary resuscitation in adults with in-hospital cardiac arrest: an observational study and propensity analysis. Lancet 2008; 372: 554–561
14) Shah M, Patnaik S, Patel B, et al: Trends in mechanical circulatory support use and hospital mortality among patients with acute myocardial infarction and non-infarction related cardiogenic shock in the United States. Clin Res Cardiol 2018; 107: 287–303
15) Moraca RJ, Wanamaker KM, Bailey SH, et al: Salvage peripheral extracorporeal membrane oxygenation using Cobe Revolution® centrifugal pump as a bridge to decision for acute refractory cardiogenic shock. J Card Surg 2012; 27: 521–527
16) Babaei A, Frederick PD, Pasta DJ, et al: Trends in management and outcomes of patients with acute myocardial infarction complicated by cardiogenic shock. JAMA 2005; 294: 448–454
17) Thiele H, Zeymer U, Neumann FJ, et al: IABP-SHOCK II Trial Investigators: Intraaortic balloon support for myocardial infarction with cardiogenic shock. N Engl J Med 2012; 367: 1287–1296
18) Sheu JJ, Tsai TH, Lee FY, et al: Early extracorporeal membrane oxygenation-assisted primary percutaneous coronary intervention improved 30-day clinical outcomes in patients with ST-segment elevation myocardial infarction complicated with profound cardiogenic shock. Crit Care Med 2010; 38: 1810–1817
19) Schmidt M, Burrell A, Roberts L, et al: Predicting survival after ECMO for refractory cardiogenic shock: The survival after venoarterial-ECMO (SAVE)-score. Eur Heart J 2015; 36: 2246–2256
20) Kato S, Morimoto S, Hiramitsu S, et al: Use of percutaneous cardiopulmonary support of patients with fulminant myocarditis and cardiogenic shock for improving prognosis. Am J Cardiol 1999; 83: 623–625
21) Chen JM, Spanier TB, Gonzalez JJ, et al: Improved survival in patients with acute myocarditis using external pulsatile mechanical ventricular assistance. J Heart Lung Transplant 1999; 18: 351–357
22) Acker MA: Mechanical circulatory support for patients with acute-fulminant myocarditis. Ann Thorac Surg 2001; 71 (3 Suppl): S73-S76
23) Duncan BW, Bohn DJ, Atz AM, et al: Mechanical circulatory support for the treatment of children with acute fulminant myocarditis. J Thorac Cardiovasc Surg 2001; 122: 440–448
24) Asaumi Y, Yasuda S, Morii I, et al: Favourable clinical outcome in patients with cardiogenic shock due to fulminant myocarditis supported by percutaneous extracorporeal membrane oxygenation. Eur Heart J 2005; 26: 2185–2192
25) Diddle JW, Almodovar MC, Rajagopal SK, et al: Extracorporeal membrane oxygenation for the support of adults with acute myocarditis. Crit Care Med 2015; 43: 1016–1025
26) McCarthy RE 3rd, Boehmer JP, Hruban RH, et al: Long-term outcome of fulminant myocarditis as compared with acute (nonfulminant) myocarditis. N Engl J Med 2000; 342: 690–695
27) Matsumoto M, Asaumi Y, Nakamura Y, et al: Clinical determinants of successful weaning from extracorporeal membrane oxygenation in patients with fulminant myocarditis. ESC Heart Fail 2018; 5: 675–684
28) Chong SZ, Fang CY, Fang HY, et al: Associations with the in-hospital survival following extracorporeal membrane oxygenation in adult acute fulminant myocarditis. J Clin Med 2018; 7, pii: E452
29) Maekawa K, Tanno K, Hase M, et al: Extracorporeal cardiopulmonary resuscitation for patients with out-of-hospital cardiac arrest of cardiac origin: a propensity-matched study and predictor analysis. Crit Care Med 2013; 41: 1186–1196
30) Sakamoto T, Morimura N, Nagao K, et al: Extracorporeal cardiopulmonary resuscitation versus conventional cardiopulmonary resuscitation in adults with out-of-hospital cardiac arrest: a prospective observational study. Resuscitation 2014; 85: 762–768

31) Link MS, Berkow LC, Kudenchuk PJ, et al: Part 7: Adult advanced cardiovascular life support: 2015 American Heart Association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation 2015; 132 (18 Suppl 2): S444-S464

32) Schrage B, Burkhoff D, Rübsamen N, et al: Unloading of the left ventricle during venoarterial extracorporeal membrane oxygenation therapy in cardiogenic shock. JACC Heart Fail 2018; 6: 1035–1043

33) Meani P, Gelsomino S, Natour E, et al: Modalities and effects of left ventricle unloading on extracorporeal life support: a review of the current literature. Eur J Heart Fail 2017; 19 (Suppl 2): 84–91

34) Ibanez B, James S, Agewall S, et al; ESC Scientific Document Group: 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2018; 39: 119–177

35) O’Gara PT, Kushner FG, Ascheim DD, et al; American College of Cardiology Foundation; American Heart Association Task Force on Practice Guidelines; American College of Emergency Physicians; Society for Cardiovascular Angiography and Interventions: 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: executive summary: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the American College of Emergency Physicians and Society for Cardiovascular Angiography and Interventions. Catheter Cardiovasc Interv 2013; 82: E1-E27

36) Li Y, Yan S, Gao S, et al: Effect of an intra-aortic balloon pump with venoarterial extracorporeal membrane oxygenation on mortality of patients with cardiogenic shock: a systematic review and meta-analysis. Eur J Cardiothorac Surg 2018; doi: 10.1093/ejcts/ezy304. [Epub ahead of print]

37) Seyfarth M, Sibbing D, Bauer I, et al: A randomized clinical trial to evaluate the safety and efficacy of a percutaneous left ventricular assist device versus intra-aortic balloon pumping for treatment of cardiogenic shock caused by myocardial infarction. J Am Coll Cardiol 2008; 52: 1584–1588

38) Ouweneel DM, Eriksen E, Sjauw KD, et al: Percutaneous mechanical circulatory support versus intra-aortic balloon pump in cardiogenic shock after acute myocardial infarction. J Am Coll Cardiol 2017; 69: 278–287

39) Pappalardo F, Schulte C, Pieri M, et al: Concomitant implantation of Impella(R) on top of veno-arterial extracorporeal membrane oxygenation may improve survival of patients with cardiogenic shock. Eur J Heart Fail 2017; 19: 404–412

40) Makdisi G, Makdisi T, Wang TW: Use of distal perfusion in peripheral extracorporeal membrane oxygenation. Ann Transl Med 2017; 5: 103