OPEN

Pheochromocytoma Crisis With Severe Cyclic Blood Pressure Fluctuations in a Cardiac Pheochromocytoma Patient Successfully Resuscitated by Extracorporeal Membrane Oxygenation

A Case Report

Xiang Zhou, MD, Dawei Liu, MD, Longxiang Su, MD, PhD, Yun Long, MD, Wei Du, MD, Qi Miao, MD, Fang Li, MD, Zhengyu Jin, MD, Zhengpei Zeng, MD, Ailun Luo, MD, and Yuguang Huang, MD

Abstract: Cardiac pheochromocytoma is relatively rare. Few reports describe the intraoperative and postoperative progression of patients experiencing a life-threatening pheochromocytoma crisis treated with extracorporeal membrane oxygenation (ECMO).

A 35-year-old man was referred to our facility for paroxysmal hypertension with a 10-year history of sweating, headaches, cardiac palpitations, and postexercise dyspnea. The patient initially underwent urine catecholamine measurement and an isotope scan, somatostatin receptor scintigraphy, and 18F-fluorodeoxyglucose positron emission tomography/computer tomography (CT), which indicated a multiple, cardiac pheochromocytoma. Echocardiography, cardiac magnetic resonance imaging (MRI), CT reconstruction, and a coronary CT angiography revealed several lesions at the aortic root and along the cardiac vasculature.

Multifocal cardiac pheochromocytoma was diagnosed and pheochromocytoma crisis with severe cyclic blood pressure fluctuation occurred during surgery.

Surgical resection of multiple pheochromocytomas in the right medial carotid sheath, mediastinum between the main and pulmonary arteries, and between the abdominal aorta and inferior vena artery was performed. To ensure cardiac perfusion and avoid severe circulatory fluctuation, the cardiac paraganglioma resection was prioritized. After resecting the cardiac pheochromocytoma, a severe pheochromocytoma crisis with rapid cyclic blood pressure fluctuation developed. ECMO and intraaortic balloon pump (IABP) were initiated to stabilize circulation and perfusion. Phenoxybenzamine, norepinephrine, epinephrine, and fluid resuscitation were administered to support cardiovascular function.

The magnitude of blood pressure fluctuation steadily decreased with treatment. IABP was discontinued after 3 days, and ECMO was discontinued after 16 days. The patient was discharged 3 months postoperatively.

This case indicates that mechanical life support with ECMO is a valuable option for pheochromocytoma-induced cardiac shock and should be considered as an effective therapeutic choice in patients with highly unstable hemodynamic function.

(*Medicine* 94(17):e790)

Abbreviations: CABG = coronary artery bypass grafting, CPB = cardiopulmonary bypass, CVP = central venous pressure, ECMO = extracorporeal membrane oxygenation, IABP = intraaortic balloon pump, ICU = intensive care unit, MAP = mean arterial pressure, MRI = magnetic resonance imaging, PET = positron emission tomography, PVS = postoperative vasoplegic syndrome, VTI = velocity time integral.

INTRODUCTION

Pheochromocytomas are catecholamine-secreting tumors originating from the stem cells of the neural crest. Approximately 1% of pheochromocytomas are intrathoracic in origin,[1] and cases of multiple pheochromocytomas containing both adrenal and extraadrenal tissue are even rarer.[2] Pheochromocytoma crisis is a life-threatening emergency with a high mortality despite aggressive treatment, mostly due to cardiovascular failure.[3,4] The clinical manifestation of pheochromocytoma crisis ranges from severe hypertension to circulatory failure and shock, but the most severe, complex, difficult, and rare form of pheochromocytoma crisis is cyclic hypertension alternating with hypotension.[5,6] Some studies have reported that extracorporeal membrane oxygenation (ECMO) was successfully used to reverse pheochromocytoma-induced, Takotsubo-like cardiomyopathy and global heart failure or cardiogenic shock.[3,7–11] However, there are no known reports describing ECMO use in cases of life-threatening pheochromocytoma crisis with rapid cyclic blood pressure fluctuation. Herein, we report a rare case of pheochromocytoma crisis presenting as rapid cyclic blood pressure fluctuation caused by multiple, cardiac pheochromocytomas that was successfully treated by ECMO.

CONSENT

Written informed consent was obtained from the patient before and after all procedures, and for the publication of this case report and accompanying images.

Editor: Alessandro Durante.
Received: January 6, 2015; revised: March 19, 2015; accepted: March 29, 2015.
From the Department of Critical Care Medicine (XZ, DL, LS, YL, WD); Department of Cardiac Surgery (QM); Department of Nuclear Medicine (FL); Department of Radiology (ZJ); Department of Endocrinology (ZZ); and Department of Anesthesiology (AL, YH), Peking Union Medical College Hospital, Peking Union Medical College and Chinese Academy of Medical Sciences, Beijing, China.
Correspondence: Prof. Dawei Liu, Department of Critical Care Medicine, Peking Union Medical College Hospital, Peking Union Medical College and Chinese Academy of Medical Sciences, Beijing 100730, China (e-mail: dwliu98@163.com).
The authors have no funding and conflicts of interest to disclose.

ISSN: 0025-7974
DOI: 10.1097/MD.0000000000000790

CASE REPORT

A 35-year-old man was referred to our facility for paroxysmal hypertension with a 10-year history of sweating, headaches, cardiac palpitations, and postexercise dyspnea. His blood pressure was 140/90 mm Hg with regular antihypertensive medication. Pheochromocytoma was preliminary diagnosed due to his significantly elevated urinary norepinephrine concentration at 259.2 μg/24 h (normal range 16.69–40.65 μg/24 h). Radionuclide examination comprising an isotope scan (iodine-131 metaiodobenzylguanidine), somatostatin receptor scintigraphy, and 18F-fluorodeoxyglucose positron emission tomography/computer tomography (CT) confirmed the diagnosis (Figure 1A–C). An echocardiography, cardiac magnetic resonance imaging (MRI), and CT reconstruction revealed several lesions at the aortic root, and a coronary CT angiography displayed coronary lesions (Figure 1D–F). The patient also had

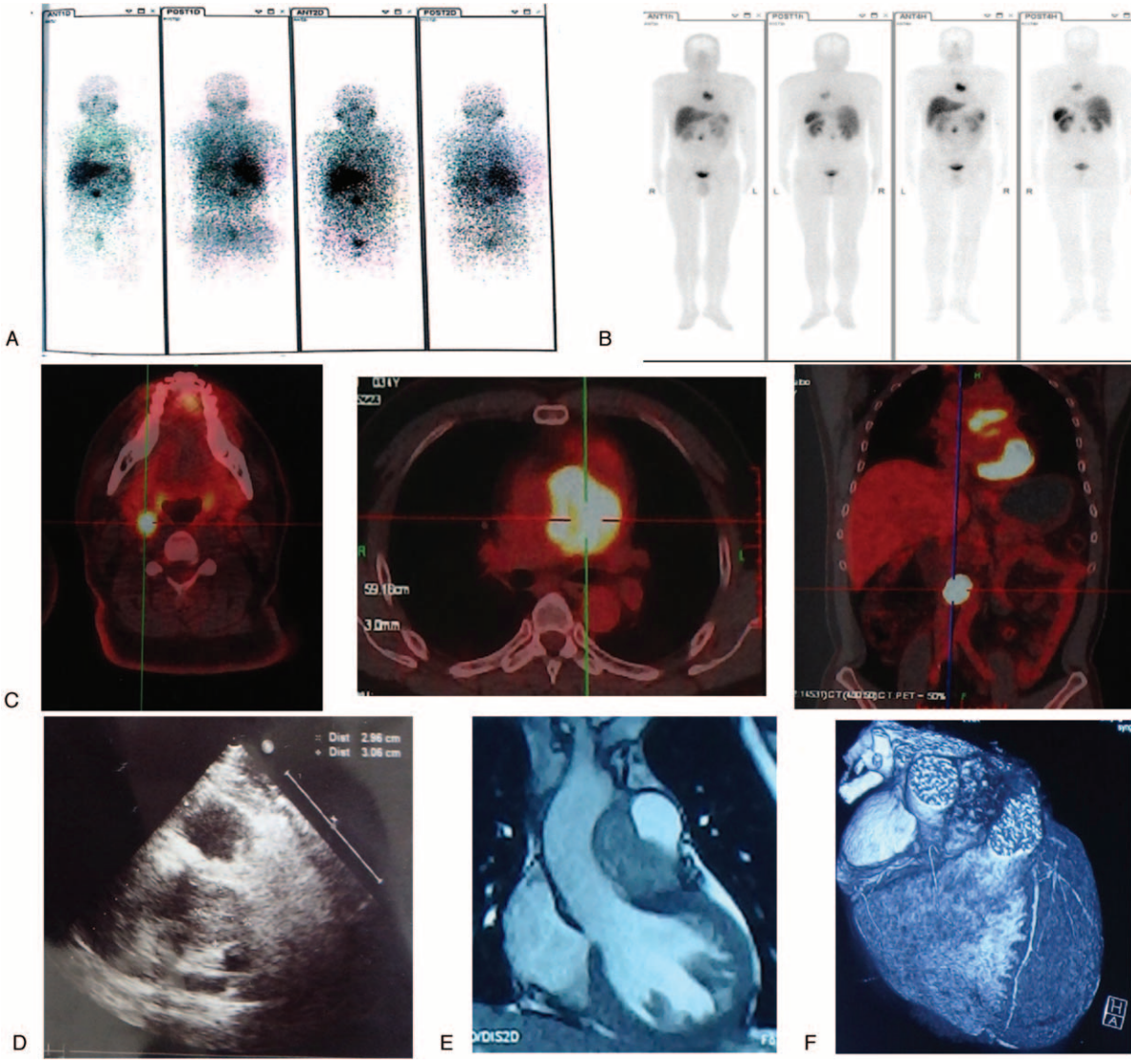

FIGURE 1. Radioisotope imaging, echocardiography, PET, CT, and MRI in a 35-year-old man. (A) Whole-body ^{131}I-MIBG imaging 24 and 48 h after tracer injection. Radioactive accumulation was observed in the right neck. Heterogeneous radioactivity was also detected in the chest and in mid-abdomen. (B) Somatostatin receptor scintigraphy at 1 and 4 h. Somatostatin expression was detected at the right medial root of the cervical carotid sheath. Expression was also detected in the mediastinum between the main and pulmonary arteries, and in the mid-abdomen. (C) PET scan. Multiple metabolic abnormalities were observed in the medial right carotid sheath (C1, SUVmax 13.6), mediastinum between the main and pulmonary arteries (C2, SUV max14.5), and between the abdominal aorta and inferior vena artery (C3, SUVmax 43.6), suggesting malignant neoplasia or malignant paraganglioma. (D) Echocardiography. The left ventricle was enlarged and had reduced function (45.1% ejection fraction). A moderate echogenic mass measuring 31 × 30 mm was found at the aortic root and left main coronary artery. (E) Cardiac MRI. A lobulated mass was found between the aortic root and main pulmonary artery extending to the aortic arch (56 × 56 × 40 mm). (F) CT angiography of the coronary vasculature. Multiple punctate calcifications were observed in the coronary arteries. A mass lesion was observed in the pericardium surrounding the left and right coronary arteries, leading to severe stenosis of the left main coronary artery and multiple stenotic areas in the left anterior descending artery. ^{131}I-MIBG = iodine-131 metaiodobenzylguanidine, CT = computed tomography, MRI = magnetic resonance imaging, PET = positron emission tomography, SUVmax = maximum standardized uptake value.

severe left ventricular (LV) dysfunction (ejection fraction 45.1%, end-diastolic/end-systolic dimension 67/51 mm), which was attributed to a suspected catecholamine-induced cardiomyopathy. His family history indicated that his mother was also diagnosed pheochromocytoma, and his sister died of pheochromocytoma. In addition, the serum total calcium (2.53 mmol/L), free calcium (1.20 mmol/L), phosphorus (1.34 mmol/L), parathyroid hormone (23.4 pg/mL), gastrin (80.9 pg/mL), calcitonin (3.96 pg/mL), and alkaline phosphatase (109 U/L) were also detected to exclude the multiple endocrine neoplasia. Finally, histopathological examination confirmed a diagnosis of pheochromocytoma, supported by AE1/AE3(−), CD56(NK-1)(+), CgA(+), Ki-67 (index 3%), S100(+), and Syn(+) results on immunohistochemistry.

After consulting with specialists across multiple disciplines, including a cardiologist, surgeon, anesthesiologist, and endocrinologist, the patient underwent a combined cardiac paraganglioma resection, coronary artery bypass grafting (CABG), aortic sinus reconstruction, main and pulmonary artery reconstruction, and main and pulmonary artery arthroplasty under cardiopulmonary bypass (CPB). Anesthesia was induced with midazolam (5 mg), fentanyl (0.05 mg), and propofol (60 mg). Following tracheal intubation with vecuronium bromide, the patient's blood pressure was 160/105 mm Hg and heart rate (HR) 82 beats/min (bpm). After beginning the CPB, his mean arterial pressure (MAP) was maintained at 80 mm Hg with norepinephrine infused at 0.8 to 1.0 μg/kg/min. The tumor was resected in 218 minutes during CPB. After the successful tumor removal, however, the patient could not be weaned from CPB. Even with aggressive fluid resuscitation (4928 mL of fluid administered, total positive fluid balance of 2650 mL, central venous pressure [CVP] of 14 mm Hg), the patient's blood pressure decreased dramatically during our attempt to discontinue CPB, dropping <60/45 mm Hg without any response to vasopressin, norepinephrine at 60 μg/kg/min, and epinephrine at 2.0 μg/kg/min. The patient also exhibited ventricular arrhythmia with a HR of 140 bpm and 3 episodes of ventricular fibrillation. The patient was successfully defibrillated and the HR restored to 50 to 60 bpm. However, myocardial contraction failed to fully recover, and thus, venoarterial (V-A)-ECMO and intraaortic balloon pump (IABP) circulatory support were initiated. With V-A-ECMO treatment, the MAP increased to 60 mm Hg, a sinus rhythm was restored, and the HR remained at 60 bpm. The patient was transferred to the intensive care unit (ICU) for further treatment. The entire surgical progression is shown in Figure 2.

Upon arriving to the ICU, the patient was still in severe cardiac shock and hypoperfusion despite receiving norepinephrine at 60 μg/kg/min and epinephrine at 2.0 μg/kg/min. The CVP, Gap mean central venous-to-arterial CO2-gap ($Pvco_2-Paco_2$), central venous oxygen saturation, and lactic acid concentration were 11 mm Hg, 10.9 mm Hg, 68.3%, and 22 mmol/L, respectively. Transthoracic echocardiography (Vivid 7; GE Medical Systems, Milwaukee, WI) showed severe LV systolic dysfunction (ejection fraction 20%), and the velocity time integral (VTI) was 7 cm with no evidence of abnormal regional wall motion, LV enlargement, or pericardial effusion. Hypothermia and dehydration therapy were initiated to protect the brain.

Thirty minutes after entering the ICU, the patient's blood pressure began fluctuating significantly despite full analgesia and sedation. At this point, norepinephrine and epinephrine were discontinued, but his blood pressure then increased rapidly, with the systolic blood pressure as high as 140 mm Hg. Phenoxybenzamine was administered to control blood pressure, but the blood pressure quickly plummeted once more, and norepinephrine and epinephrine were reinitiated at 0.98 and 0.294 μg/kg/min, respectively. His blood pressure began to exhibit an unusual rhythmic alternation between phases of relative hypertension and hypotension. This cyclic hemodynamic crisis continued for the next 10 days. However, the wave amplitude steadily decreased over time with continuous ECMO and other life support therapy; the progression of ECMO treatment and the infection index change are shown in Table 1. The VTI increased to 12 cm, and the LV rejection fraction increased to 45% on day 10. IABP was discontinued 3 days postoperatively. The patient's condition steadily

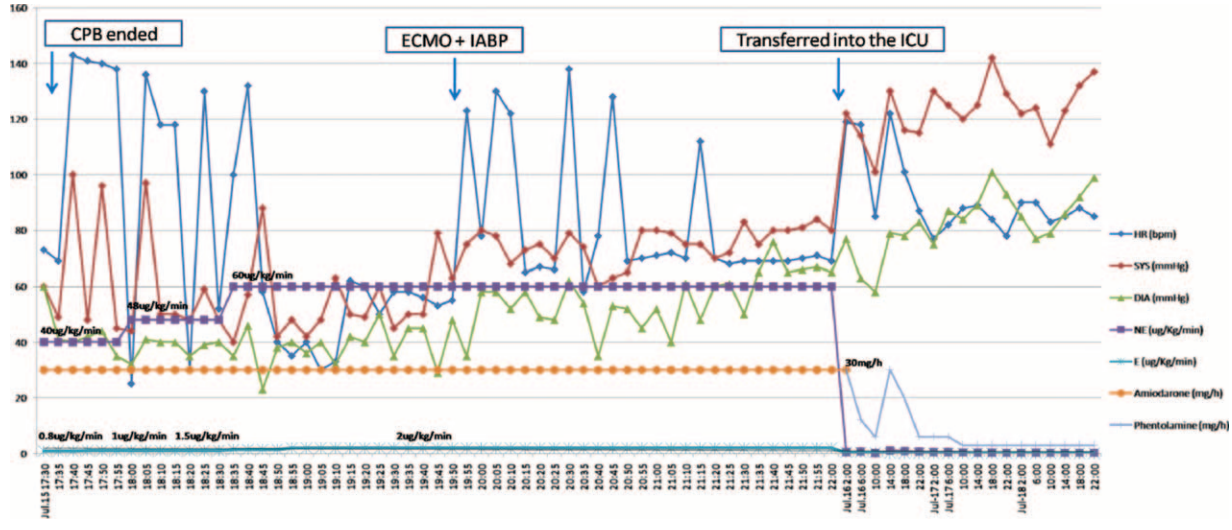

FIGURE 2. Dynamic changes in cardiac function during and after resection of multiple cardiac pheochromocytomas. The heart rate (HR), systolic blood pressure (SYS), and diastolic blood pressure (DIA), and dosages of norepinephrine (NE), epinephrine (E), amiodarone, phentolamine, and ECMO with IABP after CPB are indicated. The dramatic cyclic blood pressure fluctuation during the intraoperative and postoperative periods is particularly notable. CPB = cardiopulmonary bypass, ECMO = extracorporeal membrane oxygenation, IABP = intraaortic balloon pump, ICU = intensive care unit.

TABLE 1. Clinical Data Including Infection Indicators, Vasoactive Drug Use, and ECMO Parameters During and After Pheochromocytoma Resection

Date	July 15	July 16	July 17	July 18	July 19	July 20	July 21	July 22	July 23	July 24	July 25	July 26	July 27	July 28	July 29	July 30	July 31
Heart rate, bpm	135	115	92	91	89	125	106	108	98	82	80	101	103	89	110	121	108
BP, mm Hg	146/120	114/63	125/87	124/77	134/97	98/79	106/87	126/84	119/80	128/79	129/81	110/71	110/73	116/85	117/72	142/83	129/70
CVP, mm Hg	11	11	8–9	8	8–9	8	6	7–10	6–7	8	9–10	7–8	8–10	8	7–13	10	9
Vasoactive drugs																	
Epinephrine, μg/kg/min	2	0.294	—	—	—	0.294	0.294	0.294	0.098	0.078	—	—	—	—	—	—	—
NE, μg/kg/min	60	0.98	0.47	0.22	0.34	0.34	0.27	0.118	0.049	—	0.106	0.18	0.23	0.28	0.19	0.059	—
ECMO																	
Pump speed	4084	4000	4000	4000	3995	3775	4200	4715	4135	3735	2880	2805	2990	3405	2815	2995	2615
Blood flow, L/min	4.81	5.4	4.5	4.6	4.5	4.27	5.5	5.47	5.4	4.5	2.5	2.6	3	4	3.03	3.3	2.5
Oxygenator ΔP	<30	6–28	<30	<30	<40	<30	<40	20–28	16–29	12–23	14–27	15–19	25–33	27–41	23–27	11–27	12–20
Tissue perfusion																	
$Scvo_2$, %	68.3	85.4	81	80	70.5	81	56	65	77	72	60	64	57	67	65	76	75
Lactic acid	22	16	3	1.2	0.9	5.1	4.2	2.9	2	1.7	1	1.2	2.8	1.8	2.1	1.3	1.1
Organ function																	
Creatinine, μmol/L	106	117	129	117	101	165	145	141	122	128	127	108	117	112	108	107	99
ALT, U/L	36	46	46	39	32	24	56	32	29	24	18	18	19	11	13	19	29
CTnI, μg/L	–	159.63	82.7	36.7	24.1	24.38	14.0	12.42	6.85	4.95	3.57	2.88	2.45	1.15	0.92	0.89	0.52
VTI, cm	7	7	8	8	8	9	9	10	11	11	12	12	13	14	15	15	15

ALT = alanine aminotransferase, BP = blood pressure, CTnI = cardiac troponin I, CVP = central venous pressure, ECMO = extracorporeal membrane oxygenation, NE = norepinephrine, $Scvo_2$ = central venous oxygen saturation, VTI = velocity time integral.

improved, and ECMO was discontinued 16 days postoperatively. The tracheal cannula was extubated successfully, and the patient was transferred to the general ward 34 days postoperatively and discharged 3 months postoperatively.

DISCUSSION

The majority of pheochromocytomas are located in the adrenal glands. With <1% of tumors localized to the thoracic cavity, cardiac pheochromocytoma is extremely rare.[1] There are no known reports of multiple pheochromocytomas at the paracarotid, heart, and intraabdominal cavity as in the present case. Surgical resection is the definitive treatment for pheochromocytoma[11,12]; however, in this case, resection of the cardiac pheochromocytoma required CPB and adequate anticoagulation. Tumor resection at 3 different locations in a single surgery is extremely difficult and presents several challenges including a long surgical duration, significant hemorrhage, significant surgical trauma, and violent circulation fluctuations, all of which dramatically increase the risk of death. In this case, both the coronary and pulmonary arteries were invaded by the pheochromocytoma. Prioritizing the coronary resection may ensure cardiac perfusion, restore heart function, and avoid severe circulation fluctuations; therefore, we decided to perform the surgery in stages. The first stage comprised the cardiac paraganglioma resection, CABG, aortic sinus reconstruction, main and pulmonary artery reconstruction, and main and pulmonary artery arthroplasty. The second stage comprised the surgical removal of the remaining 2 pheochromocytomas.

Mechanical life support with ECMO is an effective treatment for refractory cardiac shock, especially when heart failure is likely reversible.[13] In the current case, the clinical progression occurred in 2 stages: severe refractory shock and hypoperfusion intraoperatively following resection of the cardiac pheochromocytoma; and severe cyclic blood pressure fluctuation postoperatively in the ICU. ECMO played a key role in addressing the hemodynamic instability during both the stages.

The acute refractory shock in this patient intraoperatively may have several causes. First, the abrupt decrease in catecholamine concentration after resecting the cardiac pheochromocytoma may have caused a catecholamine-resistant vasoplegia. The primary risk factor for this type of blood pressure abnormality is catecholamine secretion[14,15]; thus, the massive catecholamine secretion from the pheochromocytoma may have exaggerated the vasoplegia severity. Second, direct toxic effects of catecholamines on the myocardium and coronary artery may have caused catecholamine-mediated cardiomyopathy. The toxic effects of catecholamines are likely relevant in the pheochromocytoma crisis. The probable mechanisms underlying catecholamine-mediated cardiomyopathy include excess sympathetic stimulation, myocardial stunning, coronary arterial spasm, increased sarcolemmal permeability, elevated intracellular calcium concentration, and damage induced by oxygen-derived free radicals.[10] Third, postoperative vasoplegic syndrome (PVS) has been shown to contribute to refractory shock after CPB.[16–18] PVS does not usually decrease the cardiac output or trigger cyclical blood pressure fluctuations itself, but it instead causes persistent hypotension that is difficult to correct or triggers high blood pressure. Therefore, contribution from PVS cannot be excluded in the present case. Fourth, CPB performed after inducing hypothermia and CABG surgery both directly inhibit heart function. Finally, massive catecholamine release from multiple pheochromocytomas can cause peripheral vasodilation, severe cardiac depression, or distributive and cardiogenic shock.[19]

The complex mechanisms of acute refractory shock in this patient during surgery resulted in hemodynamic function characterized by extremely low cardiac output and peripheral vascular resistance unresponsive to catecholamines. In this life-threatening scenario, IABP and V-A ECMO were available as extracorporeal support systems. IABP provides only limited additional cardiac output, which is usually inadequate for acute refractory shock. V-A ECMO is an alternative option able to adequately perfuse all the organs irrespective of the lung condition. It can perform the functions of both ventricles and lungs, and can support a failing heart long term as needed. V-A ECMO can be started within 30 minutes and easily discontinued bedside in the ICU. In the present case, the MAP increased to 60 mm Hg immediately after initiating V-A-ECMO. IABP was also initiated to reduce cardiac afterload, ensure coronary artery perfusion, and maintain the pulse pressure early during V-A ECMO.

After beginning V-A ECMO and IABP, organ perfusion improved, metabolic acidosis was corrected, and the response to vasoactive drugs was restored. However, as perfusion to the 2 remaining pheochromocytomas was restored, the blood pressure began to immediately cycle between hypertension and hypotension. The mechanism for this rapid blood pressure fluctuation is unclear, but baroreflex failure may be responsible. Baroreceptors are tonically active and can respond quickly to blood pressure changes.[20,21] These patients may rapidly respond to α-blocker drugs such as phentolamine. In contrast to other cases of pheochromocytoma crisis with cyclic blood pressure fluctuation, however, the cardiac function in this patient was severely inhibited by the complex mechanisms as described. In this scenario of cyclic hemodynamic crisis, V-A ECMO can provide consistent perfusion and strengthen the cardiovascular tolerance for rapid cyclic blood pressure fluctuation and fluid resuscitation irrespective of poor cardiac function. Thus, V-A ECMO was not only key in successfully addressing the hemodynamic instability during the first refractory shock stage, but also the most important therapy ensuring adequate organ perfusion during the second stage comprising cyclic blood pressure fluctuation.

Pheochromocytoma crisis is rare but can cause refractory cardiovascular collapse and, occasionally, cyclic blood pressure fluctuation. ECMO can be used as valuable option for pheochromocytoma-induced cardiogenic shock, especially when highly unstable hemodynamics occurred. In patients experiencing a pheochromocytoma crisis with rapid cyclic blood pressure fluctuation, if acute heart failure also occurred, V-A ECMO is the most important mechanical life support to strengthen the cardiovascular tolerance for cyclic hemodynamic crisis and guarantee organs perfusion in such extreme hemodynamic status.

REFERENCES

1. Jebara VA, Uva MS, Farge A, et al. Cardiac pheochromocytomas. *Ann Thorac Surg.* 1992;53:356–361.
2. Safwat AS, Bissada NK, Seyam RM, et al. The clinical spectrum of phaeochromocytoma: analysis of 115 patients. *BJU Int.* 2008;101:1561–1564.
3. Suh IW, Lee CW, Kim YH, et al. Catastrophic catecholamine-induced cardiomyopathy mimicking acute myocardial infarction, rescued by extracorporeal membrane oxygenation (ECMO) in pheochromocytoma. *J Korean Med Sci.* 2008;23:350–354.
4. Guerrero MA, Schreinemakers JM, Vriens MR, et al. Clinical spectrum of pheochromocytoma. *J Am Coll Surg.* 2009;209:727–732.

5. Scholten A, Cisco RM, Vriens MR, et al. Pheochromocytoma crisis is not a surgical emergency. *J Clin Endocrinol Metab.* 2013;98: 581–591.

6. Ganguly A, Grim CE, Weinberger MH, et al. Rapid cyclic fluctuations of blood pressure associated with an adrenal pheochromocytoma. *Hypertension.* 1984;6 (2 pt 1):281–284.

7. Sojod G, Diana M, Wall J, et al. Successful extracorporeal membrane oxygenation treatment for pheochromocytoma-induced acute cardiac failure. *Am J Emerg Med.* 2012;30:1017.e1–1017.e3.

8. Noorani A, Vuylsteke A, Lewis C, et al. A moribund athlete. *Lancet.* 2012;380:74.

9. Banfi C, Juthier F, Ennezat PV, et al. Central extracorporeal life support in pheochromocytoma crisis. *Ann Thorac Surg.* 2012;93:1303–1305.

10. Flam B, Broome M, Frenckner B, et al. Pheochromocytoma-induced inverted Takotsubo-like cardiomyopathy leading to cardiogenic shock successfully treated with extracorporeal membrane oxygenation. *J Intensive Care Med.* 2014pii: 0885066614552992.

11. Pacak K, Eisenhofer G, Ahlman H, et al. Pheochromocytoma: recommendations for clinical practice from the First International Symposium, October 2005. *Nat Clin Pract Endocrinol Metab.* 2007;3:92–102.

12. Lenders JW, Eisenhofer G, Mannelli M, et al. Phaeochromocytoma. *Lancet.* 2005;366:665–675.

13. Hsu PS, Chen JL, Hong GJ, et al. Extracorporeal membrane oxygenation for refractory cardiogenic shock after cardiac surgery: predictors of early mortality and outcome from 51 adult patients. *Eur J Cardiothorac Surg.* 2010;37:328–333.

14. Lentschener C, Gaujoux S, Thillois JM, et al. Increased arterial pressure is not predictive of haemodynamic instability in patients undergoing adrenalectomy for phaeochromocytoma. *Acta Anaesthesiol Scand.* 2009;53:522–527.

15. Kramer CK, Leitao CB, Azevedo MJ, et al. Degree of catecholamine hypersecretion is the most important determinant of intra-operative hemodynamic outcomes in pheochromocytoma. *J Endocrinol Investig.* 2009;32:234–237.

16. Argenziano M, Chen JM, Choudhri AF, et al. Management of vasodilatory shock after cardiac surgery: identification of predisposing factors and use of a novel pressor agent. *J Thorac Cardiovasc Surg.* 1998;116:973–980.

17. Levin RL, Degrange MA, Bruno GF, et al. Methylene blue reduces mortality and morbidity in vasoplegic patients after cardiac surgery. *Ann Thorac Surg.* 2004;77:496–499.

18. Byrne JG, Leacche M, Paul S, et al. Risk factors and outcomes for 'vasoplegia syndrome' following cardiac transplantation. *Eur J Cardiothorac Surg.* 2004;25:327–332.

19. Bergland BE. Pheochromocytoma presenting as shock. *Am J Emerg Med.* 1989;7:44–48.

20. Cohn JN. Paroxysmal hypertension and hypovolemia. *N Engl J Med.* 1966;275:643–646.

21. Hamada M, Shigematsu Y, Mukai M, et al. Blood pressure response to the Valsalva maneuver in pheochromocytoma and pseudopheochromocytoma. *Hypertension.* 1995;25:266–271.