ESC HEART FAILURE
ESC Heart Failure 2016; **3**: 282–287
Published online 15 August 2016 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.12102

CASE REPORT

Continuous renal replacement therapy for haemodynamic collapse and rhabdomyolysis induced by pheochromocytoma crisis

Xi Zhou[1,3†], Chuhuan Zhao[1†], Xiafei Feng[1,3], Anweshan Samanta[2], Yi nuo Lin[3], Jun Chen[1], Xiaochun Dai[1], Xia Hong[1], Qiangli Xie[1] and Weijian Huang[1,3*]

[1]*Department of Cardiac Care Unit, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China;* [2]*Institute of Cardiovascular Research, University of Kansas Medical Center, Kansas City, KS, USA;* [3]*Department of Cardiology, The Key Lab of Cardiovascular Disease of Wenzhou, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China*

Abstract

Pheochromocytoma associated with pregnancy is not common. Caesarean section may induce pheochromocytoma crisis, resulting in a lethal condition. The clinical picture of pheochromocytoma crisis is extremely variable. In this report, we describe a case of severe pheochromocytoma crisis induced by caesarean section presenting with hyperpyrexia, haemodynamic collapse, muscle weakness, heart failure, and acute kidney injury. Furthermore, we report that the muscle weakness was a manifestation of rhabdomyolysis, resulting from the pheochromocytoma crisis. Standard medical therapy failed to halt the patient's rapidly deteriorating condition. Continuous renal replacement therapy removed catecholamines from the circulation, resulting in improvement of haemodynamics and abrogation of rhabdomyolysis.

Keywords Pheochromocytoma crisis; Continuous renal replacement therapy; Haemodynamic collapse; Rhabdomyolysis

Received: 16 February 2016; Revised: 7 June 2016; Accepted: 12 June 2016
**Correspondence to: Weijian Huang, Department of Cardiology, Department of Cardiac Care Unit, The First Affiliated Hospital of Wenzhou Medical University, Ouhai Region, Wenzhou City, Zhejiang Province 325000, China. Tel: (+86) 13806991086. E-mail: weijianhuang69@126.com*
†The first two authors contributed equally to the study.

Introduction

Pheochromocytoma associated with pregnancy is not common, without specific symptoms, but life-threatening, increasing both maternal and fetal mortality up to 50%.[1] Caesarean section has been known to induce pheochromocytoma crisis.[2] The excess release of catecholamines by the tumour can induce acute and rapidly progressive haemodynamic disturbance and a series of clinical conditions such as malignant hypertension,[3] Takotsubo cardiomyopathy,[4] and multi-organ failure. Other rare complications of pheochromocytoma crisis are spontaneous rhabdomyolysis and acute renal failure.

Early diagnosis of pheochromocytoma crisis, followed by aggressive management, is required to save the patient's life. The definitive therapy for pheochromocytoma is complete surgical resection of the tumour. For patients in pheochromocytoma crisis, the effects of excessive release of catecholamines must be counteracted to result in haemodynamic stabilization prior to surgery and improve outcomes.[5–8] Administration of α with or without β blockade is part of the standard of care. However, pheochromocytoma crisis often presents as a complicated clinical syndrome, and pharmacological intervention may not suffice, resulting in a rapid deterioration of the patient's condition.

In our case, we report a patient with severe pheochromocytoma crisis presenting with hyperpyrexia, haemodynamic collapse, heart failure, and rhabdomyolysis. Routine medical therapy was insufficient, and we administered continuous renal replacement therapy (CRRT). Surprisingly, CRRT stabilized the haemodynamics, improved cardiac output, and cured the rhabdomyolysis of the patient by means of catecholamine removal.

Case report

A 33-year-old pregnant woman, G3P2, at 39 weeks of pregnancy, without a history of hypertension, was admitted to the hospital because of vomiting and dyspnoea. The diagnosis at the referring hospital was threatened premature labour. The patient had a caesarean operation before and had few antenatal tests during this gestation. So, the patient had an emergency caesarean operation.

On the second day, the patient had hyperpyrexia, dyspnoea, convulsion, and muscle weakness. Her temperature increased to 40.2 °C, her heart rate was 160 beats per minute in sinus rhythm, and her respiratory rate was 28 times per minute. The blood pressure of the patient exhibited paroxysmal hypertension and hypotension. She demonstrated grade 2 muscle strength in her limbs. Based on the clinical presentation, we suspected that the patient was suffering from pheochromocytoma crisis and proceeded with an abdominal computed tomography scan, which revealed bilateral adrenal gland tumours.

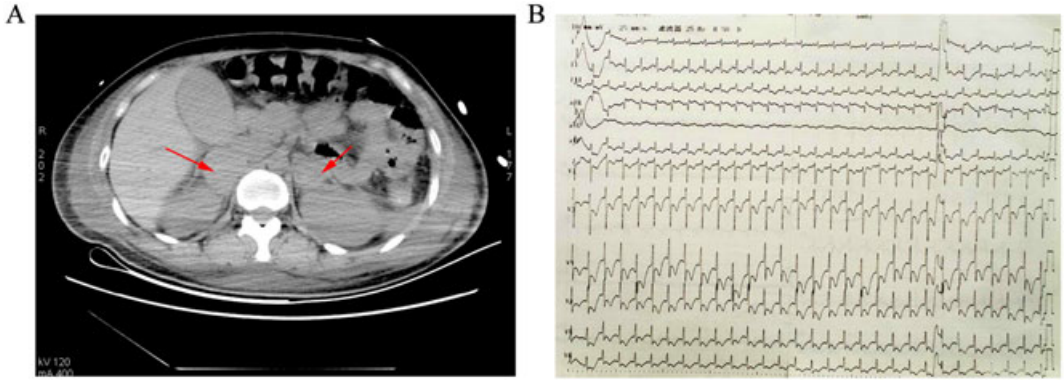
The tumour on the right was 30.28 × 32.81 mm in size, and the left one was 21.20 × 23.41 mm (*Figure 1A*). Blood analysis showed extremely elevated creatine kinase (CK: 3334 U/L, CK-MB: 24 U/L), cardiac Troponin I (cTnI: 9.94 μg/L), and serum creatinine levels (118 μmol/L). Meanwhile, thyroid function was assessed. The serum thyroxine level was 69.28 nmol/L (reference range: 78.38–157.4 nmol/L). The concentration of thyroid stimulating hormone was 1.59 mIU/L (reference range: 0.34–5.60 mIU/L). The concentration of freeT3 was 2.0 pmol/L (reference range: 3.8–6.0 pmol/L); the concentration of freeT4 was 12.8 pmol/L (reference range: 7.86–14.41 pmol/L). The electrocardiogram showed sinus tachycardia with ST segment depression and T wave inversion in leads V1–V6 (*Figure 1B*). Echocardiography showed global hypokinesis of left ventricular (LV) wall motion (the LV end-diastolic diameter was 53 mm, and the LV ejection fraction was 25%) and mild mitral valve regurgitation.

On the second and third hospital days, the patient's condition was getting worse in spite of continuous infusion of phentolamine and esmolol, ultimately resulting in altered mental status, frequent convulsions, and haemodynamic collapse. Her muscle strength was now grade 0. Creatine kinase levels increased tremendously to over 70 000 U/L, while CK-MB levels increased to 1200 U/L. Her fever was not controlled despite the use of powerful antibiotics. Furthermore, her renal function progressively deteriorated (serum creatinine: 225 μmol/L) and manifested as oliguria. Laboratory tests showed a plasma adrenaline level of 5.8 ng/mL (upper limit of normal is 0.28 ng/mL) and a plasma noradrenaline level of 32.7 ng/mL (upper limit of normal is 1.7 ng/mL).

Continuous renal replacement therapy was started on the fifth hospital day. It was surprising that the temperature of the patient decreased, the heart rate declined, and the haemodynamics stabilized (*Figure 2A*). Blood analysis showed that CK and CK-MB levels rapidly declined to normal (*Figure 2B*). Plasma catecholamine concentration also showed a similar trend (*Figure 3A*). To confirm the effect of dialysis on plasma catecholamines, we examined the catecholamine concentration in the dialysate. Concentrations of adrenaline and noradrenaline in the dialysate were 11.2 and 1.2 ng/mL, respectively, confirming the removal of these catecholamines by dialysis. Following 7 days of CRRT, her muscle strength recovered from grade 0 to grade 5, and her 24-h urine output also returned to normal. On the 12th hospital day, we performed a muscle biopsy of the right bicep muscle, which revealed deranged myofibrils, increased mitochondrial number, and damaged mitochondria (*Figure 4*). Echocardiography showed a recovery in cardiac function with a LV eject fraction of 54.4% (*Figure 3B*).

As a result, the patient was rescued from the pheochromocytoma crisis and underwent bilateral adrenalectomy.

Figure 1 Abdominal computed tomography and electrocardiography of the patient with pheochromocytoma crisis. (A) Abdominal computed tomography showed bilateral adrenal gland tumours. The tumour on the right was 30.28 × 32.81 mm in size, and the left one was 21.20 × 23.41 mm. (B) Electrocardiography showed sinus tachycardia with ST segment depression and T wave inversion in leads V1–V6.



Pathological assessment confirmed the presence of pheochromocytoma with haemorrhagic and necrotic cysts. Informed consent was obtained from the patient.

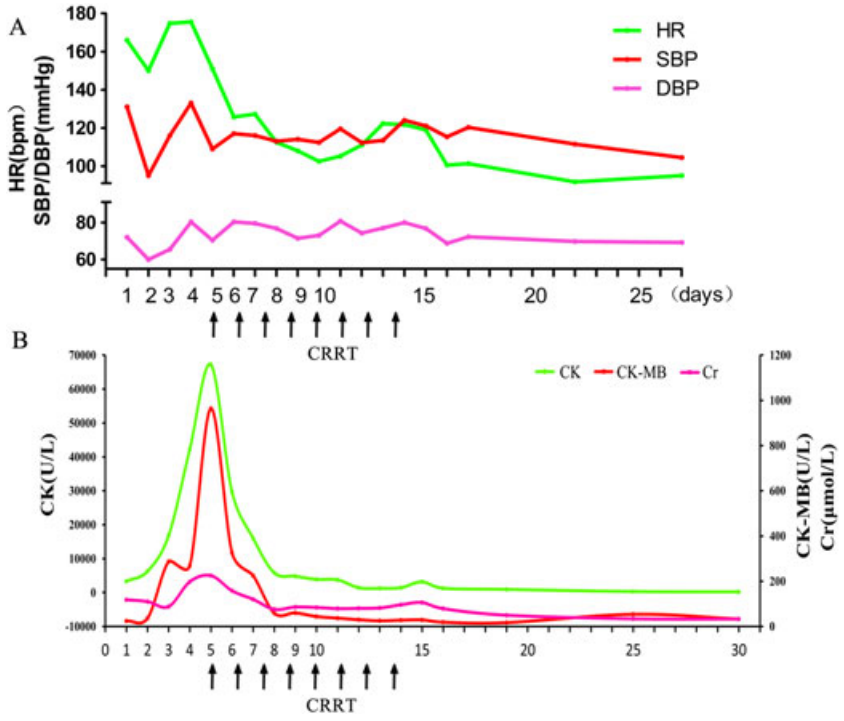
Discussion

Pheochromocytoma is a catecholamine-producing neuroendocrine tumour that arises from inside or outside the adrenal medulla. The classic triad of symptoms of pheochromocytoma are palpitations, headaches, and diaphoresis, but signs and symptoms of pheochromocytoma are wide ranging and mainly reflect the haemodynamic and metabolic actions of the catecholamines produced and secreted by the tumours.

In our case, the chief complaints of the patient were not part of the classic triad. The clinical presentation of hyperpyrexia could easily be mistaken for septicaemia, but infection was an unlikely underlying cause as a result of the ineffectiveness of a wide range of strong antibiotics. The fever and acute inflammatory symptoms could be explained by the production of interleukin-6 by the tumour, as reported previously.[9] The patient presenting with dyspnoea, paroxysmal hypertension and hypotension, sinus tachycardia, low LV ejection fraction, and increased cTnI and ST-T wave changes had extremely unstable haemodynamics that could be explained by cardiac shock or catecholamine cardiomyopathy. The assessment of thyroid function of our patient was normal, so hyperpyrexia, hypertension, tachyarrhythmia, and cardiac shock could not have been peripartum thyroid storm in the setting of a pheochromocytoma. Furthermore, malignant hypertension with multiple organ failure could also induce the similar clinical presentation. While our patient presented paroxysmal hypertension and hypotension instead of continuous elevated blood pressure, the increased cTnI and ST-T wave changes were more likely to be the result of the secretion of pheochromocytoma. Besides, rhabdomyolysis of the patient could not be explained by malignant hypertension.

Our patient exhibited a rapid rise in creatine kinase levels in addition to muscle weakness. Recently, some case reports showed that pheochromocytoma could induce rhabdomyolysis and acute renal failure with increased creatine kinase levels but had not performed biopsy.[10–12] There is just evidence in the literature of histologically proven focal myositis with degeneration of skeletal muscle fibers, increased sarcolemmal nuclei, and giant cells in a patient with a large pheochromocytoma at autopsy.[13] In our case, we performed a biopsy of the patient's bicep muscle, and electron microscopic examination revealed deranged

Figure 2 Haemodynamic parameters and levels of creatine kinase and serum creatinine in the patient before and after continuous renal replacement therapy. (A) Heart rates showed extremely sinus tachycardia before CRRT, and HR gradually decreased after CRRT. SBP and DBP fluctuated before CRRT but stabilized after CRRT. (B) Blood analysis showed extremely elevated creatine kinase and serum creatinine before CRRT, which decreased to normal after CRRT. HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; CK, creatine kinase; CK-MB, creatine kinase-MB; Cr, creatinine; CRRT, continuous renal replacement therapy.



DOI: 10.1002/ehf2.12102

Figure 3 Concentration of serum catecholamines and cardiac function before and after continuous renal replacement therapy. (A) Concentrations of noradrenaline and adrenaline were very high but decreased rapidly after starting CRRT. (B) Cardiac function, assessed by left ventricular ejection fraction, improved rapidly after starting CRRT, and eventually returned to normal. NA, noradrenaline; A, adrenaline; LAD, left atrial diameter; LV, left ventricle; EF, ejection fraction.

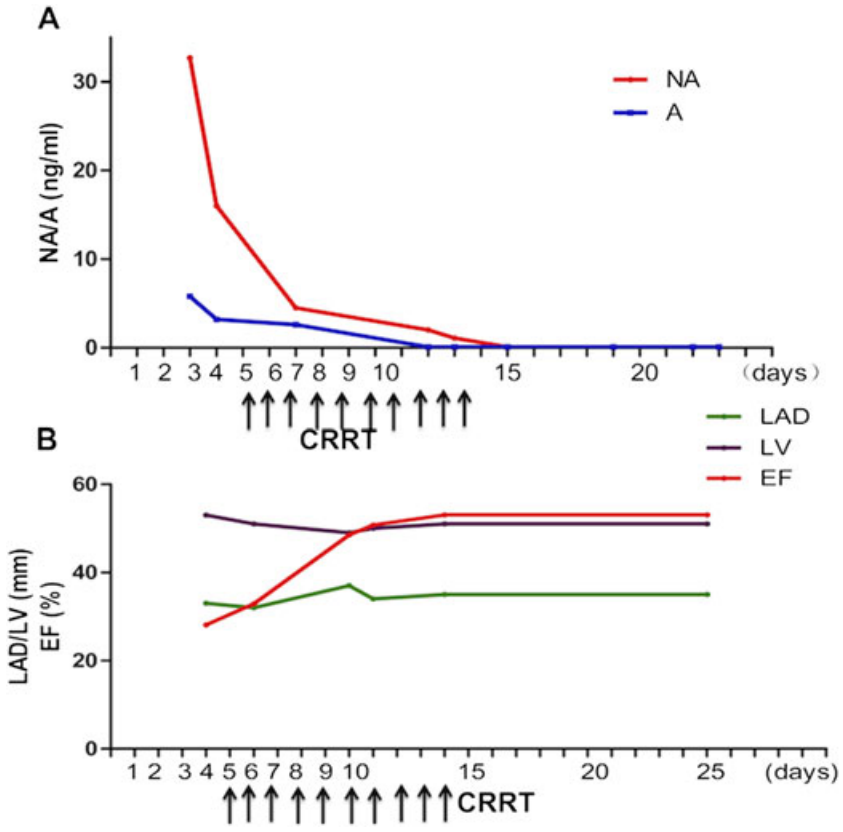
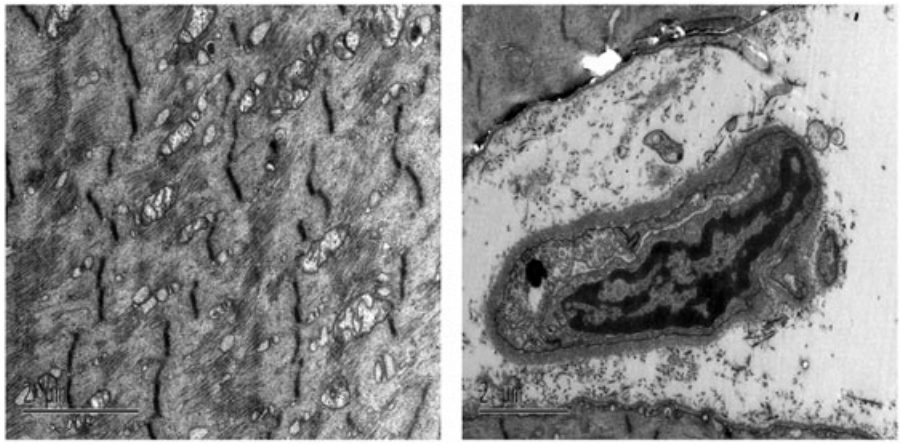


Figure 4 Biopsy of bicep muscle visualized by electron microscopy. Electron microscopy showed deranged myofibrils, increased mitochondrial number, and damaged mitochondria.



myofibrils, atrophy, increased mitochondrial number, as well as damaged mitochondria. The muscle biopsy was performed on the 12th day in the hospital, by which time CRRT had been initiated for several days, and the CK level had almost returned to normal. The pathological observation indicated that the muscle weakness and elevated CK in this patient were probably a

result of rhabdomyolysis. While CRRT remained an option for the treatment of rhabdomyolysis, it was unknown whether it would be effective in a patient with pheochromocytoma. Our patient stabilized soon after CRRT was initiated, leading us to believe that CRRT treated the rhabdomyolysis not only by the removal of the CK but also by the removal of catecholamines from the circulation.

It had previously been reported that catecholamines could be removed by CRRT in 1978.[14] Another report recently showed that CRRT could cure pheochromocytoma crisis with multiple organ failure.[15] In our report, the patient suffered not only from multiple organ failure but also rhabdomyolysis. Upon starting CRRT, the patient rapidly recovered exhibiting haemodynamic stabilization and return of muscle function. We were conclusively able to confirm the removal of catecholamines by CRRT by positively identifying it in the dialysate.

Although the definitive treatment for pheochromocytoma is surgical resection, it is often too risky to perform in the setting of pheochromocytoma crisis. It is therefore imperative to first stabilize the patient using standard medical therapy involving adequate α-blockade, followed by β-blockade. Additional medications such as nitroprusside or magnesium or alpha methyl tyrosine should be considered in controlling hypertensive crisis induced by pheochromocytoma. While nitroprusside and alpha methyl tyrosine have reported the failure use in controlling hypertensive crises in association with pheochromocytoma,[16,17] magnesium may be a good choice in stabilizing the haemodynamic of the patient by decreasing catecholamine release.[18] In our case, we supposed that magnesium may stabilise the patient from the hypertensive crisis but may fail to rescue the patient from rhabdomyolysis. Besides routine medical therapy, use of extracorporeal membrane oxygenation coupled with intra-aortic balloon pump has been reported to stabilize the haemodynamic collapse of patients.[19,20] Although extracorporeal membrane oxygenation and intra-aortic balloon pump would treat the haemodynamic collapse of our patient, it would be ineffective for the treatment of rhabdomyolysis and acute renal failure by eliminating catecholamines. We conclude from our experience that CRRT is capable of managing a wide range of complications of pheochromocytoma crisis by removing toxic catecholamines from the circulation, thereby stabilizing haemodynamics and resolving critical illness myopathy and ultimately buying valuable time to undergo elective surgery.

Conflict of Interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

This research did not receive any specific grant from any funding agency in the public, commercial, or not-for-profit sector.

References

1. Biggar MA, Lennard TW. Systematic review of phaeochromocytoma in pregnancy. *Br J Surg* 2013; **100**: 182–90.
2. Baraka A. Undiagnosed pheochromocytoma complicated with perioperative hemodynamic crisis and multiple organ failure. In Martin J. F., ed. *Pheochromocytoma—A New View of the Old Problem*. Lebanon, Beirut: InTech; 2011 p.135–148.
3. Aftab S, Yasmeen T, Hamid MH, Sarwar M, Sipra H, Qureshi A, Sheikh A, Haider N, Hanif G. Pheochromocytoma: a rare cause of childhood hypertensive encephalopathy. *J Coll Physicians Surg Pak* 2012; **22**: 536–538.
4. Assefa D, Welsch J, Laubner K, Burgdorf C, Kotzerke M. Cardiogenic shock due to atypical Tako-tsubo cardiomyopathy in a young woman with pheochromocytoma. *Dtsch Med Wochenschr* 2015; **140**: 422–425.
5. Tsirlin A, Oo Y, Sharma R, Kansara A, Gliwa A, Banerji MA. Pheochromocytoma: a review. *Maturitas* 2014; **77**: 229–238.
6. Chen H, Sippel RS, O'Dorisio MS, Vinik AI, Lloyd RV, Pacak K, North American Neuroendocrine Tumor Society (NANETS). The North American Neuroendocrine Tumor Society consensus guideline for the diagnosis and management of neuroendocrine tumors. *Pancreas* 2010; **39**: 775–783.
7. Scholten A, Cisco RM, Vriens MR, Cohen JK, Mitmaker EJ, Liu C, Tyrrell JB, Shen WT, Duh QY. Pheochromocytoma crisis is not a surgical emergency. *J Clin Endocrinol Metab* 2013; **98**: 581–591.
8. Muller G, Saint F, Hamy A, Lifante JC, Carnaille B, Sebag F, Ménégaux F, Vandwalle J, Drui D, Caillard C, Rodien P, Roy M, Peix JL, Pattou F, Brunaud L, Henry JF, Mirallié E. Pheochromocytoma revealed by acute heart failure. When should we operate? *Langenbecks Arch Surg* 2013; **398**: 729–733 Presented at the ESES Congress; May 25-26, 2012; Gothenburg, Sewden.
9. Kang JM, Lee WJ, Kim WB, Kim TY, Koh JM, Hong SJ, Huh J, Ro JY, Chi HS, Kim MS. Systemic inflammatory syndrome and hepatic inflammatory cell infiltration caused by an interleukin-6 producing pheochromocytoma. *Endocr J* 2005; **52**: 193–198.
10. Celik H, Celik O, Guldiken S, Inal V, Puyan FO, Tugrul A. Pheochromocytoma presenting with rhabdomyolysis and acute renal failure: a case report. *Ren Fail* 2014; **36**: 104–107.
11. Shemin D, Cohn PS, Zipin SB. Pheochromocytoma presenting as rhabdomyolysis and acute myoglobinuric renal failure. *Arch Intern Med* 1990; **150**: 2384–2385.
12. Anaforoglu I, Ertorer ME, Haydardedeoglu FE, Colakoglu T, Tokmak N, Demirag NG. Rhabdomyolysis and acute myoglobinuric renal failure in a patient with bilateral pheochromocytoma following open pyelolithotomy. *South Med J* 2008; **101**: 425–7.
13. Bhatnagar D, Carey P, Pollard A. Focal myositis and elevated creatine kinase levels in a patient with phaeochromocytoma. *Postgrad Med J* 1986; **62**: 197–198.
14. Zucchelli P, Catizone L, Esposti ED, Fusaroli M, Ligabue A, Zuccalà A. Influence of ultrafiltration on plasma renin activity and adrenergic system. *Nephron* 1978; **21**: 317–24.
15. Seo M, Yamada T, Ozu K, Fukunami M. Efficacy of continuous renal replacement therapy for pheochromocytoma crisis with multiple organ failure. *Am J Med Sci* 2015; **350**: 508–11.
16. Anton AH, Sherman BW, Lina AA, Acheson LS. An atrial pheochromocytoma-induced hypertensive crisis resistant to

ni-troprusside. *Int J Clin Pharmacol Ther Toxicol* 1993; **31**: 89–92.
17. Ram CV, Meese R, Hill SC. Failure of alpha-methyltyrosine to prevent hypertensive crisis in pheochromocytoma. *Arch Intern Med* 1985 Nov; **145**: 2114–5.
18. James MF, Beer RE, Esser JD. Intravenous magnesium sulfate inhibits catecholamine release associated with tracheal intuba-tion. *Anesth Analg* 1989; **68**: 772–6.
19. Suh IW, Lee CW, Kim YH, Hong MK, Lee JW, Kim JJ, Park SW, Park SJ. Catastrophic catecholamine-induced cardiomyopathy mimicking acute myocardial infarction, rescued by extracorporeal membrane oxygenation (ECMO) in pheochromocytoma. *J Korean Med Sci* 2008; **23**: 350–4.
20. Zhou X, Liu D, Su L, Long Y, Du W, Miao Q, Li F, Jin Z, Zeng Z, Luo A, Huang Y. Pheochromocytoma crisis with severe cyclic blood pressure fluctuationsin a cardiac pheochromocytoma patient successfully resuscitated by extracorporeal membrane oxygenation: a case report. *Medicine (Baltimore)* 2015; **94**: e790.