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CASE REPORT

Critical periodic systemic blood pressure fluctuations during pulmonary valve replacement cardiac surgery in a patient with an incidentally discovered normotensive pheochromocytoma-A case report

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Abstract

Standard management protocols for patients with pheochromocytoma (PHEO) have been described in current guidelines. However, the standard management approach for cardiac surgical patients with concurrent clinically silent PHEO has not been established yet. The effects of open heart surgery and cardiopulmonary bypass (CPB) on PHEO presentation are poorly documented. Here, we report in detail the anesthetic management and hemodynamic changes in a case of CPB-assisted pulmonary valve replacement surgery with an incidentally discovered normotensive PHEO. A 55-year-old male with normotensive PHEO underwent an open heart pulmonary valve replacement surgery. Blood pressure (BP) fluctuated with an inherent alternation rhythm during the whole process of the surgery with a peak at 230/130 mmHg and nadir at 40/30 mm Hg. Administration of fluids and vasoconstrictor/vasodilator was used for BP optimization. However, the BP changed intractably with delayed responses to the optimization management.
The hemodynamic instability observed in this case indicated that the risk of occurrence and severity of the PHEO crisis did not decrease in cases with previously silent PHEO and may be triggered in any clinical scenario, not in tumor removal procedures alone. Careful preoperative evaluation and preparation with multidisciplinary cooperation are of paramount importance for such patients because open chest cardiac surgery and CPB could complicate the situation. In addition, there is little evidence about the benefits of a combined cardiac surgery with PHEO resection in such a clinical scenario, which validates further investigation.

Abbreaviations:

BP	- blood pressure;
CPB	- cardiopulmonary bypass;
CVP	- central venous pressure;
LVEF	- left ventricular ejection fraction;
PHEO(s)	- pheochromocytoma(s);
VMA	- vanillylmandelic acid

INTRODUCTION

Pheochromocytomas (PHEOs) are rare catecholamine-producing neuroendocrine tumors of the adrenal medulla. Catecholamines, when released, can produce life-threatening cardiocerebral vascular complications. Refractory hypertension is the most prominent clinical sign of PHEOs. However, symptoms are absent in approximately 10% of patients (Mannelli *et al.* 2012). Although the management approach for patients with PHEO is clearly stated in the current guidelines (Chen *et al.* 2010; Lenders *et al.* 2014; Naranjo *et al.* 2017), the standard management strategy for surgical intervention in patients with concurrent, asymptomatic PHEO has not been established yet. Here, we report a case of normotensive PHEO patient who underwent open heart surgery with cardiopulmonary bypass (CPB). Dramatic blood pressure (BP) fluctuations persisted during the entire surgical procedure.

CASE PRESENTATION

A 55-year-old male, weighing 53 kg, was electively scheduled for an open heart pulmonary valve replacement surgery for infective endocarditis-induced pulmonary valve insufficiency and vegetation. His chief complaints included palpitation, short breath, chest distress, and chest pain. Cardiac ultrasonography revealed pulmonary valve prolapse and vegetation, severe pulmonary valve regurgitation, and pulmonary hypertension with a mean pulmonary pressure of 32 mmHg. Right ventricular enlargement was diagnosed with a right ventricular internal diameter of 40 mm. Left ventricular ejection fraction (LVEF) was 56%. The physical status of the patient was classified as the New York Heart Association functional class II. An adrenal mass was incidentally revealed in the preoperative computed tomography (CT) (Figure 1) with a slightly elevated 24-hr measurement of vanillylmandelic acid (VMA). The patient reported no history of hypertension and headache, and BP values were normal on five consecutive mornings. No orthostatic hypotension was detected before surgery. The plasma aldosterone level was within the normal range. Owing to the unavailability of equipment, metanephrine levels could not be measured in our hospital. After consulting with the urologists, the adrenal mass was suspected as PHEO. Because the main symptoms of the patient were related to abnormality of the intracardiac structures and corresponding physiological status and no obvious symptoms and signs related to the PHEO had been detected, urologists deferred the laparoscopic resection of PHEO until after the cardiac surgery to avoid the detrimental effects of hemodynamic fluctuations on the abnormal heart during PHEO resection.

The patient underwent isolated cardiac surgery under CPB without any preoperative preparation for

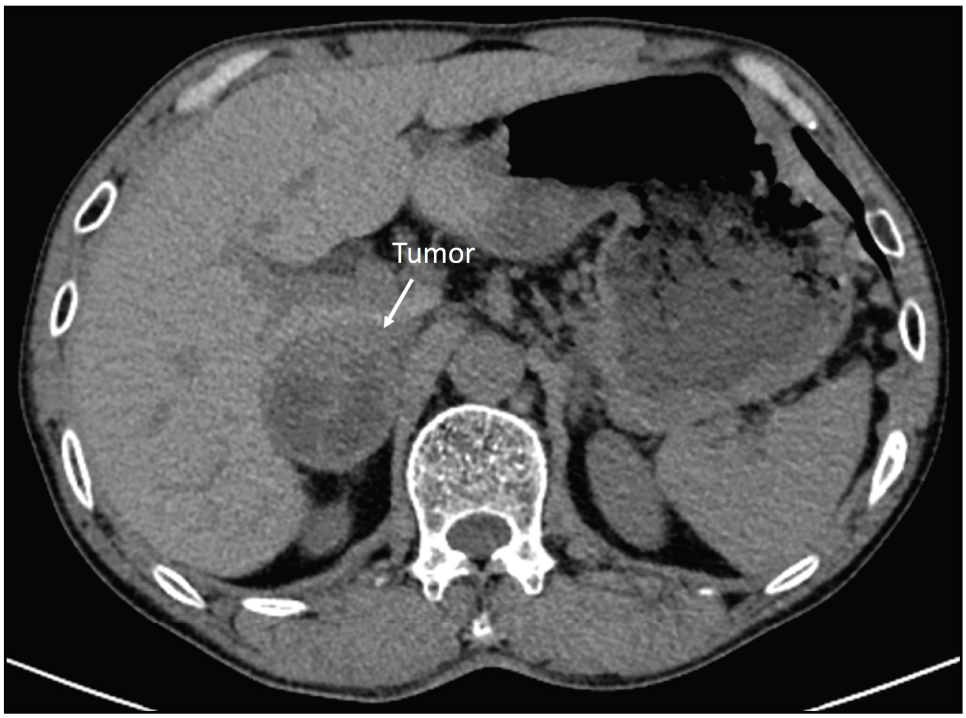

Fig. 1. Transverse view of a computed tomography (CT) scan showing a mass close to the right adrenal gland with suspected pheochromocytoma (PHEO).

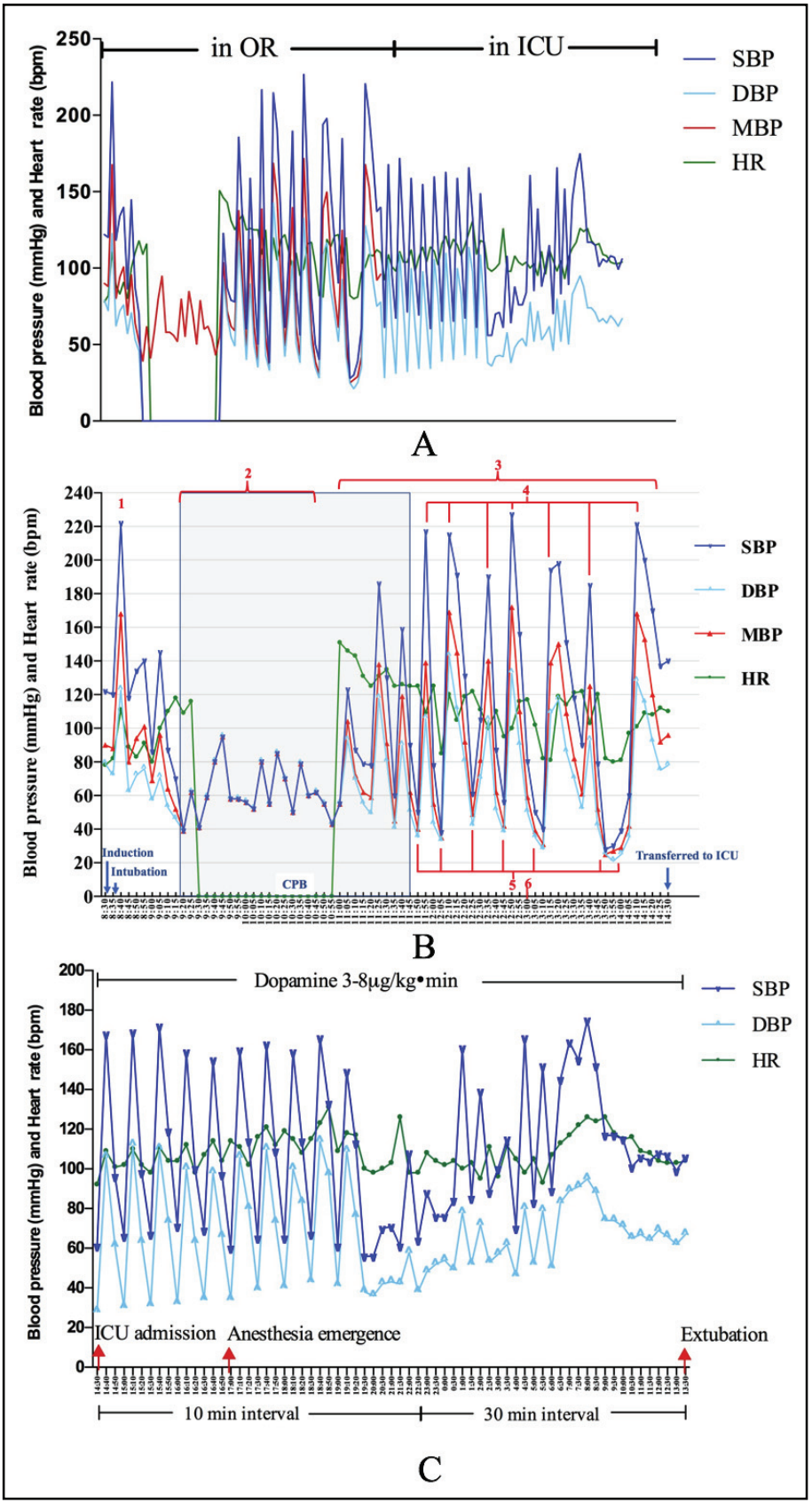

Fig. 2. Notable hemodynamic fluctuation during the surgery. A. Hemodynamic changes in the whole process; B. Hemodynamic changes during surgery; C. Hemodynamic changes after ICU admission to extubation.
SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; HR, heart rate; CPB, cardiopulmonary bypass. 1-6 labels the hemodynamics changes for corresponding events marked in Table 1.

PHEO along with invasive monitoring of BP via the right radial artery catheter and central venous pressure (CVP) using a three-lumen central venous catheter placed in the right internal jugular vein during the surgery. The baseline BP was 122/79 mmHg and heart rate (HR) was 88 bpm.

Anesthesia was induced and maintained with midazolam, sulfentanyl, rocuronium, etomidate, and propofol, following the routine institutional procedure. BP increased abruptly to 235/130 mmHg after intubation and decreased to 105/65 mmHg after 10 mg of urapidil injection. The BP varied between 140/70 and 80/50 mmHg, without the need for vasoactive drug intervention until CPB was started. Intermittent nitroglycerine injection was administered to optimize BP during CPB. After aortic declamping, BP started to fluctuate dramatically. Sodium nitroprusside (with an intermittent infusion rate of 0.5 μg/(kg·min) and urapidil (10-15 mg per injection) were administered to treat hypertension. BP then decreased slowly to an extremely hypotensive level (40/30 mmHg). Noradrenaline (5-15 μg per injection) was used to reverse the hypotension. Later on, BP increased slowly and peaked at 230/130 mmHg. The fluctuation and cadence cycle of BP seemed to be regulated with inherent rhythm, as poor responses to the vasoactive drugs were observed. The intense spike and decrease in BP occurred repeatedly till the end of surgery (detailed hemodynamic changes are shown in Figure 2). Sodium nitroprusside, phentolamine, epinephrine, noradrenaline, and metaraminol were used for BP optimization during this period (important events and treatments are shown in Table 1). The surgery lasted for 320 min; the patient was on CPB for 117

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Tab. 1. Special events and corresponding treatments during the whole surgical process.

Time	Event label	Event	Treatment
In the OR			
8:25 am		Arterial line placement (radical)	
8:30 am		Induction	
8:35 am		ETT intubation	
8:35 am	1*	Hypertension	Urapidil, 10 mg i.v. injection
8:45 am		Central venous catheterization	
9:08 am		ABG analysis	
9:18 am		CPB started	
9:25 am		Aortic cross clamping	
9:25 am to 10:55 am	2	BP optimization	Intermittent nitroglycerine injection when needed
10:50 am		Aortic de-clamping	
11:00 am to 14:30 pm	3	Hypertension	Sodium nitroprusside (with an intermittent infusion rate of 0.5 μg/(kg•min)
12:00 pm, 12:15 pm, 12:35 pm, 12:55 pm, 13:15 pm, 13:40 pm, 14:15 pm	4	Hypertension	Urapidil, 10 mg i.v. injection
			Phentolamine, 1 mg/injection
11:40 am		Wean off CPB	
11:51 am		ABG analysis indicated hypokalemia	1 g KCL, IVGTT
11:58 am, 12:05 pm, 12:24 pm, 12:43 pm, 13:03 pm, 13:45 pm	5	Hypotension	Noradrenaline, 10-15 μg i.v. injection
			Epinephrine, 10-20 μg i.v. injection
			Metaraminol, 1 mg i.v. injection
13:00 pm	6	Glucocorticoid supplementation	Hydroprednisone, 10 mg i.v. injection
12:36 pm		ABG analysis (hypokalemia, Lac 5.0 mmol/L)	1 g KCL, IVGTT
14:30 pm		OR completed	Transferred to ICU
		Total blood loss	1500 ml
		Net fluid administration	2900 ml
		Post-CPB urine output	400 ml
In CICU			
14:35 pm		ICU admission	Dopamine 3-8 μg/kg•min infusion
			Volume assessment and fluid therapy
18:30 pm		Anesthesia emergence	
Post-operative day 1			
13:30 pm		Extubation	

*The corresponding hemodynamic parameters are shown in Figure 2.

min and the aorta was cross-clamped for 75 min. Net fluid administration was 2900 ml during the surgery, total blood loss was 1500 ml, and the post-CPB urine output was 400 ml.

After surgery, the patient was transferred to the intensive care unit (ICU) with inotropic support. The BP was 61/28 mmHg on ICU admission. The BP fluctuation lasted up to 19 hrs after ICU admission with the same pattern as that during the surgery. The patient completely recovered from anesthesia 4 hrs after ICU admission and was extubated 23 hrs after ICU admission. The patient recovered uneventfully and was discharged from the ICU and hospital on postoperative day 4 and day 8, respectively.

Written informed consent for the publication of this case report and the image was obtained from the patient. A copy of written consent is available for review by the editor of this journal.

DISCUSSION AND CONCLUSIONS

PHEOs are neural crest-derived tumors arising from the chromaffin cells in the adrenal medulla. The clinical characteristics of PHEO were thought to be related to the secretory profile of the tumor and the way these hormones work on their receptors. Isaacs et al summarized the clinical characteristics of different secretion types of PHEO in a review (Isaacs & Lee, 2017). Briefly, primary norepinephrine secreting tumors typically demonstrate sustained hypertension, while epinephrine-secreting tumors present paroxysmal hypertension. Exclusively dopamine-secreting PHEO patients might present with labile BP, varying from normotension to postural hypotension and hypertension.

Resection of PHEO used to be considered as a high-risk surgery with the historical mortality rate over 40%; however, recently the mortality rate has decreased markedly to 0–3% owing to the significant improvements in diagnosis, surgery, and anesthesia (Groeben *et al.* 2017).

For years, the preoperative preparation strategy was considered important to reduce the perioperative mortality and complications in patients scheduled for PHEO resection. Guidelines recommended that all patients with hormonally functional PHEOs should receive preoperative adrenergic receptor blockers (Lenders *et al.* 2014). Alpha-blockers are the first-line drugs, while calcium antagonists are the alternatives for patients with mild hypertension or severe side effects of α-blockade. A simultaneous preoperative high-sodium diet and fluid intake could reverse catecholamine-induced volume contraction and prevent severe hypotension after tumor dissection. This strategy was recommended for 7 to 14 days to allow adequate time for BP and HR normalization (Lenders *et al.* 2014).

However, several reports have discussed the necessity of α-blockade before PHEO resection with conflicting results, especially in patients with subclinical or normotensive PHEO. Aggarwal *et al.* reported four cases of asymptomatic and biochemically negative familial PHEO, similar to our case, treated with laparoscopic adrenalectomy (Aggarwal *et al.* 2016). Compared with the patients prepared with α- and β-blockers for 2 weeks before surgery, non-prepared patients were more unstable during the surgery. In contrast, as indicated in another report, 6 of 9 normotensive PHEO patients required intraoperative sodium nitroprusside, even though all patients had received preoperative doxazosin (selective α-1 adrenoceptor antagonist) for 2 weeks (Agarwal *et al.* 2005). Nevertheless, it was suggested that preoperative α-blockade treatment would make the intraoperative hemodynamic changes easily manageable. By contrast, Shao *et al.* compared the intraoperative hemodynamic characteristics in 59 normotensive PHEO patients with or without doxazosin (Shao *et al.* 2011). They found no obvious difference in the intraoperative BP and HR between the two groups. However, the intraoperative use of vasoactive drugs and colloid fluid was significantly greater in the doxazosin group. As a result, the necessity of preoperative α-blockade administration was questionable.

Keegan suggested that α-blockade might be unnecessary based on the following reasons (Keegan, 2017). First, α-blockade was associated with a number of undesirable effects, including orthostatic hypotension, reflex tachycardia with non-selective α-blockers, nasal congestion, and sedation. Moreover, a long time is needed to regulate the BP. Second, the effectiveness of α-blockers is questionable. Undesirable hypertension could still occur with apparently adequate pretreatment with α-blockade. Third, α-blockade could exacerbate hypotension after tumor removal.

A recent study demonstrated that PHEO surgery without α-blockade was safe and feasible (Groeben *et al.* 2017). The intraoperative hemodynamics and perioperative complications were compared in 110 patients with and 166 without preoperative α-blockade administration. Propensity matching techniques were used to select 75 pairs of patients with or without α-blockade. Total mortality was 0%, and only one patient developed ischemic stroke on postoperative day 3. The mean maximal systolic pressure and the incidences of sustained severe hypertension were similar in the two groups. The incidence of systolic pressure exceeding 250 mm Hg was also similar. Comparison of the matched pairs showed a significant difference in the maximal systolic pressure (170 mm Hg in α-blocked vs. 187 mm Hg in non-α-blocked). Although the clinical significance of this difference is uncertain, the incidence of hypotension and the number of patients who received continuous administration of norepinephrine during surgery was significantly greater in α-blockade group.

In the present case, preoperative preparation strategies were not adopted based on the following reasons. First, an isolated cardiac surgery without postural changes and abdominal manipulations would not affect the abdominal pressure and thus lead to abrupt catecholamine release. Second, the risk of hypotension after α-blockade could affect cardiac function. Severe dynamic fluctuation occurred in our case, with uncontrollable periodic characteristics. The hemodynamic instability resulted from inadequate preparation, administration of anesthetics, and probably the use of CPB. We were not sure whether preoperative α-blockade and intravascular volume restoration could make this process more manageable. However, the vulnerability of the patients with primary cardiac diseases to catecholamines and constriction of blood volume should be considered. It is noteworthy that most PHEOs store excessive catecholamine, which is released when provoked by stresses, such as surgery or anesthesia (Isaacs & Lee, 2017). Vasoactive drugs should always be ready for use in all patients with PHEO.

The neural-muscular blocker rocuronium was reported to possibly induce PHEO crisis as it might

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increase norepinephrine release (Sato *et al.* 1999) and inhibit acetylcholine-induced sympatholysis and neuronal norepinephrine reuptake (Son & Waud, 1980), or direct positive inotropic effects (Gursoy *et al.* 2011). In contrast, rocuronium was also indicated to be safe in PHEO resection (Naranjo *et al.* 2017). In our case, rocuronium was not the reason of BP fluctuation as there was no obvious temporal relation to the rocuronium injection.

Generally, hypotension is most likely to occur after PHEO removal. In the present case, BP extremes occurred without tumor manipulation. Abnormal responses to the vasoactive drugs was inconsistent with the pharmacodynamics, which implied altered secretory characteristics of PHEO. A similar severe BP fluctuation was observed in Zhou's case of cardiac paraganglioma (a catecholamine-producing tumor arising outside adrenal gland) resection (Zhou *et al.* 2015), periodic changes in systolic pressure (50 to 130 mmHg) were observed during the process of CPB weaning. However, in Zhou's case, paraganglioma had been removed before CPB weaning, while the tumor persisted in our case. The effect of change in organ perfusion from pulsate blood flow to continuous flow, during CPB on the synthesis and/or secretion of hormones of PHEO is still elusive.

In the present case, the decision for staged surgery was made for an isolated pulmonary valve replacement followed by an elective laparoscopic PHEO resection. The main reason for this decision was that the urologists considered the detrimental effects of a possible violent BP fluctuation during PHEO resection on the abnormal intracardiac structures. The lack of evidence made it difficult to determine if a simultaneous operation would benefit the patient. Theoretically, a combined surgery can solve the problem at one time and prevent the patient from two courses of anesthesia. However, the compromised hemostasis related to CPB assisted cardiac surgery is the major concern for homochromous operation. Rawlins reported a case of combined procedure to resect cardiac and abdominal paraganglioma (Rawlins *et al.* 2015). In their case, paragangliomas were the primary diseases as resection of all tumors was the only treatment option. However, in the present case, the primary cardiac disease was not related to the PHEO.

From this case, we conclude that all patients with suspected PHEO are at high risk of hypertension crisis, not just during the tumor removal, but in any clinical scenario. Preoperative treatment with an α-blocker and intravascular volume restoration could not prevent a PHEO crisis, but it might make the anesthesia process more manageable, especially for those who present with severe preoperative hypertension. Close hemodynamic monitoring and blood volume evaluation are essential for precise management of intraoperative BP, such as invasive BP/CVP monitoring and transesophageal echocardiography (TEE) technology. Agents that can cause an increase in catecholamine level or trigger hypertension should be avoided.

Currently, no consensus has been reached regarding how to manage the patients undergoing cardiac surgery with concurrent PHEO. Theoretically, one-stage surgery with combined cardiac surgery and PHEO resection may have been a better choice with the PHEO resected before initiation of CPB. However, the CPB should be prepared as a standby in case of any hemodynamic compromise after PHEO removal. Additional benefit of this procedure is the avoidance of uncertain effects of CPB on catecholamine release of the tumor. Careful patient evaluation and preparation with multidisciplinary cooperation are of paramount importance to these patients for a better prognosis.

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