

## Extracorporeal Cardiopulmonary Support for Cardiogenic Shock Caused by Pheochromocytoma: A Case Report and Literature Review

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PHEOCHROMOCYTOMA is classically associated with paroxysmal hypertension but may present with various nonspecific clinical manifestations.<sup>1</sup> We describe here a patient with a pheochromocytoma causing cardiogenic shock and multiorgan failure successfully treated with extracorporeal cardiopulmonary support.

### Case Report

A 47-yr-old woman was brought to her local hospital because of nausea, vomiting, diffuse myalgias, and deterioration in mental status. She had been well until the night before, when, while dancing at a party, she had reported epigastric–retrosternal discomfort, right lumbar pain, and vomiting with an impending sense of doom.

She had no history of hypertension, diabetes, or cardiovascular diseases. She was a nonsmoker and nondrinker, had no allergies, and was not taking any regular medications.

On admission, she was alert but anxious and confused. Her blood pressure was 100/50 mm Hg, her pulse was 120/min, her respiratory rate was 28/min, and her body temperature was 39.8°C. Physical examination was unremarkable. An electrocardiogram showed a sinus tachycardia with aspecific alteration of ventricular repolarization; the corrected QT interval was 405 ms.

Echocardiography demonstrated severe biventricular dysfunction (left ventricular ejection fraction, 30–35%) and grade 2 mitral and tricuspidal regurgitation.

Laboratory values showed leukocytosis, hyperazotemia, hypocalcemia, lactic acidosis, and increased levels of transaminases, amylases, total creatine kinase and MB fraction, troponin I, and C-reactive protein (table 1). Arterial blood gas analysis showed lactic acidosis (partial pressure of oxygen [P<sub>O<sub>2</sub>], 107 mm Hg; partial pressure of carbon dioxide [P<sub>CO<sub>2</sub>], 31.9 mm Hg; pH, 7.43; bicarbonate, 22.7 mm; base excess, –2.5; lactate, 5.7 mm).</sub></sub>

The patient was given intravenous fluids and was immediately transferred to the intensive care unit. Further blood chemistry confirmed a multiorgan-failure syndrome with shock, massive rhabdomyolysis (total creatine kinase, 4,519 U/l; myoglobin, 10,790 ng/ml), progressive

renal failure, hepatic cytolysis, disseminated intravascular coagulation (platelets, 59,000/μl; prothrombin time international normalized ratio, 1.95; fibrinogen, 246 mg/dl; D-dimer, 18,446 μg/l; antithrombin III, 64%), and respiratory failure. The patient was intubated and mechanically ventilated.

The most common toxic causes of rhabdomyolysis were excluded: The patient was not taking any medication associated with myopathy (lipid-lowering drugs, antiretroviral drugs, corticosteroids, cyclosporine), and toxicologic tests on blood and urine were negative for cocaine, opiates, amphetamines, ecstasy, and alcohol.

An arterial line and pulmonary artery catheter were inserted. Blood pressure was 90/50 mm Hg; pulmonary artery pressure was 35/25 mm Hg; central venous pressure and pulmonary artery occlusion pressure were 7 and 20 mm Hg, respectively; cardiac index was 2 l · min<sup>-1</sup> · m<sup>2</sup>; and mixed venous blood saturation (S<sub>vo<sub>2</sub></sub>) was 59.7%. Inotropic support with dobutamine and norepinephrine was started.

On a presumptive diagnosis of severe septic shock, a broad spectrum antimicrobial therapy with meropenem and metronidazole was started.

Hydration, forced diuresis (with loop diuretics and fenoldopam), and urine alkalinization were instituted.

Despite initial therapy, the patient rapidly developed acute renal failure necessitating renal replacement therapy. Because this treatment was not available in the unit of admission, she was transferred to our intensive care unit.

The differential diagnosis included an acute viral infection causing myocarditis and hepatitis or an atypical presentation of a vasculitic syndrome. Complete viral and autoimmune tests yielded negative results, as well as serial cultures of blood, urine, and respiratory secretions. A computed tomography scan revealed an adrenal mass with a radiologic aspect highly suggestive of a pheochromocytoma (fig. 1).

Continuous venovenous hemofiltration was instituted to support renal function.

Hemodynamic conditions also deteriorated, with marked increase of ventricular filling pressures (up to central venous pressure values of 27 mm Hg and pulmonary artery occlusion pressure values of 37 mm Hg) and a cardiac index of 2.6 l · min<sup>-1</sup> · m<sup>2</sup> despite maximal support with vasoactive drugs.

Passive venous congestion due to right ventricular failure led to a progressive worsening of liver function, with marked increases of transaminases and bilirubin (up to 18.9 mg/dl), further impairment of coagulation, and reduction of indocyanine green clearance (plasma disappearance rate, 2.8%).

We decided to institute venoarterial extracorporeal bypass. A 24-French cannula was positioned percutaneously into the right common femoral vein, and a 12-French arterial catheter was inserted into the right common femoral artery. Venous blood was drained from inferior vena cava and propelled by a centrifugal pump (Jostra Rotaflo<sup>®</sup>; Maquet Cardiopulmonary AG, Hechingen, Germany) through an artificial lung (Jostra Quadrox<sup>®</sup>; Maquet Cardiopulmonary AG) for gas exchange before returning it into the arterial circulation. Extracorporeal blood flow was initially set to 5 l/min and gas flow through the artificial lung adjusted to maintain normal pH and P<sub>CO<sub>2</sub></sub>.

Anticoagulation was maintained with continuous infusion of unfractionated heparin, titrated to an activated clotting time of 190–210 s.

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Address correspondence to Dr. Grasselli: Department of Perioperative Medicine and Intensive Care, Ospedale San Gerardo, via Pergolesi 33, 20052, Monza, Milano, Italy. jaku71@virgilio.it. Information on purchasing reprints may be found at www.anesthesiology.org or on the masthead page at the beginning of this issue. ANESTHESIOLOGY's articles are made freely accessible to all readers, for personal use only, 6 months from the cover date of the issue.

**Table 1. Laboratory Values at Admission**

Blood Test	Value at Admission	Normal Values
Leukocytes, 10 <sup>3</sup> /μl	27,350	4–11
Hemoglobin, g/dl	15.5	12–18
Platelets, 10 <sup>3</sup> /μl	406	140–440
Plasma sodium, mEq/l	145	135–145
Plasma potassium, mEq/l	4.55	3.4–4.8
Total calcium, mg/dl	7.1	8.5–10.3
Urea nitrogen, mg/dl	88	10–50
Plasma creatinine, mg/dl	2.6	0.5–1.5
Serum glucose, mg/dl	52	70–110
Total creatine kinase, U/l	4,201	20–180
CPK-MB, ng/ml	113	<2.88
Plasma troponin T, ng/ml	13.8	<0.01
Aspartate aminotransferase, U/l	1,584	8–41
Alanine aminotransferase, U/l	1,401	8–41
Serum amylase, U/l	574	0–100
Total bilirubin, mg/dl	0.6	0.1–1

CPK-MB = creatine kinase, MB fraction.

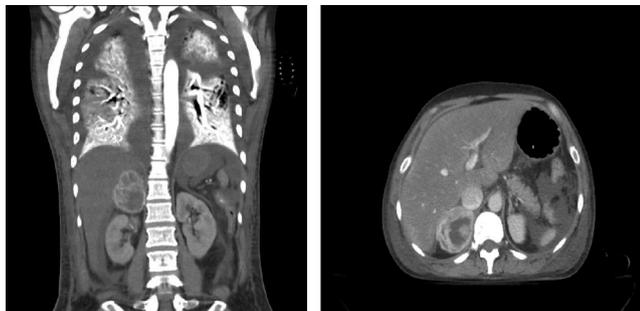
Within few hours, the patient's hemodynamics improved, with return of central venous pressure and pulmonary artery occlusion pressure to normal values and marked increase of SvO<sub>2</sub>. Unexpectedly, soon after withdrawal of catecholamine infusion, wide and rapid fluctuations in blood pressure (from 70/40 to 190/110 mm Hg) became evident (fig. 2). These variations were associated with very high plasma levels of catecholamines and of their urinary metabolites (table 2), strongly suggesting the presence of a functioning pheochromocytoma. In addition, the level of the neuroendocrine tumor marker chromogranin A was markedly increased (4,375 U/l, with normal values <70 U/l). Because of the critical conditions of the patient, a scintigraphy with metaiodobenzylguanidine could not be obtained.

Treatment with phentolamine by continuous intravenous infusion was started.

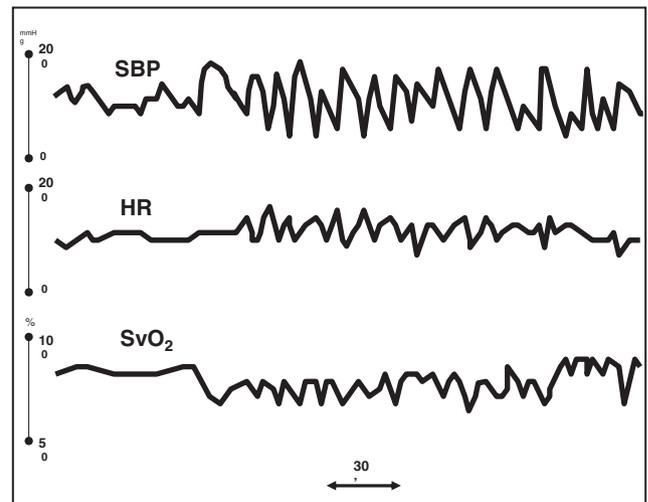
After sustained improvement of hemodynamics, the extracorporeal bypass was discontinued on day 4.

After consultation with the surgeon, we decided to perform an angiographic study with selective embolization of the tumor; the arteriographic study showed a highly vascularized adrenal mass and vasospasm of renal and hepatic arteries. In the first hours after embolization, the hypertensive-hypotensive crises transiently resolved but unfortunately reappeared approximately 24 h after the procedure.

For this reason, 2 days later, a right laparotomic adrenalectomy was performed, with radical resection of the tumor. General anesthesia was maintained with sevoflurane and remifentanyl; muscle relaxation was obtained with cisatracurium. During surgery, the patient's hemodynamic conditions remained relatively stable, except for an episode of severe hypotension (immediately after removal of the tumor) that necessitated discontinuation of phentolamine infusion and



**Fig. 1. Abdominal computed tomography scan showing a 7 × 5-cm right adrenal mass with colliquated central region and hypervascular peripheral rim.**



**Fig. 2. On-line continuous monitoring of vital parameters over a 2-h period, registered a few hours after bypass institution. Frequent and rapid oscillations of systolic blood pressure (SBP; top) are evident, with concomitant swings of heart rate (HR; middle) and mixed venous blood saturation (SvO<sub>2</sub>; bottom).**

short-term administration of norepinephrine. Pathologic examination of the mass confirmed the diagnosis of pheochromocytoma with benign histologic appearance.

After excision of the tumor, the patient's conditions rapidly improved. Treatment with vasoactive drugs was stopped, and no residual swings in blood pressure were observed. Renal function normalized, and hemofiltration was discontinued. A progressive, continuous improvement in liver function was observed (bilirubin and indocyanine green clearance at discharge were 3.7 mg/dl and 13.2%, respectively). The patient was rapidly weaned from the ventilator and discharged from our intensive care unit 29 days after admission with a residual diffuse muscular weakness and severe functional impairment; an electromyographic study showed moderate distal axonal neuropathy associated with signs of diffuse myopathy presumably related to the recent rhabdomyolysis. The muscular weakness completely resolved a few months after discharge from the hospital.

## Discussion

We report here an acute catastrophic presentation of an unrecognized case of pheochromocytoma in which we applied extracorporeal cardiopulmonary assistance for hemodynamic stabilization.

*Pheochromocytomas* are rare, catecholamine-producing tumors of chromaffin cells of the adrenal medulla (85–90% of cases) or of a paraganglion. The prevalence in hypertensive patients is 0.1–0.6%, but autopsy studies reveal a relatively high prevalence (approximately 0.05%) of unrecognized tumors. Up to 25% of pheochro-

**Table 2. Plasmatic and Urinary Levels of Catecholamines and of Their Metabolites**

Blood Test	Value	Normal Range
Plasma epinephrine, pg/ml	10,319	10–67
Plasma norepinephrine, pg/ml	26,212	95–446
Urine metanephrine, μg/24 h	3,431	52–341
Urine normetanephrine, μg/24 h	2,820	88–444

mocytomas may be familial. Hereditary pheochromocytomas occur in multiple endocrine neoplasia type 2, von Hippel-Lindau syndrome, neurofibromatosis type 1, and the familial paragangliomas. Sporadic forms of pheochromocytoma are usually diagnosed during the fifth decade of life, whereas hereditary forms are diagnosed earlier.<sup>1</sup>

Patients with pheochromocytoma typically have paroxysmal or sustained hypertension, associated with intermittent symptoms such as headache, sweating, and palpitations. Other, less frequent symptoms include anxiety, tremors, nausea, fatigue, weight loss, and dyspnea. Variability and lack of specificity of these clinical manifestations often hinder early diagnosis and treatment.

The diagnosis is based on the demonstration of catecholamine excess by dosing urinary and plasma catecholamines and metanephrines. The tumor is localized by imaging studies (computed tomography, magnetic resonance) of the adrenal glands and abdomen. Our patient had no history of hypertension or other related symptoms, and the presence of a pheochromocytoma had never been suspected. In the past five decades, few other cases of pheochromocytomas causing multiorgan failure, cardiogenic shock, and rhabdomyolysis have been reported.<sup>2-6</sup>

Rhabdomyolysis is attributed to diffuse skeletal muscle ischemia due to catecholamine-mediated vasoconstriction, but also to a focal myositis related to the direct effect of catecholamines on the skeletal muscle fibers.<sup>2</sup> Rhabdomyolysis is frequently complicated by myoglobinuric acute renal failure. In our patient, renal vasoconstriction (revealed by the angiographic scan) may also have contributed to the deterioration of renal function. Similarly, the etiology of liver failure was presumably multifactorial, with arterial vasoconstriction and passive venous congestion contributing to its development and progression. To monitor hepatic function, we used repeated assessments of indocyanine green clearance; this is a reliable and sensitive test of global liver function but cannot distinguish between failure due to splanchnic hypoperfusion or to primary hepatocyte dysfunction.<sup>7</sup>

The cause of cardiogenic shock in patients with pheochromocytoma is not completely understood, and several mechanisms have been proposed.<sup>5,8</sup> First, chronic exposure to increased epinephrine levels probably causes a down-regulation of  $\beta$  receptors on the myocardium. Second, a direct toxic effect of catecholamines leading to focal myocardial necrosis has been reported.<sup>9,10</sup> Third, hypocalcemia may play an important role: Its effect may be particularly relevant when there are rapid changes in serum calcium concentration or when hypocalcemia combines with the synergistic effect of  $\beta$  receptor down-regulation.<sup>11</sup> Olson *et al.* hypothesized that in epinephrine-secreting pheochromocytomas, hypocalcemia may be due to increased calcium utilization by the tumor or to an increase in bone calcium

deposition resulting from tumoral hypersecretion of adrenomedullin.<sup>5,12</sup>

The distinctive feature of our case is certainly the use of an extracorporeal cardiopulmonary assistance to support cardiac function. In 2000, Takagi *et al.*<sup>13</sup> reported the case of a 52-yr-old man with an occult pheochromocytoma who developed refractory cardiogenic shock after administration of dexamethasone. Initial treatment with an intraaortic balloon pump was ineffective, so a "percutaneous cardiopulmonary support system" was successfully instituted.

Likewise, our patient had refractory heart failure: Her cardiac output was in the normal range (approximately 5 l/min) but inadequate for her metabolic needs, as demonstrated by the low  $SvO_2$  and high blood lactate levels. This apparently "normal" cardiac output was obtained only at the cost of extremely high filling pressures, which, in turn, had deleterious effects on liver perfusion. Because optimal medical management did not restore heart function, we decided to apply an invasive cardiac support: We preferred a venoarterial bypass to intraaortic balloon pump because our priority was to reduce right heart preload rather than decreasing left heart afterload.

Several drugs have been reported as triggers of cardiogenic shock in patients with pheochromocytoma, such as phenothiazine, phentolamine, and propranolol.<sup>14-16</sup> In their article, Takagi *et al.*<sup>13</sup> suggested that dexamethasone might have induced the shock. Steroids may trigger acute heart failure, presumably by augmenting the sensitivity of myocardial cells to catecholamines.<sup>17,18</sup> Interestingly, our patient received therapy with methylprednisolone during the first 2 days of intensive care unit stay, but it is difficult to say whether this may have contributed to the deterioration of cardiac function.

An intriguing observation is that in our patient the marked blood pressure oscillations typical of pheochromocytoma only occurred after the institution of the extracorporeal assistance. Unstable blood pressure in pheochromocytoma is due to episodic discharge of catecholamines, and it is exaggerated by a reduced blood volume.<sup>19</sup> We can hypothesize that, before the bypass, the maximal adrenergic activation (due to the refractory heart failure and to therapeutic infusion) overrode the vasopressor effects of the tumor. The hemodynamic improvement induced by the extracorporeal support led to a reduction of the adrenergic tone and to withdrawal of catecholamine infusion with normalization of sympathetic reflexes. This, combined with the effect of blood volume reduction allowed by the bypass and continuous venovenous hemofiltration, might have unmasked the vasoconstricting activity of tumoral catecholamines pulses.

It is universally accepted that definitive treatment of pheochromocytoma consists of its surgical excision. Because manipulation of the mass during surgery can lead

to dramatic cardiovascular instability, angiographic tumor embolization has been proposed in metastatic or relapsing disease or in severely unstable patients.<sup>20,21</sup> In our patient, this approach did not obtain long-term control of pressure swings but was useful in avoiding major hemodynamic instability during the surgical removal of the tumor.

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