Variable hemodynamic fluctuations during resection of multicentric extraadrenal pheochromocytomas

[Fluctuations hémodynamiques variables pendant la résection de phéochromocytomes extrasurrénaliens multicentriques]

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Purpose: To report the perioperative management and the serious hemodynamic fluctuations during manipulation of an organ of Zuckerkandl tumour in a patient undergoing resection of multicentric extraadrenal pheochromocytomas.

Clinical findings: A 28-yr-old man who had undergone at age 12 a laparotomy for excision of an extraadrenal pheochromocytoma complained of paroxysmal headache, occasional sweating and palpitations. The arterial blood pressure (BP) was 200/100 mmHg. A 24-hr-urine collection showed catecholamines 5076 $\mu g \cdot 24\ hr^{-1}$ (normal $< 25\ \mu g \cdot 24\ hr^{-1}$). Computed tomography of the abdomen revealed two retroperitoneal masses, one adjacent to the lower pole of the right kidney and a second larger mass located at the aortic bifurcation in the region of the organ of Zuckerkandl. The patient was scheduled for excision of multiple extraadrenal pheochromocytomas. He was prepared preoperatively for two weeks with prazosin 1 mg *po* q six hours and propranolol 10 mg *tid*. Manipulation of the infrarenal tumour was uneventful but manipulation of the Zuckerkandl tumour resulted in severe hypertensive episodes with BP ranging from 200/100 to 320/120 mmHg. Surgery was interrupted temporarily; the hypertensive crisis was controlled by the infusion of sodium nitroprusside and by *iv* phentolamine and esmolol.

Conclusion: In a patient undergoing resection of recurrent multicentric extraadrenal pheochromoctyomas, severe hypertensive episodes occurred during manipulation of one tumour but not during manipulation of the other. This may be attributed to inadequate preparation of the patient, difficult surgical dissection of the large Zuckerkandl pheochromocytoma, and/or secondary to an excessive and different pattern of release of catecholamines during manipulation of the Zuckerkandl tumour.

Objectif : *Présenter le traitement périopératoire et les fluctuations hémodynamiques inquiétantes survenues pendant la manipulation d'une tumeur de l'organe de Zuckerkandl chez un patient qui devait subir la résection de phéochromocytomes extrasurrénaliens multicentriques.*

Constatations cliniques : *Un homme de 28 ans qui, à 12 ans, avait subi l'excision laparoscopique d'un phéochromocytome extrasurrénalien, se plaignait de céphalées paroxystiques, de sueurs et de palpitations occasionnelles. La tension artérielle (TA) était de 200/100 mmHg. Un prélèvement d'urine sur 24 h a montré une concentration de catécholamines de 5076 $\mu g \cdot 24\ h^{-1}$ (la normale étant $< 25\ \mu g \cdot 24\ h^{-1}$). La tomodensitométrie de l'abdomen a montré deux masses rétropéritonéales, l'une adjacente au pôle inférieur du rein droit et une seconde, plus grosse, localisée à la bifurcation aortique dans la région de l'organe de Zuckerkandl. L'excision des multiples phéochromocytomes extrasurrénaliens a été planifiée. Le patient a été préparé en recevant, deux semaines avant l'opération 1 mg de prazosin po q à prendre aux six heures et 10 mg de propranolol tid. La manipulation de la tumeur infrarénale s'est faite sans incident, mais celle de la tumeur de Zuckerkandl a entraîné des épisodes d'hypertension sévère, la TA allant de 200/100 à 320/120 mmHg. L'intervention chirurgicale a été interrompue temporairement pour permettre de traiter la crise d'hypertension par une perfusion de nitroprussiate de sodium et par de la phentolamine et de l'esmolol iv.*

Conclusion : *Des épisodes d'hypertension sévères sont survenus chez un patient subissant la résection de phéochromocytomes multicentriques récurrents pendant la manipulation d'une des deux tumeurs. Cette situation peut relever d'une préparation inadéquate du patient, de la difficulté de la dissection chirurgicale du plus gros phéochromocytome de Zuckerkandl et/ou elle peut être secondaire à une sécrétion excessive et différente de catécholamines pendant la manipulation de la tumeur de Zuckerkandl.*

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PHEOCHROMOCYTOMA is a rare disorder occurring in 0.1% of the hypertensive population.[1] It consists of a catecholamine-secreting tumour, arising from chromaffin cells, either in the adrenal medulla in 75–85% of patients or in an extraadrenal location.[2] Extraadrenal sites include any organ that contains paraganglionic tissue, along the paravertebral sympathetic chain, extending from the base of the skull to the pelvis.[3] Most of the extraadrenal pheochromocytomas or paragangliomas are located below the diaphragm.[4]

The present report describes the perioperative anesthetic management and the serious hemodynamic fluctuations observed in a patient undergoing resection of recurrent retroperitoneal multicentric extraadrenal pheochromocytomas. The report also shows that variable hemodynamic responses may occur during surgical excision of multicentric pheochromocytomas, suggesting that these tumours may be quite different functionally even if they grow concomitantly in the same patient.

Case report

The patient, a 28-yr-old man, underwent at 12 yr of age a laparotomy for the excision of an extraadrenal infrarenal pheochromocytoma adjacent to the lower pole of the left kidney. He had been free of symptoms until three months before presentation, when he presented with paroxysmal headache, occasional sweating, palpitations, and abdominal discomfort. He was found to have a blood pressure (BP) of 200/100 mmHg. A 24-hr-urine collection showed catecholamines 5076 $\mu g \cdot 24\ hr^{-1}$ (normal < 25 $\mu g \cdot 24\ hr^{-1}$), vanillylmandylic acid of 13 $mg \cdot 24\ hr^{-1}$ (normal < 8 $mg \cdot 24\ hr^{-1}$) and metanephrines 6009 $\mu g \cdot 24\ hr^{-1}$ (normal < 900 $\mu g \cdot 24\ hr^{-1}$). Computed tomography of the abdomen revealed two retroperitoneal masses, one adjacent to the lower pole of the right kidney and a second larger mass located at the aortic bifurcation in the region of the organ of Zuckerkandl.

The patient was prepared preoperatively for two weeks with prazosin 1 mg *po* q six hours (because of the unavailability of phenoxybenzamine in our hospital), and propranolol 10 mg *tid*. The BP stabilized at 120/90 mmHg supine and standing, with a regular heart rate (HR) of 68 $beats \cdot min^{-1}$. Electrocardiogram (ECG) showed normal sinus rhythm, with non-specific T wave changes in V1–V4 leads. Hematocrit (Hct) was 43% and blood sugar level was normal.

The patient was premedicated with diazepam 5 mg *po*. In the operating room, he was monitored continuously with a 5-lead ECG, pulse oximetry, capnography, intraarterial BP measurement, and pulmonary artery (PA) catheter. Prior to induction of anesthesia, BP was 145/90 mmHg and HR was 75 $beats \cdot min^{-1}$. General anesthesia was induced with *iv* lidocaine 1 $mg \cdot kg^{-1}$, propofol 3 $mg \cdot kg^{-1}$, fentanyl 2 $\mu g \cdot kg^{-1}$ and rocuronium 1 $mg \cdot kg^{-1}$. The patient was ventilated with 4% sevoflurane in 100% O_2 prior to proceeding with laryngoscopy and tracheal intubation. Anesthesia was then maintained with 4–8% sevoflurane in 100% O_2, and by incremental doses of fentanyl and rocuronium, as needed. Blood volume was expanded throughout the procedure by lactated Ringer's solution and by Haemaccel® (Hoechst Marion Roussel, Frankfurt am Main, Germany) to maintain adequate central venous pressure and urine output.

Through a midline abdominal incision, the right kidney was exposed and a mass was visualized, medial to the lower pole of the kidney, inferior to the renal hilum and lateral to the vena cava. Dissection of the tumour from its surrounding structures was performed easily. Minimal hemodynamic changes occurred and responded to increasing concentrations of sevoflurane.

The tumour of Zuckerkandl was overlying and adherent to the bifurcation of the aorta. Surgical dissection of the tumour was difficult and associated with excessive blood loss. Manipulation of the tumour resulted in severe hypertensive episodes with BP ranging from 200/100 to 320/120 mmHg. Systemic hypertension was associated with elevation of PA pressure. Surgery was interrupted temporarily; sodium nitroprusside was infused in increasing doses up to 2 $\mu g \cdot kg^{-1} \cdot min^{-1}$, and two doses of *iv* phentolamine 5 mg were administered. Hypertension also necessitated the bolus administration of esmolol 0.5 $mg \cdot kg^{-1}$ *iv* to be followed by an *iv* infusion of 30 mg esmolol over 20 min.

Ligation of the efferent vein of the tumour immediately resulted in a fall in BP which reached 70/50 mmHg. This hypotension was treated by decreasing the concentration of sevoflurane, as well as by rapid *iv* infusion of lactated Ringer's solution and 2 U of blood. In addition, a norepinephrine infusion (0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was required for 20 min. Thereafter, BP returned to normal without further treatment. The patient was kept sedated, intubated and transferred to the intensive care unit with a BP of 130/75 mmHg and a HR of 85 $beats \cdot min^{-1}$. His postoperative course was smooth and uneventful.

The hemodynamic variables immediately after induction, during manipulation and after resection of the tumours are shown in the Table.

Pathology examination of the resected tumours confirmed the diagnosis of pheochromocytoma; the first mass was slightly smaller (5 × 4 × 4 cm *vs* 6 × 4 ×

TABLE Hemodynamic parameters

	HR *beats·min^{-1}*	*BP* *mmHg*	*PAP* *mmHg*	*CO* *L·min^{-1}*	*SVR* *Dynes·sec^{-1}·cm^{-5}*
After induction	65	130/80	19/6	6	1266
Manipulation of 1st tumour	78	155/90	19/9	4.9	1795
After resection of 1st tumour	87	120/80	23/14	6.93	981
Manipulation of 2nd tumour	92	320/100	52/29	9.7	1302
Sevoflurane + SNP + phentolamine	105	132/54	32/13	9.8	587
After resection of 2nd tumour	78	71/37	24/14	7.5	426

Changes in HR, BP, PAP, CO and SVR following induction of anesthesia, during manipulation and after resection of the pheochromocytoma tumours. HR = heart rate; BP = blood pressure; PAP = pulmonary artery pressure; CO = cardiac output; SVR = systemic vascular resistance; SNP = sodium nitroprusside.

3.5 cm) and weighed less (43 g *vs* 46 g) than the second tumour. The two tumours showed no evidence of necrosis or unusual mitotic activity.

Discussion

Approximately 18% of pheochromocytomas are extraadrenal.[2] Failure of involution of chromaffin tissue may be the best explanation for the development of extraadrenal pheochromocytoma.[2] The most common location is the superior aortic region (between the diaphragm and the inferior renal poles). Approximately 46% of the extraadrenal tumours have been located in this region, particularly in and around the renal hilus. Tumours in the inferior paraaortic area (between the lower renal poles and the aortic bifurcation) have constituted 29% of the cases. Most of these tumours have arisen from the organ of Zuckerkandl, which consists of paraganglia found in the retroperitoneal region along the aorta around the inferior mesenteric artery.[4] The rate of malignancy of extraadrenal pheochromocytomas has been shown to be twice that of adrenal pheochromocytoma; however this difference did not reach statistical significance.[5] The most reliable indication of malignancy remains the demonstration of distant metastasis to areas in which paraganglionic tissue is not normally found.[2] Extraadrenal pheochromocytoma are often (15–24%) multicentric.[6,7] Multicentric extraadrenal pheochromocytomas are more frequent in children;[8] it is interesting to note that our patient was first operated for an extraadrenal pheochromocytoma at the age of 12.

It is rare for functional and nonfunctional pheochromocytoma/paragangliomas to coexist.[2] When multicentric, it is more common to find tumours at multiple extraadrenal sites rather than adrenal and extraadrenal sites.[2] Our patient had recurrent multicentric extraadrenal pheochromocytomas; one was found at the lower pole of the right kidney and the second overlying the bifurcation of the aorta, in the region of the organ of Zuckerkandl.

Most extraadrenal pheochromocytomas secrete norepinephrine exclusively.[1] If both norepinephrine and epinephrine are secreted, then the pheochromocytoma is very likely to be adrenal or Zuckerkandl in origin.[9] The main findings of the present report relate to the different hemodynamic responses noted during surgical manipulations of the two tumours. Manipulation of the upper tumour resulted in a moderate increase of BP associated with an increase of systemic vascular resistance (SVR) and a decrease of cardiac output (CO), suggesting a norepinephrine-secreting tumour.[10] In contrast, manipulation of the Zuckerkandl tumour caused a dramatic increase of BP associated with a significant increase of CO and a moderate increase in SVR, suggesting the release of both epinephrine and norepinephrine.[10]

In a retrospective study, Kinney *et al.* found that preoperative factors univariately associated with adverse perioperative events included larger tumour size, prolonged duration of anesthesia and increased levels of preoperative urinary catecholamines and catecholamine metabolites.[11] In our patient, BP fluctua-

tions were most severe during manipulation of the tumour of the organ of Zuckerkandl, which may be attributed to excessive catecholamine release secondary to its larger size and its more difficult resection and extensive manipulation.

A reduction in perioperative mortality associated with excision of pheochromocytoma from 45% down to between 0 and 3% followed the introduction of α-adrenergic antagonists for preoperative preparation of patients.[12] Preparation will not only control hypertension, but can also expand the intravascular fluid compartment. Perioperative BP fluctuation, myocardial infarction, congestive heart failure, cardiac dysrythmia, and cerebral hemorrhage all appear to be reduced in frequency when the patient has been prepared with α-adrenergic blockers.[12]

Despite preoperative pharmacologic preparation of our patient with α-adrenergic blockers, serious intraoperative hemodynamic liability occurred. Roizen *et al.* have suggested the following criteria as indicative of the adequacy of preoperative preparation of pheochromocytoma patients: 1) no BP reading > 165/90 mmHg for 48 hr, 2) presence of orthostatic hypotension, 3) absence of segment-T wave changes, 4) absence of other signs of catecholamine excess.[13] In our patient, hypertension was well controlled and the ECG was free of PVC. However, no orthostatic variation in BP was noted. In addition, the ECG showed non-specific T wave changes, and the Hct was 43%. This might suggest that the preoperative preparation of our patient was suboptimal.

Whereas norepinephrine released from sympathetic nerve fibres activates the junctional α1-receptor, it is thought that postsynaptic α2-receptors are extrajunctional, and are preferentially stimulated by circulating catecholamine.[14] Despite its selective α1-receptor antagonist effect, prazosin has little or no α2-receptor blocking effect at concentrations achieved clinically.[14] Nicholson and colleagues found that pheochromocytoma patients pretreated with prazosin exhibited marked hypertensive responses to tumour handling requiring phentolamine.[15] In another study by Russel and colleagues, phenoxybenzamine pretreatment provided superior intraoperative stability compared to prazosin.[16]

In contrast to phenoxybenzamine, prazosin has a short elimination half-life (two to three hours); therefore prazosin blood concentration may decrease to ineffective levels at the time of surgery.[17] In our patient, it seems likely that large catecholamine surges of both norepinephrine and epinephrine occurred during manipulation of the tumour arising from the organ of Zuckerkandl. These were enough to overcome the competitive α-1 blockade induced by prazosin on the blood vessels with a consequent increase of SVR, and to produce a significant increase of CO by their ß-adrenergic action on the heart.

In conclusion, the present report shows, in a patient undergoing resection of recurrent multicentric extraadrenal pheochromocytomas, the occurrence of variable hemodynamic responses during surgery. Manipulations of one tumour was associated with minor hemodynamic fluctuations suggesting the release of norepinephrine, while manipulation of the tumour arising from the organ of Zuckerkandl was associated with major hemodynamic fluctuations suggesting the release of both epinephrine and norepinephrine. The hemodynamic differences during resection of the two tumours suggest that multicentric pheochromocytomas may be functionally quite different even if they grow concomitantly in the same patient.

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