We are IntechOpen,
the world's leading publisher of
Open Access books
Built by scientists, for scientists

6,900
Open access books available

185,000
International authors and editors

200M
Downloads

154
Countries delivered to

Our authors are among the

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Undiagnosed Pheochromocytoma Complicated with Perioperative Hemodynamic Crisis and Multiple Organ Failure

Anis Baraka
American University of Beirut
Beirut
Lebanon

1. Introduction

Pheochromocytoma is a rare catecholamine secreting tumor of the chromaffin of the body derived from the neural crest tissue and accounts for 0.1% to 1% of all cases of chronic hypertension (Manger et al, 1985). The common presenting signs and symptoms are paroxysmal hypertension, headache, excessive sweating, and palpitation. The hypertension is episodic in nature in up to 50% of cases. Also, 10% of patients remain normotensive (Bravo & Gifford, 1984). Thus, pheochromocytoma may go unrecognized and up to 50% of the cases are diagnosed only at postmortem examination. A proportion of patients are diagnosed at the time of incidental surgery, when induction of anesthesia and surgical manipulations may precipitate catastrophic hemodynamic crisis and even multiple organ failure (Siddik-Sayyid et al. 2007; Dabbous et al.2007; O'Riordan JA, 1997). In this situation, mortality is close to 80% (O'Riordan, 1997). The dramatic improvement in surgical outcome of diagnosed pheochromocytoma can be attributed to adequate preoperative imaging, appropriate medical preparation, and improved surgical and anesthetic techniques (Schiff & Welsh, 2003).

2. Pheochromocytoma the "10% tumor"

Pheochromocytoma has been referred to as the "10% tumor" because 10% are extraadrenal, 10% are malignant, 10% bilateral, 10% in children, and finally 10% are hereditary. The extra-adrenal tumors are more likely to be multiple and malignant.

3. Plasma catecholamines

Plasma adrenaline concentrations >400 pg/ml, and plasma noradrenaline concentrations> 1000 pg/ml are generally diagnostic of pheochromocytoma. However, there is no significant correlation between the plasma catecholamine levels and the degree of hypertension. This may be attributed to different factors such as the decreased blood volume in the pheochromocytoma patient, the episodic secretion of catecholamines, the associated down regulation of the adrenergic receptors, as well as the paroxysmal attacks of hypertension. The presence of normotension despite an increased plasma concentration of catecholamines

presumably reflects a decrease in the number of alpha-adrenergic receptors (down regulation) in response to increased circulating concentration of the neurotransmitter. Clonidine (0.3mg orally, suppresses the plasma concentrations of catecholamines in a hypertensive patient but not in the pheochromocytoma patient. Clonidine acts as $\alpha2$-adrenergic agonist and hence can suppress an increase in the plasma catecholamine resulting from neurogenic release, but not secondary to diffusion of excess catecholamines from a pheochromocytoma into the circulation (Bravo & Gifford, 1984)

4. Preoperative preparation

Patients with pheochromocytoma are chronically vasoconstricted as a result of the high levels of circulating catecholamines, and have a secondary decrease in their blood volume. Preparation for surgery in patients with diagnosed pheochromocytoma should begin at least 2 weeks preoperatively to allow full alpha-adrenergic blockade along with the gradual restoration of blood volume. A standard protocol for adrenergic blockade is to administer phenoxyhenzamine, starting at a dose of 40mg per day, and gradually increasing to 80-120 mg per day. This single precaution may decrease perioperative mortality down from 43% to 3%. The most common side effect of phenoxybenzamine is postural hypotension. Beta-blockade can be given after starting alpha-blockade, if tachycardia or other arrhythmias develop. Beta-blockers must never be started prior to adequate alpha-blockade, since in the absence of beta2 mediated vasodilation, profound unopposed alpha-mediated vasoconstriction may lead to hypertensive crisis or pulmonary edema (MyKlejard, 2004; Kinney et al. 2002; O'Riordan, 2007; Geogheghan et al. 1998).

Whereas norepinephrine released from sympathetic nerve fibers activates the junctional α_1-adrenergic receptors, it is thought that the α_2-receptors are extrajunctional, and are preferentially stimulated by circulating catecholamines (Hamdan & Limbird, 1996). Also the α_2-receptors are located prejunctional and function as a negative feedback. Despite its selective α_1-receptor antagonist effect, prazosin has little or no α_2-receptor blocking effect at concentrations achieved clinically (Hamdan & Limbird, 1996). Nicholson and colleagues found that pheochromocytoma patients pretreated with prazosin exhibited marked hypertensive responses to tumor handling requiring phentolamine (Nicholson et al. 1983). In another study by Russel and colleagues, phenoxybenzamine, which is a nonselective α_1 and α_2-receptor blocker, provided superior intraoperative stability compared to prazosin (Russell et al. 1998). Also, in contrast to phenoxybenzamine, prazosin has a short elimination half-life (2-3 hours); therefore prazosin blood concentrations may decrease to ineffective levels at the time of surgery (Prys-Roberts, 2000).

Prys-Roberts suggested that doxazosin, a long-acting and selective α_1-adrenergic blocking agent is preferable to phenoxybenzamine when used in the dose range 2-8 mg/day. He suggests that because doxazosin does not block α_2-adrenergic activity, many patients do not require β-adrenergic blocking agents. The selective $\alpha1$-antagonsist prazosin and doxazosin have been used in the management of pheochromocytoma. They do not block the presynaptic α_2-adrenergic receptors; thus by allowing norepinephrine reuptake by nerve endings, the tachycardia following the administration of the nonselective α_1 and α_2 adrenergic blocker phenoxybenzamine does not occur. However, it has the disadvantage of being long-acting and the patient may develop postoperative hypotension refractory to norepinephrine (Nicholson et al.,1983; Hull, 1986). To help assess the adequacy of

preoperative management of pheochromocytoma, the following Roizen criteria should be met in order to reduce perioperative morbidity and mortality (Table 1) (Roizen et al., 1982).

Roizen et al proposed treatment for at least 10 days and until:
1. There are no marked symptoms
2. Arterial blood pressure does not exceed 160/90 mmHg on more than four measurements in 24hr
3. Systolic blood pressure has decreased by at least 15% when moving from lying to standing position, but was more than 80/45 mmHg
4. The ECG was free of changes in ST segment and T wave for 2 weeks

---

Table 1. Preoperative Preparation

There is no accepted rule regarding the duration of adequate preoperative preparation; however, the study of Russels et al suggested that 5-7 days will be generally sufficient. MFH James practice is to increase α-blockade on a daily basis until adequate hemodynamic control is achieved and then to proceed to surgery, rather than use any predetermined time period. Failure to achieve adequate control by medical means, particularly in patients with large tumors, may be an indication for relatively urgent surgery as the only mechanism for controlling the excessive catecholamine production. Also, catecholamine-induced cardiomyopathy, as well as ST and T-wave abnormalities appear to have little advantage in attempting to control them with medical management prior to tumor excision. These changes generally regress once the catecholamine source is removed (James, 2010).

Alpha-adrenergic blockade attenuates or prevents catecholamine-induced vasoconstriction, leading to decreased blood pressure as well as to expansion of the blood volume. Satisfactory alpha blockade is implied if the hematocrit decreases by about 5%, for example from 45% to 40%. Serial monitoring of the hematocrit is a useful method of evaluating the adequacy of intravascular volume expansion. Normalization of the intravascular blood volume and blood pressure by the alpha adrenergic blockade before surgery can decrease the risk of intraoperative hypertension during manipulation of the tumor, and may even decrease the degree of hypotension following excision of the tumor. Continuation of alpha adrenergic blockade therapy until the day of surgery is recommended in order to minimize the hypertensive response during surgery. Also, because of the expanded blood volume, concern that sustained alpha blockade could contribute to refractory hypotension when vascular isolation of the tumor is accomplished has not been substantiated (Stoelting & Dierdorf, 1993).

5. Undiagnosed pheochromocytoma

The classic symptoms of pheochromocytoma consist of the triad of excessive sweating, headache and palpitation, in addition to paroxysmal hypertension. However, all three symptoms occur together in less than 50% of patients. Also, hypertension may be sustained in 50% of patients who will be managed as essential hypertension. Also, patients who present with anxiety, palpitation, sweating and tremors may be misdiagnosed as stressed or menopausal. Abdominal pain, presumably due to bowel ischemia may lead to the erroneous diagnosis of acute abdomen. Hyperglycemia may occur and the patient is diagnosed as

diabetic (James, 2010). In all these situations, the diagnosis of pheochromocytoma may be missed, and hence the patient can develop severe pheochromocytoma crisis during incidental surgery or during pregnancy.

Anesthesia and surgery in unsuspected cases have a high reported mortality. In a postmortem series, 27% of patients with undiagnosed pheochromocytoma died during or shortly after surgery (Sutton et al, 1981). Headache, palpitation, sweating and hypertension are considered to be 90% predictive of pheochromocytoma (Bravo & Gifford, 1984). In practice, such symptoms are often dismissed as psychologic or stress related, and the diagnosis may be missed until the patient presents with hypertension. Also, excess catecholamines produce hyperglycemia, which may be mistaken for insulin-deficient diabetes mellitus. Even worse, patients may suffer a whole series of major cardiovascular "events" only to suffer an unheralded intraoperative pheochromocytoma crisis (Hull & Batchelor, 2003).

6. Pheochromocytoma crisis

Although less than 0.1% patients with hypertension actually have a pheochromocytoma, nearly 50% of deaths in patients with unsuspected pheochromocytoma occur during anesthesia and surgery or during parturition (Kirkendahl et al., 1965).

The factors triggering intraoperative pheochromocytoma crisis can be attributed to excessive release of catecholamines from the undiagnosed tumor secondary to anxiety of the awake patient, or secondary to light general anesthesia during surgery (Table 2).

- Anxiety of the awake patient
- Light anesthesia during tracheal intubation and surgery
- Mechanical Factors
  - Straining
  - Scrubbing
  - Abdominal manipulations of the tumor
  - CO_2 insufflation during laparoscopy
  - Excessive uterine contractions or fetal movements
- Excessive uterine contractions or fetal movements during pregnancy

---

Table 2. Factors precipitating pheochromocytoma crisis.

Excessive release of catecholamines may be also drug-induced secondary to histamine release, dopamine receptor blockade, or sympathomimetic action (Table 3).

In addition, excessive release of catecholamines from the pheochromocytoma may be attributed to mechanical factors such as squeeze of the tumor during straining, positioning of the patient, by scrubbing, by intraperitoneal carbon dioxide insufflations during laparoscopy, or by direct manipulation of the tumor. It should be also remembered that radiocontrast media has been also associated with pheochromocytoma crisis.

In the pregnant patient, having pheochromocytoma, excessive uterine contractions or fetal movements, as well as normal vaginal delivery or Cesarean section may precipitate the crisis; the symptoms and signs may mimic that of severe preeclampsia. However, preeclampsia is associated with hypertension and proteinuria usually after the 20th week of

gestation, while pheochromocytoma is rarely associated with proteinuria and may cause hypertension throughout pregnancy (Mudsmith et al., 2006).

Anticholinergic drugs
       e.g.   atropine
Sympathomimetic drugs
       e.g.   pancuronium
Histamine releasing drugs
       e.g.   morphine
       atracurium, mivacurium
Dopamine receptor blocker
       e.g.   droperidol (inhibits reuptake of catecholamines)
Catecholamine-sensitizing anesthetics
       e.g.   halothane
                 desflurane

Table 3. Drugs precipitating pheochromocytoma crisis.

The perioperative pheochromocytoma crisis may mimic other conditions such as thyroid storm (Hirvonen et al.,2004) or malignant hyperthermia (Crowley et al.,1988; Allen & Rosenberg, 1990). However, the absence of any increase of end-tidal CO_2, the lack of rigidity, and the near limited increase in temperature may exclude the diagnosis of malignant hyperthermia. The presentation of thyroid storm usually includes fever and tachycardia, with infection commonly being a precipitating factor. Profuse sweating with a high fever out of proportion to the infection may be a due to the presence of a thyroid storm. Systolic hypertension and widened pulse pressure is also a common occurrence. Dramatic changes in heart rate and/or blood pressure should alert the anesthesiologist to consider pheochromocytoma crisis as a possible cause. However, circulatory shock and/or pulmonary oedema may be the first manifestation of undiagnosed pheochromocytoma (3).

The anesthesiologist faced with a patient developing severe hypertension which may alternate with hypotension, with developing tachycardia, sweating, heart failure, pulmonary edema and acidosis should consider the diagnosis of pheochromocytoma. Another sign which may help to confirm the diagnosis is pupillary dilation due to high levels of catecholamines (Larson & Herman, 1992). Emergency treatment will usually involve shot-acting vasodilator such as the α-adrenergic blocker phentolamine. In the case of epinephrine-secreting tumor, the severe tachycardia can be controlled by the short-acting and selective B1-adrenergic blocker esmolol.

7. Incidental surgery

Occasionally, patients undergoing incidental surgery are found to have undiagnosed pheochromocytoma. This may occur when a tumor is found by the surgeon. Also, dramatic changes in heart rate and/or blood pressure should alert the anesthesiologist to consider pheochromocytoma as a cause. This will require judicious use of short-acting vasodilator drugs such as phentolamine or sodium nitroprusside to control the hypertension. Whenever hypertension is associated with extreme tachycardia, the use of short-acting and selective

β1-adrenergic blocker such as esmolol may be administered. Except when there is extreme tachycardia, the use of β -blockade in this acute situation without previous α-blockade is best avoided. Where surgery can be reasonably be aborted, that is likely to be the wise option (Hull & Batchelor, 2003).

7.1 Case report (Siddik-Sayyid et al.,2007)

A 43-year-old female patient was admitted to the hospital for right modified radical mastectomy. She had a past history of headache and palpitations with no hypertension: her preoperative blood pressure (BP) was 130/80 mmHg and her heart rate (HR) was 80 beats/min. Preoperative electrocardiogram and chest x-ray were normal. General anesthesia was induced with propofol, 2 mg/kg, fentanyl, 2 μg/kg, and cisatracurium, 0.15 mg/kg, and was maintained with isoflurane in a mixture of nitrous oxide and oxygen (2:1) by using intermittent positive-pressure ventilation. Thirty minutes after the start of surgery, the patient developed severe hypertension (BP 230/135 mmHg) and marked tachycardia (HR 160-180 beats/min). The anesthetic level was deepened by increasing the concentration of isoflurane and by additional doses of fentanyl (3 μg/kg) and midazolam (2 mg). Also, intravenous boluses of nitroglycerin (100 μg) and propranolol (1 mg) were given. The BP decreased to 100/50 mmHg and the HR to 130 beats/min. Right mastectomy and lymph node dissection were continued. Twenty minutes later, oxygen saturation as monitored by pulse oximetry dropped to 92%. Also, chest auscultation revealed diffuse crepitations over both lung fields. Arterial blood gas analysis showed hypoxemia associated with uncompensated metabolic acidosis. Esophageal temperature increased to 38.5ºC. Surgery lasted for 2 hours, and the patient was transferred intubated and ventilated to the intensive care unit for further management.

A chest x-ray showed widespread alveolar infiltration suggestive of pulmonary edema. Echocardiography revealed severe global hypokinesia of the left ventricle with an estimated ejection fraction of 20% to 25%. Cardiac catheterization showed normal coronaries. The patient's clinical condition deteriorated rapidly; she developed MOF including acute renal failure, hepatitis, pancreatitis, and disseminated intravascular coagulation. A computed tomography (CT) scan of the abdomen showed a 5.8cm mass in the left adrenal region, which raised suspicions of a pheochromocytoma. Spot urine vanillylmandelic acid (VMA) was 50.8 μg/mg of creatinine (normal range in this laboratory is 10.4 μg/mg of creatinine) with a creatinine of 12.6 mg/dl. A presumptive diagnosis of pheochromocytoma was made.

The patient remained on mechanical ventilation and required daily hemodialysis. She was transfused with packed cells, platelets, and fresh frozen plasma. Blood cultures grew no pathogens; however, she was started on imipenem and vancomycin. The patient had marked fluctuations of BP between 85/55 mmHg and 220/120 mmHg, which necessitated aggressive inotropic support alternating with the combination of nitroglycerin and sodium nitroprusside infusion. A pulmonary artery catheter was inserted and showed a cardiac index varying between 2.3 and 3.0 L/min/m² and a pulmonary artery pressure varying between 26/11 and 43/22 mmHg. During the following days, the patient's temperature normalized, and there was improvement of the pulmonary, hepatic, pancreatic, and coagulation systems. However, the blood urea nitrogen and creatinine remained markedly elevated despite daily hemodialysis for 3 to 4 hours. On the 13th day after the surgery, it was decided to proceed with an emergency excision of the pheochromocytoma.

Two days before surgery, prazosin was started at a dose of 1 mg orally 3 times a day. The antihypertensive regimen was maintained until the morning of surgery. The hemodynamic

profile before anesthesia showed BP of 140/70 mmHg, heart rate of 120 beats/min, and central venous pressure of 12 mmHg. In the operating room, the patient was monitored continuously with 5-lead electrocardiogram, pulse oximetry, capnography, intraarterial blood pressure, and central venous pressure measurements. Anesthesia was induced with propofol, 1 mg/kg, midazolam, 0.03 mg/kg and cisatracurium, 0.2 mg/kg, and a remifentanil infusion was initiated at a rate of 2 µg/kg.min. Anesthesia was maintained with 2% to 5% isoflurane in a mixture of air/oxygen (3:1), remifentanil, 1 to 2 µg/kg/min, and incremental doses of cisatracurium. Blood volume was expanded carefully throughout the procedure by normal saline solution to maintain an adequate central venous pressure. Through a midline abdominal incision, the left kidney was exposed, and the patient underwent resection of her left adrenal gland. During manipulation of the tumor, the BP went up to 220/120 mmHg and required increasing concentrations of isoflurane up to 6% end-tidal) and nitroprusside (1-3 µg/kg/min). The patient also developed severe tachycardia, which was controlled by intravenous esmolol, 0.5 mg/kg, followed by an intravenous infusion at a rate of 25 µg/kg/min. Ligation of the efferent vein of the tumor resulted in an abrupt fall in BP to 50/20 mmHg, which was managed with a norepinephrine infusion and rapid infusion of normal saline solution and colloid solution (Hemaccel: Hoechst Marion Roussel, Frankfurt am Main, Germany). Postoperatively, the patient made a quick recovery, and her trachea was extubated after 48 hours. Hemodialysis support was discontinued after 4 days. Pathology of the resected tissue confirmed the presence of encapsulated pheochromocytoma with focal areas of hemorrhage.

8. Pheochromocytoma during pregnancy (Hamilton,1997; Takahashi et al.,1998; Strachan et al., 2000; Mudsmith et al., 2006)

Pheochromocytoma is a dangerous condition, particularly in pregnancy, when it is difficult to diagnose, uncommon and has often been confused with preeclampsia. Pheochromocytoma during pregnancy may mimic the usual symptoms and signs of preeclampsia, either as simple hypertension or fulminant eclampsia.

Paroxysmal attacks during pregnancy may be precipitated by postural changes, the mechanical effect of the gravid uterus in the last trimester, uterine contractions during labor and increased fetal movements. Pheochromocytoma can mimic the symptoms and signs of preeclampsia and is therefore often missed. However, hypertension associated with pheochromocytoma is seldom accompanied by oedema or proteinuria, while glycosuria is often present.

The use of intravenous labetalol or hydralazine is well established in preeclampsia, and its use in combination with magnesium sulphate has been described in patients with pheochromocytoma. The pharmacodynamic properties of magnesium sulphate (direct vasodilator, inhibition of catecholamine release from the adrenal medulla) make it useful for the management of pheochromocytoma(James, 2010). Magnesium also has powerful anti-arrhythmic action in the presence of catecholamines.

When pheochromocytoma develops in pregnancy, there is a high risk of maternal and/or fetal mortality. Even vigorous fetal movements may be associated with hypertensive crisis. For cases diagnosed during pregnancy, there is a clear choice between early intervention and conservative management until fetal viability permits elective cesarean section. Hamilton et al reported the use of prazosin and propranolol followed by surgical removal of a pheochromocytoma at 7 weeks gestation, followed by an uneventful pregnancy and

delivery at 37 weeks. Nitroglycerine was used to control hypertension during surgery in preference to sodium nitroprusside on the grounds that the latter may reduce uterine blood flow. Also, phenoxyhenzamine is avoided during early pregnancy since it may have teratogenic effect.

When the pheochromocytoma is diagnosed later at 29 weeks gestation, conservative treatment using labetalol may be continued until 35 weeks when the fetus is delivered and the tumor removed at the same operation. When the parturient commences labor with unsuspected pheochromocytoma, the hypertension may be managed by intravenous phentolamine or a combination of magnesium and hydralazine until delivery, followed by oral preparation of pheochromocytoma for delayed formal resection.

9. Multicentric pheochromocytoma (Stoelting & Dierdorf, 1993; Wahlen et al., 1992; Isselbacher et al., 1994; Baraka et al., 2002)

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

Pheochromocytoma hemodynamic crisis may occur in patients with undiagnosed pheochromocytoma undergoing incidental surgery, in pregnant patients, as well as in patients with multicentric extraadrenal pheochromocytoma.

Extraadrenal sites include any organ that contains paraganglionic tissue, along the paravertebral sympathetic chain extending from the base of the skull to the pelvis. Most of the extra adrenal pheochromocytomas or paragangliomas are located below the diaphragm. Approximately 18% of pheochromocytomas are extraadrenal. The most common location is the superior aortic region between the diaphragm and the inferior renal poles, in and around the renal hilum and accounts for approximately 46% of the extra adrenal tumors. Extra adrenal tumors in the inferior paraortic area between the lower renal poles and the aortic bifurcation have constituted 24% of the cases. Most of these tumors have arisen from the organ of Zucherkandl which consists of paraganglia found in the retroperitoneal region along the aorta around the inferior mesenteric artery.

Most of extraadrenal pheochromocytoma secretes norepinephrine exclusively. If both norepinephrine and epinephrine are secreted, then the pheochromocytoma is very likely to be adrenal or Zucherkandl in origin. Serious hemodynamic fluctuations may occur during manipulations of the tumor of the organ of Zucherkandl which may be attributed to excessive catecholamine release secondary to its larger size and its more difficult resection.

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 tumors may be quite different functionally even if they grow concomitantly in the same patient.

9.1 Case report (Baraka et al. 2002)

The patient, a 28-year-old man, underwent at 12 year 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 µg.24 hr^{-1} (normal <25µg.24 hr^{-1}), vanillylmandylic acid of 13 mg.24 hr^{-1} (normal < 8 mg.24 hr^{-1}) and metanephrines 6009 µg.24hr^{-1} (normal < 900 µg.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 phenoxyenazmine 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.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.min. General anesthesia was induced with iv lidocaine 1 mg.kg, propofol 3 mg.kg, fentanyl 2 µg/kg and rocuronium 1 mg.kg. 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 Rousse. 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 helium and lateral to the vena cava. Dissection of the tumor from its surrounding structures was performed easily. Minimal hemodynamic changes occurred and responded to increasing concentrations of sevoflurane.

The tumor of Zuckerkandl was overlying and adherent to the bifurcation of the aorta. Surgical dissection of the tumor was difficult and associated with excessive blood loss. Manipulation of the tumor 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 2µg.kg^{-1}.min^{-1}, and two doses of *iv* phentolamine 5 mg were administered. Hypertension also necessitated the bolus administration of esmolol 0.5 mg.kg^{-1} *iv* to be followed by an iv infusion of 30 mg esmolol over 20 min.

Ligation of the efferent vein of the tumor 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 µg.kg.min) 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.min. His postoperative course was smooth and uneventful.

Pathology examination of the resected tumors confirmed the diagnosis of pheochromocytoma; the first mass was slightly smaller (5 x 4 x 4 cm *vs* 6 x 4 x 3.5 cm) and

weighed less (43 g *vs* 46 g) than the second tumor. The two tumors showed no evidence of necrosis or unusual meiotic activity.

10. Pheochromocytoma cardiomyopathy and multiple organ failure

A high mortality rate has been reported in pheochromocytoma patients with catecholamine-induced cardiomyopathy presenting symptoms of congestive heart failure, arrhythmia, acute pulmonary oedema and nonspecific EKG changes, as well as in pheochromocytoma complicated with multiple organ failure.

Echocardiography may reveal global cardiac hypokinesia secondary to cardiomyopathy in 25% to 50% of pheochromocytoma as a result of sustained exposure of the myocardium to high levels of catecholamines. Studies have shown a global reduction in myocardial pump function caused by a down-regulated β-adrenergic receptors and a net reduction in viable myofibrils. Rabits' hearts with catecholamine-induced cardiomyopathy have shown a reduced inotropic sensitivity to noradrenaline, and also a reduced response to calcium chloride. The pathogenesis of catecholamine-induced cardiomyopathy is probably multifactorial. Catecholamine-induced vasospasm leading to hypoxia is implicated. Excess noradrenaline also induces changes in permeability of the sarcolimmal membrane leading to increased calcium influx. Also, it has been proposed that the injury process might involve release of free radicals (Sardesai et al.,1990; Gilsanz et al.., 1983; Takaror et al., 1987; Fripp et al., 1981). Left atrial enlargement secondary to catecholamine-induced left ventricular diastolic dysfunction is quite common (around 20%), but seldom poses a management problem unless accompanied by left ventricular systolic dysfunction. Left ventricular hypertrophy is frequently seen, as are ST and T-wave abnormalities. These appear to be little advantage in attempting to correct these changes by medical management prior to tumor excision. These changes generally regress once the excess catecholamines source is removed. Left ventricular failure and pulmonary edema may be present, particularly if the patient has developed signs of catecholamine-induced cardiomyopathy (James, 2010).

Multiple organ failure (MOF) may be the initial presentation, and is called pheochromocytoma multisystem crisis. MOF may result from the high levels of circulating catecholamines, which can trigger excessive vascular spasm, volume contraction, platelet aggregation and thrombosis. The splanchnic vessels are highly susceptible to catecholamine-induced vasoconstriction, and hence the ischemic gut mucosa may allow bacterial translocation or the passage of endotoxins across the intestinal barrier to extraintestinal sites including the lung which is the first organ to fail. Also, acute renal failure can be attributed to acute tubular necrosis because of the combination of cardiogenic shock reducing the renal perfusion, associated with renal vasoconstriction induced by a surge of catecholamines (Sardesai et al.,1990; Gilsanz et al.., 1983; Takaror et al., 1987; Fripp et al., 1981).

Gut-derived factors, contained primarily in the mesenteric lymph rather than the portal system, potentiate the development of distant multiple organ failure. Because the lung is the first organ exposed to mesenteric lymph, via the thoracic duct and the subclavian vein, the lung is generally the first organ to fail in severely injured patients. The role of the gut injury and loss of gut barrier function contributes to the development of a systemic inflammatory state and distant organ injury (Fukushima et al.,1998).

During the decade from 1985 to 1995, gut barrier and the ensuing translocation of bacteria and endotoxins gained acceptance as a major contribution to the development of multiple organ dysfunction syndrome (MODS). It now appears that pheochromocytoma similar to

shock, trauma, or sepsis-induced gut injury can result in the gut becoming a cytokine-generating organ, and that the mesenteric circulation can become a priming bed for circulating neutrophils. Many of the same insults that cause intestinal mucosal injury and promote bacterial translocation also appear able to induce the gut and the gut-associated lymphatic tissue to produce cytokines and other inflammatory mediators that may contribute to MODS (Fukushima et al., 1998; Deitch,2001).

In a review of 54 autopsy-proven cases of unsuspected pheochromocytoma seen at the Mayo Clinic over a 50-year period, hypertensive or hypotensive crisis precipitated by surgery for unrelated conditions was a common cause of death. Intraoperative deaths have been ascribed variously to ventricular arrhythmias, wide fluctuations in systemic blood pressure, myocardial infarction, acute pulmonary oedema, and subarachnoid hemorrhage (St. John Sutton, et al.,1981). Barale et al., 1978 described two patients with circulatory shock, vasoconstriction, and pulmonary edema as the first manifestation of undiagnosed pheochromocytoma (Barale et al.,1978). Also, MOF may be the initial presentation of undiagnosed pheochromocytoma and has a poor prognosis (Barale et al.,1978; Kohle et al.,2001). Newell et al.,1988 reported 3 patients with unusual presentations of pheochromocytomas, which they called "pheochromocytoma multisystem crisis", a tetrad of symptoms including MOF, encephalopathy, high fever, and severe derangements in BP consisting of hypertension and/or hypotension. Siddik-Sayyid et al.,2007 reported a patient with an undiagnosed pheochromocytoma undergoing radical mastectomy; the patient developed intraoperative severe hemodynamic changes and pulmonary oedema, complicated by postoperative MOF; the postoperative hemodynamic instability and the persistent renal failure rapidly recovered after excision of the pheochromocytoma (Siddik-Sayyid et al., 2007).

Management of intraoperative pheochromocytoma crisis in patients undergoing incidental surgery consists of elimination of the triggering factors, as well as controlling hypertension by the administration of short-acting vasodilators such as the alpha-adrengergic blocker phentolamine, or sodium nitroprusside infusion. Whenever hypertension is associated with severe tachycardia, beta-adrenergic blocker can be administered; the short-acting and selective beta 1 blocker esmolol is preferred to the long-acting and nonselective propranolol. The administration of beta-adrenergic blocker without prior α-adrenergic blockade may be complicated by cardiac failure and pulmonary oedema secondary to its negative inotropic effect on the heart, associated with an increased after load. Initiation of nonselective beta blocker therapy without preceding alpha blockade in a patient with pheochromocytoma my precipitate a crisis with hemodynamic collapse. Nonselective beta blockade leads to loss of beta 2 receptor-mediated vasodilation, while the unopposed effects of alpha receptors causes vasoconstriction, resulting in increased after load, causing myocardial dysfunction and pulmonary oedema (Siddik-Sayyid et al., 2007). Thus, nonselective beta blockers should be avoided in any patient who could conceivably have a pheochromocytoma, until that possibility has been excluded. Also, unexplained cardiopulmonary dysfunction, and pulmonary oedema after the institution of beta blockade, should alert the anesthesiologist to the possibility of a pheochromocytoma (Sibal et al., 2006).

In patients with undiagnosed pheochromocytoma undergoing incidental surgery, many authors recommend urgent operation whenever their condition deteriorates despite maximal medical therapy. Newell et al.,1988 recommend urgent adrenalectomy when multisystem injury is present and in cases of progressive deterioration despite medical therapy. Also, Wood (Case 6-1986) stated that preparation for operation involves a balance

between severity of the illness and quality of α-blockade, and suggested that certain patients undergo surgical tumor excision with incomplete α--blockade. Freier et al.,1980 recommended urgent tumor excision after brief attempts at medical stabilization in patients presenting with alternating hypertension or hypotension, severe tachycardia, cardiac arrhythmias, encephalopathy, and renal failure.

11. Conclusion

In conclusion, patients with undiagnosed pheochromocytoma undergoing incidental surgery may develop intraoperative hemodynamic crisis complicated by postoperative multiple organ failure.

Management of intraoperative pheochromocytoma crisis consists of elimination of the triggering factors, as well as the administration of short-acting vasodilators such as the alpha-adrenergic blocker phentolamine, or sodium nitroprusside infusion. The administration of beta adrenergic blocker without prior α-adrenergic blockade may be complicated by cardiac failure and pulmonary edema secondary to its negative inotropic effect associated with an increased after load.

When the pheochromocytoma is surgically accessible during incidental surgery as laparotomy, the surgeon may be tempted to excise the tumor. However, tumor handling in unprepared patients may result in dramatic increases in arterial blood pressure followed by intractable hypotension after tumor excision. A safer option is planned resection of the pheochromocytoma after confirmation of the diagnosis and optimal preoperative pharmacologic preparation. However, urgent adrenalectomy is recommended whenever multisystem injury deteriorates despite maximal medical therapy.
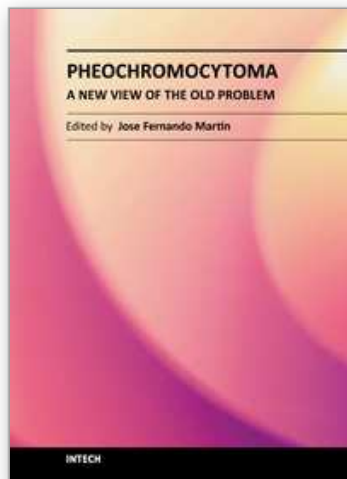
12. References

Allen, GC. & Rosenberg, H. (1990). Phaechromocytoma presenting as acute malignant hyperthermia – a diagnostic challenge. *Canadian Journal of Anaesthesia* 37, pp.593-5

Baraka,A.; Siddik-Sayyid, S., Jalbout, M. & Yacoub, S. (2002). Variable hemodynamic fluctuations During resection of   multicenteric extraadrenal pheochromocytoma. *Canadian Journal of Anesthesia* 49, No. 7, pp. 682-686

Barale, F.; Boillot, A., Neidhart, A., et al. (1978). Pheochromocytoma et reanimation d' urgence. *Anesthesia Analgesia Reanimation* 35, pp. 233-240

Bravo, EL. & Gifford, RW. (1984). Current concepts. Pheochromocytoma: diagnosis, localization and management. *N Engl J Med* 311, pp. 1298-1303

Case 6-1986, Case records of the Massachusetts General Hospital.(1986). Weekly clinicopatholgical exercises. *N Engl J Med* 314, pp. 431-439

Crowley, KJ.; Cunningham, AJ., Canroy, B. et al. (1988). Pheochromocytoma – A presentation mimicking malignan hyperthermia. Anaesthesia 43, pp. 1031-1032

Dabbous, A.; Siddik-Sayyid, S. & Baraka, A. (2007). Catastrophic hemodynamic changes in a patient with undiagnosed pheochromocytoma undergoing abdominal hysterectomy. *Anesthesia and Analagesia* 104, pp.223-224

Deitch, EA. (2001). Role of the gut lymphatic system in multiple organ failure. Curr Opin Crit Care 7, pp. 92-98, *Lippincott Williams & Wilkins, Inc.*

Freier, DT.; Eckhauser,FE. & Harrison, TS. (1980). Pheochromocytoma: A persistently problematic and still potentially lethal disease. *Arch Surg* 115, pp. 388-391

Fripp, RR.; Lee, JC. & Downing, SE. (1981). Inotropic responsiveness of the heart in catecholamine cardiomyopathy . Am Heart J 101, pp. 17-21

Fukushima, R.; Kabayashi, S. & Okinaga, K. (1998). Bacterial translocation in multiple organ failure. *Nippon Geka Gakkai Zasshi* 99, pp. 497-503

Gilsanz, FJ.; Luengo, C., Conejero, P. et al. (1983). Cardiomyopathy and pheochromocytoma. *Anaesthesia* 38, pp. 888-891

Geoghegan, JG.; Emberton ,M., Bloom, SR. & Lynn, JA. (1998). Changing trends in the management of pheochromocytoma. *Br J Surgery* 85, pp.117-120

Hamdan, JG. & Limbird, LE. (1996). *Goodman and Gilman's*. The Pharmacological Basis of Therapeutics, 9th ed. New York. McGraw-Hill Publishers, pp. 227-229

Hamilton, A.; Sirrs,S. , Schmidt, N. & Onrot, J. (1997). Anaesthesia for phaechromocytoma in pregnancy. *Canadian Journal of Anaesthesia* 44, pp. 654-657

Hirvonen, EA.; Niskanen, LK. & Niskanen, MM. (2004). Thyroid storm prior to induction of anaesthesia. *Anaesthesia* 59, pp.1020-1022

Hull, CJ. (1986). Phaechromocytoma-diagnosis, preoperative preparation and anaesthetic management. *British Journal of Anaesthesia* 58, pp. 1453-1468

Hull, CJ. & Batchelor, AM. (2003). Anesthetic management of patient with endocrine disease. *In Wylie and Churchill Davidson's.* A Practice of Anesthesia, 7th edition, Edited by Healy TEJ, Knight PR, pp. 811-827

Isselbacher, KJ.; Braunwald, E. , Wilson, JD. et al. (1994). *Harrison's principles of Internal Medicine* 14th ed Mc Graw Hill, pp. 1926-1929

James, MFM. (2010). Adrenal Medulla. The anesthetic management of pheochromocytoma. *In Anaesthesia for patients with endocrine disease.* Edited by MFM James. Oxford University Press Chapter 8, pp. 149-168

Kinney, MA.; Narr, BJ. & Warner, MA. (2002). Perioperative management of pheochromocytoma. *Journal Cardiothoracic & Vascular Anesthesia* 16, pp. 359-369

Kirkendahl, WH., Leighty, BRD. & Culp, DA. (1965). Diagnosis and treatment of patients with pheochromocytoma. *Arch Intern Med* 115, pp. 529-36

Kolhe, N., Stores ,J., Richardson, D., et al. (2001). Hypertension due to pheochromocytoma – An unusual cause of multiorgan failure. *Nephrol Dial Transplant* 16, pp.2100-2104

Larson, MD. & Herman ,WC. (1992). Bilateral dilated nonreactive pupils during surgery in a patient with undiagnosed pheochromocytoma. *Anesthesiology* 77, pp. 200-202

Manger, WM., Gifford, RW. Jr. & Hoffmann, BB. (1985). Pheochromocytoma: A clinical and experimental overview. *Curr Probl Cancer* 9, pp. 1-89

MyKlejard, DS. (2004). Undiagnosed pheochromocytoma. The Anesthesiologist Nightmare. *Clinical Medicine & Research* Volume 2, number 1, pp. 59-62

Mudsmith, JG.; Thomas, CE. & Browne, PA. (2006). Undiagnosed pheochromocytoma mimicking severe preeclampsia in a pregnant woman at term. *International Journal of Obstetric Anesthesia* 15, pp. 240-245

Newell, KA. , Porinz,RA., Pickleman, J., et al. (1988). Pheochromocytoma – multisystem crisis – A surgical emergency. *Arch Surg* 123, pp. 956-959

Nicholson, JP. Jr., Vaughn,ED., Pickering, TG., et al. (1983). Pheochromocytoma and prazasin. *Ann Int Med* 99, pp. 477-479

O.Riordan, JA. (1997). Pheochromocytoma and anesthesia. *Int Anesthesiol Clin* 35, pp. 99-127

Prys-Roberts, C. (2000). Pheochromocytoma-recent progress in its management. *British Journal of Anaesthesia* 85, pp. 44-57

Roizen, MF., Horrigan, RW., Koike, M., Eger, El. 2nd et al. (1982). Prospective trial of four anesthetic techniques for resection of pheochromocytoma. *Anesthesiology* 57, pp. A 43

Russell, WJ., Metcalfe, JR., Tankin, AL. & Frewin, DB. (1998). The preoperative management of pheochromocytoma. *Anesth Intensive Care* 26, pp.196-200

Sardesai , SH., Mourant, AJ., Sivathandon, Y. et al. (1990). Phaechromocytoma and catecholamine induced cardiomyopathy presenting as heart failure. *Br Heart J* 63, pp. 234-237

Schiff, RL. & Welsh, GA. (2003). Perioperative evaluation and management of the patient with endocrine dysfunction. *Med Clin N* Am 87, pp. 175-92

Sibal, L., Jovanovic, A., Agarwalt , SC., Peaston, RT., et al. (2006). Pheochromocytomas presenting as acute crisis after beta blockade therapy. *Clinical Endocrinology* 65, pp.186-190

Siddik-Sayyid, SM., Dabbous, AS., Shaaban,JA., Daaboul ,DG., & Baraka, AS. (2007). Catastrophic cardiac hypokinesia and multiple-organ failure after surgery in a patient with undiagnosed pheochromocytoma: Emergency excision of the tumor. *Journal of Cardiothoracic and Vascular Anesthesia* 21 (6), pp. 863-866

St. John Sutton, MG.; Sheps, SG. & Lie, JT. (1981). Prevalence of clinically unsuspected pheochromocytoma. Review of a 50-year autopsy series. *Mayo Clin Proc* 56, pp. 354-360

Stoelting, RK. & Dierdorf, SF. (1993). *Anesthesia and Co-Existing Disease*, 3rd ed New York, Churchill Livingstone pp. 363-367

Strachan, AN.; Claydon, P. & Caunt, JA. (2000). Phaechromocytoma diagnosed during labour. *British Journal of Anaesthesia* 85, pp. 635-637

Sutton,MG., Sheps, SG. & Lie, JT. (1981). Prevalence of clinically unsuspected phaeochromocytoma. Review of a 50 year autopsy series. Mayo Clinic Procedures 56, pp. 354-360

Takahashi ,K.; Sai, Y. & Nasaka, S. (1998). Anaesthetic management for Caesarean section combined with removal of pheochromocytoma. *Eur J Anaesthesiol* 15, pp. 364-366

Takaror, C.; Tanimuro, A. & Saito, Y. (1987). Catecholamine-induced cardiomyopathy accompanied with pheochromocytoma. *Acta Pathol Jpn* 37, pp. 123-132

Wahlen, RK.; Althausen, AF. & Daniels, GH. (1992). Extraadrenal pheochromocytoma. *J Urol* 147, pp. 1-10

Pheochromocytoma - A New View of the Old Problem
Edited by Dr. Jose Fernando Martin

The book is divided into six sections. The first three sections focus on the pathophysiology of the disease, showing anatomo- and histopathological aspects, experimental models and signaling pathways and programmed cell death related to pheochromocytoma. The fourth discusses some specific aspects of clinical presentation, with emphasis on clinical manifestations of headache and heart. The fifth section focuses on clinical diagnosis, laboratory and imaging, including differential diagnosis. Finally, the last section discusses the treatment of pheochromocytoma showing clinical cases, a case about undiagnosed pheochromocytoma complicated with multiple organ failure and other cases about catecholamine-secreting hereditary tumors. Thus, this book shows the disease "pheochromocytoma" in a different perspective from the traditional approach. Enjoy your reading.

How to reference
In order to correctly reference this scholarly work, feel free to copy and paste the following:

Anis Baraka (2011). Undiagnosed Pheochromocytoma Complicated with Perioperative Hemodynamic Crisis and Multiple Organ Failure, Pheochromocytoma - A New View of the Old Problem, Dr. Jose Fernando Martin (Ed.), ISBN: 978-953-307-822-9, InTech, Available from:
http://www.intechopen.com/books/pheochromocytoma-a-new-view-of-the-old-problem/undiagnosed-pheochromocytoma-complicated-with-perioperative-hemodynamic-crisis-and-multiple-organ-fa

INTECH
open science | open minds