REVIEW

Point of controversy: perioperative care of patients undergoing pheochromocytoma removal—time for a reappraisal?

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Abstract

Adrenalectomy for pheochromocytoma is reported with a mortality close to zero in recent studies. The dogma of preoperative fluid and hypotensive drug administrations is widely applied in patients scheduled for pheochromocytoma removal and is assumed to have a beneficial effect on operative outcomes. This paradigm is only based on historical studies of non-standardized practices and criteria for efficacy, with no control group. Pre- and intraoperative hypovolemia have never been demonstrated in patients scheduled for pheochromocytoma removal. Recent improvements in outcome of patients undergoing adrenalectomy for pheochromocytoma could also be the result of improvement in surgical techniques and refinement in anesthetic practices. Whether better knowledge of the disease, efficiency of available intravenous short-acting vasoactive drugs, and careful intraoperative handling of the tumor make it possible to omit preoperative preparation in most patients scheduled for pheochromocytoma removal is presently questionable. We reviewed available literature in this respect.

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Clinical and pathophysiological considerations

Pheochromocytoma symptoms result from the uncontrolled release of catecholamines: norepinephrine, epinephrine, and rarely dopamine (1–5). Compared with norepinephrine release, epinephrine has a predominant effect on β_2 -adrenoreceptors of the vessel muscles resulting in vasodilation and postural hypotension (1, 2, 5). Norepinephrine release acts predominantly on β_1 - and α_1 -adrenoreceptors resulting in vasoconstriction and hypertension (1, 2, 5). The release of both catecholamine types stimulates β_1 -adrenoreceptors resulting in an increased heart rate (1, 2, 5). Elevated blood glucose level is primarily due to stimulation of lipolysis and inhibition of glucose uptake in muscle cells and also to glycogenolysis and gluconeogenesis in the liver by epinephrine (1, 6, 7). Depending on whether catecholamines are released continuously or in shorter bursts, patients will mainly have sustained high blood pressure or a classical presentation consisting of paroxysmal episodes of hypertension associated with headache, sweating, chest pain, tachyarrhythmia, diaphoresis, and flushing (1, 2, 5). Patients with exclusively dopamine-secreting tumors present with non-specific signs such as unexplained cough, abdominal pain, flank mass, or inflammatory features and are reported to be normotensive (8). Severe high blood

pressure associated with pheochromocytoma may cause death from stroke, left-ventricular failure, myocardial infarction, or multiorgan failure (1, 5, 9). Pheochromocytoma accounts for 0.05–0.1% of patients with sustained hypertension (1, 5). This hypertension is frequently poorly controlled with standard medications (1, 5). Fifteen to twenty percent of pheochromocytomas do not secrete significant quantities of catecholamines but, however, run the same risk of life-threatening complications (1, 3). With the widespread use of cross-sectional imaging, 29.4–57% of pheochromocytomas present without clinical symptoms and are found incidentally (3). The only curative treatment for pheochromocytoma is complete surgical resection. The laboratory diagnosis of these tumors is based on the identification of excessive secretion of catecholamines and/or of their derivatives (2, 5). Most tumors are benign (1, 5, 10–12). Laparoscopic adrenalectomy has become the standard treatment for most pheochromocytomas even larger than 7 cm with, in recent studies, a mortality close to zero when performed by experienced teams (10–12).

Historical background

In early studies, life-threatening intraoperative catecholamine release has been quickly identified as

the cause of increased blood pressure, various cardiac arrhythmias including ventricular tachycardia and fibrillation, left ventricular failures, myocardial ischemias, and strokes following induction of anesthesia or tumor manipulation (13, 14). Prolonged postoperative hypotension followed the abrupt withdrawal of circulating catecholamines associated with tumor removal and accounted for most operative deaths (15). Pheochromocytoma removals were associated with a mortality rate of 20–45% in first reports (13, 14). Prolonged high preoperative levels of circulating vasopressors released from pheochromocytomas were assumed to cause a vasoconstriction, leading to arterial hypertension and a chronic decrease in blood volume (13–15). The subsequent sudden intraoperative withdrawal of vasopressors following pheochromocytoma resection was believed to cause abrupt relaxation of the vascular bed, in turn resulting in hypotension and shock unless the reduced blood volume was restored (13–15). This led to the assumption that optimal preoperative care had to include preoperative vasodilation of the previously constricted vascular compartment by a vasodilating drug along with restoring blood volume by major fluid infusion (5, 13–30).

Mortality has no longer been reported in most recent studies of patients undergoing pheochromocytoma removal (11, 12, 18, 22, 31). This improved prognosis is currently attributed to the widespread preoperative administration of vasodilating drugs and large fluid volumes, even in patients with normal or borderline elevation of catecholamine levels (5, 13–30). Nevertheless, none of these practices are evidence based, and to our opinion, a critical review of the available literature does not support this dogma.

Fluid administration

Various amounts and types of fluids have been administered to patients scheduled for pheochromocytoma removal. In 1954, Thompson & Arrowood (14) reported better intra- and post-operative hemodynamic control following the empirical administration of whole blood transfusions to a level greater than the estimated blood loss. However, at that time, estimated blood loss ranged between 500 and 26 000 ml and patients received long-acting hypotensive drugs pre- and intraoperatively (13, 14). Hypovolemia, due to delayed compensation for intraoperative blood loss intensified by long-acting α -blockade, could be the main reason for hemodynamic improvement with blood transfusion. Ulchaker *et al.* (30) reported 127 patients undergoing pheochromocytoma removal with high-volume fluid administration and no postoperative death. Patients routinely received between 1000 and 16 400 ml crystalloids and up to 5300 ml colloids, intraoperatively (30). Between 1665 and 11 665 ml fluids was infused on postoperative day 1 (30). In

addition, up to 2800 ml blood was infused (30). On the contrary, Gosse *et al.* (22) routinely infused only 2000 ml saline from 10 to 2 days prior to surgery, and Lentschener *et al.* (31) and Lebuffe *et al.* (18) administered fluids only as required when intraoperative arterial pressure decreased following adrenalectomy. Lentschener *et al.* (31) did not report any death, and Lebuffe *et al.* (18) reported only three deaths neither related to pheochromocytoma nor related to arterial hypertension. In view of these results, it seems very unlikely that major fluid administration is responsible for the improvement of outcome in pheochromocytoma surgery (18, 30–34).

Are patients with pheochromocytoma hypovolemic?

Early fundamental data do not support the concept of clinically significant hypovolemia associated with pheochromocytoma (35–37). Plasma volume was determined in 15 patients with pheochromocytoma before any therapy and in ten of these patients after hypotensive drug administration or adrenalectomy, by using human albumin labeled with ^{125}I (35). All but two patients had normal predicted plasma volume at first assessment (35). Following α -methyl-paratyrosine or phenoxybenzamine therapy, the mean plasma volume increased by 11%, and following surgery, the mean plasma volume increased by 6%, when compared with preoperative measurements (35). Finnerty *et al.* (36) showed a reversible 15% decrease in plasma volume following a 15 min infusion of levarterenol, an α -blocking drug, in ten human volunteers. Such changes in blood volume are of little clinical relevance (37). Furthermore and importantly, as early as 1977, when comparing two personal historical studies of patients undergoing adrenalectomy for pheochromocytoma, Desmond & Marty (16) reported that administering fluid only intraoperatively, whenever necessary, was as efficient as preoperative fluid infusion in regard to hemodynamic control. More recently, analysis of the arterial pressure waveform during mechanical ventilation was used to measure the negative component (Δ -down) of the respiratory systolic pressure variation in 13 patients undergoing pheochromocytoma surgery (38). During tumor removal, the stability of Δ -down and the lack of correlation between systolic arterial pressure variation and Δ -down suggest that reduced preload associated with hypovolemia is not a major mechanism of hypotension following pheochromocytoma removal (38). Furthermore, Δ -down values recorded prior to adrenal vein ligation in patients in whom arterial hypotension occurred after tumor removal overlapped those recorded in patients who remained normotensive. This suggests that the predominant mechanism of severe hypotension following tumor resection is likely to be a decrease in arterial tone and that severe hypotension

may occur in normovolemic patients (38). Further studies are warranted to assess whether hypotension associated with pheochromocytoma removal is not related to a transient drop in the sympathetic tone as is the case with hypotension associated with the onset of central neural blockade using local anesthetics (39). This situation has widely been documented in the anesthetic literature (39). Following central neural blockade using local anesthetics, after a long period of intense fluid administration, current accepted recommendations are presently focusing on vasopressor administration (39).

Preoperative hypotensive drugs

Various hypotensive drugs have been preoperatively administered to patients scheduled for pheochromocytoma removal (13, 16, 18–20, 21, 24, 26, 29, 30, 32, 40–44).

- Oral phentolamine is no longer used in the preoperative hypotensive treatment of patients scheduled for pheochromocytoma removal (20).
- Phenoxybenzamine, irreversibly bound to α_1 - and α_2 -adrenoreceptors, is still administered for preoperative management of patients undergoing adrenalectomy for pheochromocytoma (13, 21, 24, 40). Oral phenoxybenzamine has a pharmacological half-life of 24 h (13, 21, 24, 40). Phenoxybenzamine produces significant postural hypotension and reflex tachycardia due to the blockade of α_2 -receptors, along with sedation (13, 21, 24, 40). It necessitates careful dose titration (13, 21, 24, 40). It has been suggested that its long duration of action has contributed to the hypotension following pheochromocytoma removal (13, 21, 24, 40).
- Selective α_1 -antagonists such as terazosin and prazosin have a relatively short duration of action as a result of their competitive inhibition of α_1 -adrenoreceptors and therefore could minimally potentiate the risk period for the hypotension, which follows a decrease in catecholamine levels (19, 29, 30, 41). This contrasts with doxazosin, which has a half-life of 16–30 h and has also been suggested to worsen hypotension associated with adrenalectomy (19, 29, 30, 41). They have a minimal effect on cardiac function due to their α_1 -receptor selectivity (19, 29, 30, 41). Side effects of all α_1 -adrenergic blockers include postural hypotension, syncope, and nasal congestion and necessitate careful titration (19, 29, 30, 41).
- Calcium channel blockers cause smooth muscle relaxation in peripheral and coronary arteries by inhibiting norepinephrine-stimulated calcium influx into vascular smooth muscle (42). Calcium channel blockers have been used alone as primary treatment, or associated with selective α_1 -receptor blockers, to

successfully control blood pressure in patients with pheochromocytoma (18). Calcium channel blockers are often reported to produce minimal hypotension and to be safe to use in normotensive patients with occasional episodes of paroxysmal hypertension (18, 42). It was suggested that catecholamine-induced spasms of coronary arteries were prevented with preoperative calcium channel blockers (42).

- β -Receptor blockers are preoperatively administered to reduce and/or to prevent pre- and intraoperative tachycardia and cardiac arrhythmias (16, 19, 32). Propranolol, atenolol, and metoprolol have been routinely used for this purpose (16, 19, 32). In the absence of adequate α_1 -blockade, β -blockade may exacerbate epinephrine-induced constriction by blocking its vasodilator component and precipitate left ventricular insufficiency (43). Cardioselective β_1 -adrenoreceptors should be favored (44).
- Labetalol is a β -blocker with α -blocking properties (26). Labetalol, with α - and β -antagonistic activities in a ratio of about 1:7, may result in paradoxical hypertension (26).
- Structural analogs of tyrosine such as α -methyl-tyrosine are competitive inhibitors of tyrosine β -hydroxylase, a main step in catecholamine synthesis (16, 21, 45, 46). This drug significantly depletes catecholamine. It was efficiently used to control preoperative high blood pressure in patients with pheochromocytoma (16, 21). At the present time, it is used only in few institutions in association with vasodilator drugs to control high blood pressure in patients with extensive metastatic disease for which complete resection is not possible (45).

Are preoperative hypotensive drugs necessary?

Preoperative blood pressure control is believed to be one of the main causes of the decrease in mortality associated with pheochromocytoma removal. The study by Goldstein *et al.* (21), often cited as reference, illustrates the low level of evidence of this contention. From 1950 to 1998, authors observed 108 pheochromocytomas (21). Preoperative α -blockade consisting of phenoxybenzamine was first used in that institution in 1967 (21). Thereafter, since 1997, patients have received a heterogeneous drug regimen between 1 day and several weeks prior to surgery (21). Since 1973, α -methyl-tyrosine has also been used as a blocking agent in 43 patients in combination with phenoxybenzamine (21). Based on this 48-year follow-up, authors concluded that hypotensive drugs were responsible for a decrease in complications from 69 to 3% (21). However, this period saw a huge improvement of both surgical approach and anesthetic management. Before 1978, all pheochromocytomas were resected using a thoracoabdominal approach (21). After 1979,

midline abdominal incision became the preferred approach (21). Beginning in 1998, laparoscopy has been selectively used in three patients (21). All recent studies included various preoperative hypotensive drugs and preoperative fluid regimens and reported a mortality close to zero in patients undergoing pheochromocytoma removal (5, 16–19, 22, 26, 27, 29, 31, 32, 34, 41, 47). However, available reports do not comply with the rules of scientific investigation. To our knowledge, studies of preoperative hypotensive drugs did not include a non-treated or a placebo control group (13–34, 41, 45–49). In most reports, despite treatment, preoperative blood pressure control was not achieved. Thus, preoperative systolic blood pressure ranged from 95 to 183 mmHg after α -blockade in Bruynzeel *et al.* (48) report of 73 patients scheduled for pheochromocytoma removal. Two studies compared patients undergoing pheochromocytoma removal with normal and increased preoperative arterial pressures and failed to show any differences in the outcome of patients (25, 31). In a study by Lentschener *et al.* (31) on 96 patients undergoing pheochromocytoma removal with no mortality, 35 patients had high preoperative arterial pressure. In this study, a high preoperative arterial pressure was not indicative of intra- and post-operative hemodynamic instability (31). Plouin *et al.* (25) reported that high preoperative arterial pressure was independently correlated with intra- and post-operative complications. However, the emphasis in that article was on non-hypertension-related complications such as allergy, pneumothorax, postoperative bleeding, or pancreatitis (25). Others compared patients receiving preoperative hypotensive drugs to patients who did not receive any preoperative drugs. In Ulchaker *et al.* (30) report, 30% of patients received no medication in the 24 h preceding surgery. Intraoperative mean blood pressure levels were similar when comparing patients who were or were not treated preoperatively with antihypertensive medications (30). Boutros *et al.* (34) compared 31 patients receiving phenoxybenzamine or prazosin with 29 patients who did not receive any hypotensive drugs. Crystalloids were infused during the 48 h prior to surgery in all patients (34). Preoperative blood pressures were increased in most investigated patients (34). No difference in perioperative mortality or morbidity was found, although intraoperative blood pressure rise was a little higher in the untreated group (34). Desmont & Marty (16) retrospectively evaluating their practices found that, i) preoperative β -blocking drugs did not prevent intraoperative cardiac arrhythmias and ii) preoperative α -blockade was not judged necessary because available vasoactive drugs allowed intraoperative hemodynamic changes to be controlled whenever necessary. Intraoperative attention to patients' hemodynamics is likely to be more important than a specific hypotensive medication.

Cause of hemodynamic instability in pheochromocytoma surgery?

The above findings are to be expected. In patients undergoing pheochromocytoma removal, intraoperative increase in arterial pressure has been shown to be associated with plasma norepinephrine and epinephrine release, which occurs in all patients i) when moving the patient on the table; ii) during induction of general anesthesia and tracheal intubation in relationship with intraabdominal pressure changes associated with cough, light sedation, and insufficient relaxation; iii) when abdominal pressure changes due to the initiation of mechanical ventilation; iv) during the creation of pneumoperitoneum; and v) when the tumor is directly manipulated (13, 26, 48–50). Increased arterial pressure is also likely to be an exaggerated response to noxious stimuli not associated with catecholamine release such as skin incision (16, 50). These intraoperative hypertensive responses are currently and empirically limited by increasing anesthetic depth and muscle relaxation, along with careful surgical handling of tumor tissue (10–12, 16, 48–50). Whether anesthesia guided by bispectral index (BIS) monitoring could optimize anesthetic delivery and have a significant impact on intraoperative arterial pressure changes in patients undergoing pheochromocytoma removal remains to be investigated (51).

Anesthetic technique

Epidural and spinal anesthetics have been used alone or as a complement to general anesthesia for pheochromocytoma removal with satisfactory results (15, 22, 29). However, they do not provide the best comfort when carrying out an adrenalectomy (10–12), and sympathetic blockade associated with spinal anesthesia does not protect against the hemodynamic effects of catecholamine release during tumor manipulation (13, 16, 29, 35). General anesthesia is favored in most reports (5, 11–17, 24, 25, 27–35, 41, 46, 47). Induction with thiopental, propofol, and etomidate is common practice (16, 17, 32). Ketamine that increases catecholamine release should be logically avoided (15). Recent halogenated agents, including sevoflurane, desflurane, isoflurane, and nitrous oxide, have been recognized as being safe in patients undergoing pheochromocytoma removal (13, 15, 17, 24, 25, 29, 30, 34, 35). The choice among available muscle relaxants is of secondary importance (15). Succinylcholine has been used successfully either as a bolus or as a continuous infusion (13, 15). Atracurium and vecuronium are routinely used by many teams (15, 16). Tubocurarine, gallamine, and pancuronium, which have been suggested to cause catecholamine release and to have anticholinergic and histamine releasing effects, are no longer used (52). Direct and continuous monitoring of arterial pressure via an intraarterial catheter is

universally recommended (5, 16–18, 22, 23, 25–34, 41, 46, 47, 50). A central venous catheter is a routine part of patient care in many reports (18, 30, 49, 50). Some teams believe that administering a vasopressor on a peripheral venous line to control transient intra- or post-operative hypotension is not harmful (31). A pulmonary artery catheter was previously judged to be warranted to investigate hypotension following tumor removal (50). Actually, no monitoring has proved its usefulness for both interpretation and treatment of arterial hypotension following pheochromocytoma resection. Globally, many diagnostic tools have been reported to be highly predictive of fluid responsiveness in intensive care patients and during anesthesia (53–55). Invasive arterial pressure monitoring is routinely used during pheochromocytoma removal, allowing measurement of Δ -down derived from the analysis of arterial pulse pressure waveform, as mentioned earlier (38). However, fluid loading reduced non-specifically Δ -down at all times of pheochromocytoma resection similarly as in anesthetized normal patients (38). Further investigations are necessary to assess if Δ -down monitoring could efficiently guide fluid resuscitation and reduce the risk of arterial hypotension following tumor removal (38). To our knowledge, other diagnostic tools such as i) stroke volume variation derived from pulse contour analysis and ii) variation of the amplitude of the pulse oximeter plethysmographic waveform together with iii) aortic flow velocity and stroke volume assessed by Doppler echocardiography or transesophageal echocardiography have not been evaluated in patients undergoing pheochromocytoma resection (53–55).

Intraoperative hypotensive drugs

Many fast-acting intravenous drug regimens have been reported to efficiently control intra- and post-operative changes in blood pressure. Their selection mainly results from local practices.

- Increasing depth of anesthesia and muscle relaxation is a common anesthetic practice to reduce intraoperative increases in blood pressure (16, 28, 32, 50). As mentioned earlier, BIS-guided anesthesia has not been studied in pheochromocytoma surgery (51).
- Phentolamine is a competitive α_1 - and weak α_2 -adrenergic receptor antagonist that has a short duration of action (40). At the present time, continuous infusion of phentolamine is seldom administered in patients with pheochromocytoma to lower perioperative hypertensive episodes during surgical adrenalectomy (13).
- Sodium nitroprusside decreases preload and afterload (56). Its onset is immediate and recovery occurs within 1–2 min (56). It is often used as a first choice agent to treat intraoperative arterial pressure

increases in patients undergoing pheochromocytoma removal (6, 16, 30). In patients with coronary artery disease, a significant 'steal' in coronary blood flow has been documented (56). Toxic metabolites such as cyanide and thiocyanate are a concern only when the agent is administered in high doses and/or for more than 48–72 h, in patients with abnormal renal and hepatic function, and when the infusion rate is $> 2 \mu\text{g/kg per min}$ (56).

- Nitroglycerin is a rapid-acting venodilator (57). Its onset and duration of action are rapid. It reduces preload and increases coronary blood flow by dilating collateral vessels and suppressing coronary vasospasm (57). High doses of nitroglycerin produce arteriolar vasodilation (57). Nitroglycerin is a suitable drug in patients with ischemic heart disease (57). Nitroglycerine was successfully used to decrease blood pressure in patients undergoing pheochromocytoma removal (58).
- Second-generation calcium channel antagonists, especially dihydro-pyridines (nicardipine), have powerful arterial vasodilating properties (42). This results in a reduction in afterload and an improvement in left ventricular function along with the preservation of venous return (42). Potent cerebral, renal, and coronary vasodilatory activities have been reported (42). Intravenous nicardipine decreases blood pressure in a dose-dependent fashion with a response in 1–3 min (42). The half-life is 3–7 min. Gradual accumulation of nicardipine during infusions may prolong its duration of action. i.v. nicardipine infusion or bolus is currently used in patients undergoing pheochromocytoma removal (18, 50).
- Urapidil is an α -blocking agent that was judged useful in managing hypertension following the induction of anesthesia and during tumor dissection in patients undergoing pheochromocytoma removal (22). Heart rate did not change significantly (22).
- Magnesium sulfate did not consistently produce satisfactory control of arterial pressure during handling of the tumor (23).
- Intravenous lidocaine has been consistently effective in controlling intraoperative arrhythmias in many old studies (16).
- Esmolol is an ultra short-acting cardio selective β -adrenergic blocking agent, preferred over propranolol for the control of intraoperative tachycardias or tachyarrhythmias (18, 31, 59). The onset of action is 60 s with a duration of action of 10–20 min (59). The metabolism of esmolol is via the hydrolysis of ester linkages by red blood cell esterases and is not dependent on renal or hepatic function (59).

Hypotension following adrenalectomy

As can be seen from the above, various quantities and types of fluids associated with various vasopressive

drugs, mainly norepinephrine and seldom epinephrine, have been recommended to control hypotension following tumor withdrawal, resulting in a mortality close to zero in all recent studies (5, 17, 18, 22–34, 41, 46, 47, 50).

Postoperative care

Hypotension following pheochromocytoma removal is definitively controlled within a few hours following surgery in most patients (5, 16, 19, 22, 28, 30, 31). Anecdotal reports of patients requiring a 48 h vaso-pressive support are available (1, 5). High blood pressure requiring specific care has been reported to persist for a variable duration in 40% of patients (5, 16, 19, 22, 28, 30, 31). Blood glucose concentration should be monitored for at least 24 h (6, 7). Excessive rebound secretion of insulin may occur after removal of the tumor accounting for rare transient hypoglycemia reported up to 6 days postoperatively, which must not be missed in a patient drowsy as a result of general anesthesia (6, 7).

Pregnancy

Pregnancy warrants a different approach. Aggressive medical control of blood pressure with antihypertensive drugs is regarded as a major factor in accounting for the dramatic improvement in maternal and fetal outcome in patients with pheochromocytoma diagnosed during pregnancy (48, 49). Hypotensive drugs listed above have been used with good results (48, 49). Selective β_1 -blockers such as metoprolol or atenolol must be favored over non-selective β -blockers such as propranolol, which were associated with growth retardations, neonatal bradycardias, and hypoglycemia in the fetus (48, 49).

Is there a subgroup of patients who must receive hypotensive drugs, preoperatively?

Pheochromocytoma in pregnancy requires aggressive control of blood pressure (49, 50). For all other patients, few non-concordant data are available concerning factors likely to be associated with intra- and post-operative hemodynamic instability in patients undergoing adrenalectomy for pheochromocytoma. In Bruynzeel *et al.* (47) study of 73 patients undergoing adrenalectomy for pheochromocytoma between 1995 and 2007, a high plasma norepinephrine concentration, larger tumor size, postural arterial pressure decrease after α -blockade, and a preoperative mean arterial pressure above 100 mmHg are predictive of intraoperative hemodynamic instability assessed by

episodes of intraoperative mean arterial pressure decreases below 60 mmHg and systolic blood pressure increases above 160 mmHg (47). In contrast, Weismann *et al.* (60) investigated 49 patients and did not identify any factor predictive of intraoperative hemodynamic changes including tumor size larger than 7 cm. Increases in arterial pressure up to 250 mmHg have been reported in many studies of pheochromocytoma removal regardless of whether preoperative hypotensive drugs had been administered or not (16), and finally, continuous monitoring of arterial pressure and adequate intraoperative administration of fast acting drugs have allowed to achieve a mortality rate close to zero in recent studies (5, 16–19, 22, 26, 27, 29, 31, 32, 34, 41, 47).

Finally, the right issue is probably to question whether there are patients with preoperative increased arterial pressure, scheduled for general or vascular surgery, for whom surgery must be postponed (61–63). In most studies on patients undergoing general and vascular surgery, preoperative arterial hypertension is associated with an increased risk of both intraoperative hypertensive crisis and myocardial ischemias requiring a drug intervention (61–63). However, preoperative arterial hypertension is associated with an increased risk of operative mortality only if arterial hypertension coexists with i) a preexisting heart disease including coronary artery disease, ii) factors likely to favor coronary artery disease such as hyperlipidemia or diabetes, and iii) symptomatic left ventricular dilatation or hypertrophy, aortic stenosis, or arterial pressure $\geq 180/115$ mmHg (61–63). It is recommended to administer oral or i.v. hypotensive drugs prior to surgery to such patients with hypertension-associated organ dysfunctions and/or in the case of preexisting stroke, symptoms such as headache or tinnitus, and if systolic blood pressure is ≥ 180 mmHg, and diastolic blood pressure is ≥ 115 mmHg (61–63). For most patients, available data do not support postponing surgery on the sole argument that preoperative blood pressure is not normalized, provided that a coexisting heart disease is not diagnosed or increased blood pressure is functionally tolerated (61–63).

Conclusion

Increased knowledge of the disease, along with continuous arterial pressure monitoring, fast-acting vasoactive agents, and improvement of surgical approach have dramatically improved the outcome of patients undergoing adrenalectomy for pheochromocytoma. Preoperative hypotensive treatment of patients with life-threatening complications of high blood pressure such as congestive heart failure, stroke, coronary artery disease, dysrhythmia, blood pressure above 180/115 mmHg, and of patients with pheochromocytoma diagnosed during pregnancy is warranted.

Systematic preoperative administration of fluids and hypotensive drugs is not supported by any evidence-based study. Intraoperative hypertensive responses are mainly due to tumor manipulation. Careful surgical handling of tumor tissue, limited intraabdominal pressure, adequate depth of anesthesia and muscular relaxation, and the use of fast-acting vasoactive agents are the only proven means for limiting intraoperative hypertension and their consequences. Administering fluid and/or vasopressor agents intraoperatively, whenever necessary, is as efficient as preoperative fluid infusion to control hypotension following tumor withdrawal. In most cases, available data do not allow the anesthetic team to postpone or refuse surgery to patients with preoperative, uncontrolled hypertension.

Further studies are needed

Prospective, placebo-controlled studies are required to confirm our conclusions. Several intricate endpoints will have to be assessed, mainly i) is preoperative drug or fluid administration associated with a perioperative decrease in morbidity or mortality; ii) are pheochromocytoma patients hypovolemic; iii) effect of vasodilating drugs, fluid infusion, and adrenalectomy on preoperative volemia and preoperative hemodynamic changes; iv) are there hemodynamic parameters and monitoring tools likely to guide pre-, intra- and post-operative resuscitation; v) is anesthesia guided by BIS monitoring likely to limit intraoperative hemodynamic changes; vi) to provide a reliable definition of perioperative hemodynamic instability; and vii) to identify a subgroup of patients likely to benefit from preoperative drug and fluid administration.

Potential investigators must be aware of the difficulty to conduct such studies. The endpoint 'intraoperative hemodynamic instability' has no consensual definition. Such studies will have to include a huge patient sample since available data indicate a mortality rate close to zero and a very low morbidity in recent studies. Studies will have to include a stratification for the three catecholamines released and the quantity of catecholamines sometimes released in various associations, and whether catecholamine release is sustained or paroxysmal. Several classes of hypotensive drugs will have to be considered. Whether such studies will be conducted is questionable due to the rarity of the disease. Ideally, until further studies are available, historical assessments that entertain the present scientific uncertainties should no longer be considered for publication.

Declaration of interest

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

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