Clinical Endocrinology (2017) **86**, 309–314 doi: 10.1111/cen.13284

CLINICAL QUESTION

Preoperative alpha-blockade in phaeochromocytoma and paraganglioma: is it always necessary?

Michelle Isaacs* and Paul Lee*,†

*Department of Endocrinology, Garvan Institute of Medical Research, and †St Vincent's Hospital and Diabetes and Metabolism Division, Garvan Institute of Medical Research, Sydney, New South Wales, Australia

Summary

Resection of phaeochromocytoma and paraganglioma (PPGL) is traditionally preceded by alpha-blockade to prevent complications of haemodynamic instability intraoperatively. While there is general agreement on preoperative alpha-blockade for classic PPGLs presenting with hypertension, it is less clear whether alpha-blockade is necessary in predominantly dopamine-secreting tumours, normotensive PPGLs, as well as tumours that appear to be biochemically 'silent'. Preoperative management of these 'atypical' PPGLs is challenging and the treatment approach must be individualized, carefully weighing the risk of intraoperative hypertension against the possibility of orthostatic and prolonged postoperative hypotension. Consideration of antihypertensive medication pharmacology in the light of catecholamine physiology and PPGL secretory profile will facilitate the formulation of individualized preoperative preparatory strategies.

(Received 13 September 2016; returned for revision 17 October 2016; finally revised 17 October 2016; accepted 15 November 2016)

Introduction

Phaeochromocytoma and paraganglioma (PPGL) are chromaffin-cell tumours that may secrete the catecholamines adrenalin, noradrenalin and dopamine. Phaeochromocytomas arise from the adrenal medulla and account for 85% of PPGL; paragangliomas arise from sympathetic/parasympathetic ganglia and account for 15%.[1] To date, surgical resection is the only cure for PPGL. However, general anaesthesia induction, ventilation-mediated abdominal pressure fluctuations and direct tumour handling could increase catecholamine release, triggering intraoperative hypertensive crisis and potentially resulting in stroke, myocardial infarct, cardiac and/or multiorgan failure.[2]

Correspondence: Paul Lee, Department of Endocrinology, Gavan Institute of Medical Research, 384 Victoria Street, Darlinghurst, Sydney, NSW 2010, Australia. Tel.: +61 2 9295 8416; fax: +61 2 9295 8481; E-mail: p.lee@garvan.org.au

Preoperative alpha-blockade has traditionally been advocated to minimize intraoperative hypertension by preventing catecholamine-induced alpha-1 receptor-mediated vasoconstriction. Despite the recommendations from clinical guidelines,[1,3] up to one-third of patients did not receive pre-adrenalectomy blockade in one recent series.[4] Alpha-blockade may sometimes be deemed 'unnecessary' in atypical presentations, including PPGLs associated with normotension/postural hypotension, and exclusively dopamine-secreting or apparently 'nonfunctional' PPGLs. Whether alpha-blockade is indicated preoperatively in these scenarios has not been specifically addressed in the PPGL literature. Although current dogma regards the majority of sympathetic PPGL as functional, whereas 70% of parasympathetic paragangliomas are not,[1,3] dichotomizing tumour functionality into bivariate categories could be an oversimplification. PPGLs likely exhibit a spectrum of biological activity ultimately affecting clinical presentation, as governed by secretory profile and intercurrent haemodynamic stressors.

We herein discuss the cardiovascular physiology underlying PPGL presentations that will help guide preoperative management.

The spectrum of catecholamine secretion

PPGL secretory profile

The secretory profile of PPGLs varies between tumours and relates to differences in tumour enzymatic machinery and location [Fig. 1]. Adrenalin secretion is usually confined to phaeochromocytomas, whereas paragangliomas have predominant/exclusive secretion of noradrenalin.[5] The adrenergic phenotype of phaeochromocytomas arises from its proximity to adrenal glucocorticoids, which induce phenylethanolamine N-methyltransferase synthesis, the enzyme that converts noradrenalin to adrenalin.[6] Certain PPGLs can secrete dopamine, sometimes in isolation.[7] Tumoural deficiency of dopamine-β-hydroxylase diverts conversion of dopamine away from noradrenalin to 3-methoxytyramine by catechol-O-methyltransferase,[8] thereby elevating blood 3-methoxytyramine concentration, which forms the basis for quantifying this metabolite in the diagnosis of exclusively dopamine-secreting PPGLs.

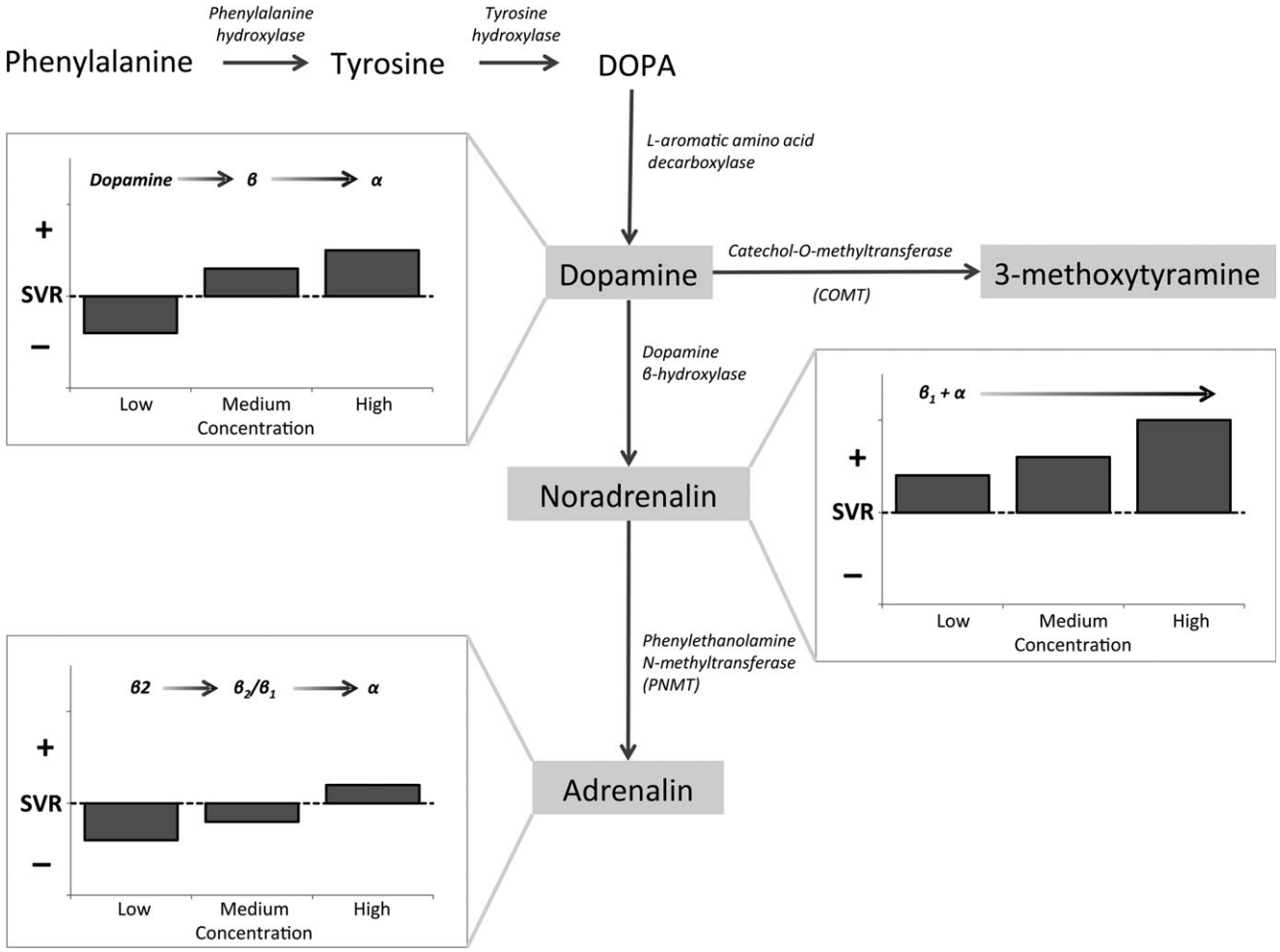

Fig. 1 Catecholamine synthetic pathway and physiology. Dopamine, noradrenalin and adrenalin exert dose-dependent effects on systemic vascular resistance (SVR) as governed by affinity to dopamine, β- and α-adreno-receptors, as shown schematically at low, medium and high circulating concentrations.

PPGL clinical phenotype

Clinical phenotype is dictated by secretory profile and can be explained by differential actions of noradrenalin, adrenalin and dopamine on alpha-adrenergic, beta-adrenergic and dopamine receptors [Fig. 1]. Noradrenalin primarily acts on alpha-1, alpha-2 and beta-1 receptors. Thus, patients with tumours secreting high concentrations of noradrenalin typically present with sustained hypertension.[9] In contrast, adrenalin mostly stimulates beta-1 and beta-2 receptors. Patients with predominantly adrenalin-secreting tumours instead present with paroxysmal hypertension attributed to episodic catecholamine release and beta-2 receptor-mediated vasodilatation in skeletal muscle.[9] On the other hand, haemodynamic effects of dopamine are dose dependent. At physiological levels, dopamine acts mainly on dopamine receptors, causing renal artery dilatation and negative cardiac inotropic action. As plasma concentration rises (such as in the case of dopamine-producing tumours), dopamine can stimulate alpha- and beta-adrenergic receptors, resulting in variable degrees of hypertension and tachycardia.[9] As a result, patients with exclusively dopamine-secreting PPGLs may exhibit labile blood pressure (BP), varying from normotension to postural hypotension and hypertension.[10]

At the other end of the spectrum are 'silent' PPGLs: tumours that are considered biochemically inactive. Their true prevalence cannot be determined as some may be undiagnosed, exclusively dopamine-secreting tumours where 3-methoxytyramine has not been measured.[7] Indeed, parasympathetic head and neck paragangliomas were once thought to be hormonally inactive, but it is now clear that 30% secrete dopamine (and 5% noradrenalin).[11] Alternatively, some biochemically silent tumours, while 'nonsecretory' in the unstimulated state, harbour significant intratumoural catecholamine reserve that may be released when provoked pharmacologically.[12] This phenomenon could potentially underpin the occurrence of catastrophic haemodynamic fluctuations during anaesthetic stress and/or surgical manipulation.

Taken together, the risk of hypertensive crisis conceivably exists for all PPGLs in a spectrum dependent on catecholamine secretory characteristics: highest in overt noradrenalin- and adrenalin-producing PPGLs, followed by exclusively dopamine-secreting tumours, and while potentially lowest in biochemically

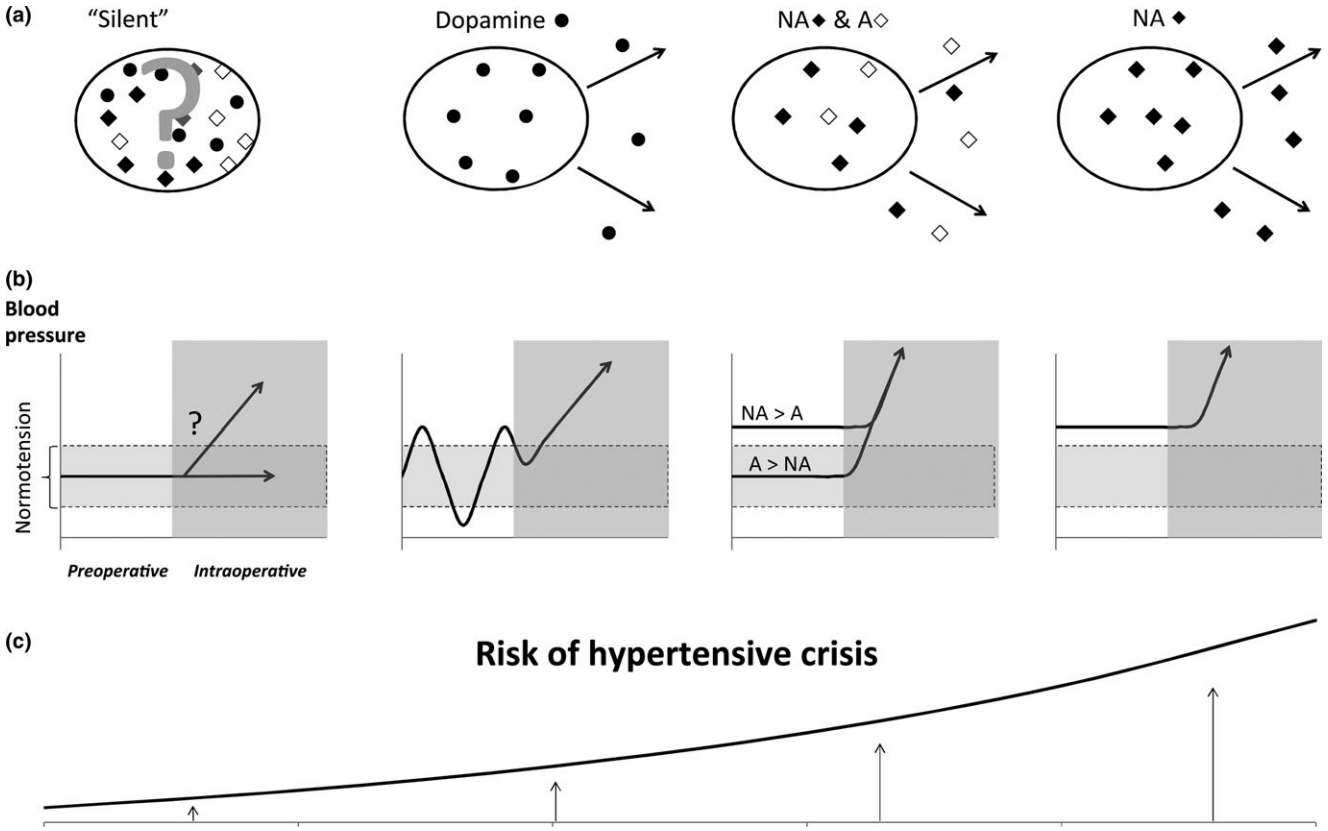

Fig. 2 Relationship between hypertensive crisis risk and catecholamine profile. Schematic diagram depicting interactions between tumour secretory profiles ('silent', exclusively dopamine, mixed noradrenaline (NA)/adrenaline (A) or predominantly NA secreting) (a), their corresponding pre- and intraoperative blood pressure phenotypes (b) and subsequent risk of intraoperative hypertensive crisis (c). Based on actions of dopamine, NA and A on systemic vascular resistance as summarized in Fig. 1, patients with predominant NA-secreting tumours present with persistent hypertension while those with mixed NA/A-secreting tumours may be normotensive as determined by relative NA/A abundance. Exclusively, dopamine-secreting tumours are associated with labile blood pressure. All tumours carry inherent risk of hypertensive crisis, including 'silent' tumours as a result of intraoperative intratumoural catecholamine release.

covert PPGLs, the risk may not be completely absent [Fig. 2]. Thus, the secretory profile of PPGL provides helpful clues when weighing the pros and cons of preoperative alpha-blockade for individual patients.

Preoperative alpha-blockade in phaeochromocytoma and paraganglioma

Traditionally, the long-acting, irreversible, nonselective alpha-blocker phenoxybenzamine is initiated 7-14 days preoperatively to achieve a seated BP <130/80 mmHg, with standing systolic BP ≥90 mmHg.[1] As phenoxybenzamine may contribute to hypotension postadrenalectomy,[2] short-acting alpha-blockers have been advocated as alternatives. The selective alpha-1 receptor blocker doxazosin is associated with less preoperative orthostatic hypotension and shorter postoperative hypotension duration compared with phenoxybenzamine, although intraoperative systolic BP is better controlled with the latter.[13] Prazosin may be associated with even less postoperative hypotension risk given its shorter duration of action.

In practice, the optimal type, dose and/or duration of alpha-blockade should be personalized to individual PPGL phenotype, with preference towards shorter acting alpha-blockers and shorter preoperative blockade duration for tumours not presenting with persistent hypertension, as discussed in each of the following scenarios.

Is preoperative alpha-blockade necessary in hypertensive PPGLs?

Mortality rates for PPGL resection have decreased from 35% to 40% in early studies,[14] to nil in recent times.[15] Mortality reduction has been attributed to widespread use of preoperative alpha-blockade.[15] This is supported by Goldstein *et al.*'s[16] series of 108 phaeochromocytomas between 1950 and 1988, showing 69% of patients who did not receive alpha-blockade had a complicated surgical course compared with 3% of those treated with phenoxybenzamine. A more recent single-centre review of 88 consecutive PPGL resection from 1992 to 2013 found that higher preoperative phenoxybenzamine dose predicted improved intraoperative haemodynamic stability.[15]

However, some authors report successful PPGL resection without alpha-blockade.[17] In the absence of placebo-controlled trials of alpha-blockade, it remains possible that advances in

preoperative localization imaging and surgical/anaesthetic techniques could have contributed to the decreased mortality associated with surgery in the modern era. Nonetheless, as the risks of alpha-blockers are minimal and not all PPGL surgeries are undertaken in specialized adrenal centres, alpha-blockade should be universal for hypertensive PPGLs aiming for the recommended preoperative BP goal.[1]

Is preoperative alpha-blockade necessary in dopamine-secreting PPGL?

No studies have examined the perioperative management of patients with exclusively dopamine-secreting PPGL, and current guidelines do not specifically address this population.[1] In one series of 14 predominantly/exclusively dopamine-secreting PPGLs, 60% developed perioperative haemodynamic disturbance.[10] Cardiovascular collapse has been reported after alpha-blockade, attributed to the unopposed hypotensive action of dopamine when pressor catecholamines are blocked.[10] This has led to some authors recommending against alpha-blockade in patients with purely dopamine-secreting PPGLs.[10,18] However, severe intraoperative hypertension has also been reported in patients who did not receive alpha-blockade. [10]

Considering the potential for serious and irreversible neurological and cardiovascular damage from drug resistant, uncontrolled intraoperative hypertension, and the fact that hypotension is generally more treatment responsive, cautious titration of a shorter acting alpha-blocker for a shorter preoperative duration may be appropriate in patients with dopamine-secreting PPGL. It is important to recognize that the traditional BP goal may not be tolerated due to orthostatic hypotension, thus necessitating slow dosage increments and careful monitoring. Calcium channel blockers and metyrosine (discussed below) may also be alternative premedication choices.

Is preoperative alpha-blockade necessary in 'normotensive phaeochromocytoma'?

Normotensive phaeochromocytoma refers to secretory tumours not manifesting spontaneous hypertension or haemodynamic instability. Normotensive phaeochromocytoma accounts for up to 40% of phaeochromocytoma detected incidentally on imaging.[19] These tumours have decreased expression of multiple genes involved in key processes of catecholamine production.[19] Patients with normotensive phaeochromocytomas have lower levels of normetanephrine and metanephrine compared with those with hypertensive phaeochromocytomas.

Trials examining the role of alpha-blockade in normotensive PPGLs are scarce. One study did not show any benefit of alpha-blockade.[20] However, another comparing 10 patients with normotensive phaeochromocytomas to 16 patients with hormonally inactive adrenal incidentalomas found that, despite similar preoperative BP, patients with normotensive phaeochromocytomas had significantly higher rates of intraoperative haemodynamic instability (including more frequent and severe hypertensive episodes); 100% of normotensive phaeochromocytomas required intraoperative antihypertensives administration compared to 5% in the incidentaloma group.[21]

Taken together, patients with normotensive secretory PPGL should receive alpha-blockade because of potential catastrophic effects of intraoperative hypertension, as recommended by the Endocrine Society.[1]

Is preoperative alpha-blockade necessary in biochemically silent 'phaeochromocytoma'?

Distinction should be made between clinically silent (i.e. normotensive) but biologically active (catecholamine-secreting) PPGLs from truly biochemically silent tumours (non-catecholamine-secreting), as they carry different intraoperative hypertensive risks. Although uncommon, intraoperative malignant hypertension has been reported in patients with biochemically silent tumours not receiving alpha-blockade.[22,23] Mechanisms leading to intraoperative haemodynamic crises from such hormonally silent tumours remain speculative. Some could be a result of undiagnosed dopamine secretion not appreciated preoperatively (as discussed above), while others potentially from uncontrolled intratumoural catecholamine discharge. Calcium channel blockers may be favoured in this setting due to lower hypotension risk while providing protection against intraoperative hypertension (discussed below). Some clinicians may choose not to premedicate, but this should be a collaborative decision with surgeon and anaesthetist, taking into account individual patient cardiovascular status, comorbidities and perceived intraoperative risks.

Are there alternatives to preoperative alpha-blockade?

Patients with 'atypical' PPGL may have a lower risk of hypertension and higher risk of medication-related hypotension; thus, alternative regimes with lesser pre- and postoperative hypotension risks may be considered.

Calcium channel blockers have been suggested as an alternative preoperative medication because of superior side-effect profile.[24] Compared with phenoxybenzamine, some,[25] but not all,[24] patients treated with nicardipine had lower incidence and duration of postoperative hypotension and required less intravenous fluid administration; however, this was offset by higher incidence and duration of severe intraoperative hypertension.[25]

Metyrosine is a tyrosine hydroxylase inhibitor which blocks the rate-limiting step of catecholamine synthesis.[26] The combination of metyrosine and phenoxybenzamine results in improved intraoperative BP control, reduced cardiovascular complications and decreased need for antihypertensive medications or pressors during surgery, compared with phenoxybenzamine alone.[27,28] There have been no studies of metyrosine monotherapy in PPGL resection, although some successful cases have been reported.[26] As metyrosine does not cause hypotension, its use has been advocated in 'atypical' PPGL, such as

those with exclusive dopamine secretion.[10] However, metyrosine is not available in all countries and its use may be limited by side effects, most commonly sedation, which occurs in the majority of patients.[26]

Collectively, alpha-blockade remains the mainstay PPGL preoperative preparation. 'Atypical' PPGLs with potentially lesser intraoperative hypertensive risk and greater concerns over treatment-related hypotension may benefit from agents such as calcium channel blockers. Treatment choice should be individualized and evaluated in multidisciplinary team discussion, taking into account secretory profile, patient comorbidities and surgical approach, and to ensure the availability of rapid-acting, intravenous, antihypertensive medication intraoperatively.

Conclusions

The potential for adverse effects of alpha-blockade have led some clinicians to question its routine preoperative use,[2] especially in 'atypical' PPGLs presenting with normotension or postural hypotension. We have provided a critical appraisal of catecholamine physiology, highlighting the inherent danger of catecholamine hypertensive crisis intraoperatively. We concur with international guidelines that recommend alpha-adrenergic receptor blockers preoperatively.[1] Although the risks may vary according to catecholamine secretory profile, and treatment regime should be individualized, we believe hypertensive risk is universal and the potential benefit of alpha-blockers in reducing the catastrophic effects of severe intraoperative hypertension outweigh the risk of medication-related side effects in most circumstances.

Acknowledgements

Paul Lee was supported by an Australian National Health Medical Research Council (NHMRC) Career Development Fellowship (APP1111944).

Conflict of interest

None of the authors have any conflict of interests to disclose.

References

1 Lenders, J.W., Duh, Q.Y., Eisenhofer, G. *et al.* (2014) Pheochromocytoma and paraganglioma: an endocrine society clinical practice guideline. *Journal of Clinical Endocrinology and Metabolism*, **99**, 1915–1942.
2 Lentschener, C., Gaujoux, S., Tesniere, A. *et al.* (2011) Point of controversy: perioperative care of patients undergoing pheochromocytoma removal-time for a reappraisal? *European Journal of Endocrinology*, **165**, 365–373.
3 Corssmit, E.P. & Romijn, J.A. (2014) Clinical management of paragangliomas. *European Journal of Endocrinology*, **171**, R231–R243.
4 Luiz, H.V., Tanchee, M.J., Pavlatou, M.G. *et al.* (2016) Are patients with hormonally functional phaeochromocytoma and paraganglioma initially receiving a proper adrenoceptor blockade? A retrospective cohort study. *Clinical Endocrinology*, **85**, 62–69.
5 Eisenhofer, G., Lenders, J.W., Goldstein, D.S. *et al.* (2005) Pheochromocytoma catecholamine phenotypes and prediction of tumor size and location by use of plasma free metanephrines. *Clinical Chemistry*, **51**, 735–744.
6 Funahashi, H., Imai, T., Tanaka, Y. *et al.* (1994) Discrepancy between PNMT presence and relative lack of adrenaline production in extra-adrenal pheochromocytoma. *Journal of Surgical Oncology*, **57**, 196–200.
7 Eisenhofer, G., Goldstein, D.S., Sullivan, P. *et al.* (2005) Biochemical and clinical manifestations of dopamine-producing paragangliomas: utility of plasma methoxytyramine. *Journal of Clinical Endocrinology and Metabolism*, **90**, 2068–2075.
8 Feldman, J.M., Blalock, J.A., Zern, R.T. *et al.* (1979) Deficiency of dopamine-beta-hydroxylase. A new mechanism for normotensive pheochromocytomas. *American Journal of Clinical Pathology*, **72**, 175–185.
9 Zuber, S.M., Kantorovich, V. & Pacak, K. (2011) Hypertension in pheochromocytoma: characteristics and treatment. *Endocrinology and Metabolism Clinics of North America*, **40**, 295–311. vii.
10 Foo, S.H., Chan, S.P., Ananda, V. *et al.* (2010) Dopamine-secreting phaeochromocytomas and paragangliomas: clinical features and management. *Singapore Medical Journal*, **51**, e89–e93.
11 van Duinen, N., Corssmit, E.P., de Jong, W.H. *et al.* (2013) Plasma levels of free metanephrines and 3-methoxytyramine indicate a higher number of biochemically active HNPGL than 24-h urinary excretion rates of catecholamines and metabolites. *European Journal of Endocrinology*, **169**, 377–382.
12 Yoshida, K., Sasaguri, M., Kinoshita, A. *et al.* (1990) A case of a clinically "silent" pheochromocytoma. *Japanese Journal of Medicine*, **29**, 27–31.
13 van der Zee, P.A. & de Boer, A. (2014) Pheochromocytoma: a review on preoperative treatment with phenoxybenzamine or doxazosin. *Netherlands Journal of Medicine*, **72**, 190–201.
14 Apgar, V. & Papper, E.M. (1951) Pheochromocytoma. Anesthetic management during surgical treatment. *AMA Archives of Surgery*, **62**, 634–648.
15 Livingstone, M., Duttchen, K., Thompson, J. *et al.* (2015) Hemodynamic stability during pheochromocytoma resection: lessons learned over the last two decades. *Annals of Surgical Oncology*, **22**, 4175–4180.
16 Goldstein, R.E., O'Neill, J.A. Jr, Holcomb, G.W. 3rd *et al.* (1999) Clinical experience over 48 years with pheochromocytoma. *Annals of Surgery*, **229**, 755–764; discussion 764–756.
17 Boutros, A.R., Bravo, E.L., Zanettin, G. *et al.* (1990) Perioperative management of 63 patients with pheochromocytoma. *Cleveland Clinic Journal of Medicine*, **57**, 613–617.
18 Poirier, E., Thauvette, D. & Hogue, J.C. (2013) Management of exclusively dopamine-secreting abdominal pheochromocytomas. *Journal of the American College of Surgeons*, **216**, 340–346.
19 Haissaguerre, M., Courel, M., Caron, P. *et al.* (2013) Normotensive incidentally discovered pheochromocytomas display specific biochemical, cellular, and molecular characteristics. *Journal of Clinical Endocrinology and Metabolism*, **98**, 4346–4354.
20 Shao, Y., Chen, R., Shen, Z.J. *et al.* (2011) Preoperative alpha blockade for normotensive pheochromocytoma: is it necessary? *Journal of Hypertension*, **29**, 2429–2432.
21 Lafont, M., Fagour, C., Haissaguerre, M. *et al.* (2015) Perioperative hemodynamic instability in normotensive patients with

incidentally discovered pheochromocytomas. *Journal of Clinical Endocrinology and Metabolism*, **100**, 417–421.
22 Song, G., Joe, B.N., Yeh, B.M. *et al.* (2011) Risk of catecholamine crisis in patients undergoing resection of unsuspected pheochromocytoma. *International Brazilian Journal of Urology*, **37**, 35–40; discussion 40-31.
23 Kota, S.K., Kota, S.K., Panda, S. *et al.* (2012) Pheochromocytoma: an uncommon presentation of an asymptomatic and biochemically silent adrenal incidentaloma. *The Malaysian Journal of Medical Sciences: MJMS*, **19**, 86–91.
24 Siddiqi, H.K., Yang, H.Y., Laird, A.M. *et al.* (2012) Utility of oral nicardipine and magnesium sulfate infusion during preparation and resection of pheochromocytomas. *Surgery*, **152**, 1027–1036.
25 Brunaud, L., Boutami, M., Nguyen-Thi, P.L. *et al.* (2014) Both preoperative alpha and calcium channel blockade impact intraoperative hemodynamic stability similarly in the management of pheochromocytoma. *Surgery*, **156**, 1410–1417; discussion 1417–1418.
26 Brogden, R.N., Heel, R.C., Speight, T.M. *et al.* (1981) alpha-Methyl-p-tyrosine: a review of its pharmacology and clinical use. *Drugs*, **21**, 81–89.
27 Steinsapir, J., Carr, A.A., Prisant, L.M. *et al.* (1997) Metyrosine and pheochromocytoma. *Archives of Internal Medicine*, **157**, 901–906.
28 Wachtel, H., Kennedy, E.H., Zaheer, S. *et al.* (2015) Preoperative metyrosine improves cardiovascular outcomes for patients undergoing surgery for pheochromocytoma and paraganglioma. *Annals of Surgical Oncology*, **22**(Suppl 3), S646–S654.