Risk Factors for Hemodynamic Instability during Surgery for Pheochromocytoma

H. Bruynzeel, R. A. Feelders, T. H. N. Groenland, A. H. van den Meiracker, C. H. J. van Eijck, J. F. Lange, W. W. de Herder, and G. Kazemier

Department of Surgery (H.B., C.H.J.v.E., J.F.L., G.K.); Department of Internal Medicine, Endocrine Section (R.A.F., W.W.d.H.); Department of Anesthesiology (T.H.N.G.); and Department of Internal Medicine, Division of Pharmacology, Metabolic and Vascular Diseases (A.H.v.d.M.), Erasmus Medical Center, 3015 CE Rotterdam, The Netherlands

Background: Surgery on pheochromocytoma carries a risk for hemodynamic (HD) instability. The aim of this study was to identify preoperative risk factors for intraoperative HD instability. In addition, efficacy of pretreatment with the α-adrenergic receptor (α) antagonists phenoxybenzamine (PXB) and doxazosin (DOX) was compared with respect to reduction of intraoperative HD instability.

Methods: Seventy-three patients operated in Erasmus Medical Center between 1995 and 2007 were included. Parameters studied were catecholamine type and concentration, tumor diameter, mean arterial pressure (MAP) before and after (MAP_α) pretreatment with α-antagonist, postural fall in blood pressure (BP) after pretreatment, type of α-blockade, type of operation, and presence of a familial polytumor syndrome. HD instability was assessed by measuring the number and time period MAP was below 60 mm Hg and systolic BP (SBP) was above 160 mm Hg.

Results: A correlation was found between the intraoperative time periods of SBP above 160 mm Hg and plasma norepinephrine levels ($r = 0.23$; $P < 0.05$), tumor diameter ($r = 0.36$; $P < 0.01$), and postural BP fall ($r = 0.30$; $P < 0.05$). MAP at presentation and after α-blockade above 100 mm Hg (BP, 130/85 mm Hg) was related to more and longer episodes with a SBP above 160 mm Hg ($P < 0.01$). Type of operation or α-blockade and presence of a familial polytumor syndrome were not related to intraoperative HD instability. Postoperative MAP was lower in the DOX group than in the PXB group ($P < 0.05$).

Conclusion: Risk factors for HD instability during surgery for pheochromocytoma include a high plasma NE concentration, larger tumor size, more profound postural BP fall after α-blockade, and a MAP above 100 mm Hg (130/85 mm Hg). Efficacy for preventing HD instability was identical for PXB and DOX. (***J Clin Endocrinol Metab* 95: 678–685, 2010**)

Pheochromocytoma is a rare neuroendocrine tumor that produces, stores, and secretes catecholamines. It usually originates from the adrenal medulla but can also develop from chromaffin cells in sympathetic ganglia. Among the hypertensive population, the estimated prevalence is 0.1–0.6% (1, 2). About 70% of pheochromocytomas are sporadic, and about 30% are associated with a familial polytumor syndrome or germ line mutation (3, 4). The classic triad of complaints resulting from uncontrolled release of catecholamines consists of headache, perspiration, and palpitations. Surgical resection, which is the only curative therapy, carries a high risk of evoking a massive release of catecholamines into the circulation during the procedure. Intubation, the creation of pneumoperitoneum, and manipulation of the adrenal gland can all induce catecholamine secretion and consequently hypertensive crises (5, 6). Resection of the tumor resulting in the acute withdrawal of catecholamines can lead to hypotension and shock (7, 8). Before the need for preoperative preparation was appreciated, reported operative mortal-

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Abbreviations: BP, Blood pressure; C, creatinine; D, dopamine; DOX, doxazosin; E, epinephrine; HD, hemodynamic; MAP, mean arterial pressure; MAP_α, MAP after α-blockade; MN, metanephrine; NE, norepinephrine; NMN, normetanephrine; PXB, phenoxybenzamine.

ity was 30–45% (7). In the second half of the last century, improvements in surgical and anesthetic techniques, improved preoperative medical management, and new imaging techniques for accurate preoperative tumor localization have contributed to a decreased mortality of 0 to 2.9% (1, 9). Although no randomized, controlled trials have been performed, preoperative pharmacological treatment is assumed to lower the risk of intraoperative hemodynamic (HD) instability (1, 5, 10–13). Antihypertensive drugs used for this purpose include (non) selective α-adrenergic receptor antagonists, calcium channel blockers, and metyrosine (1, 2, 14–16).

Despite adequate pretreatment, intraoperative HD fluctuations do still occur (12, 16). This study aimed to identify possible risk factors for HD instability during surgery of pheochromocytomas and to compare the efficacy of different types of α-adrenergic blockade to prevent this.

Patients and Methods

Patients with pheochromocytoma and paraganglioma operated for this condition in the Erasmus Medical Center between 1995 and 2007 were analyzed. Pregnant women were excluded. The diagnosis was based on the combination of clinical presentation, elevated plasma catecholamine levels [norepinephrine (NE), epinephrine (E), dopamine (D)] and elevated 24-h urinary (nor)metanephrine excretion [expressed in (nor)metanephrine/creatinine ratio (N)MN:C], the presence of an (extra) adrenal mass, and finally confirmation by pathological examination. Plasma catecholamines were always sampled with the patient in supine position, at least 30 min after insertion of an iv line. The localization of the tumor was visualized by computed tomography, magnetic resonance imaging, or both and, if necessary, by ^{131}I-meta-iodobenzyl guanidine scanning. The choice to operate via a laparoscopic or an open approach was based on the maximal tumor diameter. In case of a maximal diameter greater than 6 cm or in case of suspicion of a malignant tumor, an open procedure was performed.

Between 1995 and 2003, patients were pretreated with the nonselective and noncompetitive α-adrenergic receptor antagonist phenoxybenzamine (PXB) followed by β-adrenergic receptor blockade with propranolol. PXB exerts its maximal effect 4–6 h after administration and has a pharmacological half-life of 24 h. Two days before operation, volume was expanded by infusion of NaCl 0.9%, 2 liters/d.

Between 2003 and 2007, patients were pretreated with the selective and competitive α_1-adrenergic receptor antagonist doxazosin (DOX) followed by β-adrenergic receptor blockade with propranolol. DOX exerts its maximal effect 2–6 h after administration and has a pharmacological half-life of 16–30 h. Volume expansion was identical in the DOX and PXB groups. Both α-blockers were started at least 2 wk before operation to achieve blood pressure (BP) normalization and, if possible, some postural fall in BP. Adequate pretreatment was defined by a target BP of 130/85 mm Hg (13, 17). To correlate preoperative systolic BP (SBP) and diastolic BP (DBP) values with parameters of intraoperative hypertension, mean arterial pressure (MAP) values were used (*i.e.* the sum of the SBP and two times the DBP, total divided by 3). The calculated MAP of the target BP value of 130/85 mm Hg is 100 mm Hg, and this value was also assessed as cutoff value for adequate pretreatment in this study. The MAP values assessed at the first visit at the outpatient clinic, after α-adrenergic receptor blockade at the day before operation (MAP_α) and at the day after operation were used for analysis.

Intraoperatively systolic and diastolic arterial BP were invasively measured, monitored, and recorded every 5 min and also when marked changes were observed. Operating time is the time measured from the moment of intubation until the incision was closed. To treat undesirable elevations in BP or heart rate, iv doses of nitrates, phentolamine, ebrantil, $MgSO_4$ or β-receptor blocking agents were administered. After tumor removal, crystalloids or colloids were infused in case of hypotension. In case of persistent hypotension, NE was given, and in some patients phenylephrin or ephedrine.

Intraoperative fluctuations in BP and the amount of intraoperatively administered drugs and fluids were evaluated. Fluctuations in intraoperative BP were measured by scoring the number and time periods of episodes that the SBP was higher than 160 mm Hg, chosen as cutoff value for intraoperative hypertension.

In addition, the number of episodes that the MAP was below 60 mm Hg, chosen as cutoff value for hypotensive complications, was scored.

Analysis

The relation between preoperative and intraoperative BP control and the two different α-adrenergic receptor antagonists was analyzed. Furthermore, the relationship between the postural BP fall, defined by the difference between the BP in supine and upright position, after α-adrenergic receptor blockade was correlated to the intraoperative HD fluctuations.

In addition, patients' demographics, plasma and urinary catecholamine levels, and maximal diameter of the tumor were correlated with the intraoperative BP fluctuations. Finally, sporadic or familial tumors and open or laparoscopic approaches were compared to identify possible risk factors for HD instability.

All data were analyzed with SPSS version 11.5 (SPSS Inc., Chicago, IL). Mann-Whitney test for nonparametric variables was used for comparisons between groups. Spearman's rho bivariate correlation test was used to correlate variables. P values <0.05 were considered to indicate a significant difference. Multivariate linear regression analysis was used to adjust for confounding factors.

Results

Patients

In the period between 1995 and 2007, 73 patients were operated for a pheochromocytoma. Demographic data are listed in Table 1. Body weight, age, and operating time were not related to HD instability. None of the patients experienced long-term complications resulting from perioperative HD instability.

Malignant or benign tumor

Eight tumors were malignant. There was no difference in HD instability between malignant and benign tumors.

TABLE 1. Patient characteristics and pre-, intra-, and postoperative BP values

Patient characteristics	Median (range)
Total no.	73
No. of females	43
Age (yr)	47 (16–85)
Plasma values	
NE (pg/ml)	1,648.0 (36.5–250,378.0)
E (pg/ml)	138.0 (1.0–35,145.0)
D (pg/ml)	15.75 (1.0–500.0)
24-h urinary values	
MN μmol/mmol creat (% >150)	582 (24–11,310) (66%)
NMN μmol/mmol creat (% >400)	1,572 (145–12,179) (90%)
Producing both	53%
Tumor characteristics	
Major axis of tumor (cm)	4.2 (1.0–18.0)
Side	
Left-right	37–45%
Bilateral	8%
Extraadrenal	10%
MAP (mm Hg)	
At presentation	107 (70–180)
After α blockade	96 (67–137)
Postoperatively	84 (60–133)
SBP	
At presentation	140 (90–240)
After α blockade	130 (95–183)
Postoperatively	122 (71–180)
DBP	
At presentation	85 (55–152)
After α blockade	79 (48–113)
Postoperatively	67 (40–110)
Hemodynamic fluctuations	
MAP <60 mm Hg (min)	10 (0–150)
SBP >160 mm Hg	
Episodes	1 (0–9)
Minutes	10 (0–165)

MN μmol/mmol creat, MN:C ratio; and NMN μmol/mmol creat, NMN:C ratio as measured in 24-h urine.

All malignant tumors were removed by an open approach, two of which converted from a laparoscopic approach. Malignant tumors produced overall less concentrations of E (median, 32.0 pg/ml, and range, 9.0–476 pg/ml *vs.* 159 pg/ml and 1.0–35,145 pg/ml; $P < 0.05$). No significant difference was seen in intraoperative drug administration between both groups.

Catecholamine concentrations

The median plasma catecholamine and urinary MN and NMN concentrations are shown in Table 1. In 71% of the patients, the pheochromocytoma produced NE, in 59% only E was produced, and in 20% both were produced. NE and E were both correlated with MAP at presentation ($r = 0.57$, $P < 0.01$; and $r = 0.31$, $P < 0.05$). NE was correlated with both SBP and DBP at presentation ($r = 0.53$, $P < 0.01$; and $r = 0.57$, $P < 0.01$, respectively). E was only correlated with SBP, not with DBP at presentation ($r = 0.36$; $P < 0.05$ and $P = 0.06$, respectively). High levels of E were positively correlated with the MAP after α-blockade (MAP_α), SBP_α and DBP_α and the postoperative MAP (respectively, $r = 0.25$, $P < 0.05$; $r = 0.29$, $P < 0.05$; $r = 0.25$, $P < 0.05$; and $r = 0.40$, $P < 0.01$).

Plasma NE concentrations correlated with the duration of episodes with SBP above 160 mm Hg ($r = 0.27$; $P < 0.05$), also after adjustment for tumor size, tumor pathology (benign or malignant), and operation procedure (*i.e.* open or laparoscopic). A trend was found between the urinary NMN:C ratio and the duration of episodes with SBP above 160 mm Hg ($r = 0.27$; $P = 0.07$). In three patients, no medication at all was administered intraoperatively; 13 patients needed no antihypertensive drugs, and nine no medication to restore the BP after tumor removal. With respect to intraoperative applied medication, NE ($n = 36$), esmolol ($n = 25$), and phentolamine ($n = 28$) were most regularly administered, but no correlation was found between the dosages of these compounds and the preoperative plasma catecholamine or urinary NMN concentrations. The dosage of phenylephrine administered was positively correlated to the NE plasma concentration ($r = 0.83$; $P < 0.01$; $n = 15$). In addition, a positive relation was found between the dosage of nitroglycerine and the urinary NMN excretion ($r = 0.53$; $P < 0.05$; $n = 24$).

Tumor diameter

Median tumor diameter was 4.2 cm (range, 1–18 cm). Tumor diameter was correlated with plasma NE concentration and the urinary MN:C and NMN:C ratios ($r = 0.37$, $P < 0.05$; $r = 0.33$, $P < 0.05$; and $r = 0.62$, $P < 0.001$, respectively). In addition, tumor diameter correlated with the number and duration of episodes SBP rose above 160 mm Hg ($r = 0.28$, $P < 0.05$; and $r = 0.36$, $P < 0.01$, respectively), also after adjustment for plasma and urinary catecholamine concentrations, tumor pathology (benign or malignant), and operation procedure (*i.e.* open or laparoscopic). A tumor diameter greater than 4 cm was accompanied by a significantly increased duration of hypertensive episodes compared with a tumor diameter of 4 cm or less (20.3 ± 5.1 *vs.* 9.3 ± 2.0 min; $P < 0.05$).

BP

Pre-, intra-, and postoperative BP values are shown in Table 1. At presentation, 73% of patients had a BP above 130/85 mm Hg, and 63% of the patients had a MAP above 100 mm Hg. The general goal was to achieve a BP of 130/85 mm Hg or less after α-adrenergic receptor blockade, corresponding with a MAP of 100 mm Hg or less. After α-adrenergic receptor blockade, 48 of 73 patients (66%) were adequately pretreated with a MAP of 100 mm Hg or less, with 39 (81%) of these 48 patients having a BP

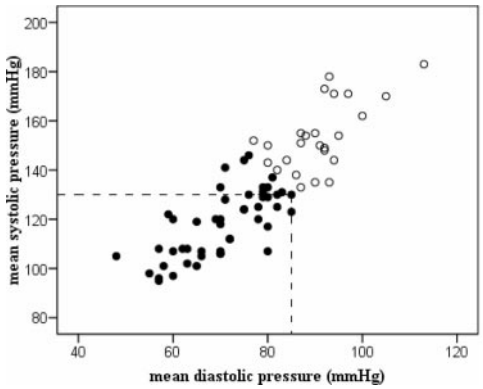

FIG. 1. Individual SBP and DBP values after α blockade in correlation to the MAP after α blockade. The *dashed lines* indicate SBP 130 mm Hg and DBP 85 mm Hg. The patients adequately pretreated according to MAP of 100 mm Hg or less are indicated by the *filled dots*.

of 130/85 mm Hg or less (Fig. 1). 25 of 73 patients (34%) still had a MAP above 100 mm Hg after α-adrenergic receptor blockade (MAP_α).

The number of times the intraoperative SBP was above 160 mm Hg correlated with MAP at presentation ($r = 0.40$; $P < 0.001$) and with MAP_α ($r = 0.31$; $P < 0.01$). In addition, the duration of episodes with a SBP above 160 mm Hg correlated with MAP at presentation and MAP_α ($r = 0.38$, $P < 0.01$; and $r = 0.29$, $P < 0.01$).

Compared with the patients with adequate pretreatment with a MAP_α of 100 mm Hg or less (n = 48), the patients with a MAP_α above 100 mm Hg (n = 25) experienced more and longer intraoperative episodes of SBP above 160 mm Hg (MAP_α <100 mm Hg, 0.5 times (0–5 times) and 2.5 min (0–45 min); and MAP_α >100 mm Hg, 2 times (0–9) and 20 min (0–165 min), both $P < 0.01$; Fig. 2), also after adjustment for tumor size, tumor pathology (benign or malignant), and operation procedure (*i.e.* open or laparoscopic).

There was no difference in the number of hypotensive episodes between the groups with a MAP_α below 100 mm Hg and the group with a MAP_α above 100 mm Hg (both were 10.0). Intraoperative infused fluids, use of vasoactive drugs, and postoperatively administered fluids were not related to the BP after α-blockade.

α-Adrenergic receptor blockade

Between 1995 and 2003, 31 patients received PXB. In the time period from 2003 until 2007, 42 patients received DOX (Table 2). In the PXB group, all but six patients and in the DOX group all but five patients received propranolol treatment. The maximal tumor diameter was not significantly different between the two groups. Plasma and urinary catecholamine concentrations, BP values, and intraoperative measurements are shown in Table 2. BP at presentation was higher in the DOX group, whereas BP after α-blockade was comparable between the two groups. Adequate pretreatment BP values were achieved in 55% of patients in the PXB group and in 53% of patients in the DOX group. There was no significant difference in BP fluctuations intraoperatively with respect to both hypertensive and hypotensive episodes. Postoperatively, the MAP in the PXB group was significantly higher than in the DOX group ($P < 0.01$). No relation was found between the PXB or DOX dosage and intraoperative BP fluctuations or postoperative hypotension. The doses of esmolol that were administered in 25 patients were significantly higher in the PXB group compared with the DOX group (314.5 mg, 25.0–5520; *vs.* 95.0 mg, 0.06–2500 mg; $P < 0.05$). However, the dosages of other vasoactive drugs as phenylephrine (n = 15), nitroglycerine (n = 24), NE (n = 36), and phentolamine (n = 28) did not differ between both groups. Intraoperatively, a comparable amount of fluids was administered.

With respect to the patients who did receive a β-blocker concomitantly with an α-blocker, there were no significant differences in intra- or postoperative HD instability compared with the group without β-blockade.

Postural fall in BP

In a subgroup of patients pretreated with DOX (n = 34) and PXB (n = 8), the presence and predictive value of the postural fall in BP after α-adrenergic receptor blockade could be evaluated. The median difference in MAP between the supine and upright positions was 7.7 mm Hg (range, −8 to 27 mm Hg). Both the plasma NE concentration and the tumor diameter correlated with the postural fall in MAP ($r = 0.37$, $P < 0.05$; and $r = 0.30$, $P = 0.05$; Fig. 3). The frequency and duration of episodes in which the SBP was above 160 mm Hg increased with the severity of postural fall in BP, also after adjustment for plasma NE levels and tumor size. A postural fall of at least

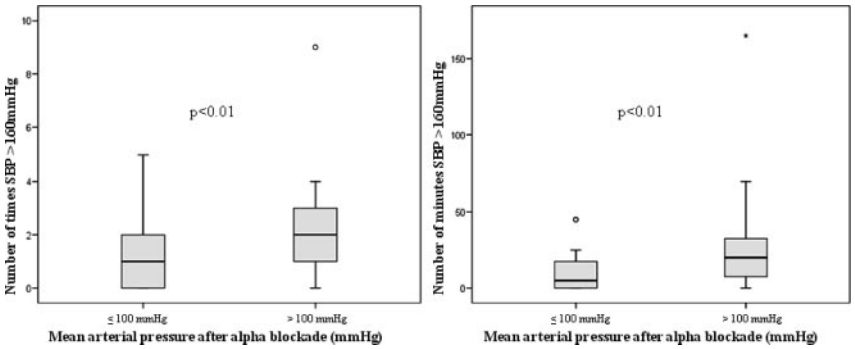

FIG. 2. Box-plots showing number of times (*left*) and duration (*right*) of episodes when SBP is above 160 mm Hg in relation to the level of MAP after α-adrenergic receptor blockade.

TABLE 2. Characteristics of patients in the PXB and DOX groups

Characteristics	PXB	DOX	*P*
n	31	42	
Age (yr)	59 (17–85)	46 (16–79)	0.09
Daily dose α (mg)	60 (20–270)	24 (8–56)	
Plasma sample			
NE (pg/ml)	792 (37–9,000)	2,350 (193–250,378)	<0.05
E (pg/ml)	170 (7–11,073)	120 (1–35,145)	0.42
D (pg/ml)	14 (1–500)	20 (1–189)	0.50
24-h urinary values			
MN μmol/mmol creat (% >150)	1,510 (44–11,310) (93%)	279 (24–4,667) (57%)	<0.05
NMN μmol/mmol creat (% >400)	979 (155–12,179) (93%)	1,668 (145–10,949) (89%)	0.82
Producing both	71% (10)	46% (17)	
MAP (mm Hg)			
At presentation (% >100)	100 (70–178) (48%)	108 (80–180) (71%)	<0.05
After α blockade (% >100)	98 (67–137) (39%)	95 (70–127) (33%)	0.53
Postoperatively	90 (60–133)	81 (64–127)	<0.01
SBP			
At presentation	140 (90–230)	150 (105–240)	0.21
After α blockade	130 (97–183)	129 (95–178)	0.85
Postoperatively	125 (90–180)	120 (71–170)	0.06
DBP			
At presentation	80 (55–152)	90 (64–150)	<0.05
After α blockade	80 (48–113)	76 (55–105)	0.21
Postoperatively	72 (45–110)	61 (40–106)	0.84
Operational approach (%)			
Open	61	48	
Laparoscopic (no. converted)	39 (6)	52 (10)	
HD fluctuations			
MAP <60 mm Hg (min)	5 (0–150)	10 (0–85)	0.16
SBP >160 mm Hg			
Episodes	1 (0–9)	1 (0–4)	0.25
Minutes	3 (0–165)	13 (0–70)	0.30

Data are expressed as median (range). MN μmol/mmol creat, MN:C ratio; and NMN μmol/mmol creat, NMN:C ratio as measured in-24 h urine.

10 mm Hg was associated with a higher number (2.0 ± 0.4 *vs.* 1.1 ± 0.2; $P < 0.05$) and increased duration (20.0 ± 4.9 *vs.* 10.8 ± 2.1 min; $P = 0.05$) of hypertensive episodes compared with a postural fall of less than 10 mm Hg.

Open *vs.* laparoscopic procedure

In 28 cases, an open procedure was performed, and in 45 cases a laparoscopic procedure was performed to remove the tumor. In six cases, a laparoscopic procedure was converted to an open procedure. The operating time for the two surgical approaches was comparable. No differences were seen in HD instability or intraoperative drug administration between the laparoscopic and open or converted procedures.

Sporadic *vs.* hereditary tumors

In 58 patients (79%), the pheochromocytoma was sporadic, whereas in 15 patients (21%) the tumor was part of a familial endocrine tumor syndrome, *i.e.* von Hippel-Lindau syndrome (n = 3), neurofibromatosis type 1 (n = 6), multiple endocrine neoplasia type 2 (n = 5), succinyldehydrogenase-B mutation (n = 1) (Table 3). Mean age of patients with a sporadic tumor was higher. The MAP at presentation in both groups was comparable; however, after α-blockade the sporadic group showed a significantly higher MAP, as well as a significantly higher SBP and DBP (Table 3). Plasma NE concentration was higher in the sporadic group, but no difference was present in urinary NMN and MN excre-

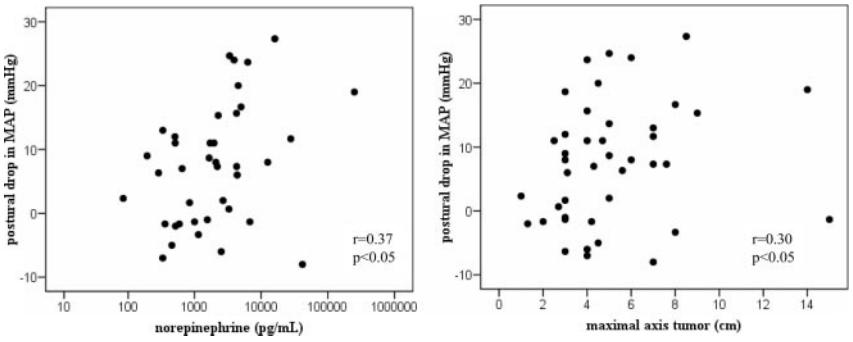

FIG. 3. Relation between plasma NE concentration (*left*) and maximal diameter of the tumor (*right*) and the postural drop in BP after α-adrenergic blockade.

TABLE 3. Characteristics of patients with sporadic pheochromocytoma and pheochromocytoma as part of a familial tumor syndrome

Characteristic	Sporadic	Hereditary	*P*
n	58	15	
Age (yr)	49 (18–85)	37 (17–82)	<0.01
Plasma values			
NE (pg/ml)	2,136 (205–250,378)	840 (37–41,614)	<0.05
E (pg/ml)	165 (1–35,145)	11 (7–9,308)	0.37
D (pg/ml)	18 (1–1,500)	14 (1–106)	0.09
24-h urinary values			
MN μmol/mmol creat	586 (24–11,310)	439 (33–4,475)	1.0
NMN μmol/mmol creat	1,847 (145–12,179)	834 (151–8,167)	0.63
MAP (mm Hg)			
At presentation	107 (67–137)	95 (73–180)	0.19
After α blockade	98 (67–137)	85 (70–119)	<0.01
Postoperatively	84 (60–133)	82 (68–102)	0.69
SBP			
At presentation	150 (90–230)	125 (110–240)	0.05
After α blockade	133 (95–183)	112 (97–171)	<0.01
Postoperatively	124 (71–180)	115 (90–161)	0.29
DBP			
At presentation	88 (60–152)	80 (55–150)	0.48
After α blockade	80 (48–113)	70 (55–94)	<0.05
Postoperatively	67 (40–110)	70 (54–77)	0.96

Data are expressed as median (range). MN μmol/mmol creat, MN:C ratio; and NMN μmol/mmol creat, NMN:C ratio as measured in 24-h urine.

tion between the two groups. Within the hereditary group, the tumors produced more NE than E, mainly in von Hippel-Lindau syndrome patients (NE, 1033 pg/ml, 840–1708 pg/ml; *vs.* E, 30.0 pg/ml, 23–32 pg/ml), but also in the multiple endocrine neoplasia type 2 group (NE, 520 pg/ml, 37–41,614 pg/ml; *vs.* E, 110 pg/ml, 7–9,308 pg/ml). No differences were found in intraoperative HD instability or administered medication between the sporadic and hereditary tumors.

Discussion

Operations on pheochromocytoma remain riskful. Although preoperative preparation and anesthetic control have improved considerably over the years, HD unstable events are still common (13). This study sought to identify risk factors for these events in a large series of pheochromocytoma operations in a single center. In addition, we compared the efficacy of two types of preoperative α-adrenergic receptor blockade. Our results revealed a number of possible risk factors for intraoperative hypertensive events: a higher preoperative plasma NE concentration, a larger maximal diameter of the tumor (>4 cm), a higher BP before and after α-adrenergic receptor blockade (cutoff, 130/85 mm Hg), and a more pronounced preoperative postural BP fall (>10 mm Hg). Risk factors for intraoperative hypotension were not identified. Reassuringly, none of the patients experienced long-term complications resulting from HD instability.

As Hull noted in 1986 in patients with a pheochromocytoma without adequate preparation for surgery, perioperative mortality was as high as 30–45% (7). Duh (18) describes the development of surgical management, evolving from α-adrenergic receptor blockade and volume expansion, innovation in localization techniques, and renewed operational and anesthetic approaches that all contributed to a marked decline in mortality. Several modes of preoperative pharmacological management have been proposed, including treatment with α-adrenergic receptor antagonists, calcium channel blockers, and metyrosine (16). Preoperative α-adrenergic receptor blockade is widely used, and most studies (16, 19–22) have shown a significant reduction in perioperative complications. It is concluded therefore that the current retrospective studies support preoperative α-adrenergic receptor blockade, notwithstanding the lack of prospective, randomized studies (13).

In our institute, PXB has been used for a long time as preoperative antihypertensive treatment to control BP intraoperatively. Due to limited availability, PXB was replaced in 2003 by DOX. PXB blocks α-adrenergic receptors noncompetitively, which avoids drug displacement by excessive increases in catecholamines during surgery; however, this could lead to prolonged hypotension postoperatively. In addition, blockade of α_2-receptors can cause an undesirable reflex tachycardia. Theoretically, DOX would be preferable for it acts only on α_1-adrenergic receptors and has a shorter half-life. Several studies com-

paring PXB with prazosin or DOX have provided conflicting results (5, 6, 8, 16, 18, 19). In the studies reported by Prys-Roberts and Farndon (23), PXB-treated patients compared with DOX-treated patients had persistent α-adrenergic receptor blockade in the postoperative period, which is evident from a higher prevalence of postoperative hypotension and a higher demand for iv fluids. In addition, intraoperative heart rate during tumor manipulation was higher in the PXB group. Finally, PXB-treated patients experienced more side effects, in particular postural hypotension (23). However, Kocak *et al.* (14) found no differences in intra- and postoperative BP values or volume replacement in patients pretreated with PXB, DOX, or prazosin.

With the limitations of a retrospective study, we found overall an equal efficacy for PXB and DOX with respect to pre- and intraoperative BP control, as indicated by comparable values for preoperative BP values after α-receptor blockade (MAP_α), the number and duration of intraoperative hyper- and hypotensive episodes, the dosages of intraoperatively administered antihypertensive or vasoactive agents, and the amount of administrated iv fluids. Intraoperatively administered esmolol doses were higher in the PXB group, which might be explained by more frequent episodes of tachycardia, possibly related to PXB-mediated blockade of α_2-receptors. Unexpectedly, the postoperative BP was lower in the DOX group compared with the PXB group (23). One explanation might be the difference in plasma NE concentration, which was significantly higher in the DOX group. This, in turn, could have resulted in a higher required α-blocker dose, leading to a more profound decrease in BP after tumor removal. Although PXB and DOX had comparable effects on perioperative BP values in this study, it should be emphasized that intraoperative pharmacological management was not standardized, although type and dose of antihypertensive or vasoactive agents as well as amount of fluid infusion was not different between both groups. Nevertheless, definitive conclusions on efficacy, safety, and adverse events of type of α-adrenergic receptor blockade applied can only be drawn through randomized, controlled trials.

It is recommended that BP values should not exceed 130/85 mm Hg (MAP, 100 mm Hg) and not fall below 85/55 mm Hg (MAP, 65 mm Hg) in the upright position during preoperative α-blockade (13, 17). In this study, we also assessed the predictive value of the calculated MAP, as a measure of an individual's average BP, of the target BP value of 130/85 mm Hg, *i.e.* 100 mm Hg. Using a cutoff value for intraoperative systolic hypertension of 160 mm Hg, we found that a MAP after α-blockade above 100 mm Hg is associated with more and longer intraoperative hypertensive episodes. On the other hand, a MAP_α of 100 mm Hg or less was not accompanied by more intra- or postoperative hypotensive periods. Because more than 80% of patients with a MAP after α-blockade of 100 mm Hg or less also had a BP of 130/85 mm Hg or less, our data support the recommended target BP value after α-blockade of 130/85 mm Hg and indicate that a target MAP_α of 100 mm Hg or less can be used as well.

Pretreatment with α-blockers is accompanied by a postural drop in BP that may indicate adequate α-adrenergic receptor blockade. Surprisingly, we found that a higher degree of postural drop after α-adrenergic receptor blockade, in particular higher than 10 mm Hg, was associated with more and longer intraoperative hypertensive episodes. Postural drop in BP itself is a clinical feature of pheochromocytoma, and it has been suggested that this results from a reduced responsiveness of the vasculature to NE due to down-regulation of α-adrenergic receptors in response to persistent elevation of the physiological agonist NE (24). Postural drop was indeed related to plasma NE levels; however, the association with intraoperative hypertension was independent of plasma NE concentrations and is therefore not yet explained. The question remains whether postural drop is a good parameter for α-adrenergic receptor blockade and whether the α-blocker dose should be adjusted according to degree of postural drop. Again, prospective studies should evaluate the predictive value of postural drop with respect to intraoperative BP control.

As mentioned, the degree of NE production was associated with intraoperative hypertension, confirming earlier reports (25). In addition, NE levels were related to tumor size and blood pressure at presentation. Tumor diameter, in particular greater than 4 cm, was also related to intraoperative hypertension, independent of preoperative plasma NE levels or surgical approach. This may indicate that intraoperative catecholamine release, due to anesthesia, tumor manipulation, *etc.*, is related to tumor size. Indeed, tissue catecholamine concentrations are very high in pheochromocytomas, and a linear relationship has been demonstrated between tumor size, tumor catecholamine content, and plasma catecholamine levels (26, 27). With respect to the surgical approach, we found no differences between laparoscopic and open procedures in intraoperative BP fluctuations, in agreement with the study of Tiberio *et al.* (28). Finally, perioperative HD instability was similar in patients with benign *vs.* malignant pheochromocytomas and in patients with sporadic pheochromocytoma and patients with a pheochromocytoma as part of a familial endocrine polytumor syndrome, despite the fact that in the sporadic group higher plasma NE levels and a higher BP after α-blockade were present in a larger proportion of patients.

In conclusion, this study shows that in patients who are operated for a pheochromocytoma, variables that predispose to intraoperative hypertension include a high NE production, a larger tumor size (>4 cm), a high BP at presentation and after α-adrenergic receptor blockade (MAP >100 mm Hg), and a more pronounced postural drop (>10 mm Hg) in BP after α-receptor blockade. In contrast, surgical approach, pathological features, and genetic causes of pheochromocytoma seem not to influence perioperative HD instability. Furthermore, preoperative treatment with PXB and DOX has a similar efficacy with respect to intraoperative HD control. Prospective studies, however, are needed to confirm the predictive value of these variables and to definitively establish which type of α-adrenergic receptor blockade most efficiently couples prevention of intraoperative hypertension to a minimum of side effects.

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Address all correspondence and requests for reprints to: Dr. G. Kazemier, M.D., Ph.D., Erasmus Medical Center, 's Gravendijkwal 230, 3015 CE Rotterdam, The Netherlands. E-mail: g.kazemier@erasmusmc.nl.

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