Primary perioperative haemodynamic effects of ß-receptor blockade in patients with catecholamine-secreting tumours

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Abstract

Introduction: Guidelines for the treatment of catecholamine-producing tumours strictly recommend starting ß-receptor blocking medication only after α-receptor blockade has been established. This recommendation is supported only by non-surgical case reports. However, in clinical practice ß-receptor blockade is often started before the diagnosis of a phaeochromocytoma is made. As we routinely treat patients with catecholamine-producing tumours without α-receptor blockade, our aim was to evaluate haemodynamic changes in such patients with and without ß-receptor blockade.

Methods: Perioperative blood pressure was assessed prospectively for all patients. The primary outcome was the highest pre-, intra-, and postoperative systolic blood pressure in patients with or without a ß-receptor blockade. Secondary outcomes were the incidence of intraoperative systolic blood pressure peaks >250 mm Hg and hypotensive episodes. Subsequently, a propensity score matching (PSM) analysis was performed.

Results: Out of 584 phaeochromocytoma and paraganglioma resections, 383 operations were performed without α-receptor blockade (including 84 with ß-receptor blockade). Before operation and intraoperatively, patients with ß-receptor blockade presented with higher systolic blood pressure (155 [25] and 207 [62] mm Hg) than patients without ß-receptor blockade (147 [24] and 183 [52] mm Hg; P=0.006 and P=0.001, respectively). Intraoperatively, patients with ß-receptor blockade demonstrated a higher incidence of hypotensive episodes (25% without vs 41% with ß-blockade; P<0.001). After propensity score matching no difference between the groups could be confirmed.

Conclusion: Overall, patients with isolated ß-receptor blockade developed higher blood pressure before operation and intraoperatively. After propensity score matching a difference could no longer be detected. Overall, ß-receptor blockade seems to be more a sign for severe disease than a risk factor for haemodynamic instability.

Keywords: adrenal surgery; adrenergic blockade; arterial hypotension; haemodynamic instability; paraganglioma; perioperative management; phaeochromocytoma; risk factors

Two of the strict recommendations in the 2014 guidelines and part of many reviews for the perioperative management of patients with catecholamine-producing tumours are to initiate a prophylactic α-receptor blockade before surgery and never to start a ß-receptor blocker before an α-receptor blockade has been established.[1–6] Catecholamine-producing tumours are rare and recommendations for perioperative management are almost exclusively based on expert experience and opinion.[1–4] Randomised studies with respect to outcome are almost impossible to conduct because of the low mortality rate of about 1–3%, the rarity of the disease, and the high number of patients that would be needed.

Pharmacologically, blockade of ß-receptors on peripheral blood vessels can lead to increased vascular tone. In phaeochromocytoma patients, this effect on peripheral vascular tone could possibly increase the effect of tumour released

catecholamines and worsen the cardiac workload, which ultimately increases the risk of acute heart failure.[6–8] Over the past decades, this theoretical consideration has been supported by some case reports.[8–11] These reports describe cases of excessive blood pressure increases and, in some cases acute heart failure, in patients with phaeochromocytoma who received a ß-receptor blocking drug (mostly propranolol) in the absence of prior α-receptor blockade. All these cases occurred in a non-surgical setting.

Although the hypothesis seems convincing, acute hypertensive crises with or without acute heart failure are typical complications of catecholamine-producing tumours and occur also in the absence of ß-receptor blockade. However, the recommendation to avoid ß-receptor blocking agents without an established α-receptor blockade may not reflect current clinical reality. It often takes a long time to come to the diagnosis of a phaeochromocytoma, at which point ß-receptor blockade may have already been started because of sustained or intermittent arterial hypertension long before the diagnosis of phaeochromocytoma was made.[8]

Since we abandoned the use of prophylactic perioperative α-receptor blockade several years ago, we have the opportunity to present haemodynamic data of patients with catecholamine-producing tumours, either without any adrenal receptor blockade or with isolated ß-receptor blockade.[12] Our primary null hypothesis was: in patients without α-receptor blockade, there is no significant difference in the maximum systolic blood pressure between patients with ß-receptor blockade compared with patients without ß-receptor blockade.

Methods

After approval by the local ethics committee (Board of Physicians 'Ärztekammer Nordrhein' reg. no.: 13–2015) 543 consecutive patients scheduled for 584 operations between January 2007 and December 2022 gave their informed written consent to have their data analysed in this observational study. Where α-receptor blockade had already been started (*n*=201), patients were not included.

Preoperative management

Over the past 15 yr, whenever our institution was contacted for referral of a patient with a catecholamine-producing tumour, the referring physician was asked not to initiate α-receptor blockade. Since then, many physicians and patients contact our institution explicitly because they wanted to avoid α-receptor blockade. Usually, patients were admitted to our hospital the day before surgery, so that patients were hospitalised before surgery. The number of antihypertensive drugs prescribed to the patients before surgery was assessed. All patients took their prescribed antihypertensive medication on the morning of surgery.

Anaesthesia and surgery

On the day of surgery, after the patients arrived in the anaesthesia induction room, noninvasive monitoring was applied and an arterial line was placed under local anaesthesia. Subsequently, general anaesthesia was induced with propofol, remifentanil, and mivacurium or rocuronium. After intubation of the patient's trachea, a three-lumen central venous catheter was placed in the right or left internal jugular vein. Depending on the surgical approach, patients were placed in the prone or supine position. Anaesthesia was maintained with isoflurane or sevoflurane at the discretion of the attending anaesthetist. Remifentanil was administered continuously.

For each patient, a sodium nitroprusside infusion was connected to one lumen of the central venous catheter and started at a minimal dose (1 mg h^{-1}) so that it was ready for rapid titration as needed. As soon as the rate was increased to treat a blood pressure increase, it was counted as a treatment. During surgery, the dose of sodium nitroprusside was adjusted once systolic blood pressure exceeded 160 mm Hg with the intention to avoid blood pressure increases above 200 mm Hg for >1 min. In addition to the administration of sodium nitroprusside, esmolol was added at the discretion of the responsible anaesthetist. The baseline maximum systolic blood pressure was recorded after arrival in the induction room. Subsequently, the highest systolic blood pressure was assessed for analysis intraoperatively and after surgery in the recovery room as was the incidence of mean arterial blood pressure episodes below 60 mm Hg for >1 min intraoperatively and in the recovery room. According to Desmonts and Marty,[13] who defined systolic blood pressure episodes >250 mm Hg as intraoperative crises, we assessed the number of systolic blood pressure episodes >250 mm Hg.

Arterial hypotension was treated at the discretion of the responsible anaesthetist. First-line treatment was infusion of crystalloid solution. Second-line treatment was the administration of norepinephrine. The volume of intraoperatively administered fluids, mean dose of norepinephrine administration, and the number of patients per group who received norepinephrine were recorded.

The incidences of complications that could have been potentially related to arterial hypertension or hypotension, such as myocardial infarction, acute congestive heart failure, pulmonary oedema, and cerebral haemorrhagic or ischaemic stroke, were assessed.

Data analysis

Data are presented as mean and 95% confidence interval. The primary null hypothesis was: in patients without α-receptor blockade, there is no significant difference in the maximum systolic blood pressure between patients with ß-receptor blockade compared and patients without ß-receptor blockade. Data were analysed as a consecutive case series with Statview software (Version 5.0.1, SAS Institute Inc., Cary, NC, USA).

Hypotheses for the three time points were tested using analysis of variance (ANOVA) for repeated measurements with Bonferroni-corrected *post hoc* tests. The analysis of the numbers of hypotensive (mean arterial blood pressure <60 mm Hg) and hypertensive (systolic blood pressure >250 mm Hg) episodes were our secondary outcomes.

Patient characteristics, tumour size, time for surgery, intraoperative fluid administration, percentage of preoperative hormone concentrations, intraoperative dose of sodium nitroprusside and norepinephrine, were tested for significant differences between groups using unpaired *t*-tests. The number of preoperative antihypertensive drug classes, aetiology of the tumour, surgical technique, number of patients with hypotensive and hypertensive episodes, number of patients who received sodium nitroprusside or norepinephrine were tested using the χ^2 test.
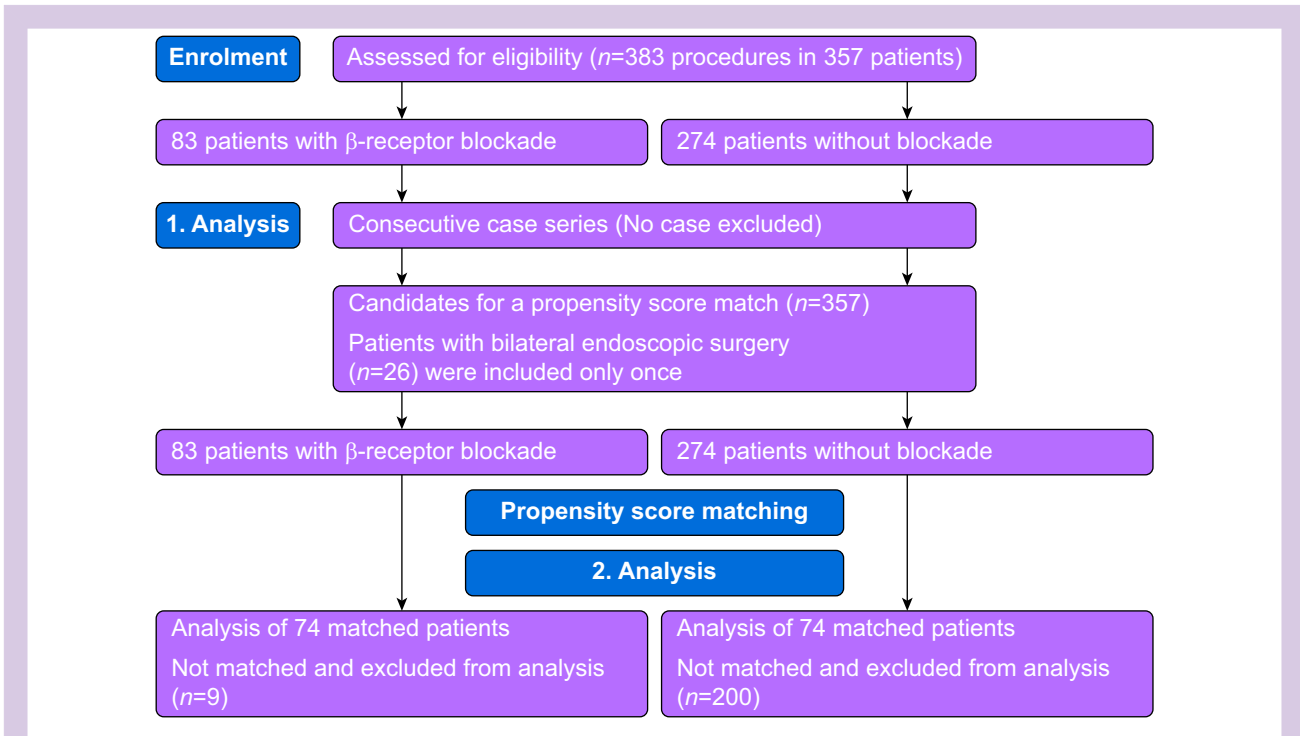
Fig 1. Consort Flow diagram.

In propensity score matching (PSM), the propensity score was estimated by fitting a logistic-regression model that included the five prognostic determinants for the primary outcome measure.

To develop a multiple linear regression model, we conducted a search to identify known predictors and their interactions from the published literature. Descriptive analysis of variables was performed to check for a normal distribution and variability of continuous variables or distribution of frequencies. Correlations between dependent and independent variables were analysed according to Pearson's correlation for continuous and normally distributed variables or Spearman's rank correlation. To avoid collinearity correlations were also tested between independent variables. The normality assumption for the residuals was assessed by QQ-plots and for checking the assumption of constant variance in the dataset, the residuals were plotted by the fitted value to exclude heteroscedasticity. Based on these analyses the variables to be included in the model were identified and the model calculated.

Thereafter, a 1:1 pair matching between patients with no adrenal blockade and patients with ß-receptor blockade was applied using the recommended method of nearest-neighbour matching without replacement. A comparison for matching on the propensity score, with a caliper width equal to 0.1 of the standard deviation of the logit of the propensity score.[14] The distribution of propensity score before and after matching was checked by histograms. After the analysis of the complete case series, propensity score matching and analysis of 74 pairs was performed (Fig 1).

Significant differences were assumed with P-values <0.05.

Results

Analysis of the closed case series

Characteristics of the patients and surgery are presented in Table 1. Patients were diagnosed with sporadic phaeochromocytoma (n=208), von Hippel–Lindau disease (VHL; n=86), multiple endocrine neoplasia type 2A (MEN 2A; n=42), or neurofibromatosis (n=6). In 26 patients, bilateral tumours were removed. In addition, 42 patients had extraadrenal paraganglioma. In six patients, with the diagnosis of an incidentaloma, the diagnosis had to be corrected to phaeochromocytoma. The tumour size did not differ significantly between groups (Table 1).

Per definition, the number of antihypertensive drugs prescribed to the patients before surgery differed between groups (Table 1). Out of 84 patients with ß-receptor blockade, 39 received bisoprolol, 34 metoprolol, seven nebivolol, three carvedilol, and one propranolol. Patients with sporadic phaeochromocytoma had significantly more antihypertensive drugs prescribed before surgery than patients with MEN II or von Hippel–Lindau syndrome.

Three hundred and seventy-five operations (95%) were performed using a retroperitoneoscopic approach, seven by the laparoscopic route (five without and two with ß-receptor blockade), and one thoracoscopically (without ß-receptor blockade). Surgical techniques of the retroperitoneoscopic and laparoscopic approach have been described in detail previously.[15,16]

Norepinephrine was more frequently administered in patients with ß-receptor blockade than in patients without blockade (Table 2). There was no difference in the amount of

Table 1 Characteristics of 357 patients with no adrenal blockade (n=274) or ß-receptor blockade (n=83) and tumour size, number of preoperative antihypertensive drugs (number of drug classes per patient), maximum preoperative plasma concentrations of epinephrine and norepinephrine (percentage of upper reference values). Data are presented as mean and confidence interval or numbers and range for age.

	No blockade	ß-receptor blockade	P-value
Height (cm)	172 (163—181)	172 (162—182)	0.690
Weight (kg)	74 (72—76)	79 (75—83)	0.016
BMI (kg m^{-2})	24.8 (24.2—25.4)	26.7 (25.2—26.9)	0.003
Age (yr)	42 (40.2—43.8)	54 (50.7—57.3)	<0.001
Sex (female/male)	165/134	45/39	0.793
Tumour size (diameter, cm)	3.4 (3.23—3.57)	3.6 (3.25—3.95)	0.125
Preoperative drugs (0/1/2/3/4/5)	232/35/24/3/4/1	0/18/35/14/10/6	<0.001
Epinephrine (%)	619 (495—746)	637 (406—869)	0.889
Norepinephrine (%)	676 (569—782)	829 (503—1154)	0.253

Fig 2. Plot of baseline arterial blood pressure in patients with no adrenoceptor blockade or isolated ß-receptor blockade (purple box=no adrenal blockade, blue box=ß-receptor blockade). There are differences over time between the two groups. *Post hoc* analysis showed higher preoperative and intraoperative maximum systolic blood pressure values for patients with isolated ß-receptor blockade (P<0.001).

intraoperative i.v. fluid administration. Blood loss was minimal (<100 ml) for all cases and not further analysed. Esmolol was used to treat tachycardia in nine patients.

Systolic arterial blood pressure before induction of anaesthesia and maximum systolic blood pressure during surgery was higher in the group with isolated ß-receptor blockade (Fig 2). Blood pressure increases were treated as described in the methods section. There were only seven patients (five without ß-receptor blockade and two with ß-receptor blockade), who had episodes of systolic blood pressure >200 mm Hg for >1 min. No episodes lasted longer than 3 min. There were more blood pressure increases >250 mm Hg (29%) in patients with an isolated ß-receptor blockade compared with patients without blockade (10%). None of the patients experienced more than one episode of a systolic blood pressure >250 mm Hg.

Hypotensive episodes, defined as episodes of mean blood pressure <60 mm Hg, occurred less often in the group of patients without any blockade (75 patients [25%]) compared with patients with ß-receptor blockade (34 patients [41%], P<0.001).

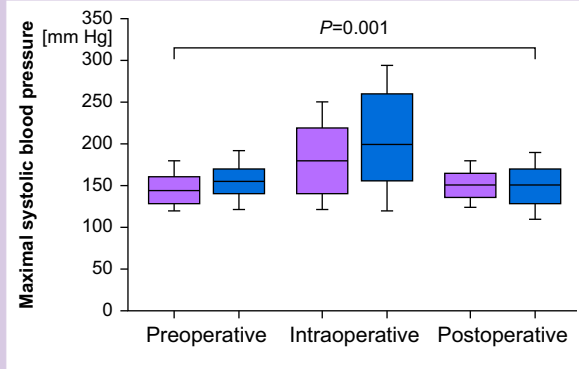Four patients were initially or secondarily operated upon by an open procedure. There were no complications that could

have been related to intraoperative blood pressure increases. All tumours were histologically verified as catecholamine-producing tumours.

Propensity score analysis

Age, tumour size, tumour aetiology, type of catecholamine produced, and presence of typical symptoms were used as matching criteria. After propensity score matching of 74 pairs, differences between the groups could no longer be detected (Fig 3), except for the number of patients who received norepinephrine (Table 3).

Discussion

Looking at the complete case series, isolated ß-receptor blockade was associated with higher systolic blood pressure before induction of anaesthesia, higher maximum systolic blood pressures intraoperatively, and a higher incidence of hypotensive episodes compared with patients without blockade. After propensity score matching no haemodynamic differences between patients with or without ß-receptor blockade could be found perioperatively.

Table 2 Intraoperative infusion volume, duration of surgery, episodes of intraoperative hypotension and excessive hypertension, intraoperative cumulative dose of sodium nitroprusside (SNP) and norepinephrine, number of cases with SNP or norepinephrine administration of 299 cases with no ß-receptor blockade and 84 cases with ß-receptor blockade. Data are presented as mean and confidence interval or numbers.

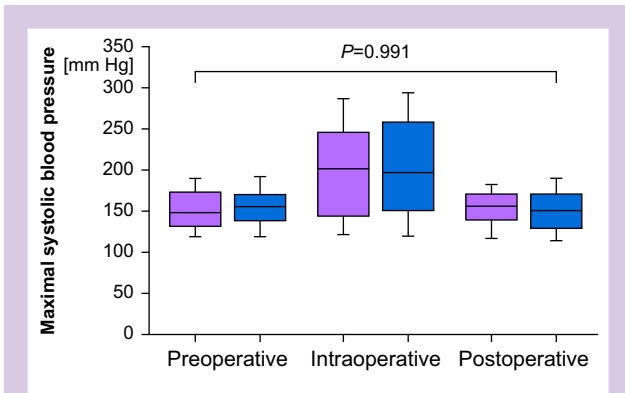|	No blockade	ß-receptor blockade	P-value
Intraoperative fluid (L)	1750 (1682—1818)	1750 (1628—1872)	0.997
Duration of surgery (min)	61 (55.7—65.5)	53 (47.2—59.2)	0.123
Intraoperative hypotension (n [%])	75 (25)	34 (41)	0.006
Systolic blood pressure peaks >250 mm Hg (n [%])	30 (10)	24 (29)	< 0.001
Dose of SNP (mg)	5.9 (4.9—6.9)	5.9 (4.7—7.1)	0.973
Number of cases with SNP administration (%)	210 (70)	63 (75)	0.394
Dose of norepinephrine (μg)	134 (82—143)	238 (227—521)	0.056
Number of norepinephrine administrations (%)	58 (19)	27 (32)	0.016

Fig 3. Box plot of baseline arterial blood pressure in patients with no adrenoceptor blockade or isolated ß-receptor blockade (purple box=no adrenal blockade, blue box=ß-receptor blockade) after propensity score matching (74 pairs). No differences between the two groups were found.

Phaeochromocytoma surgery has been burdened historically by a high mortality rate. Several factors, which could influence this rate, have been discussed.[17−22] One of these factors was the potential effect of isolated ß-receptor blockade. The blockade of peripheral arterial ß-receptors could enhance the effect of an unopposed α-stimulation and lead to increased arterial blood pressure peaks.[5−7] Therefore, guidelines for the management of catecholamine-producing tumours strictly recommend not to use ß-receptor blocking agents before α-receptor blockade has been established.[1−7,13,23] This idea was supported by some case reports, which were not related to surgical cases.[8−11] Up to now there have been no reports of the perioperative effect of isolated ß-receptor blockade. However, administration of ß-receptor blockers is one of the standard treatments for arterial hypertension. As many patients with catecholamine-producing tumours are treated for arterial hypertension long before the diagnosis of a phaeochromocytoma has been made, they may already receive ß-receptor blocking agents.[8] As we treat patients with phaeochromocytoma or paraganglioma without prophylactic α-receptor blockade, we have the unique opportunity to describe the perioperative haemodynamic behaviour of these patients and compare this with patients with no adrenal receptor blockade. Three of the patients received carvedilol, which also has weak α-receptor blocking properties (α-to ß-receptor effect with a ratio of 1−12.5).[24] As this weak effect on α-receptors is not comparable to α-receptor blockade with selective agents we included these patients in our analysis.

Designing a randomised controlled study for an adequate evaluation of the effect of ß-receptor blockers on patients undergoing phaeochromocytoma surgery seems to be impossible. Besides the difficulty to allocate enough patients, a study design enrolling patients without any adrenal blockade *vs* patients with isolated ß-receptor blockade would be completely outside the current guidelines and could not offer a theoretical benefit for patients receiving isolated ß-receptor blockade. Therefore, we suggest that our consecutive case series might be the best way to provide information about this important question. In addition, we performed a propensity score match of 74 matched pairs of patients to limit the influence of five cofounders.

There are some reports describing the perioperative management of patients with catecholamine-producing tumours without receptor blockade and without any complications, while the combination of α- and ß-receptor blockade can lead to life-threatening situations.[12,25−30] These findings raise the question of how to proceed with patients with isolated ß-receptor blockade. In asymptomatic patients, it can be argued to wait for the ß-receptor blockade to wear off, with the risk of rebound tachycardia and blood pressure increases. In symptomatic patients, it can be recommended to perform surgery as soon as possible and remove the tumour. In these patients it is inappropriate to wait for the clearing of ß-receptor blocking agents and possible rebound effects. Therefore, our policy was to proceed with surgery in the knowledge that patients with isolated ß-receptor blockade have to be monitored very closely and haemodynamic changes may have to be treated earlier and with higher doses of vasoactive substances.

In our case series of 383 patients, including 84 with isolated ß-receptor blockade, we found that patients under ß-receptor blockade demonstrated haemodynamic instability (increased number of both hypertensive and significant hypotensive episodes), although no associated increased morbidity or mortality could be detected. We previously reported that the use of long-acting α-receptor blocking agents increases the risk of sustained hypotension.[12,25,26] The combination of ß-receptor

Table 3 Intraoperative infusion volume, duration of surgery, episodes of intraoperative hypotension and excessive hypertension, intraoperative cumulative dose of sodium nitroprusside (SNP) and norepinephrine, number of cases with SNP or norepinephrine administration of 74 propensity score matched pairs with or without ß-receptor blockade. Data are presented as mean and confidence interval or numbers.

	No blockade	ß-receptor blockade	P-value
Intraoperative fluid (L)	1680 (1566−1794)	1741 (1607−1875)	0.491
Duration of surgery (min)	51 (45.4−57.0)	53 (46.2−59.2)	0.7224
Intraoperative hypotension (n [%])	18 (24)	28 (38)	0.109
Systolic blood pressure peaks >250 mm Hg (n [%])	13 (18)	20 (27)	0.236
Dose of SNP (mg)	6.8 (4.6−9.0)	5.7 (4.4−7.0)	0.435
Number of cases with SNP administration (%)	55 (74)	55 (74)	1
Dose of norepinephrine (µg)	162 (60−264)	247 (71−423)	0.494
Number of cases with norepinephrine administration (%)	12 (16)	23 (31)	0.033

blockade with α-receptor blockade could further increase the risk of significant hypotension and lead to increased periop-erative morbidity.[30]

However, after propensity score matching, which resulted in 74 matched pairs, no haemodynamic differences between patients with or without ß-receptor blockade could be found. This rather unexpected result implies that ß-receptor blockade may rather be an indicator of high tumour activity than an independent risk factor for haemodynamic instability.

There are several limitations to our observational study. Most important, the patients were not randomised for the use of ß-receptor blocking agents and we cannot exclude a bias driven by the patients' symptoms. Symptomatic patients with a sporadic phaeochromocytoma might more likely have been treated with antihypertensive drugs including ß-receptor blocking agents than patients who were asymptomatic and were diagnosed through family screening. We attempted to mitigate the risk of bias with propensity score matching.

There are several confounders for intraoperative arterial hypertension, such as tumour size and tumour aetiology, but their influence is difficult to define with low numbers of patients.[17–19] In our study, tumour size and surgical technique did not differ between the groups and should not have influ-enced the differences between the groups, while the aetiology of the tumour might have had an influence. In patients with a sporadic phaeochromocytoma it usually takes longer to make the diagnosis than in patients with hereditary disease such as von Hippel–Lindau disease. Therefore, these patients tend to have a longer time of symptomatic antihypertensive treatment with multiple drugs including ß-receptor blocking agents.

In conclusion, patients with isolated ß-receptor blockade perioperatively present with significantly higher arterial blood pressure before induction of anaesthesia and develop higher mean maximum systolic blood pressure during surgery with a higher incidence of blood pressure increases above 250 mmHg and a higher incidence of hypotensive episodes compared to patients without ß-receptor blockade. As these haemody-namic effects disappear after propensity score matching, it seems that ß-receptor blockade indicates a more severe dis-ease rather than an isolated risk factor. Patients with ß-re-ceptor blockade might need earlier and more intensified pharmacological intervention during surgery and should be regarded as high-risk patients.

Authors' contributions

Helped with the design of the work: BJN, HG.
Helped with interpretation of the data: BJN, AF, PFA, MKW, HG.
Wrote the first draft of the manuscript; revised all further versions of the manuscript until the final version: BJN.
Approved the final version: BN, AF, HG.
Helped with analysis of the data: AF, SB, HG.
Revised all versions critically; submitted the final version for publication: AF, HG.
Helped with the acquisition of the data: SB, PFA, MKW.
Revised the final version of the manuscript and approved the version for publishing: SB.
Revised the manuscript and approved it for publishing: PFA, MKW.
Accountable for all aspects of the work: all authors.

Declarations of interest

The authors declare that they have no conflicts of interest.

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