Hemodynamic instability during resection of pheochromocytoma in MEN versus non-MEN patients

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Abstract

Objective: Hemodynamic (HD) instability still underlies difficulties during pheochromocytoma resection. Little is known about HD instability in patients with multiple endocrine neoplasia (MEN) type 2-related pheochromocytoma. Our aim was to assess differences in HD during pheochromocytoma resection between MEN2 and non-MEN patients. In addition, we sought to identify risk factors for intraoperative HD instability.

Design: Retrospective cohort study.

Methods: A total of 22 MEN2 and 34 non-MEN patients underwent 61 pheochromocytoma resections at the University Medical Center Utrecht between 2000 and 2010. All MEN2-related pheochromocytomas were diagnosed by annual screening. HD instability was assessed by measuring the frequency of hypotensive (mean arterial blood pressure (MABP) < 60 mmHg) and/or hypertensive (systolic arterial blood pressure (SABP) > 200 mmHg) episodes.

Results: Compared with non-MEN patients, MEN2 patients were younger at diagnosis, had less symptoms, lower hormone levels, and smaller tumors. Intraoperatively, MEN2 patients had a similar frequency of hypertensive episodes (1.3 vs 1.9, P = 0.162, 95% confidence interval (CI): −6.7 to 35.4) and a similar maximum SABP (200 vs 220 mmHg, P = 0.180, 95% CI: −9.7 to 50.5). However, MEN2 patients experienced less frequent (1.04 vs 2.6, P = 0.003, 95% CI: 0.57 to 2.6) and less severe hypotensive episodes after tumor resection (lowest MABP: 52.5 vs 45.6 mmHg, P = 0.015, 95% CI: −12.6 to 1.16). Tumor size was an independent risk factor for HD instability for the total group after multivariate analysis.

Conclusion: MEN2 patients with pheochromocytoma, despite their smaller tumors, do not distinguish themselves from non-MEN patients in terms of hypertensive episodes during pheochromocytoma resection. Therefore, pretreatment with α- and β-blockade remains the standard of care in MEN2-related as well as in non-MEN-related pheochromocytomas.

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postural BP reduced after α-blockade were identified as risk factors for HD instability during pheochromocytoma resection (10).

Literature on perioperative care of patients undergoing adrenalectomy for pheochromocytoma is often outdated and historical without considering the improvements in perianesthetic care mentioned earlier (11). Moreover, the perioperative course concerning HD data of multiple endocrine neoplasia type 2 (MEN2) patients with pheochromocytomas has typically been reported only in conjunction with sporadic cases and patients with other familial syndromes or has included only small numbers of patients (7, 12–14).

Because of their early identification using the annual screening of mutation carriers, we questioned whether MEN2-related pheochromocytomas are associated with less HD instability during pheochromocytoma resection. Therefore, we assessed differences in intraoperative HD between MEN2 and non-MEN patients in a large cohort. In addition, we sought to identify risk factors for intraoperative HD instability.

Subjects and methods

We took the opportunity of a large database of patients for pheochromocytoma resection, at the University Medical Center Utrecht (UMCU) in The Netherlands from January 2000 to August 2010 following a homogeneous anesthetic and surgical care, to investigate whether patients with MEN have different intraoperative HD compared with non-MEN patients. A total of 56 patients were considered for this investigation after selection from the pathology database in which the pathology results were included for all operatively removed tissues. The number of episodes that the SABP was above 200 mmHg, chosen as cutoff value for intraoperative hypertension, was scored. In addition, hypotensive complications were measured according to the number of episodes that the MABP was below 60 mmHg. Intraoperative tachycardia and bradycardia were defined as an HR above 100 and below 45 beats/min respectively.

Statistical analysis

MEN2 patients were compared with the non-MEN patients regarding patients’ demographics, disease- and treatment-related features, and regarding differences in outcome of HD instability. In addition, patients’ demographics, urinary catecholamine levels, and tumor size, among other variables, were correlated with intraoperative BP fluctuations.

All data were analyzed with SPSS version 16.0 (SPSS, Inc., Chicago, IL, USA). Independent samples t-test was used for comparisons between groups. Pearson’s correlation coefficient was used to correlate variables (r value). Multivariate linear regression analysis was used to adjust for confounding factors. Statistical significance was shown at P < 0.05.

Results

Between January 2000 and August 2010, total of 56 patients underwent 61 resections for pheochromocytoma. Almost all patients (n = 52) were operated by the same surgeon (I B R). Among those, five patients underwent bilateral adrenalectomy because of bilateral pheochromocytoma. Our study population consisted of 39% MEN2 patients.

**MEN versus non-MEN**

Patient and tumor/diagnostic characteristics for the MEN2 group versus the non-MEN group are shown in
Table 1. Significant differences between both groups included a younger mean age at diagnosis, less (cardiac) symptoms, lower preoperative urinary hormone levels, and a smaller tumor size on preoperative imaging for MEN2 patients.

Preoperative differences between MEN2 and non-MEN patients in terms of BP and HR (Table 2) were diminished after preoperative medication (Table 3). Anesthesia was comparable between both groups (data not shown). Intraoperatively, MEN2 patients were similar to non-MEN patients in terms of hypertension, the maximum SABP, and the number of interventions needed to treat undesirable elevations in SABP. In contrast, MEN2 patients experienced less frequent and less severe hypotensive episodes after tumor resection (Table 2). The differences between MEN2 and non-MEN patients did not change after exclusion of patients with Von Hippel–Lindau syndrome (VHL), mutation in succinate dehydrogenase B, C, and D (SDHD), or neurofibromatosis (data not shown).

There were no significant differences between the two groups regarding postoperative course (Table 4).

Correlations with tumor size

The average tumor size based on imaging studies for the total group was 4.2 cm (range 1–12 cm). We found a correlation between tumor size and preoperative urinary hormone levels ($r=0.64$, $P<0.000$). There were weak correlations between tumor size and the number of (cardiac) symptoms and the presence of hypertension at diagnosis ($r=0.29$, $P=0.025$; $r=0.26$, $P=0.050$ respectively).

Correlations of tumor size and systolic BP were significant regarding highest SABP at tumor manipulation ($r=0.39$, $P=0.002$) and lowest SABP at tumor resection ($r=0.497$, $P<0.000$) and hypertensive ($r=0.50$, $P<0.000$) and hypotensive episodes ($r=0.60$, $P<0.000$). Tumor size also correlated with the number of interventions of the anesthesiologist, i.e. the number of episodes compared with a tumor diameter of 3 cm or less ($2.02$ vs $0.47$, $P<0.000$; $2.51$ vs $0.83$, $P<0.000$).
A larger tumor led to more hypertensive episodes after tumor resection. Although the correlation between hypertensive episodes and tumors larger than 3 cm is high, small tumors can also lead to HD instability and especially to hypertension during surgery.

**Discussion**

Due to considerable improvements in preoperative medical preparation and perioperative anesthetic control, mortality after pheochromocytoma resection is rare. However, morbidity from intraoperative HD instability remains a problem. The perioperative HD course of MEN2 patients with a pheochromocytoma has typically been reported only in case reports (6, 10, 12, 14). We report results of a large cohort study comparing patients with MEN2-related pheochromocytoma with non-MEN patients with pheochromocytoma. We mainly demonstrated that MEN2 patients with pheochromocytoma do not distinguish themselves from sporadic cases of pheochromocytoma in terms of intraoperative hypertensive episodes. In addition, we also report results on hypotension during pheochromocytoma resection, where others have only focused on rises in BP and hypertensive crisis. Importantly, reduced BP associated with reduced plasma catecholamine release after tumor resection is the major cause of death. Furthermore, we demonstrated that after multivariate analysis, tumor size is an independent risk factor for HD instability.

Clinically, pheochromocytoma in MEN2 patients differs from sporadic pheochromocytoma because they are often identified at an earlier stage because of annual screening of known mutation carriers. In most cases, earlier diagnosis leads to the identification of smaller tumors, often associated with fewer symptoms and less often and less severe hypertension. In our study, indeed 70% of the MEN2 patients were normotensive and only 43% had symptoms. Cardiovascular symptoms associated with pheochromocytoma occurred in two of our MEN2 patients. These results are in agreement with previous studies (12, 15).

However, despite preoperative differences between MEN2 and non-MEN patients, BP after preoperative medication and intraoperative HD instability in terms

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**Table 2** MEN vs non-MEN patients: hemodynamic data.

<table>
<thead>
<tr>
<th></th>
<th>MEN</th>
<th>Non-MEN</th>
<th>P value (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SABPa (mmHg, mean±s.d.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At diagnosis</td>
<td>$137 \pm 22$</td>
<td>$157 \pm 34$</td>
<td>0.014 ($4.1$ to 35.2)</td>
</tr>
<tr>
<td>After preoperative</td>
<td>$125 \pm 16$</td>
<td>$128 \pm 18$</td>
<td>0.782 ($-7.6$ to 10.0)</td>
</tr>
<tr>
<td>medication</td>
<td>$139 \pm 20$</td>
<td>$146 \pm 17$</td>
<td>0.101 ($-1.5$ to 16.8)</td>
</tr>
<tr>
<td>Pre-start</td>
<td>$93 \pm 19$</td>
<td>$87 \pm 20$</td>
<td>0.287 ($-15.5$ to 4.7)</td>
</tr>
<tr>
<td>After induction</td>
<td>$191 \pm 48$</td>
<td>$204 \pm 62$</td>
<td>0.382 ($-17.7$ to 42.8)</td>
</tr>
<tr>
<td>During tumor manipulation</td>
<td>$94 \pm 23$</td>
<td>$75 \pm 23$</td>
<td>0.001 ($-31.5$ to $-8.1$)</td>
</tr>
<tr>
<td>Intraoperative hypertension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertensive episodes</td>
<td>$1.3 \pm 1.4$</td>
<td>$1.9 \pm 2.0$</td>
<td>0.162 ($-6.7$ to 35.4)</td>
</tr>
<tr>
<td>(mean±s.d.), n</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum SABP</td>
<td>$200 \pm 57$</td>
<td>$220 \pm 55$</td>
<td>0.180 ($-9.7$ to 50.5)</td>
</tr>
<tr>
<td>(mmHg, mean±s.d.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interventions needed to</td>
<td>$11.4 \pm 9.1$</td>
<td>$14.8 \pm 18.8$</td>
<td>0.439 ($-5.31$ to 12.1)</td>
</tr>
<tr>
<td>treat undesirable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>elevations in SABP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(mean±s.d.), n</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intraoperative hypotension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypotensive episodes</td>
<td>$1.04 \pm 1.2$</td>
<td>$2.6 \pm 2.6$</td>
<td>0.003 ($0.57$ to 2.6)</td>
</tr>
<tr>
<td>(mean±s.d.), n</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimum MABP</td>
<td>$52.5 \pm 10$</td>
<td>$45.6 \pm 12$</td>
<td>0.015 ($-12.6$ to $-1.16$)</td>
</tr>
<tr>
<td>(mmHg, mean±s.d.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interventions needed to</td>
<td>$1.9 \pm 3.8$</td>
<td>$5.1 \pm 5.0$</td>
<td>0.007 ($0.9$ to 5.6)</td>
</tr>
<tr>
<td>treat undesirable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>decreases in MABP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(mean±s.d.), n</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SABP, systolic arterial blood pressure; MABP, mean arterial blood pressure. Independent sample t-test was used for comparisons between groups.

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**Table 3** MEN vs non-MEN patients: (pre)operative treatment regimes.

<table>
<thead>
<tr>
<th></th>
<th>MEN</th>
<th>Non-MEN</th>
<th>P value (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of α-blockade</td>
<td>$74 \pm 50$ (22)</td>
<td>$48 \pm 42$ (33)</td>
<td>0.047 ($-51.9$ to $-0.37$)</td>
</tr>
<tr>
<td>(days), mean±s.d. (n)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily dosage doxazosin</td>
<td>$17 \pm 12$ (22)</td>
<td>$24 \pm 20$ (31)</td>
<td>0.048 ($0.11$ to 20.43)</td>
</tr>
<tr>
<td>(mg), mean±s.d. (n)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of β-blockade</td>
<td>$115 \pm 150$ (10)</td>
<td>$56 \pm 97$ (16)</td>
<td>0.269 ($-164.8$ to 48.12)</td>
</tr>
<tr>
<td>(days), mean±s.d. (n)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Additional antihypertensive</td>
<td>1</td>
<td>12</td>
<td>0.005 ($0.09$ to 0.47)</td>
</tr>
<tr>
<td>n</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative saline infusion,</td>
<td>11</td>
<td>20</td>
<td>0.647 ($-0.22$ to 3.5)</td>
</tr>
<tr>
<td>n</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative admission</td>
<td>$3.5 \pm 3.3$</td>
<td>$3.7 \pm 3.4$</td>
<td>0.833 ($-1.68$ to 2.10)</td>
</tr>
<tr>
<td>days (mean±s.d.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laparoscopic surgery, n</td>
<td>20</td>
<td>17</td>
<td>0.004 ($-0.59$ to $-0.12$)</td>
</tr>
</tbody>
</table>

Independent sample t-test was used for comparisons between groups.
all patients were operated by the same surgeon, which
intraoperative HD instability (19). In our study, almost
skill in handling the tumor can be a risk factor in
of a familial syndrome. This correlation, as stated, is
independent of preoperative hormone levels, preopera-
tive vasoconstriction (17, 18). Patients in our study, there-
vascular volume owing to catecholamine-mediated
patients with pheochromocytoma have a reduced intra-
(11) for significant association (SABP > 160 mmHg).
However, we found a cutoff size of 3 cm instead of 4 cm
that tumor size may be correlated with HD instability.

Preoperative treatment in our study involved doxazosin
in combination with metoprolol if indicated. In all of
our patients, a mean SABP of 125 mmHg was obtained
after blockade. Multivariate analysis in our study
demonstrated that the titrated doses of doxazosin
administered preoperatively was not related to SABP
after tumor resection (P = 0.927), indicating that in our
patients higher α-blocker doses did not lead to a more
profound decrease in BP after tumor removal. Bruynzeel
et al. (10) and Prys-Roberts & Farndon (16) found similar
results for doxazosin and phenoxybenzamine in terms of
controlling arterial pressure and HR before and during
surgery, but doxazosin caused fewer undesirable side
effects both before and after surgery (16). Theoretically,
patients with pheochromocytoma have a reduced intra-
vascular volume owing to catecholamine-mediated
vasoconstriction (17, 18). Patients in our study, there-
fore, received i.v. saline infusion therapy 2 days before
surgery and a salty diet if they had tachycardia.

A recent report demonstrated a correlation between
tumor size and HD instability (SABP above 160 mmHg)
during pheochromocytoma resection (10), although
others failed to demonstrate tumor size to be a
risk factor (19, 20). The results of our study confirm
that tumor size may be correlated with HD instability.
However, we found a cutoff size of 3 cm instead of 4 cm
(11) for significant association (SABP > 200 mmHg).

Table 4 MEN vs non-MEN patients: postoperative data.

<table>
<thead>
<tr>
<th></th>
<th>MEN, n = 22</th>
<th>Non-MEN, n = 34</th>
<th>P value (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postoperative admission days (mean ± s.d.)</td>
<td>4.8±2.2</td>
<td>6.6±4.7</td>
<td>0.136 (–0.46 to 3.30)</td>
</tr>
<tr>
<td>Total admission days (mean ± s.d.)</td>
<td>8.3±3.8</td>
<td>10.3±6.2</td>
<td>0.243 (–1.14 to 4.40)</td>
</tr>
<tr>
<td>IC admission days, mean ± s.d. (n)</td>
<td>1.4±1.4 (7)</td>
<td>1.5±1.7 (8)</td>
<td>0.437 (–1.52 to 1.63)</td>
</tr>
<tr>
<td>Postoperative complications, n</td>
<td>Tension, heart rate or fluid related</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Cerebrovascular events</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Mortality</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Malignant pheochromocytoma, n</td>
<td>0</td>
<td>1</td>
<td>0.437 (–0.05 to 0.11)</td>
</tr>
</tbody>
</table>

Independent sample t-test was used for comparisons between groups.
*aIncluding hypertension during the first postoperative days requiring additional antihypertensive, direct postoperative hypotension requiring
vasopressors (mainly norepinephrine) and intravascular fluid therapy, atrial fibrillation, pulmonary edema, and cardiac stunning (caused by
relative cardiomyopathy secondary to the pheochromocytoma in combination with intraoperative fluid therapy).
*bIncluding wound infection, pneumonia, and intrauterine fetal death.

makes surgical skill less likely to play a significant role in
differences in intraoperative HD between patient groups.

Previous studies have demonstrated a direct relation-
ship between tumor size and hormone levels in plasma
and urine (21–23). Preoperative urinary hormone levels
in our study also correlated with tumor size and to an
extent intraoperative hypertension, as an independent
risk factor for HD instability. The latter is also shown in
the literature (12, 24). Our MEN2 patients had the
highest urinary hormone ratio for epinephrine compared
with (nor)metanephrine and norepinephrine. They also
had significantly less norepinephrine secretion
compared with our non-MEN patients. This is in
agreement with previous studies (25, 26).

A limitation of our study is its retrospective design.
Therefore, patients could not be randomized for different
pretreatment regimes. However, our preoperative treat-
ment protocol makes no distinction between familial
cases of pheochromocytoma and sporadic cases. This is
confirmed by the fact that dosage of α-blockade is not a
confounder in identifying risk factors for HD instability.
Because all HD data and use of medication during
pheochromocytoma resection were recorded automati-
cally, continuously, and digitally, only few data were
missing. We used the hormone ratio to account for the
differences in type of urinary hormone excreted in
highest amount by the patient. Despite this, accurate
correlation between tumor size and hormone level may
still be affected. CT and MRI were used for preoperative
imaging, which can result in size measurement
variations. In addition, multiple radiologists interpreted
the preoperative imaging scans, producing operator
variation in final size determination.

Conclusion

Despite earlier diagnosis and significantly smaller
tumors, MEN2 patients with pheochromocytoma do
not distinguish themselves from sporadic cases of
pheochromocytoma in terms of intraoperative hyperten-
sive episodes. Therefore, pretreatment with α-blockade
started at least 2 weeks before surgery in combination with β-blockade, if tachycardia is present, remains important; MEN2 patients or patients with small tumors are not excluded.

Declaration of interest

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

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