Is the Excess Cardiovascular Morbidity in Pheochromocytoma Related to Blood Pressure or to Catecholamines?

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Background: It is generally accepted that pheochromocytoma is associated with an increased cardiovascular risk. This is however not based on studies with an appropriate control group of patients with essential hypertension.

Aim of the Study: We examined whether patients with pheochromocytoma have an excess cardiovascular morbidity as compared to hypertensive patients.

Methods: In a retrospective case-control study we reviewed the medical charts of 109 pheochromocytoma patients for cardiovascular events within 5 years prior to the diagnosis. These patients were matched to control patients with essential hypertension for gender and year of birth and diagnosis. Outcome variables were ischemic heart disease, cerebrovascular accidents, and transient ischemic attacks. Classical cardiovascular risk factors were also assessed.

Results: A significantly higher rate of patients with pheochromocytoma suffered a cardiovascular event (13.8%; 95% confidence interval: 7.9%–21.6%) as compared to hypertensive patients (1.1%, 95% confidence interval: 0.1%–3.9%) ($P < .001$). Blood pressure level was lower in pheochromocytoma patients (153/91 $\pm$ 35/15 mm Hg) than in hypertensive patients (170/103 $\pm$ 18/8 mm Hg) ($P < .001$), even after correction for use of antihypertensive medication ($P < .02$). The difference in event rates could not be attributed to differences in other cardiovascular risk factors.

Conclusions: Pheochromocytoma patients have a clearly higher rate of cardiovascular events than patients with essential hypertension. This cannot be attributed to differences in blood pressure or other cardiovascular risk factors. The most likely explanation for the excess event rate is the prolonged exposure to the toxic effects of tumoral catecholamines. These data underpin the importance of a timely diagnosis and treatment of pheochromocytoma. **(*J Clin Endocrinol Metab* 98: 1100–1106, 2013)**

Pheochromocytoma (PHEO) is a rare neuroendocrine catecholamine-producing tumor in which the clinical presentation is highly variable. Although PHEO is a rare tumor with a prevalence of 0.1%–0.6% in hypertensive patients (1, 2), its prevalence in autopsy studies is not negligible (0.05%) (3). In 50% of these missed cases, it is presumed that PHEO contributed to the cause of death.

The hazardous effects of PHEO are predominantly related to the effects of catecholamines. When secreted by the tumor episodically, they are responsible for both paroxysmal symptoms and signs, such as life-threatening

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Abbreviations: AP, angina pectoris; BMI, body mass index; BP, blood pressure; CI, confidence interval; CVA, cerebral vascular accidents; MI, myocardial infarction; OR, odds ratio; PHEO, pheochromocytoma; TIA, transient ischemic attack.

blood pressure (BP) elevations and tachyarrhythmias and bradyarrhythmias. Although these spells are transient and usually short-lasting, they may evolve to catastrophic cardiovascular complications such as acute myocardial infarction (MI) or stroke (4–6). Catecholamines are however also responsible for a variety of other chronic cardiovascular and metabolic effects, such as sustained hypertension, myocarditis, cardiomyopathy, arrhythmias, impaired glucose tolerance, and overt diabetes mellitus (7). After tumor removal, rates of cardiovascular morbidity and mortality drop to the general population risk and life expectancy is not reduced in long-term follow-up studies (8–10).

Numerous case reports support the contention that cardiovascular catastrophes contribute substantially to rates of morbidity and mortality in these patients (5, 11). Although the pathophysiologic concept also predicts that the presence of PHEO is associated with an increased cardiovascular risk and although many case records and small case series have documented serious cardiovascular complications, solid data about the real prevalence of cardiovascular morbidity in PHEO patients are lacking (5). In particular, comparative studies on rates of cardiovascular morbidity, including control patients with essential hypertension, are scarce.

In this study, we examined whether patients harboring a PHEO have an excess rate of cardiovascular events prior to the diagnosis as compared to patients with essential hypertension.

Subjects and Methods

Patients

We reviewed the charts of 135 consecutive PHEO patients treated in the Radboud University Nijmegen Medical Centre between 1977 and 2010. A group of 205 newly diagnosed untreated patients with essential hypertension served as a reference group. Patients with essential hypertension were extracted from the Nijmegen Academic Practice-Based Research Network involving 9 general practices. These patients were diagnosed according to the guidelines of the Dutch College of General Practitioners (12). Matching of patients was done for year of diagnosis (±1 y), year of birth (±2 y), and gender.

Data collection

Patients' medical files were reviewed for diagnosed cardiovascular events that occurred within 5 years before the diagnosis of PHEO or essential hypertension. It was assumed that patients, having a catecholamine producing tumor, had been exposed to the effects of catecholamines for a prolonged period of time. For PHEO patients the duration and pattern of symptoms (paroxysmal or sustained) before diagnosis were retrieved from the charts.

Cardiovascular events were defined as proven MI, angina pectoris (AP), cerebral vascular accidents (CVA), and transient ischemic attacks (TIA). The diagnosis of angina pectoris was based on the reporting of typical complaints by the patient with additional classical electrocardiogram changes indicating coronary insufficiency. Essential hypertension is usually diagnosed without any preceding symptoms and therefore these patients had also been exposed to the elevated BP level for a prolonged period. Cardiovascular events in the essential hypertension patients were included if there had been a notification of an event in the Nijmegen Academic Practice-Based Research Network database.

BP levels in the PHEO patients were calculated from the average of 3 office readings at admission to the Radboud University Nijmegen Medical Centre. BP levels in the patients with essential hypertension were calculated as the average of 3 office measurements at 3 different occasions before initiation of medical treatment. Hypertensive patients with an average systolic BP of more than 160 mm Hg were considered eligible for medical treatment (13). Patients with PHEO were classified as having paroxysmal hypertension if they had documented episodes of hypertension with documented intercurrent episodes of normotension. Other patients were classified as having sustained hypertension or normotension. However in 10 patients it was impossible to classify them due to lack of reliable data on BP status.

Data were collected on additional cardiovascular risk factors, such as smoking, diabetes mellitus, body mass index (BMI), and cholesterol levels. Smoking was defined as being a present smoker or having smoked until at least 10 years before the diagnosis. Diabetes mellitus was defined as fasting blood glucose level greater than 7 mmol/L or nonfasting blood glucose level greater than 11 mmol/L. A positive family history for cardiovascular disease was defined as a first-grade family member with a cardiovascular event before the age of 60.

Finally, genetic, tumor-specific, and preoperative data on plasma and/or urinary concentrations of epinephrine and norepinephrine were collected in the PHEO patients.

Statistics

Significance of differences in proportions of events was calculated using a logistic regression model whereby the matched pairs were added as groups. This test was also performed for the number of smokers, proportion of people with a positive family history for cardiovascular disease, and number of persons with diabetes. We tested for differences in cholesterol, BMI, and BP with an ANOVA model as in the logistic regression model. The 95% confidence intervals (95% CI) and odds ratios (OR) for event rates were calculated for both groups, using estimates for standard errors from the logistic model. The Mann-Whitney U test was used for comparison of catecholamine concentrations between PHEO patients with and without a cardiovascular event. Logistic regression was used to model the effects of possible sources of confounding. Also, the group of excluded PHEO and essential hypertension patients was compared to the group of included patients to test for significant differences in event rates, BP levels, and cardiovascular risk factors. The level of significance was set at 0.05. For all analyses SAS 9.2 software (SAS, Inc, Cary, North Carolina) was used.

Results

A total of 135 patients diagnosed with a PHEO and 205 patients with untreated essential hypertension were ini-

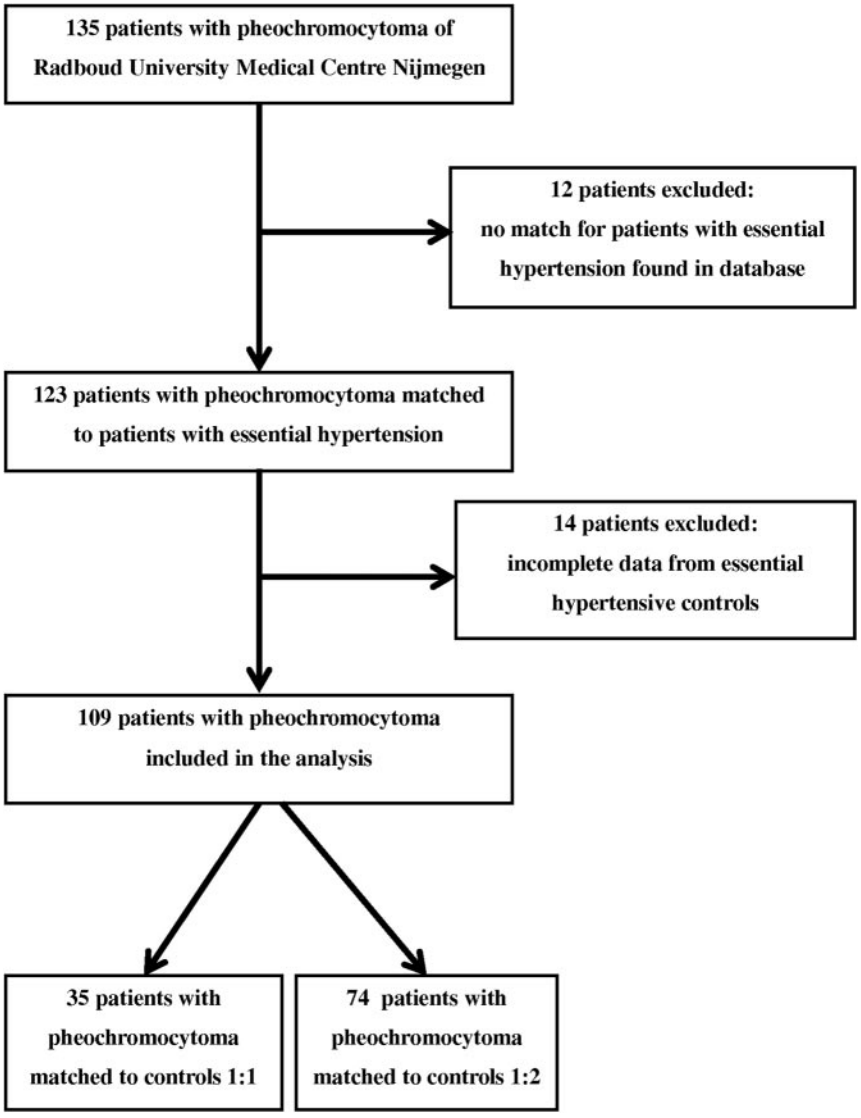

Figure 1. Flowchart of patients.

tially included for the analysis. The analysis was performed on 109 PHEO patients with 74 patients matched to 2 hypertensive controls to improve the power of the study and 35 PHEO patients matched to 1 hypertensive control subject (Figure 1). For 12 PHEO patients no matching controls were found and therefore these patients were excluded from analysis. For another 22 hypertensive control patients, there was uncertainty about the date of diagnosis and therefore these control patients and the 14 matched PHEO patients were excluded as well. There were no differences in gender, age at diagnosis, and year of diagnosis, indicating that matching was successful (Table 1). At admission 50 (45.8%) PHEO patients used antihypertensive medication, whereas it was unknown in 3 patients. All essential hypertensive patients used no antihypertensive medication at the time of diagnosis. In the PHEO group 7 patients had suffered an MI, 4 patients were diagnosed with AP, and 4 patients had a CVA or TIA within 5 years before diagnosis. In the hypertension group 1 patient had experienced a TIA and 1 patient was suffering from AP. In total, 13.8% (95% CI: 7.9%–21.6%) of PHEO patients had suffered from a cardiovascular event as compared to 1.1% (95% CI: 0.1%–3.9%) of the hypertensive patients ($P < .001$, OR for matched patients was 14.3; 95% CI: 3.2–64.4). The differences in rates of CVA/TIA and AP tended to significance ($P = .08$, OR = 6.9 and $P = .08$, OR = 6.9, respectively) (Table 2). In addition, 6 PHEO patients experienced an episode of pulmonary edema. Two PHEO patients were reported to have had an episode of supraventricular arrhythmia, whereas no arrhythmias were recorded in the essential hypertensives. There was no difference in event rate between male and female PHEO patients.

The proportion of patients with a cardiovascular event of the entire population was slightly but not significantly lower ($P = .76$) in the time period of 1977 to 1990 as compared to time periods of 1991 to 2000 and 2001 to 2010 (Table 3).

The BP level in the PHEO patients was 153/91 ± 35/15 mm Hg as compared to 170/103 ± 18/8 mm Hg in the hypertensive controls ($P < .001$). A separate analysis of PHEO patients without antihypertensive medication revealed that systolic ($P < .02$) and diastolic BP ($P < .001$) remained significantly lower than in the hypertensive patients (Table 1).

In 81 PHEO patients who presented with paroxysmal symptoms and/or paroxysmal hypertension, 13 patients had had an event. In the 28 patients who neither had paroxysmal symptoms and paroxysmal hypertension, 2 patients had had an event ($P = .18$).

There were no differences in plasma cholesterol levels or cardiovascular family history (Table 1). There was a smaller proportion of smokers ($P = .012$) among PHEO patients and they had a lower mean BMI (23.7 ± 3.9 vs 27.5 ± 4.2 kg/m^2; $P < .001$) as compared to the hypertensives. The PHEO group comprised a higher proportion of patients with diabetes ($P < .001$) (Table 1). Modeling the excess number of patients with diabetes in the PHEO

Table 1. Characteristics of Both Groups

	Patients With Pheochromocytoma	Patients With Essential Hypertension	*P* Value
Total number of patients	109	183	
Number of males, %	44 (40%)	75 (40%)	
Mean age at diagnosis, y (range)	48.3 (21–78)	48.5 (23–80)	NS
Median year of diagnosis	2001	2001	
Systolic BP, mm Hg	153 ± 35	170 ± 18	<.001
Diastolic BP, mm Hg	91 ± 15	103 ± 8	<.001
Systolic BP, mm Hg, no medication (n = 56)	161 ± 40	170 ± 18	<.02
Diastolic BP, mm Hg, no medication (n = 56)	93 ± 16	103 ± 8	<.001
Smokers, % (n = 105)[a]	37 (35%)	87 (51%)	.012
Diabetes mellitus, % (n = 106)[a]	29 (27%)	10 (5.5%)	<.001
BMI, kg/m^2 (n = 87)[a]	23.7 ± 3.9	27.5 ± 4.2	<.001
Cholesterol, mmol/L (n = 56)[a]	5.8 ± 1.4	5.8 ± 1.3	NS
Glucose, mmol/L (n = 47)[a]	7.4 ± 2.6	5.8 ± 0.8	<.001
Family history of cardiovascular disease, % (n = 103)[a]	19 (18%)	46 (26%)	NS

Abbreviation: NS, not significant. Results are presented as mean ± SD.

[a] The number of pairs of patients in whom the variable was recorded.

group did not show a significant effect on the rate of events ($P = .53$).

Plasma epinephrine and norepinephrine levels and urinary excretion of epinephrine and norepinephrine excretion did not differ between PHEO patients who had suffered an event and those who were event-free (Table 4).

Genetic data were available in 73 (67%) patients (Table 4). In 30 PHEO patients (41%) a genetic mutation or syndrome could be shown: multiple endocrine neoplasia type 2A: 17 patients; multiple endocrine neoplasia type 2B: 1 patient; succinate dehydrogenase, subunit B: 3 patients; succinate dehydrogenase, subunit D: 2 patients; and neurofibromatosis type I (based on the usual clinical diagnostic criteria): 7 patients. There was no difference in the number of patients with a cardiovascular event between the patients with (3/30) and without (7/44) a genetic mutation ($P = .21$).

No significant differences in event rate ($P = 1.00$) and systolic and diastolic BP ($P = .46$ and $P = .14$) were found between included and excluded patients. Similarly, the proportion of smokers, the number of patients with diabetes mellitus, and plasma cholesterol levels did not differ significantly. Only BMI was significantly lower in excluded patients than in the included patients ($P < .001$).

Discussion

In this comparative retrospective study we show that patients with a PHEO have a 14-fold higher rate of cardiovascular events than patients with essential hypertension. Although numerous other studies have reported on rates of cardiovascular morbidity and mortality in patients with PHEO, this is the first study to use a control group of patients with essential hypertension.

A first potential explanation for this difference in event rates is a sustained higher BP level or BP variability in the PHEO group. However, the BP level was lower in the PHEO group than in the essential hypertensives, thus making this mechanism unlikely. This lower BP level is possibly related to the fact that the PHEO group used antihypertensive medication, whereas the hypertension group did not. However, even after exclusion of the PHEO patients who were on drug treatment, the PHEO group still showed a lower BP than the essential hypertensives. An alternative explanation for the lack of a higher BP level in the PHEO patients is the previously shown downregulation and desensitization of adrenoceptors as a consequence of the prolonged elevation of plasma catecholamine levels (14). It should be noted that, because we only

Table 2. Number of Cardiovascular Complications in Both Groups Within 5 Years Before Diagnosis

Patients with CV Complications 5 y Before Diagnosis	Patients With Pheochromocytoma (n = 109)	Patients With Essential Hypertension (n = 183)	*P* Value	Odds Ratio (95% CI)
Myocardial infarction	7	0		
Angina pectoris	4	1	NS	6.9 (0.7–63.4)
CVA/TIA	4	1	NS	6.9 (0.7–63.4)
Total number of events. % (95% CI)	15 (13.8) (7.9–21.6%)	2 (1.1) (0.1–3.9%)	<.001	14.4 (3.2–64.4)

Abbreviation: NS, not significant.

Table 3. Number of Cardiovascular Events in 3 Different Time Periods in Patients With Pheochromocytoma and Patients With Essential Hypertension

	Time Period		
	1977–1990	1991–2000	2001–2010
Patients with pheochromocytoma	13	40	56
Myocardial infarction	1	4	2
Angina pectoris	0	1	3
CVA/TIA	0	1	4
Patients with essential hypertension	18	56	109
Myocardial infarction	0	0	0
Angina pectoris	0	0	1
CVA/TIA	0	0	1
Total	1/31 (3%)	6/96 (6%)	11/165 (7%)

have information on BP at the time of diagnosis, it cannot be excluded that the BP load over this entire 5-year period prior to the diagnosis was higher in the PHEO group as compared to the hypertensive group. In addition, in patients with PHEO, BP is known to be much more variable (15). This increased variability itself might also have deleterious effects on the cardiovascular system but our study cannot provide data to support this contention. The average BP level at the time of diagnosis may not be fully representative for the actual BP level and BP variability over this prolonged observation period. In contrast to the patients with essential hypertension, patients with PHEO may have suffered from severe hypertensive spells, which may be responsible for the higher event rate. Although this remains a possible explanation, an analysis within the PHEO group did not show that patients with paroxysmal hypertension had a higher event rate than the PHEO patients with sustained hypertension.

An alternative explanation for the difference in cardiovascular event rates could be a difference in other cardiovascular risk factors besides hypertension. However this possibility is unlikely because there were no significant differences in plasma cholesterol and cardiovascular family history. The essential hypertensives had an even higher BMI and contained a higher number of smokers than the PHEO group. As expected based on previous studies, only the prevalence of diabetes mellitus was higher in the PHEO patients than in the essential hypertensives. The higher rate of diabetes is caused by the β-adrenoreceptor-mediated gluconeogenesis and glycogenolysis by catecholamines and by their α-adrenoreceptor-mediated inhibitory effect on insulin secretion (16). Although the higher prevalence of diabetes might contribute to the higher cardiovascular event rate in the PHEO patients, modeling the excess of patients with diabetes in the PHEO group did not reveal a significant effect on the rate of cardiovascular events.

A major alternative factor that might help explain the high rate of cardiovascular incidents in the PHEO group are the deleterious effects of catecholamines. It has been known for a long time that catecholamines have serious toxic effects on the cardiovascular system. Catecholamines have been shown to have direct negative effects on the myocardium and coronary arteries where they can promote vasoconstriction and atherosclerosis (17, 18). In the myocardium, both epinephrine and norepinephrine can produce cardiac dysfunction by inducing intracellular calcium overload in cardiomyocytes. In addition, high concentrations of catecholamines are oxidized to form aminolutins and generate oxyradicals, leading to coronary spasm, arrhythmias, and cardiac contractile dysfunction (17, 18). Also, defects in energy production by their effect on mitochondrial function have been described (17, 18).

Cardiac risk can be enhanced further by the stimulating effect on platelet aggregation through promoting glycoprotein IIb/IIIa sites for fibrinogen binding and through enhancing phospholipase C activation (19–21). Apart from the hemodynamic effects on the coronary vasculature, animal studies have shown that even in the absence of BP and cholesterol level changes, catecholamines have a direct effect on the arterial wall and can aggravate and accelerate the atherosclerotic process (22, 23). Furthermore, it has been shown in a previous study that catecholamine injection (either bolus or continuous), after a brief dilator response, induces an increase in coronary artery resistance with a concomitant decrease in coronary oxygen tension (24). Indirect evidence for the atherogenic effects of catecholamines is provided by studies that have shown that sympatholytic agents reduce medial hypertrophy and atherogenesis, beyond the effects found by lowering BP (25, 26).

In the cerebrovascular bed, excess catecholamines are responsible for cerebral ischemia through their vasospastic effects on the cerebrovascular vessels (27, 28). Apart from vasoconstrictive effects, cerebrovascular accidents can be due to brain thromboembolism in patients with cardiomyopathy (29). Severe vasoconstriction may also occur in other vascular beds such as those in legs and mesenterium, where they give rise to mesenterial and limb ischemia (30–32).

Analysis of plasma and urine catecholamines did not show a significant difference in event rate between the PHEO patients who had suffered a cardiovascular event and those PHEO patients who had not. Although this might suggest that catecholamines do not play an etiologic role in the development of cardiovascular events, it is important to take into account that the plasma catechol-

Table 4. Clinical, Biochemical, and Genetic Characteristics and Tumor Size and Location of Pheochromocytoma Patients With and Without a Cardiovascular Event

	Patients With Pheochromocytoma With Event (n = 15)	Patients With Pheochromocytoma Without an Event (n = 94)	*P* Value	n
Clinical features				
Duration of complaints (mo)	48.0 (4.0–372)	22.5 (2.0–204)	.06	89
Paroxysmal symptoms (%)	10 (66.7)	62 (66.0)	NS	72
No paroxysmal symptoms, %	5 (33.3)	32 (34.0)	NS	37
Normotensives, %	2 (13.3)	33 (35.1)	NS	35
Paroxysmal hypertension, %	10 (66.7)	37 (39.4)	NS	47
Sustained hypertension, %	2 (13.3)	15 (16.0)	NS	17
Biochemical values				
Plasma epinephrine, nmol/L	0.71 (0.17–3.22)	1.26 (0.28–2.66)	NS	90
Plasma norepinephrine, nmol/L	11.3 (8.15–22.1)	9.01 (3.13–34.7)	NS	90
Urinary epinephrine, nmol/24 h	49 (41.0–619)	146 (72.5–743)	NS	41
Urinary norepinephrine, nmol/24 h	1741 (1546–5068)	1515 (521.0–3317)	NS	40
Number of patients with syndromal tumors				
MEN2A	1	16	—	17
MEN2B	0	1	—	1
SDHB mutation	1	2	—	3
SDHD mutation	1	1	—	2
Neurofibromatosis I	0	7	—	7
No mutation tested	5 (33.4%)	31 (33.0%)	—	36
Tumor size, cm	8.5 (7.0–9.5)	7.0 (5.0–8.0)	.033	98
Tumor location				
Left adrenal	6	33	—	39
Right adrenal	6	47	—	53
Extra-adrenal	3	11	—	14
Bilateral adrenal	0	2	—	2
Adrenal + extra-adrenal	0	1 (left side)	—	1
Metastases at presentation	0	0	—	0

Abbreviations: NS, not significant; —, not statistically tested. Duration of symptoms, plasma concentrations of plasma and urinary catecholamines and tumor size are given as median and first and third quartiles.

amine level is not representative for the exposure of the cardiovascular system over a prolonged period of time.

The data of the current study have clinical relevance because they emphasize the importance of an early diagnosis of a PHEO. Once the tumor is surgically removed, it has been repeatedly shown that life-expectancy in these patients is not substantially lower than in a comparable group of subjects from the general population. Life expectancy is only reduced in patients with a malignant PHEO (8, 9).

Several limitations of this study must be mentioned. First of all, our study may underestimate the rate of serious cardiovascular complications because we did not take into account those patients who have died of acute cardiovascular events and in whom the tumor was left undiagnosed. Therefore, the true difference in cardiovascular event rates might even be larger than what we found. The same applies to the duration of hypertension. Matching both groups for the duration of hypertension was not possible because we included only newly diagnosed hypertensive patients but, even if the hypertension would have existed for a prolonged time period before diagnosis, if anything, this should have reduced the difference between both groups instead of increasing it. Another caveat for the interpretation of our results is the effect of the proportion of PHEO patients who have a hereditary cause of the tumor. The high cardiovascular event rate may not apply to patients with a hereditary predisposition because they are diagnosed at a lower age than patients with a sporadic PHEO (33). However, the event rate was similar in the patients with and without a hereditary predisposition. Another potential limitation of this study is a change in the diagnostic quality of cardiovascular events over the wide time course of this study. Nevertheless, we could not show a significant difference in time-related event rates between the 2 groups and therefore it is unlikely that this has affected the conclusion of our study. Finally, the diagnostic systolic BP level of 160 mm Hg in the essential hypertension can nowadays be considered too high. Despite this, the cardiovascular event rate was lower in this group, reiterating that the BP level itself is unlikely to be responsible for the higher event rate in the patients with PHEO. A relatively large proportion of PHEO patients was excluded, either because matched hypertension patients had unreliable data or because no matched hypertensive patients could be found. Nevertheless,

analysis of the group of excluded patients showed no significant differences in event rate nor BP.

We conclude that PHEO patients have a clearly higher rate of cardiovascular events than patients with essential hypertension, despite a lower BP level in the PHEO patients. This difference can also not be attributed to a difference in the other conventional cardiovascular risk factors. The most likely explanation for the increased rate in cardiovascular events is the prolonged exposure to the toxic effects of tumoral catecholamines. The data of this study underpin the importance of a timely diagnosis and treatment of PHEO.

Acknowledgments

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