Long-Term Effect of Adrenalectomy on Cardiovascular Remodeling in Patients With Pheochromocytoma

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Context: Catecholamines may contribute to the accumulation of collagen fibers and extracellular matrix in the arterial and myocardial wall due to various mechanisms. Reversibility of this process has not been studied on both structures simultaneously.

Objective: To clarify the long-term effect of excess normalization of catecholamines on carotid and myocardial wall changes in patients with pheochromocytoma or functional paraganglioma (PHEO) after tumor removal.

Design, Settings, and Patients: Carotid intima-media thickness (IMT) and the left ventricular (LV) mass index were studied in 50 patients with PHEO before tumor removal and 5 years after tumor removal, and in 50 blood pressure– and age-matched essential hypertensive patients before follow-up and after 5 years of follow-up.

Main Outcome Measures: Common carotid artery (CCA)–IMT and LV mass indexed to lean body mass (LBM).

Results: Elimination of catecholamine excess in the PHEO group resulted in a significant decrease in CCA-IMT and LV mass index from 0.86 ± 0.17 to 0.83 ± 0.18 mm ($P < 0.05$) and from 3.2 ± 0.9 to 2.9 ± 0.9 g/LBM ($P < 0.001$), respectively. In contrast, CCA-IMT and LV mass index increased significantly from 0.78 ± 0.14 to 0.81 ± 0.15 mm ($P < 0.05$) and from 3.1 ± 0.7 to 3.2 ± 0.6 g/LBM ($P < 0.05$), respectively, in patients with essential hypertension.

Conclusion: In patients with PHEO, carotid IMT and LV mass index can significantly regress after tumor removal, in contrast to the impairment of these parameters in essential hypertensive patients during the same long-term period. (***J Clin Endocrinol Metab*** **102: 1208–1217, 2017)**

Pheochromocytomas or functional paragangliomas (PHEO) are tumors arising from chromaffin cells from adrenal medulla (pheochromocytoma) or from sympathetic nervous system–associated chromaffin tissue (functional paraganglioma). They have the ability to produce, metabolize, and secrete catecholamines. Catecholamines produced by the tumor cells are responsible for a large variety of signs and symptoms because of their effect on hemodynamics and metabolism (1, 2).

In vitro (3) and *in vivo* (4, 5) studies showed that catecholamines influence vascular wall growth and remodeling, independently of their hemodynamic impact. This

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Abbreviations: BP, blood pressure; CB, carotid bifurcation; CC, correlation coefficient; CCA, common carotid artery; IMT, intima-media thickness; IVS, interventricular septum; LBM, lean body mass; LV, left ventricular; LVED, left ventricular end-diastolic; LVPW, left ventricular posterior wall; PHEO, pheochromocytoma or functional paraganglioma; SD, standard deviation.

direct action of catecholamines on the vascular bed (3, 6, 7) through extracellular matrix protein activity with protein synthesis and collagen deposition (8) may consequently lead to vascular eutrophic remodeling. In contrast to experimental vascular injury (3), this process involves proliferation, hypertrophy, and migration of smooth muscle cells and adventitial fibroblasts, leading to hypertrophic remodeling.

In humans, only limited data are available concerning the effects of chronic catecholamine overproduction on the vasculature. Activation of the adrenergic system may play a relevant role in the development of eutrophic remodeling in small vessels (9), whereas both eutrophic and hypertrophic remodeling may occur in large arteries. Hypertrophic remodeling was identified by ultrasound in the form of large arterial or myocardial wall thickening. Previous studies, which enrolled relatively low numbers of patients, found no or only borderline differences (10–12). However, recently published larger studies confirmed that more advanced structural alterations of carotid arteries, represented by increased intima-media thickness (IMT) in patients with pheochromocytoma compared with those in essential hypertensive patients (13), diminished after adrenalectomy (14).

Similarly, eutrophic vascular remodeling presented by fibrosis was indirectly detected in patients with pheochromocytoma, using an ultrasonic integrated backscatter signal technique (14) or a pulse wave velocity measurement (15). This remodeling was more pronounced than that in essential hypertensive patients and diminished after adrenalectomy.

Alternatively, none of the studies described changes in both the arterial and myocardial walls after normalization of catecholamine overproduction in a relatively large group of patients, and none of the studies provided a comparison of these changes with those in essential hypertensive patients. Our prospective study was aimed at investigating the hypothesis that structural alterations of carotid arteries and of left ventricular (LV) myocardial wall, characterized by increased IMT and LV mass, diminish after tumor removal.

Methods

Study population

Patients were recruited from a prospective cohort of almost 2800 patients investigated between November 2003 and June 2011 at our tertiary hospital-based Hypertension Center because of resistant hypertension, paroxysmal symptoms suspected of pheochromocytoma, or adrenal tumors. Chronic antihypertensive therapy was discontinued at least 2 weeks before admission, and patients were switched to the treatment with α-blockers and/or slow-release verapamil. Each participant provided his/her written informed consent, and the study protocol was approved by the local Ethics Committee.

During the aforementioned period, the diagnosis of PHEO was newly confirmed in 84 patients, that is, with a 3% rate in this preselected population. The diagnosis of PHEO was based on elevated plasma metanephrine, normetanephrine, or 24-hour urine catecholamines above the upper reference limit, and positive finding on computed tomography or magnetic resonance imaging. All subjects underwent surgical removal of the tumor, and the diagnosis was confirmed histopathologically. A study flowchart is shown in Supplemental Fig. 1. Twenty patients were not enrolled due to poor quality of ultrasound images or significant comorbidities, including carotid and/or coronary atherosclerosis. Nine patients were subsequently excluded due to malignant tumor or persistent catecholamine overproduction after tumor removal, and 5 patients were not analyzed because of incomplete data or a lack of follow-up. Finally, 50 patients with PHEO, aged 30 to 77 years (25 men and 25 women), were suitable for investigation. Three of these (6%) had bilateral tumors, 5 (10%) had extra-adrenal tumors, and 6 (12%) had hereditary forms of the disease (Supplemental Table 1).

The control group of patients with essential hypertension was composed from the same prospective cohort as for PHEO patients, on the basis of matching age, sex, and office systolic blood pressure (BP). In total, 50 essential hypertensive or prehypertensive patients (25 men and 25 women) were selected, after exclusion of the main forms of secondary hypertension (primary aldosteronism, pheochromocytoma, Cushing syndrome, renal parenchymal disease, renovascular hypertension) or drug-induced hypertension. The subjects were considered hypertensive or prehypertensive when their clinic BP, an average of 3 sphygmomanometric measurements performed on 3 separate days, was $\geq$140/90 mm Hg or $\geq$130/80 mm Hg, respectively (16). Diabetes mellitus was defined as medication with oral antidiabetic drugs or repeated fasting glucose levels of $>$126 mg/dL ($>$7.0 mmol/L) (17). Insulin-dependent diabetic patients were not enrolled, except for 2 patients with PHEO who were on insulin therapy shortly before adrenalectomy. All subjects with dyslipidemia [total plasma cholesterol $\geq$ 200 mg/dL ($\geq$5.0 mmol/L) or low-density cholesterol $\geq$ 100 mg/dL ($\geq$3.0 mmol/L) or high-density lipoprotein cholesterol $\leq$ 40 mg/dL ($\leq$1.0 mmol/L) in men and $\leq$ 50 mg/dL ($\leq$1.2 mmol/L) in women or triglycerides $\geq$ 150 mg/dL ($\geq$1.7 mmol/L)] were on a diet and received lipid-lowering therapy (18).

All patients were followed at our Center and re-examined at least 4 years after the baseline examination. In all PHEO patients, this was performed as a part of a 2-day hospitalization.

BP measurement

Baseline office BP was measured in the sitting position by using a standard sphygmomanometer in all patients on their chronic antihypertensive treatment on the ambulatory visit, prior to switching to the treatment with α-blockers and/or slow-release verapamil. The measurement was repeated at the final visit at least 4 years after the enrollment.

Laboratory

Urine catecholamines were analyzed by high-performance liquid chromatography with a fluorometric detector (Agilent 1100S; Agilent Technologies, Wilmington, DE). The system was calibrated with a catecholamine standard using a ClinRep test kit (Recipe Chemicals and Instruments, Munich, Germany). Plasma-fractioned metanephrines (normetanephrine and metanephrine) were quantified by liquid chromatography

with electrochemical detection (Agilent 1100; Agilent Technologies) (19).

Blood biochemistry, including sodium, potassium, urea, creatinine, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, and plasma glucose, was analyzed using a multianalyzer (Modular SWA; Roche Diagnostics, Basel, Switzerland) in the institutional central laboratory. Creatinine clearance was calculated using the Cockcroft–Gault equation.

Echocardiography

M-mode, 2-dimensional, and Doppler echocardiography [Philips Sonos 5500 (Philips Healthcare, Andover, MA) or GE Healthcare Vivid 7 Dimension (GE Vingmed Ultrasound, Horten, Norway)] was performed according to a standard protocol. M-mode images of the left ventricle at the mitral valve tip were obtained, guided by a 2-dimensional parasternal short-axis or long-axis view, with the subjects lying down in the left lateral decubitus position, at end-expiration. The LV end-diastolic (LVED) diameter, interventricular septum (IVS) thickness, and LV posterior wall (LVPW) thickness were measured at the end of diastole according to the recommendations of the American Society of Echocardiography (20). The LVED index was calculated as the LVED diameter indexed to the body surface area in square meters (LVED diameter/body surface area). LV mass estimation using American Society of Echocardiography convention was used (21): LV mass (grams) = $0.8 \times 1.04 \times [(\text{LVED diameter} + \text{IVS thickness} + \text{LVPW thickness})^3 - (\text{LVED diameter})^3] + 0.6$ (with diameters in centimeters). Three variants of LV mass indexing were used: to the body surface area in square meters, to the 2.7th power of height in meters, and to the lean body mass (LBM) in kilograms (22). LBM was calculated using the Boer formula: LBM = $0.407 \times$ weight (kg) + $0.267 \times$ height (cm) − 19.2 (for men) and LBM = $0.252 \times$ weight (kg) + $0.473 \times$ height (cm) × 48.3 (for women) (23). Echocardiography examinations were performed by 2 cardiologists (R.H. and O.P.) blinded to participants' diagnoses.

Carotid ultrasound and IMT measurement

High-resolution B-mode carotid ultrasound was performed with a multifrequency (5 to 10 MHz) linear array transducer [Acuson Sequoia 512 (Siemens Medical Solutions, Mountain View, CA) or GE Healthcare Vivid E9 (GE Vingmed Ultrasound)]. Standardized longitudinal B-mode images of the far wall were obtained proximally from the tip of the flow divider (0 reference point). Carotid segments, carotid bifurcation (CB), and common carotid artery (CCA) were defined between 0 and 10 mm and between 10 and 20 mm from this reference point, respectively. Using a Meijer's Carotid Arc (Meyer Medical Ultrasound, Utrecht, The Netherlands), images were taken at 2 angles of 90 and 150 degrees for the right carotid artery, and 210 and 270 degrees for the left carotid artery (24). When an optimum image was obtained, it was frozen on the top of the R wave of the QRS complex, and saved in the DICOM format.

The IMT measurements were performed off-line. Frozen images were displayed on the computer screen, using an automated Image-Pro Plus version 4.0 edge detection program (Media Cybernetics, Silver Spring, MD). In each image, the visualized blood–intima and media–adventitia boundaries (including the presented plaques) of the far wall were marked with a computer mouse-controlled caliper within the defined segment (25). The maximum distance between these 2 lines was considered the representative IMT for each segment. The mean of 4 IMT measurements (from 2 angles and 2 sides) was calculated for CCA and CB segments (CCA-IMT, CB-IMT). Combined IMT per patient was calculated as an average of CCA-IMT and CB-IMT. This approach was described in detail elsewhere (26). Ultrasound examinations and the off-line IMT measurements were performed by 2 sonographers/readers (R.H. and J.R.) blinded to participants' diagnoses.

Reproducibility substudy

Cardiologists involved in the study performed identical duplicate ultrasound examinations on 20 subjects within 3 weeks. Reproducibility of individual echocardiographic and IMT indices was quantified by the assessment of coefficients of variation within the pairs of measurements for individual patients. These were subsequently averaged to obtain the mean coefficient of variation with a corresponding standard deviation (SD). Reproducibility of individual indices was as follows: 3.4% ± 1.8% for CCA-IMT, 4.4% ± 4.9% for CB-IMT, 3.2% ± 2.1% for combined IMT, 4.5% ± 3.6% for IVS thickness, 2.0% ± 2.0% for LVED diameter, 4.4% ± 3.0% for LVPW thickness, and 5.5% ± 4.8% for LV mass.

Statistical analysis

Data were analyzed using Statistica version 12.1 (StatSoft, Tulsa, OK). Depending on the normality/nonnormality of the distributions of particular variables, the results were given as mean ± SD values or median values (interquartile range). Differences between the 2 groups (before and after adrenalectomy) were analyzed using the paired *t* test or the Kruskal–Wallis test for normally or nonnormally distributed variables, respectively. A McNemar test was used for categorical data. A Pearson correlation analysis was used to assess the relationship between the IMT and other clinical parameters, as well as the relationship between their treatment-induced changes. A Spearman correlation was used for nonnormally distributed indices. A P value of <0.05 was considered significant.

Results

Clinical data

The mean follow-up was 5.0 ± 0.9 years after tumor removal and 5.1 ± 2.3 years in essential hypertensive patients. None of the investigated patients after adrenalectomy had recurrence of the disease. Age, sex, body mass index, and the distribution of major cardiovascular risk factors were comparable at baseline, except the proportion of patients with diabetes, which was higher in patients with PHEO compared with essential hypertensive patients (Table 1). Thirty-eight (76%) patients with PHEO were admitted for paroxysmal symptoms of catecholamine excess. Ten (20%) patients with PHEO had sustained hypertension and adrenal

Table 1. Baseline Clinical Characteristics

	Pheochromocytoma (n = 50)	Essential Hypertension (n = 50)	*P*
Age, y	52 ± 14	54 ± 9	NS
Sex, female/male (% female)	25/25 (50)	25/25 (50)	NS
Height, m	1.71 ± 0.09	1.73 ± 0.10	NS
Body mass index, kg/m^2	26.8 ± 5.2	27.7 ± 4.9	NS
Manifestation of the disease prior to enrollment, y	6.4 ± 4.7	6.9 ± 6.5	NS
Current cigarette smoking, n (%)	16 (32)	10 (20)	NS
Diabetes mellitus, n (%)	19 (38)	4 (8)	<0.01
Dyslipidemia, n (%)	18 (36)	24 (48)	NS
Myocardial involvement, n (%)	5 (10)	0 (0)	NS
Atrial fibrillation, n (%)	1 (2)	2 (4)	NS
Stroke, n (%)	0 (0)	1 (2)	NS

Values represent means ± SDs or absolute numbers (percentages).

Abbreviation: NS, not significant.

tumor. Pheochromocytoma was diagnosed in 1 patient with asymptomatic adrenal tumor, and paraganglioma was discovered in 1 asymptomatic patient as a part of routine screening because of mutation of the tumor susceptibility gene (succinate dehydrogenase complex subunit D) (Supplemental Table 1). Three (6%) PHEO patients had a history of non-ST elevation myocardial infarction with normal findings on coronary angiography.

After tumor removal, diabetes disappeared in 15 of 19 (79%) patients, whereas 3 patients with essential hypertension developed diabetes. The proportion of patients with dyslipidemia increased in both groups (significantly in essential hypertensive patients), and 5 patients quit smoking in both groups during the 5-year follow-up. During the study, 2 of the essential hypertensive patients experienced myocardial infarction and 4 patients had a new onset of atrial fibrillation. Alternatively, none of the patients after tumor removal experienced a new cardiovascular or cerebrovascular event.

Laboratory data

As expected, all endocrine-related laboratory data in patients with PHEO (higher plasma metanephrines, normetanephrines, as well as higher urine epinephrines, norepinephrines, and dopamine) normalized after tumor removal (Supplemental Table 2).

The patients with PHEO had a significantly lower plasma creatinine (nevertheless, only nonsignificantly higher creatinine clearance) and a significantly higher high-density lipoprotein cholesterol and fasting plasma glucose compared with those in essential hypertensive patients (Supplemental Table 3).

Lipid levels generally decreased (some of them significantly) in both groups during the follow-up. However, there were no consistent and clinically meaningful differences between the groups. As expected, fasting plasma glucose dropped significantly after tumor removal ($P < 0.001$), and between-group difference in this change was significant ($P < 0.001$) (Supplemental Table 4).

BP, antihypertensive treatment, and body weight

After tumor removal, 29 (58%) patients became normotensive, and their antihypertensive therapy was discontinued, whereas 16 patients still required antihypertensive therapy, although at smaller doses and with a fewer number of agents compared with baseline. A significant decrease was achieved in α-blockers, β-blockers, and calcium channel blockers. One patient stayed on doxazosin treatment because of benign prostatic hyperplasia, and spironolactone was started in 1 patient to treat persistent hypokalemia (Table 2).

Office systolic and diastolic BP were comparable between study groups at baseline because of BP matching. Both systolic and diastolic BP decreased significantly in both groups during follow-up, and BP reduction was significantly higher in the PHEO group (Tables 3 and 4).

The difference in the numbers of antihypertensive drugs before and after tumor removal was significant when compared with essential hypertensive patients ($P < 0.001$).

At baseline, body weight was comparable between study groups, and the significant weight gain observed during follow-up in both groups was statistically greater in patients with PHEO, which more or less projected to the different increase in LBM between groups (Tables 3 and 4).

Echocardiographic and carotid ultrasound parameters

Among echocardiographic parameters and intima-media measurement, only CCA-IMT was higher in patients with PHEO, compared with essential hypertensive patients at baseline (Table 3).

IVS thickness, LV mass, and LV mass index (irrespective of the type of indexing) significantly decreased

Table 2. Medical Treatment at Baseline and at the End of the Study

	Baseline			End of Study		
	PHEO (n = 50)	EH (n = 50)	*P*	PHEO (n = 50)	EH (n = 50)	*P*
Diuretics	10 (20)	20 (40)	<0.001	7 (14)	27 (54)[a]	<0.001
β-Blockers	21 (42)	23 (46)	NS	3 (6)[b]	20 (40)	<0.001
Calcium channel blockers	19 (38)	24 (48)	<0.01	6 (12)[c]	24 (48)	<0.001
Angiotensin-converting enzyme inhibitors	12 (24)	24 (48)	<0.001	7 (14)	24 (48)	<0.001
Angiotensin receptor blockers	9 (18)	10 (20)	NS	3 (6)	10 (10)	<0.05
α-Blockers	31 (62)	11 (22)	<0.001	1 (2)[b]	11 (22)	<0.001
Central agonists	5 (10)	12 (24)	<0.01	0 (0)	5 (10)[d]	<0.05
Aldosterone antagonists	0 (0)	4 (8)	<0.05	1 (2)	8 (16)	<0.01
Statins	12 (24)	15 (30)	NS	18 (36)[c]	28 (56)[d]	<0.001
Other lipid-lowering drugs	6 (12)	9 (18)	NS	6 (12)	9 (18)	NS
Insulin	2 (4)	0 (0)	NS	0 (0)	0 (0)	NS
Oral antidiabetic drugs	11 (22)	2 (4)	<0.01	4 (8)[b]	5 (10)	NS

Values represent absolute numbers (percentages).

Abbreviations: EH, essential hypertension; NS, not significant.

[a] $P < 0.05$ vs essential hypertension at baseline.

[b] $P < 0.01$ vs pheochromocytoma at baseline.

[c] $P < 0.05$ vs pheochromocytoma at baseline.

[d] $P < 0.01$ vs essential hypertension at baseline.

after adrenalectomy, compared with no change or increase in patients with hypertension, and between-group difference in the change was significant [Table 4; Fig. 1(A–C)].

All carotid IMT parameters decreased after adrenalectomy, but only the change measured in the common carotid artery achieved statistical significance. In essential hypertensive patients, all carotid IMT parameters increased during the follow-up and this was significant for CCA and combined IMT. Consequently, between-group differences in CCA-IMT and combined IMT were also significant [Table 4; Fig. 1(D–F)].

In the total population, IMT and LV mass indices positively correlated with age, with correlation coefficients (CCs) of 0.43 to 0.52 and 0.21 to 0.31, respectively. LV mass indices correlated with office systolic BP (CCs of 0.50 to 0.57) in patients with essential hypertension, whereas these correlations were much weaker (CCs of 0.29 to 0.34) in patients with pheochromocytoma. The association between baseline BP and IMT indices was virtually absent. We did not observe any meaningful correlations between the change in IMT or LV mass indices and the decrease in BP or reduction of urinary catecholamine levels in the subgroup of 35 patients with PHEO after tumor removal. Similarly, there was no significant correlation between the change in IMT and LV mass indices.

Discussion

The major finding of the study is the positive long-term effect of the elimination of catecholamine excess on carotid vascular and myocardial remodeling in patients with PHEO after tumor removal. The reversal of morphological changes found at baseline may represent a surrogate of the uneventful clinical follow-up that contrasted with the historical evidence of a high incidence of cardiovascular complications in patients with PHEO prior to tumor removal (27).

A systolic BP decrease (by ~15 mm Hg, or 12%) in patients with PHEO could *per se* reduce the LV mass index by ~9 g/m^2 (10%). In a large meta-analysis of treatment effects in patients with essential hypertension (28), reduction of systolic BP by 12% was associated with LV mass index reduction by 9% (weighted average across all medical therapies), that is, with an almost equally pronounced relative effect, compared with our study. However, the drop in diastolic BP (by 13% in this meta-analysis), which was found to be the main determinant of LV mass index reductions, was virtually twice as high as that observed in our study (by ~8 mm Hg, or 6%). This may still suggest other specific beneficial effects of tumor removal, that is, beyond simple BP reduction.

A regression of myocardial hypertrophy after stopping catecholamine overproduction was published by Denolle *et al.* (29). Among patients with different types of secondary hypertension, a reduction of 12 g/m^2 (5%) in LV mass index was observed in a group of 9 patients with pheochromocytoma, examined 7 months after adrenalectomy, whereas mean lowering of their 24-hour BP was by ~5/5 mm Hg (5/6%). Owing to the small size of the group, the difference did not achieve statistical significance. Contrary to findings of the study by

Table 3. Outcome Parameters at Baseline and at the End of the Study (Comparison of Study Groups)

	Baseline				End of Study			
Variable	PHEO	EH	PHEO to EH Difference Mean (95% CI)	*P*	PHEO	EH	PHEO to EH Difference Mean (95% CI)	*P*
Weight, kg	78 ± 15	82 ± 17	−4.5 (−10.8, 1.8)	0.16	82 ± 15	84 ± 18	−2.6 (−9.2, 4.0)	0.43
LBM, kg	55 ± 9	57 ± 11	−2.5 (−6.4, 1.5)	0.22	56 ± 10	58 ± 11	−1.9 (−6.0, 2.2)	0.37
Office systolic BP, mm Hg	147 ± 16	148 ± 20	−1 (−8, 6)	0.76	131 ± 12	142 ± 21	−10 (−17, −4)	<0.001
Office diastolic BP, mm Hg	91 ± 13	89 ± 12	2 (−3, 7)	0.44	82 ± 9	85 ± 10	−2 (−6, 1)	0.19
Number of drugs used	2.1 ± 1.2	2.6 ± 2.0	−0.4 (−1.1, 0.2)	0.20	0.6 ± 0.9	2.6 ± 1.8	−2.0 (−2.5, −1.5)	<0.001
IVS thickness, mm	10.1 ± 1.7	9.7 ± 1.6	0.4 (−0.3,1.0)	0.30	9.5 ± 1.4	10.0 ± 1.5	−0.4 (−1.1, 0.2)	0.18
LVED diameter, mm	48.5 ± 4.9	50.3 ± 5.0	−1.7 (−3.7, 0.3)	0.09	47.9 ± 5.6	51.4 ± 5.1	−3.5 (−5.8, −1.2)	<0.01
LVED index, mm/m^2	25.7 ± 2.7	25.5 ± 2.3	0.12 (−0.9, 1.2)	0.81	24.9 ± 2.6	26.0 ± 2.3	−1.0 (−2.1, 0.03)	0.06
LVPW thickness, mm	9.6 ± 1.6	9.6 ± 1.7	0.02 (−0.6, 0.7)	0.94	9.2 ± 1.4	9.7 ± 1.4	−0.4 (−1.0, 0.2)	0.17
LV mass, g	173 ± 50	180 ± 60	−7.3 (−29.4, 14.8)	0.51	159 ± 45	190 ± 55	−31.4 (−53.3, −9.6)	<0.01
LV mass index, g/m^2	91 ± 25	90 ± 23	1.2 (−8.5, 10.8)	0.81	83 ± 23	95 ± 20	−12.3 (−21.6, −2.9)	<0.05
LV mass index, $g/m^{2.7}$	41 ± 12	41 ± 12	0.4 (−4.5, 5.3)	0.86	38 ± 12	43 ± 11	−4.8 (−9.6, 0.03)	0.05
LV mass index, g/LBM	3.2 ± 0.9	3.1 ± 0.7	0.1 (−0.2, 0.4)	0.52	2.9 ± 0.9	3.2 ± 0.6	−0.3 (−0.7, −0.01)	<0.05
CCA-IMT, mm	0.86 ± 0.17	0.78 ± 0.14	0.08 (0.01, 0.1)	<0.05	0.83 ± 0.18	0.81 ± 0.15	0.02 (−0.04, 0.09)	0.48
CB-IMT, mm	1.24 ± 0.43	1.11 ± 0.35	0.1 (−0.04, 0.3)	0.13	1.18 ± 0.38	1.15 ± 0.31	0.03 (−0.1, 0.2)	0.68
Combined IMT, mm	1.05 ± 0.26	0.95 ± 0.23	0.1 (−0.004, 0.2)	0.06	1.00 ± 0.25	0.98 ± 0.22	0.02 (−0.07, 0.1)	0.63

Values represent means ± SDs or means (95% confidence intervals).

CI, confidence interval; EH, essential hypertension.

Denolle *et al.* (29), who observed an increase in LV volume after adrenalectomy, we cannot confirm this phenomenon, similarly to the recently published study by Ferreira *et al.* (30) using magnetic resonance imaging.

Carotid IMT regression was described by Bernini *et al.* (14) in 10 normotensive patients with pheochromocytoma examined 21 and 32 months after surgery. The authors considered the favorable effect on carotid wall remodeling directly caused by stopping the catecholamine overproduction. In our study, most patients (85%) with pheochromocytoma were hypertensive. After adrenalectomy, BP reduction was significant (by ~15/8 mm Hg), but carotid remodeling was comparable to that found in the Bernini *et al.* study. This again provokes speculations about other indirect effects induced by interruption of the catecholamine overproduction.

One of the mechanisms that can participate in vascular and cardiac structure remodeling is BP variability. In our previous study, we found that the excess of catecholamines in patients with pheochromocytoma was associated with exaggerated BP variability, compared with subjects with essential hypertension (31). An enhanced 24-hour systolic BP variability was proven as another possible risk factor leading to increased carotid intima-media thickening, and a variability in the systolic BP during the night is an independent predictor of cardiac events in initially untreated patients, independent of office BP or other cardiovascular risk factors (32).

Another mechanism that may also play a role in the acceleration of cardiovascular hypertrophy is higher fasting plasma glucose concentration in subjects with pheochromocytoma (33). There is evidence that hyperglycemia in subjects with diabetes mellitus can contribute to the proliferation of arterial smooth muscle cells (34), in particular by the accumulation of advanced glycosylation end products and protein cross-links in the arterial wall (35).

Finally, a chronic inflammatory process may also lead to a more pronounced thickening of carotid intima media (36–38). In our previous study, we showed that chronic catecholamine excess in subjects with pheochromocytoma was accompanied by an increase in inflammatory markers, which was reversed by the tumor removal (39).

Table 4. Outcome Parameters (Comparison of Treatment Effects)

	Change From Baseline in PHEO (n = 50)		Change From Baseline in EH (n = 50)		Between-Group Difference in Change	
	Mean (95% CI)	*P*	Mean (95% CI)	*P*	Mean (95% CI)	*P*
Weight, kg	3.8 (2.4, 5.2)	<0.001	1.9 (0.6, 3.2)	<0.01	1.9 (0.02, 3.8)	<0.05
LBM, kg	1.3 (0.8, 1.7)	<0.001	0.6 (0.2, 1.1)	<0.01	0.6 (0.006, 1.2)	<0.05
Office systolic BP, mm Hg	−15 (−20, −10)	<0.001	−6 (−11, −2)	<0.01	−9 (−16, −3)	<0.001
Office diastolic BP, mm Hg	−8 (−12, −4)	<0.001	−4 (−6, −2)	<0.001	−4 (−9, 0)	<0.05
Number of drugs used	−1.6 (−2.0, −1.2)	<0.001	0.02 (−0.3, 0.3)	0.90	−1.6 (−2.1, −1.1)	<0.001
IVS thickness, mm	−0.5 (−1.0, −0.08)	<0.05	0.3 (−0.08, 0.6)	0.12	−0.8 (−1.3, -0.2)	<0.01
LVED diameter, mm	−0.4 (−1.6, 0.8)	0.49	1.2 (0.2, 2.1)	<0.05	−1.6 (−3.1, −0.1)	<0.05
LVED index, mm/m^2	−0.8 (−1.4, −0.2)	<0.05	1.2 (0.4, 2.0)	<0.05	−2.0 (−2.9, −1.0)	<0.001
LVPW thickness, mm	−0.4 (−0.9, 0.08)	0.10	−0.04 (−0.4, 0.3)	0.80	−0.4 (−0.9, 0.2)	0.20
LV mass, g	−12.9 (−23.6, −2.3)	<0.05	9.1 (0.1, 18.0)	<0.05	−22.0 (−35.6, −8.4)	<0.01
LV mass index, g/m^2	−8.7 (−14.6, −2.8)	<0.01	3.3 (−3.4, 9.9)	0.33	−11.2 (−20.6, −1.8)	<0.05
LV mass index, g/m$^{2.7}$	−2.5 (−4.7, −0.3)	<0.05	2.6 (−0.1, 5.3)	0.06	−4.5 (−8.1, −0.9)	<0.05
LV mass indexed to LBM	−0.2 (−0.4, −0.04)	<0.05	0.2 (−0.05, 0.3)	0.13	−0.4 (−0.6, −0.1)	<0.01
CCA IMT, mm	−0.03 (−0.06, −0.003)	<0.05	0.02 (0.003, 0.05)	<0.05	−0.05 (−0.09, −0.02)	<0.01
CB IMT, mm	−0.1 (−0.2, 0.009)	0.07	0.008 (−0.05, 0.06)	0.80	−0.07 (−0.2, 0.03)	0.15
Combined IMT, mm	−0.08 (−0.2, 0.003)	0.06	0.03 (0.002, 0.05)	<0.05	−0.06 (−0.1, −0.01)	<0.05

Values represent means (95% confidence intervals).

Abbreviations: CI, confidence interval; EH, essential hypertension.

Owing to the lack of correlation between the difference in CCA-IMT or LV mass indexes before/after adrenalectomy and the treatment-induced effects, it is difficult to determine which of the mechanisms is the most powerful. As concerns the impact of catecholamine excess, the urinary excretion was assessed in only a 70% proportion of PHEO patients in the period prior to switching to metanephrine-based diagnostics. Therefore, the power of the study to detect the association between a drop of catecholamine level and morphological outcome measures was certainly reduced.

We tried to match the 2 study groups as closely as possible. This is, however, an elusive goal, because patients with essential hypertension are principally different from the general population; most of them have the traits of metabolic syndrome with an impact on cardiovascular health. Therefore, the group of patients with essential hypertension should be considered an indicative, rather than a comparative, group. Another limitation was the failure to achieve the sufficient BP effects in patients with essential hypertension, in whom BP reduction was significantly less prominent compared with PHEO patients (by ~6/4 vs ~15/8 mm Hg). Additionally, the final BP did not reach a target of <140/90 in a significant proportion (42%) of patients. Consequently, beneficial effects on LV mass and CCA-IMT were not observed in patients with essential hypertension. More stringent BP control and/or enrolling patients with untreated newly diagnosed hypertension would better "match" both groups in terms of BP reduction during the follow-up. If the difference in primary objectives between PHEO and hypertensive patients persisted in such a scenario, it would support the hypothesis of the direct effect of catecholamine excess.

The frequency of various antihypertensive drugs at baseline was not identical in the 2 groups of patients. Intervention studies in essential hypertensive patients found that a therapy with drugs affecting the renin–angiotensin aldosterone system and calcium channel blockers can have a superior effect on the regression of carotid atherosclerosis and LV hypertrophy to that of a therapy with diuretics and β-blockers, independent of BP lowering. In our study, essential hypertensive patients were on angiotensin-converting enzyme inhibitors or calcium channel blocker therapy in a higher percentage of cases than the patients with pheochromocytoma (54% vs 24% and 52% vs 38%). However, such an imbalance in medical therapy could have diminished the between-group difference in treatment effects, rather than biased the results in favor of the PHEO group.

The assessment of LV mass was performed by the wall thickness method only. Validation of results by the other, area–length method (40) was not performed, because the relevant echocardiographic indices were not collected in the early phase of our study. Also, LV involvement in 5 patients (10%) with PHEO found at baseline perhaps allowed for a greater extent of improvement found at the end of the study.

In summary, our long-term study in patients with pheochromocytoma confirmed that vascular and myocardial

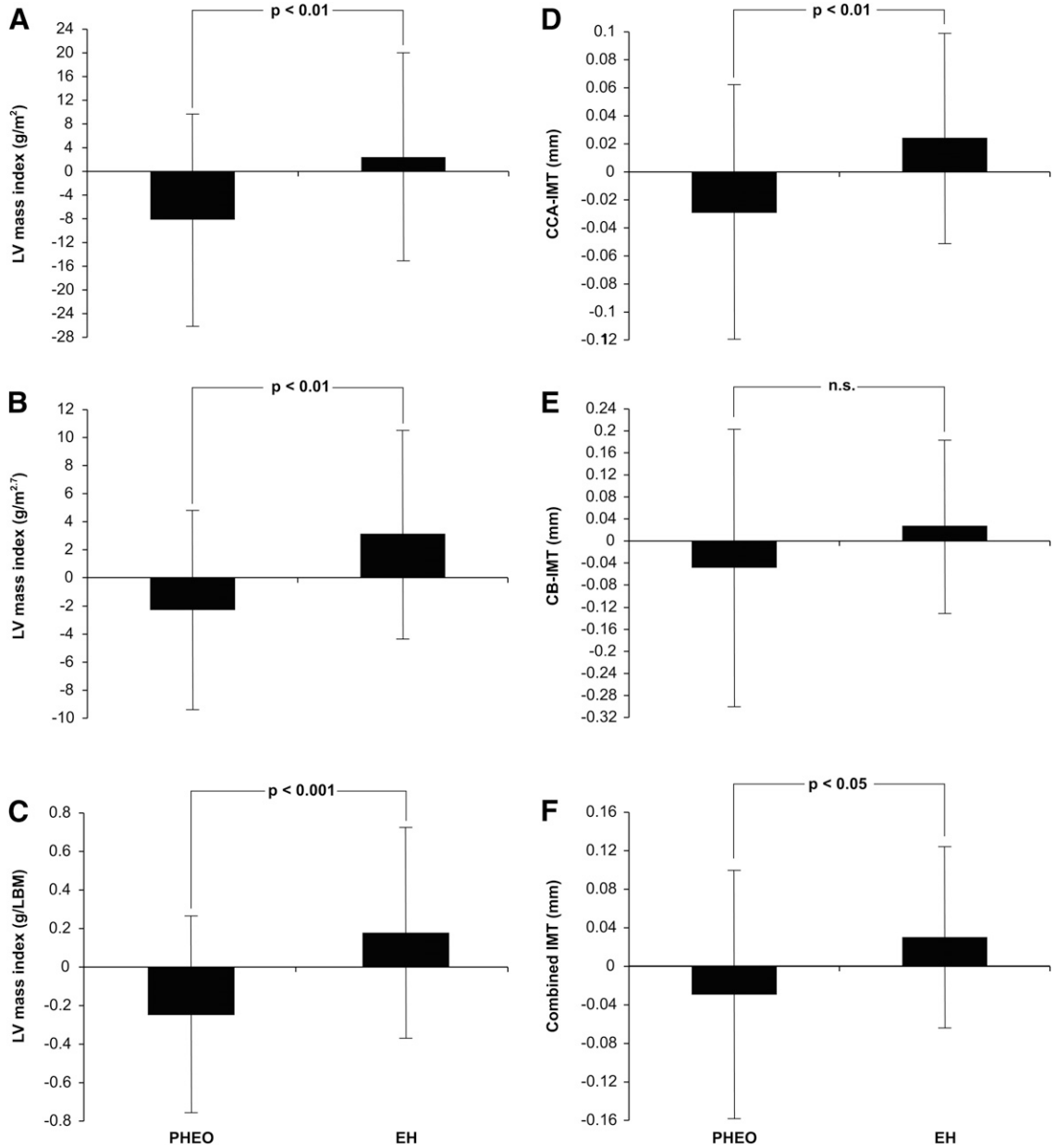

Figure 1. Changes in individual LV mass indices (A–C) and carotid IMT (D–F) at the end of the study follow-up. Patients with PHEO are compared with essential hypertensive patients (EH).

abnormalities can regress after adrenalectomy. These effects contrasted with the nearly opposite trend in patients with essential hypertension. The exact underlying mechanism of reverse remodeling after adrenalectomy remains unknown, because it was unrelated to a change in BP and catecholamine levels after surgery.

These findings may modify future decisions on the treatment of patients with other types of endocrine hypertension (*e.g.*, patients with primary aldosteronism). In such patients, a removal of the hormone-producing unilateral tumor should possibly be favored over pharmacological treatment, even in the case of a mild hypertension, to reverse the vascular/cardiac abnormalities and, potentially, improve the clinical outcome.

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