

RESEARCH

Effect of adrenalectomy on remission of subclinical left ventricular dysfunction in patients with pheochromocytoma: a speckle-tracking echocardiography study

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Abstract

Background: Pheochromocytomas (PHEO) are tumours with the ability to produce, metabolize and secrete catecholamines. Catecholamines overproduction leads to the decrease of longitudinal function of the left ventricle (LV) measured by speckle-tracking echocardiography. Patients with PHEO have a lower magnitude of global longitudinal strain (GLS) than patients with essential hypertension. GLS normalization is expected after resolution of catecholamine overproduction.

Methods: Twenty-four patients (14 females and 10 males) with a recent diagnosis of PHEO have been examined before and 1 year after adrenalectomy. An echocardiographic examination including speckle-tracking analysis with the evaluation of GLS and regional longitudinal strain (LS) in defined groups of LV segments (basal, mid-ventricular and apical) was performed.

Results: One year after adrenalectomy, the magnitude of GLS increased (-14.3 ± 1.8 to $-17.7 \pm 1.6\%$; $P < 0.001$). When evaluating the regional LS, the most significant increase in the differences was evident in the apical segment compared to mid-ventricular and basal segments of LV (-5.4 ± 5.0 vs -1.9 ± 2.7 vs -1.6 ± 3.8 ; $P < 0.01$).

Conclusions: In patients with PHEO, adrenalectomy leads to an improvement of subclinical LV dysfunction represented by the increasing magnitude of GLS, which is the most noticeable in apical segments of LV.

Key Words

- ▶ pheochromocytoma
- ▶ adrenalectomy
- ▶ global longitudinal strain
- ▶ echocardiography

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Introduction

Pheochromocytomas (PHEO) and functional paragangliomas (PGLs) are rare and mostly non-metastatic tumours originating from chromaffin tissue either from the adrenal medulla (PHEO) or from the vegetative nervous system-associated chromaffin tissue (PGLs) (1). Both types of tumours are collectively referred to as PPGLs. The prevalence of PHEO and PGLs in non-selected population of patients with arterial hypertension is between 0.2 and

0.6% (2, 3). The prevalence of PHEO is higher than the prevalence of PGLs, when 80–85% of PPGL are PHEO, whereas 15–20% are PGLs (4). The incidence has been rising due to the general ageing of the population and smaller tumour sizes at diagnosis in recent years (5).

PPGL can produce, metabolize and secrete catecholamines, which are responsible for a large variety of signs because of their hemodynamic and metabolic

effects. In particular, these signs are paroxysmal, such as headache, perspiration, palpitations and arterial hypertension (4, 6). Patients with PPGL may have more serious cardiovascular complications (even life-threatening ones, such as arrhythmias, myocardial infarction or heart failure), compared to patients with essential hypertension (EH) (7). Adrenalectomy also leads to an improvement of left ventricle (LV) mass in patients with PHEO (8). The aforementioned heart failure may be caused by the PPGL-associated catecholamine cardiomyopathy. The most severe form can be the clinical manifestation of Takotsubo syndrome (TTS) in which PPGL acts as its triggering factor. Most older diagnostic criteria for TTS preclude a diagnosis of PPGL, but the latest International Takotsubo Diagnostic Criteria (InterTAK) already directly list PPGL as a specific cause of TTS (9). These clinical conditions are usually transient and resolve after the removal of the catecholamine-producing tumour (10, 11).

An echocardiographic technique – 2D global longitudinal strain (GLS) derived from 2D speckle-tracking echocardiography – seems to be an already well-established and in certain situations more appropriate method for evaluating LV function, including myocardial motion and longitudinal deformation, than commonly used LV ejection fraction (EF) (12). GLS can also detect LV systolic impairment early on in the preclinical stage, while EF still remains in a normal range, and the analysis of regional values of longitudinal strain (LS) also allows the assessment of individual segments of the LV (13). This advantage of GLS over EF in patients with PHEO has already been confirmed by our previous study (14). Further studies have confirmed the improvement of GLS after surgical removal of PHEO (15, 16).

As mentioned above, catecholamine-induced myocardial dysfunction caused by PPGL is often compared and in some cases difficult to distinguish from TTS (11, 17). TTS is most often manifested by dysfunction of the apical segments of LV, but localization can occur anywhere in LV, as it has also been described for PPGL-triggered TTS (18). Therefore, we have designed this prospective study to confirm the positive effect of surgical removal of PPGLs on individual echocardiographic parameters and especially to evaluate the regional function of individual segments of the LV.

Methods

Subjects

The patients were recruited from a cohort of almost 1400 patients investigated because of resistant hypertension,

paroxysmal symptoms suspected of PPGL or adrenal tumours at our tertiary hospital-based Centre for Hypertension at the Third Department of Medicine, General University Hospital and First Faculty of Medicine, Charles University in Prague between November 2015 and November 2019. Each participant provided their written informed consent, and the study protocol was approved by the local Ethics Committee which took place during the grant approval (on 21 May 2015, code 20/15). The study was conducted in accordance with the Declaration of Helsinki.

The diagnosis of PPGL was newly confirmed in 62 patients during the aforementioned period, which represents circa a 4% rate in this preselected population. The diagnosis of PPGL was based on elevated plasma metanephrines and normetanephrines above the upper reference limit, and a positive finding of adrenal tumour on CT or MRI and/or a positive study with PET/CT with fluorodopa/fluorodeoxyglucose or ¹²³I-metaiodobenzylguanidine scintigraphy. After examination, all subjects underwent surgical removal of the tumour and the diagnosis was confirmed histopathologically. The noradrenergic (NA) biochemical phenotype was defined as a predominant increase in normetanephrine only, accompanied by either normal plasma concentrations of metanephrine or by an increase of <5% in metanephrine, relative to the sum of increments for both metabolites. Conversely, the adrenergic (A) biochemical phenotype was defined by an increase of plasma metanephrine above the upper reference limits and associated increments, relative to the combined increments of both metabolites, of >5% in metanephrine (19, 20).

Thirty-eight patients were excluded from this group due to various circumstances. The flow chart for enrolling patients in the study is shown in Fig. 1.

The subjects were considered hypertensive when their office BP was $\geq 140/90$ mmHg or $\geq 130/80$ mmHg; an average of three measurements was calculated based on measurements performed on three individual days or $\geq 130/80$ mmHg measured with 24-h ambulatory blood pressure monitoring (21). Diabetes mellitus was defined as medication with oral antidiabetic drugs or repeated fasting glucose levels of ≥ 7.0 mmol/L (22). All subjects with dyslipidemia (LDL ≥ 3.0 mmol/L) were on a diet and received lipid-lowering therapy (23).

All patients were initially examined during a short 3-day hospitalization on therapy that did not affect the renin-angiotensin-aldosterone system. Therefore, 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.

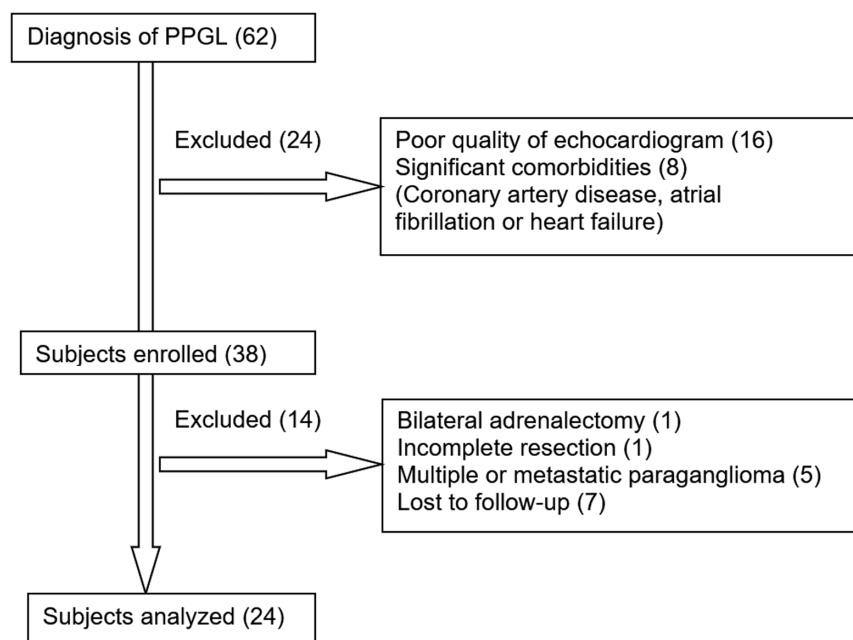


Figure 1
Study flowchart in patients with pheochromocytoma or functional paraganglioma (PPGL).

A diagnosis of PPGL was followed by standard pharmacological treatment with α -blockers followed by β -blockers until surgical treatment. Another 2-day hospitalization, including control echocardiography examination, was performed 12 months after the first examination.

BP measurement

Office blood pressure was measured using an oscillometric device (Omron M6, Shimogyo-ku, Kyoto, Japan). The measurement was made in a quiet room with the patient's arm positioned at the heart level and on chronic antihypertensive treatment during the first ambulatory visit, prior to switching to the treatment with α -blockers and/or slow-release verapamil. Blood pressure was measured three times in a sitting position after 5 min of rest. The final value of causal systolic and diastolic blood pressure was calculated as the average from the second and third measurements. The patient's 24-h blood pressure was measured during their stay in the hospital using an oscillometric device (SpaceLabs 90207, SpaceLabs Medical, Redmond, WA, USA) already on the replaced medication. Monitors were programmed to measure BP at 20-min intervals from 06:00 to 22:00 h and at 30-min intervals from 22:00 to 06:00 h. Fixed-clock time periods, rather than actual in-bed and out-of-bed periods, were statistically analysed to ensure similar day- and night-time periods for comparison between individuals. Moreover, patients were investigated during a short hospitalization with the same

daily hospital regime where the day and night periods ranged from 06:00 to 22:00 h and from 22:00 to 06:00 h, respectively. At a follow-up 1 year after the adrenalectomy, office blood pressure was measured in the same manner again during the outpatient visit and 24-h blood pressure was measured during a 2-day rehospitalization on chronic treatment.

Laboratory

Plasma catecholamines were analysed by HPLC with a fluorometric detector (HPLC/FLD 1100S, Agilent Technologies Inc.). The system was calibrated with a catecholamine standard using the ClinRep test kit (Recipe Chemicals and Instruments GmbH, Munich, Germany). Plasma-fractionated metanephrine (metanephrine and normetanephrine) was quantified by liquid chromatography with electrochemical detection (HPLC/ED 1100, Agilent Technologies Inc.) in the Laboratory for Endocrinology and Metabolism at the Third Department of Medicine, General University Hospital and First Faculty of Medicine, Charles University in Prague (24). Blood biochemistry, including sodium, potassium, urea, creatinine, total cholesterol, LDL, HDL, triglycerides and plasma glucose, was analysed using a multi-analyser (Modular SWA; Roche Diagnostics) in the Institute of Medical Biochemistry and Laboratory Diagnostics of the General University Hospital and First Faculty of Medicine, Charles University in Prague with international accreditation. Creatinine clearance was determined during 24 h of urine collection.

Echocardiography

2D Doppler and 2D speckle-tracking echocardiography was performed according to the recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging (25) on Vivid E9 ultrasound system (GE Healthcare). This approach was described in detail elsewhere (14).

The 2D speckle-tracking analysis was performed by automated detection of the endocardial border after manually defining the basal and apical points of the LV myocardium. The 17-segment ventricular model was obtained from 3 projections at end-expiration: apical 4-chamber view, 2-chamber view and apical long-axis view. Then GLS was computed as the mean of peak LS values from each of these segments according to the consensus of the American Society of Echocardiography and the European Association of Echocardiography endorsed by the Japanese Society of Echocardiography (26). As recommended, patients were excluded if tracking was insufficient in more than one segment due to suboptimal visualization or artefacts. The mid-wall GLS and peak LS in individual segments were evaluated. Individual segments, like basal, mid-ventricular and apical, were unified for simplification. The normal range of GLS using GE Healthcare system was from -18.0 to $-21.5\% \pm 3.7\%$ (27).

Reproducibility sub-study

Echocardiographic images were recorded by two cardiologists with over 20 years of echocardiography experience (R H and O P) during the hospitalization of patients in our ward.

Furthermore, these two cardiologists performed offline identical duplicate measurement and evaluation of the basic echocardiographic parameters using the EchoPAC working station (v.113, Advanced Analysis Technologies; GE Healthcare) within 3 weeks. Reproducibility was quantified by the assessment of coefficients of variation within the pairs of measurements for individual patients, identically as in our previous work (8). These were subsequently averaged in order to obtain the mean coefficient of variation with a corresponding s.d. Reproducibility of individual parameters was as follows: $4.5 \pm 3.6\%$ for interventricular septum thickness (IVS), $2.0 \pm 2.0\%$ for LV end-diastolic diameter (LVED), $2.4 \pm 1.9\%$ for LV end-systolic diameter (LVES), $4.4 \pm 3.0\%$ for posterior wall thickness (PWT) and $5.5 \pm 4.8\%$ for left atrium diameter (LA).

The 2D speckle-tracking analysis was performed again offline using the EchoPAC working station by one

cardiologist (J K) with over 7 years of experience using this method. Reproducibility sub-study was not performed as GLS should be an objective method with little dependence on inter-observer variability (28).

Statistical analysis

The statistical analysis was performed by STATISTICA software version 12.5 (Statsoft, Tulsa, Oklahoma, USA). Normally distributed data were described by mean \pm s.d. *P*-values of <0.05 were considered statistically significant. Continuous variables with clearly nonnormal distributions (Shapiro–Wilks *W*-test) were described as medians (interquartile range). The paired measurements (PHEO before adrenalectomy and after adrenalectomy) were compared using either *t*-test for dependent samples or Wilcoxon matched-pairs test, as appropriate. The difference between two treatment groups was analysed by *t*-test for independent samples. Multiple-group comparisons were performed by one-way ANOVA, followed by the Scheffe's multiple range test. Changes from the baseline of regional LS measurement were assessed by two-way ANOVA. Pearson's correlation analysis was used to assess the relationship between the GLS and other clinical parameters as well as the relationship between their treatment-induced changes. Spearman's correlation was used for non-normally distributed indices.

Results

Clinical data

The final group included 24 patients with a biochemically and histologically confirmed diagnosis of PHEO (18 subjects with adrenergic phenotype and 6 subjects with noradrenergic phenotype), aged from 29 to 78 years (14 females and 10 males). Clinical characteristics of the final group of patients are shown in Table 1. The follow-up was 12 months. After the adrenalectomy, an increase in the patients' body weight was observed and therefore their BMI significantly increased ($P < 0.05$). Sixteen patients (67%) became normotensives, and their antihypertensive therapy was discontinued, whereas eight patients still required antihypertensive therapy although at reduced doses and with a lower number of agents compared to baseline (Table 2). A significant reduction in the number of antihypertensive drugs was achieved with α -blockers, β -blockers and calcium channel blockers ($P < 0.01$) (Table 3).

Table 1 Clinical characteristics of patients at the beginning of the study.

Clinical characteristics		n	(%)
Localization of tumours	Right side	13	54
	Left side	11	46
	Bilateral	0	0
	Extra-adrenal	0	0
Phenotype	Elevated plasma adrenaline and noradrenaline (or plasma metanephrine and normetanephrine)	18	75
	Elevated only plasma noradrenaline (or only plasma normetanephrine)	6	25
Hereditary forms	Neurofibromatosis type 1	1	4
	Transmembrane protein 127 gene	1	4
Severity of hypertension	Normotension	6	25
	Mild grade	10	42
	Moderate grade	5	21
Myocardial involvement	Severe grade	3	12
	Myocardial infarction	1	4
	Takotsubo-like cardiomyopathy	1	4
Paroxysmal symptoms (as a reason for clinical examination)	Hypertension crisis	1	4
	Sweating	11	46
	Headache	10	42
	Palpitation	7	30
	Hypertension	6	25
	Vertigo	5	21
	Intestinal symptoms	5	21
	Vomiting	3	12
	Colour changes	1	4
	Chest pain	1	4
No symptoms	7	30	

Moreover, 24-h systolic and diastolic BP significantly decreased ($P < 0.005$ and $P < 0.05$, respectively) although the office blood pressure values insignificantly increased. Both office and 24-h heart rate ($P < 0.05$) significantly decreased (Table 2).

Laboratory data

As expected, after the tumour removal, plasma-fractionated metanephrines also normalized ($P < 0.001$) (Table 4).

Six patients with PHEO met the criteria for a diagnosis of diabetes, and after the tumour removal, diabetes disappeared in three patients. The overall improvement in glucose metabolism resulted in the discontinuation of insulin by all patients who had been on such treatment, and the three remaining patients with diabetes mellitus were only continued on oral hypoglycaemic agents. Moreover, the fasting blood glucose showed a significant decrease ($P < 0.001$), while lipid levels and renal function did not change (Table 5).

Table 2 Clinical characteristic of the study population. Variables are shown as means \pm s.d.

	Before adrenalectomy (n = 24)	After adrenalectomy (n = 24)	P-value
Age (years)	54 \pm 12	55 \pm 12	<0.001
Height (cm)	169 \pm 9	169 \pm 9	NS
Weight (kg)	76 \pm 15	79 \pm 16	<0.05
Body mass index (kg/m ²)	26 \pm 4	27 \pm 4	<0.05
Systolic office BP (mmHg)	131 \pm 10	134 \pm 13	NS
Diastolic office BP (mmHg)	81 \pm 9	83 \pm 7	NS
Heart rate office (BPM)	79 \pm 10	74 \pm 5	<0.05
24-h ABPM systolic BP (mmHg)	131 \pm 11	122 \pm 8	<0.005
24-h ABPM diastolic BP (mmHg)	78 \pm 7	74 \pm 5	<0.05
24-h ABPM heart rate (BPM)	77 \pm 8	71 \pm 6	<0.05
Number of used antihypertensive drugs	1.9 \pm 1.2	0.6 \pm 0.8	<0.001

ABPM, ambulatory blood pressure monitoring; BP, blood pressure; NS, non-significant; PHEO, pheochromocytoma.

Table 3 Use of antihypertensive, antidiabetic and lipid-lowering drugs in study population. Values are represented as absolute numbers (percentages).

	Before adrenalectomy (n = 24)	After adrenalectomy (n = 24)	P-value
Diuretics (n (%))	6 (25)	3 (13)	NS
β-blockers (n (%))	11 (46)	3 (13)	<0.005
Calcium channel blockers (n (%))	7 (29)	0 (0)	<0.005
Angiotensin-converting enzyme inhibitors (n (%))	7 (29)	5 (21)	NS
Angiotensin receptor blockers (n (%))	4 (17)	1 (4)	NS
α-blockers (n (%))	8 (33)	0 (0)	<0.005
Central agonists (n (%))	2 (8)	0 (0)	NS
Aldosterone antagonists (n (%))	1 (4)	0 (0)	NS
Statins (n (%))	8 (33)	8 (33)	NS
Insulin (n (%))	3 (13)	0 (0)	<0.05
Oral antidiabetic drugs (n (%))	4 (17)	3 (13)	NS

NS, non-significant.

Echocardiographic parameters

One year after adrenalectomy, there was a significant decrease in IVS from 10.3 ± 1.7 mm to 9.3 ± 1.1 mm ($P < 0.005$) and PWT from 10.1 ± 1.5 mm to 9.2 ± 0.8 mm ($P < 0.05$). As the LVED and the LVES remained unchanged, the RWT decreased from 0.43 ± 0.08 to 0.39 ± 0.05 ($P < 0.05$). These changes in diameters of the LV also affected its total mass. There was a significant decrease in both indexed left ventricular masses LVMi/BSA (left ventricular mass index to the body surface area) from 95.3 ± 18.7 g/m² to 83.6 ± 17.8 g/m² ($P < 0.05$) and LVMi (left ventricular mass index) from 43.2 ± 10.6 g/m^{2.7} to 37.9 ± 9.7 g/m^{2.7} ($P < 0.05$). There was also a reduction in the LA 1 year after adrenalectomy from 37.6 ± 5.0 mm to 35.2 ± 3.9 mm ($P < 0.05$). The above data are listed in Table 6.

As we expected, the basic parameter of systolic function – LV EF remained unchanged after 1 year, as patients with PHEO already had normal values of LV EF before the adrenalectomy. The estimation of the LV filling pressures expressed as the E/e' ratio also remained unchanged.

When evaluating LV function using 2D speckle-tracking echocardiography, we observed a significant increase of GLS from -14.3 ± 1.8 to -17.7 ± 1.6 ($P < 0.001$). This increase was evident in all groups of LV segments (basal, mid-ventricular and apical), when evaluating the

regional LS (Table 7). Overall, the highest values of regional LS were reached in apical segments compared to mid-ventricular and basal segments (-20.7 ± 3.2 vs -17.5 ± 2.1 ; -16.2 ± 2.1 ; $P < 0.01$; $P < 0.001$), and subsequently, the most significant increase in the differences between the regional LS was also evident after adrenalectomy in apical segments compared to mid-ventricular and basal segments (-5.4 ± 5.0 vs -1.9 ± 2.7 ; -1.6 ± 3.8 ; $P < 0.05$; $P < 0.01$) (Fig. 2 and Table 8). Typical examples of an echocardiographic pattern with GLS ‘bull’s-eye’ diagrams and values of regional LS, including deformation curves before and 1 year after adrenalectomy, are shown in Figs 3 and 4.

Discussion

Our study confirmed previous results that normalization of catecholamine in patients with PHEO leads to a positive LV remodelling (8) and an improvement in the longitudinal LV function and deformation represented by GLS (15). Moreover, we primarily focused on the evaluation of regional LS in individual LV segments and the effect of adrenalectomy on their final function. In our study, we have shown that the most significant improvement in regional LS values occurs in the apical segments of LV.

Table 4 Endocrine laboratory data. Values are shown as medians (interquartile range).

	Before adrenalectomy (n = 24)	After adrenalectomy (n = 24)	P-value
Plasma metanephrine (nmol/L)	4.28 (0.83–10.42)	0.12 (0.09–0.19)	<0.001
Plasma normetanephrine (nmol/L)	6.57 (3.74–22.13)	0.23 (0.19–0.38)	<0.001
Plasma adrenaline (nmol/L)	2.00 (0.35–2.82)	NA	
Plasma noradrenaline (nmol/L)	7.96 (3.95–15.37)	NA	
Plasma dopamine (nmol/L)	0.24 (0.15–0.29)	NA	

NA, not available.

Table 5 Laboratory data of the study population. Variables are shown as means ± s.d.

	Before adrenalectomy (n = 24)	After adrenalectomy (n = 24)	P-value
Creatinine (µmol/L)	71 ± 16	75 ± 12	NS
Creatinine clearance (mL/min)	135 ± 34	119 ± 26	NS
Total cholesterol (mmol/L)	4.4 ± 0.6	4.4 ± 0.7	NS
HDL cholesterol (mmol/L)	1.4 ± 0.2	1.4 ± 0.4	NS
LDL cholesterol (mmol/L)	2.6 ± 0.7	2.8 ± 0.8	NS
Triglycerides (mmol/L)	1.3 ± 0.5	1.3 ± 0.5	NS
Fasting plasma glucose (mmol/L)	6.1 ± 1.0	5.0 ± 0.5	<0.001

HDL, high-density lipoprotein; LDL, low-density lipoprotein; NS, non-significant.

Regional discrepancies between individual LV segments are already known in clinical practice. For example, hypertrophic cardiomyopathy (HCM) is characterized by an overall reduction in GLS, but a regional reduction in LS correlates with the HCM phenotype (29). In the case of cardiac amyloidosis, regional LS is reduced mainly in the basal and mid-ventricular segments of the LV and this pattern is called ‘apical sparing’ (30). Fabry’s disease also shows a decrease in regional LS, especially in the basal posterior and lateral segments (31). In patients with PHEO, no typical echocardiographic patterns of regional LS have been described.

In the case of patients with PHEO, however, a pathophysiological resemblance to TTS is presented. PHEO is considered a specific cause of TTS and is listed as one of the InterTAK Diagnostic Criteria for the diagnosis of TTS (9). The exact pathophysiology of TTS remains unclear, but certainly, the main mechanism includes sympathetic

stimulation due to emotional or physical trigger or due to catecholamine excess because of CNS disorders (32, 33) or due to PPGL like the disease itself (34). This activation leads to myocardial dysfunction by multiple mechanisms. The first presumptive mechanism is myocardial microcirculation dysfunction, which is most likely caused by the effect of catecholamines on α₁-receptors and subsequently by endothelin on its receptor type A (35). The second probable mechanism leading to myocardial damage is the direct toxic effect of catecholamine on cardiomyocytes. This extreme catecholamine overproduction is characterized by contraction band necrosis, hypercontracted sarcomeres and interstitial mononuclear inflammation in endomyocardial biopsies (36). These histopathological changes in PPGL-triggered TTS are then difficult to distinguish from the changes caused by ‘common’ TTS (37, 38). The myocardial response to catecholamines overproduction is mediated through β₁- and β₂-receptors. The highest density of β-receptors is more often located in the apical segment of the LV than in other segments and therefore an excess of catecholamine more often affects this region (17, 39). Therefore, TTS is morphologically manifested most often by an apical kinetics disorder, called ‘apical ballooning’, where severe dysfunction of the apical segments of the LV occurs (40, 41).

In our group of patients with PHEO before adrenalectomy, a diffuse decrease in LS was observed in all segments of the LV. Twelve patients had the lowest regional LS values in the apical segments of LV and 12 in the basal segments. TTS may not only affect the apical segments but may also appear in other segments or focal points throughout the heart (9). Atypical localization of the kinetics disorder in TTS is relatively rare and varies around 18% (42). The reverse form of TTS proves to be very rare, at around 1–2.2%, while the occurrence of mid-ventricular forms is more common, around 14.6–17% (42, 43). Our results are consistent with the analysis of Y-Hassan that confirmed a more frequent occurrence of reverse forms of PPGL-triggered TTS with a prevalence of 30% vs

Table 6 Echocardiographic parameters and Doppler-derived indexes of the study population. Variables are shown as means ± s.d.

	Before adrenalectomy (n = 24)	After adrenalectomy (n = 24)	P-value
IVS (mm)	10.3 ± 1.7	9.3 ± 1.1	<0.005
LVED (mm)	47.8 ± 5.0	48.3 ± 3.9	NS
LVES (mm)	29.7 ± 3.9	28.9 ± 4.3	NS
PWT (mm)	10.1 ± 1.5	9.2 ± 0.8	<0.05
RWT	0.43 ± 0.08	0.39 ± 0.05	<0.05
LA (mm)	37.6 ± 5.0	35.2 ± 3.9	<0.05
LVMi/BSA (g/m ²)	95.3 ± 18.7	83.6 ± 17.8	<0.05
LVMi (g/m ^{2.7})	43.2 ± 10.6	37.9 ± 9.7	<0.05
LVEF	0.66 ± 0.07	0.65 ± 0.05	NS
E/e'	9.0 ± 2.1	9.4 ± 2.7	NS

E/e', pulsed-wave Doppler/tissue Doppler imaging ratio of E and e' wave velocity; IVS, interventricular septum end-diastolic diameter; LA, left atrium; LVED, left ventricle end-diastolic diameter; LVEF, left ventricle ejection fraction; LVES, left ventricle end-systolic diameter; LVMi, left ventricular mass index to the 2.7th power of height in metres; LVMi/BSA, left ventricular mass index to the body surface area; NS, non-significant; PWT, posterior wall thickness end-diastolic diameter; RWT, relative wall thickness.

Table 7 Longitudinal strain parameters of the study population. Variables are shown as means ± s.d.

	Before adrenalectomy (n = 24)	After adrenalectomy (n = 24)	P-value
Global LS (%)	-14.3 ± 1.8	-17.7 ± 1.6	<0.001
Basal LV LS (%)	-14.6 ± 2.7	-16.2 ± 2.1	<0.05
Mid-ventricular LV LS (%)	-15.6 ± 1.8	-17.5 ± 2.1	<0.005
Apical LV LS (%)	-15.3 ± 3.4	-20.7 ± 3.2	<0.001

EF, ejection fraction; GLS, global longitudinal strain; LV LS, left ventricle longitudinal strain.

above-mentioned 2.2% in the unselected population with TTS (34). This study also describes the relatively common occurrence (around 20%) of the so-called global TTS, which is specific for myocardial dysfunction because of PPGL and which is also consistent with our finding of a more global decline of regional LS in analysed segments before adrenalectomy.

After adrenalectomy, all but one patient had an improvement in GLS. The overall values of the regional LS also improved, with these positive changes being most evident in the apical segments of the LV. A decrease in regional LS was observed in three patients in the mid-ventricular segments and, surprisingly, even in nine patients in the basal segments of LV. The most significant changes in the apical segments of LV could be related to the above-mentioned hypothesis of a higher density of β-receptors in this area. On the other hand, the minor increase or even partial decrease of regional LS in basal and mid-ventricular segments remains unclear. The explanation could be in the different pathophysiological influence of catecholamines on

individual LV segments. While arterial hypertension leads to a more diffuse decrease in LS in all LV segments (44), an excessive amount of catecholamines can cause myocardial dysfunction by its own cardiotoxic effect and at the same time by the haemodynamic effect leading to increased afterload. Because subsequent upregulation of β-receptors after removal of an excess of catecholamines is relatively fast (45), changes in the mainly hypertension-damaged tissue may subside more slowly or the pathological effect of concomitant arterial hypertension on LS values may persist even after adrenalectomy. The negative hemodynamic effect of arterial hypertension is evident by a statistically significant reduction in wall dimensions and regression of LV mass in our patients with PHEO after adrenalectomy. Another factor may be the increased variability of blood pressure in patients with PPGL (46) and the absence of a nocturnal decrease (non-dipping) on 24-h blood pressure monitoring or even a reversal increase (reverse dipping), which is associated with a higher incidence of target organ damage (47).

Despite the similar pathophysiological effect of PPGL and TTS on LV function, there are several differences to be aware of. PPGL are more often manifested by a more chronic course, while TTS is more often an acute disease. In addition, PPGL cause other complex metabolic changes, some of which could be related to a smaller increase in regional strain in some segments of the LV. The role of arterial hypertension has been mentioned above. Another pathological phenomenon in patients with PHEO is impaired glucose tolerance up to the development of diabetes (48). It is known that patients with type 2 diabetes have a significant reduction in GLS, which is associated with a worse prognosis (49). Although glucose metabolism improves after adrenalectomy (50, 51), it cannot be ruled out that subclinical involvement of LV may persist to some extent. Finally, the decline of GLS is well documented in patients with the systemic inflammatory response syndrome and the magnitude of the decline of GLS is related to the prognosis of these patients (52). In our previous study, we showed that chronic catecholamine excess in subjects with PHEO was accompanied by an

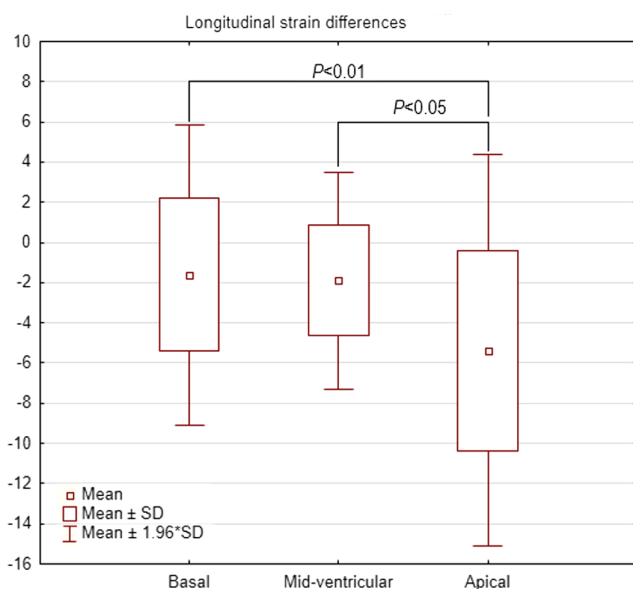


Figure 2 Left ventricle longitudinal strain differences before and after adrenalectomy.

Table 8 Differences in longitudinal strain among left ventricle segments. Variables are shown as means ± s.d.

LV segment	Apical LS (%) (n = 24)	Mid-ventricular LS (%) (n = 24)	Basal LS (%) (n = 24)	ANOVA P-value
Before adrenalectomy	-15.3 ± 3.4	-15.6 ± 1.8	-14.6 ± 2.7	0.600
After adrenalectomy	-20.7 ± 3.2**###	-17.5 ± 2.1	-16.2 ± 2.1	<0.001
Difference	-5.4 ± 5.0*##	-1.9 ± 2.7	-1.6 ± 3.8	<0.01

*P < 0.05, **P < 0.01, vs mid-ventricular; ##P < 0.01, ###P < 0.001 vs basal. LS, longitudinal strain; LV, left ventricle.

increase in inflammatory markers, which was reversed by the tumour removal (53), therefore systemic inflammation may also influence our results.

We are aware of the limitations of our study. PHEO is a rare disease, and we are not able to enroll a larger number of patients into the study. Moreover, speckle-tracking analysis requires good quality of echocardiographic records and therefore patients with poor recording quality had to be excluded from the study. The second limitation of our study is the absence of free urinary catecholamine values; therefore, it was not possible to correlate catecholamine levels with various echocardiographic, biochemical and clinical data, which are usually of high significance. In that way, we are not able to evaluate causality between influences of urine catecholamine levels on GLS changes. The third limitation is the insufficient representation of patients with noradrenergic biochemical phenotype. The representation of only six patients with the noradrenergic biochemical phenotype did not allow us to sufficiently evaluate the influence of the biochemical phenotype on regional changes in LS values. These regional changes may be caused by the

different affinity of adrenaline and noradrenaline for β_1 - and β_2 -receptors since adrenaline has a higher affinity for β_2 - and noradrenaline for the β_1 -receptor. Basal segments of the LV have fewer β_2 -receptors. As opposed to the apical segments, where the β_2 -receptors can be found in abundance. There is a sufficient β_2 -receptor stimulation in patients with adrenergic phenotype and there is a ‘molecular switch’ from the positive inotropic G_s to the negatively inotropic G_i pathway (41, 54). This may spare the apical segments from excessive contraction and contraction band necrosis and therefore allow for better recovery of systolic function. On the other hand, basal segments of the LV have more β_1 -receptors. Therefore, patients with the noradrenergic phenotype do not have a sufficient β_2 -receptor stimulation but an abundance of β_1 -receptor stimulation, so there is a lack of G_s to the G_i pathway switch. This can lead to excessive contraction, contraction band necrosis and a diminished ability to recover systolic function at the basal segments.

Despite the above limitations, it can be concluded that our study confirmed the positive effect of adrenalectomy on the regression of subclinical LV impairment

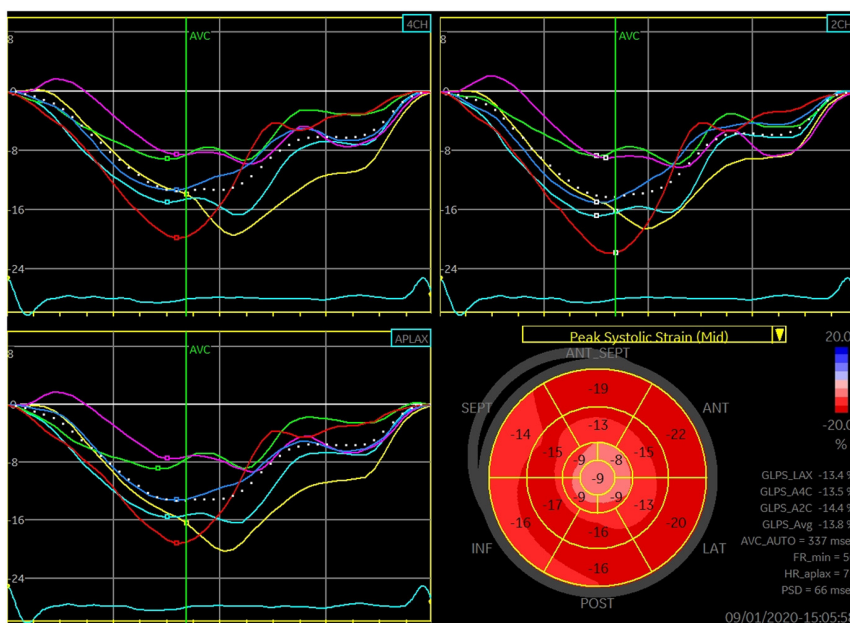


Figure 3 Global longitudinal strain before adrenalectomy. The green and purple curves represent apical segments. GLPS, global longitudinal peak strain; 4CH, apical four chamber view, 2CH, apical two chamber view; APLAX, apical long-axis view; MID, mid-wall; AVC, aortic valve closure; ANT-SEPT, anterior-septal; ANT, anterior; LAT, lateral; POST, posterior; INF, inferior; SEPT, septal; HR, heart rate.

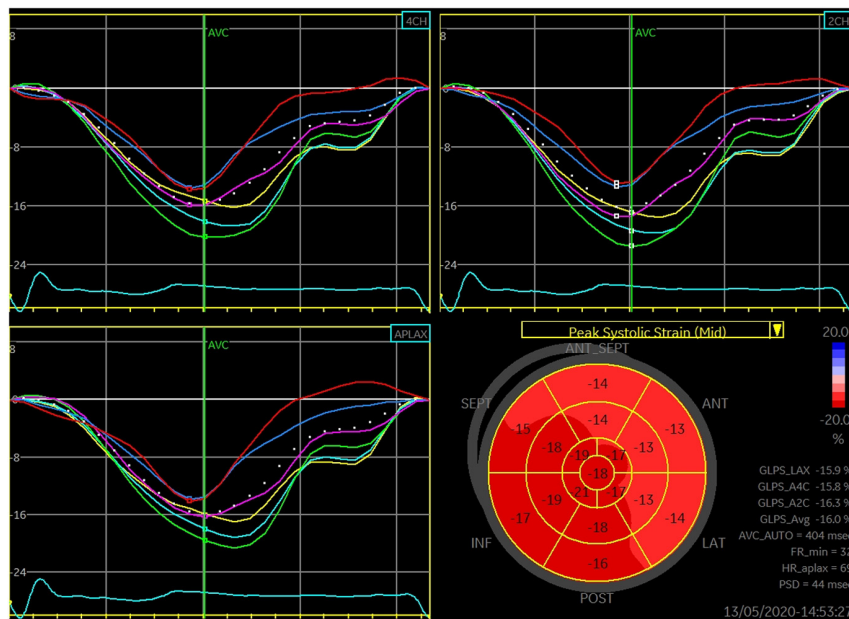


Figure 4 Global longitudinal strain after adrenalectomy. The green and purple curves represent apical segments. GLPS, global longitudinal peak strain; 4CH, apical four chamber view; 2CH, apical two chamber view; APLAX, apical long-axis view; MID, mid-wall; AVC, aortic valve closure; ANT-SEPT, anterior-septal; ANT, anterior; LAT, lateral; POST, posterior; INF, inferior; SEPT, septal; HR, heart rate.

characterized by improvement of GLS values. The main original finding of our study is that the most pronounced changes in regional LS after adrenalectomy occurred in the apical segments of the LV. The most likely explanation is the higher concentration of specific β -receptors in this LV area manifested with the higher direct toxic effect of catecholamines on the myocardium.

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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Institutional review board statement

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of General University Hospital and First Faculty of Medicine, Charles University in Prague (on 21 May 2015, code 20/15).

Informed consent statement

Informed consent was obtained from all subjects involved in the study.

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