cancers

MDPI

Article

Catecholamines Induce Left Ventricular Subclinical Systolic Dysfunction: A Speckle-Tracking Echocardiography Study

Jan Kvasnička [1], Tomáš Zelinka [1], Ondřej Petrák [1], Ján Rosa [1], Branislav Štrauch [1], Zuzana Krátká [1], Tomáš Indra [2], Alice Markvartová [1], Jiří Widimský Jr. [1] and Robert Holaj [1,*]

1 3rd Department of Medicine, Centre for Hypertension, General University Hospital and 1st Faculty of Medicine, Charles University in Prague, Ovocný trh 5, 116 36 Prague 1, Czech Republic; jan.kvasnicka3@vfn.cz (J.K.); tzeli@lf1.cuni.cz (T.Z.); ondrej.petrak@vfn.cz (O.P.); jan.rosa@vfn.cz (J.R.); branislav.strauch@vfn.cz (B.Š.); zuzana.kratka@vfn.cz (Z.K.); alice.vrankova@vfn.cz (A.M.); jwidi@lf1.cuni.cz (J.W.J.)

2 Department of Nephrology, General University Hospital and 1st Faculty of Medicine, Charles University in Prague, Ovocný trh 5, 116 36 Prague 1, Czech Republic; tomas.indra@vfn.cz

* Correspondence: robert.holaj@vfn.cz or rholaj@hotmail.com; Tel.: +420-224-963-509

Received: 9 January 2019; Accepted: 28 February 2019; Published: 6 March 2019

Abstract: *Background*: Pheochromocytomas (PHEO) are tumors arising from chromaffin cells from the adrenal medulla, having the ability to produce, metabolize and secrete catecholamines. The overproduction of catecholamines leads by many mechanisms to the impairment in the left ventricle (LV) function, however, endocardial measurement of systolic function did not find any differences between patients with PHEO and essential hypertension (EH). The aim of the study was to investigate whether global longitudinal strain (GLS) derived from speckle-tracking echocardiography can detect catecholamine-induced subclinical impairments in systolic function. *Methods*: We analyzed 17 patients (10 females and seven males) with PHEO and 18 patients (nine females and nine males) with EH. The groups did not differ in age or in 24-h blood pressure values. *Results*: The patients with PHEO did not differ in echocardiographic parameters including LV ejection fraction compared to the EH patients (0.69 ± 0.04 vs. 0.71 ± 0.05; NS), nevertheless, in spackle-tracking analysis, the patients with PHEO displayed significantly lower GLS than the EH patients (-14.8 ± 1.5 vs. -17.8 ± 1.7; $p < 0.001$). *Conclusions*: Patients with PHEO have a lower magnitude of GLS than the patients with EH, suggesting that catecholamines induce a subclinical decline in LV systolic function.

Keywords: pheochromocytoma; catecholamine; global longitudinal strain; speckle-tracking echocardiography; subclinical systolic dysfunction

1. Introduction

Pheochromocytomas (PHEO) and functional paragangliomas (PGLs) are rare and mostly non-metastatic tumors originating from chromaffin cells either from the adrenal medulla (PHEO) or from the sympathetic nervous system–associated chromaffin tissue (PGLs) [1]. The prevalence of PHEO and PGLs in non-selected population of patients with arterial hypertension is between 0.2 and 0.6% [2,3] and the prevalence of PHEO is higher than the prevalence of PGLs, when 80 to 85% of chromaffin-cell tumors are PHEO, whereas 15 to 20% are PGLs [4]. Due to the higher age of the population and smaller tumor sizes at diagnosis, the incidence has increased in recent years [5].

These tumors have the ability to produce, metabolize, and secrete catecholamines. Catecholamines produced by the tumor cells are responsible for a large variety of signs, in particular paroxysmal effects, such as headache, sweating, palpitations, and hypertension because of their effect on

hemodynamics and metabolism [4,6]. In vitro [7] and in vivo studies [8] showed that catecholamines influence vascular wall growth and remodeling, independently of their hemodynamic impact. In general, patients with pheochromocytoma have a higher risk of cardiovascular complications (even life-threatening like arrhythmias, heart failure and myocardial infarction), than patients with essential hypertension (EH) [9]. The aforementioned heart failure may be manifested by a decrease in the ejection fraction (EF) or, in some patients, by a transient left ventricle (LV) dysfunction due to the so-called catecholamine-induced myocarditis, also called pheochromocytoma-associated catecholamine cardiomyopathy [10]. Adrenalectomy also leads to an improvement of LV mass in patients with PHEO in contrast to the impairment of this parameter in EH patients [11]. A reduction of LV EF or even heart failure are signs of already developed clinical impairment. We therefore focused on the detection of subclinical impairment before the onset of cardiac damage.

In recent years, global longitudinal strain (GLS) derived from two-dimensional speckle-tracking echocardiography seems to be a better parameter for evaluating LV systolic performance including myocardial motion and longitudinal deformation than LV EF [12]. GLS can also detect LV systolic impairment already in the preclinical stage, when EF remains in normal range [13]. Recently, GLS has been used for the assessments of LV subclinical systolic function in many indications. In clinical practice, it is most often the evaluation of various forms of LV hypertrophy such as hypertrophic cardiomyopathy, amyloidosis [14] or primary aldosteronism [15] and evaluation of cardiotoxicity in patients with oncological diseases undergoing chemotherapy [16]. Therefore, we designed a prospective study to detect catecholamines-induced myocardial impairment of LV systolic function in patients with PHEO already in the subclinical stage.

2. Results

2.1. Characteristic of Groups

The final group included seventeen patients with a diagnosis of PHEO (11 subjects with adrenergic phenotype and six subjects with noradrenergic phenotype), aged 28 to 67 years (10 females and seven males) and eighteen patients (nine females and nine males) with a diagnosis of EH. The patient subgroups do not significantly differ in age, body mass index, in presumptive duration of disease or in heart rate and blood pressure values measured casually or using 24-h ambulatory monitoring (ABPM).

Thirteen patients with PHEO (76%) had a history of sustained hypertension and used at least one antihypertensive drug. Four patients with PHEO (24%) had developed only paroxysmal symptoms in the history and displayed normal blood pressure levels during measurements in the hospital. On the contrary, two patients with PHEO (12%) showed repeatedly very high blood pressure levels. The other patients with PHEO showed only a mild form of hypertension. The average values of heart rate in patients with PHEO were only about +7 mmHg higher than those in patients with EH. Nevertheless, this slight difference did not achieve statistical significance. The patients with EH used a higher number of antihypertensive drugs before switching to the treatment with α-blockers and/or slow-release verapamil than the patients with PHEO ($p < 0.01$) (Table 1). Significantly higher proportion of EH patients were treated by β-blockers ($p < 0.01$), calcium channel blockers ($p < 0.01$), and diuretics ($p < 0.05$). Four patients with PHEO had diabetes (two of them were on insulin and three of them were on oral antidiabetic drugs) and seven patients in both groups were treated for dyslipidemia (Table 2).

Table 1. Clinical characteristic of the study population.

Clinical Characteristic	PHEO (n = 17)	EH (n = 18)	p-Value
Age (years)	50 ± 11	49 ± 6	NS
Gender: F/M (% female)	10/7 (58%)	9/9 (50%)	NS
Height (cm)	170 ± 8	173 ± 7	NS
Weight (kg)	82 ± 14	88 ± 11	NS
Body mass index (kg/m^2)	29 ± 5	30 ± 4	NS
Systolic office BP (mmHg)	141 ± 13	140 ± 8	NS
Diastolic office BP (mmHg)	88 ± 6	89 ± 5	NS
Heart Rate office (BPM)	81 ± 9	74 ± 8	NS
24 h ABPM systolic BP (mmHg)	127 ± 9	132 ± 8	NS
24 h ABPM diastolic BP (mmHg)	76 ± 7	80 ± 5	NS
24 h ABPM Heart Rate (BPM)	77 ± 10	71 ± 6	NS
Number of used antihypertensive drugs	1.5 ± 1.1	3.6 ± 1.4	<0.001
Manifestation of symptoms (years)	5.8 ± 3.4	6.7 ± 3.6	NS

Variables are shown as means ± SD, or absolute values and relative values in percent. PHEO, pheochromocytoma; EH, essential hypertension; BP, blood pressure; BPM, beats per minute; ABPM, ambulatory blood pressure monitoring; NS, non-significant.

Table 2. Use of antihypertensive, antidiabetic and lipid-lowering drugs in the study population.

Antihypertensive, Antidiabetic and Lipid-Lowering Drugs	PHEO (n = 17)	EH (n = 18)	p-Value
Diuretics [n (%)]	3 (18)	10 (56)	<0.05
β-blockers [n (%)]	3 (18)	11 (61)	<0.01
Calcium channel blockers [n (%)]	5 (29)	14 (78)	<0.01
Angiotensin-converting enzyme inhibitors [n (%)]	5 (29)	10 (56)	NS
Angiotensin receptor blockers [n (%)]	2 (12)	7 (39)	NS
α-blockers [n (%)]	4 (24)	2 (11)	NS
Central agonists [n (%)]	3 (18)	6 (33)	NS
Aldosterone antagonists [n (%)]	1 (6)	4 (22)	NS
Statins [n (%)]	7 (41)	7 (39)	NS
Insulin [n (%)]	2 (12)	0 (0)	NS
Oral antidiabetic drugs [n (%)]	3 (18)	0 (0)	NS

Values are presented in absolute numbers (in percents). PHEO, pheochromocytoma; EH, essential hypertension; NS, non-significant.

2.2. Laboratory Results

The patient subgroups did not differ in lipid parameters, in plasma creatinine or in creatinine clearance. As expected, all endocrine-related laboratory values in patients with PHEO (fasting plasma glucose, plasma metanephrines, normetanephrines) were higher than in patients with EH (Table 3).

Table 3. Laboratory data of the study population.

Laboratory Data	PHEO (n = 17)	EH (n = 18)	p-Value
Plasma creatinine (μmol/L)	69 ± 12	75 ± 12	NS
Creatinine clearance (mL/min)	135 ± 34	119 ± 25	NS
Plasma cholesterol (mmol/L)	4.4 ± 0.5	4.8 ± 0.5	NS
HDL cholesterol (mmol/L)	1.5 ± 0.3	1.5 ± 0.3	NS
LDL cholesterol (mmol/L)	2.4 ± 0.5	2.5 ± 0.5	NS
Triglycerides (mmol/L)	1.2 ± 0.5	1.4 ± 0.5	NS
Fasting plasma glucose (mmol/L)	6.0 ± 0.9	5.2 ± 0.5	<0.05
Plasma metanephrines (nmol/L)	4.87 ± 4.30	0.16 ± 0.09	<0.01
Plasma normetanephrines (nmol/L)	13.65 ± 13.80	0.27 ± 0.12	<0.05

Variables are shown as means ± S.D.; PHEO, pheochromocytoma; EH, essential hypertension; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NS, non-significant.

2.3. Echocardiography Parameters

The patient subgroups did not differ in the LV and left atrial dimensions, LV mass indexes or Doppler-derived indexes characterizing diastolic function (Table 4).

Table 4. Echocardiographic parameters and Doppler-derived indexes of the study population.

Echocardiographic Parameters	PHEO (n = 17)	EH (n = 18)	p-Value
IVS (mm)	9.7 ± 1.6	9.6 ± 1.1	NS
LVED (mm)	49.6 ± 4.7	49.3 ± 3.1	NS
LVES (mm)	30.3 ± 2.6	29.1 ± 2.9	NS
PWT (mm)	9.6 ± 1.6	9.8 ± 1.1	NS
RWT	0.39 ± 0.05	0.40 ± 0.05	NS
LA (mm)	38.2 ± 5.1	37.0 ± 2.9	NS
LVMi/BSA (g/m^2)	91.2 ± 23.3	86.4 ± 16.2	NS
LVMi ($g/m^{2.7}$)	42.2 ± 12.1	40.3 ± 9.1	NS
LVEF	0.69 ± 0.04	0.71 ± 0.05	NS
E/A	1.04 ± 0.30	1.06 ± 0.25	NS
E/e′	8.5 ± 1.9	8.9 ± 1.6	NS

Variables are shown as means ± SD; LVEF, left ventricle ejection fraction; IVS, interventricular septum; LVED, left ventricle end-diastolic diameter; LVES, left ventricle end-systolic diameter; PWT, posterior wall thickness; RWT, relative wall thickness; LVMi/BSA, left ventricular mass index to the body surface area; LVMi, left ventricular mass index to the 2.7th power of height in meters; LA, left atrium; E/e′, Pulsed-Wave Doppler/Tissue Doppler Imaging ratio of E wave velocity, NS, non-significant.

When evaluating systolic function, the two groups did not differ in LV EF (0.69 ± 0.04 in the PHEO group vs. 0.71 ± 0.05 in the EH group, $p = 0.25$), nevertheless, in the speckle analysis, a significantly lower magnitude of GLS was found in patients with PHEO compared to those with EH.

The patients with PHEO displayed significantly lower strain than those with EH in all three views including: apical two-chamber view (−14.9 ± 1.6% in the PHEO group vs. −18.2 ± 2.1% in the EH group, $p < 0.001$), apical long axis view (−15.0 ± 1.7% in the PHEO group vs. −18.0 ± 1.9% in the EH group, $p < 0.001$), apical four-chamber view (−14.5 ± 1.4% in the PHEO group vs. −17.8 ± 1.7% in the EH group, $p < 0.001$), and GLS (−14.8 ± 1.5% in the PHEO group vs. −17.8 ± 1.7% in the EH group, $p < 0.001$, Figure 1). Comparing the individual LV segments, patients with PHEO showed a significantly reduced peak longitudinal strain in all segments (apical, mid-ventricular and basal, $p < 0.001$) compared to patients with EH (Table 5).

Table 5. Longitudinal strain parameters of the study population.

Longitudinal Strain Parameters	PHEO (n = 17)	EH (n = 18)	p-Value
Global LS (%)	−14.8 ± 1.5	−17.8 ± 1.7	<0.001
Basal LV LS (%)	−14.8 ± 2.1	−17.3 ± 2.3	<0.05
Mid-ventricular LV LS (%)	−15.7 ± 1.9	−18.9 ± 2.1	<0.001
Apical LV LS (%)	−16.1 ± 2.6	−19.9 ± 3.9	<0.05

Variables are shown as means ± SD; EF, ejection fraction; GLS, global longitudinal strain, LV LS, left ventricle longitudinal strain.

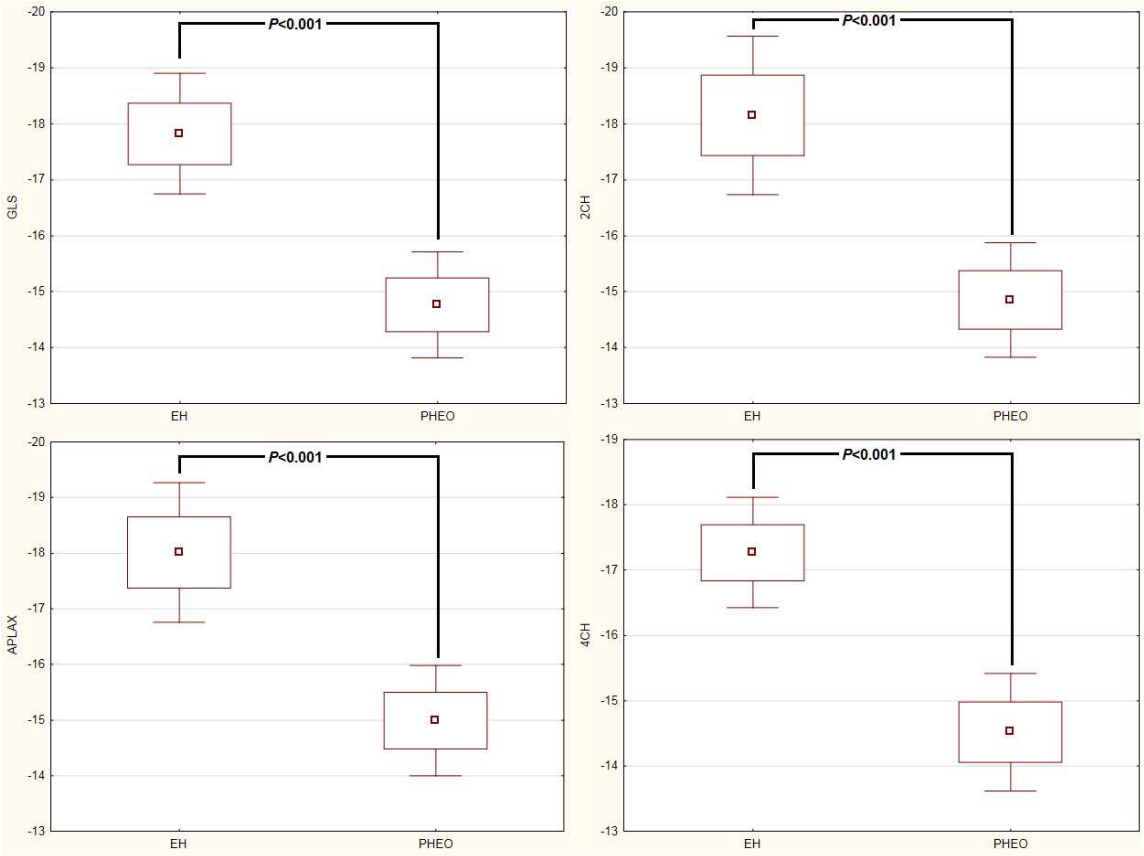


Figure 1. Speckle-tracking analysis in patients with pheochromocytoma and essential hypertension. The patients with pheochromocytoma showed significantly lower global longitudinal strain (GLS), strain in apical two-chamber view (2CH), strain in apical long axis view (APLAX), and strain in apical four-chamber view (4CH).

3. Discussion

Our results demonstrate that the patients with PHEO display a lower magnitude of GLS than patients with EH, although they display the same hemodynamic parameters and no difference in LVEF. Our study therefore indicates that the overproduction of catecholamines in patients with PHEO may cause subclinical LV systolic impairment.

A conventional approach to the assessment of LV systolic function usually involves measurement of LVEF and endocardial fractional shortening. Both of these methods are derived from endocardial movement without considering myocardium deformation [17]. However, an evaluation using the EF cannot detect LV affection in hypertrophic patients and thus distinguish these patients from healthy controls [18,19].

In contrast to the conventional methods of measuring LV from endocardial movement, methods taking myocardium deformation into consideration, such as mid-wall endocardial fractional shortening or speckle-tracking echocardiography, have the advantage of being able to detect systolic function impairments with a higher degree of sensitivity [12]. For example, in hypertensive patients, an impairment of LV longitudinal strain and geometric changes (such as concentric remodeling or hypertrophy) occur prior to a decrease in LVEF [20], and increased afterload-related cardiomyocyte hypertrophy and collagen deposition in the extracellular matrix may cause the deterioration in strain in hypertensive myocardium [21].

It is well known that catecholamine overproduction has an adverse effect on cardiac structure [22]. Catecholamine stimulates cell growth and cardiomyocyte hypertrophy, which may lead to cardiac wall thickening and LV mass increase. In addition, in animal studies, catecholamine infusion has been

shown to induce cardiac hypertrophy and myocardial interstitial fibrosis and scarring in both left and right ventricles [23]. In our previous studies, we found that the patients with PHEO displayed higher LVMI than patients with essential hypertension in echocardiography and that adrenalectomy led to a reduction of cardiovascular remodeling [11]. Catecholamine-induced cardiomyocyte hypertrophy, elevated cardiac wall thickness and collagen deposition in the extracellular matrix may explain the decrease in GLS in patients with PHEO in the current study. With a more contemporary tool, cardiac magnetic resonance imaging, Ferreira at al. [24] demonstrated that patients with PHEO had broader extent of myocardial fibrosis and myocardial dysfunction than patients with EH and elevated LV mass, and cardiac fibrosis improved after the removal of catecholamine excess (after adrenalectomy). Taken together, these findings indicate that patients with PHEO had a more severe cardiac fibrosis. This reduction in GLS is well known from patients with hypertrophic cardiomyopathy in whom reductions in longitudinal strain may be found prior to the reduction in EF [12].

An important factor is the direct toxic effect of catecholamines on the myocardium. Long-term high levels of catecholamines lead to β-adrenergic receptor downregulation. This degrades the function of the myofibers and gradually leads to their necrosis [25]. A similar mechanism, where β-adrenergic receptors are stimulated, occurs in stress cardiomyopathy, also referred to as Takotsubo cardiomyopathy [26]. Also, patients with PHEO may develop Takotsubo-like cardiomyopathy [27] due to the overproduction of catecholamines or develop a different form of another cardiac dysfunction (inverted Takotsubo cardiomyopathy and diffuse hypokinesis of LV) [10,28], which may often be transient [29]. Known cardiotoxic effects have been also observed in different types of chemotherapeutics used in the treatment of oncological diseases (although not mediated through β-adrenergic receptors), and GLS is used for an early detection of this cardiotoxicity [30]. It is therefore suggested that the decrease in GLS is related to the direct toxic effect of catecholamines on the myocardial muscle fibers through β-adrenergic receptors.

Another mechanism that may also play a role in the acceleration of cardiovascular hypertrophy is the higher fasting plasma glucose concentration in subjects with PHEO [31]. Asymptomatic patients with type 2 diabetes mellitus have a significant reduction in GLS, which is associated with a worse prognosis in these groups of patients [32]. Similarly, patients with type 2 diabetes mellitus have lower GLS after ST-segment elevation myocardial infarction [33] than non-diabetic patients.

Finally, a chronic inflammatory process may also lead to vascular damage [34,35]. In our previous study, we showed that chronic catecholamine excess in subjects with PHEO was accompanied by an increase in inflammatory markers, which was reversed by the tumor removal [36]. The decline of GLS is well documented in patients with the systemic inflammatory response syndrome and the magnitude of decline of GLS is related to the prognosis of these patients [37], which can be also related to the results of our work.

There are several limitations to this study. First, the number of patients was relatively small, which prevented finding any association between GLS and catecholamine overproduction. However, this is the first study to demonstrate subclinical systolic functional changes in patients with PHEO using speckle-tracking echocardiography. Further large-scale studies are needed to confirm the link between the magnitude of GLS and the overproduction of catecholamines. Secondly, we tried to match the group of subjects with PHEO with the EH group as closely as possible. This is, however, an elusive goal, because the overproduction of catecholamines leads not only to hypertension and weight loss but also to abnormalities in glucose metabolism. This makes the exact matching of the two groups unachievable. Therefore, the possible impact of diabetes on the magnitude of GLS in subject with PHEO cannot be excluded. On the other hand, EH patients had definitely higher atherogenic risk profiles, namely longer duration of hypertension, higher 24 h ABPM systolic blood pressure and higher body weight which may counteract the GLS differences between the two groups. Thirdly, the frequency of various antihypertensive drugs was not identical in the two groups of patients. Intervention studies in EH 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 LV hypertrophy than a therapy

with diuretics and β-blockers independently of BP lowering. In our study, the proportions of EH patients on angiotensin-converting enzyme inhibitors or calcium channel blockers therapy were higher than those of PHEO patients (56% vs. 29% and 78% vs. 29%, respectively). Fourthly, postoperative speckle-tracking data were not available at the time of the study. Therefore, we could not resolve whether the impaired subclinical systolic function was reversible or not. A follow-up study involving postoperative findings of speckle-tracking analysis is under way.

4. Materials and Methods

Patients were recruited from a cohort of almost 1100 patients investigated for severe or resistant hypertension and for suspected secondary hypertension at our tertiary hospital-based Centre for Hypertension at the 3rd Department of Medicine, General University Hospital and 1st Faculty of Medicine, Charles University in Prague between November 2015 and October 2018. Each participant provided his/her 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 diagnosis of PHEO was newly confirmed in 35 patients during the aforementioned period, which is about 3% rate in this preselected population. The diagnosis of PHEO was based on elevated plasma metanephrines and normetanephrines above the upper reference limit, and positive finding of adrenal tumor on computed tomography or magnetic resonance imaging. After examination all subjects underwent surgical removal of the tumor, and the diagnosis was confirmed histo-pathologically.

Ten patients were not enrolled due to the poor quality of echocardiography images or impossibility of GLS determination and seven due to significant comorbidities, including coronary atherosclerosis, atrial fibrillation or cardiac dysfunction for reasons other than PHEO. One patient was excluded for persistent overproduction of catecholamines after surgical removal because of the generalization of metastatic PHEO.

The control group of patients with essential hypertension (EH) was composed of the same prospective cohort as for the PHEO patients, on the basis of matching age, gender, body mass index, office and 24 h systolic blood pressure (BP). The patients were selected, after exclusion of the main forms of secondary hypertension (primary aldosteronism, PHEO, Cushing syndrome, renal parenchymal disease, renovascular hypertension), non-compliance or drug-induced hypertension. The subjects were considered hypertensive or pre-hypertensive when their clinic BP, an average of 3 sphygmomanometric measurements performed on 3 separate days, was $\geq$140/90 mmHg or $\geq$130/80 mmHg, respectively [38]. 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. Diabetes mellitus was defined as medication with oral antidiabetic drugs or repeated fasting glucose levels of >7.0 mmol/L [39]. There were two insulin-dependent patients in the PHEO group and none in the control group. All subjects with dyslipidemia (total plasma cholesterol $\geq$5.0 mmol/L or low-density cholesterol $\geq$3.0 mmol/L or high-density lipoprotein cholesterol $\leq$1.0 mmol/L in men and $\leq$1.2 mmol/L in women or triglycerides $\geq$1.7 mmol/L) were on a diet and received lipid-lowering therapy [40]. All patients were examined during a short three-day hospitalization.

4.1. BP Measurement

Casual blood pressure was measured using an oscillometric device (Omron M6, Shimogyo-ku, Kyoto, Japan). The measurement was made in a silent, quiet room with the patient's arm situated 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 sitting position after five minutes of rest. The resulting 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 switched medication.

4.2. Laboratory

Plasma-fractioned metanephrines (metanephrine and normetanephrine) were quantified by liquid chromatography with electrochemical detection (Agilent 1100; Agilent Technologies, Wilmington, DE, USA) in the Laboratory for Endocrinology and Metabolism at the 3rd Department of Medicine, General University Hospital and 1st Faculty of Medicine, Charles University in Prague [41].

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 Institute of Medical Biochemistry and Laboratory Diagnostics of the General University Hospital and 1st Faculty of Medicine, Charles University in Prague. Creatinine clearance was calculated using the Cockcroft–Gault equation.

4.3. Echocardiography

M-mode, 2-dimensional, Doppler and speckle tracking echocardiography were performed according to a standard protocol on Vivid 9 ultrasound system (GE Healthcare, Chicago, IL, USA). The records were analyzed offline using the EchoPAC working station (v.113, Advanced Analysis Technologies; GE Healthcare) by one cardiologist (J.K.) blinded to participants final diagnoses due to at least a fourteen-day period for the analysis of plasmatic metanephrines. M-mode images of the left ventricle at the mitral valve tip were obtained, guided by 2-dimensional parasternal long-axis and short-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 and relative wall thickness (RWT) was measured with the formula 2 × LVPW thickness/LVED according to the recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging [42].

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 [43]: 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). Two variants of LV mass indexing were used: to the body surface area in square meters and to the 2.7th power of height in meters. The LV EF was measured by the biplane method of disks (modified Simpson's rule) according to the last published recommendations [42]. Before the speckle-tracking analysis was performed, the image quality, frame rate and foreshortening were optimized. The speckle-tracking analysis was performed by automated detection of endocardial border after manually defining the basal and apical points of the LV myocardium. If necessary, a manual adjustment was applied. The seventeen ventricular segment model was obtained from three projections: apical four-chamber view, two-chamber view and apical long-axis view and then the GLS was computed as the mean of peak longitudinal strain values from each of these segments according to consensus of American Society of Echocardiography and European Association of Echocardiography endorsed by the Japanese Society of Echocardiography (Figure 2) [44]. As recommended, patients were excluded if tracking was insufficient in more than one segment because of not clear visualization or artefacts [45]. If tracking in only one segment was unsuccessful, this segment was discarded and not used when calculating the GLS. The mid-wall GLS and also peak longitudinal strain in individual segments were evaluated. Individual segments were unified like basal, mid-ventricular and apical for simplification. The normal range of GLS using GE Healthcare system was -18.0 to $-21.5\% \pm 3.7\%$ [45].

4.4. Statistical Analysis

Data were analyzed using the Stata 13.5 program (StataCorp LP, College Station, TX, USA). Differences between the two groups (PHEO and EH) were analyzed with the help of the χ^2 test for categoric data and with the help of non-paired t-test for normal distribution of variables for the two patient groups. Depending on the normality/nonnormality of the distributions of particular variables, the results were given as mean ± SD values or median values (interquartile range). A *p*-values of <0.05 were considered statistically significant.

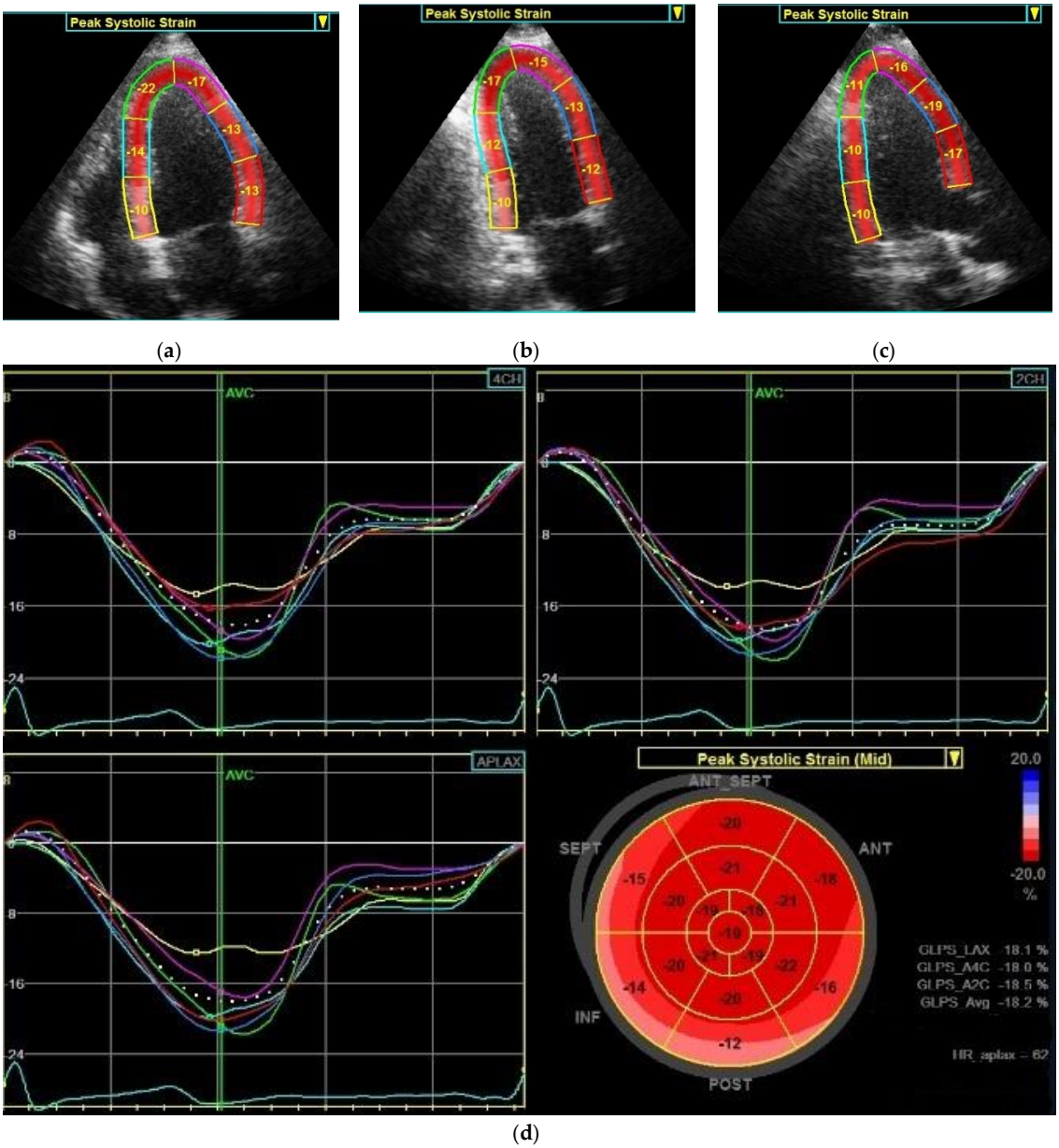
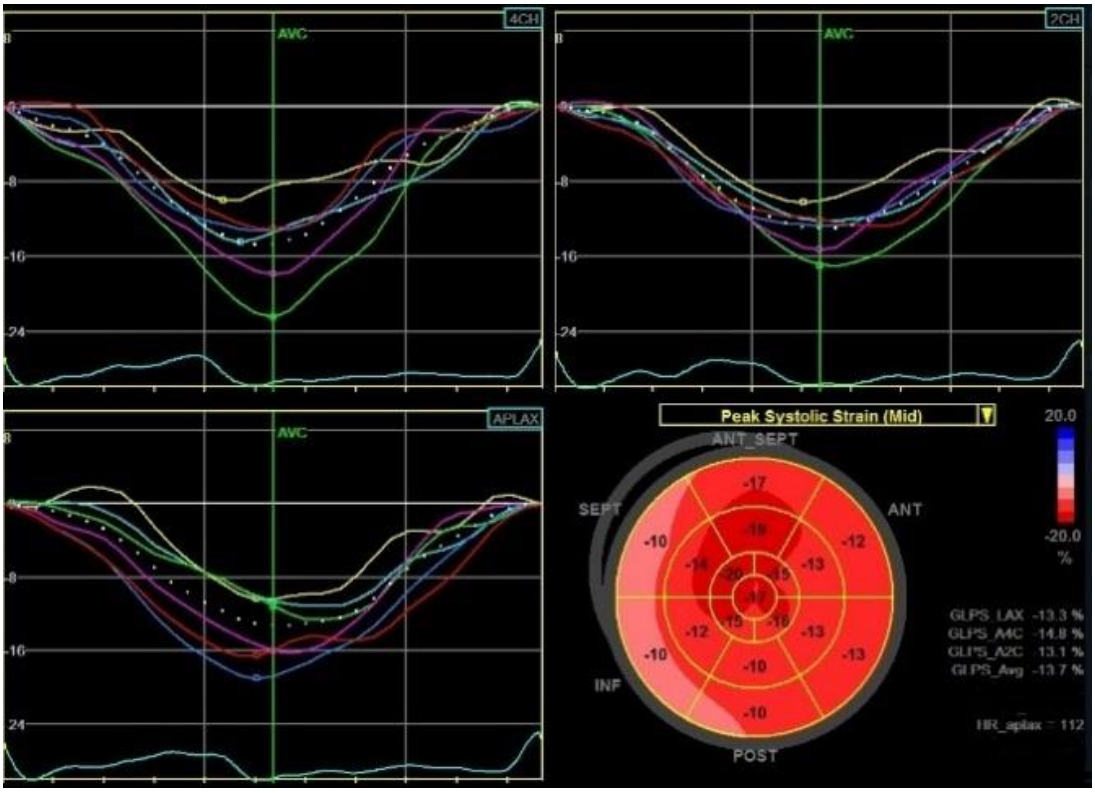


Figure 2. *Cont.*



(**e**)

Figure 2. Distribution of individual left ventricular segments in which peak systolic strain is analyzed in apical four-chamber view (**a**), apical two-chamber view (**b**) and apical long-axis view (**c**). The resulting peak systolic strain-expressing curves in individual segments that correspond to the color designation of the segments in images a-c in a patient with essential hypertension (**d**) and in a patient with pheochromocytoma (**e**). The GLS (or GLPS) is calculated for the whole LV from each segment peak systolic strain and is expressed as the LV seventeen-segment model also called "bull eye" which is shown at the bottom right of images d-e. 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

5. Conclusions

In conclusion, the patients with PHEO revealed lower magnitudes of GLS than the patients with EH. This finding is possibly caused by catecholamine-induced subclinical decline in LV systolic function, nevertheless, the link between the magnitude of GLS and the overproduction of catecholamines has not been proved in this study. At this stage, we can only express a suspicion of the diagnosis of PHEO in hypertensive patients based on measured lower magnitudes of GLS during routine echocardiographic examination.

Author Contributions: J.K., and R.H. designed the study and drafted the manuscript. J.K. performed and evaluated all echocardiographic examinations. T.Z., O.P., J.R., B.Š., T.I., Z.K. and J.W.J. collected clinical samples, patient information and provided statistical analysis. A.M. performed a laboratory analysis of plasma-fractioned metanephrines. R.H., as the corresponding author, made the final editing of the article. All authors were involved in the revision of the manuscript and approved the final version of the submitted manuscript.

Funding: This study was supported by grant projects AZV 16-30345A and AZV 15-27109A from the Ministry of Health of the Czech Republic and by research projects Progres Q25 and Q28 of Charles University in Prague.

Acknowledgments: The authors wish to express special thanks to nurses Terezie Holajová and Eva Straková of the echocardiography laboratory at the 3rd Department of Medicine for their assistance during the study.

Conflicts of Interest: The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analysis, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

References

1. Pacak, K.; Keiser, H.R.; Eisenhofer, G. Pheochromocytoma. In *Endocrinology*, 5th ed.; DeGroot, L.J., Jamenson, J.L., Eds.; Elsevier Saunders: Philadelphia, PA, USA, 2006; pp. 2501–2534.
2. Ariton, M.; Juan, C.S.; AvRuskin, T.W. Pheochromocytoma: Clinical observations from a Brooklyn tertiary hospital. *Endocr. Pract.* **2000**, *6*, 249–252. [CrossRef] [PubMed]
3. Omura, M.; Saito, J.; Yamaguchi, K.; Kakuta, Y.; Nishikawa, T. Prospective study on the prevalence of secondary hypertension among hypertensive patients visiting a general outpatient clinic in Japan. *Hypertens. Res.* **2004**, *27*, 193–202. [PubMed]
4. Lenders, J.W.; Eisenhofer, G.; Mannelli, M.; Pacak, K. Phaeochromocytoma. *Lancet* **2005**, *366*, 665–675. [CrossRef]
5. Berends, A.M.A.; Buitenwerf, E.; de Krijger, R.R.; Veeger, N.; van der Horst-Schrivers, A.N.A.; Links, T.P.; Kerstens, M.N. Incidence of pheochromocytoma and sympathetic paraganglioma in the Netherlands: A nationwide study and systematic review. *Eur. J. Intern. Med.* **2018**, *51*, 68–73. [CrossRef] [PubMed]
6. Zelinka, T.; Eisenhofer, G.; Pacak, K. Pheochromocytoma as a catecholamine producing tumor: Implications for clinical practice. *Stress* **2007**, *10*, 195–203. [PubMed]
7. Zhang, H.; Faber, J.E. Trophic effect of norepinephrine on arterial intima-media and adventitia is augmented by injury and mediated by different alpha1-adrenoceptor subtypes. *Circ. Res.* **2001**, *89*, 815–822. [PubMed]
8. Nakaki, T.; Nakayama, M.; Yamamoto, S.; Kato, R. Alpha 1-adrenergic stimulation and beta 2-adrenergic inhibition of DNA synthesis in vascular smooth muscle cells. *Mol. Pharm.* **1990**, *37*, 30–36.
9. Zelinka, T.; Petrák, O.; Turková, H.; Holaj, R.; Štrauch, B.; Kršek, M.; Vrankova, A.B.; Musil, Z.; Dušková, J.; Kubinyi, J.; et al. High incidence of cardiovascular complications in pheochromocytoma. *Horm. Metab. Res.* **2012**, *44*, 379–384. [CrossRef] [PubMed]
10. Park, J.H.; Kim, K.S.; Sul, J.Y.; Shin, S.K.; Kim, J.H.; Lee, J.H.; Choi, S.W.; Jeong, J.O.; Seong, I.W. Prevalence and patterns of left ventricular dysfunction in patients with pheochromocytoma. *J. Cardiovasc. Ultrasound* **2011**, *19*, 76–82. [CrossRef] [PubMed]
11. Majtan, B.; Zelinka, T.; Rosa, J.; Petrák, O.; Kratka, Z.; Štrauch, B.; Tuka, V.; Vránková, A.; Michalský, D.; Novák, K.; et al. Long-Term Effect of Adrenalectomy on Cardiovascular Remodeling in Patients With Pheochromocytoma. *J. Clin. Endocrinol. Metab.* **2017**, *102*, 1208–1217. [CrossRef] [PubMed]
12. Kalam, K.; Otahal, P.; Marwick, T.H. Prognostic implications of global LV dysfunction: A systematic review and meta-analysis of global longitudinal strain and ejection fraction. *Heart* **2014**, *100*, 1673–1680. [PubMed]
13. Smiseth, O.A.; Torp, H.; Opdahl, A.; Haugaa, K.H.; Urheim, S. Myocardial strain imaging: How useful is it in clinical decision making? *Eur. Heart J.* **2016**, *37*, 1196–1207. [CrossRef] [PubMed]
14. Sun, J.P.; Stewart, W.J.; Yang, X.S.; Donnell, R.O.; Leon, A.R.; Felner, J.M.; Thomas, J.D.; Merlino, J.D. Differentiation of hypertrophic cardiomyopathy and cardiac amyloidosis from other causes of ventricular wall thickening by two-dimensional strain imaging echocardiography. *Am. J. Cardiol.* **2009**, *103*, 411–415. [CrossRef] [PubMed]
15. Chen, Z.W.; Huang, K.C.; Lee, J.K.; Lin, L.C.; Chen, C.W.; Chang, Y.Y.; Liao, C.W.; Wu, V.C.; Hung, C.S.; Lin, Y.H. Aldosterone induces left ventricular subclinical systolic dysfunction: A strain imaging study. *J. Hypertens.* **2017**, *36*, 353–360.
16. Plana, J.C.; Galderisi, M.; Barac, A.; Ewer, M.S.; Ky, B.; Scherrer-Crosbie, M.; Ganame, J.; Sebag, I.A.; Agler, D.A.; Badano, L.P.; et al. Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: A report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J. Am. Soc. Echocardiogr.* **2014**, *27*, 911–939. [PubMed]
17. Park, K.; Chang, S.A.; Kim, H.K.; Park, H.E.; Na, S.H.; Kim, Y.J.; Sohn, D.W.; Oh, B.H.; Park, Y.B. Normal ranges and physiological changes of midwall fractional shortening in healthy korean population. *Korean Circ. J.* **2010**, *40*, 587–592. [PubMed]

18. Krzesinski, P.; Uzieblo-Zyczkowska, B.; Gielerak, G.; Stanczyk, A.; Kurpaska, M.; Piotrowicz, K. Global longitudinal two-dimensional systolic strain is associated with hemodynamic alterations in arterial hypertension. *J. Am. Soc. Hypertens. JASH* **2015**, *9*, 680–689. [CrossRef] [PubMed]
19. Mayet, J.; Ariff, B.; Wasan, B.; Chapman, N.; Shahi, M.; Senior, R.; Foale, R.A.; Thom, S.A. Midwall myocardial shortening in athletic left ventricular hypertrophy. *Int. J. Cardiol.* **2002**, *86*, 233–238. [PubMed]
20. Kouzu, H.; Yuda, S.; Muranaka, A.; Doi, T.; Yamamoto, H.; Shimoshige, S.; Hase, M.; Hashimoto, A.; Saitoh, S.; Tsuchihashi, K.; et al. Left ventricular hypertrophy causes different changes in longitudinal, radial, and circumferential mechanics in patients with hypertension: A two-dimensional speckle tracking study. *J. Am. Soc. Echocardiogr.* **2011**, *24*, 192–199. [CrossRef] [PubMed]
21. Ishizu, T.; Seo, Y.; Kameda, Y.; Kawamura, R.; Kimura, T.; Shimojo, N.; Xu, D.; Murakoshi, N.; Aonuma, K. Left ventricular strain and transmural distribution of structural remodeling in hypertensive heart disease. *Hypertension* **2014**, *63*, 500–506. [PubMed]
22. Galetta, F.; Franzoni, F.; Bernini, G.; Poupak, F.; Carpi, A.; Cini, G.; Tocchini, L.; Antonelli, A.; Santoro, G. Cardiovascular complications in patients with pheochromocytoma: A mini-review. *Biomed. Pharm.* **2010**, *64*, 505–509. [CrossRef] [PubMed]
23. Johnson, M.D.; Grignolo, A.; Kuhn, C.M.; Schanberg, S.M. Hypertension and cardiovascular hypertrophy during chronic catecholamine infusion in rats. *Life Sci.* **1983**, *33*, 169–180. [PubMed]
24. Ferreira, V.M.; Marcelino, M.; Piechnik, S.K.; Marini, C.; Karamitsos, T.D.; Ntusi, N.A.; Francis, J.M.; Robson, M.D.; Arnold, J.R.; Mihai, R.; et al. Pheochromocytoma Is Characterized by Catecholamine-Mediated Myocarditis, Focal and Diffuse Myocardial Fibrosis, and Myocardial Dysfunction. *J. Am. Coll. Cardiol.* **2016**, *67*, 2364–2374. [CrossRef] [PubMed]
25. De Miguel, V.; Arias, A.; Paissan, A.; de Arenaza, D.P.; Pietrani, M.; Jurado, A.; Jaén, A.; Day, P.F. Catecholamine-induced myocarditis in pheochromocytoma. *Circulation* **2014**, *129*, 1348–1349. [CrossRef] [PubMed]
26. Lyon, A.R.; Rees, P.S.; Prasad, S.; Poole-Wilson, P.A.; Harding, S.E. Stress (Takotsubo) cardiomyopathy—A novel pathophysiological hypothesis to explain catecholamine-induced acute myocardial stunning. *Nat. Clin. Pract. Cardiovasc. Med.* **2008**, *5*, 22–29. [CrossRef] [PubMed]
27. Chiang, Y.L.; Chen, P.C.; Lee, C.C.; Chua, S.K. Adrenal pheochromocytoma presenting with Takotsubo-pattern cardiomyopathy and acute heart failure: A case report and literature review. *Medicine* **2016**, *95*, e4846. [CrossRef] [PubMed]
28. Tafreshi, S.; Naqvi, S.Y.; Thomas, S. Extra-adrenal pheochromocytoma presenting as inverse takotsubo-pattern cardiomyopathy treated with surgical resection. *BMJ Case Rep.* **2018**, *11*, e226384. [PubMed]
29. Brilakis, E.S.; Young, W.F., Jr.; Wilson, J.W.; Thompson, G.B.; Munger, T.M. Reversible catecholamine-induced cardiomyopathy in a heart transplant candidate without persistent or paroxysmal hypertension. *J. Heart Lung Transplant.* **1999**, *18*, 376–380. [CrossRef]
30. Thavendiranathan, P.; Poulin, F.; Lim, K.D.; Plana, J.C.; Woo, A.; Marwick, T.H. Use of myocardial strain imaging by echocardiography for the early detection of cardiotoxicity in patients during and after cancer chemotherapy: A systematic review. *J. Am. Coll. Cardiol.* **2014**, *63*, 2751–2768. [PubMed]
31. Turnbull, D.M.; Johnston, D.G.; Alberti, K.G.; Hall, R. Hormonal and metabolic studies in a patient with a pheochromocytoma. *J. Clin. Endocrinol. Metab.* **1980**, *51*, 930–933. [PubMed]
32. Holland, D.J.; Marwick, T.H.; Haluska, B.A.; Leano, R.; Hordern, M.D.; Hare, J.L.; Fang, Z.Y.; Prins, J.B.; Stanton, T. Subclinical LV dysfunction and 10-year outcomes in type 2 diabetes mellitus. *Heart* **2015**, *101*, 1061–1066. [CrossRef] [PubMed]
33. Hoogslag, G.E.; Abou, R.; Joyce, E.; Boden, H.; Kamperidis, V.; Regeer, M.V.; van Rosendael, P.J.; Schalij, M.J.; Bax, J.J.; Marsan, N.A.; et al. Comparison of Changes in Global Longitudinal Peak Systolic Strain After ST-Segment Elevation Myocardial Infarction in Patients With Versus Without Diabetes Mellitus. *Am. J. Cardiol.* **2015**, *116*, 1334–1339. [CrossRef] [PubMed]
34. Wang, T.J.; Nam, B.H.; Wilson, P.W.; Wolf, P.A.; Levy, D.; Polak, J.F.; D'agostino, R.B.; O'donnell, C.J. Association of C-reactive protein with carotid atherosclerosis in men and women: The Framingham Heart Study. *Arterioscler. Thromb. Vasc. Biol.* **2002**, *22*, 1662–1667. [CrossRef] [PubMed]
35. Magyar, M.T.; Szikszai, Z.; Balla, J.; Valikovics, A.; Kappelmayer, J.; Imre, S.; Balla, G.; Jeney, V.; Csiba, L.; Bereczki, D. Early-onset carotid atherosclerosis is associated with increased intima-media thickness and elevated serum levels of inflammatory markers. *Stroke J. Cereb. Circ.* **2003**, *34*, 58–63. [CrossRef]

36. Zelinka, T.; Petrák, O.; Štrauch, B.; Holaj, R.; Kvasnička, J.; Mazoch, J.; Pacak, K.; Widimský, J., Jr. Elevated inflammation markers in pheochromocytoma compared to other forms of hypertension. *Neuroimmunomodulation* **2007**, *14*, 57–64. [CrossRef] [PubMed]
37. Sanfilippo, F.; Corredor, C.; Fletcher, N.; Tritapepe, L.; Lorini, F.L.; Arcadipane, A.; Vieillard-Baron, A.; Cecconi, M. Left ventricular systolic function evaluated by strain echocardiography and relationship with mortality in patients with severe sepsis or septic shock: A systematic review and meta-analysis. *Crit. Care* **2018**, *22*, 183. [CrossRef] [PubMed]
38. Mancia, G.; Fagard, R.; Narkiewicz, K.; Redon, J.; Zanchetti, A.; Boehm, M.; Christiaens, T.; Cifkova, R.; De Backer, G.; Dominiczak, A.; et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J. Hypertens.* **2013**, *31*, 1281–1357. [CrossRef] [PubMed]
39. Force IDFCGT. Global Guideline for Type 2 Diabetes: Recommendations for standard, comprehensive, and minimal care. *Diabet. Med.* **2006**, *23*, 579–593.
40. Graham, I.; Atar, D.; Borch-Johnsen, K.; Boysen, G.; Burell, G.; Cifkova, R.; Dallongeville, J.; De Backer, G.; Ebrahim, S.; Gjelsvik, B.; et al. European guidelines on cardiovascular disease prevention in clinical practice: Executive summary: Fourth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (Constituted by representatives of nine societies and by invited experts). *Eur. Heart J.* **2007**, *28*, 2375–2414. [PubMed]
41. Lenders, J.W.; Eisenhofer, G.; Armando, I.; Keiser, H.R.; Goldstein, D.S.; Kopin, I.J. Determination of metanephrines in plasma by liquid chromatography with electrochemical detection. *Clin. Chem.* **1993**, *39*, 97–103. [PubMed]
42. Lang, R.M.; Badano, L.P.; Mor-Avi, V.; Afilalo, J.; Armstrong, A.; Ernande, L.; Flachskampf, F.A.; Foster, E.; Goldstein, S.A.; Kuznetsova, T.; et al. Recommendations for cardiac chamber quantification by echocardiography in adults: An update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur. Heart J. Cardiovasc. Imaging* **2015**, *16*, 233–270. [CrossRef] [PubMed]
43. Devereux, R.B.; Alonso, D.R.; Lutas, E.M.; Gottlieb, G.J.; Campo, E.; Sachs, I.; Reichek, N. Echocardiographic assessment of left ventricular hypertrophy: Comparison to necropsy findings. *Am. J. Cardiol.* **1986**, *57*, 450–458. [PubMed]
44. Mor-Avi, V.; Lang, R.M.; Badano, L.P.; Belohlavek, M.; Cardim, N.M.; Derumeaux, G.; Galderisi, M.; Marwick, T.; Nagueh, S.F.; Sengupta, P.P.; et al. Current and evolving echocardiographic techniques for the quantitative evaluation of cardiac mechanics: ASE/EAE consensus statement on methodology and indications endorsed by the Japanese Society of Echocardiography. *Eur. J. Echocardiogr.* **2011**, *12*, 167–205. [CrossRef] [PubMed]
45. Farsalinos, K.E.; Daraban, A.M.; Unlu, S.; Thomas, J.D.; Badano, L.P.; Voigt, J.U. Head-to-Head Comparison of Global Longitudinal Strain Measurements among Nine Different Vendors: The EACVI/ASE Inter-Vendor Comparison Study. *J. Am. Soc. Echocardiogr.* **2015**, *28*, 1171–1181.e2. [CrossRef] [PubMed]

RESEARCH

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

Jan Kvasnička[1], Ondřej Petrák[1], Tomáš Zelinka[1], Judita Klímová[1], Barbora Kološová[1], Květoslav Novák[2], David Michalský[3], Jiří Widimský Jr[1] and **Robert Holaj[1]**

[1]3rd Department of Medicine, General University Hospital and 1st Faculty of Medicine, Charles University in Prague, Praha, Czech Republic
[2]Department of Urology, General University Hospital and 1st Faculty of Medicine, Charles University in Prague, Praha, Czech Republic
[3]1st Department of Surgery, General University Hospital and 1st Faculty of Medicine, Charles University in Prague, Praha, Czech Republic

Correspondence should be addressed to R Holaj: robert.holaj@vfn.cz

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 ± 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

Endocrine Connections (2021) **10**, 1538–1549

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

https://ec.bioscientifica.com
https://doi.org/10.1530/EC-21-0462

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 ^{123}I-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 ≥140/90 mmHg or ≥130/80 mmHg; an average of three measurements was calculated based on measurements performed on three individual days or ≥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.

https://ec.bioscientifica.com
https://doi.org/10.1530/EC-21-0462

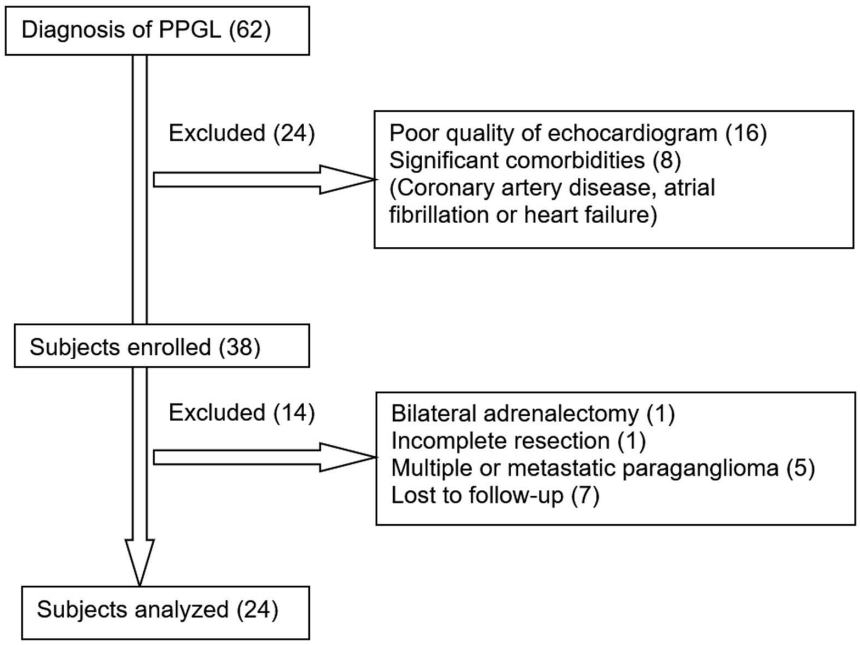


Figure 1
Study flowchart in patients with pheochromocytoma or functional paraganglioma (PPGL).

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-fractioned 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.

https://ec.bioscientifica.com
https://doi.org/10.1530/EC-21-0462

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% ± 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 ± 3.6% for interventricular septum thickness (IVS), 2.0 ± 2.0% for LV end-diastolic diameter (LVED), 2.4 ± 1.9% for LV end-systolic diameter (LVES), 4.4 ± 3.0% for posterior wall thickness (PWT) and 5.5 ± 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 ± 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 12months. 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).

https://ec.bioscientifica.com
https://doi.org/10.1530/EC-21-0462

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
	Severe grade	3	12
Myocardial involvement	Myocardial infarction	1	4
	Takotsubo-like cardiomyopathy	1	4
	Hypertension crisis	1	4
Paroxysmal symptoms (as a reason for clinical examination)	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-fractioned 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 ± SD.

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

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

https://ec.bioscientifica.com
https://doi.org/10.1530/EC-21-0462

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/m^2 to 83.6 ± 17.8 g/m^2 ($P < 0.05$) 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.

https://ec.bioscientifica.com
https://doi.org/10.1530/EC-21-0462

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 α_1-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 β_1- and β_2-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).

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.

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

https://ec.bioscientifica.com
https://doi.org/10.1530/EC-21-0462

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

	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 pathophysiologic 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).

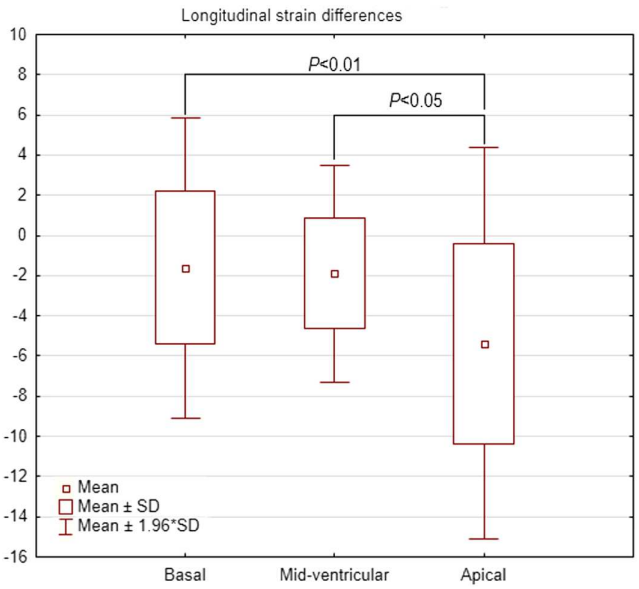


Figure 2
Left ventricle longitudinal strain differences before and after adrenalectomy.

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

https://ec.bioscientifica.com
https://doi.org/10.1530/EC-21-0462

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 β1-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

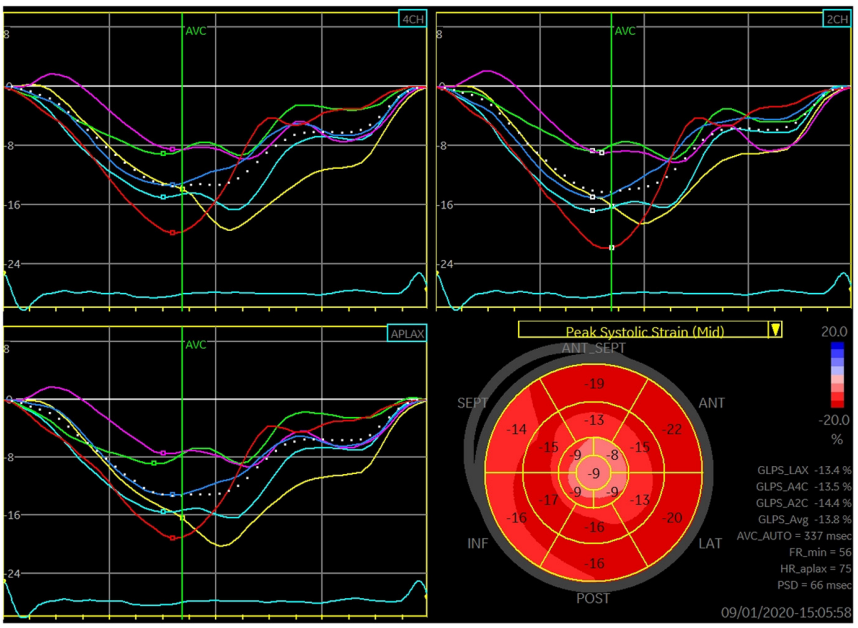


Figure 3
Global longitudinal strain before adrenalectomy. The green and purple curves represent apical segments. GLPS, global longitudinal peak strain; 4CH, apical four chamber view, 2CH, apical two chamber view; APLAX, apical long-axis view; MID, mid-wall; AVC, aortic valve closure; ANT-SEPT, anterior-septal;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

https://ec.bioscientifica.com
https://doi.org/10.1530/EC-21-0462

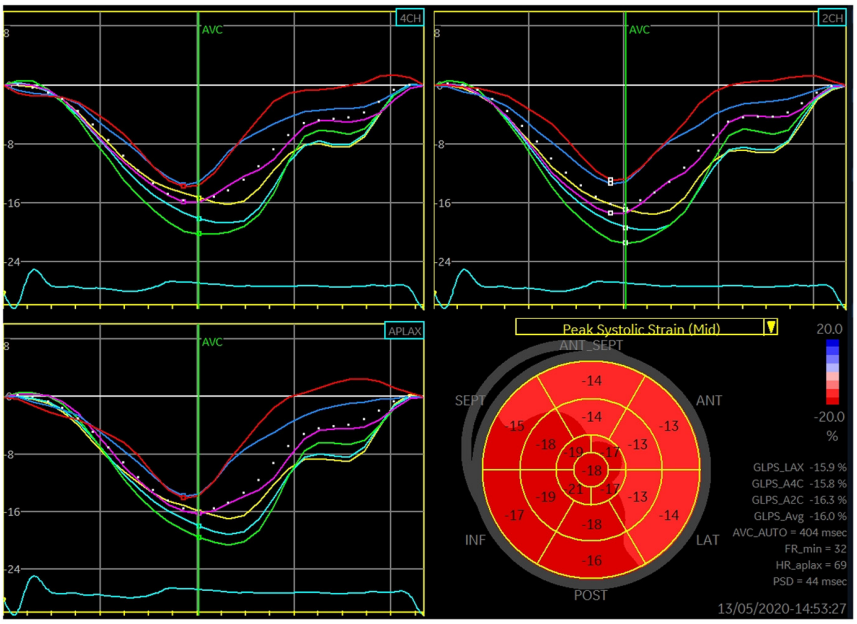


Figure 4
Global longitudinal strain after adrenalectomy. The green and purple curves represent apical segments. GLPS, global longitudinal peak strain; 4CH, apical four chamber view, 2CH, apical two chamber view; APLAX, apical long-axis view; MID, mid-wall; AVC, aortic valve closure; ANT-SEPT, anterior-septal;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

Funding
This study was supported by Research Projects of the Charles University in Prague: Progres Q25 and Q28 and by research grant #NV19-01-00083 from the Ministry of Health of the Czech Republic; Ministry of Health, Czech Republic – conceptual development of research organization 64165, General University Hospital in Prague, Czech Republic.

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.

Acknowledgements
Special thanks go to the nurses Terezie Holajová and Eva Straková from the echocardiography laboratory at the Third Department of Medicine for assistance during the study.

References

1 Pacak K, Keiser HR & Eisenhofer G. Pheochromocytoma. In *Endocrinology*, 5th ed., pp. 2501–2534. Eds LJ DeGroot & JL Jamenson. Philadelphia: Elsevier Saunders, 2006.
2 Ariton M, Juan CS & AvRuskin TW. Pheochromocytoma: clinical observations from a Brooklyn Tertiary Hospital. *Endocrine Practice* 2000 **6** 249–252. (https://doi.org/10.4158/EP.6.3.249)
3 Omura M, Saito J, Yamaguchi K, Kakuta Y & Nishikawa T. Prospective study on the prevalence of secondary hypertension among hypertensive patients visiting a general outpatient clinic in Japan. *Hypertension Research* 2004 **27** 193–202. (https://doi.org/10.1291/hypres.27.193)
4 Lenders JW, Eisenhofer G, Mannelli M & Pacak K. Phaeochromocytoma. *Lancet* 2005 **366** 665–675. (https://doi.org/10.1016/S0140-6736(05)67139-5)
5 Berends AMA, Buitenwerf E, de Krijger RR, Veeger NJGM, van der Horst-Schrivers ANA, Links TP & Kerstens MN. Incidence of pheochromocytoma and sympathetic paraganglioma in the Netherlands: a nationwide study and systematic review. *European Journal of Internal Medicine* 2018 **51** 68–73. (https://doi.org/10.1016/j.ejim.2018.01.015)
6 Zelinka T, Eisenhofer G & Pacak K. Pheochromocytoma as a catecholamine producing tumor: implications for clinical practice. *Stress* 2007 **10** 195–203. (https://doi.org/10.1080/10253890701395896)
7 Zelinka T, Petrák O, Turková H, Holaj R, Štrauch B, Kršek M, Brabcová-Vránková AB, Musil Z, Dušková J, Kubinyi J, *et al.* High incidence of cardiovascular complications in pheochromocytoma. *Hormone and Metabolic Research* 2012 **44** 379–384. (https://doi.org/10.1055/s-0032-1306294)
8 Majtan B, Zelinka T, Rosa J, Petrák O, Krátká Z, Štrauch B, Tuka V, Vránková A, Michalský D, Novák K, *et al.* Long-term effect of adrenalectomy on cardiovascular remodeling in patients with pheochromocytoma. *Journal of Clinical Endocrinology and Metabolism* 2017 **102** 1208–1217. (https://doi.org/10.1210/jc.2016-2422)
9 Ghadri JR, Wittstein IS, Prasad A, Sharkey S, Dote K, Akashi YJ, Cammann VL, Crea F, Galiuto L, Desmet W, *et al.* International expert consensus document on takotsubo syndrome (Part I): clinical characteristics, diagnostic criteria, and pathophysiology. *European Heart Journal* 2018 **39** 2032–2046. (https://doi.org/10.1093/eurheartj/ehy076)

10 Park JH, Kim KS, Sul JY, Shin SK, Kim JH, Lee JH, Choi SW, Jeong JO & Seong IW. Prevalence and patterns of left ventricular dysfunction in patients with pheochromocytoma. *Journal of Cardiovascular Ultrasound* 2011 **19** 76–82. (https://doi.org/10.4250/jcu.2011.19.2.76)

11 Chiang YL, Chen PC, Lee CC & Chua SK. Adrenal pheochromocytoma presenting with takotsubo-pattern cardiomyopathy and acute heart failure: a case report and literature review. *Medicine* 2016 **95** e4846. (https://doi.org/10.1097/MD.0000000000004846)

12 Sun JP, Stewart WJ, Yang XS, Donnell RO, Leon AR, Felner JM, Thomas JD & Merlino JD. Differentiation of hypertrophic cardiomyopathy and cardiac amyloidosis from other causes of ventricular wall thickening by two-dimensional strain imaging echocardiography. *American Journal of Cardiology* 2009 **103** 411–415. (https://doi.org/10.1016/j.amjcard.2008.09.102)

13 Lee SH, Park JH, Lee JY, Lee SR, Rhee KS, Chae JK, Kim WH, Sul JY, Oh JK, Kwon HJ, *et al.* Clinical profiles of patients with surgically resected pheochromocytoma and paraganglioma. *Korean Journal of Internal Medicine* 2019 **35** 351–359. (https://doi.org/10.3904/kjim.2018.231)

14 Kvasnička J, Zelinka T, Petrák O, Rosa J, Štrauch B, Krátká Z, Indra T, Markvartová A, Widimský J & Holaj R. Catecholamines induce left ventricular subclinical systolic dysfunction: a speckle-tracking echocardiography study. *Cancers* 2019 **11** 318. (https://doi.org/10.3390/cancers11030318)

15 Dobrowolski P, Januszewicz A, Klisiewicz A, Gosk-Przybylek M, Peczkowska M, Kabat M, Kwapiszewska A, Warchol-Celinska E, Ambroziak U, Doroszko A, *et al.* Left ventricular structural and functional alterations in patients With pheochromocytoma/paraganglioma before and after surgery. *JACC: Cardiovascular Imaging* 2020 **13** 2498–2509. (https://doi.org/10.1016/j.jcmg.2020.07.017)

16 Elenkova A, Shabani R, Kinova E, Vasilev V, Goudev A & Zacharieva S. Global longitudinal strain as a marker for systolic function in patients with pheochromocytomas. *Endocrine-Related Cancer* 2020 **27** 561–570. (https://doi.org/10.1530/ERC-20-0137)

17 Lyon AR, Rees PS, Prasad S, Poole-Wilson PA & Harding SE. Stress (takotsubo) cardiomyopathy – a novel pathophysiological hypothesis to explain catecholamine-induced acute myocardial stunning. *Nature Clinical Practice: Cardiovascular Medicine* 2008 **5** 22–29. (https://doi.org/10.1038/ncpcardio1066)

18 Tafreshi S, Naqvi SY & Thomas S. Extra-adrenal pheochromocytoma presenting as inverse takotsubo-pattern cardiomyopathy treated with surgical resection. *BMJ Case Reports* 2018 **11** e226384. (https://doi.org/10.1136/bcr-2018-226384)

19 Eisenhofer G, Lenders JW, Goldstein DS, Mannelli M, Csako G, Walther MM, Brouwers FM & Pacak K. Pheochromocytoma catecholamine phenotypes and prediction of tumor size and location by use of plasma free metanephrines. *Clinical Chemistry* 2005 **51** 735–744. (https://doi.org/10.1373/clinchem.2004.045484)

20 Eisenhofer G, Timmers HJ, Lenders JW, Bornstein SR, Tiebel O, Mannelli M, King KS, Vocke CD, Linehan WM, Bratslavsky G, *et al.* Age at diagnosis of pheochromocytoma differs according to catecholamine phenotype and tumor location. *Journal of Clinical Endocrinology and Metabolism* 2011 **96** 375–384. (https://doi.org/10.1210/jc.2010-1588)

21 Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, Clement D, Coca A, De Simone G, Dominiczak A, *et al.* 2018 Practice Guidelines for the management of arterial hypertension of the European Society of Hypertension and the European Society of Cardiology: ESH/ESC Task Force for the management of arterial hypertension. *Journal of Hypertension* 2018 **36** 2284–2309. (https://doi.org/10.1097/HJH.0000000000001961)

22 Ramaraj R & Movahed MR. Reverse or inverted takotsubo cardiomyopathy (reverse left ventricular apical ballooning syndrome) presents at a younger age compared with the mid or apical variant and is always associated with triggering stress. *Congestive Heart Failure* 2010 **16** 284–286. (https://doi.org/10.1111/j.1751-7133.2010.00188.x)

23 Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, Chapman MJ, De Backer GG, Delgado V, Ference BA, *et al.* 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *European Heart Journal* 2020 **41** 111–188. (https://doi.org/10.1093/eurheartj/ehz455)

24 Lenders JW, Eisenhofer G, Armando I, Keiser HR, Goldstein DS & Kopin IJ. Determination of metanephrines in plasma by liquid chromatography with electrochemical detection. *Clinical Chemistry* 1993 **39** 97–103. (https://doi.org/10.1093/clinchem/39.1.97)

25 Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, *et al.* Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *European Heart Journal: Cardiovascular Imaging* 2015 **16** 233–270. (https://doi.org/10.1093/ehjci/jev014)

26 Mor-Avi V, Lang RM, Badano LP, Belohlavek M, Cardim NM, Derumeaux G, Galderisi M, Marwick T, Nagueh SF, Sengupta PP, *et al.* Current and evolving echocardiographic techniques for the quantitative evaluation of cardiac mechanics: ASE/EAE consensus statement on methodology and indications endorsed by the Japanese Society of Echocardiography. *European Journal of Echocardiography* 2011 **12** 167–205. (https://doi.org/10.1093/ejechocard/jer021)

27 Farsalinos KE, Daraban AM, Unlu S, Thomas JD, Badano LP & Voigt JU. Head-to-head comparison of global longitudinal strain measurements among nine different vendors: the EACVI/ASE inter-vendor comparison study. *Journal of the American Society of Echocardiography* 2015 **28** 1171–1181, e2. (https://doi.org/10.1016/j.echo.2015.06.011)

28 Cheng S, Larson MG, McCabe EL, Osypiuk E, Lehman BT, Stanchev P, Aragam J, Benjamin EJ, Solomon SD & Vasan RS. Reproducibility of speckle-tracking-based strain measures of left ventricular function in a community-based study. *Journal of the American Society of Echocardiography* 2013 **26** 1258.e2–1266.e2. (https://doi.org/10.1016/j.echo.2013.07.002)

29 Inoue K, Okayama H, Nishimura K, Nagai T, Suzuki J, Ogimoto A, Saito M, Yoshii T, Hiasa G, Sumimoto T, *et al.* Impact of septal curvature on regional strain in patients with hypertrophic cardiomyopathy. *Circulation Journal* 2013 **77** 1040–1045. (https://doi.org/10.1253/circj.cj-12-0752)

30 Phelan D, Collier P, Thavendiranathan P, Popovic ZB, Hanna M, Plana JC, Marwick TH & Thomas JD. Relative apical sparing of longitudinal strain using two-dimensional speckle-tracking echocardiography is both sensitive and specific for the diagnosis of cardiac amyloidosis. *Heart* 2012 **98** 1442–1448. (https://doi.org/10.1136/heartjnl-2012-302353)

31 Kramer J, Niemann M, Liu D, Hu K, Machann W, Beer M, Wanner C, Ertl G & Weidemann F. Two-dimensional speckle tracking as a non-invasive tool for identification of myocardial fibrosis in Fabry disease. *European Heart Journal* 2013 **34** 1587–1596. (https://doi.org/10.1093/eurheartj/eht098)

32 Finsterer J & Wahbi K. CNS disease triggering takotsubo stress cardiomyopathy. *International Journal of Cardiology* 2014 **177** 322–329. (https://doi.org/10.1016/j.ijcard.2014.08.101)

33 Templin C, Ghadri JR, Diekmann J, Napp LC, Bataiosu DR, Jaguszewski M, Cammann VL, Sarcon A, Geyer V, Neumann CA, *et al.* Clinical features and outcomes of takotsubo (stress) cardiomyopathy. *New England Journal of Medicine* 2015 **373** 929–938. (https://doi.org/10.1056/NEJMoa1406761)

34 Y-Hassan S. Clinical features and outcome of pheochromocytoma-induced takotsubo syndrome: analysis of 80 published cases. *American Journal of Cardiology* 2016 **117** 1836–1844. (https://doi.org/10.1016/j.amjcard.2016.03.019)

35 Cohen RA, Shepherd JT & Vanhoutte PM. Prejunctional and postjunctional actions of endogenous norepinephrine at the sympathetic neuroeffector junction in canine coronary arteries. *Circulation Research* 1983 **52** 16–25. (https://doi.org/10.1161/01.res.52.1.16)

36 Wittstein IS. Stress cardiomyopathy: a syndrome of catecholamine-mediated myocardial stunning? *Cellular and Molecular Neurobiology* 2012 **32** 847–857. (https://doi.org/10.1007/s10571-012-9804-8)

37 Frustaci A, Loperfido F, Gentiloni N, Caldarulo M, Morgante E & Russo MA. Catecholamine-induced cardiomyopathy in multiple endocrine neoplasia. A histologic, ultrastructural, and biochemical study. *Chest* 1991 **99** 382–385. (https://doi.org/10.1378/chest.99.2.382)

38 Samuels MA. The brain-heart connection. *Circulation* 2007 **116** 77–84. (https://doi.org/10.1161/CIRCULATIONAHA.106.678995)

39 Mori H, Ishikawa S, Kojima S, Hayashi J, Watanabe Y, Hoffman JI & Okino H. Increased responsiveness of left ventricular apical myocardium to adrenergic stimuli. *Cardiovascular Research* 1993 **27** 192–198. (https://doi.org/10.1093/cvr/27.2.192)

40 Lyon AR, Bossone E, Schneider B, Sechtem U, Citro R, Underwood SR, Sheppard MN, Figtree GA, Parodi G, Akashi YJ, *et al.* Current state of knowledge on Takotsubo syndrome: a position statement from the taskforce on Takotsubo Syndrome of the Heart Failure Association of the European Society of Cardiology. *European Journal of Heart Failure* 2016 **18** 8–27. (https://doi.org/10.1002/ejhf.424)

41 Paur H, Wright PT, Sikkel MB, Tranter MH, Mansfield C, O'Gara P, Stuckey DJ, Nikolaev VO, Diakonov I, Pannell L, *et al.* High levels of circulating epinephrine trigger apical cardiodepression in a beta2-adrenergic receptor/Gi-dependent manner: a new model of takotsubo cardiomyopathy. *Circulation* 2012 **126** 697–706. (https://doi.org/10.1161/CIRCULATIONAHA.112.111591)

42 Eitel I, von Knobelsdorff-Brenkenhoff F, Bernhardt P, Carbone I, Muellerleile K, Aldrovandi A, Francone M, Desch S, Gutberlet M, Strohm O, *et al.* Clinical characteristics and cardiovascular magnetic resonance findings in stress (takotsubo) cardiomyopathy. *JAMA* 2011 **306** 277–286. (https://doi.org/10.1001/jama.2011.992)

43 Ghadri JR, Cammann VL, Napp LC, Jurisic S, Diekmann J, Bataiosu DR, Seifert B, Jaguszewski M, Sarcon A, Neumann CA, *et al.* Differences in the clinical profile and outcomes of typical and atypical takotsubo syndrome: data from the international takotsubo registry. *JAMA Cardiology* 2016 **1** 335–340. (https://doi.org/10.1001/jamacardio.2016.0225)

44 Trivedi SJ, Altman M, Stanton T & Thomas L. Echocardiographic strain in clinical practice. *Heart, Lung and Circulation* 2019 **28** 1320–1330. (https://doi.org/10.1016/j.hlc.2019.03.012)

45 Wang X, Sentex E, Saini HK, Chapman D & Dhalla NS. Upregulation of beta-adrenergic receptors in heart failure due to volume overload. *American Journal of Physiology: Heart and Circulatory Physiology* 2005 **289** H151–H159. (https://doi.org/10.1152/ajpheart.00066.2005)

46 Zelinka T, Štrauch B, Petrák O, Holaj R, Vránková A, Weisserová H, Pacák K & Widimský Jr J. Increased blood pressure variability in pheochromocytoma compared to essential hypertension patients. *Journal of Hypertension* 2005 **23** 2033–2039. (https://doi.org/10.1097/01.hjh.0000185714.60788.52)

47 Petrak O, Rosa J, Holaj R, Strauch B, Kratka Z, Kvasnicka J, Klimova J, Waldauf P, Hamplova B, Markvartova A, *et al.* Blood pressure profile, catecholamine phenotype, and target organ damage in pheochromocytoma/paraganglioma. *Journal of Clinical Endocrinology and Metabolism* 2019 **104** 5170–5180. (https://doi.org/10.1210/jc.2018-02644)

48 La Batide-Alanore A, Chatellier G & Plouin PF. Diabetes as a marker of pheochromocytoma in hypertensive patients. *Journal of Hypertension* 2003 **21** 1703–1707. (https://doi.org/10.1097/00004872-200309000-00020)

49 Holland DJ, Marwick TH, Haluska BA, Leano R, Hordern MD, Hare JL, Fang ZY, Prins JB & Stanton T. Subclinical LV dysfunction and 10-year outcomes in type 2 diabetes mellitus. *Heart* 2015 **101** 1061–1066. (https://doi.org/10.1136/heartjnl-2014-307391)

50 Komada H, Hirota Y, So A, Nakamura T, Okuno Y, Fukuoka H, Iguchi G, Takahashi Y, Sakaguchi K & Ogawa W. Insulin secretion and insulin sensitivity before and after surgical treatment of pheochromocytoma or paraganglioma. *Journal of Clinical Endocrinology and Metabolism* 2017 **102** 3400–3405. (https://doi.org/10.1210/jc.2017-00357)

51 Wiesner TD, Bluher M, Windgassen M & Paschke R. Improvement of insulin sensitivity after adrenalectomy in patients with pheochromocytoma. *Journal of Clinical Endocrinology and Metabolism* 2003 **88** 3632–3636. (https://doi.org/10.1210/jc.2003-030000)

52 Sanfilippo F, Corredor C, Fletcher N, Tritapepe L, Lorini FL, Arcadipane A, Vieillard-Baron A & Cecconi M. Left ventricular systolic function evaluated by strain echocardiography and relationship with mortality in patients with severe sepsis or septic shock: a systematic review and meta-analysis. *Critical Care* 2018 **22** 183. (https://doi.org/10.1186/s13054-018-2113-y)

53 Zelinka T, Petrák O, Štrauch B, Holaj R, Kvasnička J, Mazoch J, Pacák K & Widimský Jr J. Elevated inflammation markers in pheochromocytoma compared to other forms of hypertension. *Neuroimmunomodulation* 2007 **14** 57–64. (https://doi.org/10.1159/000107289)

54 Heubach JF, Ravens U & Kaumann AJ. Epinephrine activates both Gs and Gi pathways, but norepinephrine activates only the Gs pathway through human beta2-adrenoceptors overexpressed in mouse heart. *Molecular Pharmacology* 2004 **65** 1313–1322. (https://doi.org/10.1124/mol.65.5.1313)

Received in final form 14 October 2021
Accepted 3 November 2021
Accepted Manuscript published online 4 November 2021