Brief Report

Is treated hypopituitarism associated with increased left ventricular strains?—detailed analysis from the three-dimensional speckle-tracking echocardiographic MAGYAR-Path Study

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Abstract: Reduced secretion of one or more of the hormones normally produced by the pituitary gland is called hypopituitarism, which is a rare and frequently underdiagnosed condition. Hypopituitarism can be present at birth called congenital or may develop due to acquired causes like tumor, infection, infiltration, vascular or other causes. Symptoms of hypopituitarism are highly dependent on which hormones are insufficient. The present prospective study was designed to test whether treated hypopituitarism is associated with changes in 3DSTE-derived LV strains in patients without known cardiovascular disorder. We investigated 38 patients with treated hypopituitarism who were in sinus rhythm (57.0±13.6 years, 19 males), 6 patients were excluded from the study due to inferior image quality. The remaining patient group consisted of 16 patients with congenital hypopituitarism and 16 patients with acquired form of hypopituitarism. Their results were compared to age- and gender-matched controls (mean age: 55.3±4.7 years, 14 males). Out of the 32 patients with hypopituitarism, 30 patients had growth hormone deficiency, 27 patients had central adrenal insufficiency, 12 patients had central hypothyroidism, 12 patients had hypogonadotropic hypogonadism and 5 patients had diabetes insipidus. Only LV longitudinal and area strains proved to be significantly increased in patients with hypopituitarism, other LV strains did not differ between patients and controls. No significant differences could be confirmed in LV strains between patients with congenital and acquired hypopituitarism. It could be concluded that longitudinal LV strains are increased in both congenital and acquired treated hypopituitarism.

Keywords: Left ventricular strain; three-dimensional; echocardiography; hypopituitarism

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Introduction

Reduced secretion of one or more of the hormones normally produced by the pituitary gland is called hypopituitarism, which is a rare and frequently underdiagnosed condition. Hypopituitarism can be present at birth called congenital or may develop due to acquired causes like tumor, infection, infiltration, vascular or other causes. Symptoms of hypopituitarism are highly dependent on which hormones are insufficient (1,2). Absence or reduced level of certain hormones could be theorized to be associated with changes in myocardial mechanics. Mostly acromegaly was investigated (3-7), but limited information is available with other endocrine diseases (8). Three-dimensional (3D) speckle-tracking echocardiography (3DSTE) is a promising new validated imaging technique with capability of 3D volumetric and functional assessment of certain heart chambers (9-12). The present prospective study was designed to test whether treated hypopituitarism is associated with changes in 3DSTE-derived LV strains in patients without known cardiovascular disorder. It was also aimed to compare data of patients with congenital *vs*. acquired hypopituitarism.

Patients and methods

Patient population

The study comprised of 38 patients with treated hypopituitarism (mean age: 57.0±13.6 years, 19 males), the patients were in sinus rhythm, 6 patients were excluded from the study due to inferior image quality. The remaining group consisted of 16 patients having congenital hypopituitarism and 16 patients having acquired form of hypopituitarism. Patients originate from the outpatient clinic of the Division of Endocrinology at the University of Szeged, which is a tertiary endocrine center responsible for the treatment of patients with severe or/and rare endocrine disorders like hypopituitarism. Their results were compared to age- and gender-matched controls (mean age: 55.3±4.7 years, 14 males), who were considered to be healthy, no acute or chronic disease was present, there were no electrocardiographic and echocardiographic abnormalities and they had no history of regular drug use. Complete two-dimensional Doppler echocardiography and 3DSTE were performed in all patients and controls. The presented work is a part of the Motion Analysis of the heart and Great vessels bY three-dimensionAl speckle-tRacking echocardiography in Pathological cases (MAGYAR-Path) Study. It was organized to assess diagnostic and prognostic value of 3DSTE-derived LV deformation parameters among others in different disorders ('magyar' means 'Hungarian' in Hungarian language). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional ethics committee of the University of Szeged (No. 71/2011) and informed consent was taken from all the patients.

Two-dimensional echocardiography

Toshiba Artida™ echocardiographic tool (Toshiba Medical Systems, Tochigi, Japan) was used for completion of 2D Doppler studies attached with a PST-30SBP (1–5 MHz) phased-array transducer by experienced sonographers. Echocardiographic chamber quantifications were performed according to clinical standards (13). LV ejection fraction was calculated by using the Simpson's formula. Valvular regurgitations and stenoses were evaluated by Doppler measurements. Mean pulmonary artery pressure was estimated by Doppler jet velocity. Mitral and tricuspid annular plane systolic excursion (MAPSE and TAPSE, respectively) parameters were also calculated.

3DSTE

3DSTE was performed as described in more details in previous studies (9-12). Shortly, the same Toshiba Artida™ imaging equipment (Toshiba Medical Systems, Tochigi, Japan) was used with a PST-25SX matrix-array transducer. Full volume pyramid-shaped 3D echocardiographic datasets were digitally acquired from the apical window during breath suspension during 6 cardiac cycles. LV strains were assessed by offline image analysis using 3D Wall Motion Tracking software version 2.7 (Ultra Extend, Toshiba Medical Systems, Tochigi, Japan). Following selection of apical four- (AP4CH), two-chamber (AP2CH) and 3 cross-sectional views at different levels of the LV mitral annular septal and lateral edges and LV apex were defined, then sequential analysis and automatic contour detection were performed. LV was analyzed using a 3D virtual LV model (*Figure 1*).

Global unidirectional longitudinal (LS), circumferential (CS), radial (RS) and complex/multidirectional area (AS) and 3D strains (3DS) were assessed. Using 16-segment LV model, segmental and mean segmental LV strains were also assessed. LV regional strains were measured from segmental LV strains calculated for each apical, midventricular and basal LV regions (9-12).

Statistical analysis

Mean ± standard deviation or number and percentage formats were used for data presentations. $P<0.05$ was considered to be statistically significant. Categorical variables were tested by Fisher's exact test. To test normality of distribution for continuous variables, Shapiro-Wilks test was performed. Levene's Test for Equality of Variances was used for Homogeneity of Variance. Student's *t*-test was used in the presence of normal distribution, in case of non-normal distribution Mann-Whitney-Wilcoxon test was performed. Bonferroni correction of the significance level for multiple testing. Statistical analyses were performed with an RStudio (RStudio Team 2015). RStudio: Integrated Development for R. RStudio, Inc., Boston, MA). For offline

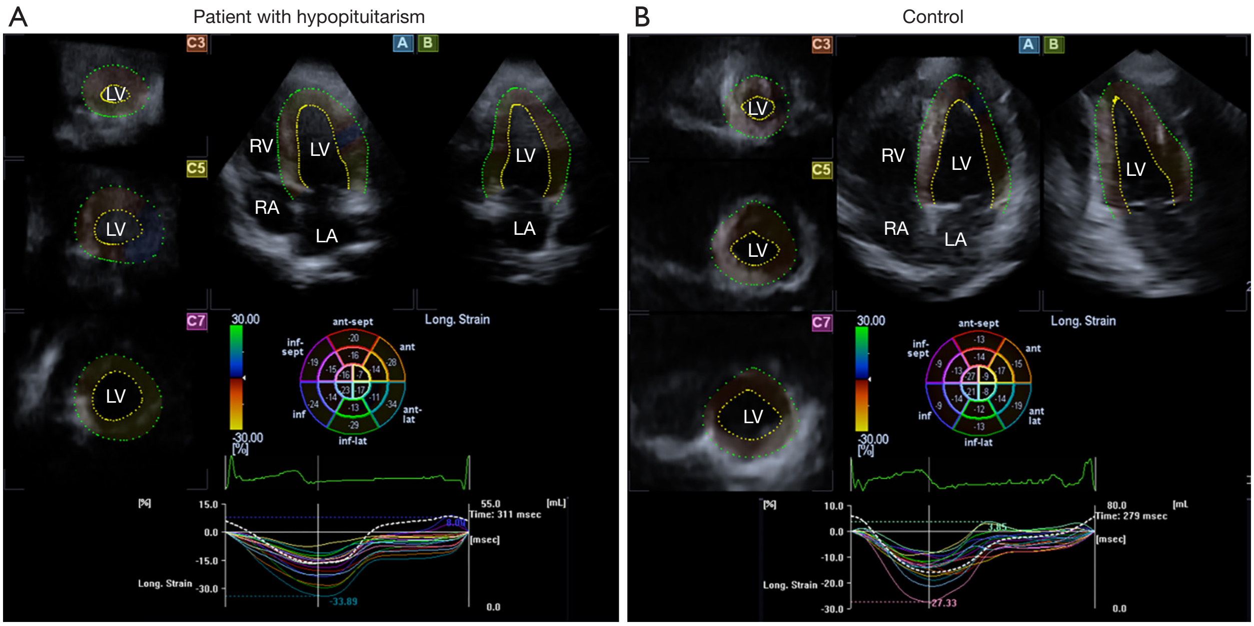

Figure 1 Images from a three-dimensional (3D) speckle-tracking echocardiographic analysis in a healthy subject (A) and in a patient with hypopituitarism (B) are demonstrated presenting an apical four-chamber view (A), apical two-chamber view (B) and apical (C3), mid-ventricular (C5) and basal (C7) left ventricular (LV) short-axis views together with LV volumetric data in respect with cardiac cycle and time – LV segmental longitudinal strain curves (coloured lines) with bull's eye display and a time-volume changes curve (dashed line) during the cardiac cycle. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

data analysis and graph creation, MATLab was used (The MathWorks Inc, Natick, Massachusetts).

Results

Demographic and two-dimensional echocardiographic data

Out of the 32 patients with hypopituitarism, 30 patients had growth hormone deficiency, 27 patients had central adrenal insufficiency, 12 patients had central hypothyroidism, 12 patients had hypogonadotropic hypogonadism and 5 patients had diabetes insipidus. Among cardiovascular risk factors, only hypertension proved to be more frequent in the group of patients with hypopituitarism. All hypertensive patients were treated with normo- or combined antihypertensive treatment. From routine 2D echocardiographic parameters, only LV walls were found to be thickened in patients with hypopituitarism compared to that of negative controls (*Table 1*). None of the healthy subjects or patients showed more than grade 1 valvular regurgitation or significant stenosis on any valves. Systolic mean pulmonary artery pressure proved to be 24.3±3.4 mmHg. The hormone levels of all patients were within their gender- and age-specific reference ranges.

3DSTE

Only global and mean segmental LV-LS and LV-AS proved to be significantly increased in patients with hypopituitarism, other LV strains did not differ between patients and controls. No significant differences could be seen in LV strains between patients with congenital and acquired hypopituitarism. 3DSTE-derived LV global and mean segmental strains are demonstrated in *Table 2*, while LV regional strains are depicted in *Table 3*. No differences in LV strains could be detected between patients with hypopituitarism with *vs.* without treated hypertension (*Table 4*).

Discussion

Increased LV-LS and LV-AS could be demonstrated in patients with hypopituitarism being on optimal hormone replacement therapy (HRT) without overt cardiovascular symptoms and alterations. No significant alterations could be demonstrated between patients with congenital versus

Table 1 Demographic, clinical and two-dimensional echocardiographic data of patients with hypopituitarism and controls

Parameters	Controls (n=30)	Treated patients with hypopituitarism (n=32)	P value
Risk factors			
Age (years)	55.3±4.7	57.0±13.6	0.5
Male gender, n (%)	14 (47.0)	19 (59.0)	0.4
Hypertension, n (%)	0 (0.0)	17 (53.0)	<0.0001
Hypercholesterolemia, n (%)	0 (0.0)	4 (13.0)	0.1
Diabetes mellitus, n (%)	0 (0.0)	2 (6.0)	0.5
Systolic blood pressure (mmHg)	120.6±4.2	127.2±3.4	0.8
Diastolic blood pressure (mmHg)	81.2±2.3	82.5±3.4	0.8
Two-dimensional echocardiography			
LA diameter (mm)	39.2±3.7	38.8±4.9	0.7
LV end-diastolic diameter (mm)	48.3±2.8	48.9±3.0	0.4
LV end-diastolic volume (mL)	110.0±18.4	115.0±22.5	0.4
LV end-systolic diameter (mm)	31.9±2.6	30.0±2.9	0.1
LV end-systolic volume (mL)	38.9±7.7	38.0±11.5	0.7
Interventricular septum (mm)	9.5±1.3	10.0±1.0	0.06
LV posterior wall (mm)	9.6±1.6	10.1±1.0	0.04
E (cm/s)	67.1±16.7	74.7±18.3	0.1
A (cm/s)	71.8±17.6	74.2±16.6	0.6
E/A	0.97±0.25	1.06±0.38	0.5
LV ejection fraction (%)	64.6±3.8	66.3±5.9	0.6
MAPSE (mm)	14.3±1.1	13.1±2.0	0.8
TAPSE (mm)	22.5±4.2	20.7±3.6	0.8

LA, left atrium; LV, left ventricle; E, early transmitral flow velocity; A, late transmitral flow velocity; MAPSE, mitral annular plane systolic excursion; TAPSE, tricuspid annular plane systolic excursion.

acquired forms of hypopituitarism. Moreover, differences in LV strains could not be detected between patients with hypopituitarism with *vs.* without hypertension. In recent studies, similar LV abnormalities represented by LV strains were found in acromegaly (4), lipedema (14) and highly trained sportsmen (15), where these alterations were theorized to be a compensatory mechanism for abnormalities related to the underlying disease- or condition-related changes in myocardial architecture.

Growth hormone (GH) deficiency, which causes alterations in body composition, lipid profile, insulin resistance, vascular atherosclerosis, endothelial and cardiac (systolic) function, is the main factor of increased mortality in hypopituitary patients, when appropriate standard replacement of the pituitary hormone deficiencies is given (16). These cardiovascular comorbidities in hypopituitarism (and GH deficiency) could affect myocardial mechanics via cellular dysfunction, hypertrophy, fibrosis or increased wall stress (16,17). Adults with GH deficiency had reduced LV-LS and LV-CS with preserved LV-RS compared with controls (18). GH-HRT in adult-onset GH deficiency demonstrated to have beneficial effects on strain and strain rate parameters, but these parameters returned to baseline levels after the withdrawal of GH (19). In our study, we demonstrated increased LV-LS and LV-AS, and these results can be explained by a number of theories. Similarly to acromegaly, changes in LV rotational mechanics could be assumed to be present demonstrating

Table 2 Comparison of three-dimensional speckle-tracking echocardiography-derived left ventricular volumetric, global and mean segmental strain parameters in patients with hypopituitarism and in controls

Parameters	Controls (n=30)	Treated patients with hypopituitarism (n=32)	Treated patients with congenital hypopituitarism (n=16)	Treated patients with acquired hypopituitarism (n=16)
3DSTE-derived LV volumetric parameters				
EDV (mL)	82.3±20.2	78.8±29.5	77.6±27.9	80.0±31.9
ESV (mL)	35.6±10.9	34.4±18.0	32.8±15.4	36.0±20.6
EF (%)	56.8±6.8	58.1±8.4	58.8±7.1	57.5±9.8
3DSTE-derived LV global strains				
Radial (%)	26.9±10.8	25.8±13.0	25.0±13.1	26.6±13.3
Circumferential (%)	–26.5±5.6	–27.4±7.1	–28.4±7.1	–26.4±7.2
Longitudinal (%)	–15.5±2.8	–19.4±3.2*	–19.7±3.1*	–19.2±3.5*
3D (%)	29.2±10.8	29.5±12.4	29.0±12.2	30.0±12.9
Area (%)	–38.8±5.3	–42.2±7.4*	–43.2±6.7*	–41.2±8.0
3DSTE-derived LV mean segmental strains				
Radial (%)	29.6±10.1	29.9±11.7	29.1±11.6	30.8±12.2
Circumferential (%)	–27.9±5.3	–28.7±6.7	–29.6±6.9	–27.9±6.5
Longitudinal (%)	–16.5±2.8	–20.5±3.0*	–20.7±2.9*	–20.4±3.2*
3D (%)	31.5±10.0	33.0±11.4	32.3±11.1	33.8±11.9
Area (%)	–40.0±5.1	–43.4±6.9*	–44.2±6.5*	–42.6±7.4

*, P<0.05 *vs.* controls. 3D, three-dimensional; 3DSTE, three-dimensional speckle-tracking echocardiography; EDV, end-diastolic volume; ESV, end-systolic volume; EF, ejection fraction; LV, left ventricular.

Table 3 Comparison of three-dimensional speckle-tracking echocardiography-derived left ventricular regional strain parameters between hypopituitary patients and controls

Parameters	Controls (n=30)	Treated patients with hypopituitarism (n=32)	Treated patients with congenital hypopituitarism (n=16)	Treated patients with acquired hypopituitarism (n=16)
RS_{basal} (%)	36.7±14.7	32.6±16.0	32.0±14.9	33.1±17.5
RS_{mid} (%)	30.9±12.7	30.2±14.0	27.6±11.7	32.8±16.0
RS_{apex} (%)	16.9±8.2	25.7±12.6*	27.1±12.6*	24.3±12.9
CS_{basal} %)	–27.0±5.9	–24.6±6.0	–25.3±5.1	–23.9±7.0
CS_{mid} (%)	–28.7±7.4	–28.1±6.2	–28.3±6.4	–27.8±6.3
CS_{apex} (%)	–28.1±11.0	–36.0±14.0*	–38.1±13.2*	–33.9±14.9
LS_{basal} (%)	–20.8±5.4	–23.6±4.0*	–24.1±2.7*	–23.1±5.1
LS_{mid} %)	–13.4±4.5	–17.3±4.4*	–16.3±3.9*	–18.4±4.7*
LS_{apex} (%)	–14.7±5.8	–20.8±7.9*	–22.1±8.8*	–19.4±6.9*
$3DS_{basal}$ (%)	39.2±13.9	36.9±15.8	35.9±14.5	37.8±17.4
$3DS_{mid}$ (%)	32.0±12.5	32.7±13.5	30.8±11.7	34.7±15.3
$3DS_{apex}$ (%)	19.1±9.3	27.8±13.2*	29.0±12.8*	26.6±14.0
AS_{basal} (%)	–41.3±7.0	–41.0±6.9	–41.7±4.6	–40.3±8.7
AS_{mid} (%)	–38.9±8.0	–41.5±6.6	–41.2±6.7	–41.9±6.7
AS_{apex} (%)	–39.7±13.7	–50.0±16.1*	–52.7±13.4*	–47.3±18.3

*, P<0.05 *vs.* controls. RS, radial strain; CS, circumferential strain; LS, longitudinal strain; 3DS, three-dimensional strain; AS, area strain.

Table 4 Comparison of three-dimensional speckle-tracking echocardiography-derived left ventricular volumetric, global and mean segmental strain parameters in normotensive and hypertensive patients with hypopituitarism and in controls

Parameters	Controls (n=30)	Normotensive treated patients with hypopituitarism (n=15)	Hypertensive treated patients with hypopituitarism (n=17)
Congenital/acquired	0/0	8/7	8/9
3DSTE-derived LV volumetric parameters			
EDV (mL)	82.3±20.2	87.8±29.6	70.8±27.9
ESV (mL)	35.6±10.9	37.8±18.3	31.4±17.7
EF (%)	56.8±6.8	59.1±8.6	57.3±8.4
3DSTE-derived LV global strains			
Radial (%)	26.9±10.8	26.8±16.7	25.0±9.1
Circumferential (%)	−26.5±5.6	−28.4±6.6	−26.6±7.7
Longitudinal (%)	−15.5±2.8	−19.6±3.3*	−19.3±3.2*
3D (%)	29.2±10.8	29.6±16.0	29.4±8.6
Area (%)	−38.8±5.3	−43.1±6.6*	−41.4±8.1
3DSTE-derived LV mean segmental strains			
Radial (%)	29.6±10.1	30.1±15.5	29.8±7.4
Circumferential (%)	−27.9±5.3	−29.4±6.5	−28.2±7.0
Longitudinal (%)	−16.5±2.8	−20.5±3.3*	−20.6±2.9*
3D (%)	31.5±10.0	32.5±14.9	33.5±7.5
Area (%)	−40.0±5.1	−44.0±6.4*	−42.9±7.5

*, $P<0.05$ *vs.* controls. 3D, three-dimensional; 3DSTE, three-dimensional speckle-tracking echocardiography; EDV, end-diastolic volume; ESV, end-systolic volume; EF, ejection fraction; LV, left ventricular.

significant reduction or absence of LV twist proceeding into a compensatory mechanism represented by the increased LV strains (3,4). Increase of LV apical segmental strains could be theoretically an adaptational/compensatory effect for reduced LV apical rotation. It is important to emphasize that treated hypopituitarism seems to be asscociated with altered myocardial mechanism, but further studies are warranted to confirm our findings in larger populations with selective hypopituitarism. Moreover, different forms of hypopituitarism and modes of HRT should be compared with each other.

Limitation section

(I) The study population was relatively low. However, hypopituitarism is considered to be a rare disease. All subjects alive who were able and willing to participate in this study was enrolled from South-East Hungary.
(II) 3DSTE is accompanied with lower frame rate and spatial resolution as compared to 2D echocardiography, which could affect image quality and therefore measurement of data.
(III) The present study was designed to assess only 3DSTE-derived LV strains. We did not aim to evaluate other variables including LV rotations and twist and deformation parameters of other heart chambers.
(IV) Validation of 3DSTE-derived LV strain measurements were not aimed due to their validated nature.

Conclusions

Increased longitudinal LV strains could be demonstrated in both congenital and acquired treated hypopituitarism.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/qims-21-113). Dr. AN serves as an unpaid editorial board member of *Quantitative Imaging in Medicine and Surgery*. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional ethics committee of the University of Szeged (No. 71/2011) and informed consent was taken from all the patients.

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