



RĪGAS STRADIŅA  
UNIVERSITĀTE

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POSSIBILITIES OF THE  
ULTRASOUND FOR THE  
ASSESSMENTS OF THE LEFT  
ATRIAL DEFORMATION IN  
HEALTHY INDIVIDUALS AND  
PATIENTS WITH LEFT  
VENTRICULAR HYPERTROPHY

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## ABBREVIATIONS

|            |   |
|------------|---|
| 2DS        | – two-dimensional strain                      |
| 4ch        | – apical 4-chamber                            |
| 2ch        | – apical 2-chamber                            |
| 3ch        | – apical 3-chamber                            |
| 4ch-avPALS | – average 4ch peak atrial longitudinal strain |
| 2ch-avPALS | – average 2ch peak atrial longitudinal strain |
| Ao         | – aorta                                       |
| Ao asc     | – aorta ascendens                             |
| AH         | – arterial hypertension                       |
| AS         | – aortic valve stenosis                       |
| ASE        | – American Society of Echocardiography        |
| AV         | – aortic valve                                |
| AF         | – atrial fibrillation                         |
| BSA        | – body surface area                           |
| c          | – conduit                                     |
| DD         | – diastolic dysfunction                       |
| DCM        | – dilatation cardiomyopathy                   |
| DT         | – deceleration time                           |
| EAE        | – European Association of Echocardiography    |
| Echo-cg    | – echocardiography                            |
| ECG        | – electrocardiogram                           |
| ESC        | – European Society of Cardiology              |
| ESH        | – European Society of Hypertension            |
| HCM        | – hypertrophic cardiomyopathy                 |
| HF         | – heart failure                               |
| globPALS   | – global peak atrial longitudinal strain      |

|           |  |
|-----------|--|
| IVC       | – inferior vena cava                     |
| IVRT      | – isovolumic relaxation time             |
| LVH       | – left ventricular hypertrophy           |
| LV        | – left ventricle                         |
| LA        | – left atrium                            |
| LA AEF    | – left atrial active emptying fraction   |
| LA IE     | – left atrial expansion index            |
| LA PEF    | – left atrial passive emptying fraction  |
| LA Vi max | – left atrium maximal volume index       |
| LA Vmax   | – left atrial maximal volume             |
| LA Vp     | – left atrial volume P wave on ECG       |
| LA Vmin   | – left atrial minimal volume             |
| LV EDD    | –left ventricular end diastolic diameter |
| LV EF     | – left ventricular ejection fraction     |
| LV ESD    | – left ventricular end systolic diameter |
| LVMI      | – left ventricular mass index            |
| MI        | – myocardial infarction                  |
| MV        | – mitral valve                           |
| PALS      | – peak atrial longitudinal strain        |
| PALSR     | – peak atrial longitudinal strain rate   |
| PH        | – pulmonary hypertension                 |
| PVv       | – pulmonary veins                        |
| RV        | – right ventricle                        |
| RA        | – right atrium                           |
| r         | – reservoir                              |
| S         | – strain                                 |
| SR        | – strain rate                            |
| s         | – systolic (contractile)                 |

- segPALS – segmental peak atrial longitudinal strain
- TDI – Tissue Doppler Imaging
- TPLS – time to peak atrial longitudinal strain
- TR – tricuspid regurgitation
- TV – tricuspid valve



# 1. INTRODUCTION

One of the most essential manifestations of the arterial hypertension (AH) is a heart injury, which directly influence the prognosis and the stage of the disease. The changes of heart caused by AH can be considered as the model to research heart diastolic dysfunction. These changes are especially important when necessary to define the hypertensive heart disease.

In the development of the heart failure (HF) the most important key is the AH [1]. The results of the numerous clinical researches about AH patients prove that the risk of the development of HF reliably declines in accordance with the lowering of the arterial pressure (AP) [2, 3]. However, the prognosis and the clinical manifestations of the patients with AH, depend not only from the levels of increasing of AP, but also from the injury of the target organ, including the myocardial left ventricular hypertrophy (LVH). Nowadays LVH is considered as the independent predictor of the early coronary artery disease and mortality. The patients with AH and LVH are more likely to develop the cardiovascular event than the AH patients without LVH [4, 5, 6]. 30-40% of patients with aortic stenosis (AS) have AH [7, 8]. The combination of AH and AS increases the risk of the pressure overload in the left ventricular (LV), which will lead to the fast progression of the LV dysfunction and worse patient prognosis [9].

In case of LVH, the function of the left atrial (LA) can be disturbed [10]. The LV myocardial relaxation disturbance and decreasing of the compliance cause problems in blood transfer from LA to LV. In order to increase the LV diastolic volume, the increasing of LV filling pressure is required. This is the one of the reason for the increase of the LA in moderate and severe AH and AS [11, 12].

The results of Framingham researches [13] show, that the increase of the LA is a significant predictor of the cardiovascular complications, particularly important in case of AH, because the above mentioned aspects can be developed before having the noticeable LV changes. However, a great number of researches are devoted to the investigation of LV changes in AH cases. Often these researches do not include the other modified parts of the heart in the "hypertensive heart" manifestation, neither do they evaluate the injury of the target organ and the stratification risk. However, the structural-functional changes of the LA do influence the number of clinical and instrumental symptoms. Therefore they need to be thoroughly investigated. Today the most researched are the LA structural-functional rates; in echocardiography the measurements of the volume of LA are widely used. The changes of the volume of the LA can be found even in the patients with the slight hypertension and insignificant LV hypertrophy, however, only 22 % of the patients have LA enlargement (LA maximum volume index enlargement) [14]. The size, volume and other derivatives of the LA (LA functional index, LA volume index, LA injection time, LA enlargement index), are theoretically significant parameters in diastolic dysfunctions, AH, atrial fibrillation and heart attack [2, 3, 4, 5].

However, the LA volume is the cumulative index and these changes (LA volume enlargement) are developed in the concrete period of time and circumstances. Therefore, the question is raised about the early LA dysfunction diagnostics, which can be seen even before the LA volume enlargement.

During the last years the researchers are interested in the atrial function. This is due to the new method in echocardiography, which allows evaluating the mechanical function of the atrial: the Tissue Doppler imaging (TDI) and Two-dimensional speckle tracking echocardiography (2DS) method. The above mentioned methods allow evaluating the deformation and the

velocity of deformation of the LV and LA. Deformation (latin. *deformation*) is a change in the shape or size of an object due to an applied force. Different deformation modes may occur under different conditions: elastic (reversible) or plastic (irreversible) deformation ([http://en.wikipedia.org/wiki/Deformation\\_\(engineering\)](http://en.wikipedia.org/wiki/Deformation_(engineering))). Myocardial deformation is elastic deformation type - a change in dimensions of myocardium under load that is fully recovered when the load is removed.

With the help of the TDI it is possible to assess precisely the velocity of displacement of the atrial myocardium. In some researches the normal velocity of displacement of the atrial myocardium, strain (S, describes myocardial deformation) and strain rate (SR, is the speed at which deformation occurs) were presented [15-17]. The present issues were investigated in the pathological cases too, for instance, the LV hypertrophy, heart ischemic diseases and the atrial fibrillation [18-21]. However, the TDI has some limitations – the angle dependency, the data registration with a lot of frames, a time-consuming process, due to which the method cannot be widely used.

Two-Dimensional Speckle tracking Echocardiography (2DS) is a new quantitative approach to the assessment of myocardial function. 2DS method providing sensitive and reproducible indexes of myocardial dysfunction that overcome most of limitations (angle-independent, non-Doppler) of TDI derived strain measures [22, 23].

### **1.1. Relevance of the scientific research**

1. 2DS method – a new non-invasive method with a high reliability and the ability to assess atrial function at once. The importance of the assessment of the atrial function in the clinical cardiology is rising, especially in the cases of early (pre-clinical) heart function disturbances.

2. 2DS is an interesting method to evaluate the mechanic function of both artials, which has the predictably important role in the development of the heart disease.
3. Today there are no data about the AH patients with the atrial function disturbances having various degrees of the LV hypertrophy.

### **1.2. Aim of the study**

To study possibility applying the ultrasound (2DS method) in order to evaluate left atrial deformation in healthy individuals and patients with LV hypertrophy.

### **1.3. Objectives of the study**

1. To examine 120 patients using 2DS method, to perform the conventional echocardiography study and to compare gained data.
2. To research opportunity of 2DS method to evaluate the left atrial deformation.
3. To research data of left and right atrial deformation in healthy individuals of different age.
4. To evaluate 2DS data reproducibility.
5. To evaluate the influence of LV myocardial hypertrophy on atrial deformation.
6. To identify early abnormalities of LA deformation in AH patients with mild LV hypertrophy.
7. To evaluate LA deformation abnormalities in AS patients.
8. To compare abnormalities of LA deformation between 2 groups: AH patients and AS patients.

## **1.4. Scientific novelty of the research**

The present scientific paper is the first research conducted in Latvia, which not only examines the atrial structural-functional condition, but also evaluates the mechanic function (LA deformation) of the atrial using the 2DS method.

## **1.5. Hypothesis of the research**

1. The 2DS is an ultrasound method with an early sensitivity to the changes of the myocardial structure.
2. The 2DS method allows evaluating the LA and RA longitudinal deformation and the velocity of the deformation.
3. By applying the 2DS method in patients without any clinical manifestations to the cardiovascular diseases, it is possible to improve and optimize the plan of examinations in patients with the heart diseases.
4. Overload of the pressure caused by LVH is occurring together with the atrial deformation abnormalities.
5. The 2DS method allows to diagnose the changes of the atrial deformation in patients with the AH and even mild LVH.

## **1.6. Approval of the work**

Approbation of the paper has been performed at the meeting of the RSU Internal diseases department on 16 April, 2012.

### **1. Full publications in indexed journals:**

- Kalinin A., Bahs G., Šipačovs P., Alekhin M. N.  
Atrial myocardial deformation in healthy individuals of two-dimensional strain. *Kardioloģija* 2010; 50(2):62-8. *Pub Med* (PMID: 20146681).

- Kalinin A., Bahs G., Kalnins A., Šīpačovs P., Alekhin M. N.  
Assessment of the state of atrial myocardium by two-dimensional grey-scale deformation in patients with arterial hypertension and mild left ventricular hypertrophy. *Kardioloģija* 2010; 50(8):13-20. *Pub Med* (PMID: 21105324).
- Kalinin A., Bahs G., Lejnieks A., Kalnins A., Shipachovs P., Alekhin M. N.  
Left atrial deformation in hypertensive patients with aortic stenosis and left ventricular hypertrophy of different severity. *Ter Arkh.* 2012; 84(4):23-9 *Pub Med* (PMID: 22774486).

## **2. Poster presentations (abstracts) at international conferences:**

- Kalinin A., Bahs G., Šīpačovs P., Alekhin M. N. Assessment of left and right atrial regional and global mechanical function by two-dimensional speckle tracking echocardiography: a feasibility study on healthy individuals. EUROECHO 2009: XIII Annual Meeting of The European Association of Echocardiography, Madrid, Spain. *Eur J Echocardiogr* 2009; 10: (suppl 2) ii184-ii196.
- Kalinin A., Bahs G., Šīpačovs P., Alekhin M. N. Feasibility of two-dimensional strain for the assessment of regional atrial myocardial deformation in healthy individuals. RSU Scientific Conference 2010. g., Riga.
- Kalinin A., Trenin A. Huge left atrium thrombus and chronic pulmonary artery thrombus due to critical mitral valve stenosis. Pasaules Kardioloģijas kongress 2010. g. China, Beijing. *Circulation* 2010;122;e295-e296.
- Kalinin A., Bahs G., Lejnieks A., Kalvelis A., Kalnins A., Šīpačovs P., Zakharova E., Blumentale G., Alekhin M. N. Left atrial myocardial longitudinal function in hypertensive patients with a various degree of

the left ventricular hypertrophy: a two-dimensional speckle tracking study. EUROECHO 2010. XIV Annual Meeting of The European Association of Echocardiography, Denmark, Copenhagen. *Eur J Echocardiography*, 2010; 11: 343- ii31.

- Kalinin A., Bahs G., Lejnicks A., Šipačovs P., Zakharova E., Alekhin M. N. Differences in Left atrial longitudinal function in patients with aortic stenosis and in hypertensive patients with a severe degree of the left ventricular hypertrophy: Two-Dimensional speckle tracking study. XV Pasaules Ehokardiogrāfijas kongress 2011. g. october, India, Delhi.

### **3. Oral presentations at international conferences:**

- Kalinin A. Light arterial hypertension and the function of the left atrium. International Congress “Cardiology at a Crossroad of Sciences” Russia, Tyumen, 19.05.2010.
- Kalinin A. Assessment of the left atrium myocardium deformation. International Congress “Contemporary Cardiology: age of innovations” Russia, Tomsk, 25.06.2010.
- Kalinin A. Two-dimensional speckle-tracking echocardiography for assessment of left atrial myocardial deformation. International Symposium “The possibilities of new technologies in functional diagnostic” Russia, Moscow, 24.09.2010.
- Kalinin A. Left atrial function and Left ventricular diastolic function. International Congress “Cardiology at Crossroad of Sciences” Russia, Tyumen, 20.05.2011.
- A. Kalinin. Left atrial deformation in hypertensive patients with a mild degree of the left ventricular hypertrophy: Two-Dimensional speckle tracking study. RSU Scientific Conference, Riga 29.03.2011.

- A. Kalinin. 2-D speckle tracking echocardiography for assessment of left atrial deformation. XV World Congress of Echocardiography, India, Dheli, 02.10.2011.
- A. Kalinin. Left atrial function in patients with arterial hypertension and left ventricular hypertrophy. International Congress „VI Russian National Congress of Radiology” Russia, Moscow, 19.10.2011.
- A. Kalinin. Differences in left atrial longitudinal function in patients with aortic stenosis and in hypertensive patients with a severe degree of the left ventricular hypertrophy: 2D speckle tracking study. RSU Scientific Conference, Riga 30.03.2012.



## 2. MATERIALS AND METHODS

### 2.1. Study population

A total of 118 individuals were included: 52 patients with AH and LVH, 16 patients with AS and LVH and 50 healthy individuals. Study group participants are enough to make a reliable statistical analysis of the data.

The study was approved by the Riga Eastern Clinical University Hospital Medical Ethics Committee (Resolution 6-A/12). Written informed consent was obtained from all participants following a thorough discussion of the study.

#### 2.1.1. Healthy individuals

The control group consisted of 50 healthy individuals (mean age  $45 \pm 14$  years, 25 female and 25 male). After that, the group was divided according to age:

- 1 group – 30 healthy individuals aged under 50 years (mean age  $36 \pm 11$  years, 14 female and 16 male, BSA  $1.89 \pm 0.23$  m<sup>2</sup>, Body Surface Area was calculated:  $BSA = (\text{weight}^{0.425}) \times (\text{height}^{0.725}) \times 0.007184$  [41]);
- 2 group – 20 healthy individuals aged over 50 years (mean age  $58 \pm 7$  years, 11 females and 9 male, BSA  $1.83 \pm 0.22$  m<sup>2</sup>).

Such a division of age groups were related to: 1) effect of age on LA function and morphology [24]; 2) assessment of LA deformation data in healthy individuals aged under 50; 3) for the statistical analyzing, control group (healthy individuals aged over 50 years) was compared to a corresponding age group with LVH.

All subjects had no symptoms or history of cardiovascular disease, normal physical examinations, no chronic and systemic diseases, no medications, no smokers, no alcohol. For inclusion in the study LVMI was

defined as normal 43–95 g/m<sup>2</sup> for female and 49–115 g/m<sup>2</sup> for male [25]. All subjects had normal laboratory tests (glucose, full lipid spectrum), normal systolic and diastolic blood pressure, normal sinus rhythm between 50 and 85 beats/min without conduction abnormalities on ECG.

### **2.1.2. Study group with LV hypertrophy**

We studied 68 patients with LVH.

Hypertensive patients with LV hypertrophy:

- 3 group – 30 patients (17 female, 13 male, mean age  $57 \pm 8$  years, BSA  $2.03 \pm 0.18$  m<sup>2</sup>). LVMI was defined as mildly abnormal 95–108 g/m<sup>2</sup> for female, 115–131 g/m<sup>2</sup> for male [25];
- 4 group – 22 patients (14 female, 8 male, mean age  $60 \pm 7$  years, BSA  $1.92 \pm 0.23$  m<sup>2</sup>). LVMI was defined as severely abnormal  $\geq 121$  g/m<sup>2</sup> for female and  $\geq 148$  g/m<sup>2</sup> for male [25].

Inclusion criteria for hypertensive patients included:

1. documented history of hypertension  $\geq 140/90$  mm Hg st.;
2. no regular antihypertensive treatment;
3. negative exercise test on ischemia;
4. no history of Diabetes mellitus;
5. sinus rhythm on ECG, between 50 and 85 beats/min.

Patients with aortic valve stenosis and LV hypertrophy:

- 5 group – 16 patients with AS (7 female, 9 male, mean age  $70 \pm 6$  years, BSA  $1.83 \pm 0.18$  m<sup>2</sup>).

Inclusion criteria for patients with AS included:

1. aortic valve area (AVA)  $\leq 1$  cm<sup>2</sup>;
2. sinus rhythm on ECG, between 50 and 85 beats/min;
3. without moderate or severe aortic regurgitation;
4. no history of myocardial infarction, stroke, diabetes mellitus;

5. no regular antihypertensive treatment.

## 2.2. Methods

### 2.2.1. Standard Echocardiography

Standard echocardiography with 2DS analyses was performed. All studies were performed using a high-quality echocardiograph GE Vivid7 Dimension (*GE Medical Systems, Horten, Norway*) equipped M4S (1.5-4.3 MHz) phased-array transducers.

All patients were examined at rest in the left lateral decubitus position. The values for standard and 2DS echocardiography parameters were obtained and saved after 3 consecutive cycles.

Standard LV measurements – LV end-diastolic and end-systolic diameters (LV EDD, LV ESD), LV ejection fraction (EF), LV end-diastolic and end-systolic thickness of the interventricular septum (IVSd, IVSs) and LV posterior wall (PWd, PWs), aortic root diameter, LA diameter – were measured by M-mode echocardiography from the long-axis parasternal view. We calculated the LV mass and LV mass index as follows: LV masa =  $0.8 \times \{1.04 [(EDD + IVSd + PWd)^3 - (ESD)^3]\} + 0.6$  [25]; LV mass/ BSA.

LA volumes were calculated from apical four-chamber and two-chamber views using the biplane area-length (A-L) method. The following volumes of LA were calculated:

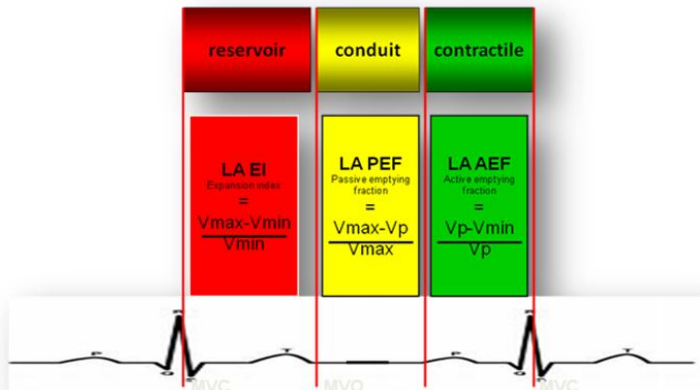
1. maximal LA volume in ventricular systole just before mitral valve opening – LA Vmax;
2. minimal LA volume after mitral valve closure – LA Vmin;
3. volume just before P-wave on ECG – LA Vp.

The following indexes of LA function were calculated:

1. maximal LA volume index (LAVi – LA Vmax / BSA);

2. minimal LA volume index (LAV<sub>min</sub> / BSA);
3. LA volume index just before P-wave on ECG(LAV<sub>p</sub> / BSA);
4. LA passive emptying fraction (PEF) was defined as:  $PEF = (V_{max} - V_p) / V_{max} \times 100\%$ ;
5. LA active emptying fraction (AEF) was defined:  $AEF = (V_p - V_{min}) / V_p \times 100\%$ ;
6. LA expansion index (EI):  $EI = (V_{max} - V_{min}) / V_{min} \times 100\%$ .

LA indexes correspond to LA mechanical function phases: LA conduit function (*conduit*, c) characterized by PEF, LA pump function (*contractile*, s) characterized by AEF and LA reservoir function (*reservoir*, r) characterized by EI (Figure 2.1).



**Figure 2.1 Left atrial mechanical function phases**

1. during left ventricular systole – „reservoir”;
2. during passive filling of the left ventricular – „conduit”;
3. during active filling of the left ventricular, left atrial systole – „contractile”

The following pulsed-wave Doppler measurements were obtained in the apical four-chamber view with the sample volume at the tip of MV (transmitral flow), pulmonary vein (right superior pulmonary vein): maximal

early (peak E, cm/s) and late (peak A, cm/s) transmitral velocities, E/A ratio, transmitral E wave deceleration time (DT, ms), transmitral A wave duration (Adur, ms), LV isovolumic relaxation time (IVRT, ms); pulmonary venous flow atrial reversal wave duration (Ar dur, ms), Ar dur – A dur wave duration.

The following pulsed-wave Tissue Doppler measurements were obtained in apical four-chamber view at the septal and lateral mitral annulus: early diastolic tissue velocities (peak E` lat, peak E` sep MV, peak E` mean MV), E/E` mean MV ratio was calculated.

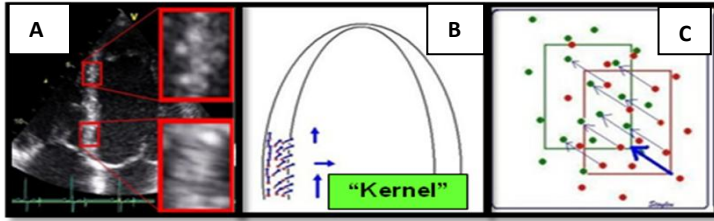
### **2.2.2. Two-dimensional Speckle Tracking Echocardiography (2DS)**

Two-dimensional speckle tracking echocardiography is a new technique and this tool based on tracking the motion of a myocardium in grayscale mode (Non-Doppler). It analyzes motion by tracking speckles (natural acoustic markers) in the ultrasonic image in two dimensions. The speckle pattern remains reasonably stable, and the speckles follow the myocardial motion. The size of these elements (*kernels*) is 20 to 40 pixels. Blocks or kernels of speckles can be tracked from frame to frame using block matching, and provide local displacement information, from which parameters of myocardial function such as strain (S) and strain rate (SR) can be derived. (Figure 2.2).

Strain, in daily language means, “stretching”. In scientific usage, the definition is extended to mean “deformation”. The concept of strain is complex, but linear strain can be defined by the *Lagrangian* formula:

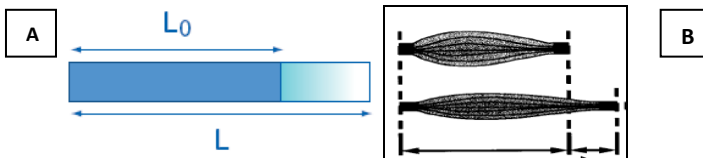
$$\varepsilon = (L - L_0)/L_0 \quad (1)$$

where  $\varepsilon$  (epsilons, %) is strain,  $L_0$  = baseline length and L is the instantaneous length at the time of measurement as shown below. Thus strain is deformation of an object, relative to its original length (Figure 2.3.).



**Figure 2.2 Acoustic speckle tracking (author pictures and text MD Asbjørn Støylen)**

(A) – Demonstrating the difference between two different regions of the myocardium by their different random speckle pattern. The two enlarged areas show completely different speckle patterns. (B) - This creates an unique pattern for any selected region that can identify this region and hence, the displacement of the region in the next frame. (C) Defining a kernel in the myocardium will define a speckle pattern within (red). Within a defined search area (blue), the new position of the kernel in the next frame (green) can be recognised by finding the same speckle pattern in a new position. The movement of the kernel (thick blue arrow) can then be measured



**Figure 2.3 Linear strain of the object (myocardium)**

A – an object undergoing strain. In this case there is a 25% elongation from the original length ( $L_0$ ), thus, according to the Lagrangian formula there is positive strain of 25%; B – example of the myocardial strain. Myocardial changes are not pathological anatomical changes, but only the inherent cyclical changes in the myocardium

It should be noted that atrial myocardial deformation analysis, compared with ventricular, has its own characteristics. Atrial myocardium is significantly thinner than ventricular myocardium, the LA myocardial fascicles do not have strong orientations, endocardial contours is unclear and interrupted (pulmonary veins, left atrial appendage), heterogeneous atrial septum. Therefore, the deformation can be assessed only in the longitudinal directions, to define atrial longitudinal deformation [15].

2DS for LA longitudinal function analyses (off-line) were performed using commercially available software (*EchoPac PC Dimension 06, version 6.x.x., GE Healthcare, Norway*). Apical 4ch, 3ch, 2ch views images were obtained using conventional two dimensional gray scale echocardiography, during breath hold and with stable ECG recording (good P and R waves on ECG). The frame rate was set between 50 and 80 frames per second. Three consecutive heart cycles (loops) were recorded in 4ch, 3ch or 2ch apical views.

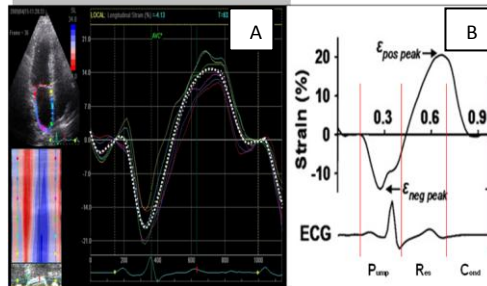
For 2DS analysis, a line was manually drawn along the LA endocardium when the LA was at its minimum volume after contraction (onset on the P wave of ECG as the reference point). The software then automatically generates additional lines near the atrial epicardium and mid-myocardial line, with a region of interest

default width of 15 mm. Before processing, a cine loop preview feature visually confirms (score system from 1 to 3, approved > 2,5) that the internal line follows the LA endocardium throughout the cardiac cycle. If tracking of the LA endocardium is unsatisfactory, manual adjustments or changing software parameters (eg, region of interest size or smoothing functions) can be made. Segments in which adequate tracking quality could not be obtained despite manual adjustment were excluded from the analysis. The LA myocardium was divided into 6 equidistant regions. Longitudinal strain curves were then generated for each atrial segment. After that, the user can obtain segmental, average (averaging values observed in all six segments) and global (averaging values observed in all segments from 4ch, 3ch or 2ch apical views) peak atrial longitudinal strain (PALS) (Figure 2.4).

Peak atrial longitudinal strain (PALS, %) were calculated:

1. LA systole phase (from P-wave on ECG until MV closure) – PALSs (contractile phase);

- during LV systole (from MV closure until AV closure) – PALSr (reservoir phase);
- during early LV diastole (from MV opening until P-wave on ECG) – PALSc (conduit phase).



**Figure 2.4 Left atrial longitudinal strain in a normal subject obtained from an apical 4ch view**

A – each LA segment corresponds to their color curve, segmental longitudinal deformation. Dotted line – mean value for all 6 segments. B – typical example of regional LA strain: The use of the P-wave as the reference point to allow the measurement of a first negative peak LA longitudinal strain (LA systole, contractile phase (*Pump*), myocardial shortening,  $\epsilon$  neg peak, PALSs), of a second positive peak LA longitudinal strain (LV systole, reservoir phase (*Res*), myocardial lengthening,  $\epsilon$  pos peak, PALSr). During the next LA conduit phase (*Cond*) occurs myocardial shortening and just before LA systole curve of deformation approaching zero. We hypothesized that during conduit phase LA deformation is not too much significant, because LV early filling is a passive blood transfer through LA

### 2.2.2.1. Evaluation of the LA deformation in healthy individuals aged under 50 years

Segmental PALS (segPALS) parameters were measured in following LA and RA segments:

- apical 4ch view – LA and RA lateral wall mid-segments, atrial septum mid-segment;
- apical 3ch view – LA posterior wall mid-segment;



3. apical 2ch-view – LA inferior wall mid-segment and LA anterior wall mid-segment.

Average PALS (avPALS) parameters were measured in apical 2ch and 4 ch views: averaging values observed in all six segments apical 4ch or 2ch views during reservoir phase (4ch-avPALSr un 2ch-avPALSr, %) and contractile phase (4ch-avPALSs un 2ch-avPALSs, %).

#### **2.2.2.2. Evaluation of the LA deformation in healthy individuals aged over 50 years and in patients with LV**

Segmental, average and global left atrial peak longitudinal strain parameters were measured in study groups.

Segmental peak atrial longitudinal strain (segPALS) was measured in the following LA walls (mid-segment): LA lateral, LA inferior, LA posterior, LA anterior and septal.

Average peak atrial longitudinal strain (avPALS) was calculated by separately averaging values observed in 4- and 2-chamber views: 6 segments in 4ch view and 6 segments in 2ch view during LA reservoir phase (4ch-avPALSr un 2ch-avPALSr, %) and LA contraction phase (4ch-avPALSs un 2ch-avPALSs, %).

Global peak atrial longitudinal strain (globPALS) was calculated by averaging values observed in all 15 LA segments (global PALS): 6 segments in 4ch view, 6 segments in 2ch view, 3 segments in 3ch view during LA reservoir phase (globPALSr, %) and LA contraction phase (globPALSs, %).

#### **2.2.3. Statistical analysis**

Established descriptive statistical methods were used for characterisation of the study groups (*Bland, J.M., 1986; Altman, D.G., 2000*).

All variables were expressed as mean  $\pm$  standard deviation.

The different S/SR, PLD indicators for the longitudinal deformation of the RA and LA wall were compared between the LA anterior, LA posterior, septal, RA lateral, LA lateral and LA inferior walls with repeated-measures ANOVA (for  $> 2$  groups) followed by posthoc comparisons using Student's t-tests corrected according to Bonferroni. The 95% confidence interval was calculated and reported both as an absolute value and as a percentage of the mean value.

Correlations between variables were tested by simple linear regression analysis (Pearson's correlation).

Two-sided p value  $< 0.05$  was regarded as statistically significant result.

The estimation of intra-observer reproducibility was performed using the Bland-Altman analysis

Sensitivity and specificity were calculated using standard definitions, receiver operating characteristic curves were constructed and the area under the curve was calculated for the prediction.

Analyses were performed using the *SPSS for Windows* (Statistical Package for the Social Sciences) software Release 12.0 and *MS Excel* 2003.

## 3. RESULTS

### 3.1. Healthy individuals aged under 50 years

Results – standard echocardiographic characteristics and deformation parameters – were obtained from 30 healthy individuals.

#### 3.1.1. Standard echocardiographic characteristics

The general and standard echocardiographic characteristics of the study population are presented in Table 3.1 and show normal values according to their age.

Table 3.1

**General and standard echocardiographic characteristics in healthy individuals aged under 50 years (M ± SD)**

| Variable                    | Healthy individuals (n=30) | Normal values* |
|-----------------------------|----------------------------|----------------|
| Age (years)                 | 36 ± 11                    |                |
| BSA (m <sup>2</sup> )       | 1.89 ± 0.2                 |                |
| HR, (bpm)                   | 71.5 ± 11,5                |                |
| LV EF, %                    | 65.5 ± 4.1                 | > 55 %         |
| LVMI, g/m <sup>2</sup>      | 84.4 ± 14.1                | 43–115         |
| LA, mm                      | 32 ± 3.8                   | 27–40          |
| LA max volume, ml           | 33.1 ± 8.4                 | 18–58          |
| LAVI max, ml/m <sup>2</sup> | 17.3 ± 3.1                 | 16–28          |

BSA – Body Surface Area; LV EF – left ventricular ejection fraction; LVMI – left ventricular mass index; LA – left atrium; LAVI<sub>max</sub> – left atrial maximal volume index;

\* ASE and EAE recommendations [25, 38-40]

#### 3.1.2. Peak atrial longitudinal strain

Among a total of 420 LA and RA segments, the software was unable to track 18 (4.3 %) segments. Average post-processing time per patient was

2.2 ± 1.0 min. PALS of RA and LA in mid-segments during reservoir, conduit and contractile phases are reported in Table 3.2.

Table 3.2

**Strain indices of longitudinal deformation for the RA and LA walls mid-segments during different phases of the cardiac cycle in healthy individuals aged under 50 years (M ± SD)**

| Atrial phase (Index) | LATla                     | SEP                      | POS                       | INF                       | ANT                       | LATra                     |
|----------------------|---------------------------|--------------------------|---------------------------|---------------------------|---------------------------|---------------------------|
| <b>Contraction</b>   |                           |                          |                           |                           |                           |                           |
| PALS, %              | -<br>13.89±3.29<br>n = 30 | -<br>13.88±3.5<br>n = 29 | -<br>15.11±4.97<br>n = 30 | -<br>17.59±4.53<br>n = 30 | -<br>13.80±4.94<br>n = 30 | -<br>19.49±9.08<br>n = 30 |
| <b>Reservoir</b>     |                           |                          |                           |                           |                           |                           |
| PALS, %              | 23.87±7.94<br>n = 30      | 21.60±7.3<br>n = 30      | 21.01±8.63<br>n = 29      | 21.54±6.96<br>n = 30      | 16.99±8.35<br>n = 28      | 21.07±12.96<br>n = 26     |

Left atrial walls mid-segments: LATla – lateral; SEP – septal; POS – posterior; INF – inferior; ANT – anterior; Right atrial wall mid-segment – lateral; PALS – peak atrial longitudinal strain

**3.1.3. Contraction phase**

The peak values for PALS during the contraction phase for the three LA walls (lateral, anterior, inferior) are presented in Table 3.3. and for the two LA walls (lateral, septal) and one RA wall (lateral) are presented in Table 3.4.

During the LA and RA contraction period, the myocardium shortens to a peak value that and then starts to lengthen.

A significant difference between walls was obtained for the PALS values, with the value for the LA inferior wall (-17.59 ± 4.53%) significantly higher than the values for the LA anterior (-13.80 ± 4.94%; p < 0.01) and lateral walls (-13.89 ± 3.29%; p < 0.01, Table 3.3).

Table 3.3

**Strain indices of longitudinal deformation for the three LA walls mid-segments during different phases of the cardiac cycle in healthy individuals aged under 50 years (M ± SD)**

| Atrial phase | Index   | LATla*        | ANT           | INF                  |
|--------------|---------|---------------|---------------|----------------------|
| Contraction  |         |               |               |                      |
|              | PALS, % | -13.89 ± 3.29 | -13.80 ± 4.94 | -17.59 ± 4.53 ##\$\$ |
| Reservoir    |         |               |               |                      |
|              | PALS, % | 23.87±7.94    | 16.99±8.35 ## | 21.54 ± 6.96         |

## p < 0.01, compared to the lateral wall; \$\$ p < 0.01, compared to the anterior wall. Left atrial walls mid-segments: LATla – lateral; INF – inferior; ANT – anterior; PALS – peak atrial longitudinal strain; LA – left atrium

Using the 4ch apical view it possible simultaneously analyze three walls: LA and RA lateral walls and atrial septum. The RA lateral wall had significantly highest PALS (-19.49 ± 9.08%) when compared with LA lateral wall (-13.89 ± 3.29%; p < 0.05) (Table 3.4).

Table3.4

**Strain indices of longitudinal deformation for the three LA and RA walls mid-segments during different phases of the cardiac cycle in healthy individuals aged under 50 years (M ± SD)**

| Atrial phase | Index   | LATla *       | SEP           | LATra           |
|--------------|---------|---------------|---------------|-----------------|
| Contraction  |         |               |               |                 |
|              | PALS, % | -13.89 ± 3.29 | -13.88 ± 3.56 | -19.49 ± 9.08 # |
| Reservoir    |         |               |               |                 |
|              | PALS, % | 23.87 ± 7.94  | 21.60 ± 7.34  | 21.07 ± 12.96   |

# p < 0.05, compared to the LA lateral wall.

Left atrial and Right atrial walls mid-segments: LATla – LA lateral; SEP – septum; LATra – RA lateral; PALS – peak atrial longitudinal strain; LA – left atrium; RA – right atrium

### **3.1.4. Reservoir phase**

For the reservoir phase the strain profiles indicated atrial lengthening with a peak value occurring during the LV ejection period. During reservoir phase there was a significant difference between the three LA walls for PALS, with PALS value for the LA lateral wall ( $23.87 \pm 7.94\%$ ) significantly higher than the LA anterior wall ( $16.99 \pm 8.35\%$ ;  $p < 0.01$ , respectively) (Table 3.3).

### **3.1.5. Conduit phase**

For the conduit period the strain profiles indicated atrial myocardial shortening during early LV filling. It should be noted, that during the conduit phase strain parameters (50% from studied patients) were zero regardless of segment position and the quality of visualization.

### **3.1.6. Average PALS in LA 6 segments during contraction and reservoir phases**

The following results were obtained for the average PALS values: during reservoir phase in 4ch apical view had the highest average PALS (4ch-avPALSr  $22.00 \pm 6.64\%$ ) when compared with average PALS in 2ch apical view (2ch-avPALSr  $17.71 \pm 5.94\%$ ,  $p < 0.05$ ).

During contraction phase average PALS were: in 2ch apical view –  $15.24 \pm 3.91\%$  (2ch-avPALSs) and in 4ch apical view –  $13.55 \pm 2.95\%$  (4ch-avPALSs).

### **3.1.7. Observer variability**

Table 3.5 shows intra-observer agreement assessed separately for each parameter of LA and RA wall deformation (*CV, coefficient of variation*).

Table 3.5

**Intra-observer variability for Strain measurements for the longitudinal LA and RA walls deformation in healthy individuals (n = 10) aged under 50 years**

| Indicator                   | Mean   | CV (%) |
|-----------------------------|--------|--------|
| PALS ( <i>reservoir</i> )   | 19.92  | 6.34   |
| PALS ( <i>conduit</i> )     | -1.20  | 39.44  |
| PALS ( <i>contractile</i> ) | -15.97 | 6.85   |

PALS – peak atrial longitudinal strain; *reservoir* – reservoir phase; *contractile* – contraction phase; *conduit* – conduit phase

For the conduit phase intra-observer variability were high for the PALS (39.44%). It appears that those atrial myocardial deformation measurements in this phase are limited or impractical. During reservoir and contraction phases intra-observer variability was significantly better: CV were from 6.34% (PALS) for the reservoir phase until to 6.85% (PALS) for the contractile phase.

### **3.2. Comparison of the results between two groups: healthy individuals aged under 50 and over 50 years**

It necessary take in account, that this method is not widely used today and only few studies were performed for assessment of atrial deformation in healthy individuals. That's why, the healthy individuals aged under 50 years was the first group in study and the aim was to to determine the feasibility and reference ranges of atrial longitudinal strain indices measured by 2DS in a population of normal subjects. In order to evaluate the atrial deformation in patients with hypertrophy established second group of healthy individuals aged over 50, because mean age in the group of patients with AH was also over of 50 years.

Comparison of the echocardiography and 2DS results was performed between two groups of healthy individuals in order to confirm some of the

readings that could affect the accuracy of the statistical analysis. Table 3.6 shows the results of comparison between two groups healthy individuals.

Table 3.6

**Echocardiographic characteristics in the two groups of healthy individuals aged under 50 and over 50 years (M ± SD)**

| Variable                     | Healthy individuals aged under 50 years (n = 30)           | Healthy individuals aged over 50 years (n = 20) | p       |
|------------------------------|--|---|---------|
|                              | LA structural-functional indices                           |   |         |
| LA, mm                       | 32 ± 3.8   | 34.7 ± 3.0                                      | <0.01   |
| LA max volume, ml            | 33.1 ± 8.4   | 38.0 ± 8.2                                      | <0.05   |
| LA VI max, ml/m <sup>2</sup> | 17.3 ± 3.1   | 20.4 ± 4.0                                      | <0.003  |
|                              | Transmitral flow, E/E', LV mass index                      |   |         |
| LV DT, msec                  | 189.7 ± 32.3   | 221.1 ± 59.5                                    | <0.02   |
| LV Peak A, cm/s              | 0.5 ± 0.1  | 0.69 ± 0.16                                     | <0.0001 |
| MV E/E' mean                 | 5.5 ± 1.1  | 7.0 ± 1.5                                       | <0.0001 |
| LV MI, g/m <sup>2</sup>      | 84.4 ± 14.1  | 89.6 ± 11.5                                     | NS      |
|                              | Average peak atrial longitudinal strain, reservoir phase   |   |         |
| 4ch-avPALSr                  | 22.00 ± 6.64   | 17.9 ± 4.4                                      | <0.02   |
| 2ch-avPALSr                  | 17.71 ± 5.94   | 14.9 ± 3.4                                      | <0.05   |
|                              | Average peak atrial longitudinal strain, contraction phase |   |         |
| 4ch-avPALSs                  | -13.55 ± 2.95  | -14.2 ± 2.7                                     | NS      |
| 2ch-avPALSs                  | -15.24 ± 3.91  | -16.4 ± 2.9                                     | NS      |

LA – left atrium; LA max volume – left atrial maximal volume; LA VI max – left atrial maximal volume index; LV DT – left ventricular deceleration time; LV Peak A – left ventricular maximal late transmitral velocity; MV E/E' mean – ratio: maximal early transmitral velocity (E) to tissue Doppler mitral annulus (septal and lateral – average value) early diastolic velocity (E'); LV MI – left ventricular mass index; 4ch-avPALS – average peak atrial longitudinal strain in 4ch apical view; 2ch-avPALS – average peak atrial longitudinal strain in 2ch apical view; r (*reservoir*)– reservoir phase; s (*contractile*) – contraction phase.

As the table 3.6 shows, there is a logical difference between two groups in indices of the transmitral blood flow and LA sizes. LA diameter, LA



maximal volume and LA maximal volume index in healthy individuals aged under 50 years group were significantly lower than in healthy individuals aged over 50 years. Also, in healthy individuals aged over 50 years group significantly longer was DT time and significantly higher peak A and E/E` ratio. No differences between groups for the LV and LV dimensions were obtained. A significant difference between two groups was obtained for the average PALS during resrvoir phase. The 4ch-avPALSr and 2ch-avPALSr were significantly lower in healthy individuals aged over 50 year’s group and oppositely, during contraction phase average PALS did not show any difference.

### 3.3. Results comparisons between two groups - the healthy individuals aged over 50 years and patients with LV hypertrophy

Comparisons of indices between two healthy individuals groups confirmed correctness of the choices of this healthy group (aged over 50 years) for the comparisons with group patients with LV hypertrophy.

#### 3.3.1. Standard echocardiographic characteristics

Table 3.7 shows standard echocardiographic characteristics of the four groups.

Table 3.7

**Echocardiographic characteristics in the four study groups. (M ± SD)**

| Variable              | Healthy individuals<br>(n = 20) | AH and mild LVH<br>(n = 30) | AH and severe LVH<br>(n = 22) | AS and severe LVH<br>(n = 16) |
|-----------------------|---------------------------------|-----------------------------|-------------------------------|-------------------------------|
| Age (years)           | 57.6 ± 6.8                      | 56.9 ± 7.5                  | 60.4 ± 7.2                    | 70.0 ± 5.9*                   |
| BSA (m <sup>2</sup> ) | 1.83 ± 0.2                      | 2.03 ± 0.2 ††               | 1.92 ± 0.2                    | 1.82 ± 0.2                    |
| HR<br>(beats/min)     | 70.9 ± 8.8                      | 71.4 ± 7.2                  | 71.7 ± 6.4                    | 69.8 ± 8.1                    |

End of Table 3.7

| Variable                 | Healthy individuals (n = 20) | AH and mild LVH (n = 30) | AH and severe LVH (n = 22) | AS and severe LVH (n = 16) |
|--------------------------|------------------------------|--------------------------|----------------------------|----------------------------|
| LVMI (g/m <sup>2</sup> ) | 89.6 ± 11.5                  | 118.2 ± 11.8 †††         | 143.8 ± 14.4 ††† ‡         | 156.7 ± 38.6 †††           |
| LV EF, %                 | 65.4 ± 3.7                   | 60.9 ± 3.3 †             | 61.6 ± 3.1 †               | 63.0 ± 2.4 †               |
| LV peak E, m/s           | 0.73 ± 0.13                  | 0.72 ± 0.15              | 0.77 ± 0.20                | 0.99 ± 0.20 *              |
| LV peak A, m/s           | 0.69 ± 0.16                  | 0.79 ± 0.19 †            | 0.84 ± 0.19 ††             | 1.17 ± 0.20 *              |
| LV DT, ms                | 221.1 ± 59.5                 | 235.1 ± 70.0             | 241.6 ± 74.8               | 288.4 ± 77.0 †             |
| MV E` mean, m/s          | 0.11 ± 0.03                  | 0.07 ± 0.02 †††          | 0.06 ± 0.01 ††† ‡          | 0.05 ± 0.01 ††† *          |
| MV E/E` mean             | 7.0 ± 1.5                    | 10.0 ± 3.3 †††           | 13.6 ± 3.4 ††† ‡           | 19.7 ± 3.3 ††† *           |
| LV IVRT, ms              | 82.5 ± 8.5                   | 91.3 ± 15.6 †            | 90.8 ± 17.0 †              | 100.8 ± 7.3 ††† †          |
| LV E/A                   | 1.14 ± 0.41                  | 0.98 ± 0.38              | 1.0 ± 0.52                 | 0.86 ± 0.17†               |
| Ar dur – A dur, ms       | 12.3 ± 7.3                   | 27.3 ± 14.6†             | 21.2 ± 18.3 †              | 41.1 ± 21.2*               |

\* p < 0.001 compared to three groups; † p < 0.05, compared to healthy individuals group; †† p < 0.01, compared to healthy individuals group; ††† p < 0.001, compared to healthy individuals group; ‡ p < 0.001, compared to AH and mild LVH group; † p < 0.05, compared to AH and mild and severe LVH groups;

HR – heart rate; AH – arterial hypertension; AS – aortic valve stenosis; LVH – left ventricular hypertrophy; BSA – body surface area; LV MI – left ventricular mass index; LV EF – left ventricular ejection fraction; LV *Peak E* – maximal early transmitral velocity; LV *Peak A* – maximal late transmitral velocity; LV DT – left ventricular deceleration time; MV E` *mean* – mitrālā vārstuļa fibrozā gredzena diastoliskās kustības vidējais (mediālā un laterālā mitrālā vārstuļa gredzena) ātrums; MV E/E` *mean* – ratio: maximal early transmitral velocity (E) to tissue Doppler mitral annulus (septal and lateral – average value) early diastolic velocity (E`); LV IVRT – left ventricular isovolumic relaxation time; E/A – ratio: maximal early transmitral velocity (E) to maximal late transmitral velocity (A); Ar dur – A dur – the time difference between atrial reversal velocity (Ar dur) duration and late transmitral velocity duration (A dur)

As the table 3.7 shows, the oldest were patients group with AS. BSA was significantly higher in patients with AH and mild hypertrophy. LV EF was significantly lower in patients with AH and AS. LV diastolic function indices changes were observed: significantly decreased E`mean MV (p < 0.001) and

E/E`mean ratio ( $p < 0.001$ ), significantly increased LV transmitral peak A ( $p < 0.001$ ), LV isovolumic relaxation time and time difference Ar dur – A dur in patients in studies groups.

### 3.3.2. LA structural – functional indices

LA structural – functional indices are shown in table 3.8.

Table 3.8

**LA structural – functional indices in four study groups (M ± SD)**

| Variable                    | Healthy individuals<br>(n = 20) | AH and mild LVH<br>(n = 30) | AH and severe LVH<br>(n = 22) | AS and severe LVH<br>(n = 16) |
|-----------------------------|---------------------------------|-----------------------------|-------------------------------|-------------------------------|
| LA diametr, mm              | 34.7 ± 3.0                      | 37.6 ± 2.1 †††              | 38.9 ± 4.1 †††                | 39.6 ± 2.4 †††                |
| LA Vmax, ml                 | 38.0 ± 8.2                      | 42.6 ± 7.8 †††              | 51.6 ± 13.8 †††<br>*          | 59.3 ± 8.2 †††                |
| LAVImax, ml/m <sup>2</sup>  | 20.4 ± 4.0                      | 21.6 ± 4.6 ††               | 26.7 ± 5.7 ††† *              | 32.4 ± 3.4 ††† ††             |
| LA Vmin, ml                 | 10.7 ± 3.5                      | 15.9 ± 4.8 †††              | 19.4 ± 6.5 †††<br>**          | 25.0 ± 5.6 ††† ††             |
| LAVI min, ml/m <sup>2</sup> | 4.8 ± 1.4                       | 7.9 ± 2,5 ††                | 10.1 ± 3.7 ††                 | 13.7 ± 3.9 †† ††              |
| LA Vp, ml                   | 18.4 ± 5.5                      | 26.5 ± 6.2 †††              | 31.3 ± 10.2 †††<br>**         | 37.8 ± 8.5 ††† ††             |
| LAVI p, ml/m <sup>2</sup>   | 8.5 ± 2.1                       | 13.1 ± 3.1 ††               | 16.3 ± 3.9 †††<br>**          | 20.8 ± 4.1 ††† ††             |
| LA PEF, %                   | 45.1 ± 9.5                      | 37.7 ± 8.5 ††               | 39.3 ± 7.1 †                  | 35.6 ± 7.1 ††                 |
| LA AEF, %                   | 43.0 ± 7.6                      | 40,3 ± 9.0                  | 37.7 ± 6.4 †                  | 34.1 ± 5.4 †††                |
| LA EI, %                    | 229.1 ± 61.1                    | 179.5 ± 51.2<br>††          | 167.4 ± 34.5 †††              | 139.8 ± 31.2 †††<br>†         |

†  $p < 0.05$ , compared to healthy individuals group; ††  $p < 0.01$ , compared to healthy individuals group; †††  $p < 0.001$ , compared to healthy individuals group; \*  $p < 0.01$ , compared to AH and mild LVH group; \*\*  $p < 0.05$ , compared to AH and mild LVH group; ††  $p < 0.01$ , compared to AH and mild and severe LVH groups; †††  $p < 0.001$ , compared to AH and mild and severe LVH groups;

AH – arterial hypertension; AS – aortic valve stenosis; LVH – left ventricular hypertrophy; LA – left atrium; LA V max – left atrial maximal volume;

End of Table 3.8

LA VI max – left atrial maximal volume index; LA V min – left atrial minimal volume; LA VI min – left atrial minimal volume index; LAV p – left atrial volume just before P-wave on ECG; LA VI p – left atrial volume index just before P-wave on ECG; LA PEF – left atrial passive emptying fraction; LA AEF – left atrial active emptying fraction; LA EI – left atrial expansion index

As the table 3.8 shows, LA diameter, LA volumes and volumes indexes significantly increased in patients in studies groups. But only in patients group with AS was abnormal value of the LA maximum volume index. LA EI was significantly lower in patients with AH and AS. It should be noted that the most pronounced structural functional abnormalities were found in patients with AS.

### 3.3.3. LA segmental deformation

Among a total of 264 segments in five LA walls (lateral, septal, inferior, anterior, posterior), the software was unable to track 6 (1.9 %) segments. It should be noted, that those segments were from LA anterior wall. LA segmental deformation indices during reservoir and contractile phases are shown in table 3.9.

Table 3.9

#### LA segmental peak longitudinal strain during reservoir (segPALSR) and contraction (segPALSCs), phases in four study groups, % (M ± SD)

| Atrial wall (mid-segment)  | Healthy individuals (n = 20) | AH and mild LVH (n = 30) | AH and severe LVH (n = 22) | AS and severe LVH (n = 16) |
|----------------------------|------------------------------|--------------------------|----------------------------|----------------------------|
| Reservoir phase (segPALSR) |                              |                          |                            |                            |
| LATla                      | 19.8 ± 5.4                   | 10.1 ± 3.0 ††            | 9.6 ± 3.3 ††               | 8.5 ± 4.3 ††               |
| SEP                        | 17.4 ± 4.9                   | 11.4 ± 3.8 ††            | 11.5 ± 3.8 ††              | 9.6 ± 3.2 ††               |
| POS                        | 16.3 ± 5.3                   | 10.7 ± 3.1 ††            | 10.4 ± 4.3 ††              | 8.3 ± 3.5 †† ‡             |
| INF                        | 18.3 ± 4.8                   | 12.9 ± 4.7 ††            | 10.7 ± 4.0 ††              | 9.5 ± 3.0 †† ‡             |
| ANT                        | 13.4 ± 3.3                   | 9.2 ± 3.8 ††             | 8.6 ± 2.9 ††               | 6.4 ± 2.9 †† ‡             |

| Atrial wall (mid-segment)    | Healthy individuals (n = 20) | AH and mild LVH (n = 30) | AH and severe LVH (n = 22) | AS and severe LVH (n = 16)     |
|------------------------------|------------------------------|--------------------------|----------------------------|--------------------------------|
| Contraction phase (segPALSs) |                              |                          |                            |                                |
| LATla                        | -14.6 ± 3.5                  | -16.4 ± 4.6 ††           | -15.8 ± 4.5 ††             | -12.2 ± 4.4 <sup>d</sup>       |
| SEP                          | -14.8 ± 3.7                  | -14.8 ± 5.3              | -13.9 ± 4.1                | -12.8 ± 3.0                    |
| POS                          | -15.5 ± 4.6                  | -15.2 ± 4.7              | -14.6 ± 4.8                | -11.4 ± 3.9 † <sup>d</sup>     |
| INF                          | -18.0 ± 3.1                  | -16.8 ± 4.2              | -17.6 ± 4.5                | -13.7 ± 3.7 ††<br><sup>d</sup> |
| ANT                          | -15.6 ± 3.8                  | -14.1 ± 4.1              | -13.8 ± 5.4                | -10.2 ± 2.9 †† <sup>d</sup>    |

† p < 0.05, compared to healthy individuals group; †† p < 0.001, compared to healthy individuals group; <sup>d</sup> p < 0.05, compared to AH with mild and severe LVH groups; <sup>d</sup> <sup>d</sup> p < 0.01, compared to AH with mild and severe LVH groups.

AH – arterial hypertension; LA – left atrium; AS – aortic valve stenosis; LVH – left ventricular hypertrophy; LA walls mid-segments: LATla – lateral left atrium; SEP – septum; POS – posterior; INF – inferior; ANT - anterior; segPALS – segmental peak atrial longitudinal strain; r – reservoir phase; s – contraction phase

Table 3.9 shows that segmental LA peak longitudinal strain (segPALSr) was decreased in all patients with LVH (p < 0.001, in all groups compared with healthy individuals). Already in patients with mild LVH were significantly decreased segPALSr, but segPALSr was not significant different between patients groups with mild LVH compared to patients with severe LVH and AS. Only in patients with AS significantly decreased segPALSr compared to patients with mild and severe LVH (p < 0.05, LA inferior, anterior, posterior walls mid-segments).

During contraction phase segPALSs was not different between AH patients groups, only segPALSs LA lateral wall was significantly higher in patients groups with AH (p < 0.001, compared to healthy individuals). SegPALSs LA posterior, inferior and anterior walls were significantly lower in patients with AS (p < 0.001, compared to healthy individuals and p < 0.01, compared to groups with AH).

### 3.3.4. LA average peak longitudinal deformation

Table 3.10 shows average peak atrial longitudinal strain (avPALS) values during LA reservoir and contraction phases. Among a total of 1232 segments, the software was able to track 1202 (97.6 %) segments.

Table 3.10

**LA average and global peak longitudinal strain (avPALS, globPALS) values during LA reservoir and contraction phases in four study groups, % (M ± SD)**

| PALS              | Healthy individuals<br>(n = 20) | AH and mild<br>LVH<br>(n = 30) | AH and<br>severe LVH<br>(n = 22) | AS and<br>severe LVH<br>(n = 16) |
|-------------------|---------------------------------|--------------------------------|----------------------------------|----------------------------------|
| Reservoir phase   |                                 |                                |                                  |                                  |
| 4ch-avPALSr       | 17.9 ± 4.4                      | 9.9 ± 2.4††                    | 9.4 ± 3.1††                      | 7.9 ± 3.4†† †                    |
| 2ch-avPALSr       | 14.9 ± 3.4                      | 9.8 ± 2.7††                    | 8.5 ± 2.7††                      | 6.5 ± 2.2†† ††                   |
| globPALSr         | 16.4 ± 4.4                      | 9.9 ± 2.1††                    | 9.0 ± 2.6††                      | 7.2 ± 2.0†† ††                   |
| Contraction phase |                                 |                                |                                  |                                  |
| 4ch-avPALSs       | -14.2 ± 2.7                     | -14.1 ± 4.5                    | -13.2 ± 4.1                      | -11.8 ± 2.9†                     |
| 2ch-avPALSs       | -16.4 ± 2.9                     | -14.7 ± 3.6                    | -13.6 ± 4.4                      | -11.4 ± 1.8††                    |
| globPALSs         | -15.3 ± 2.3                     | -14.4 ± 3.7                    | -13.4 ± 5.3                      | -11.5 ± 2.0†† †                  |

† p < 0.05, compared to healthy individuals group; †† p < 0.001, compared to healthy individuals group; † p < 0.05, compared to AH with mild and severe LVH groups; †† p < 0.001, compared to AH with mild and severe LVH groups.

AH – arterial hypertension; AS – aortic valve stenosis; LVH – left ventricular hypertrophy; 4chPALS, 2 ch-avPALS – average peak atrial longitudinal strain in 4ch or 2ch apical views; globPALS – global peak atrial longitudinal strain; r – reservoir phase; s – contraction phase

As the table 3.10 shows, during LA reservoir phase avPALSr in 2ch and 4ch apical views were significantly lower in all study groups (p < 0.001, in all groups compared to healthy individuals).

It should be noted that, as in the case of segmental PALSr, average PALSr in patients with AH and mild hypertrophy was no different compared to patients with AH and severe hypertrophy. Average PALSr in 4ch and 2 ch apical views were significantly lowest only in patients group with AS (4ch-

avPALSr  $p < 0.05$ ; 2ch-avPALSr  $p < 0.001$ , compared to AH group with mild and severe LVH).

During contraction phase avPALSs in 4ch and 2 ch apical views were not different between healthy individuals group and AH groups. However, avPALSs in patients with AS was significantly lower than in healthy individuals ( $p < 0.05$ , for 4ch-avPALSs and  $p < 0.001$ , for 2ch-avPALSs).

### **3.3.5. LA global peak longitudinal deformation**

Comparisons of the global peak longitudinal strain (globPALS) values between groups are shown in table 3.10.

During reservoir phase globPALSr was significantly lower in all patients ( $p < 0.001$ , compared to healthy individuals). The lowest globPALSr values were in patients with AS.

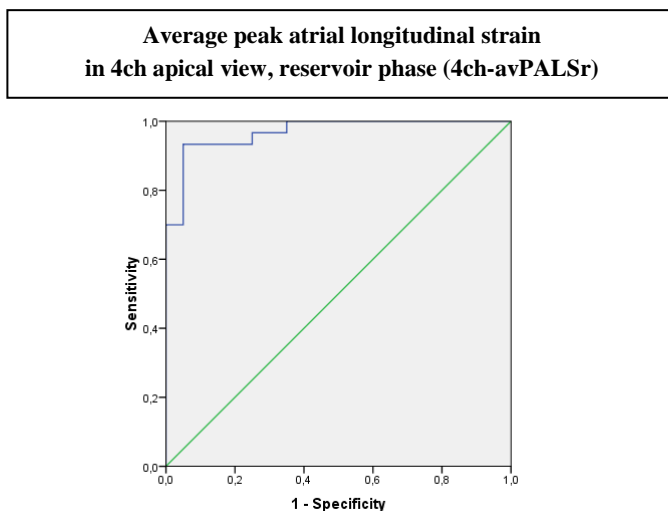
During contraction phase globPALSs was not different between patients with AH and healthy individuals. However, globPALSs in patients with AS was significantly lower than in healthy individuals ( $p < 0.001$ ) and in patients with AH and mild or severe LVH ( $p < 0.05$ ).

GlobPALSr and globPALSs did not show significant correlation with age and LV ejection fraction. There was a significant negative correlation between globPALSr reservoir phase and LVMI ( $r = -0.56$ ,  $p < 0.001$ ) and LA volume indexes (LAVI max,  $r = -0.42$ ,  $p < 0.05$ ; LAVI min,  $r = -0.45$ ,  $p < 0.01$ ; LAVIp,  $r = -0.38$ ,  $p < 0.05$ ). There was a significant positive correlation between globPALSr reservoir phase and E`mean MV ( $r = 0.64$ ,  $p < 0.001$ ).

There was a moderate positive correlation during contraction phase between globPALSs and LVMI ( $r = 0.40$ ,  $p < 0.05$ ) and LAVI min ( $r = 0.51$ ,  $p < 0.01$ ). There was a moderate negative correlation between globPALSs and LA active emptying fraction ( $r = -0.41$ ,  $p < 0.05$ ) and LA expansion index ( $r = -0.46$ ,  $p < 0.01$ ).

### 3.3.6. Average and global peak atrial longitudinal strain indices for predicting of the LA deformation abnormalities

To further investigate the value of these echocardiographic indices to predict the early LA deformation abnormalities in patients with AH and mild LVH, we performed receiving operating characteristics (ROC) curve analyses. Area under the curve (AUC), optimal cutoff values and corresponding sensitivities and specificities are presented in figure 3.1 and 3.2.



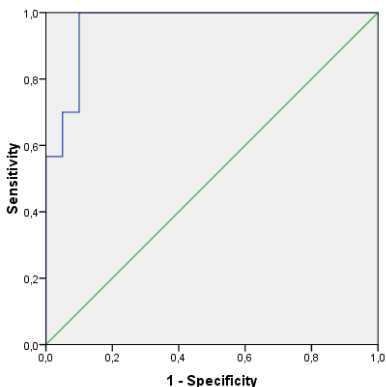
**Figure 3.1 Receiver operating characteristics analysis (AUC = 0.968). Sensitivity 93 % and specificity 95 % to predict LA deformation abnormalities in AH patients with mild LVH using a cutoff value of 4ch-avPALS 12.5 %**

Among all echocardiographic parameters analyzed, global PALSr and 4ch-avPALSr showed the highest diagnostic accuracy.

4ch-avPALSr presented diagnostic accuracy with AUC = 0.968 and excellent sensitivity and specificity of 93 % and 95 %, respectively, to predict LA deformation abnormalities using a cutoff value less than 12.5 %.



**Global peak atrial longitudinal strain,  
reservoir phase (globPALSr)**



**Figure 3.2 Receiver operating characteristics analysis (AUC = 0.963). Sensitivity 97 % and specificity 90 % to predict LA deformation abnormalities in AH patients with mild LVH using a cutoff value of globPALS 12.6 %**

GlobPALSr presented diagnostic accuracy with AUC = 0.963 and sensitivity and specificity of 97 % and 90 %, respectively, to predict LA deformation abnormalities using a cutoff value less than 12.6 %.

Given a significant positive correlation between the 4ch-avPALSr and globPALSr ( $r = 0.93$ ,  $p < 0.001$ ), and also excellent sensitivity and specificity of 4ch-avPALSr value, it can be assumed that for detection of the early LA deformation abnormalities in AH patients with mild LVH in clinical daily practise may be used value of 4ch-avPALSr parameter.

### 3.3.7. Intra-observer variability

During reservoir phase coefficient of variation (CV) was 6.34 % for PALSr and 2.84 % for PALSs.

## **4. DISCUSSION**

After the development of the new technologies in echocardiography, such as TDI and 2DS, the research of the regional atrial myocardium became possible. In the previous scientific papers the usage of the TDI for the identification of the atrial strain was described. Moreover, the time analysis of the atrial systole has been conducted [15-17]. However, the above mentioned method did not gain a lot of success.

Recently a new method of the identification of the myocardial strain (non-Doppler 2DS), which is not connected to the Doppler effect and had well responds regarding the analysis of the global and segmental function of LV, has been presented. The main advantages of the present method in comparison with the TDI, are as follows: independence of the scanning angle, possibility to use the frames with the lower frame frequency as well as the independence of the heart beat in general.

By applying the 2DS method, the changes of the longitudinal atrial strain, having the cardiomyopathy, the LV myocardial hypertrophy and the dilatation cardiomyopathy in patients, who underwent the heart resynchronization, were presented [26-28]. Besides, the correctness of the present method has been proved by the patients with the occluder in the atrial septum. In this case the strain in the occluder segment was not present [29].

### **4.1. Evaluation of the results of the group of healthy individuals aged under 50 years**

In the present scientific paper the author provides data of the atrial longitudinal strain of the LA and RA walls of the healthy individuals. During all the phases of the atrials cycle, the results have been gained (the strain curves). It is worth mentioning that the biggest strain values have been noticed in the reservoir phase, because during this period the myocardial length

significantly prolongs and there is a significant blood flow from the pulmonary veins. The compliance of the LV myocardium during the reservoir phase determines the blood volume flowing and the pressure in the atrials.

The conduit phase, as it has been mentioned earlier, the PALS data of the 50% of the responder's equals 0. Perhaps it is due to the lack of the myocardial deformation during this period. As it is known, during the conduit phase the atrial transfers the blood passively through itself. Therefore the displacement of the atrial myocardium is practically not visible. It has been proved by the tensocardiogram and the mechanocardiogram of the myocardial atrials [30].

During the contraction phase, which is the important starting point for the beginning of the ventricular systole, the biggest strain values have been registered in the inferior and lateral walls of the LA and the lateral wall of the RA. Perhaps, during the contraction phase, the lateral wall of the RA has higher results than the LA due to the low pressure in the RA and more massive *mm. pectinati*, than in the LA [30, 31].

Comparing the gained results with the other researches that has been using the TDI method in order to identify the strain, there was found both similarities and the difference. Would like to stress, that the analysis of the atrial mechanical function were different in every paper. One group of authors has been using only three walls of the LA [15], and compared the strain data in all the phases, the other group, on the contrary, compared the data of strain of the LA and RA, but only in the contraction phase [16, 17]. In the present paper, in order to compare, tried to sum up the LA and RA walls with the data in all phases of the atrials cycle.

The same results of the lateral wall of the RA have been gained during the contraction phase, which had higher rates of the myocardial contraction and the myocardial strain than in the walls of the LA [16]. During the analysis only

of the walls LA, the various results have been gained. According to the research, conducted by *M. Quintana et al.* [17], no reliable differences of the maximum strain of the LA wall in the contraction phase, have been presented.

In the research done by *C. Sirbu et al.* [15] while analyzing the three walls of the LA during the contraction phase, the myocardium of the inferior wall has been deformed (became shorter) less if to compare with the lateral and the anterior walls. The author of the present paper got another results: during the contraction phase the strain and the strain rate of the inferior wall appeared to be higher if to compare with the lateral and the anterior walls.

More differences have been found in the conduit phase. In the research done by *C. Sirbu et al.* [15] during the conduit phase the numbers of the maximal longitudinal strain were rather high (till -41,72%), but the present paper claimed that the PALS of the 50% of the examined healthy individuals equals 0. As it has been mentioned earlier, during the conduit phase myocardial strain is minimal.

It is also important to observe the differences of the analyzing methods. In the basis of the TDI and the non-Doppler 2DS there are different ways of the assessment of the myocardial strain. It can also have some impact on the final results.

#### **4.2. Evaluation of the results of the group of the patients with the LV hypertrophy**

In the present research the author has investigated the function of the atrial with patients having AH and AS with the different degree of the LV hypertrophy. The group of the AH patients were compared with the group of the healthy individuals according to the age. The group of the AS patients were older, which is logical. It is worth mentioning that the main inclusion criteria in

the research, was the fact of the irregular usage of the medicine, because this point could influence the results.

In the group of the AH and AS patients the LVMI was higher, but EF LV lower. The obvious reason of the reduction of the pumping function of the LV was the increase of the afterload due to the constantly rising and the non-corrected by the medicine of the blood pressure or because of the AS.

The Doppler-echocardiography data of the diastolic function of the LV reflect the disturbances of relaxation of the LV myocardium in all the groups: the reliable increase of the peak velocity A of the transmitral flow, the augmentation of the deceleration time (DT), the extension of the isovolumic relaxation time (IVRT), the decrease of the MV E' average, the increase of the MV E/E' ratio average and the increase in the difference between the duration of the LA systole and the duration of the retrograde flow from the atrial to the pulmonary vein ( $A_r \text{ dur} - A \text{ dur}$ ). It is worth mentioning, that only the E'av. MV and E/E'av. MV indexes were reliably different in all the groups. The decrease of the MV E'av. and the increase of the correlation of the E/E'av. were not associated with the reduction of the EF of the LV ( $r=0.28$ ), but these indexes probably was associated with the increase of the LVMI ( $r=0.6$ ,  $p<0.001$ ). In the group of the patients with the AS, E/E'av. was reliably the highest, if to compare with others groups ( $19.7 \pm 3.3$ ), that has been indicating about the joining of the LV relaxation disturbances the reduction of the myocardial compliance of the LV and the increase of the filling pressure of the LV [33].

#### **4.2.1. Structural-functional indexes of left atrium**

The volume of the atrial is viewed as the cumulative indexes that present the long-term impact of the various factors. In the present situation this is the arterial blood pressure and the LV hypertrophy or AS.

In the present research all the volumes of the LA and the volume indexes were reliably higher in the patient groups with the AH and AS in comparison with the control group. The highest expected indexes were registered in the patient group having the AS, which is confirmed by other researches [34, 35].

In all volume indexes of the LA the reliably negative correlative connection with the globPALS during the reservoir phase (longitudinal extension of the LA) has been registered and only the index of the minimal volume of the LA had shown the positive correlative connection with the globPALS ( $r=0.51$ ,  $p<0.01$ ) during the contraction phase (the LA systole). The present data allow assuming that with the increase of the volume the extension of the LA becomes worse and the contraction of the LA increases compensative. The present process has been proved by Frank-Starling's law: the volume increase of the LA is associated with the increase of the myocardial contraction of the LA. At the same time, the increase of the LA active emptying fraction in the patient groups with the AH and AS has not been found. It can be proved from the mathematic point of view by the reliable increase of the volume not only of the  $V_p$  LA, but also by the  $V_{min}$  LA in all the researched groups. The display of the compensatory abilities of the LA is the reliable increase of the peak A of the transmitral flow. In another words, with the increase of the LV filling pressure, that confirms the increase of the E/E' interrelation of the LV), the systole of the LA extends in order to provide the normal filling of the LV compensatory.

## **4.2.2. Segmental, average and global peak atrial longitudinal strain of left atrium**

### **4.2.2.1. Reservoir phase (LA lengthening)**

During the reservoir phase the results of the segmental, average and global peak atrial longitudinal strain (PALS) of the LA were lower in all of the researched groups, namely the LA is not relaxed completely after the atrial systole, and thereby it does not fully perform the function of the blood pumping from the pulmonary veins. Perhaps, in return of the hypertrophy of the LV, the myocardium of the atrium has been responding by the relaxation disturbances right as well as the LV. It is worth mentioning that the significant decrease of the PALS has been already seen in the hypertonic patient group with a mild hypertrophy, but in the hypertonic patient group the PALS did not reliably differ, and only in the group with AS the reliably lower PALS has been registered. Such processes as the disturbances of the myocardial relaxation and the deterioration of the compliance of the LV caused the aggravation of the LA dysfunction. Our results have been proved by other researches. *D'Andrea A. et al.* [27] have researched the AH patients with the moderate hypertrophy of the LV and a slight dilatation of the LA, and showed reliable decrease of the segmental maximal strain of the LA by the patients with the AH in comparison with the control group. Even more interesting results have been provided in the *Mondillo S. et al.* [36] and *Miyoshi H. et al.* [37] researches, the goal of which was to find out the early symptoms of the LA function disturbance (with normal size of the LA) by the AH patients with a mild hypertrophy of the LV and the diabetes mellitus [36] and the patients with the one or more cardiovascular risk factors [37]. The results were the same in the both researches: during the reservoir phase, already on the early stage of the AH or the patients with the risk factor, the reliable decrease of the avPALSr [37] and globPALSr [36] have been registered. Adding the diabetes mellitus to the AH

decrease the strain abilities of the LA even more [36]. Perhaps, the decrease of the PALS (the decrease of the lengthening during the reservoir phase) of the LA, is the early symptom of the heart function disturbance having the unchanged or slightly changes echocardiographic standard indexes.

As it has been mentioned earlier, the main disturbance of the LA strain has been seen in the patient group with the AS and more distinctive hypertrophy of the myocardial LV. In another words, in this patient group plus to the overload of the pressure the overload of the volume has been added (due to the disturbance of blood outflow through stenotic aortic valve), which led to the significant decrease of the LA deformation.

It is interesting to observe the correlative association of global PALS during the reservoir and the contraction phases with the average and the segmental PALS. The segmental PALS in middle segments of lateral, posterior, inferior walls of the LA during the reservoir phase showed significant positive correlation with globPALSr ( $r=0.83$ ;  $0.66$ ;  $0.66$  respectively,  $p<0.001$ ). The reliably positive correlation is also viewed in between 4ch-avPALSr and 2ch-avPALSr and globPALSr indexes ( $r=0.93$  and  $0.90$  respectively,  $p<0.001$ ). The similar situation has been viewed during contraction phase too. Perhaps, these results allowed using segmental or average strain indexes (avPALS and segPALS) as the surrogate marker of global strain (globPALS). As it is known, one of the disadvantages of the assessment of LA strain is the blurring and broken contour of atrial endocardium: the pulmonary veins, the appendage of LA. Generally, those disadvantages are not present in middle segments of lateral, posterior, inferior walls of LA, where endocardium as well as the thickness of LA walls are distinctly visualized. Besides, exactly these three segments are included in the apical 4ch, 3ch and 2ch views, in which the assessment of average (avPALS) and global strain (globPALS) occur.



#### **4.2.2.2. Contractile phase (shortening, systole of LA)**

Summarizing results associated with the contraction phase, the author can conclude that PALS indexes did not have any reliable differences in the AH and the control groups. Perhaps, in hypertonic groups on the increase of LA volume the compensation reaction in the form of the strengthening of LA PALSs did not happen. The increase of peak A transmitral blood flow have been noticed. Only patient group with AS the author have viewed the reliable decrease of the segmental, average and global strain in comparison with the healthy individuals and with hypertonic groups. Having the AH, degree of the increase of LA volume, before the beginning of the contraction phase, is not probably so important, if to compare with the increase of LA volume having the AS. Perhaps, the reaction of the myocardial LA in the present case will be different, namely the depletion of compensation function of LA myocardium is taking place, in associations with increase of the filling pressure of LV, which resulted in increase of the tension of LA walls [12].

Thus, the application of 2DS method allows analyzing the atrial deformation as well as opens us the perspectives for the further researches with the goal to understand the changes, which occur in LA.

### **4.3. Study limitations**

Some limitations of this study should be considered.

Because dedicated software for LA strain analysis has not yet been released, we used the software for LV analysis to study LA strain.

Another limitation is the relatively small amount of the researched individuals, which could affect the processing of the statistic data.

One of the significant criteria for patients with LVH to enter research was the irregular usage of medications, but still this fact can affect LA deformation properties.

## 5. CONCLUSIONS

1. Having analyzed data of 118 patients, we concluded, that 2DS method may be considered a useful tool to detect early LA disfunction.
2. 2DS method allows assessing atrial longitudinal strain.
3. Normaly atrial myocardium characterized by heterogeneous deformation and asinhronisms in different walls, and with age LA longitudinal deformation decrease in reservoir phase (decrease compliance of LA myocardium).
4. During reservoir and contractile phase was demonstrated good reproducibility of peak longitudinal strain indexes.
5. In case of LV hypertrophy, abnormalities of LA deformation occur simultaneously.
6. LA longitudinal deformation is significantly impaired in patients with AH and even with mild LV hypertrophy: during reservoir phase LA longitudinal deformation are decreased.
7. LA longitudinal deformation are most impaired in patients with AS.
8. In patients with AH and AS LA longitudinal deformation was most impaired during reservoir phase. In contraction phase, left atrial deformation deterioration occurred only in patients with AS.

## 6. PRACTICAL RECOMMENDATIONS

On the basis of the results obtained using 2DS method was developed recommendations for the Latvian echocardiography specialists:

1. 2DS method is effective and widely introduced tool for early detection of LA dysfunction in healthy individuals under the age of 50 years and in patients with AH and mild LVH;
2. During LA reservoir phase is recommended to use parameter value of peak longitudinal strain (average, 6 segments, apical 4-chamber view, 4ch-avPALS) less than 12.5 % (AUC = 0.968, sensitivity: 93%, specificity: 95%), which indicates deterioration of LA deformation in patients with AH and mild LVH.

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