Aus dem

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Innovative imaging modalities in the evaluation of hypertensive heart disease

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Content

1. Introduction

The evaluation of left ventricular (LV) function represents a cornerstone in decision-making in the broad range of cardiovascular and non-cardiovascular diseases. Conventional two-dimensional and Doppler echocardiography has long been a fundamental segment in evaluation of LV function. The central and most commonly used echocardiographic parameter in determination of LV systolic function is LV ejection fraction. This is a purely numeric parameter that can be obtained by all echocardiographic methods, from M-mode to three-dimensional echocardiography and this is the reason why ejection fraction is widely calculated measure in clinical routine. However, this parameter it not reliable due to high inter- and intra-observer variability and this is why nowadays many indices of LV global systolic are available, but with limited usage [1].

Over the years it has become obvious that the percentage of changes in LV diameters or volumes is not representative enough for complex cardiac motion that occurs during a cardiac cycle [1]. Tissue Doppler imaging represents a better method in evaluation of LV mechanics because it takes into account myocardial velocity in the portion of myocardium involved in a sample volume [1]. Nevertheless, tissue Doppler imaging is an age, angle- and load-dependent technique and it could provide information about cardiac mechanics in only a small heart segment [2].

A new echocardiographic method that appeared almost two decades ago was strain [3]. It is an angle independent, highly reproducible and significantly less age- and load-dependent technique that provides accurate insight into cardiac mechanics of the whole heart thickness unlike tissue Doppler imaging that enables information about only a small portion of myocardium [2-4]. Tissue Doppler-derived strain was used at the beginning, but rapid development in this field soon provided speckle tracking-derived strain which is still being used in both, clinical practice and research nowadays [5].

1.1 Left ventricular mechanics

Left ventricular motions include shortening, lengthening, thickening, rotation, and twisting. The timing and the power of the motion determine the direction of the principal motion. The best echocardiographic method for evaluation of the complex

cardiac motion is strain which basically represents a percentage difference in myocardial longitudinal diameter, circumference and thickness - longitudinal, circumferential and radial strain, respectively [4-7]. Apical and basal rotations are additional cardiac motions that enable efficient cardiac contraction. The cardiac base rotates clockwise, whereas the apical segment rotates in the opposite direction - more prominent counterclockwise. Twist is the calculation as the sum of the rotations of the cardiac base and apex [8].

This complex cardiac motion can be explained by cardiac layer architecture and myocyte organization. LV myocardial wall consists of three layers: endocardium, mid-myocardium and epicardium [9]. Subendocardial and subepicardial myocites have mostly longitudinal direction, whereas mid-myocardial myocites are circumferentially directed [9]. The subepicardial fibers are directed at an angle of –60° to the horizontally directed mid-myocardial myocites and make a counterclockwise helix. The subendocardial fibers together with the mid-myocardial fibers form the clockweise helix with angulation of approximately +60° [9]. The spherical fibers of the cardiac base are also responsible for LV contraction and rotation. A mathematical model showed that if LV possessed only longitudinal or circumferential myofibers, then the contraction of these fibers would generate ejection fraction of 15% and 28%, respectively [10]. Instead, the same model revealed that fibers with 60° angle from the horizontal plane could produce ejection fraction higher than 60%, which is the case with the normal LV.

In the last several years the software development has made so much progress that nowadays we are able to distinguish and determine layers-specific strain [11]. This novel approach confirmed the old hypothesis that myocardial remodeling develops in the endocardium – epicardium direction. This was previously demonstrated only in an animal model [12].

The evaluation of global LV strain has been adopted in everyday clinical practice, especially in the patients with cardiovascular diseases, but it has also become important in other disorders. The reason for this broad acceptance of a relatively new method lies in the fact that LV longitudinal strain, global and layer-specific, has a high predictive value in patients with a wide range of cardiovascular

diseases including arterial hypertension, but also in general population [13,14]. Interestingly, it was also reported that LV longitudinal strain represented a better predictor of cardiovascular and global mortality than LV ejection fraction which was considered as a "gold standard" parameter of LV systolic function [15].

1.2 Left ventricular mechanics and arterial hypertension

The development of arterial hypertensive disease could be roughly divided into two stages: the first stage with increased preload and normal afterload and the second stage with relatively normal preload and increased afterload. The adaptation of the LV occurs simultaneously [16]. Therefore, the initial phase of LV remodeling considers minor LV dilatation which is in line with Frank-Starling law – achieving force for the ejection of higher stroke volume by increased myofibers stretching. In the second phase the increase of afterload is remarkable and the LV response is hypertrophy [16]. According to the law of LaPlace LV wall thickness increases as a compensatory mechanism to reduce wall stress and oxygen demand [16].

Traditionally arterial hypertension has been related to concentric LV hypertrophy and only chronic hypertensive disease could induce LV dilatation and consequent eccentric LV hypertrophy and eventually reduced LV pump function [16]. However, new evidence in the field of hypertension showed that progression of LV changes could be different and start with LV concentric remodeling and LV eccentric hypertrophy, whereas LV concentric hypertrophy develops later in the course of arterial hypertension [17]. The updated classification of LV geometry patterns is providing more detailed information regarding LV remodeling and could be easily applied in hypertensive patients. Namely, this classification for the first time included LV dilatation and separated LV eccentric and concentric hypertrophy into two subsets: (i) with and (ii) without LV dilatation [18]. This classification revealed that the patients with dilated eccentric and concentric LV hypertrophy had significantly higher total and cardiovascular mortality than their non-dilated counterparts [19,20]. Studies conducted in the hypertensive population showed that the patients with eccentric dilated LV hypertrophy, concentric non-dilated and

dilated LV hypertrophy were related with a significantly higher cardiovascular risk [21,22].

There are several possible mechanisms that might potentially clarify the relation between LV function and arterial hypertension and all of them could be separated into two different sets: direct mechanical and indirect biohumoral [9,23]. Arterial hypertension is initially associated with increased preload and subsequently with elevated afterload, which have direct unfavorable influence on LV mechanics. On the other hand, sympathetic autonomic nervous system, renin-angiotensin-aldosterone system and oxidative stress are responsible for interstitial myocardial changes, predominantly fibrosis that is related with worsening of LV elasticity and consequently with reduced LV deformation [12]. In patients with additional cardiovascular risk factors, such as diabetes, obesity, obstructive sleep apnea, hypercholesterolemia, metabolic syndrome, or chronic renal failure, LV mechanics is even more deteriorated than in the patients with isolated arterial hypertension and the effect of these risk factors is not additive, but synergistic negative [24].

1.3 Left ventricle in patients with white-coat and masked hypertension

White-coat hypertension is defined as increased office blood pressure and normal values of ambulatory blood pressure. The prevalence varies from 13% to 32% [25]. Its influence on target organ damage, cardiovascular and general morbidity and mortality is still unclear [26]. Earlier investigations demonstrated that white-coat hypertension was related with LV hypertrophy and LV diastolic dysfunction [27]. A recently published meta-analysis revealed that white-coat hypertension was related with LV remodeling [28].

Masked hypertension is characterized by normal office blood pressure in combination with increased blood pressure detected by ambulatory blood pressure [25]. The influence of masked hypertension on target organ is still controversial. However, majority of studies agree that masked hypertension is related with LV hypertrophy [29,30]. Recently a large meta-analysis reported a gradual increase in LV mass from the normotensive across the masked hypertension to the hypertensive patients [31].

The impact of white-coat and masked hypertension on LV mechanics has not been studied so far.

1.4 Right ventricular function

The right ventricular (RV) shape and structure is specific and significantly different from the LV. Namely, the RV is divided into three anatomically separated parts: the inflow segment, the outflow segment, and the apex. The RV structure is also very different from the LV because it must enable unique contraction of the RV. The unique structure of the RV prevents the simultaneous contraction of the inflow and outflow tract that would be fatal. RV free wall consists mainly of transverse myofibers, the interventricular septum includes predominantly oblique myofibers and the RV outflow tract comprises oblique myofibers, which is why these fibers could not form the RV helix, as in the LV [32].

RV pump function is the result of contraction of transverse and oblique fibers that are responsible for longitudinal and radial motion. Furthermore, magnetic resonance imaging demonstrates RV twist. The RV contraction involves in two stages: (i) shortening of RV oblique myofibers, (ii) shortening of RV ascending and descending myofibers [32].

The evaluation of the RV mechanics is still not straightforward primarily because of the complex RV shape and retrosternal position in the mediastinum that makes the RV difficult for echocardiographic evaluation. Similarly to LV strain, RV longitudinal strain represents a useful diagnostic tool for detecting the initial stage of myocardial dysfunction. Studies showed that RV longitudinal strain had a high predictive value in a large number of cardiovascular conditions (pulmonary hypertension, valvular heart disease, obstructive sleep apnea, heart failure and congenital heart disease) [33,34].

1.5 Right ventricular function in arterial hypertension

The first time changes in pulmonary circulation in patients with arterial hypertension were reported almost 70 years ago [35]. Several decades passed until investigators reported that the pulmonary resistance is positively associated with the peripheral resistance in the systemic circulation in the hypertensive subjects [36].

More recently echocardiographic researches demonstrated that arterial hypertension was associated with RV remodeling – increased RV free wall thickness and impaired RV diastolic function [37]. Pedrinelli et al. revealed that hypertensive individuals had mild damage of RV systolic function assessed with tissue Doppler imaging [38], but also detected the impairment of RV longitudinal strain in the same population [39].

Numerous mechanisms might connect RV remodeling with arterial hypertension [40]. First, the overactivation of biohumoral systems such as autonomous sympathetic nervous system and renin-angiotensin-aldosterone could deteriorate RV structure and function, as well as pulmonary circulation. Second, oxidative stress and endothelial damage may induce impaired vascular relaxation. Third, the mechanical mechanism that could be the most important one is the interaction between the ventricles. On the one hand, pure mechanical interaction achieved by the interventricular septum is extremely important because septum is already known as "the lion of the RV function" [41]. On the other hand, increased filling pressure of the LV in the hypertensive patients is retrogradely transmitted through pulmonary veins to pulmonary circulation and finally to the RV, which could further induce RV functional and structural changes [41].

1.6 Right ventricular function and diabetes

The association between RV remodeling and diabetes is still a matter of debate. Studies revealed that diabetic patients had increased RV thickness comparing with healthy controls [42], and negative correlation between diabetes and RV volume [43]. There is agreement in findings regarding the impaired RV diastolic function in diabetic patients [42,44]. The evaluation of RV systolic function is not an easy task in everyday clinical practice. The usage of traditional echocardiographic indices of RV systolic function like TAPSE and RV fractional shortening in most research did not show important difference between diabetics and controls [45,46]. Results were significantly different when speckle tracking imaging was used for evaluation of RV systolic function in the diabetic patients [47,48].

Mechanisms that could clarify the association between diabetes and RV changes are various. Raised production of free oxygen radicals induces the interstitial collagen deposition with subsequent myocardial fibrosis, reduction of elasticity, increase of filling pressure, hypertrophy and ultimately RV systolic dysfunction [49]. Additionally, the cross talk among insulin resistance, autonomic nervous system and renin-angiotensin-aldosterone system might contribute to RV functional and structural remodeling in diabetes [50,51]. Obesity is commonly seen in diabetic patients, which could be a contributing factor for RV impairment because of increase preload in obese patients and its influence on RV function and structure [52]. The ventricular interaction remains the most important mechanism that could explain RV remodeling in diabetes. Namely, diabetes is responsible for LV dysfunction and hypertrophy, which is associated with increased LV filling pressure that retrogradely increases pulmonary capillary wedge pressure and furthermore deteriorates RV function and structure [52].

2. Aims

The present paper aimed to investigate several important topics regarding left and right ventricular mechanics in the hypertensive population:

1. The potential influence of left ventricular geometry patterns on left ventricular deformation in hypertensive population
2. The impact of white coat and masked hypertension on left ventricular mechanics
3. The association between functional capacity and right ventricular remodeling in hypertensive patients
4. Right ventricular mechanics in the metabolic syndrome and diabetes

3.1 The relationship between left ventricular deformation and different geometric patterns according to the updated classification: findings from the hypertensive population

Background: Systemic hypertension is connected with left ventricular (LV) hypertrophy. Concentric remodeling and concentric hypertrophy have long been considered as the most prevalent LV geometry patterns among patients with arterial hypertension. An updated LV geometry classification for the first time introduced LV dilatation as one of the parameters which is used in determination of LV geometry pattern. Therefore, concentric and eccentric LV hypertrophy (LVH) patterns were separated into two subgroups: dilated and non-dilated form.

Objective: LV mechanics was evaluated in patients with increased blood pressure and different LV geometry patterns by novel echocardiographic techniques.

Methods: All 197 hypertensive subjects were divided in 6 different groups using 3 different parameters: LV mass index, LV end-diastolic diameter and relative wall thickness. Instead of 4 LV geometry patterns used in the conventional classification 6 geometry groups were observed: (i) normal LV geometry, (ii) concentric remodeling, (iii) eccentric non-dilated LVH; (iv) concentric LVH, (v) dilated LVH, (vi) concentric-dilated LVH. Anthropometric measures and laboratory parameters (level of fasting glucose, blood creatinine, serum lipids level) were analyzed in all participants.

Results: LV mechanics, assessed by 2D and 3D speckle tracking, was the most impaired in the patients with concentric LVH and dilated LVH patterns. Hypertensive patients with normal LV geometry had the least impaired LV mechanics. LV deformation during systole and early diastole was also the most impaired in the patients with concentric LVH and dilated LVH patterns. LV twist and torsion were the highest in hypertensive patients with concentric LVH (with or without dilatation). Concentric and dilated LVH geometry patters were independently related with deteriorated LV mechanics.

Conclusion: LV mechanics in all directions is the most impaired in patients with increased blood pressure and concentric LVH irrespective of LV dilatation. The new classification of LV geometry is providing new and useful information about

hypertensive-induced LV changes. However, the present investigation is cross-sectional and could not provide follow-up data regarding the predictive value of new LV geometric patterns in constantly increasing hypertensive population. **[Original article A]** /53/

Original article A: Tadic M, Cuspidi C, Majstorovic A, Kocijancic V, Celic V. The relationship between left ventricular deformation and different geometric patterns according to the updated classification: findings from the hypertensive population. J Hypertens. 2015;33(9):1954-61.

Tadic M, Cuspidi C, Majstorovic A, Kocijancic V, Celic V (2015):

The relationship between left ventricular deformation and different geometric patterns according to the updated classification: findings from the hypertensive population.

J Hypertens. 33(9):1954-61.

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3.2 Influence of white-coat hypertension on left ventricular deformation: two- and three-dimensional speckle tracking study

Background: The findings regarding the impact of white-coat hypertension on the left ventricular (LV) structure and function are still conflicting. Although majority of studies showed that white-coat hypertension is related with LV diastolic dysfunction and LV hypertrophy, there are also investigations that failed to demonstrate the significant difference between white-coat hypertensive patients and sustained normotensive individuals. To our knowledge there are no data about the effect of white-coat hypertension on LV mechanics.

Objective: The aim of the current study was to investigate LV mechanics in individuals with white-coat hypertension and compare them to subjects with normal and constantly increased blood pressure.

Methods: This study involved 139 untreated subjects who underwent 24-hour ambulatory blood pressure monitoring and echocardiographic examination. White-coat hypertension was defined according to the guidelines.

Results: 2D LV longitudinal and circumferential functions were the most impaired in the sustained hypertensive group. Systolic, early and late diastolic longitudinal and circumferential strain rates were not different between the normotensive participants and the white-coat hypertensive patients. Nevertheless, LV mechanics was deteriorated in each part of the cardiac cycle in the patients with sustained hypertension. Radial LV strain was not significantly different among the observed groups. LV twist was the highest in the patients with sustained hypertension. Subendocardial and mid-myocardial longitudinal and circumferential strains progressively reduced from the normotensive controls to the sustained hypertensives. Subepicardial strain was similar among the three observed groups. 3D longitudinal and circumferential strain reduced progressively from the normotensive controls to the hypertensives. 3D radial and area strains were reduced in the hypertensive individuals. However, the difference between the subjects with white-coat hypertension and the controls was not perceived. Clinic and 24-hour systolic blood pressure were related with LV longitudinal, circumferential and longitudinal endocardial layer strain independently of LV mass index and LV diastolic function.

Conclusion: This investigation demonstrated deteriorated LV mechanics in the participants with white-coat hypertension and sustained hypertension. Multidirectional strain gradually worsened from the normotensive participants, throughout the white-coat hypertension individuals, to the hypertensive patients. The study revealed that white-coat hypertension and sustained hypertension predominantly influenced subendocardial and mid-myocardial layers, which further shows that LV remodeling in hypertensive heart disease occurs in a certain direction – from endocardium to epicardium, which concurs with other pathological cardiovascular conditions such as coronary artery disease. Future follow-up investigations are required to establish a potential predictive value of LV strain in the individuals with white-coat hypertension and a possible value of medical treatment of this condition. **[Original article B]** /54/

Original article B: Tadic M, Cuspidi C, Ivanovic B, Ilic I, Celic V, Kocijancic V. Influence of white-coat hypertension on left ventricular deformation 2- and 3-dimensional speckle tracking study. Hypertension. 2016;67(3):592-6.

Tadic M, Cuspidi C, Ivanovic B, Ilic I, Celic V, Kocijancic V (2016).

Influence of white-coat hypertension on left ventricular deformation 2- and 3-dimensional speckle tracking study.

Hypertension. 67(3):592-6.

https://doi.org/10.1161/HYPERTENSIONAHA.115.06822

3.3 Does masked hypertension impact left ventricular deformation?

Background: The influence of masked hypertension on cardiovascular morbidity and mortality is not fully understood. Previous studies revealed the association between masked hypertension and left ventricular (LV) hypertrophy and LV diastolic dysfunction, which could contribute to unfavorable outcome in these individuals. The greatest problem remains the absence of antihypertensive treatment in this group of patients. There are no available data regarding LV strain in subjects with masked hypertension.

Objective: We sought to investigate LV mechanics in the subjects with masked hypertension and to compare them with the normotensive controls and the patients with sustained hypertension.

Methods: Investigation involved 185 never treated subjects. 24-hour ambulatory blood pressure monitoring and echocardiographic examination were performed to all. Masked hypertension was defined by the guidelines.

Results: LV longitudinal and circumferential mechanics, assessed by strain and strain rates, were the most deteriorated in the subjects with persistent hypertension. However, LV mechanics in masked hypertensive patients were in between normotensive and persistent hypertensive subjects. LV radial strain was decreased in the sustained hypertensive patients but only when they were compared with the controls, not when they were compared with the masked hypertensive patients. Endocardial and mid-myocardial longitudinal and circumferential strains progressively deteriorated from the controls to the individuals with sustained hypertension. On the other hand, longitudinal and circumferential epicardial strains were reduced in the sustained hypertensive patients in comparison with the normotensive controls, but there was no difference between the masked hypertensive subjects and the controls or the sustained hypertensive patients. 24-hour systolic blood pressure was at the same time related with 2D LV longitudinal and circumferential endocardial strain.

Conclusion: The present investigation showed that conventional echocardiographic indices used in the evaluation of LV remodeling could not fully elucidate the

influence of masked hypertension on the LV. Speckle tracking imaging showed that the impairment of LV mechanics in masked hypertension was between the normotensive controls and the sustained hypertensive patients. Longitudinal and circumferential LV strains progressively deteriorated from the normotensive controls, across the subjects with masked hypertension, to the individuals with sustained hypertension. Masked hypertension and sustained hypertension have a particularly negative effect on endocardial and mid-myocardial layers. The latest research about increased mortality in patients with masked hypertension together with our findings displays the importance of detailed evaluation of LV mechanics in the patients with masked hypertension. **[Original article C]** /55/

Original article C: Tadic M, Cuspidi C, Vukomanovic V, Celic V, Tasic I, Stevanovic A, Kocijancic V. Does masked hypertension impact left ventricular deformation? J Am Soc Hypertens. 2016;10(9):694-701.

Tadic M, Cuspidi C, Vukomanovic V, Celic V, Tasic I, Stevanovic A, Kocijancic V (2016).

Does masked hypertension impact left ventricular deformation?

J Am Soc Hypertens. 10(9):694-701.

https://doi.org/10.1016/j.jash.2016.06.032

3.4 Is there a relationship between right ventricular and right atrial mechanics and functional capacity in hypertensive patients?

Background: Previous investigations revealed that arterial hypertension impacts right ventricular (RV) structure and function. Studies also revealed that functional capacity is reduced in the subjects with arterial hypertension. However, there are no data regarding the potential relationship between RV deformation and functional capacity in the patients with arterial hypertension.

Objective: The purpose of this investigation was to investigate RV and right atrial (RA) deformation in the patients with arterial hypertension using 2D strain and three-dimensional echocardiography (3DE), as well as to determine the association between RV deformation and exercise capacity in the study population.

Methods: Investigation included patients with hypertension and different level of blood pressure control, as well as control group. All participants underwent echocardiographic examination and cardiopulmonary exercise testing.

Results: 3D RV volumes were the largest in patients with uncontrolled blood pressure. The RV stroke volume was similar between the observed groups. The 3D RV ejection fraction was significantly lower in the untreated hypertensive subjects compared with the normotensive controls.

RV free wall longitudinal strain was not different between the controls and the satisfactory-controlled hypertensive subjects, but still higher than in the untreated and the inadequately treated individuals. RV free wall systolic and early diastolic strain rates were decreased, whereas late diastolic strain rate was increased, in the uncontrolled hypertensive subjects comparing with the normotensive controls or the satisfactory-controlled patients. Equivalent results were shown for interventricular septum strain. The longitudinal RA strain was not different between the untreated and the unsatisfactory controlled hypertensive patients. However, RA longitudinal strain was reduced in contrast to the normotensive controls and the satisfactory-controlled patients.

Peak oxygen uptake and oxygen pulse were significantly decreased in the untreated and uncontrolled hypertensive patients in contrast with normotensive subjects and individuals with well-controlled hypertension.

Conclusion: Hypertensive patients with untreated and uncontrolled blood pressure had the most impaired functional capacity, RV and RA strain. Hypertension-induced RV changes were related with functional capacity. **[Original article D]** /56/

Original article D: Tadic M, Cuspidi C, Suzic-Lazic J, Andric A, Stojcevski B, Ivanovic B, Hot S, Scepanovic R, Celic V. Is there a relationship between right-ventricular and right atrial mechanics and functional capacity in hypertensive patients? J Hypertens. 2014;32(4):929-37.

Tadic M, Cuspidi C, Suzic-Lazic J, Andric A, Stojcevski B, Ivanovic B, Hot S, Scepanovic R, Celic V (2014).

Is there a relationship between right-ventricular and right atrial mechanics and functional capacity in hypertensive patients?

J Hypertens. 32(4):929-37.

https://doi: 10.1097/HJH.0000000000000102

3.5 Effects of the metabolic syndrome on right heart mechanics and function

Background: The metabolic syndrome (MS) represents a cluster of cardiovascular risk factors (abdominal obesity, increased blood pressure, dyslipidemia and increased fasting glucose level) associated with cardiovascular morbidity and mortality. Recent investigations showed that MS is associated with right ventricular (RV) remodeling. However, the existing investigations did not research RV strain in this population of patients.

Objective: This study aimed to investigate RV and right atrial (RA) strain assessed by 2D speckle tracking imaging and 3D echocardiography in MS individuals, as well as the relationship between different MS criteria with parameters of the right heart remodeling.

Methods: The present cross-sectional investigation involved 108 subjects with the MS and 75 healthy controls with similar gender and age distribution. The MS was defined by the presence ≥3 AHA-NHLB criteria. All participants underwent necessary laboratory analyses and comprehensive 2D and 3D echocardiographic investigation.

Results: 2D RV global longitudinal strain was significantly reduced in the MS subjects comparing with the healthy controls (-24 ± 5 *vs.* -27 ± 5 %, $p<0.001$). RA longitudinal strain was also significantly decreased in the MS group than in the control group (40 ± 5 *vs.* 44 ± 7 %, $p<0.001$). Interventricular longitudinal strain generally showed similar changes as the RV free wall. However, interventricular septal longitudinal strain did not differ between the MS individuals and the healthy controls. Systolic and early diastolic RV and RA strain rates were reduced, while late diastolic strain rate was elevated among the MS patients. 3D RV ejection fraction was significantly reduced in the MS participants (55 ± 4 *vs.* 58 ± 4 %, $p<0.001$). Systolic blood pressure, waist circumference and fasting glucose level were independently of other MS criteria related with RV and RA strain. Interestingly, global longitudinal left ventricular strain did not show correlation with 3D RV ejection fraction ($r=0.11$, $p>0.05$). On the other hand, left ventricular longitudinal strain correlated significantly with global RV strain ($r=0.43$, $p<0.01$) and global RA strain ($r=0.25$, $p=0.037$).

Conclusion: The current investigation revealed deteriorated RV and RA function and deformation in the individuals with the MS. All criteria of the MS were associated with RV and RA remodeling (structure, function and mechanics). However, only systolic blood pressure, waist circumference and fasting glucose level were independently of other MS criteria associated with RV and RA longitudinal strain. Future follow-up investigation with a larger sample size is necessary to determine the impact of impaired RV and RA strain on cardiovascular and total morbidity and mortality in the large population of patients with the MS. **[Original article E]** /57/

Original article E: Tadic M, Cuspidi C, Sljivic A, Andric A, Ivanovic B, Scepanovic R, Ilic I, Jozika L, Marjanovic T, Celic V. Effects of the metabolic syndrome on right heart mechanics and function. Can J Cardiol. 2014;30(3):325-31.

Tadic M, Cuspidi C, Sljivic A, Andric A, Ivanovic B, Scepanovic R, Ilic I, Jozika L, Marjanovic T, Celic V (2014).

Effects of the metabolic syndrome on right heart mechanics and function.

Can J Cardiol. 30(3):325-31.

https://doi.org/10.1016/j.cjca.2013.12.006

3.6 The influence of type 2 diabetes and arterial hypertension on right ventricular layer-specific mechanics

Background: Diabetes mellitus (DM) is associated with significant left ventricular (LV) remodeling that ultimately might induce heart failure with preserved ejection fraction, an entity which has drawn attention in the last decade. The relationship between DM and right ventricular (RV) remodeling is less known. Recent advantages in the imaging, and especially echocardiographic field, enable the detection of subtle myocardial changes significantly before any clinical manifestation. A layer-specific strain analysis provides information regarding each RV layer separately and could indicate the direction of RV remodeling in the myocardial wall.

Objective: This investigation aimed to research multilayer RV strain in normotensive and hypertensive patients with type 2 diabetes mellitus (DM).

Methods: Investigation involved 129 individuals diabetic patients with or without DM and healthy controls. Echocardiographic study was performed to all participants.

Results: Hypertensive diabetic patients had the most deteriorated RV global, RV free wall and RV layer-specific longitudinal strain. Normotensive diabetic patients had RV mechanics between controls and hypertensive diabetic patients.

Fasting glucose level correlated with body mass index, left ventricular diastolic function (E/e'_m), left ventricular mass index, RV diastolic function (E/e'_t), and RV mid-myocardial global longitudinal strain. HbA1c correlated with body mass index, left ventricular diastolic function (E/e'_m), left ventricular mass index, RV wall thickness, RV diastolic function (E/e'_t), and RV endo- and mid-myocardial longitudinal strain.

Conclusion: The current study revealed deterioration of RV mechanics in diabetic patients irrespective of arterial hypertension existence. RV changes in function and deformation gradually deteriorated from healthy controls, throughout diabetic patients without hypertension, to hypertensive diabetic subjects. Nevertheless, significant difference was not noticed in comparison with the normotensive and the hypertensive diabetic patients. Diabetes and arterial hypertension negatively influenced the whole thickness of the RV meaning that all layer-specific longitudinal

strains were decreased. The most widely used parameters of diabetes control (fasting glucose and HbA1c) correlated with RV endocardial and mid.-myocardial strain. Further longitudinal investigations are required in order to determine a possible predictive value of RV strain in diabetic and hypertensive population. **[Original article F]** /58/

Original article F: Tadic M, Cuspidi C, Vukomanovic V, Ilic S, Celic V, Obert P, Kocijancic V. The influence of type 2 diabetes and arterial hypertension on right ventricular layer-specific mechanics. Acta Diabetol. 2016;53(5):791-7.

Tadic M, Cuspidi C, Vukomanovic V, Ilic S, Celic V, Obert P, Kocijancic V (2016).

The influence of type 2 diabetes and arterial hypertension on right ventricular layer-specific mechanics.

Acta Diabetol. 53(5):791-7.

https://doi.org/10.1007/s00592-016-0874-9

4. Discussion

4.1 The association between left ventricular geometry patterns and left ventricular mechanics in arterial hypertension

For a long time hypertension-induced cardiac changes were considered as insufficiently important for cardiovascular or total morbidity and mortality. Left ventricular hypertrophy has been the only valid echocardiographic parameter used in the assessment of these patients [16]. However, technical development encouraged implementation of more sophisticated echocardiographic parameters in hypertensive patients [59]. Two decades ago tissue Doppler-derived parameters were used in evaluation of cardiac function and deformation [59]. However, in the last decade the appearance of speckle tracking imaging has significantly changed our perspective regarding myocardial mechanics assessment.

Echocardiography still remains the best, most common and first-line method for cardiac assessment in hypertensive population. This was confirmed in the latest guidelines [25,59], which for the first time recommended the usage of LV strain for evaluation of LV remodeling in the hypertensive patients. This might be especially significant in patients with different etiologies of LV hypertrophy.

The updated DALLAS criteria of LV geometry for the first time included LV dilatation that provided completely new patterns – dilated and non-dilated concentric LV patterns, as well as dilated and non-dilated eccentric LV patterns [19,20], and showed that the patients with dilated concentric LV hypertrophy have the highest cardiovascular morbidity and mortality comparing with other LV patterns. However, this new classification revealed that the patients with dilated patterns (concentric or eccentric) had higher mortality than their non-dilated counterparts.

Our findings revealed that multidirectional 2D and 3D LV strain gradually reduced from the hypertensive patients with normal geometry, throughout the participants with concentric remodeling, eccentric non-dilated and dilated LV hypertrophy, to the hypertensive individuals with non-dilated and dilated concentric LV hypertrophy patterns [53]. On the other hand, LV twist and torsion were elevated

in the hypertensive patients with concentric and dilated LV hypertrophy. Interestingly, the right ventricular and left atrial function and strain gradually deteriorated in the same direction [60,61]. These findings agree with previous reports in the similar population. However, earlier studies did not use the updated DALLAS criteria for LV geometry and therefore these investigations could only show that the hypertensive patients with concentric LV hypertrophy have the worst LV multidirectional strain [62,63].

Our results demonstrated increased LV twist and torsion in hypertensive individuals with concentric and dilated LV hypertrophy. This is probably a compensatory mechanism that enables maintenance of cardiac systolic function which became impaired, which is confirmed by reduced multidirectional strain in the patients with dilated and concentric-dilated LV hypertrophy.

4.2 The interaction between obesity, biohumoral systems and left ventricular mechanics in hypertensive patients

The interaction between obesity, hypertension and LV mechanics has been investigated in our recent investigation [64]. The findings revealed that LV mechanics in overweight and obese hypertensive patients is even more deteriorated than in patients with isolated hypertension [64].

Furthermore, our results demonstrated that blood pressure and blood pressure variability gradually increased from normal-weight, across overweight to obese hypertensive patients. A possible clinical implication of this result is that reduction in weight might reduce blood pressure, as well as blood pressure variability in overweight and obese hypertensive individuals. Other authors also reported the synergic negative influence of various cardiovascular risk factors such as age, body weight, blood pressure and cholesterol on LV mechanics [65]. The association between deteriorated LV strain and increased body weight in untreated hypertensive individuals in our investigation could be also related with somewhat increase LV mass index and relative wall thickness in these groups. However, gradual and statistically significant impairment from lean subjects, across overweight individuals to obese hypertensive patients was noticed only for 2D LV longitudinal and 3D LV area strain. Nevertheless, 2D and 3D circumferential and radial strains

were not significantly different between normal weight and overweight hypertensive participants.

The association between blood pressure variability and LV strain in obese hypertensive individuals could be explained by elevated sympathetic drive, humoral and inflammation factors, reduced cardiopulmonary reflex, evidently decreased physical activity, and sleeping disorders such as obstructive sleep apnea syndrome in obese patients with arterial hypertension [66].

The influence of elevated activity of biohumoral systems, and especially autonomic sympathetic nervous system, on cardiac remodeling has always been an interesting topic for investigation. There are several invasive techniques that could evaluate the sympathetic nervous system such as direct measurements of muscle sympathetic nerve activity. However, these techniques are not useful for everyday clinical practice. The assessment of 24-h blood pressure variability and blood pressure patterns, as well as 24-h heart rate variability could serve as good surrogates for autonomic function evaluation. Investigations previously showed that non-dipping and reverse dipping blood pressure patterns, which are characterized by increased nighttime blood pressure, were associated with increased sympathetic nervous system activity and deteriorated left and right ventricular structure and function [67]. Studies also showed that renin-angiotensin activity is also increased in these subjects [68]. Our recent study revealed that nighttime hypertension was associated with significant reduction in LV multidirectional strain [69]. The deterioration of LV mechanics developed from normotensive individuals throughout subjects with isolated daytime and nighttime hypertension to day-nighttime hypertensive patients [69]. This could partly explain higher cardiovascular and total morbidity and mortality in patients with nighttime hypertension [70,71].

The sympathetic nervous system drive could also partly explain the negative influence of some 24-h blood pressure patterns such as white-coat hypertension and masked hypertension on LV function and mechanics. Our recent investigations showed that both blood pressure patterns negatively influence LV mechanics by decreasing multidirectional LV strain [54,55].

Usage of conventional echocardiographic parameters showed that parameters of LV hypertrophy gradually increased, while the parameters of LV diastolic function gradually deteriorated from the normotensive subjects, across the white-coat and masked hypertensive patients, to the sustained hypertensive patients [54,55]. The same was valid for 2D and 3D LV longitudinal and circumferential strains, but not for radial strain. Interestingly, LV twist gradually increased in the same direction. What is more important, our studies showed that endocardial and mid-myocardial longitudinal and circumferential strains are more affected by white-coat and masked hypertension than other layers [54,55]. All functional and mechanical changes were more pronounced in the subjects with masked hypertension than in the white-coat hypertensive patients [54,55].

4.3 The impact of white-coat and masked hypertension on left ventricular strain

Cardiac remodeling in the patients with white-coat and masked hypertension might be explained by two large groups of mechanisms. The first group includes biohumoral mechanisms: increased activation of the sympathetic autonomic nervous and renin-angiotensin-aldosterone system, and their interactions. The hyper-activation of these systems induces the elevation of peripheral resistance and consequently afterload increase. Oxidative stress and endothelial damage are present in both, white-coat and masked hypertension, and could contribute to decreased vascular relaxation and further cardiac remodeling. Stimulation of both biohumoral systems provokes the production of interstitial collagen and myocardial fibrosis that could induce cardiac hypertrophy and myocardial functional changes. The second group of reasons is more mechanical. Namely, patients with white-coat and particularly with masked hypertension have significantly higher preload and afterload, which consequently worsens LV function and mechanics.

The clinical importance of these findings is considerable because most of the individuals with white-coat and masked hypertension are untreated for arterial hypertension. Our studies showed that the current guidelines regarding treatment of white-coat hypertension should possibly be reconsidered by introducing antihypertensive therapy in the patients with white-coat hypertension with other

cardiovascular risk factors (diabetes, obesity, hyperlipidemia, etc.). The problem with the lack of antihypertensive treatment in the patients with masked hypertension is even more important because these patients remain undiagnosed for a long time, which is why they could develop severe target organ damage (ischemic heart disease, stroke, renal failure, LV hypertrophy). This is the reason why 24-h blood pressure monitoring should be used more often in everyday clinical practice in patients with prehypertension, metabolic syndrome or in those patients whose symptoms could be related with increased blood pressure, but with normal values in ambulant conditions.

4.4 Association between functional capacity and right ventricular remodeling in arterial hypertension

Arterial hypertension is related not only to LV remodeling, but also to right ventricular changes. Our recent investigation showed that right ventricular (RV) and right atrial (RA) longitudinal strain were significantly reduced in hypertensive patients [56]. In this study we included normotensive controls, untreated, well-controlled, and uncontrolled hypertensive patients and showed that RV and RA longitudinal strain was significantly reduced in the untreated and the uncontrolled hypertensive participants. Furthermore, 3D RV volumes were increased, while 3D RV ejection fraction was reduced in the uncontrolled hypertensive subjects [56]. 3D RV volumes differences disappeared after adjustment for body size. Global RV strain ($\beta = 0.29$, $p = 0.018$) and 3D RV stroke volume ($\beta = 0.22$, $p = 0.041$) were independently associated with functional capacity - peak oxygen uptake (VO2) in the whole study population [56]. Another important finding is that VO2 was significantly reduced in the untreated and poorly controlled hypertensive individuals comparing with the normotensive controls and well-controlled hypertensive patients.

Similar findings regarding reduced RV longitudinal strain were published earlier [38]. However, we went one step further by showing the relationship between arterial hypertension and decreased functional capacity in hypertensive population. This association could be explained in several possible ways [72]. Pulmonary circulation is changed in the patients with arterial hypertension due to

vascular overreactivity caused by catecholamines-induced vasoconstriction [73]. These findings could be associated with changes in the number and quality of adrenergic receptors in pulmonary circulation [74]. Oxidative stress and endothelial damage caused by oxidative stress stimulates vasoconstriction, which could also contribute to impaired pulmonary circulation in patients with arterial hypertension and ultimately to reduced functional capacity in these patients.

4.5 Metabolic syndrome and right ventricular mechanics

Besides arterial hypertension, other cardiovascular risk factors are also associated with RV remodeling. The metabolic syndrome represents a cluster of these risk factors: arterial hypertension, abdominal obesity, insulin resistance, and dyslipidemia. Our investigation showed that RV global longitudinal strain was significantly impacted by metabolic syndrome (-24 ± 5 vs -27 ± 5%; $p < 0.001$) [57]. Interestingly, 3D RV ejection fraction was significantly reduced in the individuals with metabolic syndrome (55 ± 4 vs. 58 ± 4%; $p < 0.001$). The multivariate regression analysis that included all criteria of the metabolic syndrome demonstrated that systolic blood pressure, waist circumference and fasting glucose level were independently associated with RV and RA longitudinal strain [57].

The association between RV remodeling and arterial hypertension was already commented. However, other parameters of metabolic syndrome should be further discussed.

The relationship between obesity and RV mechanics could be partly explained by increased preload, elevated afterload, biohumoral and hormonal effects, as well as direct obesity-related myocardial effects [40,75]. The association between insulin resistance and RV remodeling in metabolic syndrome might be related with aggregation of advanced glycation end products in myocardial interstitium with subsequent damage in Ca^{2+} handling in cardiomyocytes and finally with cardiac dysfunction [76]. The impact of dyslipidemia on cardiac remodeling and particularly on RV structure and function is not easy to understand and explain. Our findings showed that HDL cholesterol level was associated with RV longitudinal strain. Interestingly, the level of triglycerides did not correlate with RV thickness, diastolic function or longitudinal strain [57]. Dalen et al. reported a significant

correlation between HDL cholesterol and RV function assessed by tissue Doppler in women, but not in men in a large sample of participants free from cardiovascular diseases or rick factors [65].

The number of subjects with metabolic syndrome is constantly increasing due to the obesity epidemic. However, a majority of subjects with metabolic syndrome still remain unrecognized and more importantly untreated until they develop severe target organ damage. The metabolic syndrome represents preventable and modifiable condition that deserves our attention and rapid action. The present study showed the significance of lifestyle changes, particularly weight loss, regulation of blood pressure, insulin resistance and dyslipidemia.

4.6 Diabetes and right ventricular mechanics in hypertensive individuals

Diabetes is an important cardiovascular risk factor responsible for RV remodeling. Our study showed not only that diabetes impacts RV longitudinal strain, but also that its influence is layer-specific [58]. We demonstrated that RV global longitudinal endcardial, mid-myocardial and epicardial strains were decreased in the normotensive and hypertensive diabetic patients comparing with the normotensive and normoglycemic controls. However, when RV free wall was analyzed separately, we obtained that multilayer strain was decreased in the hypertensive diabetic participants, but with no statistically significant difference between the healthy controls and the normotensive diabetic patients [58]. From the clinical point of view, possibly the most important finding of this study discovers that parameters of diabetes control (fasting glucose and HbA1c) correlated with 2D RV global longitudinal strain, which emphasizes the importance of tight glucoregulation in diabetic patients with other cardiovascular risk factors such as arterial hypertension. This study also emphasized the importance of a new strategy in cardiac imaging in patients with cardiovascular risk factors and particularly the usage of strain in evaluation of cardiac remodeling during the first visit and also during the follow-up.

9. Conclusion

Echocardiography is the first-line imaging technique that has been used for a long time in the assessment of hypertensive heart disease. However, development of new techniques within echocardiography demands reconsideration of the present approach to the patients with different cardiovascular risk factors such as arterial hypertension, diabetes, dyslipidemia and metabolic syndrome. Speckle tracking imaging enables the detection of subtle and subclinical damage of myocardial function and mechanics.

In conclusion, our studies have shown that arterial hypertension, diabetes and metabolic syndrome are associated with significant cardiac remodeling that involves both ventricles. Furthermore, it has been demonstrated that unfavorable 24-hour blood pressure patterns and left ventricular geometry patterns were associated with myocardial impairment in hypertensive population. It has been showed that white coat and masked hypertension were associated with left ventricular mechanical damage.

Another important finding was the layer-specific impact of arterial hypertension and diabetes on left ventricular deformation. Our results showed that endocardial and mid-myocardial left ventricular layers were more affected by these cardiovascular risk factors than the epicardial layer, which suggests that heart remodeling in hypertensive heart disease develops in the endocardial-epicardial direction, as it was previously shown in the animal model with the invasive techniques.

As it was indicated in the latest guidelines for the management of arterial hypertension, the assessment of left ventricular strain should become a routine parameter in every echocardiographic report in the patients with different cardiovascular risk factors such as arterial hypertension. However, the assessment of right ventricular strain should also be considered as the part of more comprehensive echocardiographic examination in hypertensive patients.

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Erklärung

§ 4 Abs. 3 (k) der HabOMed der Charité

Hiermit erkläre ich, dass

- weder früher noch gleichzeitig ein Habilitationsverfahren durchgeführt oder angemeldet wurde,

- die vorgelegte Habilitationsschrift ohne fremde Hilfe verfasst, die beschriebenen Ergebnisse selbst gewonnen sowie die verwendeten Hilfsmittel, die Zusammenarbeit mit anderen Wissenschaftlern/Wissenschaftlerinnen und mit technischen Hilfskräften sowie die verwendete Literatur vollständig in der Habilitationsschrift angegeben wurden,

- mir die geltende Habilitationsordnung bekannt ist.

Ich erkläre ferner, dass mir die Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis bekannt ist und ich mich zur Einhaltung dieser Satzung verpflichte.

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Datum Unterschrift