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PhD THESIS

UTILITY OF GLOBAL LONGITUDINAL STRAIN FOR MEASUREMENT OF SYSTOLIC FUNCTION AND VENTRICULO-ARTERIAL COUPLING IN SYSTEMIC HYPERTENSION

A B S T R A C T

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GENERAL PART

Hypertension is one of the traditional risk factors, being an important contributor to cardiovascular morbidity and mortality worldwide (1). It is estimated that by 2025, the number of hypertensives will increase to 1.5 billion (2). In Romania, arterial hypertension has a prevalence of more than 34.0%.

In systemic hypertension, diastolic dysfunction occurs before impairment of LVEF, although systolic dysfunction with normal ejection fraction might be present, a condition classified as heart failure with preserved ejection fraction (HFpEF) (3).

Despite their widespread use in current diagnostic guidelines of heart failure (4), conventional echocardiographic markers of left ventricular function have significant disadvantages. HFpEF became the dominant presentation and with an incidence of 11-23% (5, 6), systemic hypertension is the main cause of HfpEF, requiring a reliable assessment tool of LV function. A more refined method to detect subclinical LV systolic dysfunction is represented by two-dimensional speckle tracking echocardiography, which measures global and regional longitudinal strain in 17 segments of the LV. GLS has been shown to distinguish the different degrees of subclinical LV dysfunction, constantly improving the risk stratification of patients with heart failure (7).

Ventricular-arterial coupling (VAC), defined by the interaction between the left ventricle (LV) and the arterial system, is now recognized as a key determinant of overall cardiovascular performance (8). In hypertensive patients myocardial and arterial stiffness increase in parallel. Arterial PWV measurement is a reproducible and simple method of determining arterial stiffness (9). For the determination of VAC, the PWV/GLS ratio has been recently proposed, because it seems to correlate better with subclinical target organ damage (10).

In this context, we considered the opportunity to identify subclinical left ventricular systolic dysfunction by determining GLS in hypertensive patients with and without HFpEF secondary to coronary artery disease versus control. GLS and segmental regional strain values were significantly reduced in patients with HFpEF vs HTN patients vs control age-matched healthy subjects.

In a second study we evaluated the potential of the PWV/GLS ratio to detect altered ventricular-arterial coupling in hypertensive patients *vs* age-matched control. The results demonstrated the benefit of these measurements in clinical practice. The

performance of GLS in predicting HFpEF in hypertensive patients was very good. Also, the PWV/GLS ratio showed good discrimination ability to predict altered VA coupling.

The novelty of the two studies resided in extending the pathophysiological concept of ventricular and vascular rigidity to comprehensive, non-invasive and easy to apply measurements in hypertensive patients.

The perspectives of the future use of GLS and PWV/GLS could include monitoring of earlier development of multiple organ damage and efficacy of different hypertensive medications. Extensive prospective studies are needed to confirm this hypothesis.

SPECIAL PART

A new approach to the arterial stiffness-subclinical systolic dysfunction-hypertension relationship is warranted by evidence-based medicine.
This research aims to provide answers to the following questions:

- Does GLS measurement in hypertensive patients with or without HFpEF secondary to coronary artery disease identify subclinical left ventricular systolic dysfunction?
- Can GLS be used in predicting HFpEF in hypertensive patients?
- Can the PWV/GLS ratio become a reliable tool in detecting altered ventricular-arterial coupling in hypertensive patients?

Types of study: cross-sectional.
Populations studied are represented by:

- Patients with hypertension staged based on definitions of hypertension grade from the 2018 ESC/ESH Guidelines for the management of arterial hypertension (11);
- Patients with hypertension and coronary artery disease in stable condition diagnosed based on angiocoronarographic criteria;
- Healthy subjects defined according to the World Health Organization criteria (12).

This research design started from following assumptions:

a) Hypertension is a chronic disease with a constantly increasing global prevalence, being reported by the registries of 2 large studies dedicated to HF as a dominant risk factor for HFpEF, with an incidence of 11-23% (5, 6).

b) Recently, the evidence from the studies (13-15) demonstrated a higher sensitivity of GLS than LVEF measurement to detect early impairment of left ventricular systolic function and also to provide additional prognostic information. The technology is validated, widely available and reproducible within an acceptable range (16, 17).

c) GLS has been shown to detect and distinguish different degrees of subclinical LV dysfunction, consistently improving risk stratification in heart failure patients (7).

Overall Objectives:

1. To provide evidence to support the integration of GLS into routine clinical practice in hypertensive patients and to confirm that such approaches will improve therapy selection for these patients and, consequently, outcomes.
2. To maximize clinical assessment of hypertensive patients by incorporating available data from GLS (ventricular parameter) and PWV (arterial stiffness parameter) to as an integral part of a comprehensive strategy in cardiovascular prevention.

Specific objectives include:

1. To analyze GLS contribution in detecting subclinical left ventricular systolic dysfunction in hypertensive patients.
2. To evaluate the potential of the PWV/GLS ratio to detect altered ventricular-arterial coupling in hypertensive patients.

The first part of personal research: **"Contribution of global and regional longitudinal strain for clinical assessment of HFpEF in coronary vs. hypertensive patients"** analyzed if GLS can be integrated to the assessment of HFpEF in hypertensive patients. The aim of this part of research was to identify

subclinical left ventricular dysfunction in hypertensive subjects compared to subjects with confirmed HFpEF secondary to coronary artery disease versus controls. This study was challenging and could be useful in differentiating patients at higher risk of developing HF. Therefore, it was interesting to study this aspect.

Furthermore, this study aimed to demonstrated that GLS may be a suitable target for preventive strategies because it detects systolic dysfunction that occurs before LVEF abnormalities, and also, to support the contribution of GLS to the clinical evaluation of HFpEF in coronary and hypertensive patients and to promote GLS assessment in routine clinical practice in all these patients.

This first study included 3 groups of patients (n=148), as follows: group 1 (HFpEF) enrolled 62 coronary patients with heart failure with preserved LVEF (> 50%) in stable condition, group 2 (HTN) enrolled 46 hypertensive patients, and group 3 (CON) represented the control group consisting of 40 age-matched subjects.

The second part of personal research: **"Ventricular-arterial coupling assessed by PWV/GLS ratio in hypertensive patients",** is based on the fact that during the progression of hypertensive disease, the stiffer the aortic tree, the higher the PWV, while at the same time, subclinical LV dysfunction leads to higher GLS values (less negative) and further decreases the ratio. Therefore, a superior marker of VAC in predicting hypertensive target organ damage and its association with clinical outcomes may become the PWV/GLS ratio, probably because the PWV/GLS ratio incorporates the gold standard methods for assessment of both aortic stiffness and LV function (18, 19). Thus, this study aimed to provide additional evidence for the complex relationship between arterial stiffness, LV remodeling and diastolic dysfunction.

This second part of the study included a total of 135 patients divided into 3 groups: group 1 (HT + CAD) enrolled 54 hypertensive patients with coronary artery disease, group 2 (HT) included 43 hypertensive patients and group 3 (CON) was the control group comprising 38 age-matched subjects.

The third part of personal research: **"Evolution of uncontrolled hypertension in a diabetic patient with multivessel atherosclerotic disease"** analyzes a case chosen for its complexity determined by the association of two pathologies with high cardiovascular risk, hypertension and diabetes, poorly medicated. As consequence, the patient already had associated coronary artery

disease and suffered a stroke. The evolution of this case demonstrates that systematic investigation of all possible sites of atherosclerosis and secondary prevention treatment must have been performed earlier in this case to prevent treatment-resistant renovascular hypertension and renal failure caused by advanced atherosclerosis of the renal arteries.

For the entire research, eligible patients were selected from the databases of the Institute of Cardiovascular Diseases Timisoara and Cardiovascular Prevention and Rehabilitation Clinic. This PhD study took place between 2019-2022.

This study conformed to the Declaration of Helsinki, was approved by the Ethics Committee of the Institute of Cardiovascular Diseases in Timisoara and all patients provided written informed consent.

RESULTS

Study 1

By appling Kruskal-Wallis and One-Way ANOVA tests to analyze echocardiographic data for all patients (n = 148), no statistically significantly differences were found regarding LVEF (%) between the three groups (55.0 ± 5.0% for HFpEF group vs. 56.0 ± 8% for HTN group vs. 56.0 ± 4.0% for CON group, p = 0.262). Values of IVSd (cm) and LVPWd (cm) were not statistically significant when compared with HTN and HFpEF groups. LVEDV (mL) values were significantly lower in the CON group compared with HTN group ($p < 0.001$) and with HFpEF group (p = 0.004) and in the HFpEF group compared with HTN group (p = 0.002). LVESV (mL) values were significantly lower in the CON group compared with HTN group and with HFpEF group ($p < 0.001$). E-mitral wave values were significantly lower in the HTN group compared with CON group (p = 0.029) and with HFpEF group (p = 0.001), and also in the CON group compared with HFpEF group (p = 0.042). Regarding A-mitral wave values, significantly lower values were observed in the CON group vs. HFpEF (p = 0.002) and vs. HTN group ($p < 0.001$) and also when HFpEF and HTN groups (p = 0.007) were compared. In the HTN group, 30 patients had diastolic dysfunction (E/A < 1), while 36 had LVH. In the CON group two patients had diastolic dysfunction, probably due to age.

There were significant differences between GLS (%) values between the 3 groups (One-Way ANOVA test, p <0.001); marked increased values (more negative) were observed in the control group (-20.2±1.4) compared to the HFpEF + CAD group (-17.6±2.3) (Scheffe PostHoc test, p <0.001) and to the HTN group (-18.4±3.0), p = 0.031). By applying the One-Way ANOVA test, it was observed that GLS (%) values decreased (were more positive) as arterial hypertension stages increased (p=0.012).

To analyze the predictive performance of global longitudinal strain for the diagnosis of HFpEF, a ROC curve analysis was performed (table 8, figure 16A and B). We determined the predictive value of GLS in HFpEF + CAD patients from HFpEF+CAD+HTN+CON and also in HFpEF+CAD+HTN with diastolic dysfunction) (n=30) + CON with diastolic dysfunction (n=2) from HFpEF+CAD+HTN+CON. When HFpEF+CAD was analyzed, the performance of GLS in predicting HFpEF was satisfactory. The optimal cutoff of GLS in this case was -19.45%, with sensitivity=79.03%, specificity =46.97%, PPV=58.33%, NPV=70.45%. An optimal cutoff of GLS of -19.35%, with sensitivity=77.42%, specifity=80.00%, PPV=92.31%, NPV=53.33%, an AUC=0.833, p<0.001, and a very good performance of GLS in predicting HFpEF was also obtained when HFpEF+CAD+HTN with diastolic dysfunction (n=30) + CON with diastolic dysfunction (n=2) from HFpEF+CAD+HTN+CON was anayzed.

Study 2

Although there were no significant differences between groups regarding LVEF and left atrial diameter, surface or volume, the evaluation of diastolic dysfunction by pulsed-wave and tissue Doppler showed significant differences between groups. According to mean mitral inflow E/A ratio, stage I diastolic dysfunction was present in 37 patients in the HT group and 14 patients in the HT+CAD group, while stage II diastolic dysfunction was present in 6 patients in the HT group and 40 patients in the HT+CAD group.

The control group presented normal diastolic function. There was a significant difference between both groups and control (p<0.001). The E/e' ratio ranged from 0.6 to 15.9 with means of 8.7±2.1 in the HT+CAD group to 6.5±1.2 in the HT group (p<0.001). GLS values were significantly reduced in HT+CAD (-17.50±7.2) *vs* HT (-17.95±5.3) *vs* control (-20.13±4.6) (p<0.001).

PWV values were higher in HT+CAD (9.90±3.1) and HT (9.70±2.5) *vs* control (7.85±3.2) ($p<0.001$). VA coupling measured by the PWV/GLS ratio showed significantly lower values in HT+CAD and HT *vs* control ($p<0.001$).

Post-hoc analysis of vascular and cardiac parameters comparing the HT+CAD group and the HT group was statistically significant for IMT ($p=0.002$), while GLS ($p=0.521$), PWV ($p=0.850$) and PWV/GLS ratio ($p=0.408$) did not register significant differences. Post-hoc analysis between the HT+CAD group and the CON group showed statistical significance for GLS, IMT, PWV and PWV/GLS ratio ($p<0.001$). Significance threshold was also reached for GLS ($p=0.004$) and for the other parameters ($p<0.001$) when comparing the HT and CON groups.

The ROC curve identified a threshold of -0.054 of the PWV/GLS ratio to discriminate between cardiac pathology (HT+CAD and HT) and healthy controls AUROC = 0.836, 95% CI [0.762; 0.909].

CASE REPORT

The third part of the study, a case report, is focus on the evolution of an uncontrolled hypertension in a diabetic patient with multivessel atherosclerotic disease. So, we present the case of 73-year-old man with a history of arterial hypertension essential grade 3 and coronary artery disease presented to our clinic with insufficiently controlled blood pressure (BP), dyspnea on mild exertion, and fatigue. CAD was previously diagnosed following a prior ST-elevation myocardial infarction for which percutaneous transluminal coronary angioplasty with Multi Link 2.5/18 mm stenting of the left anterior descending artery (LAD) was performed in 2014. Prior to this condition, she suffered a right sylvian stroke in 2010 and is known to have type 2 diabetes since 2001. The patient also had multiple cardiovascular risk factors in addition to age, sex, hypertension and diabetes, being a smoker active for 25 years (600 packages/year) diagnosed with chronic obstructive pulmonary disease (COPD) and atherogenic dyslipidemia.

During hospitalization in our clinic the patient underwent a Ambulatory Blood Pressure Monitoring (ABPM) that was showing a non-dipper profile with mild nocturnal hypertension (mean nocturnal BP=133/77 mmHg compared to the upper limit of normal 120/70 mmHg). The ankle-brachial index (ABI) test on the right side was 0.9 and on the left side was 1.2 (normal values between 0.9-1.3). The carotid Doppler ultrasonography showed a left common carotid artery (LCCA) following a rectilinear path and intima media-thickness (IMT) = 1.1 m (normal values < 0.9 mm), while the left internal carotid artery presented a

calcified plaque with 75% stenosis. The right common carotid artery also followed a rectilinear path and IMT=1 mm, without significant plaques or stenosis. Two-dimensional speckle tracking echocardiography that analysed global left ventricular strain revealed a value of - 7.7 %, significantly decreased in the antero-septal segments. A control angio-coronarography was performed and revealed a left main coronary artery without significant lesions, patent stent in the mid-segment of the left anterior descending artery (LAD), 40% proximal stenosis of the I diagonal, 30% stenosis of the intermediate coronary artery, 40-50% ostial stenosis of the left circumflex artery (LCX) and insignificant serial stenosis of the right coronary artery (RCA). On abdominal ultrasound hepatic steatosis and a small left kidney of 66/38 mm were found, while the right kidney had normal dimensions (128/54 mm), without urolithiasis or hydronephrosis. As a next step of investigation, the patient underwent abdominal and peripheral arterial computed tomography angiography that revealed an abdominal aorta with small atherosclerotic plaques and circumferential peripheral calcifications, without dilatation or aneurysmal dissection. Calcareous atheromatosis at the origin of the left renal artery, small cortical cysts and delayed secretion in the left kidney were found. The appearance suggested severe chronic stenosis of the left renal artery.

The positive diagnosis was reformulated to include all vascular territories affected: severe chronic stenosis of the left renal artery with grade 3 secondary reno-vascular hypertension and very high additional risk; bivascular coronary artery disease (LAD, LCX); ectatic ascending aorta; ischemic dilative cardiomyopathy; NYHA II heart failure with moderate ejection fraction (LVEF = 48%); right sylvian artery stroke; left internal carotid artery stenosis; type 2 diabetes mellitus; chronic kidney disease stage G3B A2 KDIGO; chronic obstructive pulmonary disease GOLD 2.

The complexity of this case is nevertheless regarding the association of high cardiovascular risk pathologies, such as hypertension and diabetes mellitus with a poor medication management in a patient who already associated coronary artery disease and suffered a stroke. Perhaps systematic investigation of all possible atherosclerosis sites and secondary prevention treatment should have been conducted earlier in this case in order to prevent treatment-resistant renovascular hypertension and kidney failure. However, the lack of treatment compliance combined with absolutely no lifestyle changes increase the risk for further atherosclerotic complications, which further lead to a higher disability and mortality. Also, kidney failure in a diabetic patient should be investigated more extensively due to the high risk of renal artery stenosis secondary to atherosclerotic plaques.

GENERAL CONCLUSIONS

1. In systemic hypertension adaptive responses include remodelling of the left ventricle, of the endothelium and of vascular smooth muscle cells. Therefore, the study of clinical consequences of these mechanisms expressed by parameters of systolic and diastolic dysfunction, vascular rigidity and ventricular-arterial coupling is expected to bring supplemental data for differentiating patients at higher risk for development of HF.

2. The first study contributed to identify subclinical left ventricular systolic dysfunction by determining GLS in hypertensive patients with and without HFpEF secondary to coronary artery disease versus control. The second study evaluated the potential of the PWV/GLS ratio to detect altered ventricular-arterial coupling in hypertensive patient's *vs* age-matched control.

3. The novelty of the two studies resided in extending the pathophysiological concept of ventricular and vascular rigidity to comprehensive, non-invasive and easy to apply measurements in hypertensive patients. The results demonstrated the benefit of these measurements in clinical practice.

4. GLS and segmental regional (basal, mid, and apical) strain values were significantly reduced in patients with HFpEF vs HTN patients vs control age-matched healthy subjects. The study demonstrated that although LVEF is still widely used in expressing LV function, the addition of GLS allows a more detailed and improved assessment of systolic function, making it a valuable and reliable tool for early detection of subclinical systolic dysfunction in hypertensive patients. We find it necessary to promote GLS evaluation in routine clinical practice in all these patients.

5. The performance of GLS in predicting HFpEF in hypertensive patients was very good. The optimal cutoff of GLS was -19.35 (%), with sensitivity=77.42%, specificity=80.00%, PPV=92.31%, NPV=53.33%, an AUC=0.833, $p<0.001$. Prior to our study, GLS proved to be a powerful diagnostic tool to assess the early systolic dysfunction only in stable coronary heart disease with normal LVEF.

6. In hypertensive patients arterial stiffness increases in parallel with myocardial stiffness. In our study PWV was calculated according to guidelines and GLS was calculated from standard echocardiographic measurements. Our study demonstrated that the PWV/GLS ratio was significantly associated with LV wall thickness in hypertensive patients. The PWV/GLS ratio showed good discrimination ability to

predict altered VA coupling. The ROC curve identified a threshold of -0.054 of the PWV/GLS ratio to detect altered ventricular-arterial coupling AUROC = 0.836, 95% CI [0.762; 0.909].

7. The high prevalence of systemic hypertension in the general population requires thorough investigations to detect subjects at risk to develop target organ damage earlier. Since LVEF is affected only in more advanced stages of the disease, we consider that a pathophysiological approach of these patients should be part of routine clinical practice and include measurements of GLS, PWV and VA coupling expressed by the PWV/GLS ratio. The results of our two studies are proofs of this concept.

8. Non-invasive assessment of left ventricular-arterial coupling continues to remain an underexplored area and should be the focus for future research. Our results proved that PWV/GLS ratio can be used to detect altered VA coupling in hypertensive patients. The perspectives of its future use could include besides monitoring of earlier development of multiple organ damage, also the efficacy of different hypertensive medications. Extensive prospective studies are needed to confirm this hypothesis.

9. In the future, more complex and all the more adequate approaches in systemic hypertension would be represented by a time varying evaluation of LV function and arterial pulse, or wave separation analysis looking at the interaction between early and late ejection, isovolumic relaxation, and time and amplitude of the reflected waves.