European Review for Medical and Pharmacological Sciences 2022; 26: 7024-7035

Ventricular-arterial coupling assessed by PWV/GLS ratio in hypertensive patients

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Abstract. – OBJECTIVE: The physiological interaction between the left ventricle (LV) and the arterial system, defined as ventricular-arterial coupling (VAC), facilitates the optimal volume of cardiac work and cardiovascular performance. The aim of this study was to evaluate the benefit of PWV/GLS ratio associated with other vascular and cardiac performance parameters in hypertensive patients compared to age-matched healthy controls.

PATIENTS AND METHODS: We calculated the ratio of pulse wave velocity (PWV), as a marker of arterial stiffness, to global longitudinal strain (GLS), as a marker of left ventricular function in 135 patients divided in 3 groups, as follows: group 1 (HT + CAD) enrolled 54 hypertensive patients with coronary artery disease, group 2 (HT) enrolled 43 hypertensive patients and group 3 (CON) represented the control group consisting of 38 age-matched healthy subjects.

RESULTS: 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*-value <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*-value <0.001). VA coupling measured by the PWV/GLS ratio showed significantly lower values in HT+CAD and HT *vs.* control (*p*-value <0.001). 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].

CONCLUSIONS: This study demonstrated that assessment of the PWV/GLS ratio represents a useful tool to detect altered ventricular-arterial coupling in hypertensive patients. The perspectives of future use could include monitoring of earlier development of multiple organ damage in hypertensive patients and the efficacy of the different hypertensive medications. Extensive prospective studies are needed to confirm this hypothesis.

Key Words:
Ventricular-arterial coupling, Hypertension, PWV/GLS ratio, Speckle-tracking echocardiography.

Introduction

Hypertension can affect the heart due to pressure overload with subsequent left ventricular (LV) remodeling in terms of LV hypertrophy (LVH) or concentric remodeling, increased LV oxygen requirements, and LV dysfunction. Cardiovascular risk factors and disease (CVD) can affect the heart and the arterial tree and negatively impact their interaction leading to subclinical and clinical overt CVD and adverse outcomes.

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[1]. The concept of ventricular-arterial coupling therefore follows from the logical notion that the arterial system and the heart are inherently connected, being anatomically and functionally linked structures, and refers to the pumping action of the heart when connected to the load opposed by the arterial system[2,3]. Thus, for the functional analysis of the cardiovascular system, the concept of VAC offers many potential benefits, defining the complex behavior of the heart and arterial system as interconnected structures and not as isolated ones, which makes it a valuable method of assessing overall cardiovascular performance that integrates both cardiac and arterial functions[4,5].

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Several invasive and non-invasive methods have been developed to measure VAC. Assessing the interaction of cardiac contractility with the arterial system would help us to understand more comprehensively the cardiovascular energetics and function, not only in cardiovascular diseases, but also in normal physiological states[6,7]. For example, age-related increase in vascular stiffness is a known physiological phenomenon and its consequence is increased arterial blood pressure in the elderly[8]. This vascular stiffness produces a compensatory change in the LV structure at rest, but with a low cardiovascular reserve during exertion, as demonstrated in numerous studies[7,9]. Moreover, these changes are exacerbated even more by comorbidities such as hypertension, kidney disease, rheumatic diseases, atrial fibrillation and diabetes[7,10-15].

Due to hypertension, there are early changes in LV dynamics that cause preclinical LV systolic dysfunction, even before the onset of LV hypertrophy (LVH)[16]. Therefore, an accurate assessment of the influence of hypertension on subclinical LV systolic and diastolic functions is clinically important for the prevention of development of obvious cardiovascular disease. Global longitudinal strain (GLS) has been extensively studied in hypertensive patients and is considered as an early marker of subclinical LV contractile dysfunction in newly diagnosed cases of hypertension and heart failure with preserved ejection fraction (HFpEF). GLS measured by speckle-tracking echocardiography can detect subtle changes in myocardial function that cannot be detected with conventional echocardiography, before the onset of overt LVH.

Due to mechanical coupling with the aorta, LV function has a close relation to aortic stiffness leading to remodeling that follows the concentric pattern in hypertension[17]. Increased arterial stiffness affects cardiac function in both systole and diastole and determines symptoms particularly during exercise, contributing to CV complications[18]. Age related arterial stiffening is inevitable. In addition to this, the aorta can also become rigid due to the influence of cardiovascular risk factors. Central arterial stiffness can be measured by aortic distensibility index, stiffness index, impedance of the proximal aorta, echocardiography (PP/SVi), and MRI, but the most reliable method remains carotid-femoral PWV by applanation tonometry.

Pulse wave velocity (PWV) is defined as the speed at which the pressure wave is produced by the heartbeat[19]. In the last decades, carotid–femoral pulse wave velocity (PWVcf) has been linked to cardiovascular events in hypertensive patients and is recommended as a "gold standard" measure of aortic stiffness. In addition, as an early marker of subclinical contractile dysfunction of LV in hypertensive patients, the global longitudinal strain (GLS) has been proposed by numerous studies[20-22]. During the progression of hypertensive disease, the stiffer the aortic tree, the higher the PWVcf, 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[5,23].

Based on this, and due to the fact, that there are a limited number of studies[10,24-27] that have examined VAC in hypertensive individuals with different conclusions and assessment tools of VAC, the present study evaluated the potential of the PWV/GLS ratio to become a useful tool to detect altered ventricular-arterial coupling in hypertensive patients *vs.* age-matched control.

Patients and Methods

Study Design and Populations

This study included a total of 135 patients recruited from a database of 500 consecutive patients hospitalized during 2019-2021 in the Clinic of Cardiovascular Prevention and Rehabilitation, Institute of Cardiovascular Diseases Timisoara, Romania. The patients were 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. All patients from groups 1 and 2 were in stable condition and maintained the previously prescribed cardiac medications at the same doses. Informed consent was obtained in all cases. The study obtained the approval of the Ethics Committee of the Institute of Cardiovascular Diseases Timisoara (approval certificate 1432/20.02.2019), and respected the principles of the Declaration of Helsinki.

All coronary patients had documented previous diagnostic coronary angiographies and various revascularization procedures (PTCA, coronary by-pass surgery). The exclusion criteria were

the diagnosis of acute heart failure, congenital heart disease, degenerative valve disease, cardiomyopathies with other causes than CAD, pulmonary, pericardial or rheumatic inflammatory diseases, active infections or known neoplasms, anemia, renal or hepatic disease (due to similar or identical disease symptoms).

Patients with hypertension without LV systolic dysfunction were evaluated based on the 2018 ESC/ESH Guidelines for the management of arterial hypertension[28]. Only the patients with preserved LVEF (>50%) were included.

Healthy subjects included in the control group were age-matched to the HT + CAD group and have been previously addressed for cardiovascular screening from primary care. These subjects were free of cardiovascular and/or inflammatory diseases, neoplasms and familial dyslipidemias. Their lipid profile parameters and blood pressure values were within normal limits without specific treatment. Fasting blood glucose was lower than 100 mg/dL.

Clinical Examinations

The clinical examination of the patients included measurement of systolic blood pressure (SBP), diastolic blood pressure (DBP) and body mass index (BMI). Blood pressure (BP) was determined with an usual tensiometer (Riester, Germany) with a suitable cuff for the arm of each subject. The formula for body mass index was: BMI = weight (kg) ÷ height^2 (m^2). For each patient the body weight was determined using a mechanical scale and the height with a metal taliometre (Fazzini, Italy). All patients with diabetes mellitus were diagnosed previously according to criteria of the European Association for the Study of Diabetes (EASD) and of the American Diabetes Association (ADA). The criteria include either fasting plasma glucose values above 126 mg/dL or plasma glucose values above 200 mg/dL 2 h after an oral glucose tolerance test (OGTT)[29]. The diagnosis of chronic kidney disease (CKD) was based on the 2021 Clinical Practice Guidelines for the Evaluation and Management of CKD and on estimated glomerular filtration rate (eGFR) calculated based on the MDRD (Modification of Diet in Renal Disease) formula[30]: eGFR = 186 × (Creatinine/88.4)$^{-1.154}$ × (Age)$^{-0.203}$ × (0.742 if female).

Echocardiographic Parameters and Speckle-Tracking Echocardiography Strain Analysis

In all patients enrolled in the study echocardiography was performed on the GE VIVID E9 ultrasound system (GEMS Ultrasound, Horten, Norway) using a phased-array M5S transducer. The 2D echocardiographic images were obtained from parasternal long-axis and short-axis views, as well as from the three standard apical views. The LV chamber size and wall thickness were measured according to guidelines of the American Society of Echocardiography (ASE, 2005)[31]. Trans-mitral blood flow was recorded in the apical four-chamber view using pulsed-wave Doppler and the rates of the E, of mitral peak velocity of late filling A, the E/A ratio, and the deceleration time (DT) of the E wave were measured. Tissue Doppler was used in the septum and the lateral annulus and e' was measured in order to calculate the E/e' ratio. Speckle-tracking analysis was determined by a dedicated wall motion tracking system from GE Vingmed Ultrasound AS, Horten, Norway using a 17-segment model for the LV. The detected region of interest (ROI) is visually assessed and manually modified, if necessary, for accurate speckle tracking. Normal GLS is considered - 18%[32].

Determination of Carotid Intima-Media Thickness

Carotid intima-media thickness (IMT) was measured with carotid artery ultrasound (7.0-10 MHz, linear array transducer, GE VIVID E9 ultrasound system). Determination of carotid IMT was performed with patients lying on their backs with a slight hyperextension and rotation of the head and neck on the opposite side, by the average of three measurements in each of the three successive segments of both carotid arteries, according to the Mannheim consensus as follows: at the level of the common carotid artery (1 cm proximal to the carotid bulb), at the level of the carotid bulb (the segment between the carotid dilation and flow divider) and at the level of the internal carotid artery (arterial segment 1 cm distal to the carotid bifurcation). The mean IMT of six (three on each side) segments was calculated for each patient to obtain a mean IMT. A carotid IMT value> 0.9 mm was considered abnormal[33].

Aortic Stiffness and Ventricular-Arterial Coupling

The PWV was performed with the Medexpert Arteriograph 3.0.0.3 version (TensioMedKft., Budapest, Hungary). The central pressure, the augmentation index (Aix) and the pulse wave velocity in the aorta (PWVao) were measured after a minimum rest of 10 min in a supine position in a quiet room. Repeated measurements were tak-

Table I. Characteristics of the study population (n=135).

	HT+CAD (n=54)	HT (n=43)	CON (n=38)	*p*-value
Age, years	64.0 (60.0, 70.5)	63.5 (60.8, 66.3)	62.0 (58.0, 64.8)	0.094[a]
Male sex, n (%)	37 (68.5%)	22 (51.1%)	16 (42.1%)	0.209[b]
BMI, kg /m^2	30.1 (27.6, 33.4)	28.2 (26.0, 31.7)	25.3 (23.8, 27.3)	< 0.001[a*]
SBP, mmHg	140.0 (130.0, 153.8)	130.0 (121.2, 150.0)	130.0 (120.0, 132.5)	0.016[a*]
DBP, mmHg	80.0 (71.2, 90.0)	80.0 (70.0, 90.0)	82.0 (70.0, 84.5)	0.360[a]
HR, bpm	70.0 (61.0, 75.0)	70.0 (63.2, 75.8)	71.5 (67.0, 82.5)	0.388[a]
HTN, stage				
0	0	0	38 (100.0%)	< 0.001[*]
1	3 (5.5%)	3 (6.9%)	0	
2	22 (40.7%)	27 (62.8%)	0	
3	29 (53.7%)	13 (30.2%)	0	
T2DM, n (%)	13 (24.1%)	11 (25.6%)	0	0.028[*]
CKD, n (%)	5 (9.26%)	7 (16.2%)	0	0.099

BMI, Body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; HTN, arterial hypertension; T2DM, type 2 diabetes mellitus; CKD, chronic kidney disease. [a] Kruskal-Wallis test; [b] Chi-square test; Chi-square/Fisher exact tests; [*] significance threshold reached.

en. Smoking and caffeine were not permitted 3 h prior to investigation. Alcohol consumption was interrupted at least 10 h prior to the investigation. Patients were not allowed to fall asleep during the measurements, in order to not influence arterial diameter and stiffness. Patients did also not speak.

The index of AV coupling was calculated as the ratio of the arterial stiffness measured with PWV and the myocardial performance estimated with GLS (PWV/GLS ratio) calculated by echocardiography as described above.

Statistical Analysis

Continuous variables are presented as median with interquartile range (IQR), and categorical variables as frequency and percentages. Considering that the results of the normality test (Shapiro-Wilk) showed a non-Gaussian distribution, we used further nonparametric tests for our analysis. Kruskal-Wallis's test was employed for comparing study population's characteristics, and the Mann-Whitney U Test was applied as a post-hoc test. Chi-square or Fisher's exact test were employed to evaluate the significance of differences in the proportions of nominal variables. We employed Spearman's correlation test to assess the potential connection between transthoracic echocardiography parameters. Receiver Operating Characteristic (ROC) curve was used to illustrate the identification ability, and the thresholds to discriminate between cardiac pathology (HT, CAD) and healthy controls. It was determined with Youden's index. A p-value of < 0.05 was considered to indicate a statistically significant difference. Data analysis was performed using R: A Language and Environment for Statistical Computing (R Core Team, Vienna, Austria).

Results

Patient Population and Characteristics

Patients with HT+CAD had a higher BMI compared to the other groups (p-value <0.001). No differences between groups were observed regarding age and gender (p-value=0.094, respectively p-value=0.209). Although no statistically significant differences were observed between groups in terms of diastolic blood pressure (p-value=0.768) and heart rate (p-value=0.388) values, systolic blood pressure registered significant differences (p-value =0.016). When we compared the groups based on arterial hypertension staging, we observed a statistically significant difference (p-value <0.001) between them. Also 24.1% patients (n=13) from the HT+CAD group had type 2 diabetes mellitus, compared with 25.6% (n=11) from HT group (p-value=0.028). No statistically significant difference was observed between HT+CAD *vs.* HT groups regarding chronic kidney disease (p-value=0.099) (Table I).

The comparison of prevalent use of medications in the 3 groups (n=135) is reported in Table II. In the HT+CAD group 68.51% (n=37) used ACEi or ARBs compared with 74.41 % (n=32) in the HT group and 0% in the CON group (p-value =0.042), 75.92% (n=41) used beta-blockers compared with 41.86% (n=18) in the HT group and with 0% in the CON group (p-value <0.001); and 31.48% (n=17) used calcium channel blockers compared with 20.93 % (n=9) in the HT group and 0% in the CON group

Table II. Comparison of prevalent use of medications in the 3 groups (n= 135).

Variables	HT+ CAD (n=54)	HT (n=43)	CON (n=38)	*p*-value
Medications				
ACEi or ARB	37 (68.51%)	32 (74.41%)	0 (0.0%)	0.042*
Beta-Blocker	41 (75.92%)	18 (41.86%)	0 (0.0 %)	<0.001*
Aspirin	46 (85.18%)	24 (55.81%)	0 (0.0%)	<0.001*
Antiplatelet Agent	40 (74.07%)	19 (44.18%)	0 (0.0%)	<0.001*
Statin	50 (92.59%)	36 (83.72%)	0 (0.0%)	<0.001*
Calcium Channel Blocker	17 (31.48%)	9 (20.93%)	0 (0.0%)	0.002*
Oral antidiabetic agents (metformin, sitagliptin)	12 (22.22%)	11 (25.58%)	0 (0.0%)	<0.001*

ACEi or ARB, angiotensin converting enzyme inhibitors or angiotensin receptor blockers. Values were expressed as mean± standard deviation (SD). [test] – used statistical Test; Kruskal-Wallis test; *significance threshold reached

(*p*-value= 0.002). Statistically significant differences were found between the 3 groups regarding the use of aspirin (*p*-value< 0.001), antiplatelet agents (*p*-value <0.001) and statin (*p*-value < 0.001). Also, 22.22% (n=12) in the HT+CAD group and 25.58% (n=11) in the HT group used oral antidiabetic agents (metformin, sitagliptin) (*p*-value< 0.001).

Echocardiographic Parameters, Vascular Rigidity and Ventricular-Arterial Coupling

Relevant echocardiographic parameters and comparisons between groups are represented in Table III. Both systolic and diastolic diameters and volumes of the left ventricle were significantly increased in the HT+CAD group compared to the HT group (*p*-value <0.001). 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,

Table III. Echocardiographic and vascular parameters in the study population (n=135).

	HT+CAD (n=54)	HT (n=43)	CON (n=38)	*p*-value
Echocardiography				
LA diam, cm	4.05 (3.88, 4.30)	3.92 (3.70, 4.18)	3.92 (3.8, 4.0)	0.101
IVS, cm	1.10 (1.00, 1.20)	1.12 (1.05, 1.20)	0.95 (0.90, 1.00)	<0.001*
LVEDD, cm	4.65 (4.40, 5.00)	4.65 (4.22, 4.90)	4.50 (4.30, 4.60)	0.141
PW, cm	1.10 (1.00, 1.16)	1.10 (1.00, 1.20)	1.00 (0.90, 1.00)	<0.001*
LVEDV, ml	103.50 (90.50, 120.75)	90.0 (84.00, 98.75)	86.0 (81.0, 88.5)	<0.001*
LVESV, ml	40.0 (35.00, 43.75)	39.0 (36.00, 42.0)	32.0 (31.75, 34.0)	<0.001*
LVEF, %	55.0 (50.0, 55.0)	55.0 (50.00, 60.0)	55.0 (55.0, 55.0)	0.336
LA surface cm²	24.0 (20.25, 28.0)	24.0 (22.0, 24.5)	22.0 (18.0, 26.0)	0.276
LAV, ml	38.5 (32.25, 42.0)	37.0 (34.00, 40.75)	36.0 (34.0, 38.0)	0.429
E m/sec	0.82 (0.71, 0.90)	0.6 (0.50, 0.84)	0.78 (0.72, 0.81)	0.002*
A m/sec	0.60 (0.50, 0.70)	0.7 (0.60, 0.82)	0.52 (0.46, 0.57)	<0.001*
E/A ratio	1.36 (1.20, 1.60)	0.82 (0.71, 1.23)	1.50 (1.35, 1.59)	<0.001*
E/e' ratio	8.7 (3.8, 15.9)	6.5 (5.1, 8.1)	5.7 (0.6, 7.0)	<0.001*
GLS, %	-17.50 **(-19.17, -16.62)**	-17.95 **(-20.62, -16.05)**	-20.13 **(-21.15, -19.48)**	<0.001*
Carotid intima-media thickness				
IMT mm	1.00 (0.90, 1.20)	0.90 (0.80, 1.10)	0.60 (0.50, 0.70)	<0.001*
Aortic stiffness – VA coupling				
PWV m/sec	9.90 (9.20, 10.50)	9.70 (9.22, 10.20)	7.85 (7.40, 8.20)	<0.001*
PWV/GLS ratio	-0.67±0.22	-0.52±0.17	-0.43±0.12	<0.001*

LA, left atrium; IVS, interventricular septum; LVEDD, left ventricular end diastolic diameter, PW, posterior wall; LVEDV, left ventricular end diastolic volume; LVESV, left ventricular end sistolic volume; LVESD, left ventricular end systolic diameter; LVEF, left ventricular ejection fraction; LAV, left atrium volume, E, early diastolic mitral inflow velocity; A, mitral peak velocity of late filling e', early diastolic mitral annulus velocity; GLS, global longitudinal strain; IMT, intima-media thickness; PWV, pulse wave velocity. Kruskal-Wallis test; * significance threshold reached

Table IV. Post-hoc analysis between groups with *p*-values (Mann-Whitney U Test).

Variables	GLS, %	IMT, MM	PWV, M/SEC	PWV/GLS, RATIO
HT+CAD *vs.* HT	0.521	0.002*	0.850	0.408
HT+CAD *vs.* CON	<0.001*	<0.001*	<0.001*	<0.001*
HT *vs.* CON	0.004*	<0.001*	<0.001*	<0.001*

* significance threshold reached.

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*-value <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*-value <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*-value<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*-value<0.001). VA coupling measured by the PWV/GLS ratio showed significantly lower values in HT+CAD and HT *vs.* control (*p*-value<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*-value=0.002), while GLS (*p*-value=0.521), PWV (*p*-value=0.850) and PWV/GLS ratio (*p*-value=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*-value<0.001). Significance threshold was also reached for GLS (*p*-value =0.004) and for the other parameters (*p*-value<0.001) when comparing the HT and CON groups (Table IV).

The boxplots inside the violin graphs in Figure 1 represent the median and the interquartile range for IMT, PWV, GLS and PWV/GLS distribution

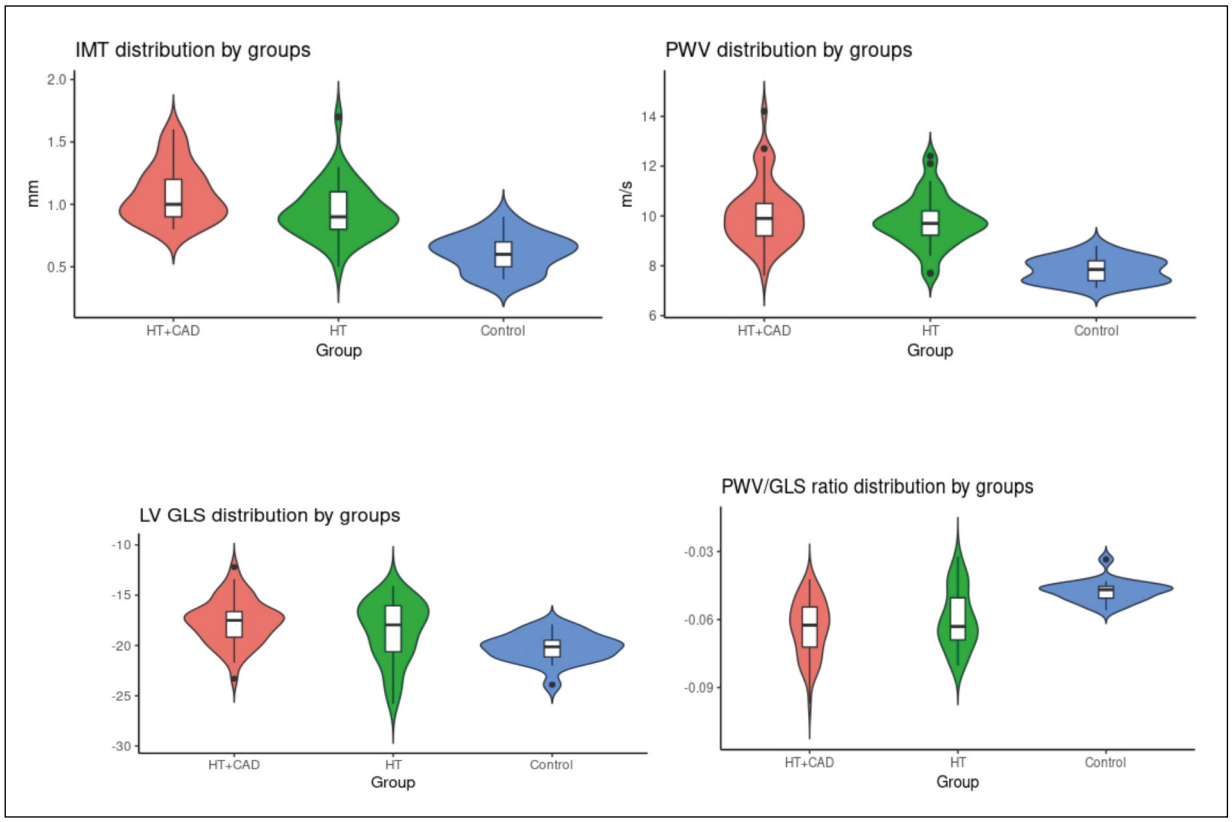

Figure 1. Boxplots for IMT, PWV, GLS and PWV/GLS distribution by groups (median and interquartile range).

Table V. Comparison of echocardiographic and vascular parameters between genders from all groups (n=135).

Variables	Feminine (n=60)	Masculine (n=75)	*p*-value
LA diameter, cm	3.9 (3.7, 4.0)	4.0 (3.8, 4.1)	0.046*
IVS, cm	1.0 (0.9, 1.2)	1.0 (1.0, 1.2)	0.398
LVEDD, cm	4.5 (4.2, 4.8)	4.7 (4.4, 5.0)	0.008*
PW, cm	1.0 (1.0, 1.1)	1.1 (1.0, 1.2)	0.185
LVEDV, ml	90.0 (80.0, 104.5)	90.0 (86.0, 104.2)	0.652
LVESV, ml	37.0 (32.0, 41.5)	38.0 (34.0, 42.0)	0.343
LVEF, %	55.0 (55.0, 55.0)	55.0 (50.0, 60.0)	0.997
LA surface, cm²	22.5 (19.2, 25.8)	23.5 (20.0, 26.0)	0.677
LAV, ml	36.0 (33.2, 42.0)	37.0 (34.0, 40.0)	0.967
E, m/sec	0.7 (0.6, 0.8)	0.8 (0.6, 0.9)	0.049*
A, m/sec	0.6 (0.5, 0.7)	0.6 (0.5, 0.7)	0.603
E/A ratio	1.3 (0.8, 1.4)	1.3 (0.9, 1.6)	0.192
E/e, ratio	7.9 (4.4-13.9)	8.3 (3.9-16.0)	0.180
GLS, %	-19.6 (-20.8, -17.1)	-17.9 (-19.3, -16.6)	0.005*
IMT, mm	0.9 (0.8, 1.1)	0.9 (0.8, 1.2)	0.405
PWV, m/sec	9.6 (8.4, 10.4)	9.4 (8.8, 10.2)	0.616
PWV/GLS ratio	-0.1 (-0.1, -0.0)	-0.1 (-0.1, -0.1)	0.009*

LA, left atrium; IVS, interventricular septum; LVEDD, left ventricular end diastolic diameter, PW, posterior wall; LVEDV, left ventricular end diastolic volume; LVESV, left ventricular end sistolic volume; LVESD, left ventricular end systolic diameter; LVEF, left ventricular ejection fraction; LAV, left atrium volume, E, early diastolic mitral inflow velocity; A, mitral peak velocity of late filling e', early diastolic mitral annulus velocity; GLS, global longitudinal strain; IMT, intima-media thickness; PWV, pulse wave velocity. Kruskal-Wallis test; *significance threshold reached

by groups (Figure 1). The *p*-values in Table III apply.

The comparison of echocardiographic and vascular parameters between genders (feminine, n=60 and masculine, n=75) from all groups revealed statistically significant differences regarding LA diameter (*p*-value=0.046), LVEDD (*p*-value=0.008), E (*p*-value=0.049), GLS (*p*-value=0.005), and PWV/GLs ratio (*p*-value=0.009) (Table V).

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] (Figure 2 and Table VI).

Correlation plots between PWV/GLS ratio and parameters of LV geometry PW and IVS are demonstrated in Figure 3. The PWV/GLS ratio had significant correlations with posterior wall thickness (r=-0.797, 95% CI [-0.851; -0.725], *p*-value<0.001), interventricular septum thickness (r=-0.643, 95% CI [-0.732; -0.531], *p*-value<0.001) and LVESV (r=-0.350, 95% CI [-0.489; -0.192], *p*-value<0.001).

Discussion

Hypertension has a very high prevalence in the general population, being a major cardiovascular risk factor, which can lead to coronary heart disease and death. Early detection of subtle changes in cardiac performance could contribute substantially to stopping or delaying irreversible damage to heart and vascular structures. The critical role of ventricular-arterial coupling in the physiology of cardiac and aortic mechanics and in the pathophysiology of cardiac disease has long been recognized. We evaluated the ventricular-arterial coupling (VAC) as the ratio of pulse wave velocity (PWV) to global longitudinal strain (GLS) in 135 patients divided in 3 groups: group 1 (HT + CAD), including 54 hypertensive patients with coronary artery disease; group 2 (HT), including 43 hypertensive patients; and group 3 (CON) as control group, consisting of 38 age-matched normal subjects.

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*-value <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*-value<0.001). VA coupling measured by the PWV/GLS ratio showed significantly lower values in HT+CAD and HT *vs.* control (*p*-value<0.001).

Diastolic dysfunction of the left ventricle is a common pathophysiologic consequence of hypertension that appears even before LV hypertrophy and can be detected in early stages[34]. Together with LV diastolic dysfunction, myocardial

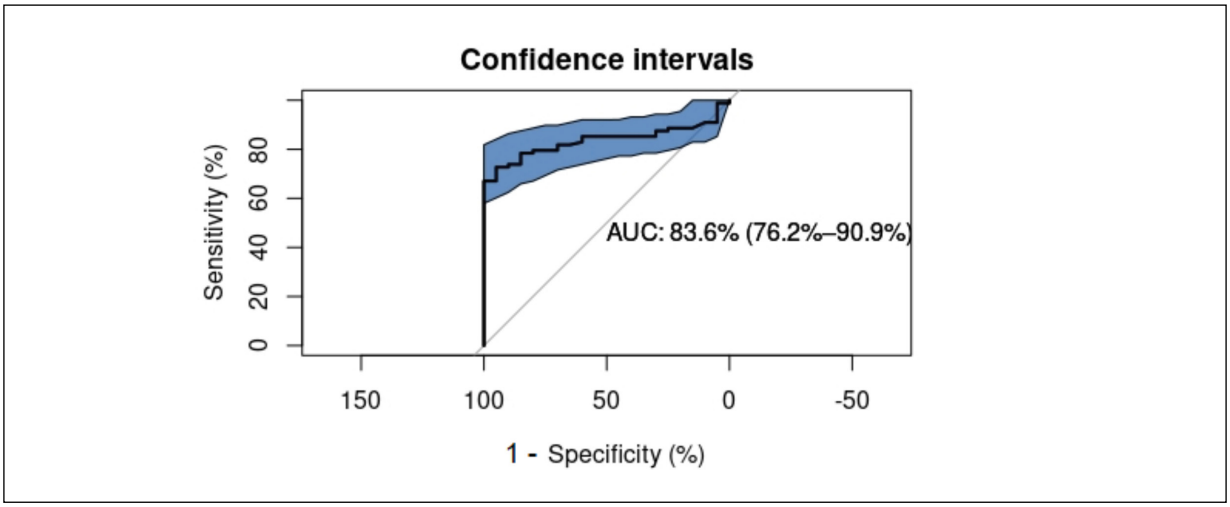

Figure 2. ROC curve for predictive performance of PWV/GLS ratio to detect altered ventricular-arterial coupling.

ischemia can also be present in hypertensive patients, determining especially the stage I delayed relaxation pattern[35]. In our study, we did expect to find a higher E/e' ratio in the HT+CAD group compared to the HT group. The E/e' ratio means were 8.7±2.1 in the HT+CAD group compared to 6.5±1.2 in the HT group (p-value<0.001). There is conflicting evidence about the clinical relevance of this ratio as marker of diastolic dysfunction. Previtali et al[36] consider that the suboptimal sensitivity and specificity of the E/e' ratio for predicting increased LV diastolic pressure in their study is suggestive of the fact that it is of limited clinical value in patients without heart failure. However, in our study, the difference between HT+CAD and HT regarding this marker of diastolic dysfunction was significant.

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[37]. Post-hoc analysis of vascular and cardiac parameters comparing the HT+CAD group *vs.* the HT group was statistically significant only for IMT (p-value=0.002), while GLS (p-value=0.521), PWV (p-value=0.850) and PWV/GLS ratio (p-value=0.408) did not register significant differences. This may be due to the limited number of patients included in the study and to the fact that systolic function was preserved in all cases, even when CAD was present. Also, the role of different medications and the duration of hypertension and diabetes may explain these results. Microvascular disease present in hypertensives without confirmed CAD may also contribute. However, the PWV/GLS ratio was significantly correlated with posterior wall thickness (r=-0.797, 95% CI [-0.851; -0.725], p-value<0.001), and interventricular septum thickness (r=-0.643, 95% CI [-0.732; -0.531], p-value<0.001), as well as LVESV (r=-0.350, 95% CI [-0.489; -0.192], p-value <0.001), suggesting that vascular and myocardial stiffness are present in hypertensive patients even in the absence of CAD. The common denominators for both PWV and GLS impairment in hypertension are represented by endothelial dysfunction, renin-angiotensin system activation, abnormal collagen turnover, increased metalloproteinase activity and fibrosis, which are all linked from pathophysio-

Table VI. Predictive performance of PWV/GLS ratio to detect altered ventricular-arterial coupling.

Variables	Estimate	95% CI lower limit	95% CI upper limit
Cutoff	**-0.054**	-	-
Se	0.72	0.62	0.81
Sp	0.95	0.75	0.99
PPV	0.98	0.91	0.99
NPV	0.44	0.32	0.97

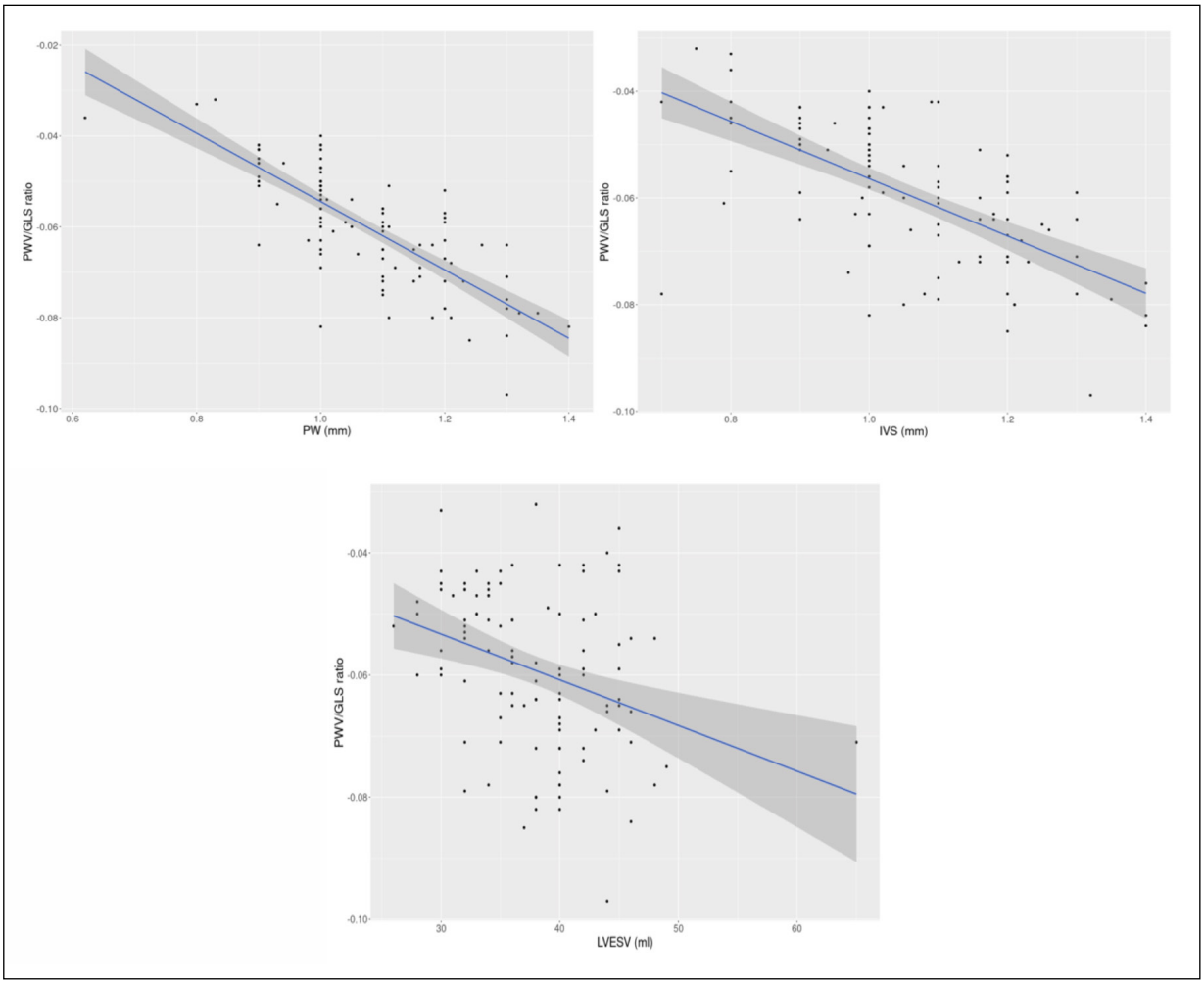

Figure 3. Correlation plots showing the associations of PWV/GLS ratio with indices of LV geometry. Each dot indicates an individual patient's data. Linear regression line (blue line) and 95% confidence interval (shaded area) are depicted. PW, posterior wall, IVS, interventricular septum, LVESV, left ventricular end-systolic volume.

logical point of view. These mechanisms explain the correlation of PWV/GLS ratio with parameters of LV geometry and with markers of vascular damage like carotid IMT. Our results are similar to the findings of Ikonomidis et al[27], done on 299 newly-diagnosed untreated hypertensive cases, where PWVcf, IMT, GLS, coronary-flow reserve and arterial elastance/left ventricular elastance (E A/E LV) index were measured and correlated with markers of left ventricular diastolic function (E/A and E'). PWV/GLS ratio was lower in hypertensives than controls (p-value< 0.001). Similar to our findings, low PWV/GLS values were associated with carotid-intima media thickness > 0.9 mm (p-value=0.003), after adjustment for age, sex and mean arterial pressure. Low PWV/GLS was also associated with increased left ventricular mass and left atrial volume in the univariate model (p-value=0.003 and 0.038). No significant association of E A/E LV index with carotid IMT, coronary flow reserve, E/A, E', or left atrial volume was found, and the authors conclude that PWV/GLS ratio provides a better measurement for ventricular-arterial coupling than the E A/E LV index.

Our study demonstrated that the PWV/GLS ratio had significant associations with LV wall thickness in hypertensive patients. The PWV/GLS ratio showed fair 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]. The results of our study provide additional evidence for the complex relationship between arterial stiffness, LV remod-

eling and diastolic dysfunction. As confirmed in the study of Ikonomidis et al[27], early detection of subclinical disease progression in newly onset hypertension using PWV/GLS may be possible. They observed a significant association with target organ damage in hypertensive subjects. The PWV/GLS ratio has also been shown to correlate better with subclinical target organ damage than the traditional echocardiographic method (Ea/Ees) in the study of Saeed et al[5]. Hypertensives with IMT>0.9 mm were compared with patients with IMT<0.9 mm, demonstrating lower PWV/GLS values (-0.69±25 *vs*.-0.58±19, *p*-value <0.001) in their study.

A consensus document for the importance of assessment of VA coupling and its implications in heart disease was issued by the European Society of Cardiology Working Group on Aorta & Peripheral Vascular Diseases, European Association of Cardiovascular Imaging, and Heart Failure Association[38]. All lumped measurements, such as the most popular one represented by the elastance ratio (E A/E LV), and the total arterial compliance (SV/PP) are considered an oversimplification to estimate the VA coupling. In the future, more adequate approaches 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.

Limitations

Our study is not without limitations. This has been a retrospective cross-sectional analysis. More insight could be obtained in the future by prospective longitudinal studies in order to better explain the complex relationship between ventricular-arterial coupling and diastolic dysfunction in hypertensive and coronary patients. This would allow a thorough evaluation of patients at risk for faster progression of atherosclerotic disease.

Conclusions

Non-invasive assessment of left ventricular-arterial coupling is currently an underexplored area and should be the focus of future research. This study showed that PWV/GLS ratio can be used to detect the altered ventricular arterial coupling in hypertensive patients. The perspectives of its future use could include monitoring of earlier development of multiple organ damage in hypertensive patients and of the efficacy of different hypertensive medications. Extensive prospective studies are needed to confirm this hypothesis. Also, further studies are needed to evaluate whether alterations in ventricular-arterial coupling can provide any prognostic information for adverse outcomes, including that for HF.

Conflicts of Interest

The authors declare that they have no conflict of interest.

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

Institutional Review Board Statement

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of Institute of Cardiovascular Diseases Timisoara, Romania approval certificate 1432/20.02.2019).

Author Contributions

Conceptualization, G.S.-H.; R.C. and S.D.; methodology, G.S.-H. and N.F.B.; software, G.N.P. and A.T.; validation, N.R.K., R.C. and S.D.; investigation, G.S.-H.; P.B.; D.D. and A.E.; resources, G.S.-H.; R.C. and S.D.; data curation, G.N.P. and A.T.; writing–original draft preparation, G.S.-H., N.F.B., P.B. and A.E.; writing–review and editing, N.R.K., R.C.; and S.D.; visualization, N.F.B. and N.R.K.; supervision, S.D.; project administration, G.S.-H.; R.C. and S.D. All authors have read and agreed to the published version of the manuscript.

Funding

None.

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