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ORIGINAL PAPER

Left atrial, ventricular and atrio-ventricular strain in patients with subclinical heart dysfunction

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Abstract
Arterial hypertension (AH) and diabetes mellitus (DM) are the most common causes of heart deterioration because of their high prevalence in the population. The aim of this study was to evaluate peak left atrial (LA), longitudinal strain (PALS), left ventricular (LV), longitudinal strain (LS) and global atrial-ventricular strain (GAVS), by speckle-tracking echocardiography (STE), in asymptomatic patients with AH or/and DM and normal LA, LV size and ejection fraction (EF), to analyze their capability to detect early subclinical dysfunction. We enrolled 162 patients affected by AH and/or DM with normal indexed LA volume, LV end-diastolic diameter and a LVEF > 52% (females) or > 54% (males) (60 hypertensives, 52 diabetics and 50 both) and 60 healthy controls. All subjects underwent standard and advanced STE. PALS, LS and GAVS were measured. GAVS was calculated as the algebraic sum of absolute PALS and LS values in four- and two-chambers views. LS, although with lower values in hypertensives, diabetics and both, did not show significant differences between groups. PALS and GAVS were significantly reduced in AH (31.9 ± 10.3% and 49.7 ± 11.2%, respectively) and DM (26.2 ± 7.1% and 42.6 ± 9.8%) compared to controls, and even more if the two coexisted (20.4 ± 6.5% and 37.1 ± 8.4%). PALS had the highest statistical significance and was able to identify subclinical damage independently from LS value. PALS was reduced in patients with AH and/or DM without alteration of standard echo indexes. The value of PALS was independent from LS and was sufficient to identify heart dysfunction in an earlier stage.

Keywords Speckle tracking · Left heart function · Arterial hypertension · Diabetes mellitus

Introduction

Arterial hypertension (AH) and type 2 diabetes mellitus (DM) currently have huge social and economic impact on national health care services with a prevalence of about 30 to 45% [1] and 8% [2] in the general population, respectively. They have widely been associated to both left ventricular (LV) and left atrial (LA) impairment. To control and possibly treat a functional deterioration of the heart, an early identification of cardiac dysfunction could be useful, when the damage is still subclinical and reversible. In this phase, alterations of standard echocardiographic indexes are usually not visible. Hypertensive heart disease includes several ventricular alterations, from LV remodeling, with typical concentric hypertrophy and diastolic alterations, to systolic dysfunction, arrhythmogenic potential and heart failure (HF) [3, 4]. During the progression of DM, important changes in the myocardial interstitium lead to higher LV mass and concentric geometry that might cause cardiovascular events and definitely have an impact on short and long term prognosis, also in asymptomatic subjects [5–7]. AH and DM influence LA size [8–11] and, mostly, LA function. LA microstructural alterations precede macroscopic ones: in fact, an atrium with normal area and volume could have already lost its compliance and contractility [12]. Speckle tracking echocardiography (STE) has emerged as a valuable tool for the assessment of myocardial function [13]. It allows a direct analysis of myocardial deformation and is independent from in-plane translation movements and insonification angle,

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overcoming most of the limitations of Doppler-derived strain analysis. STE has been applied firstly to left ventricle and successively to the other cardiac chambers, including left atrium, with high reproducibility and feasibility [14, 15]. In recent years, numerous papers have described the STE-derived parameters LV global longitudinal strain (GLS) and peak atrial longitudinal strain (PALS) in patients with AH [16–19] and DM [20–23]. However, this evaluation has always been performed analyzing separately LA and LV alterations. Nevertheless, these two chambers represent a single functional unit and the impairments caused by different systemic pathologies, like AH and DM, advance by damaging both simultaneously. The aim of this study was to assess, in addition to LA and LV strain, a new STE-derived parameter, called global atrial-ventricular strain (GAVS), that inspected for the first time the deformation and the atrio-ventricular coupling of the left heart in asymptomatic patients with AH and/or DM, normal LA and LV size and preserved ejection fraction (EF).

Materials and methods

Study population

For this study, we enrolled asymptomatic patients with AH and/or type 2 DM, accessing our echocardiographic laboratory between January 2012 and December 2016. To be included in the protocol, the subjects needed to have: normal LA volume, defined as maximum LA volume indexed to body surface area < 34 mL/m^2; absent LV dilation, that is LV end diastolic diameter < 58 mm (male) or < 52 mm (female); preserved LV systolic function [EF ≥ 52% (female), ≥ 54% (male)]. Moreover, the patients had not to show symptoms of suspected cardiac origin. AH was defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg on three or more occasions or as antihypertensive treatment in the presence of a documented history of AH, according to the latest guidelines of European Society of Hypertension and European Society of Cardiology [1]. DM was instead diagnosed in accordance with the World Health Organization (WHO) definition as a fasting glucose ≥ 126 mg/dL or the use of hypoglycemic medications in subjects with documented history of diabetes [24]. Exclusion criteria included: malignant hypertension; uncontrolled DM (glycosylated hemoglobin ≥ 7.0%) [25], manifest coronary artery disease (that is at least one between: history of effort angina, acute coronary syndromes, or revascularization procedures, evidence of positive exercise stress test, segmental wall abnormalities at echocardiography); mitral regurgitation of higher degree than mild; aortic regurgitation; any degree of valve stenosis; previous valve surgery; history of atrial fibrillation, atrial flutter, or other major arrhythmias; hypertrophic cardiomyopathy; left bundle branch block; pacemaker implantation; heart transplantation; severe renal failure (calculated creatinine clearance < 30 mL/min); chronic obstructive pulmonary disease; abnormal thyroid function; other significant systemic chronic disease; inadequate acoustic windows; and refusal to participate in the study. During enrollment, 180 patients met the selection criteria: 65 subjects had AH but not DM, 58 presented DM but a normal blood pressure, and 57 had both DM and AH. These patients were compared to a control group, composed of 60 age-matched healthy individuals with no history of any cardiovascular or systemic disease, normal findings on clinical examination, electrocardiography, and echocardiography who visited our laboratory during the same period. Control population consulted the laboratory mainly because of preoperative assessment of risk before minor non-cardiac surgery (n = 21), preparticipation sports examination for noncompetitive physical activities (n = 16), palpitations without significant abnormalities on Holter ECG recording (n = 8). Age-matching was performed using a 1:4 scheme and to within ± 5 years. Procedure was performed by obtaining randomly arranged subsets of four non-control patients, calculating mean age in each subset, and then matching one control subject to this age by considering the age criterion. Thus, 60 age-matched healthy subjects entered the control group. All subjects signed an informed consent for inclusion in the study. All procedures were conducted in accordance with the Declaration of Helsinki.

Standard Echocardiography

Patients were studied using a high-quality echocardiographic machine (Vivid E9; GE Medical Systems, Milwaukee, WI) equipped with a 1.5-MHz and 3.6-MHz transducer. The standard LV diameters were measured in long-axis parasternal view. LV and LA volumes were calculated from apical four-chambers and two-chambers views using the biplane modified Simpson's rule, according to the current American Society of Echocardiography recommendations [26]. Maximum, pre-atrial systole, and minimal LA volumes were measured just before mitral valve opening, at the beginning of the P wave, and at mitral valve closure, respectively. LV mass was calculated from 2D images by the Truncated ellipsoid technique [26]. LV relative wall thickness (RWT) was obtained by the formula (2 × posterior wall thickness)/(LV internal diameter at end diastole). LV diastolic phase was assessed using pulsed Doppler (PW), placing the sample volume at leaflets' tips level. E wave occurs immediately after mitral valve opening and represents diastolic rapid filling. LV long-axis function was assessed by pulsed tissue Doppler from apical four-chambers view, placing the sample volume at the junction between LV wall and septal and lateral mitral annulus [27]. Successively, peak systolic (s′),

early diastolic (e′), and late diastolic (a′) annular velocities were obtained by averaging values recorded at the septal and lateral positions. The E/e′ ratio was used as an index of LV filling pressures [28].

Speckle tracking echocardiography

For STE analysis, echocardiographic images were acquired in apical four- and two-chambers, in conventional two-dimensional grayscale, during breath hold and with a stable ECG recording. All images were carefully recorded optimizing the visualization of both LA and LV cavities, avoiding foreshortening of the left atrium and including endocardial LA and LV border and LV apex in all cardiac cycles. Frame rate was set between 60 and 80 frames/s. Three consecutive heart cycles were recorded and averaged. STE analyses were performed offline, using the latest commercially available software (EchoPAC; GE Medical Systems). For LV strain quantification, the region of interest (ROI) was manually defined by tracing the endocardial border by a point-and-click approach. The automatic tracking of the endocardial contour was carefully verified, and the ROI was manually corrected to ensure an optimal tracking of the entire myocardium. LV images were divided into six segments both in two- and in four-chambers views (12 total segments). Longitudinal strain (LS) represents the myocardial deformation along the base-apex plan: during systole, LV myocardial fibers shorten from the base to the apex with a reduction of the distance between the speckles, determining a negative curve. GLS value was obtained by averaging the 12 (6 + 6) segments' deformation curves [13]. Then, in the same cardiac cycles, LA endocardial border was again manually traced at end-systole in both apical views. An epicardial surface tracing was automatically generated by the software, delineating a ROI of six segments per view (12 total segments). Then, the ROI was again manually adjusted to include the thickness of LA myocardium, and an automated segmental tracking quality analysis was obtained. A longitudinal curve was generated for each atrial segment. Left atrium fills and stretches during its reservoir phase so the atrial strain increases up to a positive peak at the end of atrial filling, before the opening of mitral valve [15]. Peak atrial longitudinal strain (PALS) was measured at the end of reservoir phase. Global PALS was then obtained by averaging all the single LA strain segments' values. GAVS was calculated as the sum of absolute values of PALS and LV LS in four- and two-chambers views (Fig. 1). The segments in which an adequate tracking quality could not be obtained despite ROI manual adjustments, were excluded from the analysis. Whether the patient had an inadequate tracking quality in more than three LA or LV segments, it was excluded from the study.

Data collection and reproducibility

Strain analyses were performed by four experienced and independent investigators who were blinded to clinical and other echocardiographic characteristics of patients. All indexes were obtained by averaging the measurements from three consecutive cardiac cycles. To assess the reproducibility of LV GLS, patients were randomly selected and Bland–Altman analysis [29] was performed to evaluate the intra- and inter-observer agreements by repeating the analysis 1 week later by the same observer and a second independent observer. On the contrary, our center has a great experience in LA strain and high reproducibility and feasibility have already been reported [15].

Statistical analysis

All data are expressed as means ± SD (for continuous variables) or as numbers and percentages (for binary variables). Comparisons of continuous variables were performed using analysis of variance (ANOVA), with

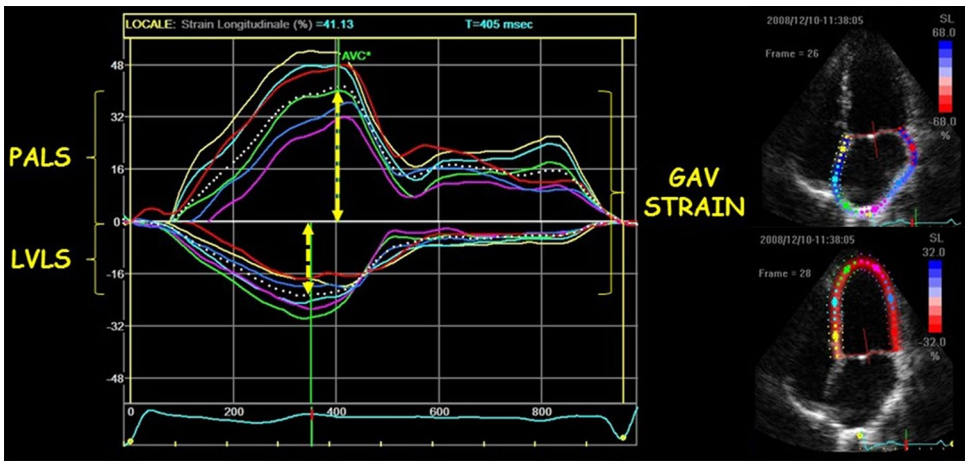

Fig. 1 Measurement of global atrio-ventricular (GAV) strain: it is composed by the algebraic sum of peak atrial longitudinal strain (PALS) and left ventricular longitudinal strain (LV LS), evaluated in the same cardiac cycle

Scheffé post hoc test being used to determine comparisons between two individual variables. Categorical variables were compared using Chi-squared test, with or without continuity correction depending on the circumstances. Linear regression analysis was used to find multivariate correlations of the three measures (PALS, GLS, GAVS) with DM and AH. Three models were tested for each of the three measures: the first model only included DM and AH as covariates. The second model introduced age, gender and body mass index as confounding covariates. The third model included even more confounding covariates: heart rate, systolic blood pressure, EF, indexed LV mass, RWT, E/A, e′, E/e′, LA area, maximum indexed LA volume, end-diastolic LV diameter, end-diastolic LV volume and end-systolic LV volume. Independence of PALS and GLS was determined using the Pearson correlation test: first without corrections, then with age, gender and BMI taken as confounders, and finally with the same variables as in linear regression's third model, plus DM and AH added as further confounders. The significance level was set at 0.05 for all analyses. GraphPad Prism 6 (GraphPad La Jolla CA, USA) and RStudio (RStudio Boston MA, USA) were used to perform all the analyses.

Results

General characteristic of the study population

During off-line strain analysis, in the overall study population, 18 subjects (seven controls and eleven patients) were excluded due to the impossibility of obtaining an adequate tracking quality in more than three LA or LV segments. Among a total of 5328 segments analyzed in the remaining 222 subjects (60 controls, 60 patients with AH but not DM, 52 diabetic patients and 50 patients with both DM and AH) a strain curve was obtained in 5019 segments (94.2%) with an average postprocessing time of 4.1 ± 0.7 min. Table 1 shows clinical characteristics of the study population and Table 2 shows standard echocardiographic findings. As expected, no difference was found in LA antero-posterior diameter, area and volume and in LV dimensions and function while body mass index, blood pressure values, LV mass and geometry and diastolic function were statistically significant between the groups.

Strain indexes

It was found that GAVS had an accuracy comparable with PALS, although it was not superior. Mean PALS values

Table 1 Clinical characteristics of the study population (n = 222)

	Controls (N = 60)	Hypertension (N = 60)	Diabetes (N = 52)	Both (N = 50)	p
Age (years)	59.8 ± 9.1	61.3 ± 10.7	59.3 ± 14.9	62.5 ± 9.9	0.44
Women	39 (65.0%)	31 (51.7%)	22 (42.3%)	22 (44.0%)	0.064
BSA (m^2)	1.7 ± 0.2	1.8 ± 0.2	1.8 ± 0.2	1.9 ± 0.2*	0.012
BMI (kg/m^2)	25.0 ± 4.9	26.2 ± 2.8	26.8 ± 5.3	28.1 ± 5.2	0.0047
Smoker	14 (23.3%)	12 (20.0%)	12 (23.1%)	14 (28.0%)	0.81
Former smoker	11 (18.3%)	16 (26.7%)	14 (26.9%)	13 (26.0%)	0.66
Heart rate (bpm)	73.7 ± 10.9	72.3 ± 9.7	70.7 ± 9.1	75.0 ± 12.0	0.18
Syst BP (mmHg)	125.5 ± 13.3	138.7 ± 16.8*	130.7 ± 15.0	142.4 ± 16.2*	< 0.0001
Diast BP (mmHg)	80.3 ± 9.0	84.1 ± 8.9	79.0 ± 8.5†	84.4 ± 9.6	0.0026
Hyperchol	21 (35.0%)	33 (55.0%)*	26 (50.0%)	36 (72.0%)*	0.0016
Hypertrigl	–	8 (13.3%)	6 (11.5%)	9 (18.0%)	0.63
Medications					
ACE inibitors	–	47 (78.3%)	–	38 (76.0%)	0.95
B-blockers	–	17 (28.3%)	–	8 (16.0%)	0.19
CCB	–	11 (18.3%)	–	15 (30.0%)	0.23
Statin	7 (11.7%)	11 (18.3%)	16 (30.8%)*	23 (46.0%)*	0.0002
OAD	–	–	27 (51.9%)	40 (80.0%)	0.0055
Insulin	–	–	18 (34.6%)	14 (28.0%)	0.61

Data are expressed as mean ± SD (continuous) or as numbers and percentages (binary)

BMI body mass index; *BP* blood pressure; *BSA* body surface area; *CCB* calcium channel blockers; *OAD* oral antidiabetic therapy

*p < 0.5 versus "controls" group

Table 2 Conventional echocardiographic characteristics of the study population (n = 222)

	Controls (N = 60)	Hypertension (N = 60)	Diabetes (N = 52)	Both (N = 50)	p
LA diameter (mm)	32.6 ± 5.0	33.9 ± 4.5	33.5 ± 5.4	34.9 ± 4.5	0.15
LA Area (cm^2)	15.6 ± 1.8	16.1 ± 2.5	16.2 ± 2.3	16.4 ± 2.2	0.16
LA volumes					
Indexed maximum (mL/m^2)	22.5 ± 3.3	23.4 ± 3.4	23.2 ± 3.8	24.0 ± 3.7	0.13
Indexed precontraction (mL/m^2)	12.0 ± 3.3	13.4 ± 4.0	12.5 ± 4.1	12.7 ± 3.2	0.18
Indexed minimal (mL/m^2)	6.6 ± 2.2	7.3 ± 2.9	7.4 ± 2.9	7.3 ± 2.8	0.37
End-diastolic LV diameter (mm)	44.4 ± 5.3	46.6 ± 3.4	45.9 ± 5.0	46.5 ± 4.0	0.034
End-systolic LV diameter (mm)	27.1 ± 5.6	28.2 ± 3.9	28.8 ± 5.1	29.6 ± 5.1	0.053
Indexed end-diastolic LV volume (mL)	45.0 ± 10.8	47.4 ± 10.7	47.2 ± 9.8	47.4 ± 11.8	0.54
Indexed end-systolic LV volume (mL)	17.3 ± 5.1	19.0 ± 5.6	18.7 ± 4.0	19.0 ± 5.6	0.24
RWT	0.42 ± 0.06	0.45 ± 0.07	0.43 ± 0.08	0.46 ± 0.06*	0.0026
Indexed LV mass (g/m^2)	80.4 ± 18.8	101.9 ± 15.7*	88.4 ± 16.7†	102.7 ± 20.6*	< 0.0001
EF (%)	61.1 ± 3.7	59.9 ± 4.7	59.7 ± 4.0	58.9 ± 3.8*	0.037
Mitral E/A ratio	0.99 ± 0.39	0.85 ± 0.28	0.99 ± 0.32	0.77 ± 0.26*	0.0006
S′	0.10 ± 0.06	0.09 ± 0.02	0.10 ± 0.02	0.09 ± 0.02	0.071
A′	0.11 ± 0.02	0.11 ± 0.02	0.11 ± 0.02	0.12 ± 0.03	0.032
E′	0.10 ± 0.03	0.09 ± 0.03	0.10 ± 0.03	0.09 ± 0.02	0.0019
E/e′	7.3 ± 2.0	7.6 ± 2.5	7.7 ± 2.0	8.6 ± 3.1	0.036
MAPSE	15.7 ± 2.1	15.4 ± 2.1	16.1 ± 2.3	15.4 ± 2.3	0.33

Data are expressed as mean ± SD (continuous) or as numbers and percentages (binary)

EF ejection fraction; *LA* left atrial; *LV* left ventricular; *MAPSE* mitral annular plane systolic excursion; *RWT* relative wall thickness

*p < 0.5 versus "controls" group

†p < 0.5 versus "hypertension" group and "both" group

were 39.2 ± 8.7% in healthy subjects, 31.9 ± 10.3% in hypertensive group, 26.2 ± 7.1% in diabetics and 20.4 ± 6.5% in patients with DM and AH. Also GLS had the lowest values in combined DM + AH group (− 16.5 ± 3.6%), and was − 17.6 ± 3.3% in isolated AH, − 16.7 ± 3.7% in DM and higher (− 17.9 ± 3.7%) in controls even if no statistical significance was found between the groups (Fig. 2). GAVS was lower in patients with AH (49.7 ± 11.2%) and DM (42.6 ± 9.8%) than in the control group (57.5 ± 10.1%), and patients with both DM and AH showed the lowest values (37.1 ± 8.4%), following the same trend (Table 3; Fig. 3).

Table 4 shows the results of the univariate correlation analysis between PALS, GLS, GAVS and main study population characteristics and echocardiographic indexes, DM and AH. Moreover, the regression analysis (Table 4) showed that, for all the three models, PALS was far superior to GLS and slightly superior to GAVS as a predictor of heart subclinical damage in both diabetes and hypertension.

Independence of PALS and GLS was assessed through the Pearson correlation test with various levels of confounders. The more complex model showed that PALS and GLS were essentially uncorrelated (R = − 0.13, p = 0.072 > 0.05). GAVS, on the other hand, was highly correlated with both GLS (R = − 0.49) and especially PALS (R = 0.95), which is

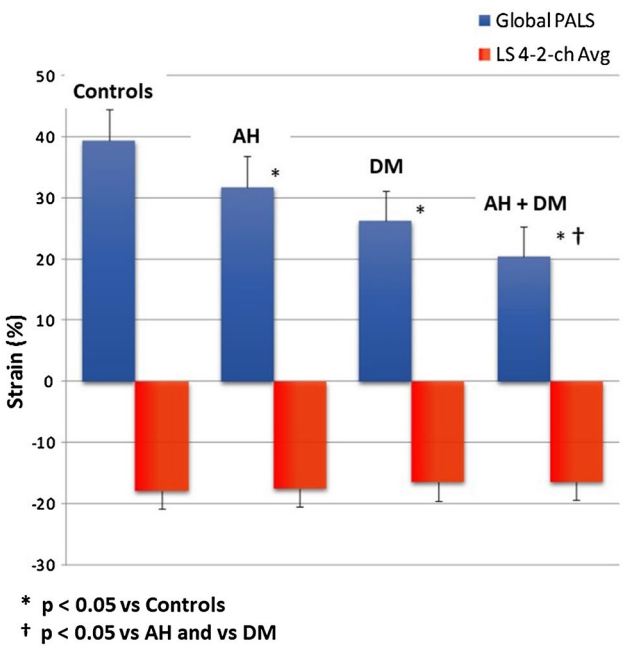

Fig. 2 Global peak atrial longitudinal strain (PALS, blue) and averaged 4- and 2-chambers left ventricular longitudinal strain (LS 4-2-ch Avg, red) values in the four study groups. *AH* arterial hypertension; *DM* diabetes mellitus

Table 3 Strain indexes of the study population (n = 222)

	Controls (N = 60)	Hypertension (N = 60)	Diabetes (N = 52)	Both (N = 50)	p
PALS (%)	39.2 ± 8.7	31.9 ± 10.3	26.2 ± 7.1	20.4 ± 6.5	< 0.0001
GLS (%)	− 17.9 ± 3.7	− 17.6 ± 3.3	− 16.7 ± 3.7	− 16.5 ± 3.6	Ns
GAVS (%)	57.5 ± 10.1	49.7 ± 11.2	42.6 ± 9.8	37.1 ± 8.4	0.001

Data are expressed as mean ± SD

GAVS global atrioventricular strain; *GLS* global longitudinal strain; *PALS* peak atrial longitudinal strain

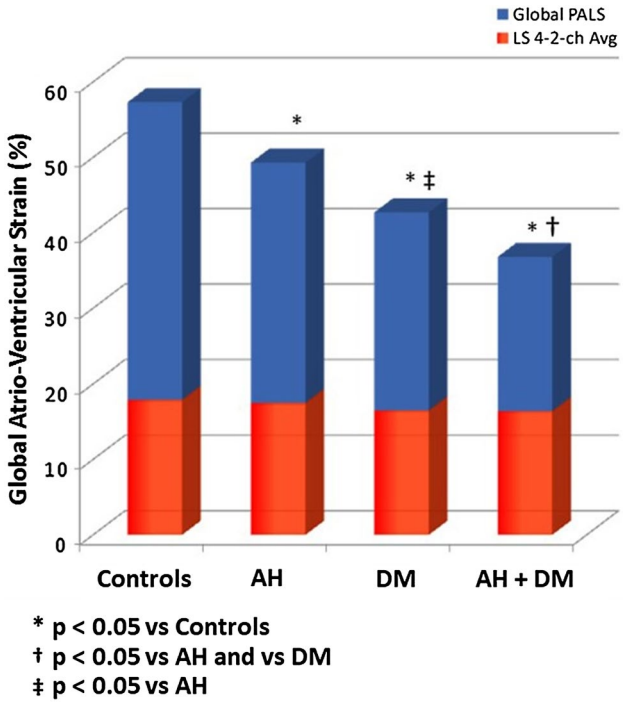

Fig. 3 Global atrio-ventricular strain (GAVS) values in the population study. It can be noticed how GAV strain is composed by global peak atrial longitudinal strain (PALS, blue) and averaged 4- and 2-chambers left ventricular longitudinal strain (LS 4-2-ch Avg, red). *AH* arterial hypertension; *DM* diabetes mellitus

not surprising given that a large fraction of GAVS is composed of the PALS itself (Table 5).

Discussion

Main study findings

Our work focused on the research of subclinical cardiac damage, by the analysis of LA and LV function, singularly and globally, in asymptomatic patients with DM and/or AH with normal chambers' size and EF. It revealed that: (1) both atrial and ventricular longitudinal functions are impaired in these subjects compared to age- and gender-matched healthy controls, confirming the previous literature findings, with higher alterations if the two diseases coexist; (2) new STE-derived parameter, GAVS, evaluates combined function of the two left heart chambers and shows the same trend in the study population; (3) PALS and GAVS are far superior to GLS in the prediction of heart subclinical damage in diabetes and hypertension; (4) PALS is superior to the other two analyzed strain parameters, with high statistical significance and independence from GLS value.

Left chambers function in subclinical heart damage

We decided to study asymptomatic patients with conventional 2D echo parameters within the normal range to detect the best strain tool to identify the potential presence of an early cardiac damage. We focused our attention on those subjects suffering from AH, DM or both, diseases that currently are the commonest responsible of subclinical cardiac dysfunction in the general population. The involvement of the heart can be considered part of the natural pathological course in these patients. An early assessment of the contractile alterations could pave the way to new therapeutic approaches that might slow or change their clinical history, impacting on their quality of life and mortality. Further new studies could be developed, evaluating early behavioral or pharmacologic effects on left heart deformation. The negative effects of AH on left heart deformation have already been widely illustrated. Chronically high blood pressure negatively impacts on normal LV geometry and function, determining typical concentric hypertrophy, increase of LV filling pressure and eventually deterioration of the EF up to HF [3, 30, 31]. Simultaneously, increased LA size [9, 32] and impaired LA function appear as also proved by the analysis of LA dynamic volumes [33], PW transmitral flow pattern [34, 35], TDI and strain rate [36, 37]. In the last years, STE emerged as an accurate tool for the assessment of the damage induced by AH on cardiomyocyte also in an early phase, before alterations of the conventional echocardiographic parameters [16]. In hypertensive cardiomyopathy, subendocardial myocardial fibers are the first to be involved, so GLS shows untimely impairment [17], with a strong correlation with myocardial fibrosis detected by late Gadolinium enhancement (LGE) in cardiac magnetic resonance too [38]. Equally, LA strain reduces, together with

Table 4 Univariate correlations and multivariate linear regression analysis

	p	GLS:R	p	GAVS:R	p
Age	0.0068	0.05	0.48	−0.18	0.0071
Women	0.043	0.14	0.034	−0.18	0.0069
BMI (kg/m^2)	<0.0001	0.22	0.0011	−0.29	<0.0001
Smoker	0.84	−0.12	0.067	0.01	0.85
Heart Rate (bpm)	0.38	0.22	0.0008	−0.11	0.1
Syst. BP (mmHg)	0.0004	0.13	0.062	−0.24	0.0003
Diast. BP (mmHg)	0.36	0.09	0.17	−0.09	0.18
EF (%)	0.0031	0.18	0.0088	0.24	0.0004
Indexed LV mass (g/m^2)	0.0032	0.21	0.0019	−0.24	0.0004
RWT	0.011	0.12	0.075	−0.18	0.0059
E/A	0.0082	−0.10	0.14	0.18	0.0066
S′	0.27	−0.09	0.2	0.10	0.14
A′	0.16	−0.11	0.11	−0.04	0.55
E′	0.06	−0.20	0.031	0.18	0.0075
E/e′	0.057	0.06	0.34	−0.14	0.039
LA diameter (mm)	<0.0001	0.13	0.056	−0.29	<0.0001
LA area (cm^2)	<0.0001	0.13	0.052	−0.33	<0.0001
Indexed LA maximal volume (mL/m^2)	<0.0001	0.14	0.03	−0.36	<0.0001
Indexed LA precontraction volume (mL/m^2)	<0.0001	0.04	0.52	−0.26	<0.0001
Indexed LA minimal volume (mL/m^2)	<0.0001	0.02	0.76	−0.28	<0.0001
End-diastolic LV diameter (mm)	0.11	0.11	0.09	−0.13	0.053
End-systolic LV diameter (mm)	0.14	−0.01	0.94	−0.09	0.19
End-diastolic LV volume (mL)	0.19	0.12	0.069	−0.12	0.067
End-systolic LV volume (mL)	0.1	0.15	0.028	−0.16	0.019
MAPSE	0.47	−0.03	0.65	0.04	0.59
Diabetes	<0.0001	−0.16	0.015	0.55	<0.0001
Hypertension	<0.0001	−0.03	0.59	0.26	<0.0001

	Model 1		Model 2		Model 3	
	β	p	β	p	β	p
PALS						
Diabetes	−1.129	<0.0001	−1.067	<0.0001	−1.116	<0.0001
Hypertension	−0.612	<0.0001	−0.516	<0.0001	−0.510	<0.0001
GLS						
Diabetes	0.328	0.0147	0.214	0.115	0.305	0.028
Hypertension	0.077	0.5639	−0.021	0.878	−0.256	0.084
GAVS						
Diabetes	−1.099	<0.0001	−1.005	<0.0001	−1.079	<0.0001
Hypertension	−0.536	<0.0001	−0.415	0.0002	−0.337	<0.0001

EF ejection fraction; *GAVS* global atrioventricular strain; *GLS* global longitudinal strain; *LA* left atrial; *LV* left ventricular; *PALS* peak atrial longitudinal strain; *RWT* relative wall thickness

Table 5 Correlation and independence

	Model 1		Model 2		Model 3	
	R	p	R	p	R	p
PALS vs. GLS	−0.22	0.0007	−0.16	0.021	−0.13	0.072
GAVS vs. PALS	0.95	<0.0001	0.95	<0.0001	0.93	<0.0001
GAVS vs. GLS	−0.49	<0.0001	−0.44	<0.0001	−0.45	<0.0001

GAVS global atrioventricular strain; *GLS* global longitudinal strain; *PALS* peak atrial longitudinal strain

the worsening of the LV function, before visible increases of area and volume or other structural abnormalities appear [18, 19]. Moreover, the chronically elevated levels of serum glucose in DM patients cause the development of a real cardiomyopathy as a component of systemic involvement, mostly due to interstitial remodeling led by advanced glycation end-products and reactive oxygen species [39]. Minor studies have been conducted on LA function in these subjects by real-time 3D echocardiography [11], where a trend to a decrease of compliance and contractility emerged in addition to chamber dilation [40]. In DM, once again, GLS is the first deteriorating index [21], with a gradual reduction along with the progression of the disease [20] and in conjunction with typical complications [41]. It has been demonstrated how LA strain is reduced in DM patients [23], before shape and size remodeling, impacting on outcomes [42]. A previous clinical investigation developed in our center proved that PALS was lower in patients with DM and AH and normal LA volume, even more if the two pathologies coexist [12]. Moreover, PALS demonstrated the ability to accurately predict LV filling pressure [43, 44] and so it could represent a valuable added value for a complete evaluation of LA in this setting, avoiding simple size assessment, from diagnostic to therapeutic stages. The present study confirmed these points. PALS emerged as a strong index of LA dysfunction with gradually reduced values in DM and AH, comparing to controls emphasizing that a normal LA size is indicative of a preserved deformation. The atrial dysfunction was higher in subjects with both diseases testifying a probable additive negative effect, as beforehand demonstrated. On the contrary, as explained before, DM and AH alter LV longitudinal function, but our findings demonstrated that, in a so early stage of the cardiomyopathy, GLS did not represent the most accurate parameter to detect myocardial damage in these patients. Hereto, we supposed that one of the possible explanation might be attributable to an anatomic matter: LA is structured with a thin, single-layer wall that results to be very sensitive to even minimal untimely stimuli. LA and LV longitudinal strain have never been globally evaluated. We thought that it was not properly correct to consider these chambers as two independent entities, given that they represent a true single morpho-functional unit, beyond an anatomic continuum. Starting from these considerations, we decided to apply strain analysis on LA and LV in the same cardiac cycle and to evaluate LA–LV coupling and deformation by a new index, the GAVS, as the sum of the absolute PALS and GLS values in two- and four-chambers views during the same cardiac cycle indeed. As expected, GAVS resulted to be reduced in diabetic and hypertensive patients and even more in the combined group, keeping a statistical significance, like PALS. Therefore, in the examined diseases, left heart is already affected by a global dysfunction even in asymptomatic patients albeit standard echocardiographic parameters (LA size, LV size and EF) within normal ranges. PALS emerged as the most valuable STE-derived index in this subset of patients. Moreover, it resulted to be independent from GLS alteration, so the message is that LA impairment could appear even earlier than LV one. It is possible to affirm that, to guarantee the best evaluation of subclinical left heart damage in hypertensive and diabetic patients, it is currently sufficient to analyze atrial deformation, not only for a matter of ease and practicality, but also because it is superior to global LA–LV assessment. Our results could pave the way for further fields of GAVS applications in specific primitive and secondary cardiomyopathies, in acute setting and in prognostic field, searching for correlations with major cardiovascular events and outcomes.

Study limitations

Our study focused only on diabetic and/or hypertensive patients, mainly because of their high prevalence worldwide, while subclinical heart dysfunction includes many other conditions. Moreover, considering the extreme diffusion of DM and AH in the general population, the study should have been performed in a biggest sample and taking into consideration female differences due to confounding sex factors too. Currently, a dedicated software for the analysis of LA strain is not available so we used the same software of the left ventricle. Moreover, for PALS assessment, we employed QRS, and not P wave, as reference point given that it represents the most used method. The use of different vendors' software could determine small difference in GAVS values in future studies with consequent bias. However, STE-derived indexes have shown a higher reproducibility than standard echocardiographic parameters between operators [45].

Conclusions

STE confirmed to be an excellent method for the evaluation of early heart organ damage in asymptomatic patients affected by AH and/or DM, with standard echocardiographic parameters within the range values. GAVS, the new global deformation index of left cardiac chambers, showed high sensitivity in differentiating impairment between the study groups. However, PALS was superior to GAVS and GLS in predicting a subclinical loss of longitudinal function in this subset of subjects, independently from GLS value itself.

Compliance with ethical standards

Conflict of interest Authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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