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Association of Subclinical Atherosclerosis Using Carotid Intima-Media Thickness, Carotid Plaque, and Coronary Calcium Score with Left Ventricular Dyssynchrony: The Multi-Ethnic Study of Atherosclerosis

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Abstract

Background—The role of atherosclerosis in the progression of global left ventricular dysfunction and cardiovascular events has been well recognized. Left ventricular (LV) dyssynchrony is a measure of regional myocardial dysfunction. Our objective was to investigate the relationship of subclinical atherosclerosis with mechanical LV dyssynchrony in a population-based asymptomatic multi-ethnic cohort.

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Clinical trials info: MESA; <http://www.mesa-nhlbi.org>

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Methods and Results—Participants of the Multi-Ethnic Study of Atherosclerosis (MESA) at exam 5 were evaluated using 1.5T cardiac magnetic resonance (CMR) imaging, carotid ultrasound (n=2,062) for common carotid artery (CCA) and internal carotid artery (ICA) intima-media thickness (IMT), and cardiac computed tomography (n=2,039) for coronary artery calcium (CAC) assessment (Agatston method). Dyssynchrony indices were defined as the standard deviation of time to peak systolic circumferential strain (SD-TPS) and the difference between maximum and minimum (max-min) time to peak strain using harmonic phase imaging in 12 segments (3-slices × 4 segments). Multivariable regression analyses were performed to assess associations after adjusting for participant demographics, cardiovascular risk factors, LV mass, and ejection fraction. In multivariable analyses, SD-TPS was significantly related to measures of atherosclerosis, including CCA-IMT (8.7msec/mm change in IMT, $p=0.020$), ICA-IMT (19.2 msec/mm change in IMT, $p<0.001$), carotid plaque score (1.2 msec/unit change in score, $p<0.001$), and log transformed CAC+1 (0.66 msec/unit log-CAC+1, $p=0.018$). These findings were consistent with other parameter of LV dyssynchrony i.e. max-min.

Conclusion—In the MESA cohort, measures of atherosclerosis are associated with parameters of subclinical LV dyssynchrony in the absence of clinical coronary event and left-bundle-branch block.

Keywords

Left Ventricular Dyssynchrony; Carotid IMT; Coronary Calcium Score; Atherosclerosis

Introduction

Atherosclerosis is a major cause of cardiovascular morbidity and mortality and one of the primary causes of heart failure.[1] Identification of individuals with subclinical atherosclerosis at risk of cardiovascular events is essential in initiating primary preventive measures so as to delay the onset of global LV systolic and diastolic dysfunction and thereby heart failure.[2] Carotid artery intima-media thickness is an established marker of subclinical arterial injury and is associated with increased risk of cardiovascular events,[3, 4] coronary risk factors,[5] and serves as an atherosclerotic surrogate end-point for therapeutic interventions.[6, 7, 8] Furthermore, presence of carotid plaque either enhances the predictive power of carotid IMT [9] or is itself a better predictor of coronary events than carotid IMT.[10] Similarly, coronary artery calcium (CAC) measured by computed tomography (CT) represents a quantifiable marker of coronary atherosclerosis.[11, 12]

LV dyssynchrony in an asymptomatic population with narrow QRS (<120 msec) has emerged as a marker of regional myocardial dysfunction and is associated with increased risk of an adverse cardiovascular event.[13] Cardiac magnetic resonance (CMR) imaging allows accurate and detailed analyses of regional LV function using myocardial tagging.[14, 15] The Multi-ethnic Study of Atherosclerosis (MESA) offers a unique opportunity to assess the relationship between subclinical atherosclerosis and incipient alterations of regional myocardial function in a large epidemiologic cohort. Therefore, the main aim of this study is to investigate the association between subclinical atherosclerosis—defined by carotid IMTs, carotid plaque score, and CAC—and subclinical LV dyssynchrony independent of myocardial scar in participants with no prior history of a clinical coronary event.

Methods

Study Population

MESA is a prospective cohort study designed to investigate the subclinical characteristics and underlying mechanisms involving cardiovascular disease in asymptomatic individual. [16] A total of 6,814 individuals 45 to 84 years of age from different ethnic backgrounds (White, African-American, Hispanic, and Chinese-American) were enrolled. Individuals with cardiac symptoms or known cardiovascular disease were excluded during initial recruitment. During the longitudinal follow-up of the fifth examination from April 2010 to February 2012, 2,062 participants underwent tagged CMR for regional function and carotid ultrasound; 2,039 participants underwent CMR and cardiac computed tomography (CT) at six clinical sites (Johns Hopkins University, Baltimore, MD; University of Minnesota, Minneapolis, MN; Northwestern University, Chicago, IL; Wake Forest University, Winston Salem, NC; and UCLA, Los Angeles, CA; Columbia University, NY). Individuals with an interim coronary event (n=32) or left bundle-branch-block (LBBB) (n=6) were preemptively excluded from the statistical analyses. Institutional review boards at each participating site approved study protocol, and informed consent was obtained from each participant.

CMR studies

Tagged CMR images were acquired by whole body 1.5T scanners with ECG-triggered, segmented K-space fast spoiled gradient-echo pulse sequence during breath hold. After the standard protocol, 3 tagged short-axis slices (base to apex) were obtained using spatial modulation of magnetization encoding gradients. Detailed scanning parameters include the following: field of view 360×360 mm, slice thickness 10 mm, repetition time 5msec, echo time 2.5 msec, flip angle 10–12 degrees, phase encoding views per segment 9, temporal resolution 40–45 msec, tag spacing 7 mm.

LV mass and functional analyses were performed using CIM software (version 6.2, University of Auckland, New Zealand).

Late gadolinium enhancement (LGE) analyses—Contrast enhanced images were acquired 15 min after gadolinium contrast administration using inversion-recovery fast gradient-echo pulse sequences, in the same short-axis locations as the cine images. The LGE analysis was performed using Medis research software (Leiden University, Netherlands) using a semi-automated method; a visual selection step followed by manual adjustment of scar delineation. An experienced observer first assesses all short and long-axis LGE images to determine the presence or absence of LGE areas. For the image analysis, one set of epicardial and endocardial contours were manually traced to define specific myocardial regions, proceeding then by drawing a region of interest in the remote myocardium (defined as a region with no enhancement and normal wall motion) and obtaining separated sets of planimetric scars delineated by automatic software computations defined as those areas with signal (SI) intensity between 1 SD and 10 SD above remote myocardium SI. The planimetry output that best fits the observer's visual assessment of scar is chosen and manually corrected to remove regions of blood pool or epicardial fat and evident artifacts, as well as to include areas of microvascular obstruction.

Dyssynchrony analysis

Harmonic phase imaging (HARP, Diagnosoft, Palo Alto, CA) was used to analyze 3 short-axis slices (basal, mid-ventricular, and apex) and 4 regions (septum, anterior, posterior, and lateral) (Fig. 1). HARP is a standard method for assessment of myocardial strain.[15] Times from end-diastole to peak systolic circumferential strain was measured. Standard deviation of time to peak systolic strain (SD-TPS) and difference between the maximum and minimum time to peak systolic strain (max-min) in 12 regions (3 slices $\times$ 4 regions) were determined to be the measures of myocardial dyssynchrony. Rosen et al.[17] described these parameters as equivalent to the echocardiographic method described by Yu et al.[18]

Carotid artery measurements

B-mode ultrasound longitudinal images of the right and left common, bifurcation, and internal carotid artery segments were obtained with a Logiq 700 ultrasound system using the M12L transducer (General Electric Medical Systems, CCA frequency 13 MHz). The video stream output was digitized at high resolution and frame rates using a Medical Digital Recording device (PACSGEAR, Pleasanton, CA) and converted into DICOM compatible digital records. Trained and certified sonographers from all 6 MESA sites performed all exams. MESA exam-5 ultrasound images were reviewed and interpreted at the MESA Air Carotid Ultrasound Reading Center (UW AIRP, Madison, WI). Digitized images were imported into *syngo* Ultrasound Workplace 3.5B reading stations loaded with Arterial Health Package software (Siemens Medical, Malvern, PA) for carotid IMT measurement and plaque scoring.

The distal CCA was defined as the distal 10mm of the vessel. The proximal ICA was defined as the initial 10mm of the ICA after the flow divider. CCA-IMT was defined as the intima-media thickness measured as the mean of the left and right far wall distal CCA wall thicknesses. Similarly, ICA-IMT was defined by the mean intima-media thickness of the left and right far wall proximal ICA. Carotid plaque burden was defined by the carotid plaque scored as the number of plaques (0-12) in the internal, bifurcation, and common segments of both carotid arteries.[19] Carotid plaque was defined as a discrete, focal wall thickening 1.5 mm or focal thickening at least 50% greater than the surrounding IMT.[20]

The intra-class correlation coefficient (ICC) for *intra*-reader reproducibility for mean CCA IMT was 0.99; ICC for *inter*-reader CCA IMT reproducibility was 0.95. For mean ICA, *intra*-reader reproducibility was between 0.98 and 0.99; *inter*-reader reproducibility was 0.93. For carotid plaque presence and score, *intra*-reader reproducibility was kappa=0.83 (95% confidence interval [CI] 0.70-0.96) and *inter*-reader reproducibility was kappa=0.89 (95% CI 0.72-1.00).

Coronary artery calcium score assessment

CAC score was obtained using either a cardiac-gated electron-beam computed tomography scanner or a multidetector CT system as previously described.[21] Mean CAC (Agatston) score[11] was used for all analyses after adjustment for known calcium concentrations in a phantom that was included in the field of view. Images were interpreted using an interactive

scoring system at the MESA CT reading center (Los Angeles Biomedical Research Institute-UCLA, Torrance, CA).

Statistical analysis

Baseline characteristics were described as mean $\pm$ standard deviation or percentages, as appropriate. SD-TPS and max-min were regressed against common and internal carotid IMT, and plaque score as continuous variables. Participants with missing data in multivariable models were excluded. Multivariable linear regression analysis was performed as follows: model 1, unadjusted; model 2, adjusted for age, gender, ethnicity, and heart rate; model 3, model 2 with further adjustment for traditional cardiovascular risk factors such as diabetic status, hypertension status, antihypertensive medication, total cholesterol, HDL-cholesterol, body mass index, smoking status (never, former, current), education level. For model 4, in addition to covariables in model 3, statistical adjustment was performed for LV end-diastolic mass, ejection fraction as measures of LV structure and global function. Further sub-analyses in 1244 participants with LGE analyses was performed with further adjustment for the presence or absence of myocardial scar based on LGE analyses.

The Shapiro-Wilk test for normality revealed a positively skewed coronary calcium score ($p < 0.001$). Therefore, for CAC analyses, (1) we treated natural logarithm ($\log$) of (CAC+1) as a continuous variable and (2) categorized CAC into 3 groups (bottom 33% and 2 upper tertiles) to account for the fact that 667 participants (~33%) of participants had CAC of zero. The cut off for Agatston CAC score in each of the 1st, 2nd, & 3rd tertiles were 0,

131.8, and >131.8, respectively. The $\log(\text{CAC}+1)$ transformation better normalized the CAC distribution. Multivariable regression analyses for $\log(\text{CAC}+1)$ using hierarchical models were performed as detailed above. Analysis of variance with Bonferroni's correction was done to determine the difference between the means of SD-TPS among the groups categorized based on tertiles of CAC distribution.

For comparative analyses to determine the best atherosclerotic predictor of dyssynchrony using SD-TPS, the CCA-IMT, carotid plaque score, and $\log(\text{CAC}+1)$ were included in the same model, with further adjustment for covariables as in model 3. All statistical analyses were performed using STATA 12.0 (StataCorp, College Station, Texas, USA). All reported p-values are 2-tailed and values < 0.05 were considered as significant. The authors had full access to the data and take full responsibility for its integrity. All authors have read and agreed to the manuscript as written.

Results

A total of 2,062 participants (mean age 69 years, women 54.2%) were analyzed for carotid plaque score after excluding participants with prior history of myocardial infarction and presence of left bundle branch block on 12-lead ECG; 2,015 individuals for CCA-IMT and 1,333 participants for ICA-IMT were analyzed; 2,039 participants were evaluated for correlation between CAC and LV dyssynchrony. Subset characteristics of the study population were similar to that of the MESA cohort. Mean QRS duration of study participants was 95.14 msec with mean ejection fraction of 62%. Detailed participant characteristics are described in Table 1.

Mean $\pm$ SD (median, inter-quartile range) for SD-TPS was 92.45 ± 29.56 msec (91.51, 72.28 – 112.34 msec) and for max-min was 287.04 ± 90.79 msec (280.0, 210.0– 350.0 msec).

Carotid IMT and plaque score

Mean CCA-IMT was 0.85 ± 0.19 mm (25-75th percentile, 0.72-0.95 mm); 368 individuals had mean CCA-IMT >1.0 mm. Mean ICA-IMT was 0.71 ± 0.26 (25-75th percentile, 0.54-0.78 mm); 1,374 individuals had presence of plaque on carotid ultrasound examination. Mean plaque score was 2.15 ± 2.33 (median 1.0, 25th-75th percentile 0-4).

Relationship of common carotid and internal carotid artery IMT with LV dyssynchrony

In multivariable regression analysis, CCA-IMT was significantly associated with SD-TPS (β -coefficient 8.71 msec/mm change in IMT, $p=0.020$) and max-min (β -coefficient 32.53 msec/mm IMT, $p=0.005$) (Table 2).

Similarly, in the multivariable regression model, ICA-IMT was also related to parameters of LV dyssynchrony; SD-TPS (β -coefficient 19.23 msec/mm change in IMT, $p<0.001$) and max-min (β -coefficient 49.67 msec/mm, $p<0.001$).

Relationship of carotid artery plaque score and LV dyssynchrony parameters

Using multivariable regression, plaque score as a continuous variable was significantly associated with SD-TPS (β -coefficient 1.24 msec/unit change in plaque score, $p<0.001$) and max-min (β -coefficient 3.85 msec/unit change in plaque score, $p<0.001$).

Coronary artery calcium score and LV dyssynchrony

Mean CAC was 256 ± 539 (median 35, 25th-75th percentile 0-247). 667 (32.7 33%) participants had CAC of zero.

Unadjusted $\log(\text{CAC}+1)$ was significantly related to SD-TPS (β -coefficient 1.489 msec/unit $\log(\text{CAC}+1)$, $p<0.001$) and max-min (β -coefficient 3.882 msec/unit $\log(\text{CAC}+1)$, $p<0.001$). The relationship persisted for SD-TPS (β -coefficient 0.664 msec/unit $\log(\text{CAC}+1)$, $p=0.018$) and max-min (β -coefficient 2.040 msec/unit change in $\log(\text{CAC}+1)$, $p=0.019$) after adjustment for traditional and non-traditional cardiovascular risk factors including LV mass and ejection fraction (Table-3). In multivariable analyses, ICA-IMT, carotid artery plaque score, and coronary artery calcium score were not related to LV ejection fraction (data not shown).

Participants categorized in tertiles based on incremental CAC score showed worsening dyssynchrony with mean SD-TPS of 87.84 ± 29.98 msec ($n=667$), 92.10 ± 29.28 msec ($n=686$), and 96.67 ± 29.46 msec ($n=686$) in 1st, 2nd, & 3rd tertiles, respectively. ANOVA test with Bonferroni's correction revealed a statistically significant difference of mean SD-TPS between the tertile groups (Fig.-2).

Effect of myocardial scar based on LGE analyses

In multivariable regression analyses with further adjustment for presence of myocardial scar based on LGE analyses revealed improved relationship between CCA-IMT and LV

dyssynchrony (β -coefficient 9.25 msec/mm change in IMT, $p=0.014$), carotid plaque score – LV dyssynchrony (β -coefficient 1.29 msec/unit change in plaque score, $p<0.001$) and coronary calcium score (β -coefficient 0.674msec/unit log(CAC+1), $p=0.017$). (Table 4)

Participants with absence of coronary artery calcium and myocardial scar on LGE (calcium score=0, no scar) had lowest values of SD-TPS ($n=415$, mean $\pm$ SD 87.27 $\pm$ 29.14msec). In contrast, higher values of LV dyssynchrony were noted in participants with calcium score >0 and no scar ($n=738$, 93.27 $\pm$ 27.65msec, $p<0.01$) while participants with presence of coronary calcium and myocardial scar had highest values of SD-TPS ($n=87$, 94.38 $\pm$ 32.46msec, $p<0.01$ vs. Calcium score=0 and no scar group).

Comparative analysis of atherosclerosis parameters and association with dyssynchrony

A multivariable linear regression analyses with variable selection model including all three atherosclerosis parameters predicting LV dyssynchrony revealed that carotid plaque score was better correlated with SD-TPS (β -coefficient 1.255 msec/unit change in plaque score, $p<0.001$, R^2 0.145). CCA-IMT (β -coefficient 4.176 msec/mm change in IMT, $p=0.294$, R^2 0.138) and CAC score (β -coefficient 0.287 msec/unit log(CAC+1), $p=0.345$, R^2 0.143) had attenuation of statistical significance in the model.

Discussion

This study demonstrates a relationship between subclinical atherosclerosis and impaired regional LV function expressed as dyssynchronous myocardial contraction in a multi-ethnic population of asymptomatic individuals. The CCA-IMT, ICA-IMT, carotid plaque score as surrogate markers of coronary atherosclerosis were consistently related to the extent of LV dyssynchrony independent of the presence of myocardial scar. Similarly, coronary calcium score as a measure of atherosclerotic burden in the coronary arterial system was associated with parameters of mechanical dyssynchrony. These findings illustrate a potential role of early atherosclerosis in inflicting subclinical myocardial damage in the absence of a discrete clinical event. To our knowledge, these findings are the first to exhibit the correlation of subclinical atherosclerosis with LV dyssynchrony as a distinct parameter of regional myocardial impairment using CMR in a population-based cohort—way before the occurrence of global LV dysfunction.

The natural history of ischemic heart failure associated with global enlargement and dysfunction focuses on patients who develop heart failure mediated by clinical coronary events triggering structural alterations and compensatory mechanisms that lead to LV dilation and remodeling. LV dyssynchrony-related impairment in cardiac function has been primarily considered in relevance to HF due to reduced ejection fraction, based on the potential for therapeutic intervention (e.g., cardiac resynchronization therapy). We found that alterations in the synchronization of LV myocardial contraction precede impairment in global LV function. Therefore, our results may have significant implications in regards to preventive efforts and management of ischemia-related LV dysfunction.

The mechanisms of atherosclerosis-induced dyssynchrony are complex. Carotid IMT represents early atherosclerotic changes in the vascular system and is considered as a

surrogate end-point of atherosclerosis in epidemiology-based studies,[6, 22, 23] or clinical studies gauging efficacy of therapeutic interventions.[4, 8, 24] Therefore, IMT reflects an increased burden of atherosclerosis with greater incidence of epicardial vessel CAD and possible small vessel microembolization secondary to plaque rupture. In hypertensive patients without coronary artery disease, Takiuchi et al.[25] demonstrated an inverse relationship of carotid IMT with coronary flow reserve linked to early phase atherosclerosis. Furthermore, the presence of early subclinical atherosclerosis—even in the absence of stenotic CAD—is associated with increased resistance in smaller microvessels[26, 27], reduced coronary flow reserve[25, 28, 29], and endothelial dysfunction, causing repeated myocardial stunning from recurrent ischemia, thereby altering local myocardial contractility. [30] Using CMR perfusion imaging in the MESA study, Rosen et al. illustrated that reduced myocardial perfusion is accompanied by worsening of LV dyssynchrony.[17] LV dyssynchrony is also related to myocardial remodeling that occurs in response to cardiovascular risk burden[31, 32] as a common denominator for atherosclerosis as well as myocardial deformation.

Fernandes et al.[33] reported that, with greater carotid IMT, there is a decrease in segmental myocardial strain and diastolic function as a marker of incipient regional myocardial dysfunction that precedes global reduction of ejection fraction and symptoms in the heart failure continuum. In a similar MESA subset, Edvardsen et al. demonstrated a decrease in segmental myocardial strain with an increase in CAC.[34] Our study significantly extends this paradigm by demonstrating a distinctive mechanism of myocardial functional impairment.

Aging, LV mass and regional myocardial dysfunction

Since age and LV end-diastolic mass are directly related to subclinical LV dyssynchrony, [17] we performed supplementary analyses to control for the influence of aging and increased LV mass as potential confounders to the atherosclerosis-LV dyssynchrony relationship. Additional analyses (Tables 2 & 3) showed that even though age and LV mass affect dyssynchrony, the associations of IMT and CAC with LV dyssynchrony persist despite statistical control for age (model 2) and LV mass (model 4). The participants with LBBB were also excluded from the analyses to account for LBBB as a potential confounder in the induction of LV dyssynchrony. Moreover, the subclinical atherosclerosis-dyssynchrony relationship did not alter after adjusting for hypertension and other established cardiovascular risk factors contributing towards incipient regional dysfunction.[35, 36]

Methodological considerations

Our study demonstrates the relationship of carotid IMT with LV dyssynchrony as a marker of regional myocardial dysfunction in more than 2000 individuals with no previous history of clinical coronary event or left-bundle-branch block using tagged CMR, which is considered as a standard for assessment of regional LV function. Hence, the prevalence of risk factors and severity of carotid IMT may not reflect that found in the general population, and extrapolation of our study results must be considered in the context of the study design and the population examined. Moreover, the basic mechanisms involving myocardial dyssynchrony and atherosclerosis are complex and are beyond the scope of this paper.

Finally, since our study is cross-sectional in nature, causal temporality cannot be determined.

In summary, our study demonstrates that subclinical atherosclerosis determined by carotid IMT, carotid plaque score, and coronary artery calcium score in the absence of clinical cardiovascular event are significantly associated with parameters of left ventricular dyssynchrony as a marker of subclinical regional myocardial dysfunction. These findings in a population based asymptomatic cohort provide important insights into the mechanisms and pathways of atherosclerosis-related incipient LV dysfunction and heart failure.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

LV	Left ventricular
CMR	Cardiovascular magnetic resonance
CCA	Common carotid artery
ICA	Internal carotid artery
IMT	Carotid intima-media thickness
CAC	Coronary artery calcium
CT	Computed tomography
HF	Heart failure
LBBS	Left bundle-branch block
SD	Standard deviation

SD-TPS	SD time to peak strain
Max-min	Maximum to minimum time to peak strain
HDL	High-density lipoprotein
eGFR	estimated glomerular filtration rate

Highlights

- Our study demonstrate that in a multi-ethnic population free of clinical cardiovascular disease, subclinical atherosclerotic markers such as carotid intima-media thickness, carotid plaque score, and coronary calcium score are related to left ventricular dyssynchrony as a measure of regional myocardial dysfunction, independent of presence of myocardial scar and left bundle branch block.
- These findings are the first to exhibit the correlation of subclinical atherosclerosis with LV dyssynchrony as a distinct parameter of regional myocardial impairment using cardiac magnetic resonance imaging in a population-based cohort—way before the occurrence of global LV dysfunction.
- Of the atherosclerotic parameters, carotid plaque score was better correlated with subclinical left ventricular dyssynchrony.
- These findings illustrate a potential role of early atherosclerosis in inflicting subclinical myocardial damage in the absence of a discrete clinical event and provide important insights into the mechanisms and pathways of atherosclerosis-related incipient LV dysfunction and heart failure.

Figure 1.

Sample representation of cardiac magnetic resonance study with myocardial tagging and analysis of circumferential strain curves using harmonic phase imaging. In the graph, the x-axis represents time (cine frame number) and the y-axis represents circumferential strain (%).

Figure 2.

Box plot representing distribution of SD-time to peak systolic strain categorized by tertiles of coronary artery calcium score.

P-values denote the statistical significance of difference between SD-TPS mean among the groups using analysis of variance test with Bonferroni's correction.

Table 1
Participant demographics and characteristics

Parameters	(n=2062)
Age, years	69.10 ± 9.20
Gender- female, n (%)	1117 (54.2)
Race, n (%)	
White	843 (40.9)
Chinese-American	283 (13.7)
African-American	529 (25.7)
Hispanic	407 (19.7)
Body mass index, kg/m ²	28.01 ± 5.16
Body surface area, m ²	1.83 ± 0.22
Risk factors	
Diabetes mellitus, n (%)	
Impaired fasting glucose	446 (21.6)
Untreated	26 (1.3)
Treated	340 (16.5)
Heart rate, bpm	61.44 ± 9.49
Systolic blood pressure, mm Hg	123.15 ± 19.82
Diastolic blood pressure, mm Hg	68.30 ± 9.85
Antihypertensive medication, %	1118 (54.22)
Total cholesterol, mg/dL	184.13 ± 36.81
LDL cholesterol, mg/dL	106.08 ± 32.37
HDL cholesterol, mg/dL	56.19 ± 16.74
Glomerular filtration rate, ml/min/1.73m ²	80.73 ± 19.93
Cigarette smoking, %	
Never smoked	1045 (50.67)
Former smoker	888 (43.06)
Current smoker	129 (6.27)
EKG parameters	
LBBB, number of participants, n	6
QRS duration, msec	95.14 ± 15.58
Global parameters	
LV ejection fraction, %	62.08 ± 7.25
LV mass-indexed to BSA, gm/m ²	65.79 ± 13.41
LV end-diastolic volume, mL	118.36 ± 31.05
LV end-systolic volume, mL	45.57 ± 17.71

HDL, high-density lipoprotein, LBBB, left-bundle-branch block, LV, left ventricular.

Table 2
Relationship of carotid artery (common and internal) intima-media thickness and carotid plaque score with parameters of left ventricular dyssynchrony

CCA-IMT							
Model-1 (2015)		Model-2 (1989)		Model-3 (1965)		Model-4 (1954)	
B-coefficient (95% CI)	p-value	B-coefficient (95% CI)	p-value	B-coefficient (95% CI)	p-value	B-coefficient (95% CI)	p-value
SD-TPS	18.62 (11.91 – 25.32)	<0.001	12.95 (5.71 – 20.19)	<0.001	9.26 (1.84 – 16.68)	0.014	8.71 (1.37 – 16.04)
Max-min	57.05 (36.48 – 77.63)	<0.001	43.96 (21.62 – 66.3)	<0.001	33.18 (10.28 – 56.09)	0.005	32.53 (9.82 – 55.24)
ICA-IMT							
Model-1 (1333)		Model-2 (1317)		Model-3 (1302)		Model-4 (1295)	
B-coefficient (95% CI)	p-value	B-coefficient (95% CI)	p-value	B-coefficient (95% CI)	p-value	B-coefficient (95% CI)	p-value
SD-TPS	19.36 (13.49 – 25.23)	<0.001	18.41 (12.43 – 24.38)	<0.001	17.62 (11.52 – 23.73)	<0.001	19.23 (13.24 – 25.22)
Max-min	47.62 (29.35 – 65.89)	<0.001	46.21 (27.51 – 64.9)	<0.001	44.73 (25.63 – 63.83)	<0.001	49.67 (30.9 – 68.45)
Carotid plaque score							
Model-1 (2062)		Model-2 (2036)		Model-3 (2011)		Model-4 (2000)	
B-coefficient (95% CI)	p-value	B-coefficient (95% CI)	p-value	B-coefficient (95% CI)	p-value	B-coefficient (95% CI)	p-value
SD-TPS	2.2 (1.66 – 2.74)	<0.001	1.59 (1.02 – 2.16)	<0.001	1.22 (0.634 – 1.8)	<0.001	1.24 (0.66 – 1.82)
Max-min	6.18 (4.53 – 7.83)	<0.001	4.72 (2.97 – 6.48)	<0.001	3.78 (1.97 – 5.59)	<0.001	3.85 (2.06 – 5.64)

CCA, common carotid artery; ICA, Internal carotid artery; IMT, intima-media thickness. Unit of β -coefficient, msec/mm change in IMT. CI, confidence interval. SD-TPS, standard deviation of time to peak systolic circumferential strain. Max-min, Difference between the earliest and latest time to peak segmental systolic circumferential strain. Model 1, unadjusted; Model 2, adjusted for age, gender, ethnicity, and heart rate; Model 3, model 2 plus diabetic status, hypertension status, antihypertensive medication, total cholesterol, HDL-cholesterol, body mass index, smoking status (never, former, current), education level; Model 4; model 3 plus end-diastolic LV mass and LV ejection fraction.

Relationship of phantom adjusted coronary calcium score with parameters of left ventricular dyssynchrony.

Table 3

Parameters	Model-1 (n=2039)		Model-2 (n=2013)		Model-3 (n=1986)		Model-4 (n=1975)	
	β -coefficient (95% CI)	p-value	β -coefficient (95% CI)	p-value	β -coefficient (95% CI)	p-value	β -coefficient (95% CI)	p-value
SD-TPS	1.489 (1.011 - 1.968)	<0.001	0.894 (0.358 - 1.431)	0.001	0.571 (0.013 - 1.130)	0.045	0.664 (0.113 - 1.215)	0.018
Max-min	3.882 (2.407 - 5.358)	<0.001	2.528 (0.867 - 4.189)	0.003	1.751 (0.021 - 3.481)	0.047	2.040 (0.330 - 3.749)	0.019

SD-TPS, standard deviation of time to peak systolic circumferential strain, Max-min, Difference between the earliest and latest time to peak segmental systolic circumferential strain. For adjustment parameter, please refer Table-2.

Table 4
Table representing multivariable regression analyses to assess correlation between atherosclerotic markers and LV dyssynchrony, adjusted for presence of myocardial scar on delayed enhanced MRI

Parameters	B-coefficient (95% CI)	p-value
CCA-IMT		
SD-TPS	9.25 (1.85 - 16.65)	0.014
Max-min	34.18 (11.28 - 57.08)	0.003
ICA-IMT		
SD-TPS	19.50 (13.51 - 25.49)	<0.001
Max-min	50.59 (31.79 - 69.39)	<0.001
Carotid plaque score		
SD-TPS	1.29 (0.71 - 1.86)	<0.001
Max-min	3.98 (2.18 - 5.76)	<0.001
Coronary calcium score		
SD-TPS	0.67 (0.12 - 1.23)	0.017
Max-min	2.10 (0.38 - 3.83)	0.017

CCA, common carotid artery, ICA, Internal carotid artery, IMT, intima-media thickness. Unit of β -coefficient, msec/mm change in IMT. CI, confidence interval. SD-TPS, standard deviation of time to peak systolic circumferential strain, Max-min, Difference between the earliest and latest time to peak segmental systolic circumferential strain. Model adjusted for age, gender, ethnicity, and heart rate, diabetic status, hypertension status, antihypertensive medication, total cholesterol, HDL-cholesterol, body mass index, smoking status (never, former, current), education level, end-diastolic LV mass, LV ejection fraction and presence of myocardial scar on LGE.