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Functional myocardial assessment in cine cardiac computerized tomographic angiography using echocardiographic feature-tracking software in patients with and without significant coronary disease

Adi Hertz [a,b], Michael Jerdev [a,b], Liza Grosman-Rimon [g], Itiel Ben-Zakai [d], Jordan Rimon [c,f], Offer Amir [e], Gabby Elbaz Greener [e,1], Shemy Carasso [a,b,*,1]

[a] The Azrieli Faculty of Medicine in the Galilee, Bar-Ilan University, Zefat, Israel
[b] Cardiovascular Institute, B Padeh Medical Center, Poriya, Israel
[c] Division of Cardiology, Ottawa Heart Institute, Ottawa, Canada
[d] Department of Radiology, B Padeh Medical Center, Poriya, Israel
[e] Department of Cardiology, Hadassah Medical Center, Faculty of Medicine, Hebrew University of Jerusalem, Israel
[f] Faculty of Health, York University, Toronto, Ontario, Canada
[g] Levinsky-Wingate Academic College, Wingate Institute, Tel Aviv, Israel

A R T I C L E I N F O

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Coronary arteries
Velocity Vector Imaging (VVI)
Global longitudinal strain (GLS)
Global circumferential strains (GCS)

A B S T R A C T

Introduction: Cardiac computerized tomographic angiography (CCTA) is perceived as a non-invasive tool for assessment of coronary vessel anatomy. Feature tracking echocardiography has recently emerged as a tool for assessment of regional and global left ventricular function. We aimed to explore the applicability of echocardiographic strain on CCTA cine clips and assess whether global and regional strain parameters are associated with the extent of coronary stenosis.

Methods: CCTA studies of 61 consecutive patients were reconstructed to yield cine images in classic echocardiographic long and short views. Siemens Velocity Vector Imaging (VVI) software was applied to generate strain and displacement results. Volumetric and mechanics parameters were compared among patients with no or non-significant coronary artery disease (CAD) and patients with significant CAD. Finally, a comparison of the degree of coronary stenosis to regional segmental strain was performed.

Results: Myocardial mechanics parameters could be generated in 60 cases. Ejection fraction (EF) and left ventricular end diastolic volume (LVEDV) were within the normal range in both groups. VVI values were lower in the CAD group (VVI LVEF 59 $\pm$ 6 vs. 50 $\pm$ 11, $p = 0.0002$). Global longitudinal and global circumferential strain both were significantly lower in this group. Regional segmental strain was lower in segments affected by coronary stenosis in comparison to unaffected segments.

Conclusion: While CT segmentation derived LVEF did not differ among groups, patients with significant coronary stenosis had reduced longitudinal and circumferential contraction. This suggests that application of VVI to CCTA cine clips tracking may help to differentiate significant and non-significant coronary stenosis, adding functional value to anatomic findings in CCTA.

1. Introduction

Coronary Computed Tomography Angiography (CCTA) offers a non-invasive, high sensitivity approach to depict the extent and severity of coronary atherosclerosis [1]. The extremely high sensitivity of this approach offers a very effective means of excluding coronary artery disease (CAD), assessment of coronary anatomy and severity of stenosis. Narrowing of the arteries, however, is not synonymous to myocardial ischemia, and its clinical significance may need to be ascertained to avoid unnecessary coronary angiographies with subsequent revascularizations [2]. Complementary tests (Stress/Dobutamine echocardiography or Thallium nuclear stress test) [3] or fractional flow

* Corresponding author at: Non-invasive cardiac imaging, Division of Cardiovascular Medicine, B Padeh Medical Center, Poriya, Lower Galilee 15208, Israel.
E-mail address: shemyca@szmc.org.il (S. Carasso).

[1] Authors contributed equally to this study and manuscript preparation.

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reserve derived from coronary computed tomography angiography [4] may be used for this purpose.

Assessment of local myocardial function, especially sub-endocardial, may provide insight regarding the presence of myocardial ischemia. Myocardial deformation (linear strain) evaluates the percent change in myocardial length unit from relaxed to contractile state [5]. Myocardial strain measurement is usually applied to echocardiography cine images [6]. By measuring myocardial strain, one can quantitatively measure global and regional myocardial systolic function [7]. Alteration of strain was found to occur in the setting of normal ejection fraction (EF) and provide greater prognostic value than EF alone in myocardial and valvular heart diseases and assessment of chemotherapy induced cardiotoxicity [8,9].

While echocardiography cannot visualize coronary stenosis [10] the application of strain imaging to cine CCTA could confirm the significance of a coronary stenosis by recognition of subclinical regional functional impairment in the subtended myocardium. Specific biplane strain patterns may be helpful in the diagnosis of non-CAD specific cardiomyopathies [11,12]. Three dimensional CCTA datasets were utilized to generate longitudinal strain (LS), circumferential strain (CS) and displacement curves when analyzed by a specific experimental algorithm [13] with comparable results to global and regional echocardiographic measurements [14]. Application of a commercial echocardiographic strain analysis software Velocity Vector Imaging (VVI, Siemens, Mountain View, CA, USA) on steady-state free precession (SSFP) MRI cine images has been validated with echocardiography in patients with hypertrophic cardiomyopathy [15]. Finally, a recent study found that strain measurements using another commercially available CT strain software were feasible in patients with advanced valve heart disease [16].

The aim of this study was to explore the feasibility of application of echocardiographic strain on CCTA cine clips and assess whether global and regional strain parameters are associated with the extent of coronary stenosis. We applied VVI strain imaging software on CCTA cine clips to validate its measurements internally and against an age and gender-matched echocardiographic cohort of normal subjects. Finally, we carried a comparison between the degree of coronary stenosis and regional segmental strain.

2. Methods

The study was approved by the institutional research ethics board at the Poriya Medical Center.

2.1. Subjects

We selected 61 consecutive patients referred for ambulatory CCTA for the evaluation of various indications, mostly for exclusion of CAD (n = 56, 92 %). The final cohort included 60 patients while one patient was excluded due to rapid atrial fibrillation with extremely irregular rhythm (Table 1). The whole group was tested for consistency of CT segmentation and VVI generated parameters. For an initial feasibility/validation assessment of feature-tracking on cine CCTA images, 26 patients with normal LV function (EF $\geq$ 50 %) and no or minimal coronary disease by CCTA (coronary artery calcium score < 10 Agatston Units (AU), narrowing < 35 %), were selected and the results compared to strain measurements in echocardiograms of age and sex-matched healthy patients with normal echocardiograms.

Table 1
Cardiac CT referral indications.

CCTA referral indication (n, %)	
Exclusion of coronary artery disease	44, 72
Dyspnea, Fatigue	4, 6
Follow up aortic dilation	4, 6
Evaluation of coronary stent patency	2, 3
Palpitations	1, 2
Other	6, 10

The control patients were selected from a group of 120 consecutive healthy patients referred for elective echocardiography for sport activity clearance, evaluate minor symptoms (not chest pain or dyspnea) or incidental murmurs during 2009 [15]. Pre-test probability of the presence of coronary artery disease in these patients was estimated to be very low. All patients had myocardial mechanics previously analyzed. A test to control matching (age and sex) was performed in a 1-test to 2-controls ratio.

2.2. CCTA

The CCTA was performed according to hospital protocol using a Philips 256 iCT (Koninklijke Philips N.V., The Netherlands). Data sets were acquired retrospectively over two consecutive heart beats using a dose-reduction protocol in which full tube current was applied only for the end systolic (35 %) and end diastolic (75 %) phases. Dose modulation was applied to the remaining cardiac phases. Image sets were created from phase 0 % to phase 95 % using an iterative reconstruction algorithm to reduce image noise (20 phases per cardiac cycle). These time-resolved image sets were subsequently used for functional and strain evaluation. Coronary and left ventricular volumetric evaluations were performed using the Philips Intellispace portal version 10.

Left ventricular cine clips were generated automatically in an echocardiography pattern (longitudinal axis – 4, 3 and 2 chambers; short axis – base, mid-myocardial and apex) and saved for blinded offline analysis by VVI.

2.3. CT strain measurement

CT images were converted from DICOM format to AVI format by DIC2AVI software by Siemens – 6 videos of 20 phases each, per case (4, 2 and 3 chambers long axis and base, mid and apical short axis views).

CT cine loops were analyzed by Velocity Vector Imaging US 3.0.1.45b 140,211 software (Siemens, Mountainview, CA, USA) and the measurements were transferred to a dedicated excel table, which automatically calculated all the motion components, as well as global and regional strain – according to the different segments, regions and coronary arteries. EF, LVESV and LVEDV were calculated by the software and recorded.

2.4. The comparison between volume and strain parameters was calculated using VVI in CCTA cine images of patients with and without significant CAD

The subjects were divided into two groups, based on the degree of coronary stenosis determined by CCTA. The group with no or non-significant coronary narrowing, defined as a narrowing of less than 50 %, includes 44 patients. The second group, with significant narrowing, defined as a narrowing of 50 % and more, includes 16 patients.

The following parameters were compared: (1) calcium score (2) volume parameters (LVEDV and EF) (3) LV mechanics parameters – longitudinal and circumferential global and regional strain were compared according to the different segments, regions and coronary perfusion territories (4) rotation displacement angles and direction.

2.5. Comparison of the degree of coronary stenosis to regional segmental strain

A comparison between the degree of coronary stenosis, derived from the CCTA results to regional segmental strain was performed, in the aim of addressing our hypothesis that an inverse association exists between the two variables. First, we applied a grading system according to the degree of coronary narrowing: Grade 0 – no coronary narrowing, Grade

2 – < 50 % narrowing, and Grade 3 – 50–100 % narrowing. Next, we constructed a table presenting the segments supplied by each coronary and the grade allocated to them. We used the standard AHA segmentation. We constructed an additional table presenting the data of all the segmental grades and the peak regional strain of each segment as calculated by VVI. Finally, we conducted a comparison between the two data sets.

2.6. Statistical analysis

Continuous variables were reported as means ± 1 SD and frequencies as integers (percentages). Volume parameters, which included left ventricle end diastolic volume (LVEDV) and left ventricle end systolic volume (LVESV), acquired from the CCTA, were compared to volume parameters calculated by the VVI software using linear regression, Pearson correlation and Bland Altman analyses. The CT-calculated LVEF was correlated to VVI-measured global longitudinal strain (GLS) and global circumferential strains (GCS). LV mechanics parameters, including average longitudinal strain, average circumferential strain, myocardial rotation angles and direction, were compared using ANOVA. Tests of 26 test subjects (no/insignificant CAD on CT) were compared to that of the test 52 healthy age and sex matched echocardiographic control for volumes and average strains using ANOVA. P values of < 0.05 were considered statistically significant.

All assessments were done using MedCalc® Statistical Software version 19.8 (MedCalc Software Ltd, Ostend, Belgium).

3. Results

The final cohort included 60 patients, of whom VVI could track their left ventricular myocardium. One patient with rapid atrial fibrillation was excluded due to excessively variable cycle lengths that hindered the ability to perform reconstructions.

Table 1 discloses the CCTA referral indications, most of whom were for the evaluation of presence of CAD. The mean age was 55 + 12 years, with male predominance (Table 2) and most had multiple risk factors for CAD. Their average coronary calcium score was 184 ± 317 Agatston units. The calcium score of the group with a narrowing of 50 % and above was significantly higher than the group without significant CAD (403 ± 422 and 107 ± 229 respectively, $p = 0.001$).

3.1. Comparison of Volumetrics derived from CT and VVI software

The CT calculated 3-dimensional LVEDV median was 160 ml (IQR 132–181), LVESV was 62 ml (IQR 53–83), and LVEF was 59 % (IQR 55–66, range 42–82 ml). Fig. 1 demonstrates an example of typical VVI tracking and longitudinal strain in echocardiography and CCTA in a patient with normal contraction. Video 1 shows strain parametric tracking in CCTA in a patient with normal contraction, Video 2 is in a patient with infero-septal reduced contraction. Strain curves demonstrate typical characteristics at end diastole, end systole, and diastasis.

Table 2
Characteristics of Patients.

Patients Clinical Features	
Age (average)	55 ± 12
Sex male, n, (%)	36, (59)
Hypertension	21
Diabetes Mellitus	10
Hyperlipidemia	25
Smoking	10
Previous Myocardial Infraction	3
Obstructive Sleep Apnea	3
Overweight	46
Family History of Coronary Artery Disease	4
Malignancy	2
Prior Percutaneous Coronary Intervention	5

Moderate correlations were found between automatically segmented 3D CT and biplane VVI tracked volumes. LVESV demonstrated better correlation than LVEDV. Both demonstrated a positive bias for VVI-calculated volumes (Fig. 2).

The correlation between CT LVEF and global longitudinal and circumferential strains are shown in Fig. 4 (Fig. 3). Both were significant ($p < 0.0001$) but the R^2 was lower than correlation for volumes. The circumferential strain correlated better with CT LVEF than longitudinal strain.

3.2. Comparison of strain parameters in patients without CAD to age and sex matched echocardiographic controls

In 26 subjects under CCTA, there was no evidence of significant coronary narrowing. The coronary artery calcium score average was 0.6 ± 1.7 (CI −1.3 to 1.3) and extra luminal plaques were demonstrated in 3 of the subjects. Their CT LVEF was ≥ 50 %, and there were no visually detected regional wall motion abnormalities in their 20 phases CTA cine clips. From the 120 echocardiographic controls, 52 subjects were age and gender matched, and strain parameters were compared (Table 3).

Longitudinal strain was minimally lower in CT derived strain while circumferential strain was higher; both changes were statistically significant. Principal strain calculated as the geometric mean of global strain in both directions was, however, identical, (34 ± 5 % vs. 34 ± 4 %, for CCTA vs. Echo, respectively, p = ns). Basal and apical circumferential strains were not different between cases and control while mid (papillary muscle level) strain was statistically significantly higher in the CT group. Regarding rotation displacement peak angles and systolic rotation direction, these were similar between groups, with preservation of the clockwise direction of the base, and counter − clockwise direction of the mid and apical levels.

3.3. Comparison of volume and strain parameters calculated using VVI in CCTA cine images of patients with and without significant CAD

3.3.1. Volume parameters

EF and LVEDV were both within the normal range in both groups. LVEDV was slightly higher in the significant CAD group (163 ± 33 vs. 155 ± 30, p = ns). LVEF was lower in the significant CAD group, but only VVI calculated values was statistical significance (VVI LVEF 59 ± 6 vs. 50 ± 11, $p = 0.0002$). CT EF was higher than VVI calculated EF (Table 4).

3.3.2. LV mechanics

Global longitudinal and global circumferential strain were both significantly lower in the group with significant CAD. The decrease in GLS is more prominent than the decrease in GCS. Longitudinal strain is also lower in the significant CAD group when compared to LV region and coronary perfusion territories. Peak circumferential strain was lower in all views, except the apical.

Rotation displacement angles and direction shows no significant difference between the two groups.

3.4. Comparison of the degree of coronary stenosis to regional segmental strain

Segmental strain according to coronary obstruction is shown in Fig. 4 within three subgroups; no narrowing vs. narrowing < 50 % vs. narrowing > 50 %.

Following the allocation of the segmental grading system, we obtained 756 normal segments, 268 segments with narrowing < 50 % and 37 segments with narrowing ≥ 50 %. Fig. 4 exhibits the gradual decrease in segmental strain (less negative, smaller absolute values) as the grade of coronary artery narrowing increase. Statistical significance was found in the comparison of the first group (no narrowing) vs. the second and third group (Narrowing < 50 % and Narrowing > 50 % respectively)

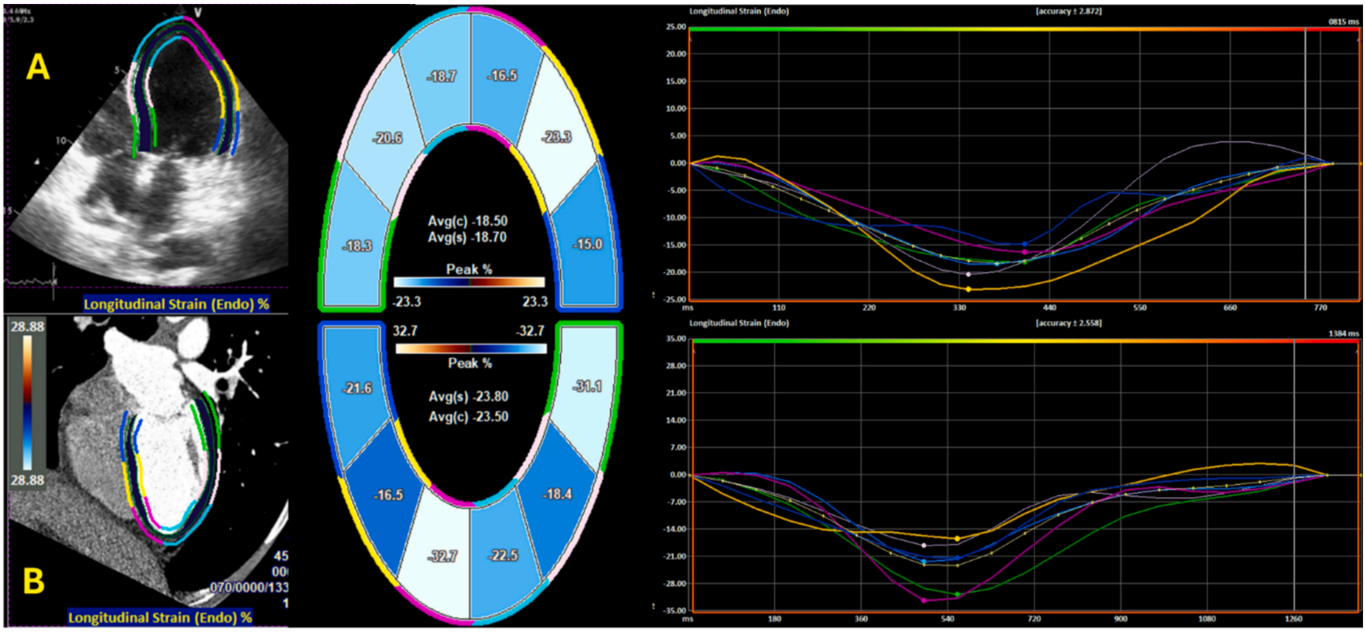

Fig. 1. Typical Strain Output Screen. Taken from a 4-Chamber View of a Normal Subject without CAD, A – Echocardiography and B – CCTA. Left panels show the source image with color coded segmentation, middle panels show segments and peak segmental systolic strain, right panels show cycle (R to next R wave) strain curves for each segment analyzed.

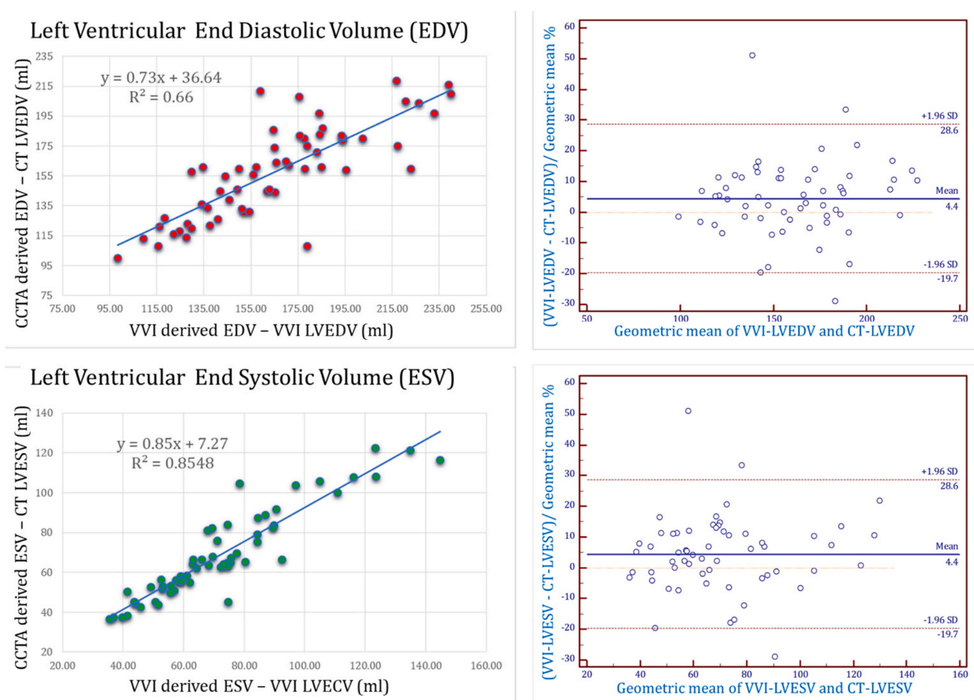

Fig. 2. Comparisons of LV Volumes Calculated by 3D CT and Biplane VVI.

(Fig. 4).

4. Discussion

In this study, we have incorporated the use of cine CT images for the determination of myocardial mechanics by application of a commercial echocardiographic feature tracking software on 20-phases cine CT clips of the heart of standard long and short axis echocardiographic views. In the first stage, we compared CT volumetric measurement to feature tracking volumetric and functional measurements in an unselected group of patients. Secondly, we compared CT feature tracking measurements in patients without CAD to a measurement derived from an age and sex matched echocardiographic cohort of healthy subjects analyzed by the same echocardiographic feature tracking software (VVI).

Volume measurement by 3D CT segmentation and biplane VVI measurement were closely correlated, with somewhat larger measurements (~5ml) for VVI. As VVI volume measurement is related to endocardial contour tracking in echocardiography, this probably means that the algorithm did the same in CT images and identified trackable

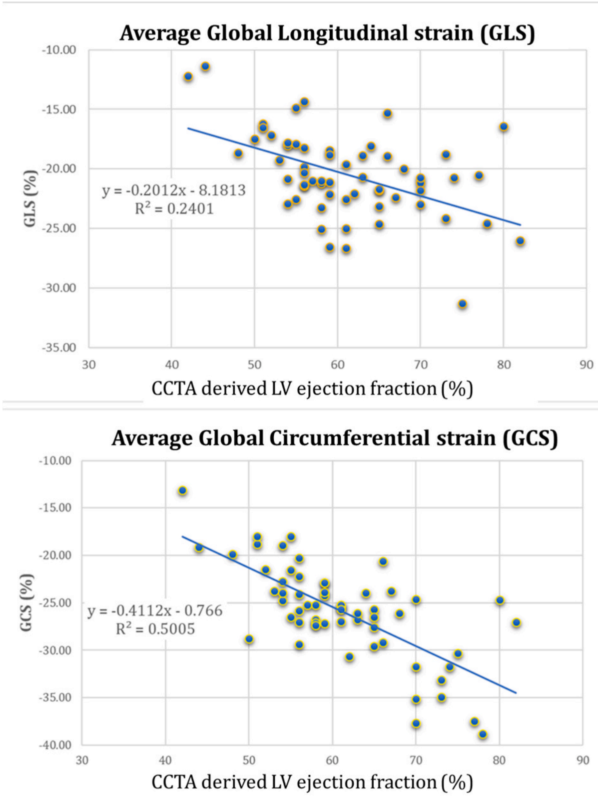

Fig. 3. Correlation Between CT LVEF and Global Longitudinal and Circumferential Strain.

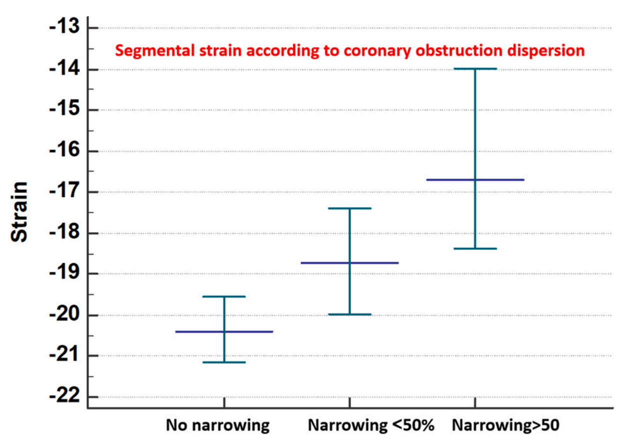

Fig. 4. Segmental Strain According to Coronary Obstruction.

features in the cine-CT images and was able to accurately follow them from frame to frame [13]. Correlations for ESVs were stronger than for EDVs. This may result from the initial contour (manually drawn) for VVI tracking being set at end systole (as done for echocardiography), with some detachment from features as tracking progressed to end diastole. As demonstrated in Fig. 2 the typical contraction stages could be identified in CT cine loop VVI-derived strain and volume curves (end diastole, systole to end systole, rapid filling, diastasis, late filling back to end diastole) confirming tracking of a physiologic pattern of the cardiac cycle [18].

Assessment of LV function, using global volumes to derive ejection fraction, has been shown to be less accurate than contraction assessment using strain analysis [19–21]. Although GLS may grossly correlate with LVEF, it has been shown to decrease before LVEF does in patients

Table 3
Test vs. Control Myocardial Strain Parameters.

Parameter	CCTA − VVI	ECHO-VVI	ANOVA p-Value
n	26	52	
Age	52.5 ± 8.7	52.3 ± 8.1	0.6514
Sex male n, (%)	12, (48)	27, (52)	0.7569
Longitudinal Strain	−19.7 ± 1.9	−21.7 ± 3.3	0.0138
Circumferential Strain	−28.7 ± 3.4	−26.3 ± 4.1	0.0313
Base	−24.2 ± 3.6	−23.1 ± 3.6	0.0909
Mid	−27.3 ± 3.5	−22.3 ± 3.5	0.0002
Apex	−34.2 ± 6.3	−33.0 ± 8.4	0.5395
Rotation			
Base (°)	−3.8 ± 2.0	−3.0 ± 2.3	0.0972
Mid (°)	+3.4 ± 3.9	+2.5 ± 2.1	0.3658
Apex (°)	+7.7 ± 3.4	+8.4 ± 4.6	0.4576

Table 4
Comparison of Volume and Motion Parameters.

Parameter	Non-Significant CAD	Significant CAD	ANOVA p-Value
n	44	16	
Age	57.4 ± 10.3	56.2 ± 15.3	0.73
Sex male n, (%)	52	75	0.11
Calcium score	107 ± 229	403 ± 422	<0.001
CT LVEDV (ml)	155 + 30	163 + 330	0.37
CT EF	62 ± 6	58 ± 12	0.19
VVI EF	59 ± 6	50 ± 11	<0.001
Longitudinal Strain	−21.5 ± 2.8	−17.3 ± 4.2	<0.001
LAD	−22.8 ± 3.4	−17.8 ± 4.6	<0.001
LCX	−22.4 ± 3.5	−18.6 ± 4.6	<0.001
RCA	−18.9 ± 2.8	−15.1 ± 4.5	<0.001
Circumferential strain	−26.6 + 4.0	−23.3 + 7.4	0.03
Base	−23.1 ± 3.9	−18.3 ± 7.6	0.006
Mid	−22.5 ± 2.8	−18.9 ± 6	0.002
Apex	−32.3 ± 10	−27.8 ± 10.8	0.14
Rotation Base (^{0})	−3.3 ± 2.6	−2.8 ± 3.2	0.58
Mid	−3.9 ± 4.4	−3.9 ± 4.9	0.99
Apex	−9.5 ± 4.5	−11.2 ± 8.9	0.31

receiving cardiotoxic chemotherapy [9,22]. A similar modest correlation between GLS and LVEF was demonstrated in this study. As this group included patients with CAD and its risk factors, it is not surprising that strains only weakly correlated with LVEF.

GCS correlated more strongly with LVEF than with GLS. This may be due to the presence of CAD mostly influencing sub-endocardial tissue that selectively includes longitudinally directed fibers, while mid myocardial, more circumferential fibers were less affected, preserving LV systolic function.

It was previously shown that both longitudinal and circumferential strain rates were independent predictors of outcomes after MI, while only circumferential strain rate was predictive of remodeling, suggesting that preserved circumferential function might serve to limit ventricular enlargement after MI [24,25].

In the subgroup of patients without significant CAD, strain measurements were compared to sex and age matched controls assessed by echocardiography with the same feature tracking algorithm. We found similar values for GLS, GCS (global, base and apex), circumferential displacement parameters (peak systolic rotation angles and their directions). Although changes were small, they demonstrated statistically significant differences in opposite directions (less longitudinal contraction, higher circumferential contraction in the CT group compared to the Echo group). Principal strain (the geometric average of GLS and GCS), however, remained similar. There are two possible explanations for this finding. One is clinical, our patients were matched for sex and age, yet the CT cohort included patients with CAD risk factors, while the echocardiographic cohort did not. Conditions with elevated afterload such as hypertension, aortic stenosis and obstructive hypertrophic cardiomyopathy tended to decrease the amplitude of GLS and increase it for GCS and maintained a normal principal strain similar to what we have shown in this study [26–29]. The other possibility is merely technical. Automatic 3D segmentation by CT software creates non-foreshortened "echocardiographic" images, while echocardiographic 2D apical images are usually foreshortened to some extent [10,17]. That may diminish the longitudinal shortening vector.

In the study, we can see a clear gradual decrease in strain as the severity of coronary narrowing increases. The difference in sub-endocardial longitudinal strain between segment supplied by 0-narrowed vessels and segments supplied by vessels with < 50 % narrowing was prominent. Similarly, the difference between the latter and strain of segments supplied by vessels with ≥ 50 % was somewhat less prominent This may be the result of greater heterogeneity in the degree of coronary narrowing in the third group with some segments' strain closer in value to the second group, due to less severe coronary stenosis and some segments with very low strain value, due to much more severe narrowing. Additional studies are required to confirm this inverse relation between strain and coronary narrowing, using a greater sample size and sub-division of the ≥ 50 % into a 50–69 % and ≥ 70 % subgroups.

Almost all segments display strain values within the normal range. It implies that during this stage of CAD we may not be able to visually identify any wall motion abnormalities. This is potentially acceptable as strain changes were shown to be early indicators of myocardial dysfunction appearing before noticeable visual decreases are present and before overt decline in EF can be identified. In the setting of normal strain values, strain analysis can still possess a clinical value by comparing the values of the different segments in serial measurements over time to detect a trend indicating reduction in myocardial function, like the routine evaluation of patients receiving cardio-toxic chemotherapy.

The more prominent decrease in longitudinal strain may be a result of ongoing ischemic myocardial injury in the significant CAD group, mostly influencing sub-endocardial tissue that selectively includes longitudinally directed fibers. The circumferential shortening involves the sub-epicardial fibers, which are less affected at early stages and maintain normal or high mechanics in order to compensate for the longitudinal dysfunction and to preserve normal EF [23].

In the apex, most of the fibers are circumferential, thus they are not prone to injury and work to compensate for other areas with reduced function, which coincide with our results showing no significant difference between the two groups [23,30].

Our study should be interpreted in the contexts of several limitations. Coupled echocardiographic and CT strain evaluations for each subject might have provided the best methodology for validation of CT derived strain analysis. Echocardiographic studies were not available for most of our CCTA subjects. Comparison to age and sex matched normal controls may be the reason for the small yet statistically significant differences, as discussed above.

Most of the images and data were acquired at reduced tube current, resulting in coarse resolution in most image phases. This may have reduced the ability to draw precise endocardial and pericardial contours for tracking. Yet, it may have improved VVI tracking by making the images coarser, more "echocardiographic" that might have been more suitable for the VVI algorithm.

5. Limitations

This was a retrospective study of patients referred to for CCTA, most of whom did not have a corresponding echocardiogram available for analysis. Thus a direct comparison of CCTA and echocardiography strain parameters could not be done. Moreover, patients' selection bias may have been introduced. Only 1061 AHA segments were available for assessment of narrowing vs. strain, only 37 of which were in territories supplied by vessels with significant (>50 %) narrowing. This did not allow us for per coronary vessel (left main/Left anterior descending/Left circumflex/ Right) analysis.

6. Conclusion

Myocardial Mechanics analysis by feature-tracking on cine-CT angiography clips yielded comparable results to echocardiography for volumes, strain (longitudinal and circumferential) and rotation (extent and direction). Volume and strain curves depicted ejection and filling stages as seen in echocardiographic analysis. Like echocardiography strain modestly correlated with EF, likely providing more functional information than EF alone. Applying VVI on multiphase cine-CT clips may be used to assess systolic left ventricular function and may add important global and regional physiological data beyond the net anatomy gathered in CCTA. A large prospective CCTA vs. Echocardiography study would be needed to validate our finding, and define CCTA strain sensitivity and specificity across the coronary vessels tree.

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CRediT authorship contribution statement

Adi Hertz: Writing – original draft, Data curation. **Michael Jerdev:** Writing – review & editing, Data curation. **Liza Grosman-Rimon:** Writing – review & editing, Validation, Methodology. **Itiel Ben-Zakai:** Writing – review & editing, Data curation. **Jordan Rimon:** Writing – review & editing. **Offer Amir:** Writing – review & editing, Supervision, Resources. **Gabby Elbaz Greener:** Writing – review & editing. **Shemy Carasso:** Writing – original draft, Visualization, Validation, Supervision, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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The corresponding author affirms that he has listed everyone who contributed significantly to the work. The authors had access to all the study data, and were responsible for the accuracy of the analysis, and had authority over manuscript preparation and the decision to submit the manuscript for publication. The corresponding author confirms that all authors read and approve the manuscript.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2024.101586.

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