Longer Life Foundation Final Research Report

Title: Patients with Diabetes and Significant Coronary Artery Disease have Increased Systolic Left Ventricular Apical Rotation and Rotation Rate at Rest.

P.I.: Ravi Rasalingam MD

Abstract

Background: Diabetes is associated with an increased risk of coronary artery disease (CAD) related morbidity and mortality. Significant CAD may be associated with abnormal left ventricular function expressed as altered myocardial deformation characteristics. The purpose of this study was to determine whether resting myocardial deformation and rotation may be altered in diabetic patients with significant CAD with normal left ventricular ejection fraction.

Methods and Results: Diabetic patients suspected of CAD scheduled for cardiac catheterization had a resting echocardiogram performed prior to their procedure. An echocardiographer blinded to the cardiac catheterization results performed analysis of longitudinal strain, strain rate, apical rotation and rotation rate. Echocardiographic measurements were compared between patients with and without significant CAD as determined by cardiac catheterization. 84 patients were studied, 39 (46.4%) of whom had significant CAD. Global peak systolic apical rotation was significantly increased (14.9±5.1 versus 11.0±4.8 degrees, $p<0.001$) in patients with CAD along with faster peak systolic apical rotation rate (90.4±29 versus 68.1±22.2 degrees/sec, $p<0.001$). These findings were further confirmed through multivariate logistic regression analysis (global peak systolic

apical rotation OR=1.16, p=0.004 and peak systolic apical rotation rate OR=1.05, p<0.001).

Conclusions: In conclusion, diabetic patients with significant CAD and normal LVEF exhibit an increase in peak systolic apical counter-clockwise rotation and rotation rate detected by echocardiography suggesting that significant CAD and its associated myocardial effects in patients with diabetes may be detected non-invasively at rest.

Background

Patients with diabetes are at increased risk of coronary artery disease and have a higher morbidity and mortality associated with initial presentation than patients without diabetes[1 2]. Early diagnosis and treatment of CAD is therefore critical in this patient population although no effective screening strategy currently exists to detect the presence of significant CAD[3].

A recent evolution in non-invasive imaging technology has allowed more sophisticated and accurate assessment of myocardial function in patients with CAD. Measurement of strain, defined as the degree of deformation of myocardium over the heart cycle relative to its initial dimension, has been shown to be abnormal by magnetic resonance imaging in patients with CAD in the absence of previous myocardial infarction[4]. The authors hypothesized that this was related to the myocardial effects of coronary atherosclerotic plaque evolution

in particular involving small vessel disease, distal micro-embolization and repetitive myocardial stunning. A novel alternative approach to measuring myocardial strain has been developed using 2-dimensional echocardiographic images and the tracking of the relative positions of localized 'speckle' patterns seen within the myocardium as acoustic markers of deformation[5]. The degree of cardiac twisting or rotation can also be measured by tracking the speckle pattern over the heart cycle.

Myocardial deformation is related to the fiber orientation between the different myocardial layers as well as the basal to apical levels of the heart[6 7]. Endocardial fibers are predominantly oriented in a longitudinal direction and in a right-handed helix causing left ventricular shortening and clockwise rotation (as viewed from the apex) respectively[8]. Epicardial fibers are oriented in an opposing left-handed helix and exert a greater effect on myocardial twisting because of a larger radius of curvature[9]. The subendocardial layer and left ventricular apex is most vulnerable to the downstream effects of CAD remodeling, particularly in patients with diabetes prone to diffuse small vessel disease, microvascular obstruction and clinically silent myocardial ischemia and infarction[10 11]. Therefore we hypothesized that longitudinal deformation may be decreased and counter-clockwise myocardial rotation (as viewed from the apex) would be increased in the setting of significant CAD in patients with diabetes where the contributions from the subendocardial fibers may be compromised to a greater extent than would be the case for subepicardial fibers.

Methods

Subjects:

Patients with either type 1 or type 2 diabetes scheduled for diagnostic cardiac catheterization for suspected CAD as part of their clinical care were eligible to be enrolled in this study under a human studies protocol approved by the Washington University Human Research Protection Office (HRPO). Diagnosis of diabetes was established by personal history and/or evidence from laboratory testing showing a random plasma glucose >200mg/dL, by fasting plasma glucose>126mg/dL, or by 2 hour oral glucose tolerance test plasma glucose >200mg/dL. Subjects were excluded from this study if they had a prior history of coronary intervention or evidence of acute or prior myocardial infarction by cardiac enzyme elevation (troponin-I ≥ 0.25 ng/ml, CK > 200 IU/L), electrocardiogram abnormality (significant Q waves, ST segment elevation or depression >1 mm in 2 contiguous leads unrelated to left ventricular hypertrophy or conduction abnormality) or resting left ventricular wall motion abnormality. Other potential confounding conditions such as significant left ventricular hypertrophy defined as end-diastolic left ventricular wall thickness >1.5 cm or severe hypertension defined as systolic and diastolic blood pressures greater than 200 mmHg and 110 mmHg, respectively or ventricular conduction abnormalities at the time of acquisition were also excluded.

Cardiac catheterization:

An experienced angiographer blinded to the echocardiographic data interpreted the results of coronary angiographic studies. The degree of stenosis was quantified by percent occlusion of the lumen as determined in two orthogonal views. For this study ≥50% of any major coronary artery indicated the presence of significant CAD as defined by the American College of Cardiology consensus document on the performance of cardiac catheterization for evaluation of CAD[12].

Echocardiography:

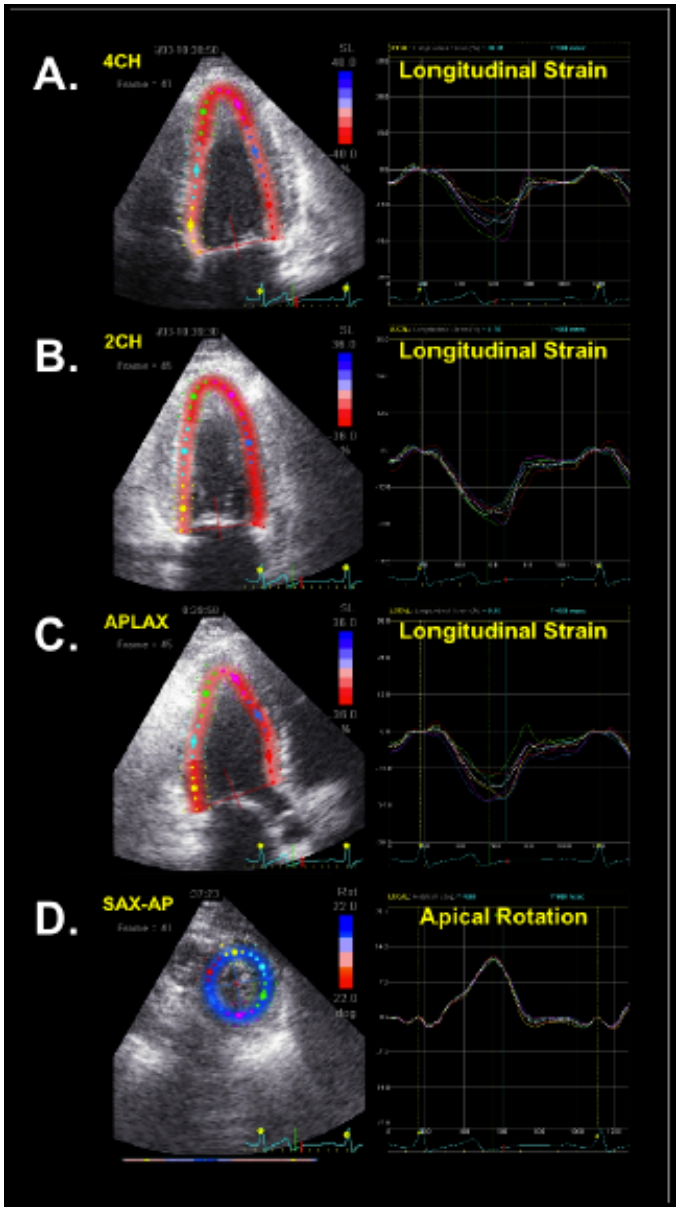
Transthoracic echocardiographic images were acquired using a GE Vivid 7™ imaging system (General Electric Medical Systems, Milwaukee, WI) immediately prior to coronary angiography. All images were obtained by an experienced sonographer and digitally archived for subsequent analyses and interpretation by a single cardiologist. Echocardiographic examination was performed which included Doppler assessment for valvular disease as well as apical four chamber (4CH), two chamber (2CH), and long axis (APLAX) and parasternal short axis images of the apical region (SAX-AP). The ejection time, based on the timing of aortic valve opening and closure, was determined by analysis of the spectral Doppler waveform obtained from a sample gate positioned in the left-ventricular outflow tract. These images were acquired for three consecutive heart cycles and downloaded to a GE EchoPac™ echocardiographic image analysis system (General Electric Medical Systems, Milwaukee, WI) for further analyses as described below, including left ventricular ejection fraction.

Measurements of Myocardial Strain, Strain Rate, and Apical Rotation:

Myocardial strain (%), strain rate (s^{-1}), apical rotation (degrees) and rotation rate (degrees/sec) were obtained by analyzing the acquired images using the GE EchoPac^{TM} analysis software by a trained investigator blinded to the patient's clinical data. Myocardial borders were delineated using the automated algorithm available on the EchoPac^{TM} system to track the myocardial thickness over the acquired heart cycles. Tracking of the myocardial borders was verified visually prior to approving the data for subsequent analysis.

Global and segmental longitudinal strain and strain rate data curves over the heart cycle were automatically measured for each apical 4CH, 2CH and APLAX echocardiographic view. The peak values for each of the global longitudinal strain (GLS) and strain rate curves (GLSr), for each of the segments in each apical view, were obtained and averaged. Also global apical rotation (GAR) and rotation rate (GARr) curves, representing the mean of the measured segments in the SAX-AP view, were generated (**Figure 1**).

Figure 1. Global longitudinal strain from three apical views (Panel A, B, C). Global apical rotation was measured from a short axis view at the apex of the heart (Panel D).



Statistical Analysis:

Univariate analysis, using t-tests for independent groups, was conducted for echocardiographic variables comparing patients with significant CAD to those without. Significant CAD was defined as any stenosis ≥50% as determined by cardiac catheterization. For each echocardiographic measure a logistic regression model was built with the presence or absence of significant CAD as the dependent variable. Independent variables included the echocardiographic measurement along with covariates associated with significant CAD. To help identify covariates, the relationship between available demographic and clinical variables and significant CAD were examined through univariate analyses. Categorical variables were evaluated with chi-square tests (or Fisher's exact test in the case of small sample size cell counts). Continuous variables were evaluated with t-tests. Variables with p-values<0.10 were included as model covariates. Odds ratios and 95% confidence intervals were reported from the multivariate logistic regression analysis with one model built for each measurement. A Bonferroni correction was performed to limit the effect of multiple comparisons and type I error. Therefore, since eight variables were evaluated, echocardiographic measures were found to be significantly associated with CAD when the p-value fell below 0.05/8=0.006.

After multivariate analysis, those echocardiographic measurements that remained significant were tested for ability to identify patients with CAD, using

receiver operating characteristics (ROC) analysis and the area under the curve (AUC). The Youden index was used to identify the optimal cut-point for sensitivity and specificity[13]. Reproducibility was assessed by inter-observer and intra-observer reliability using the intra-class correlation coefficient (ICC)[14]. All statistical analyses were conducted using SAS® 9.2 (SAS Institute Inc., Cary, North Carolina).

Results

Demographic Data:

A total of 89 subjects were enrolled of which **84** (**37** male, **47** female) ranging in age from **35** to **82** years were eligible. Poor echocardiographic windows disqualified five of them. Indication for cardiac catheterization was an abnormal cardiac stress test in 89% of patients with the remainder evaluated for anginal symptoms without preceding cardiac stress testing. **Table 1** provides the clinical characteristics and conventional echocardiographic measurements of the study population. Resting heart rate tended to be lower in patients with significant CAD compared to those without significant CAD (71±13 versus 77±12 beats/minute, p=0.039) likely secondary to increased beta-blocker use (44% versus 31%, p=0.020). All other variables were similar between both groups including septal wall thickness (p=0.776) and LVEF (p=0.089). Variables with a p value <0.1 were used as covariates in subsequent multivariate logistic models.

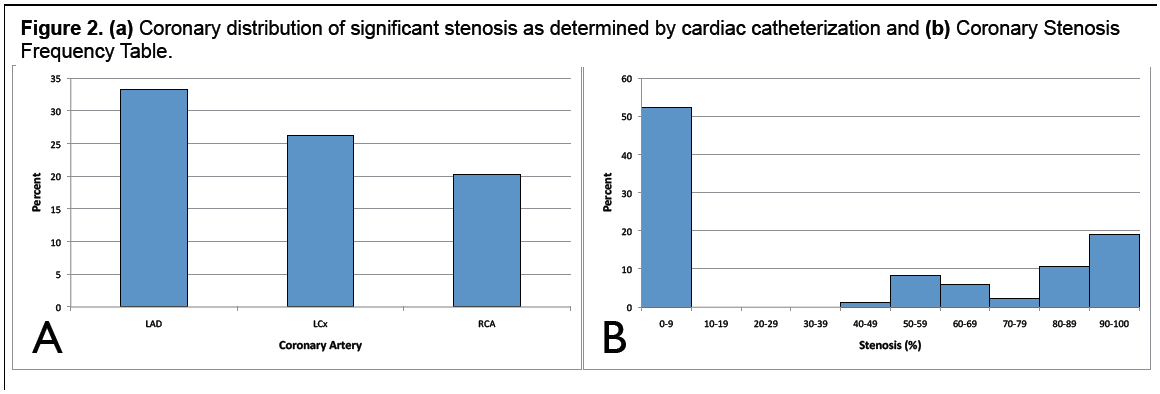
Table 1. Clinical and echocardiographic characteristics of the study population.

	No Significant CAD		Significant CAD		
	N	Mean (± std. dev) or Count	N	Mean (± std. dev) or Count	p-value
Demographics					
Age (years)	45	58.6 (±9.3)	39	62.2(±10.6)	0.103
Male	45	19	39	18	0.717
Caucasian	45	32	39	28	1.000
Vital signs					
BMI (kg/m2)	41	36.5 (±12.3)	37	34.2 (10.1)	0.373
Height (cm)	41	168.3 (±14.9)	37	168.9 (15.4)	0.860
SBP (mmHg)	45	136 (18)	39	143 (17)	0.077
DBP (mmHg)	45	77 (11)	39	78 (12)	0.574
HR (beats/minute)	44	77 (12)	39	71 (±13)	0.039*
Risk factors					
Dyslipidemia	45	33	39	32	0.341
Smoking-current	45	11	39	9	0.960
Hypertension	45	42	39	32	0.176
Family History of CAD	44	13	39	18	0.119
Laboratory Values					
Glucose (mg/dL)	45	164.8 (±70.3)	39	185.3 (±87.3)	0.238
HgbA1c (%)	31	7.4 (±1.6)	29	8.2 (±2.7)	0.186
Creatinine (mg/dL)	44	1.13 (±1.33)	39	0.96 (±0.30)	0.436
Echocardiogram					
LVEDV (mL)	45	103.6 (±32.0)	39	100.8 (±28.7)	0.673
LVESV (mL)	45	37.4 (±13.4)	39	38.3 (±12.2)	0.754
Septum (mm)	45	1.0 (±0.1)	39	1.0 (±0.1)	0.776
LVEF (%)	45	64 (±5)	39	62 (±5)	0.089
Current Medications					
Beta-Blocker	45	14	39	22	0.020*
Calcium Channel Blocker	45	17	39	11	0.353
Angiotensin Converting Enzyme inhibitor	45	32	39	24	0.353
Oral Hypoglycemic	45	34	39	30	0.883
Insulin	45	14	39	13	0.828

Cardiac Catheterization Results:

39 (46.4%) patients had evidence of significant CAD by cardiac catheterization. The vascular distribution of significant lesions for the study population is shown in **Figure 2a**, with 19% having multi-vessel disease. The distribution of stenosis severity is shown in **Figure 2b**.

Figure 2. (a) Coronary distribution of significant stenosis as determined by cardiac catheterization and **(b)** Coronary Stenosis Frequency Table.



Apical Rotation and Rotation Rate:

Global apical rotation (GAR) was greater (14.9 versus 11.0 degrees) and its rate (GARr-S) was faster (90.4 versus 68.1 degrees/second) in diabetic patients with significant CAD versus those without significant CAD. After multivariate analysis controlling for systolic blood pressure, heart rate, left ventricular ejection fraction and beta-blocker use, both echocardiographic indices remained significant **(Table 2)**. GAR had an odds ratio of 1.166 ($p=0.004$) and GARr-S had an odds ratio of 1.050 ($p<0.001$). .

Longitudinal Strain and Strain Rate:

Longitudinal strain and strain rate were not significantly different between the two groups (**Table 2**).

Table 2. Univariate and Multivariate analysis

	Univariate				Multivariate model (for having CAD)		
	No CAD		Significant CAD				
Variable	N	Value±SD	N	Value±SD	Odds Ratio	P value	95% CI†
GAR	45	11.0±4.8	36	14.9±5.1	1.17	0.004*	1.01-1.35
GARr-S	45	68.1±22.2	36	90.4±29.0	1.05	<0.001*	1.01-1.10
GARr-E	45	-77.8±35.0	36	-89.4±39.0	0.99	0.164	0.97-1.01
GARr-A	45	-39.6±19.7	36	-50.6±33.9	0.10	0.036	0.95-1.01
GLS	45	-18.5±4.0	39	-18.0±2.5	0.97	0.647	0.78-1.19
GLSr-S	45	-1.0±0.2	39	-0.9±0.2	0.76	0.100	0.49-1.20
GLSr-E	45	1.1±0.4	39	1.0±0.2	0.96	0.616	0.77-1.20
GLSr-A	45	0.9±0.2	38	1.0±0.3	1.40	0.021	0.94-2.08

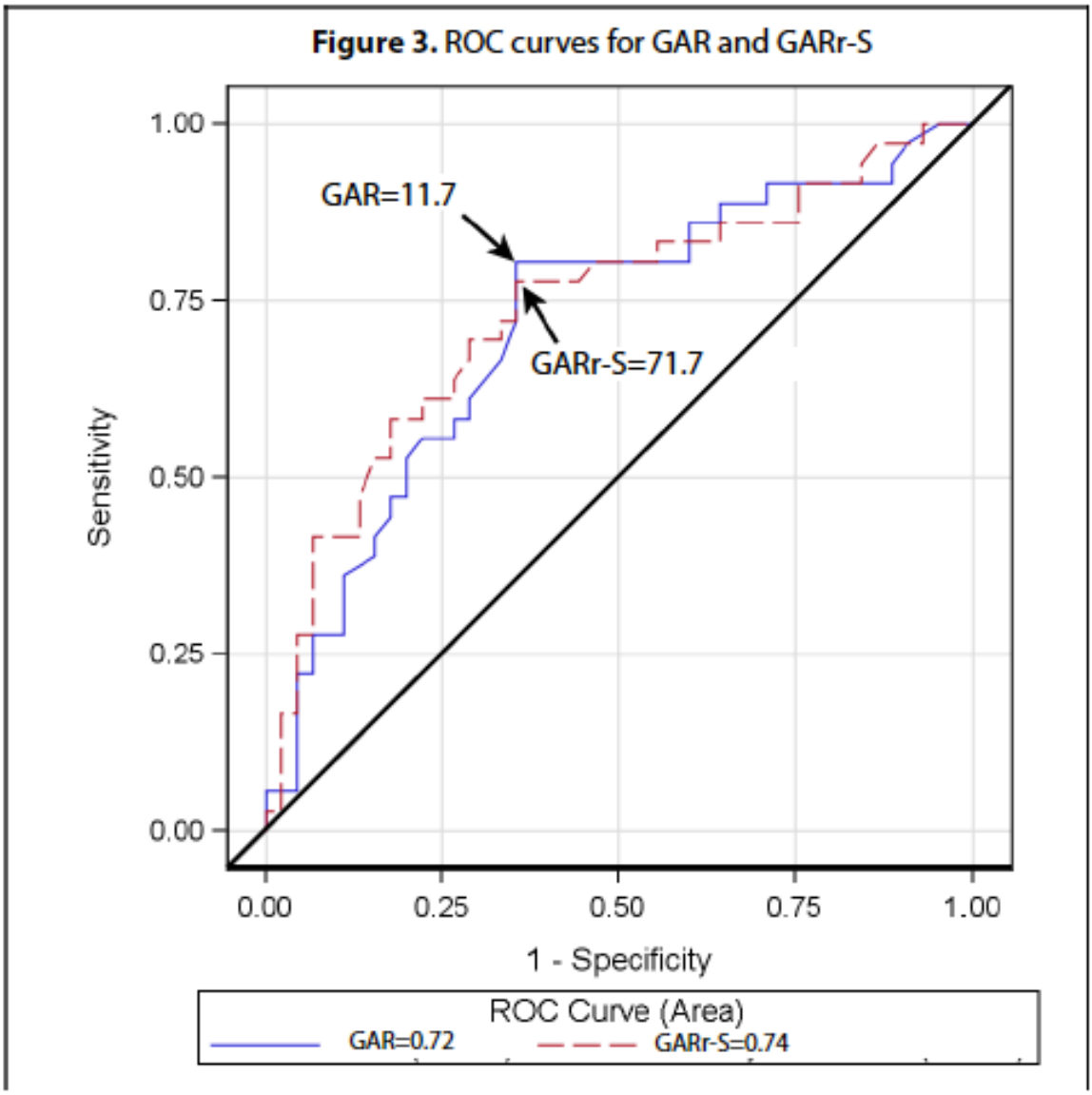
GAR=peak systolic global apical rotation, GARr-S=peak systolic global apical rotation rate, GARr-E, peak early diastolic global apical rotation rate, GARr-A=peak late diastolic global apical rotation rate, GLS=peak systolic global longitudinal strain, GLSr-S=peak systolic global longitudinal strain rate, GLSr-E= peak early diastolic global longitudinal strain rate, GLSr-A=peak late diastolic global longitudinal strain rate

** Significant at .05/8=0.006*

† Confidence intervals calculated with Bonferroni correction

ROC Analysis

FIGURE 3 shows ROC analyses for GAR and GARr-S. Accuracies of these parameters to detect significant CAD in the study population were assessed by measurement of the AUC; for GAR it was 0.72 (CI=0.60-0.83) and for GARr-S was 0.74 (CI=0.63-0.85). The optimal cut-point for peak GAR was 11.7 degrees providing a sensitivity and specificity of 80.6% and 64.4% respectively. For GARr-S 71.7 seconds^{-1} provided a sensitivity and specificity of 77.8% and 64.4% respectively.



Reproducibility of Strain and Rotation Measurements:

Re-analysis of a subset of the echocardiographic images was performed to assess inter- and intra-observer reproducibility of measurements. GAR and GLS were examined for reproducibility. Both showed good agreement with ICC values near 1. For GAR, the inter-observer and intra-observer ICC values were 0.95 (95% CI = (0.84, 0.99)) and 0.97 (95% CI = (0.9, 0.99)), respectively. For

4CH GLS, ICC = 0.97 (95% CI = (0.88, 0.99)) for inter-observer and ICC = 0.97 (95% CI = (0.89, 0.99)) for intra-observer.

Discussion:

Results of our study demonstrate that the extent and rate of myocardial function expressed as apical rotation were increased in diabetic patients when afflicted by significant CAD. These changes were found by analysis of standard, resting echocardiographic images.

Although LVEF remains the most commonly used measurement of LV systolic function, and is a strong predictor of prognosis in patients with CAD and heart failure[15], this parameter depends on endocardial radial thickening and LV geometry and is insensitive to changes related to other directions of deformation[16]. Using cardiac magnetic resonance imaging, resting myocardial function has been previously shown to be abnormal in patients with sub-clinical CAD and no documented history of myocardial infarction or reduction in left ventricular ejection fraction. These studies demonstrated that patients with increased coronary artery calcification scores and carotid intimal thickness, had regional alterations in myocardial deformation and increased risk of morbidity and mortality[4 17 18]. In our study despite a trend for LVEF to be lower in patients with significant CAD (p=0.09) it was still within normal limits.

Alteration of longitudinal deformation with significant CAD

There have been relatively few studies using resting echocardiography to demonstrate alteration in myocardial deformation in patients with either suspected or known CAD and normal LVEF and no studies evaluating patients with diabetes exclusively. Shimoni et al. demonstrated that patients presenting with angina had a significant reduction in longitudinal strain compared to a control group of patients at low risk of CAD[19]. Choi et al. also demonstrated similar findings with increased accuracy in segmental analysis of basal and mid peak longitudinal strain values rather than GLS for detection of significant left main or three vessel CAD in patients presenting for cardiac catheterization[20]. Nucifora et al. demonstrated that a cut-point of ≥-17.4% GLS provided a high degree of accuracy in identifying patients with significant CAD (sensitivity=83% and specificity=77%)[21].

In our group of patients we did not find a significant reduction in GLS and GLSr in patients with stable angina and significant CAD. One major reason for this may be attributed to difference in study populations and design. Shimoni et al. compared a population, of patients with acute coronary syndrome and evidence of myocardial damage (troponin elevation), with asymptomatic patients presenting for stress test (therefore very low likelihood for CAD), increasing the odds that differences in myocardial deformation would be detected. In their study[19] the accuracy of longitudinal strain to detect significant CAD was decreased when analyzing only patients with stable angina and using GLS as in

our study. Choi et al. similarly evaluated a higher risk population with a third of their population having significant left main or three vessel CAD. In our group of patients sub-clinical diabetic cardiomyopathy and the propensity for small vessel CAD may also have reduced the differences, with mean GLS in normal versus CAD patients (-18.5% versus -18%) compared to Nucifura et al. (-19.5% versus -15.8%)[21].

Alteration of apical rotation with significant CAD

Apical myocardial rotation and its rate were significantly increased in patients with significant CAD in our study. Patients with coronary stenosis of ≥ 50% had a mean GAR of 14.9 versus 11.0 degrees and GARr-S of 90.4 versus 68.1 degrees/second. Apical rotation in animal and human models of ischemia has been shown to transiently increase and then reduce with prolonged ischemia although the time course of these events remains unclear[22-24]. In the setting of myocardial infarction Bertini et al. demonstrated an incremental effect on subendocardial and subepicardial layers resulting in reduction of apical rotation based on the size and clinical severity of myocardial damage[25]. In patients with small infarctions compared to normal controls, subendocardial rotation was reduced (12.6±5.2 versus 15.3±2.7 degrees) while subepicardial rotation was increased (9.6±3.6 versus 8.9±1.9 degrees). The overall effect on apical rotation specifically was not reported. There have been no studies evaluating the effects of repetitive ischemia without infarction (such as it occurs with angina) on left

ventricular rotation.

Interestingly, patients with diabetes without CAD have increased left ventricular apical rotation when compared to normal controls. In our study the mean GAR for patients without CAD (11±4.8 degrees) was higher than the control group in the study performed by Bertini et al (7.4±2.1 degrees) for example[25]. Fonseca et al. found a 17% increase in torsion and 20% increase in torsion rate in patients with diabetes compared to controls using cardiac MR[26]. Chung et al. found similar changes in a diabetic population with optimal diabetes control and lack of diabetic related co-morbidities using the same imaging modality[27]. Shivu et al. demonstrated a reduction in myocardial perfusion reserve index (MPRI) using cardiac MR in the setting of increased ventricular torsion in patients with diabetes proposing that this alteration in myocardial mechanics is related to coronary microangiopathy[28]. A reduction in MPRI has been also been demonstrated to be an accurate non-invasive measure for the presence of significant CAD[29]. Our results extend these findings suggesting that in diabetic patients with significant CAD resting apical rotation and rotation rate detected by echocardiography are increased.

The mechanism that underpins the observed increase in apical rotation and rate cannot be ascertained by our study. It is unlikely that these findings are related to resting myocardial ischemia with the majority of patients with significant CAD (59%) having stenoses between 50 and 90%, a severity that is unlikely to alter

resting myocardial blood flow[30]. We hypothesize that in diabetic patients, small vessel CAD, repetitive myocardial ischemia, vessel remodeling and distal micro-embolization may cause a permanent reduction in sub-endocardial function resulting in a compensatory increase in subepicardial function[31-33]. This reduction in sub-endocardial function and increase in the counter-balancing sub-epicardial function has been proposed by others as a mechanism for increased apical rotation[34 35]. In our study longitudinal deformation was already significantly decreased in diabetic patients irrespective of the presence of CAD in comparison to published studies evaluating patients without diabetes[19-21]. We believe this represents primarily the effect of diabetes on the myocardium as well as other CAD related risk factors such as arterial hypertension. As reported by a model created by Beyar et al. an increase in left ventricular rotation may provide a mechanism to reduce transmural myocardial energy requirements in the setting of reduced longitudinal deformation and sub-clinical cardiomyopathy[10]. This may be especially important in diabetic patients where the effects of significant CAD may further affect already impaired myocardial energetics[36]

Limitations

In this prospective study of patients with diabetes presenting for cardiac catheterization we utilized standard resting echocardiographic images acquired in a clinical setting to derive strain measurements. The relatively small study population may have affected statistical power to detect differences in the variables tested. Utility in lower risk populations will need to be performed due to

referral bias in the study population tested. We chose select strain and rotation parameters to minimize processing time and also to reflect sub-endocardial function, which is most likely to be affected by the effects of CAD. For example, we measured left ventricular apical rotation rather than twist, which requires additional calculation of basal rotation. Apical rotation is the predominant determinant of twist and has shown comparable accuracy when assessing myocardial contractility[37]. Comprehensive data on diabetes control was not available in our population however in the study by Chung et al. diabetes control and duration did not appear to affect the finding of increased resting torsion[27]. Finally neither quantitative angiography nor assessment of coronary flow reserve was performed to confirm lesion hemodynamic signficance, raising the possibility of misclassification of study participants. However, recognizing the pitfalls in accuracy of visual estimation of coronary stenosis, this study was designed to reflect current cardiology practice and data used for decision management.

Summary

In diabetic patients with significant CAD and normal left ventricular ejection fraction myocardial function was characterized by an increase in LV apical counter-clockwise systolic rotation and rotation rate, providing a distinct feature that may be useful to identify the coexistence of CAD in diabetes. Further studies are needed to better define the mechanisms responsible for these changes, and to evaluate their potential diagnostic applicability and accuracy in a broader

patient population.

Future Plans

This study has provided preliminary data for a new line of investigation designed to use both imaging and biomarker evidence for sub-clinical CAD events. A private industry sponsored biomarker pilot study will begin in October 2011 testing whether using a novel high sensitivity troponin assay in patients with stable CAD can detect sub-clinical CAD events and predict future risk of death and myocardial infarction. An NIH RO1 has been submitted to allow a fully powered study to be performed.

References:

1. Hu FB, Stampfer MJ, Solomon CG, Liu S, Willett WC, Speizer FE, et al. The impact of diabetes mellitus on mortality from all causes and coronary heart disease in women: 20 years of follow-up. *Arch Intern Med* 2001;161(14):1717-23.
2. Malmberg K, Yusuf S, Gerstein HC, Brown J, Zhao F, Hunt D, et al. Impact of diabetes on long-term prognosis in patients with unstable angina and non-Q-wave myocardial infarction: results of the OASIS (Organization to Assess Strategies for Ischemic Syndromes) Registry. *Circulation* 2000;102(9):1014-9.
3. Bax JJ, Young LH, Frye RL, Bonow RO, Steinberg HO, Barrett EJ. Screening for coronary artery disease in patients with diabetes. *Diabetes Care* 2007;30(10):2729-36.
4. Fernandes VR, Polak JF, Edvardsen T, Carvalho B, Gomes A, Bluemke DA, et al. Subclinical atherosclerosis and incipient regional myocardial dysfunction in asymptomatic individuals: the Multi-Ethnic Study of Atherosclerosis (MESA). *J Am Coll Cardiol* 2006;47(12):2420-8.
5. Perk G, Tunick PA, Kronzon I. Non-Doppler two-dimensional strain imaging by echocardiography--from technical considerations to clinical applications. *J Am Soc Echocardiogr* 2007;20(3):234-43.
6. Greenbaum RA, Ho SY, Gibson DG, Becker AE, Anderson RH. Left ventricular fibre architecture in man. *Br Heart J* 1981;45(3):248-63.
7. Sengupta PP, Korinek J, Belohlavek M, Narula J, Vannan MA, Jahangir A, et al. Left ventricular structure and function: basic science for cardiac imaging. *J Am Coll Cardiol* 2006;48(10):1988-2001.

8. Narula J, Vannan MA, DeMaria AN. Of that Waltz in my heart. *J Am Coll Cardiol* 2007;49(8):917-20.
9. Ingels NB, Jr., Hansen DE, Daughters GT, 2nd, Stinson EB, Alderman EL, Miller DC. Relation between longitudinal, circumferential, and oblique shortening and torsional deformation in the left ventricle of the transplanted human heart. *Circ Res* 1989;64(5):915-27.
10. Beyar R, Sideman S. Left ventricular mechanics related to the local distribution of oxygen demand throughout the wall. *Circ Res* 1986;58(5):664-77.
11. Pfeffer MA. Left ventricular remodeling after acute myocardial infarction. *Annu Rev Med* 1995;46:455-66.
12. Bashore TM, Bates ER, Berger PB, Clark DA, Cusma JT, Dehmer GJ, et al. American College of Cardiology/Society for Cardiac Angiography and Interventions Clinical Expert Consensus Document on cardiac catheterization laboratory standards. A report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. *J Am Coll Cardiol* 2001;37(8):2170-214.
13. Youden WJ. Index for rating diagnostic tests. *Cancer* 1950;3(1):32-5.
14. Lachin JM. The role of measurement reliability in clinical trials. *Clin Trials* 2004;1(6):553-66.
15. Volpi A, De Vita C, Franzosi MG, Geraci E, Maggioni AP, Mauri F, et al. Determinants of 6-month mortality in survivors of myocardial infarction after thrombolysis. Results of the GISSI-2 data base. The Ad hoc Working Group of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-2 Data Base. *Circulation* 1993;88(2):416-29.
16. Cramariuc D, Gerdts E, Davidsen ES, Segadal L, Matre K. Myocardial deformation in aortic valve stenosis: relation to left ventricular geometry. *Heart* 2010;96(2):106-12.
17. Edvardsen T, Detrano R, Rosen BD, Carr JJ, Liu K, Lai S, et al. Coronary artery atherosclerosis is related to reduced regional left ventricular function in individuals without history of clinical cardiovascular disease: the Multiethnic Study of Atherosclerosis. *Arterioscler Thromb Vasc Biol* 2006;26(1):206-11.
18. Yan RT, Bluemke D, Gomes A, Burke G, Shea S, Liu K, et al. Regional Left Ventricular Myocardial Dysfunction as a Predictor of Incident Cardiovascular Events MESA (Multi-Ethnic Study of Atherosclerosis). *J Am Coll Cardiol* 2011;57(17):1735-44.
19. Shimoni S, Gendelman G, Ayzenberg O, Smirin N, Lysyansky P, Edri O, et al. Differential effects of coronary artery stenosis on myocardial function: the value of myocardial strain analysis for the detection of coronary artery disease. *J Am Soc Echocardiogr* 2011;24(7):748-57.
20. Choi JO, Cho SW, Song YB, Cho SJ, Song BG, Lee SC, et al. Longitudinal 2D strain at rest predicts the presence of left main and three vessel coronary artery disease in patients without regional wall motion abnormality. *Eur J Echocardiogr* 2009;10(5):695-701.
21. Nucifora G, Schuijf JD, Delgado V, Bertini M, Scholte AJ, Ng AC, et al. Incremental value of subclinical left ventricular systolic dysfunction for the identification of patients with obstructive coronary artery disease. *Am Heart J* 2010;159(1):148-

57.
22. Jamal F, Kukulski T, Strotmann J, Szilard M, D'Hooge J, Bijnens B, et al. Quantification of the spectrum of changes in regional myocardial function during acute ischemia in closed chest pigs: an ultrasonic strain rate and strain study. *J Am Soc Echocardiogr* 2001;14(9):874-84.
23. Knudtson ML, Galbraith PD, Hildebrand KL, Tyberg JV, Beyar R. Dynamics of left ventricular apex rotation during angioplasty: a sensitive index of ischemic dysfunction. *Circulation* 1997;96(3):801-8.
24. Kroeker CA, Tyberg JV, Beyar R. Effects of ischemia on left ventricular apex rotation. An experimental study in anesthetized dogs. *Circulation* 1995;92(12):3539-48.
25. Bertini M, Delgado V, Nucifora G, Ajmone Marsan N, Ng AC, Shanks M, et al. Left ventricular rotational mechanics in patients with coronary artery disease: differences in subendocardial and subepicardial layers. *Heart* 2010;96(21):1737-43.
26. Fonseca CG, Dissanayake AM, Doughty RN, Whalley GA, Gamble GD, Cowan BR, et al. Three-dimensional assessment of left ventricular systolic strain in patients with type 2 diabetes mellitus, diastolic dysfunction, and normal ejection fraction. *Am J Cardiol* 2004;94(11):1391-5.
27. Chung J, Abraszewski P, Yu X, Liu W, Krainik AJ, Ashford M, et al. Paradoxical increase in ventricular torsion and systolic torsion rate in type I diabetic patients under tight glycemic control. *J Am Coll Cardiol* 2006;47(2):384-90.
28. Shivu GN, Abozguia K, Phan TT, Ahmed I, Weaver R, Narendran P, et al. Increased left ventricular torsion in uncomplicated type 1 diabetic patients: the role of coronary microvascular function. *Diabetes Care* 2009;32(9):1710-2.
29. Nagel E, Klein C, Paetsch I, Hettwer S, Schnackenburg B, Wegscheider K, et al. Magnetic resonance perfusion measurements for the noninvasive detection of coronary artery disease. *Circulation* 2003;108(4):432-7.
30. Gould KL, Hamilton GW, Lipscomb K, Ritchie JL, Kennedy JW. Method for assessing stress-induced regional malperfusion during coronary arteriography. Experimental validation and clinical application. *Am J Cardiol* 1974;34(5):557-64.
31. Dokainish H, Pillai M, Murphy SA, DiBattiste PM, Schweiger MJ, Lotfi A, et al. Prognostic implications of elevated troponin in patients with suspected acute coronary syndrome but no critical epicardial coronary disease: a TACTICS-TIMI-18 substudy. *J Am Coll Cardiol* 2005;45(1):19-24.
32. Topol EJ, Yadav JS. Recognition of the importance of embolization in atherosclerotic vascular disease. *Circulation* 2000;101(5):570-80.
33. Kloner RA, Jennings RB. Consequences of brief ischemia: stunning, preconditioning, and their clinical implications: part 2. *Circulation* 2001;104(25):3158-67.
34. Nakatani S. Left ventricular rotation and twist: why should we learn? *J Cardiovasc Ultrasound* 2011;19(1):1-6.
35. Sengupta PP, Tajik AJ, Chandrasekaran K, Khandheria BK. Twist mechanics of the left ventricle: principles and application. *JACC Cardiovasc Imaging* 2008;1(3):366-76.
36. Shivu GN, Phan TT, Abozguia K, Ahmed I, Wagenmakers A, Henning A, et al.

Relationship between coronary microvascular dysfunction and cardiac energetics impairment in type 1 diabetes mellitus. *Circulation* 2010;121(10):1209-15.

37. Kim WJ, Lee BH, Kim YJ, Kang JH, Jung YJ, Song JM, et al. Apical rotation assessed by speckle-tracking echocardiography as an index of global left ventricular contractility. *Circ Cardiovasc Imaging* 2009;2(2):123-31.