Increased Coronary Tortuosity Is Associated with Increased Left Ventricular Longitudinal Myocardial Shortening

Andrew C. Oehler, MD, Jessica Minnier, PhD, and Jonathan R. Lindner, MD, *Portland, Oregon*

Background: The mechanistic basis for tortuosity of the coronary arteries (TCA) is unclear. The aim of this study was to test the hypothesis that the relative degree of systolic longitudinal shortening of the left ventricle that deforms coaxially oriented coronary arteries is associated with TCA.

Methods: Adult subjects undergoing coronary angiography and comprehensive echocardiography within 3 months were classified dichotomously as with ($n = 32$) or without ($n = 42$) TCA defined on the basis of number and severity of coronary angles. Systolic left ventricular (LV) longitudinal deformation was determined by mitral annular plane systolic excursion (MAPSE) from both B-mode displacement and tissue Doppler time-velocity integral; data were indexed to LV diastolic long-axis length.

Results: There were no differences between groups with respect to age, gender, hypertension, or coronary artery disease. Patients with TCA had significantly ($P < .01$) lower LV mass index and a shorter total LV diastolic long-axis length (mean, 8.3 ± 1.9 vs 9.1 ± 2.2 cm; $P < .01$). Despite having a shorter length, those with TCA had greater MAPSE by both methods. MAPSE normalized to diastolic length was significantly greater ($P < .01$) in those with TCA, which remained the case after excluding subjects with reduced LV ejection fraction. Multiple linear regression found that lateral annular MAPSE had the largest effect size, with a 13-fold increase in likelihood for TCA for every 0.1 of normalized MAPSE.

Conclusions: TCA is not associated with increased LV mass but rather with smaller hearts that have greater relative longitudinal shortening of the left ventricle. This finding suggests that TCA could represent an adaptive response to longitudinal systolic distortion of coaxially oriented coronary arteries that dynamically produce shear stresses associated with expansive coronary remodeling. (J Am Soc Echocardiogr 2017;30:1028-34.)

Keywords: Coronary anatomy, Coronary tortuosity, Longitudinal shortening

Excessive tortuosity of the coronary arteries (TCA) is a somewhat common finding in patients referred for coronary angiography, reported in 14% to 40% of patients referred for angiography.[1-4] The presence of TCA has been associated with chest pain and myocardial perfusion abnormalities during stress in the absence of obstructive coronary artery disease.[2,5,6] Fluid dynamic modeling suggests that stress-induced ischemia may be attributable to a reduction in distal coronary artery perfusion pressure from viscous and turbulence energy losses.[7,8] The physiologic reasons for TCA are unclear. Preclinical studies in which elastases and collagenases were used to alter arterial morphology together with genetic and pathologic analysis of rare clinical disorders such as arterial tortuosity syndrome have indicated that arterial tortuosity arises from abnormalities in arterial elastin fibers and extracellular matrix.[9,10] Apart from inherited disorders, some but not all studies have linked TCA with hypertension and female sex[1,4,11] and with increased left ventricular (LV) mass from pressure but not volume overload and smaller heart size, suggesting that this form of coronary remodeling is not from increased LV mass alone.[12] Dynamic forces on the coronary arteries have not been studied.

During ventricular systole at rest, there is normally a 15% to 25% longitudinal shortening of the LV and right ventricular dimensions. Accordingly, epicardial arteries oriented along the ventricular long axis, which are those that are most likely to develop TCA, must dynamically deform. Fluid dynamic models predict that systolic hinging of vessels during longitudinal shortening would be expected to produce excessive wall shear stress.[13,14] High shear stress at coronary bends predisposes to what has been termed "expansive remodeling," which likely involves shear-dependent pathways, including regional production of proteases, fragmentation of the elastic laminae, and smooth muscle cell apoptosis.[15,16] Accordingly, we hypothesized that TCA is associated with the relative degree of longitudinal shortening, particularly in small but hypertrophic hearts that produces a scenario of increase in flow demand at rest yet an

From the Knight Cardiovascular Institute, Oregon Health & Science University, Portland, Oregon.

Dr. Lindner is supported by grants R01-HL078610 and R01-HL130046 from the National Institutes of Health and grant 14NSBRI1-0025 from the National Space Biomedical Research Institute (NSBRI).

Reprint requests: Jonathan R. Lindner, MD, Cardiovascular Division, UHN-62 Oregon Health & Science University, 3181 SW Sam Jackson Park Road, Portland, OR 97239 (E-mail: *linderj@ohsu.edu*).

0894-7317/$36.00

http://dx.doi.org/10.1016/j.echo.2017.06.007

Abbreviations

2D = Two-dimensional

LAD = Left anterior descending coronary artery

LASSO = Least absolute shrinkage and selection operator

LV = Left ventricular

LVEF = Left ventricular ejection fraction

MAPSE = Mitral annular plane systolic excursion

TCA = Tortuosity of the coronary arteries

TI = Tortuosity index

TVI = Time-velocity integral

economy of epicardial space during systole. To test this hypothesis, echocardiographic measurements of LV geometry and longitudinal shortening were compared in subjects referred for coronary angiography with and without TCA.

METHODS

Subjects

The study was approved by the investigational review board at Oregon Health & Sciences University. The design was a retrospective case-control study. Medical records from 450 consecutive adult patients (>19 years of age) undergoing elective diagnostic coronary angiography during a 6-month time interval were screened to identify 76 subjects who underwent comprehensive echocardiography within 30 days of angiography. Patients were excluded for acute coronary syndrome at the time of coronary angiography, prior coronary artery bypass surgery, mitral valve prosthesis, connective tissue disease, moderate or greater valvular regurgitation, major cardiovascular event (death, acute coronary syndrome, coronary revascularization, or hospitalization for heart failure), or change in any medical therapy that could influence inotropic status (β-blockers, calcium channel blockers) between study angiography and echocardiography or inadequate echocardiographic views to make accurate measurements.

Patient demographics were obtained from review of the electronic medical record documented at the time of angiography. Hypertension was defined as a past or current history of hypertension requiring medication. Coronary artery disease was defined as a history of myocardial infarction, revascularization, or coronary stenosis >50% on angiography.

Coronary Angiography

Digitized images of selective coronary angiography were analyzed by an experienced reader blinded to the results of echocardiography. The presence of TCA was defined according to previously suggested criteria as three or more abrupt turns of >45° in at least one major epicardial coronary artery supplying the left ventricle.[1] Because of nonlongitudinal orientation, the left circumflex and right coronary arteries were not included in the analysis, whereas the left anterior descending coronary artery (LAD), major diagonal, major obtuse marginal arteries, and posterior descending arteries were included. ImageJ (National Institutes of Health, Bethesda, MD) was used to quantify the length and span of each target coronary at end-diastole, as previously described. Length was defined as the true distance each coronary artery traversed from its origin to the most distal visualized portion of the vessel during diastole. Span was measured as the shortest distance each artery could potentially traverse if linear in geometry. Tortuosity for each artery was calculated using previously published criteria by dividing length by span, and a tortuosity index (TI) for each subject was calculated by combining data for all vessels and weighting according length.[12,17] Intraobserver variability of TCA measurement was assessed by reanalysis of TI >6 months later in 15 randomly selected subjects from the total population.

Echocardiography

Quantitative two-dimensional and Doppler echocardiographic data on LV dimensions, mass, relative wall thickness, and systolic function were made according to American Society of Echocardiography guidelines,[18] except that normal LV ejection fraction (LVEF) was defined as >50%. Previously published criteria based on LV mass and dimensions were used to characterize LV mass as normal, concentric remodeling, concentric hypertrophy, or eccentric hypertrophy.[18] Stroke volume was calculated as the product of LV outflow tract diameter and time-velocity integral (TVI). From the apical four-chamber view, LV length was defined as the distance from the mitral annular plane to the apical epicardium at end-diastole. Two-dimensional longitudinal excursion of the lateral mitral annulus from end-diastole to the maximal end-systolic descent (mitral annular plane systolic excursion [MAPSE]) was measured using digital video calipers. Doppler-based MAPSE was also calculated by measuring the TVI of the systolic tissue Doppler velocity (S′) of the medial and lateral mitral annulus.[19] For all measurements, an average of five beats was used for subjects in atrial fibrillation. Reproducibility of MAPSE measurement from Doppler-derived and two-dimensional (2D) methods was assessed by reanalysis >6 months later in 15 randomly selected subjects from the total population.

Statistical Analysis

Statistical analysis was performed using SPSS version 23.0 (SPSS, Chicago, IL) and R version 3.2.2 (R Foundation for Statistical Computing, Vienna, Austria). Continuous variables are expressed as mean ± SD except for skewed data, which are expressed as median and interquartile range. Groupwise comparisons were made using a nonpaired Student's *t* test or a Mann-Whitney *U* test. For multiple comparisons, one-way analysis of variance with post hoc Student's *t* test and Bonferroni correction were used. Categorical variables are summarized as frequencies and percentages and were analyzed using the χ^2 test. P values < .05 were considered to indicate statistical significance. Multivariate prediction models for TI and binary TCA status were built with linear and logistic regressions, respectively. The best predictive subset of associated variables (see the Online Supplement, available at www.onlinejase.com) was chosen using the regularized regression method of least absolute shrinkage and selection operator (LASSO).[20,21] LASSO models were fit with tuning parameter chosen by the cross-validation method in the R package glmnet.[22] Prediction accuracy measures were estimated with fivefold cross-validation to remove the overfitting bias from prediction accuracy measures estimated on the same data set that was used to train the regression models. The best-fitting and most predictive models for TI and TCA status were chosen with cross-validation. Variability of measurements from reanalysis of TI and MAPSE data was assessed using intraclass correlation coefficient.

RESULTS

Patient Characteristics and Coronary Angiography

In the study cohort, there were 33 subjects categorized as having TCA and 43 without TCA. Age and sex were not different between the two patient cohorts (Table 1). Those with TCA were characterized