

Impaired aortic distensibility measured by computed tomography is associated with the severity of coronary artery disease

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Abstract Impaired aortic distensibility index (ADI) is associated with cardiovascular risk factors. This study evaluates the relation of ADI measured by computed tomographic angiography (CTA) with the severity of coronary atherosclerosis in subjects with suspected coronary artery disease (CAD). Two hundred and twenty-nine subjects, age 63 ± 9 years, 42% female, underwent coronary artery calcium (CAC) scanning and CTA, and their ADI and Framingham risk score (FRS) were measured. End-systolic and end-diastolic (ED) cross-sectional-area (CSA) of ascending-aorta (AAo) was measured 15-mm above the left-main coronary ostium. ADI was defined as: $[(\Delta \text{lumen-CSA}) / (\text{lumen-CSA in ED} \times \text{systemic-pulse-pressure}) \times 10^3]$. ADI measured by 2D-trans-thoracic echocardiography (TTE) was compared with CTA-

measured ADI in 26 subjects without CAC. CAC was defined as 0, 1–100, 101–400 and 400+. CAD was defined as luminal stenosis 0, 1–49% and 50%+. There was an excellent correlation between CTA- and TTE-measured ADI ($r^2 = 0.94$, $P = 0.0001$). ADI decreased from CAC 0 to CAC 400+; similarly from FRS 1–9% to FRS 20%+ ($P < 0.05$). After adjustment for risk factors, the relative risk for each standard deviation decrease in ADI was 1.66 for CAC 1–100, 2.26 for CAC 101–400 and 2.32 for CAC 400+ as compared to CAC 0; similarly, 2.36 for non-obstructive CAD and 2.67 for obstructive CAD as compared to normal coronaries. The area under the ROC-curve to predict significant CAD was 0.68 for FRS, 0.75 for ADI, 0.81 for CAC and 0.86 for the combination ($P < 0.05$). Impaired aortic distensibility strongly correlates with the severity of coronary atherosclerosis. Addition of ADI to CAC and traditional risk factors provides incremental value to predict at-risk individuals.

Keywords Aortic distensibility index · Computed tomographic angiography · Coronary artery calcium score · 2D Trans-thoracic echocardiography

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Introduction

Vascular dysfunction has been shown to be an independent predictor of adverse cardiovascular events [1–3]. Impaired vascular function is associated

with coronary artery disease [4], hypertension [5], diabetes [6, 7], and hypercholesterolemia [8–10].

Arterial distensibility, a measure of vascular function, can serve as a marker of coronary heart disease risk in humans [11, 12]. In addition animal studies suggest that reduced arterial distensibility is an early sign of atherosclerotic change [13]. Previous studies revealed an inverse relationship between aortic distensibility and cardiovascular risk factors and may predict outcome [14–16].

The aorta maintains low left ventricular after-load, promotes optimal subendocardial coronary blood flow [17], and transforms pulsatile into more luminal blood flow. Impaired aortic distensibility leads to higher left ventricular systolic pressures, diminished subendocardial blood supply [17] and may ultimately contribute to left ventricular dysfunction [18, 19].

Coronary artery calcium (CAC) is a marker of overall atherosclerotic burden and correlates well with the total plaque burden, the presence of obstructive coronary artery disease (CAD) and future cardiovascular events in both genders across ethnicities [20–22]. Systemic vascular dysfunction measured through reactive hyperemia procedure is strongly correlated with increasing Framingham risk score (FRS) and CAC independent of age, sex, and traditional cardiac risk factors and is superior to FRS for the prediction of significant CAC [23].

This study evaluates whether impaired aortic distensibility index (ADI) is associated with the severity of coronary atherosclerosis in at-risk individuals.

Methods

Subjects and study design

Two hundred and twenty-nine consecutive subjects referred for coronary artery calcium (CAC) scanning and CTA for suspected coronary artery disease (CAD) were enrolled. Patients with established cardiovascular disease, stroke, diabetic retinopathy, Raynaud's syndrome, infection, cancer, immunosuppression, systemic inflammation, advanced renal or liver disease, creatinine >1.4 mg/dl, and triglyceride >400 mg/dl were excluded. In a sub-study, 26 patients with normal coronaries and CAC 0 underwent 2D trans-thoracic echocardiography (TTE). The ascending aorta diameter and cross-sectional area

measured by CTA and TTE were compared. Risk factors were determined, and FRS was calculated to assess the risk of developing total coronary disease events (angina, myocardial infarction, or cardiovascular death) over the next 10 years [24].

CAC scanning

The coronary arteries were imaged with 30–40 contiguous 3 mm slices during mid-diastole using ECG-triggering during a 15 s breath hold. CAC was considered present in a coronary artery when a density of >130 Hounsfield units (HU) was detected in ≥ 3 contiguous pixels ($>1 \text{ mm}^2$) overlying that coronary artery and quantified using the previously described Agatston scoring method [25].

Cardiac CTA

Beta blockers were administered for pulses greater than 65 bpm. CTA was performed according to standard clinical technique with retrospective ECG gating and ECG pulsing applied. Mean heart rate during the scan was 57 ± 2 bpm.

Data acquisition

A 64-Multi-detector Computed Tomography (MDCT) scanner (Lightspeed VCT, General Electric Healthcare Technologies, Milwaukee, WI) was used for all subjects. Imaging was started 1 inch above the left main ostium and continued to 1 inch below the bottom of the heart. The following imaging and reconstruction parameters were applied: data acquisition collimation $0.625 \text{ mm} \times 64 = 4 \text{ cm}$; 120 kVp; 220–670 mAs; pitch 0.18–0.24 (depending on heart rate); rotation time 0.35 s; slice width 0.625 mm; matrix 512×512 and pixel size 0.39 mm^2 . ECG-triggered dose modulation was applied in each case with 400–600 mA in 60–80% R–R interval and 250–350 mA for the rest of the cardiac cycle (81 to 59% of the next cycle).

Cardiac data were reconstructed from 5 to 95% of R–R interval and with 10% intervals. Coronary vessels were reviewed (AW Volume Share™, GE Medical Systems, Milwaukee, WI) and volume renderings and curved multi-planar reformations were done. CAC was defined as CAC 0, CAC 1–100, CAC 101–400 and CAC 400+. CAD was defined as normal coronaries, non-obstructive and obstructive CAD (luminal

stenosis 1–49 and 50%, respectively). Two skilled cardiologists blinded to the clinical data measured the CAC and interpreted CTA separately.

Measurements

Cardiac CTA

The principle of aortic distensibility measurement is illustrated in Fig. 1. The window level and width of 300 and 800 HU was used. True CSA and diameter of ascending aorta (AAo) was measured both manually and with the automated software (Workstation AW 4.4, GE Medical Systems, Milwaukee, WI) using the

aligned and adjusted planes. The CSA and diameter of AAo were measurements 15 mm above the ostium of left main artery [26]. AAo diameter and CSA were measured from 5 to 95% of the R–R interval in 10% increments. Maximum AAo diameter and CSA was observed at end-systolic phase, 35% of R–R interval in individuals with a heart rate ≤ 60 bpm. AAo diameter and CSA decreased linearly from end-systole to end-diastole phases from 35 to 95% of R–R interval; which the minimum AAo diameter and CSA was observed at the end-diastolic (95% of R–R interval) phase.

Consensus was reached with a third expert measurement in case of disagreements between the manual and automated measures (2 cases).

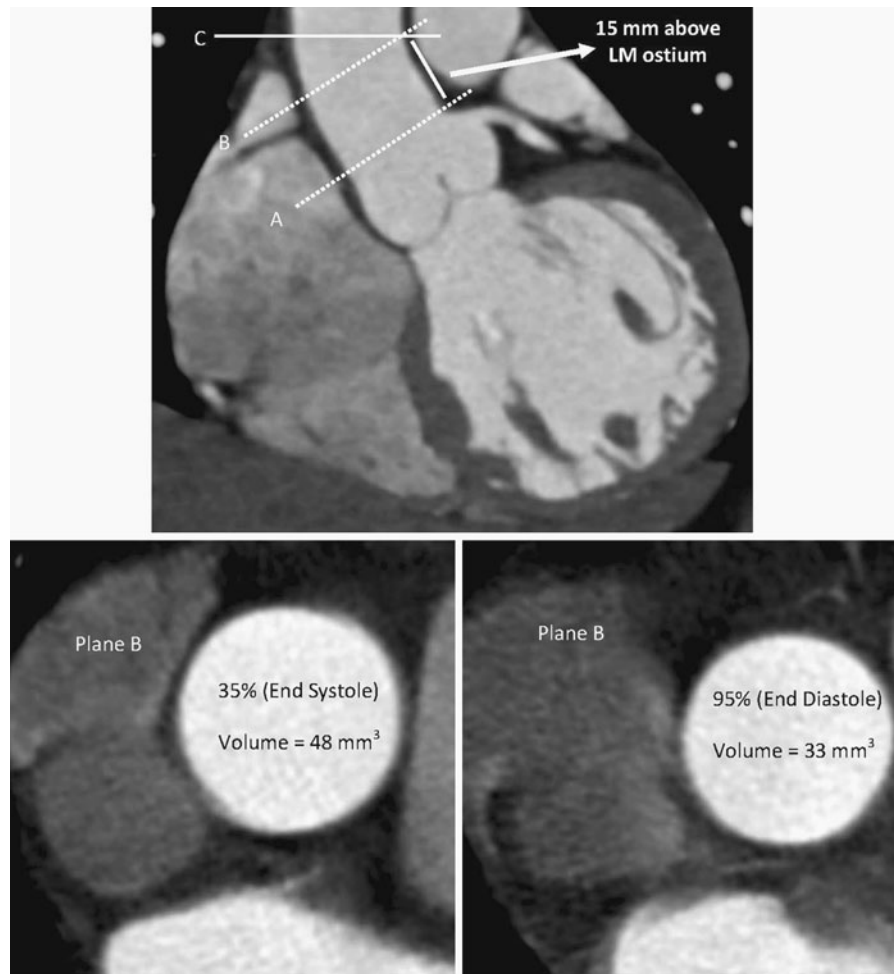


Fig. 1 Changes in the volume of ascending aorta (AAo) at the end systolic and end diastolic phase, 35% and 95% of R–R interval respectively, 15 mm above LM ostium using axial and coronal views. Using axial image, AAo image 15 mm above

LM ostium was assessed (C), then perpendicular diameter and volume of AAo was measured using coronal and oblique views (B) at end systole and diastole, respectively

ADI was defined as: $[\text{ADI} = (\Delta \text{lumen AAO CSA}) / (\text{end-diastole AAO CSA} \times \text{systemic pulse pressure}) \times 10^3]$ [27, 28]. $\Delta \text{lumen AAO CSA}$ is defined as: end-systolic AAO CSA – end-diastolic AAO CSA. Brachial artery blood pressure was measured before and after CTA acquisition, and the mean value was calculated.

Trans-thoracic echocardiography

In a sub-study, 26 subjects with normal coronaries and CAC 0 underwent TTE within a week after cardiac CTA. AAO diameter was measured 15 mm above sinotubular junction in the M-mode tracings, guided by the two-dimensional long parasternal axis [29] using Hewlett-Packard Sonos 5,500 echocardiographic system (Hewlett-Packard Corporation, Palo Alto, CA). Simultaneous recording of the ECG during TTE permitted evaluation of changes in AAO diameter during various phases of cardiac cycle, and reliable comparison with CTA measured AAO diameter. AAO cross section area (CSA) was calculated from 35%, end-systolic-, and 95%, end-diastolic-phase, of echocardiogram measured diameter with the assumption that the CSA is circular ($\text{area} = (\text{diameter}/2)^2 \times (\pi)$). TTE and CTA measured ADI was driven from calculated and measured AAO CSA, respectively.

Statistical analysis

Mean \pm SD and proportions were used to summarize the characteristics of the study group. Continuous variables were compared by ANOVA, and categorical variables were compared by the Kruskal–Wallis multivariate analysis. Inter-observer and inter-modality (CTA vs. TTE) variability of AAO diameter measurement were calculated using intra-class correlation coefficient (ICC), and Bland & Altman plots [30]. Relative risk regression analyses were employed to assess the association between the severity of CAC and ADI, also the association between ADI and CAD before and after adjustment for conventional cardiovascular risk factors, as well as for Framingham risk score. ROC curves were constructed and the area under the ROC curve (AUC) was calculated to predict the ability of each model to detect a) significant CAC (CAC 100+), and B)

significant CAD (obstructive CAD), respectively. All statistical analyses were performed with PASW version 18.0 (SPSS Institute Inc, Chicago, IL, <http://www.spss.com>). The level of significance was set at $P < 0.05$ (two-tailed). The study protocol was approved by the IRB Committee Board of the Los Angeles Biomedical Research Institute at Harbor UCLA, Torrance, California and all patients provided written informed consent.

Results

Aortic distensibility index (ADI)

CTA measured ADI was compared to the TTE measured ADI. There was excellent correlation between CTA and TTE measured ADI ($r^2 = 0.94$, ICC = 0.99, $P = 0.0001$). However, CTA measured ADI was 3.4% higher than TTE. (Figure 2a) There was excellent inter-observer agreement in measuring ADI using TTE and CTA. The inter-observer variability was higher with TTE than CTA (Fig. 2b).

Patient characteristics and aortic artery distensibility

Patients were characterized based upon the severity of CAC and placed into one of 4 groups (CAC 0, 1–100, 101–400 and 400+) (Table 1). There were no significant differences in gender, smoking status, diabetes mellitus, hypertension, hypercholesterolemia, lipid profile, and family history of premature CAD between the cohorts. The mean age was higher in patients with significant CAC as compared to normal cohort. The Framingham risk score increased substantially with increasing CAC. In a sub-study in subjects with CAC zero, ADI decreased with the metabolic status from normal cohorts to diabetes mellitus ($P < 0.05$).

There was strong inverse correlation between ADI and CAC ($r^2 = -0.69$, $P = 0.0001$). ADI decreased proportionally from CAC 0 to CAC 1–100 to CAC 101–400 to CAC 400+ in both genders (Fig. 3a and b). Furthermore, severity of CAC increased incrementally in each FRS category as ADI decreased; similarly, in each ADI category as FRS increased. The highest CAC was noted with the combination of the lowest tertile of ADI and FRS 20%+; The lowest ADI was observed in subjects with highest CAC and

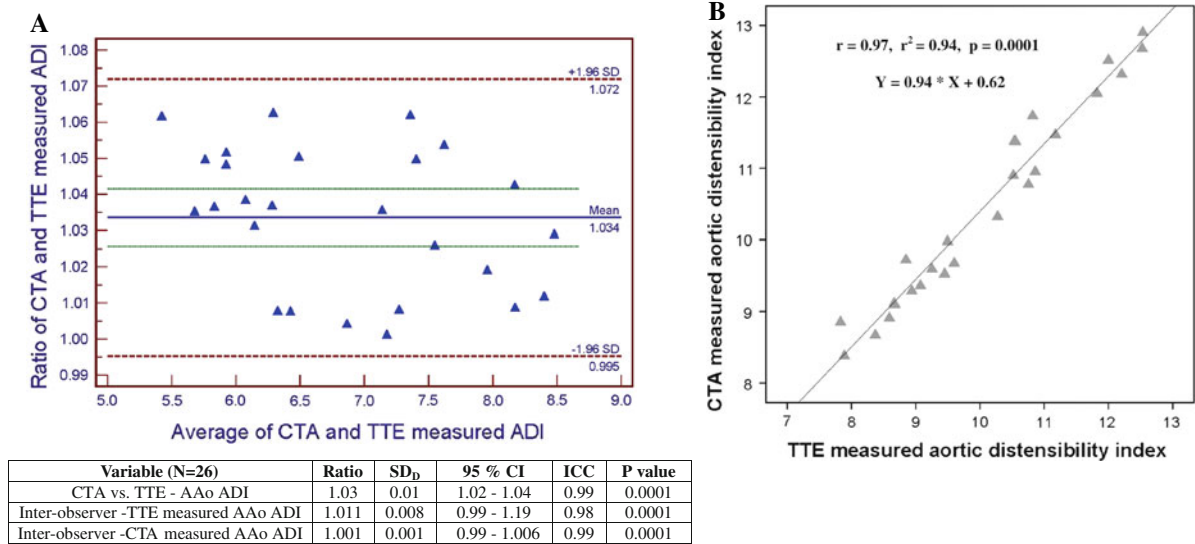


Fig. 2 **a** The variability between TTE and CTA in measured aortic distensibility index. **b** CTA measured aortic artery distensibility (ADI) correlated well with TTE measured ADI

FRS (Fig. 3b). ADI decreased with the severity of metabolic status in each CAC category in which diabetics with CAC 400+ had the least ADI. (Figure 3c) After adjustment for age, gender, conventional cardiac risk factors, and FRS by relative risk regression analyses, the risk of each standard deviation decrease in ADI was 1.66 for CAC 1–100, 2.26 for CAC 101–400 and 2.32 for CAC 400+ as compared to CAC 0. (Table 2) Multivariate regression analysis showed that ADI was an independent predictor of the severity of CAC.

Increasing severity of CAD was associated with increase in CAC and FRS, and decrease in ADI (Table 1). After adjustment for age, gender, conventional cardiac risk factors, and CAC, ADI was independent predictor of significant CAD. (Table 3).

ROC curves were constructed to assess the ability of cardiovascular risk factors and ADI to predict: a) significant CAC, and b) significant CAD. The AUC for proposed models is summarized in Fig. 4. Addition of ADI to FRS increased the area under the ROC curve to predict significant CAC significantly from 0.63 to 0.84 ($P < 0.05$) and provided the largest contributor to significant CAC prediction. Similarly, addition of ADI to CAC and traditional risk factors increased the area under the ROC curve to predict significant CAD from 0.68 to 0.86.

Discussion

The current study demonstrates that: 1. Excellent correlation exists between TTE and CTA measured ADI, 2- ADI decreased with the severity of metabolic status, 3. CTA measured ADI decreased proportionally with the severity of CAC independent of cardiovascular risk factors, and 4. Addition of ADI to FRS improved the ability to detect significant CAC from 0.63 to 0.84.

There is considerable heterogeneity in the magnitude of vascular dysfunction in individuals with similar risk factor profiles [31, 32]. In this regard, vascular dysfunction may be seen as an important “integrative factor” of the inherent atherosclerotic risk of an individual which takes into account the cumulative effects of various risk and protective factors [31]. In addition to improving risk assessment for the prediction of cardiovascular outcomes, another important application of vascular function assessment is to evaluate response to therapies [33–37].

Arterial distensibility serves as a marker of the structure and function of the artery (i.e. vascular function) and has been shown to diminish with advancing age and with increasing cardiovascular risk factors [38]. Recent studies have demonstrated that oxidative modification of LDL particles, and

Table 1 Cardiovascular risk factors and the severity of coronary artery calcium

Coronary artery calcium	Normal (N = 78)	CAC 1–100 (N = 42)	CAC 101–400 (N = 40)	CAC 400+ (N = 69)	P value
Age (years)	55 ± 10	55 ± 9	57 ± 9	61 ± 8	0.001
Male gender	67%	61%	69%	68%	0.8
Smoking	0	0	3%	3%	0.4
Hypertension [†]	46%	35%	57%	55%	0.2
High cholesterol	46%	41%	51%	38%	0.6
Diabetes mellitus [§]	16%	19%	19%	15%	0.7
Family history of CHD	40%	43%	57%	58%	0.1
Statin therapy	7%	12%	25%	27%	0.1
BMI (kg/m ²)	28.1 ± 3.6	28.8 ± 3.9	27.6 ± 5.1	28.4 ± 4.7	0.6
Total Cholesterol (md/dL)	191 ± 42	186 ± 37	171 ± 27	178 ± 43	0.7
HDL-C (mg/dL)	50 ± 10	46 ± 11	50 ± 14	46 ± 12	0.5
LDL-C (mg/dL)	116 ± 34	120 ± 26	100 ± 34	105 ± 39	0.4
Triglyceride (mg/dL)	112 ± 37	115 ± 28	96 ± 34	120 ± 32	0.2
SPB (mm Hg)	121 ± 11	129 ± 10	128 ± 15	132 ± 18	0.1
DBP (mm Hg)	75 ± 9	76 ± 8	76 ± 9	76 ± 9	0.9
Framingham risk score (%)	4.6 ± 2.6	5.2 ± 2.8	6.1 ± 3.3	8.9 ± 4.6	0.001
AAo 35% CSA (mm ³)	49.71 ± 2.10	48.82 ± 1.77	47.02 ± 1.68	46.66 ± 1.75	0.08
AAo 95% CSA (mm ³)	32.76 ± 1.91	33.34 ± 1.81	33.69 ± 1.69	34.14 ± 2.01	0.8
Δ AAo CSA/AAo 95% CSA ^Ω	0.57 ± 0.10	0.50 ± 0.07	0.39 ± 0.07	0.34 ± 0.06	0.003
ADI ^Δ	10.7 ± 1.31	8.87 ± 1.13	7.29 ± 1.09	6.18 ± 0.92	0.003
CTA-Diagnosed coronary artery disease	Normal (N = 78)	CAD 1–29% (N = 35)	CAD 30–49% (N = 61)	CAD 70% (N = 55)	P value
Framingham risk score (%)	4.6 ± 2.6	5.2 ± 2.5	7.4 ± 4.7	9.8 ± 5.7	0.001
Coronary artery calcium	0	43 ± 26	279 ± 115	385 ± 220	0.0001
ADI ^Δ	10.7 ± 1.31	8.62 ± 1.19	7.26 ± 1.21	5.71 ± 1.21	0.0001

Values presented as mean ± SD or %

NS = Non-significant ($P > 0.05$)

[†] Self-reported diagnosis of hypertension, prescribed medication for hypertension, or current blood pressure >140 mmHg systolic or >90 mmHg diastolic (>130/80 mmHg if diabetic)

[‡] Self-reported diagnosis of high cholesterol, prescribed medication for high cholesterol, or current total cholesterol >200 mg/dL

[§] Self-reported diagnosis of diabetes (type 1 or 2) or prescribed medication for diabetes

^{||} First degree relative; female < 65 yrs, male < 55 years

^Ω Δ AAo CSA = (AAo 35% CSA - AAo 95% CSA)/AAo 95% CSA

^Δ ADI = (Δ AAo CSA/systemic pulse pressure) $\times 10^3$

vascular wall remodeling induced by hyperglycemia may play a pathophysiological role in reducing arterial distensibility and revealed that aortic distensibility decreased with increasing cardiovascular risk factors [6, 8–10, 18, 19, 39].

Previous studies provided evidence that reduced arterial distensibility predicts future cardiovascular events [10, 15, 40]. Haluska et al. studied the

association of arterial distensibility and long-term clinical outcome of 719 patients. They reported that impaired arterial distensibility independently correlated with poor outcome in patients with varying degrees of cardiovascular risk, and arterial distensibility can identify patients at risk of future fatal and non-fatal events [41]. Finally, recent studies have shown that functional changes in arteries

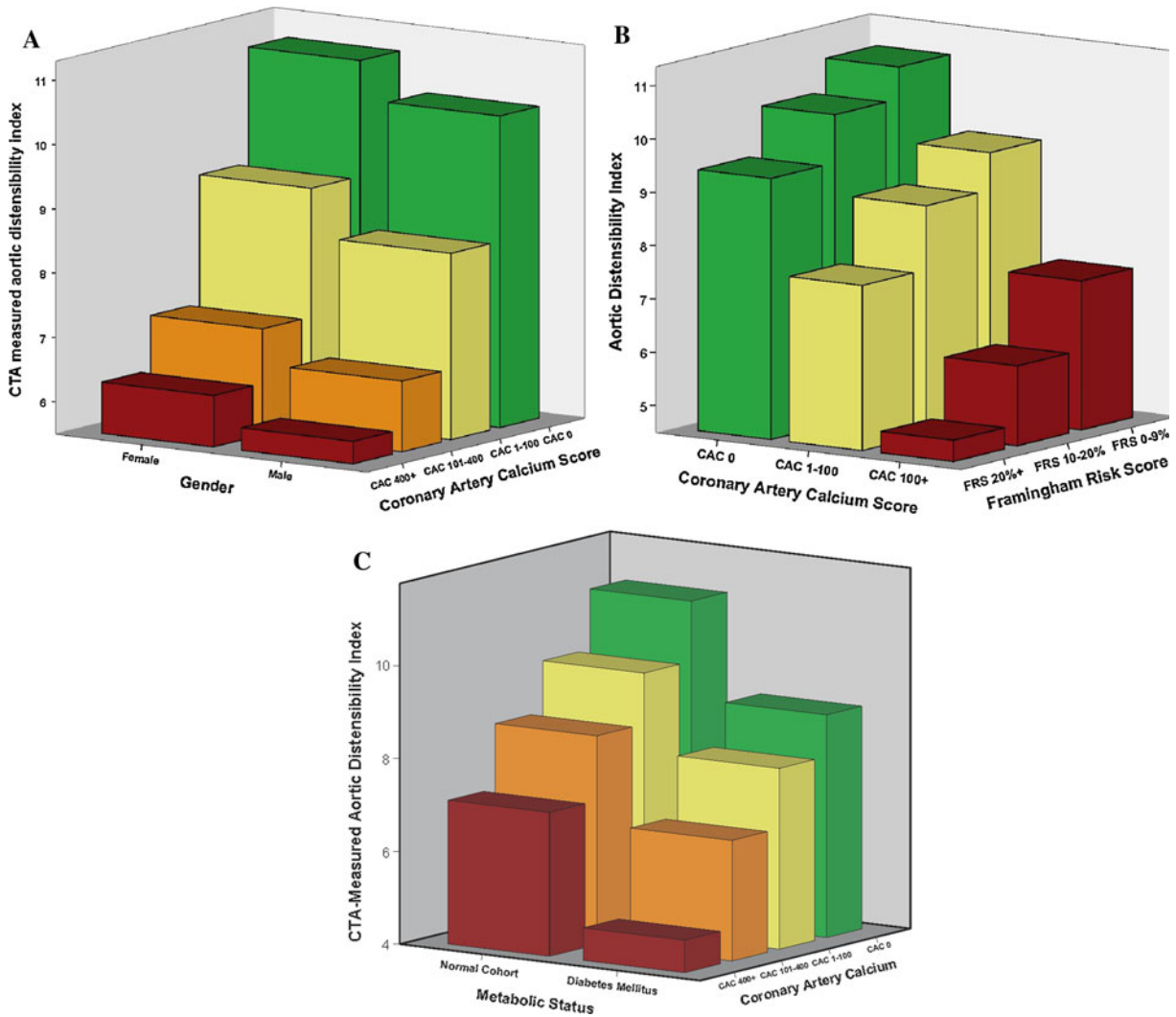


Fig. 3 **a** Aortic distensibility index (ADI) decreased proportionally with increasing the severity of coronary artery calcium (CAC) in both genders. **b** ADI decreased with increasing CAC and Framingham risk score, and **c** ADI decreased proportionally with the severity of metabolic status

Table 2 Multivariate relative risk regression analysis of the relationship between the extent of coronary artery calcium and aortic artery distensibility

Model	Normal	CAC 1–100	CAC 101–400	CAC 400+
Unadjusted				
ADI ^y	1 (ref)	1.57 (1.28–1.93), <i>P</i> = 0.0001	2.18 (1.69–2.82), <i>P</i> = 0.0001	2.23 (1.78–2.78), <i>P</i> = 0.0001
Adjusted for age, gender, diabetes mellitus, hypertension, hypercholesterolemia, family history of CHD, and smoking status				
ADI ^y	1 (ref)	1.66 (1.39–3.46), <i>P</i> = 0.0001	2.26 (1.73–3.28), <i>P</i> = 0.0001	2.32 (1.85–5.62), <i>P</i> = 0.0001

Relative risk for each standard deviation (SD) decrease in ADI (SD: 1.2)

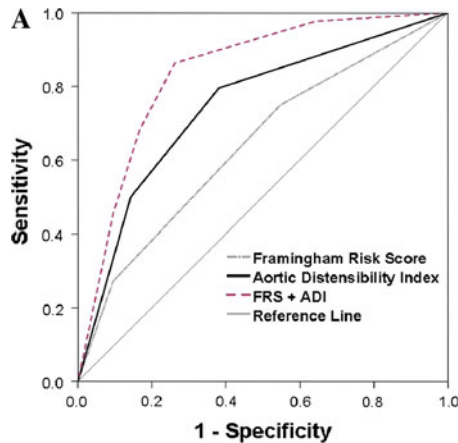
precede the development of structural changes and also reverse more quickly in response to therapies [37, 42–44].

Clinical guidelines recommend risk management based on the Framingham score [45, 46] followed by goal-directed therapy when necessary [47–49] in

Table 3 Multivariate relative risk regression analysis of the relationship between the severity of coronary artery diseases and aortic artery distensibility

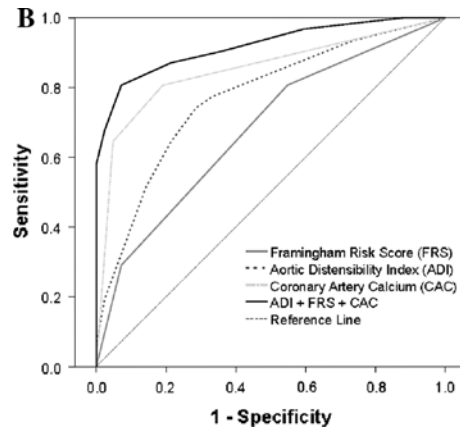
Model	Normal	Non-obstructive CAD	Obstructive CAD
Unadjusted			
ADI [‡]	1 (ref)	2.29 (1.26–2.75), <i>P</i> = 0.0001	2.56 (1.94–3.36), <i>P</i> = 0.0001
Adjusted for age, gender, diabetes mellitus, hypertension, hypercholesterolemia, family history of CHD, smoking status and CAC			
ADI [‡]	1 (ref)	2.36 (1.35–3.15), <i>P</i> = 0.0001	2.67 (1.93–3.56), <i>P</i> = 0.0001

Relative risk for each standard deviation (SD) decrease in ADI (SD: 1.2)



Variable	AUC±SD	95% CI	P	Comparison P
FRS [‡]	0.63 ± 0.04	0.53 - 0.82	0.001	--
ADI [‡]	0.74 ± 0.04	0.63 - 0.85	0.0001	0.01
FRS + ADI	0.84 ± 0.03	0.74 - 0.91	0.0001	0.001

[‡] FRS: Framingham risk score – FRS: 1-9%, 10-20%, and 20%+
[‡] ADI: Aortic distensibility index – per each standard deviation decrease



Variable	AUC±SD	95% CI	P	Comparison P
FRS [‡]	0.68 ± 0.04	0.59 - 0.78	0.0001	--
ADI [‡]	0.75 ± 0.03	0.67 - 0.85	0.0001	0.001
CAC [‡]	0.81 ± 0.02	0.79 - 0.90	0.0001	0.001
FRS + ADI + CAC	0.86 ± 0.01	0.81 - 0.92	0.0001	0.001

[‡] FRS: Framingham risk score – FRS: 1-9%, 10-20%, and 20%+
[‡] ADI: Aortic distensibility index – per each standard deviation decrease
[‡] CAC: Coronary Artery Calcium- CAC: 0, 1-100, 101-400, and 400+

Fig. 4 a ROC curves for 3 models created to assess the ability of a combination of clinical variables to predict significant coronary artery calcium (CAC 100+). **b** ROC curves for 4

models created to assess the ability of a combination of clinical variables to predict significant coronary artery disease

patients without known prior CAD. Recent studies have showed that FRS has significant limitation in identifying high risk subjects without known CAD [50, 51]. Current findings revealed that CTA provides an accurate measure for vascular function rather than just anatomical studies; Furthermore, in this study aortic distensibility decreased substantially with the severity of coronary atherosclerosis in both genders. The excellent correlations between impaired aortic distensibility measured by CTA and FRS, and, in particular, the superior independent and incremental value of aortic distensibility for predicting significant coronary atherosclerosis, highlight the role of

vascular function assessment as a part of cardiovascular risk assessment to improve identification of high risk individuals and optimizing patient management.

Limitations

Beta blockers which are vasoactive medications were administered for heart rates greater than 65 bpm. However, recent studies demonstrated that concomitant therapy with non-nitrate vasoactive drugs has no significant effect on vascular function assessment

[52]. The effect of data acquisition and analysis during a breath-hold is another potential source of error. Nonetheless, the CTA measurements correlated well with the TTE measurements, suggesting that potential errors introduced by non-simultaneous blood pressures and breath-hold are minimal.

Conclusion

Aortic distensibility measured by CTA correlates well with corresponding values measured by TTE. Impaired aortic distensibility is associated with the severity of coronary atherosclerosis independent of age, gender, and cardiovascular risk factors. Furthermore, addition of ADI to traditional risk factors and CAC provided the largest contribution to detect significant coronary atherosclerosis, and highlights the diagnostic utility of ADI in the early detection and monitoring of patients with atherosclerotic cardiovascular disease by a single noninvasive diagnostic study.

Disclosures Matthew Budoff has a financial disclosure in relationship to this study, as he is on the speaker's bureau for General Electric, whereas other authors have no conflicts to disclose.

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