CT-Based Diagnosis of Diffuse Coronary Artery Disease in Patients Based on Scaling Power Laws

Advances in Knowledge:
Patients with metabolic syndrome had significantly different CT-determined morphometry from the controls. The CT-based scaling analysis showed that more than 65% of metabolic syndrome patients have coefficient ≥ 23 for the coronary vascular length-volume scaling power law, while approximately 90% of the controls have coefficient < 23.

Implications for Patient Care:
This retrospective study suggests that an increase of coefficient of the coronary vascular length-volume scaling power-law (≥ 23) can be a CT-based diagnostic index of DCAD.

ABSTRACT
Purpose: To provide proof of concept for a diagnostic method to assess diffuse coronary artery disease (DCAD) based on coronary computerized tomography angiography (CTA).
Materials and Methods: The study was approved by the Cleveland Clinic Institutional Review Board and the subjects gave informed consent. Morphometric data of the epicardial coronary arterial tree, determined from CTA of 120 subjects (89 with metabolic syndrome and 31 age and gender matched controls), were analyzed based on the scaling power law. The results between metabolic syndrome and control groups were compared statistically.
Results: Patients with metabolic syndrome had mean lumen CSA of 0.039 ± 0.015 cm^2 (i.e., lumen CSA averaged over each vessel of an epicardial coronary arterial tree) and sum of intravascular volume of 2.71 ± 1.75 cm^3, which were significantly less than those of controls $(0.054\pm0.015$ cm^2 and 3.29 ± 1.77 cm^3, respectively, p values < 0.05). The length-volume power law showed coefficients of 27.0 ± 9.0 ($R^2=0.91\pm0.08$) and 19.9 ± 4.3 ($R^2=0.92\pm0.07$) for metabolic syndrome and control groups, respectively (p value < 0.05). The probability frequency shows that more than 65% of metabolic syndrome patients have coefficient ≥ 23 for the length-volume scaling power law, while approximately 90% of the controls have coefficient < 23.
Conclusion: The retrospective scaling analysis provides a quantitative rationale for diagnosis of DCAD.

Keywords: Diffuse disease, scaling power law, CT angiography

INTRODUCTION

Diffuse coronary artery disease (DCAD) without severe segmental stenosis is a substrate for plaque rupture (1-3). Hence, DCAD is associated with unstable coronary syndromes or myocardial infarctions, which have significant clinical implications (4-6). In contrast with severe segmental stenosis, DCAD is difficult to diagnose angiographically given the absence of a "normal" reference vessel (7). Although intravascular ultrasound (IVUS) has been used to visualize plaque burden in the vessel wall for diagnosis of DCAD (8,9), it is an interventional tool requiring an invasive procedure. Hence, there is a need for a non-invasive method to quantify DCAD.

There have been previous attempts to apply global morphological features of the coronary arterial tree to assess DCAD (7,10,11). Several experimental reports have also documented a direct relation between coronary artery lumen size and heart weight or size of distal myocardial bed (12-18) and between myocardial mass and the sum of arterial branch lengths that perfuse the region (18,19). Based on the principle of minimum energy, we have recently deduced scaling power laws between length and volume and between length and cross sectional area (CSA) in an entire tree structure of various organs in different species (20,21). In particular, these scaling power laws have self-similar nature (20-22) which implies that they can be clinically applied to a partial tree, e.g., an epicardial coronary arterial tree obtained from an angiogram, computerized tomography (CT), or magnetic resonance imaging (MRI). Hence, we hypothesize that the length-volume scaling power law (i.e., scaling relation and power-law distribution for the sum of intravascular lengths and volumes in a tree) provides the signature of "normal" vasculature and deviations from which can be used to quantify the extent of DCAD. The purpose of this study is to provide proof of concept for a diagnostic method to assess DCAD based on coronary CT angiography (CTA).

MATERIALS AND METHODS

Study Design: To assess the extent of DCAD, human subjects of metabolic syndrome (a high-risk population for DCAD) as well as age and gender matched controls underwent coronary CTA at Cleveland Clinic during the period of 2007-2009. The CT reconstruction and scaling analysis were performed at Indiana University-Purdue University Indianapolis (IUPUI) with the help from another independent laboratory at Wright State University. The study was approved by the Cleveland Clinic Institutional Review Board (IRB) and the subjects gave informed consent.

Patients: A total of 93 patients who met US National Cholesterol Education Program Adult Treatment Panel III (NCEP III) criteria for metabolic syndrome (23) as well as 31 age and gender matched control patients were identified and recruited from a large database at Cleveland Clinic if they had none of the following symptoms: 1) rhythm other than sinus; 2) contraindication to iodinated contrast agents; and 3) end stage renal disease requiring dialysis. Four subjects with severe segmental stenoses (i.e., diameter stenosis > 50% or area stenosis > 75%) were excluded from metabolic syndrome group. Hence, we retrospectively evaluated 89 metabolic syndrome patients (Age: 56 ± 9.2; Male: 68%; Symptom: cardiac chest pain) and 31 controls (Age: 55 ± 9; Male: 68%; Symptom: cardiac chest pain without metabolic syndrome). The NCEP III diagnosed metabolic syndrome if patients fulfilled at least three of the following conditions: 1) waist circumference ≥ 102 cm for male or ≥ 88 cm for female, 2) triglycerides ≥ 150 mg/dl, 3) high-density lipoprotein (HDL) cholesterol < 40 mg/dl for male or < 50 mg/dl for female, 4) blood pressure ≥ 130/85 mmHg, or 5) fasting plasma glucose ≥ 110 mg/dl. The control subjects, who did not fulfill the NCEP III criteria, underwent coronary CTA study for

evaluation of cardiac chest pain, but had no heart attack, angina, or severe segmental stenoses. The control group had significantly lower body mass index (BMI) and triglycerides and higher HDL than the metabolic syndrome group. Table 1 summarizes patient demographics for metabolic syndrome and control groups. A flow chart in Figure 1 shows the imaging acquisition and data analysis protocol.

Imaging Acquisition: Electrocardiograms (ECG) and blood pressures were monitored. Prior to imaging acquisition, patients were given repeated doses of intravenous metoprolol of 5 mg every 5 minutes until heart rate was ≤ 65 bpm or a maximum dose of 15 mg was given (mean±SD dose: 10±3 mg, where SD refers to the standard deviation). If patients had contraindications to beta blockers, they were given intravenous diltiazem of 10 mg followed by additional dose of 5 mg every 5 minutes up to a maximum of 20 mg. All patients received sublingual nitroglycerin tablet (0.4 mg) 3-5 minutes before CT examination.

All studies were performed on a dual-source CT scanner (Siemens Definition, Forchheim Germany). After an initial survey scan, a retrospectively gated contrast-enhanced scan was obtained using 80 ml of iodinated contrast (Iopromide-Ultravist 370, Bayer Healthcare, Morristown USA) injected through an antecubital vein at 3.5 ml/s followed by 50 ml of normal saline at the same rate. The scan parameters were: $2 \times 64 \times 0.6$ mm collimation, tube voltage – 120 kV; tube current – average 620 mAs adjusted to body size; gantry rotation time – 330 msec; pitch – 0.2-0.43 depending on heart rate. The entire heart was scanned from the carina to the diaphragm within a single breath-hold of approximately 10 seconds. To reduce radiation dose, electrocardiogram pulsing was used to reduce tube current by 80% outside a time window between 30% and 75% of the cardiac cycle. The mean±SD effective radiation dose ($E = DLP \times k$) was 11.7±4 mSv, where DLP refers to the dose length product and k is the region-specific (chest) normalized coefficient (0.017 mSv/mGy·cm).

Images were reconstructed with a slice thickness/increment of 0.7/0.4 mm with B26f (a Siemens reconstruction kernel) at temporal resolution of 83 msec (half-scan). The initial data window was positioned at 70% of the R-R interval, with additional data sets reconstructed at ±5% intervals to compensate for motion artifacts in coronary arteries if necessary.

Imaging Analysis: As shown in Figure 2, the morphometry (i.e., centerlines, CSA and lengths) of the left main coronary artery (LMCA) and right coronary artery (RCA) trees was extracted from CTA images of both control and metabolic syndrome groups by a validated software algorithm (24,25). Briefly, the algorithm first segmented the vessels within the volumetric image based on the image gradients (Fig. 1). To get a more accurate representation of the vessel boundary, the points resulting from the segmentation step were moved along the gradient direction in such a way that they were located at the maximal gradient. This determines the most likely location of the vessel boundary at sub-voxel precision and reduces a jagged appearance of the vessel boundary. Thus it provides a more precise and smoother representation of the boundary as compared with using the original voxel locations. This is important because representation of the boundary at a subvoxel level improves the accuracy of the morphometric measurements. A vector field was then computed in such a way that all vectors were pointing inward to the center of the vessel. Based on a tetrahedrization of all the boundary points and their image gradient vectors, a vector field was computed using a trilinear interpolation. Finally, points on the centerlines were determined utilizing a topological analysis of the vector field within the CSA of the vessels and connected based on the topology of the tetrahedrization. This provides the centerline at a subvoxel precision, which further contributes to the enhanced accuracy of this approach and results in a precise representation of the centerlines of all vessels

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within the volumetric image. The algorithm was validated by comparing optical microscope measurements of the same coronary casts imaged with CT and processed by the previously described algorithm (24). The RMS error between optical and CT measurements was 0.16 mm (<10% of the mean value) with an average deviation of 0.13 mm (24).

Scaling Power laws: We defined a vessel segment as a stem and the tree distal to the stem as a crown, as shown in Fig. A1. The epicardial coronary arterial tree has many stem-crown units. Based on the principle of minimum energy (20-22), we derived the length-volume scaling power law as:

$$L_c = K_{LV} V_c^{\frac{7}{9}}$$ [1]

where K_{LV} is a constant (Unit: cm$^{-4/3}$) and L_c and V_c are the crown length and volume (Unit: cm and cm^3, respectively). The mathematical derivation of Eq. [1] is provided in the Appendix. The length-volume scaling power law of Eq. [1] represents the relationship between the total length and the total intravascular volume in a stem-crown system of epicardial coronary arterial tree (see Fig. A1). Furthermore, the length-CSA scaling power law is given as:

$$L_c = K_{LA} A_s^{\frac{7}{6}}$$ [2]

where K_{LA} is a constant (Unit: cm$^{-4/3}$) and A_s is the CSA of the stem (Unit: cm^2) in a stem-crown unit (see Fig. A1). The length-SCA scaling power law of Eq. [2] represents the relationship between the total length of each vessel and the stem CSA in the stem-crown system of epicardial coronary arterial tree.

We determined the coefficients K_{LV} and K_{LA} of the two scaling power laws for the epicardial coronary arterial tree of each patient in the metabolic syndrome and control groups reconstructed from CTA. Briefly, the centerlines formed the skeleton of the epicardial coronary arterial tree, which stretched over a consecutive sequence of vessels segments (Fig. 1). The mother and daughter vessels were labeled and indexed. The stem-crown system was then generated in the epicardial coronary arterial tree. Finally, we determined the following parameters: 1) both coefficient K^0 and exponent X in a power law relation: $M = K^0 \cdot Y^X$ (defined as two-parameter model) and 2) coefficient K with exponent X equal to the theoretical value (i.e., $\frac{7}{9}$ in Eq. 1 and $\frac{7}{6}$ in Eq. 2) in a power law relation: $M = K \cdot Y^{\text{theoretical value}}$, (defined as one-parameter model) by a least-square fit of all stem-crown units in an epicardial coronary arterial tree to the corresponding power laws.

Data Analysis: The mean and standard deviation (SD) were computed by averaging over all epicardial coronary arterial trees in each group. Coefficient of variation ($CV = \frac{SD}{mean} \times 100\%$) was also calculated in the one-parameter model. The 2-sample student's *t* test (Excel 2010) was used to compare coefficients and exponents in metabolic syndrome group with those in control group, where p value < 0.05 represented statistically significant difference.

For patients in metabolic syndrome and control groups, we defined the probability frequency as $\frac{\text{Patient number for } K_i < K < K_{i+1}}{\text{Total patient number}} \times 100\%$ (where $K_0 = K_{Minimum}$, $K_i < K_{i+1}$, and $K_N = K_{Miaximum}$, $i = 0 \cdots N-1$) and plotted the probability frequency as a function of K. We

also defined the accumulative probability frequency as $\dfrac{\text{Patient number for } K < K_{i+1}}{\text{Total patient number}} \times 100\%$ and

plotted the accumulative probability frequency vs. coefficient K.

RESULTS
Table 2 shows morphometric data of the reconstructed epicardial coronary arteries for metabolic syndrome and control groups in Table 1. There is significant difference of mean lumen CSA (averaged over each vessel in a tree structure) and sum of intravascular volume (p value < 0.05), but no statistical difference of inlet CSA (p value $= 0.96$) and sum of vessel length (p value $= 0.19$) in epicardial coronary arterial trees between metabolic syndrome and control groups.

Table 3 summarizes the mean$\pm$SD values (averaged over individual patients) of coefficients and exponents for the length-volume (Eq. 1) and length-CSA (Eq. 2) scaling power laws, which show significant difference between metabolic syndrome and control groups (p value < 0.05). Moreover, the least-square fit of all the measurements to the one-parameter model for the length-volume and length-CSA scaling power laws results in K_{LV} values of 26.6 ($R^2 = 0.85$) and 19.9 ($R^2 = 0.88$) and K_{LA} values of 363 ($R^2 = 0.50$) and 278 ($R^2 = 0.55$) for metabolic syndrome and control groups, respectively, where $\left\lfloor \dfrac{26.6 + 19.9}{2} \right\rfloor = 23$. Coefficients K_{LV} and K_{LA} in the one-parameter model are significantly increased in metabolic syndrome group as compared with those in control group.

In comparison with the length-CSA scaling power law, the length-volume scaling power law fits well to CT data ($R^2 > 0.9$ in Table 3). Moreover, Figure 3 shows the probability frequency as a function of coefficient K_{LV} and Figure 4 shows the accumulative probability frequency as a function of coefficient K_{LV} in the length-volume scaling power law, where the solid and dash lines represent control and metabolic syndrome groups, respectively. The two figures imply that approximately 90% of patients in control group have $K_{LV} < 23$ and $> 65\%$ patients in metabolic syndrome group have $K_{LV} \geq 23$.

DISCUSSION
The major finding of the study is that patients with metabolic syndrome that have higher predilection to DCAD had significantly increased K_{LV} values of the length-volume scaling power law (i.e., $L_c = K_{LV} V_c^{\frac{7}{9}}$).

Morphometry of Epicardial Coronary Arterial Trees: Coronary atherosclerosis is usually diffuse along the length of large arteries (7,26). Here, we reconstructed epicardial coronary arterial trees of metabolic syndrome and control patients from CTA. In general, metabolic syndrome precedes the onset of full-blown diabetes but has a similar, albeit lesser, impact on growth of plaque (27). The morphometric data showed no severe segmental stenoses in the two groups. The patients with metabolic syndrome demonstrated a 28% decrease of mean lumen CSA (i.e., lumen CSA averaged over vessels of the entire epicardial coronary arterial tree) as compared with the controls. Given similar inlet CSAs, the decrease of mean lumen CSA in metabolic syndrome patients was a result of decrease of lumen CSA in distal coronary arteries. Moreover, the sum of intravascular volume of the entire epicardial coronary arterial tree was

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reduced by 18%. The decrease of mean CSA and sum of intravascular volume reflected the extent of diffuse disease in the epicardial coronary arterial tree of metabolic syndrome patients.

Scaling power laws: We theoretically derived the length-volume and length-CSA scaling power laws in the stem-crown system of epicardial coronary arterial tree (see Appendix). The length-volume and length-CSA scaling power laws have theoretical exponents of $\frac{7}{9} = 0.78$ and $\frac{7}{6} = 1.17$, respectively. From the quantitative coronary arteriographic (QCA) analysis of coronary arterial trees, Seiler et al. showed an exponent of 1.22 for the length-CSA scaling power law, which is consistent with the theoretical prediction (4.5% difference from theoretical value) (7). From the CTA analysis, Craiem et al. supported the length-volume scaling power law, but showed an exponent of 2.28 (94.9% difference from theoretical value) for the length-CSA scaling power law in normal patients (28). If a single terminal vessel was considered as a stem-crown unit (which occupies more than half of the total stem-crown numbers and predominates the exponent of the length-CSA scaling power law), then such a large exponent is expected. Unfortunately, this violates the concept of crown because the minimal crown is comprised of a bifurcation and a single terminal vessel is not a stem-crown unit. Moreover, most terminal vessels have unknown truncated length and should not be considered in the analysis. When the correct stem-crown unit is adopted, we found the length-volume exponent of 0.77±0.11 and length-CSA exponent of 1.05±0.3 for patients in the control group, which agrees well with the theoretical predictions. Therefore, the CTA and QCA analysis supports the theoretical predictions for the length-volume and length-CSA scaling power laws in normal human epicardial coronary arterial tree.

Scaling Diagnosis of DCAD: Patients with metabolic syndrome demonstrated a significant deviation of both exponents and coefficients in the two-parameter model from the control group for the length-volume and length-CSA scaling power laws. To eliminate the potential interaction of exponent and coefficient in power law, we combined the two-parameter model into the one-parameter model and only determined K_{LV} and K_{LA} values with the exponents equal to the corresponding theoretical values. There were significant differences of K_{LV} and K_{LA} between metabolic syndrome and control groups in the one-parameter model.

The least-square fit of CT data to the length-volume scaling power law showed higher correlation coefficient (R^2=0.91±0.08 for metabolic syndrome group and R^2=0.92±0.07 for control group) and lower coefficient of variation (CV=33.3% for metabolic syndrome group and CV=21.6% for control group) as compared with the fit to the length-CSA scaling power law. This can be explained by the integrated properties of both crown volume and crown length (i.e., the sum of the intravascular volume or the length of each vessel segment in a crown). Hence, we selected the length-volume scaling power law in the one-parameter model as the index of DCAD. Since the least-square fit of all the measurements to the one-parameter model for the length-volume scaling power law results in K_{LV} values of 26.6 (R^2=0.85) and 19.9 (R^2=0.88) for metabolic syndrome and control groups, respectively, the mean value of 23 ($= \left\lfloor \left| \frac{26.6 + 19.9}{2} \right| \right\rfloor$) was selected as a demarcation value between patient groups. Moreover, the frequency analysis showed that > 65% of metabolic syndrome patients had $K_{LV} \geq 23$, but approximately 90% of

normal patients had $K_{LV} < 23$. Hence, $K_{LV} \geq 23$ in Eq. [1] is a good index for the diagnosis of DCAD in patients.

To rule out the effect of number of patients which differed significantly between the two groups (89 metabolic syndrome patients vs. 31 control subjects), the same number of metabolic syndrome patients as the controls were randomly selected to calculate K_{LV} value. The K_{LV} values vary in the range of 25-31 in the one-parameter model. This further supports the DCAD index of $K_{LV} \geq 23$.

Study Limitations: Although severe segmental stenosis was suggested to not affect the scaling power laws (28), the combined effect of segmental stenosis and DCAD remains unknown. Future studies are needed to determine at what point the scaling power laws no longer hold during the progression of disease severity (segmental stenosis). Once severe stenosis is present, however, diagnosis of DCAD with coronary CTA may become less clinically relevant.

Coronary artery spasm can also lead to diffuse coronary narrowing (29). In contrast with invasive procedures (29), CTA seldom results in coronary artery spasm since the contrast media is injected through an intravenous (IV) line. Hence, the effect of diffuse coronary artery spasm on the scaling diagnosis of DCAD is likely negligible. Furthermore, intramyocardial smaller arteries that are less accurately determined by CTA were not considered given their lack of atherosclerosis (30).

Although a significant decrease of mean lumen CSA and sum of intravascular volume implies the presence of diffuse disease in the epicardial coronary arterial tree of metabolic syndrome patients in the retrospective group, it is necessary to validate the diffuse disease using IVUS in future studies. Furthermore, future prospective studies should be carried out to investigate the relation between the length-volume scaling power law and progression of DCAD. Here, we only showed a proof of concept that in a cohort of patients with higher risk of DCAD, a scaling power law analysis confirmed a greater probability of disease as compared to a normal cohort.

In Conclusion: This study provided a clinical rationale for the non-invasive diagnosis of DCAD and warrants future prospective clinical trials.

APPENDIX
Scaling power laws
We defined a proximal vessel segment as a stem and the tree distal to the stem as a crown, as shown in Fig. A1. A tree structure (e.g., the epicardial coronary arterial tree) has many stem-crown units. In a stem-crown unit, the crown volume (V_c; Unit: ml) is defined as the sum of the intravascular volume of each vessel segment and the crown length (L_c; Unit: cm) is defined as the sum of the lengths of each vessel segment in the crown from the stem to the most distal vessels. Here, the smallest stem-crown unit corresponds to a terminal bifurcation (i.e., $Stem_n$ and $Crown_n$ in Fig. A1) of epicardial coronary arterial tree obtained from CTA with the diameter of terminal vessels in the range of 0.6-1 mm.

To derive the volume-length scaling power law, a cost function for an integrated system of stem-crown units was proposed, which consists of two terms: viscous and metabolic power dissipation. The cost function, F_c (Unit: erg), is written as (22):

$$F_c = Q_s \cdot \Delta P_c + K_m V_c \quad \text{[A1]}$$

where Q_s and $\Delta P_c = Q_s \cdot R_c$ are the flow rate through the stem (Unit: ml/s) and the pressure drop in the distal crown (Unit: dynes/cm^2), respectively. K_m is a metabolic constant of blood in a crown (Unit: dynes/cm^2·s). Two important structure-structure scaling power laws as well as a flow-structure scaling power law are needed to perform the minimum energy analysis in the cost function. First, we have shown that the resistance of a crown (Unit: dynes·s/cm^5) has the following form (22):

$$R_c = K_R \frac{L_c}{D_s^4} \quad \text{[A2]}$$

where D_s is the stem diameter (Unit: cm) and K_R is a flow resistance constant in a crown (Unit: dynes·s/cm^2), which depends on the branching ratio and total number of tree generation in a crown. Second, the crown volume is found to scale with the stem diameter as (21):

$$V_c = K_{VD} D_s^3 \quad \text{[A3]}$$

where K_{VD} is a morphometric constant in a crown. Finally, the flow-length scaling power law is given as (21):

$$Q_s = K_{QL} L_c \quad \text{[A4]}$$

where K_{QL} is a functional constant in a crown (Unit: cm^2/s).

When resistance (Eq. A2), volume-diameter (Eq. A3), and flow-length (Eq. A4) scaling power laws are substituted into the energy cost function, Equation [A1] can be written as:

$$F_c = Q_s^2 \cdot R_c + K_m V_c = \left(K_R \cdot K_{QL}^2 \cdot K_{VD}^{4/3} \right) \frac{L_c^3}{V_c^{4/3}} + K_m V_c \quad \text{[A5]}$$

Similar to Murray's approach (31), we minimize the cost function with respect to crown volume at a fixed crown length to obtain the following equation (21):

$$\frac{\partial F_c}{\partial [V_c]} = 0 \Rightarrow -\frac{4}{3} \left(K_R \cdot K_{QL}^2 \cdot K_{VD}^{4/3} \right) \frac{L_c^3}{V_c^{7/3}} = -K_m \quad \text{[A6]}$$

Equation [A6] can be written as:

$$L_c = \sqrt[3]{\frac{3K_m}{4K_R \cdot K_{QL}^2 \cdot K_{VD}^{4/3}}} V_c^{7/9} = K_{LV} V_c^{\frac{7}{9}} \qquad \text{[A7]}$$

where $K_{LV} = \sqrt[3]{\dfrac{3K_m}{4K_R \cdot K_{QL}^2 \cdot K_{VD}^{4/3}}}$ is a constant (Unit: cm$^{-4/3}$). Equation [A7] provides the length-volume scaling power law, which forms the theoretical basis for the diagnosis of DCAD. Moreover, a combination of Eqs. [A3] and [A7] results in:

$$L_c = K_{LA} A_s^{\frac{7}{6}} \qquad \text{[A8]}$$

where A_s is the cross-sectional area (CSA) of the stem (Unit: cm^2) and K_{LA} is a constant (Unit: cm$^{-4/3}$). Equation [A8] refers to the length-CSA scaling power law.

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Table 1
Baseline demographics of the study population

	Metabolic Syndrome (n=89)	Control Group (n=31)	p value
Age, years	56 ± 9.2	55 ± 9	0.69
Male gender	52 (68%)	21 (68%)	1
BMI, kg/m^2	34.8 ± 7.3	26.9 ± 3.3	< 0.05
SBP, mmHg	133 ± 18	127 ± 16	0.05
DBP, mmHg	80 ± 10	78 ± 10	0.12
Hypertension	63 (83%)	7 (24%)	< 0.05
Diabetes mellitus	25 (33%)	None	< 0.05
Active smoker	11 (14%)	5 (16%)	0.53
Family history of CAD	26 (34%)	13 (42%)	0.08
Total cholesterol, mg/dL	188 ± 48	199 ± 37	0.05
Triglycerides, mg/dL	190 ± 133	108 ± 51	< 0.05
LDL, mg/dL	105 ± 38	117 ± 33	0.05
HDL, mg/dL	45 ± 14	60 ± 15	< 0.05
Fasting glucose, mg/dL	119 ± 45	92 ± 14	< 0.05

n: patient number
BMI: Body mass index
SBP: Systolic blood press
DBP: Diastolic blood pressure
CAD: Coronary artery disease
LDL: Low density lipoprotein
HDL: High density lipoprotein
The values were mean ± SD (averaged over the patients)

Table 2
Morphometric data reconstructed from CTA

Morphometry of Epicardial Arteries	Metabolic Syndrome (n=89)	Control Group (n=31)	p value
$A_{s\,max}$ (cm^2)	0.16 ± 0.09	0.16 ± 0.07	0.96
$A_{s\,mean}$ (cm^2)	0.039 ± 0.015	0.054 ± 0.015	< 0.05
$L_{c\,max}$ (cm)	46.1 ± 24.4	50.2 ± 24.6	0.19
$V_{c\,max}$ (cm^3)	2.71 ± 1.75	3.29 ± 1.77	< 0.05

$A_{s\,max}$: CSA at the inlet of coronary arterial trees (i.e., LMCA or RCA)

$A_{s\,mean}$: Mean CSA averaged over vessels of the entire epicardial coronary arterial tree

$L_{c\,max}$: Sum of vessel length of the entire epicardial coronary arterial tree

$V_{c\,max}$: Sum of intravascular volume of the entire epicardial coronary arterial tree

The values were mean $\pm$ SD (averaged over arterial trees)

Table 3

Coefficients and exponents for the length-volume and length-CSA scaling power laws in epicardial coronary arterial trees of metabolic syndrome and control groups

Scaling power laws		Metabolic Syndrome (n=89)	Control (n=31)	p value
Least-squares fit of both K^0 and X values (two-parameter model)				
Length-Volume Scaling law $(L_c = K_{LV}^0 V_c^{X_{LV}})$	K_{LV}^0 (cm$^{-4/3}$)	20.7 ± 5.7	18.2 ± 3.4	< 0.05
	X_{LV}	0.62 ± 0.12	0.77 ± 0.11	< 0.05
	R^2	0.91 ± 0.08	0.92 ± 0.07	
Length-CSA Scaling law $(L_c = K_{LA}^0 A_s^{X_{LA}})$	K_{LA}^0 (cm$^{-4/3}$)	125 ± 129	255 ± 199	< 0.05
	X_{LA}	0.76 ± 0.30	1.05 ± 0.30	< 0.05
	R^2	0.63 ± 0.20	0.58 ± 0.21	
Least-squares fit of K values with X equal to theoretical values (one-parameter model)				
Length-Volume Scaling law $(L_c = K_{LV} V_c^{\frac{7}{9}})$	K_{LV} (cm$^{-4/3}$)	27.0 ± 9.0	19.9 ± 4.3	< 0.05
	CV	$33.3\ \%$	$21.6\ \%$	
	R^2	0.91 ± 0.08	0.92 ± 0.07	
Length-CSA Scaling law $(L_c = K_{LA} A_s^{\frac{7}{6}})$	K_{LA} (cm$^{-4/3}$)	390 ± 203	279 ± 70	< 0.05
	CV	$52.1\ \%$	$25.1\ \%$	
	R^2	0.63 ± 0.20	0.58 ± 0.21	

$CV = \dfrac{SD}{mean} \times 100\%$: Coefficient of variation

The values were mean $\pm$ SD (averaged over arterial trees).

FIGURE LEGEND

Figure 1: A flow chart of experimental procedures and data analysis

Figure 2: Schematic representation of epicardial coronary arterial trees for metabolic syndrome and control patients reconstructed from CTA. (a-b) Axial CT images for metabolic syndrome and normal patients respectively and (c-d) reconstructed arterial trees accordingly.

Figure 3: (a) The probability frequency as a function of coefficient K_{LV} in the one-parameter model of length-volume scaling power law. The solid and dash lines represent the control and metabolic syndrome groups, respectively. Since the least-square fit of all the measurements to the one-parameter model for the length-volume scaling power law results in K_{LV} values of 26.6 (R^2=0.85) and 19.9 (R^2=0.88) for metabolic syndrome and control groups, respectively, the mean value of 23 ($= \left\lfloor \dfrac{26.6 + 19.9}{2} \right\rfloor$) was selected as a demarcation value between the two groups.

Figure 4: The accumulative probability frequency as a function of coefficient K_{LV} in the one-parameter model of length-volume scaling power law. The solid and dash lines represent the control and metabolic syndrome groups, respectively.

Figure A1: Schematic illustration of the definition of stem-crown units in the epicardial coronary arterial tree. Three stem-crown units are shown successively (1, 2 and n), with the smallest unit corresponding to a resolution of CT of ~ 1 mm (i.e., $Stem_n$ and $Crown_n$) of epicardial coronary arterial tree.