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Airway remodeling measured by multidetector computed tomography is increased in severe asthma and correlates with pathology

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Abstract

Background—To prospectively apply an automated, quantitative 3-D approach to imaging and airway analysis to assess airway remodeling in asthma.

Methods—Using the Pulmonary Workstation (VIDA Diagnostics) that enables quantitative airway segment measurements of low-dose, thin section (0.625-1.25 mm) multidetector-row CT (MDCT), we compared airway wall thickness (WT) and area (WA) in 123 subjects participating in a prospective multicenter cohort study, NIH Severe Asthma Research Program (SARP): severe asthma (n=63), mild-moderate asthma (n=35), and normal (n=25). A subset of these subjects underwent fiberoptic bronchoscopy and endobronchial biopsies (n=32). WT and WA were corrected for total airway diameter and area - WT%, WA%.

Results—Subjects with severe asthma had significantly greater WT% than mild-moderate asthma and normals [17.2 ± 1.5 v 16.5 ± 1.6 , $p=0.014$ and 16.3 ± 1.2 , $p=0.031$, respectively] and greater WA% compared to mild-moderate asthma and normal [56.6 ± 2.9 v 54.7 ± 3.3 , $p=.005$ and 54.6 ± 2.4 , $p=0.003$, respectively]. Both WT% and WA% were inversely correlated with baseline FEV₁% ($r=-0.39$, $p<0.0001$ and -0.40 , $p<0.0001$, respectively) and positively correlated with response to bronchodilator ($r=0.28$, $p=0.002$ and $r=0.35$, $p<0.0001$, respectively). Airway epithelial thickness on biopsy correlated with WT% ($r=0.47$, $p=0.007$) and WA% ($r=0.52$, $p=0.003$). In the same individual, there is considerable regional heterogeneity in airway wall thickness.

Conclusion—Severe asthmatics have thicker airway walls on MDCT than mild asthmatics or normals, which correlates with pathologic measures of remodeling and the degree of airflow obstruction. MDCT may be a useful technique for assessing airway remodeling in asthma, but overlap among groups limits the diagnostic value in individual subjects.

Keywords

Asthma; airway remodeling; chest CT

INTRODUCTION

Studies of airways of patients who die from asthma demonstrate thickened airway walls, due to increases in smooth muscle mass, infiltration with inflammatory cells, deposition of connective tissue, vascular changes and mucous gland hyperplasia, termed airway

remodeling¹⁻⁴. Airway remodeling may be a feature of milder and even asymptomatic asthma⁵⁻⁷. Remodeling of airways can result in worsening of airway narrowing, airflow obstruction and disease progression^{8,9}.

Airway remodeling in asthma has been studied *in vivo* by performing endobronchial biopsies that can then be evaluated for structural and inflammatory changes¹⁰⁻¹². Multi-detector computed tomography (MDCT) studies have recently been used to evaluate the extent of airway wall thickening as a non-invasive, highly reproducible method for studying individual airways. Several studies using MDCT have demonstrated that the airway walls of asthmatics are thicker than normals and that airway wall thickness is related to severity of disease and airflow obstruction^{7,13-15}. This thickening may be partially reversible with inhaled corticosteroid (ICS) treatment in steroid naïve patients and may increase in the absence of ICS. The airway lumen area of stable patients with asthma is not narrowed compared with that of healthy controls and may even be dilated in those with more severe disease¹⁶. These studies are often limited by the number of airways studied, small subject numbers or by the use of semi-quantitative techniques. Thus, the purpose of our study was to apply an automated airway analysis software comparing airway wall measurements among severe and mild-moderate asthmatics and normals and to correlate this with remodeling measurements on biopsies of matched airway segments.

METHODS

Study Design

As part of the NIH Severe Asthma Research Program (SARP), a prospective cohort of subjects, following informed consent, underwent a detailed testing and MDCT – using a standardized protocol developed by the SARP¹⁷. MDCT data was analyzed and compared on a total of 123 subjects: severe asthma (n=63), mild-moderate asthma (n=35), normals (n=25). In a subset whom underwent airway biopsies (n=32), we correlated segmental airway WT and area (WA) from MDCT with measures of airway remodeling from biopsies, including epithelial and lamina reticularis (LR) thickness, from the corresponding segment. All subjects at the Washington University SARP site were given the option of participating in the airway biopsy substudy. The study was approved by each site's Institutional Review Board and monitored by an independent Data and Safety Monitoring Board.

Human Subjects

The inclusion criteria by group were: *Normals*: 18 – 60 years of age, in good overall health, no smoking within past 5 years and <5 pack years smoking, and PC₂₀ >16 mg/ml. *Mild to moderate asthma*¹⁸: 18 - 60 years of age, physician diagnosis of asthma, on asthma therapy >12 months, daytime asthma symptoms > 2 times per week but less than continual, and/or nocturnal asthma symptoms > 2 times per month but less than nightly, no smoking within past 5 years and <5 pack years smoking, no concurrent lung disease, and PC₂₀ 8mg/ml or 15% improvement in FEV₁ post bronchodilator. *Severe asthma*: 18 - 60 years of age subjects with one or both of two major criteria and two of the minor criteria (American Thoracic Society workshop¹⁹). The major criteria include (in order to achieve control to a level of mild-moderate persistent asthma): (1) Treatment with continuous or near continuous (≥50% of the previous year) oral corticosteroids; or (2) Treatment with high dose inhaled corticosteroids: beclomethasone (>1,260 µg/d), budesonide (>1,200 µg/d), flunisolide (>2,000 µg/d), fluticasone (>880 µg/d), or triamcinolone (>2,000 µg/d). The minor criteria include: (1) daily treatment with a long term controller medication in addition to inhaled corticosteroids (e.g. long-acting -agonist, theophylline, or leukotriene antagonist), (2) asthma symptoms requiring short-acting -agonist use on a daily or near daily basis, (3) persistent airflow obstruction (FEV₁ <80% predicted; diurnal peak flow variability >20%),

(4) one or more urgent care visits for asthma per year, (5) three or more oral corticosteroid “bursts” per year, (6) prompt deterioration with 25% reduction in oral or inhaled corticosteroid dose; and (7) near fatal asthma event in the past. In these subjects with severe asthma, conditions other than asthma were excluded, exacerbating factors were treated, and the subject did not have a history of poor adherence.

CT technique

All subjects underwent MDCT chest with 16 or 64 detector rows (GE Light Speed Ultra 16 or Siemens Volume Zoom, Sensation 16 or 64) after maximal bronchodilation with albuterol (540-720 mcg) to minimize the effect of acute bronchoconstriction on airway dimensions. Subjects were administered increasing doses of albuterol till the FEV₁% difference was 5% or a maximal dose of albuterol (8 puffs or 720 mcg) was reached. Suspended full inspiratory measurements were obtained at the following settings: GE: 1.675-1.75 pitch, 0.6 sec rotation time, 120 kV, 0.625-1.25 mm reconstructed slice thickness, medium smooth “standard” reconstruction algorithm; Siemens: 1.5 pitch, 0.5 sec rotation time, 120 kV, 1mm reconstructed slice thickness, a medium smooth reconstruction algorithm, effective mAs was 30-57. To obtain isotropic voxels, the slice reconstruction interval was set to equal the inplane spatial resolution (field of view in mm/512 pixels).

MDCT airway evaluation software

MDCT scans were analyzed using automated, quantitative software designed to reliably label and segment the first five to six airway generations and allow accurate measurement of airway wall and lumen diameters obtained perpendicular to the long axis of each airway (Pulmonary Workstation, Version 0.139, VIDA Diagnostics)²⁰⁻²³. Previous studies have validated the lung and airway segmentation methods when compared to manual measurements^{24,25}. Airway measurements for each segment were made at each centerline voxel and averaged over the middle third of the segment. The specific MDCT measurements used included airway WT, percent WT (WT%), WA, percent WA (WA%), luminal area (LA) and percent LA (LA%). The calculations are as follows: WT = Average Outer Diameter – Average Inner Diameter, WT% = (WT/Average Outer Diameter) x 100, WA = Total Area (TA) – LA, WA% = (WA/TA) x 100, LA% = (LA/TA) x 100, (Figure 1).

In the primary analysis, we averaged third generation airway wall measurements for all automatically segmented and labeled airways in each subject. An average of 18 third generation airways per subject were measured (9 for each lung). In the secondary analysis of subjects who underwent biopsies, we obtained cross-sectional CT measurements of each biopsied airway in a plane perpendicular to the airway long-axis at a distance 30% of the segment length distal to the origin of the airway segment. Two independent readers trained in the use of Pulmonary Workstation were blinded to the subject status or the results of the biopsy measurements. Inter-rater reliability on a random sample of 50 subjects between these two readers was excellent (intraclass correlation (ICC) = 0.98).

Pulmonary Function Tests

Spirometry, methacholine bronchoprovocation and plethysmographic lung volumes were performed within 1-2 days of the MDCT scan among the SARP sites in accordance with standardized ATS criteria^{26,27}. Subjects were asked to abstain from long-acting β_2 agonists for 12 hours and short acting β_2 agonists for 4 hours prior to assessment. Spirometry was performed before and after shorting-acting β_2 agonist (4 puffs/360 mcg of albuterol) was delivered by metered dose inhaler and spacer.

Endobronchial Biopsies

A subset of 32 subjects (15 severe asthma, 9 mild-moderate asthma, and 8 normals) underwent bronchoscopy and 12-16 endobronchial biopsies were obtained from the third generation segmental carinas of the upper lobes. Three readers independently measured the areas of epithelium and LR of at least 3 biopsies with intact airway epithelium using the ImageJ software for morphometric analysis. The areas of the epithelium and LR were normalized for the length of the basement membrane yielding an epithelial and LR ratio²⁸. The average of these measurements made in triplicate was then used for subsequent analysis.

Statistical methods

All data were analyzed using analysis of variance and chi square tests to compare continuous and categorical variables across groups (SAS v9). Stepwise multiple linear regression identified variables that had independent significant associations with outcome measures that included FEV₁%_{pred}, WA%, and WT%. Variables were retained in these models if they had a significant ($p < 0.05$) or borderline significant ($p < 0.1$) association with the outcome measure.

RESULTS

Demographics

The characteristics of the subjects in our study (Table 1) demonstrated that those with severe persistent asthma were on average: older, reported more frequent symptoms of allergies, had elevated levels of IgE, increased airway hyperresponsiveness and decreased baseline FEV₁%_{pred} compared to mild-moderate asthmatics and normals. Subjects in the biopsy subset were representative of the overall cohort (Table 1) with the exception that mild-moderate asthmatics had earlier onset of asthma (11.6 v 13 yrs, $p=0.01$) and greater ED visits within the last 12 months (50% v 5.6%, $p=0.02$).

MDCT Airway WT/WA/LA

There was no significant difference in average WT among groups. To account for differences in airway size, we calculated the WT% (Figure 1) for the labeled airways in each subject. Severe asthmatics had significantly greater WT% than those with mild-moderate asthma and normals (Figure 2, Table 2). There was no significant difference between mild-moderate asthmatics and normals for WT%. The increase in WT% inversely correlated with baseline FEV₁%_{pred} ($r = -0.39$, $p < 0.0001$), and positively correlated with change in FEV₁% postbronchodilator ($r = 0.28$, $p = 0.002$). This finding was primarily due to the relationship between WT% and FEV₁%_{pred} ($r = -0.47$, $p = 0.0003$) in severe asthma. There was no significant relationship between WT% and FEV₁%_{pred} in mild-moderate asthmatics and normals. There was no significant correlation between WT% with FEV₁ PC₂₀.

There was no statistically significant difference in WA among groups. The analysis of WA% showed that severe asthmatics had greater WA% compared to mild-moderate asthmatics and normals. There was no significant difference in WA% between mild-moderate asthmatics and normals (Figure 2, Table 2). WA% was inversely correlated with baseline FEV₁%_{pred} ($r = -0.4$, $p < 0.0001$), and positively correlated with change in FEV₁% postbronchodilator ($r = 0.35$, $p < 0.0001$). The correlation between WA% and baseline FEV₁%_{pred} was due to the relationship in severe asthmatics ($r = -0.49$, $p = 0.0001$). There was a significant inverse correlation between WA% with FEV₁ PC₂₀ ($r = -0.29$ in all asthmatic subjects, $p = 0.02$, and $r = -0.48$ in those with severe asthma, $p = 0.01$).

LA was not significantly different between groups. Severe asthmatics did have smaller LA% compared to mild-moderate asthmatics and normals. There was no significant difference in LA% between mild-moderate asthmatics and normals ($p = ns$).

Segmental MDCT Comparisons

Individual airways segments were compared among the three groups in regards to WT% and WA%. WT% in a few airways, and WA% in most airways were significantly greater in severe asthmatics compared to mild-moderate asthma and normals (**Table 3**). Because segmental WT measurements are not independent of each other, we calculated a slope of airway WT% and WA% from the apex to the base of the lung in each individual subject²¹. The slopes for WT% and WA% were not significantly different between groups.

The range (minimum-maximum measurement) in airway thickness across segments per subject for WT% was 9.7-29.9 (normals), 9.7-29.6 (mild-moderate asthma), and 9.8-30.1 (severe asthma) and for WA% was 38.6-65.5 (normals), 38.9-64.7 (mild-moderate asthma) and 39.0-67.3 (severe asthma). The range of WA% across segments was significantly different between groups, with the severe asthmatics (28.3 ± 3.4) having more variability than the mild-moderate asthmatics (25.8 ± 3.4) or normals (26.9 ± 4.0 , $p = 0.0035$) but not for WT% ($p = 0.92$). The WT% and WA% range in an individual's segmental airways is highly variable and is dependent on the underlying disease status. However, if one focuses on the RUL apical segment (previously used in other studies^{5,15}), there was a statistically significant correlation between the RUL apical segment WA% (Pearson correlation coefficient $r=0.75$, $p<0.0001$) and WT% ($r=0.52$, $p<0.0001$) with all other segments (up to 19).

Multivariate analysis of WA/WT

The variables that distinguished severe asthmatics from mild-moderate asthmatics and normals included: age, baseline FEV₁%_{pred} and FVC%_{pred}, log IgE, and change in FEV₁ post-bronchodilator. We also found that WT% and WA% were significantly greater in severe asthmatics versus subjects with mild-moderate asthma and normals. Stepwise multiple regression models used FEV₁%_{pred}, WA% and WT% as dependent variables. The only significant independent predictors of FEV₁%_{pred} were WT% ($P = 0.0004$) and group ($p < 0.0001$) ($R^2 = 0.48$). When WT% was the dependent variable in the stepwise regression, the significant independent correlates were FEV₁%_{pred} ($p < 0.0001$) and history of intubation ($p = 0.04$, $R^2 = 0.415$). The only significant independent correlate of WA% was FEV₁%_{pred} ($p < 0.0001$, $R^2 = 0.331$).

Correlation between MDCT airway indices and remodeling

Epithelial thickness ratio was positively correlated with both WT% and WA% ($r = 0.47$, $p = 0.007$ and $r = 0.52$, $p = 0.003$ respectively) (Figure 3). The relationship between LR thickness ratio and WT% and WA% demonstrated a similar trend ($r = 0.33$, $p = 0.07$ and $r = 0.33$, $p = 0.06$ respectively). The sum of epithelial and LR ratios was also positively correlated with WT% and WA% ($r = 0.46$, $p = 0.008$ and $r = 0.49$, $p = 0.004$ respectively).

DISCUSSION

Airway remodeling describes structural changes, that in the asthmatic airway collectively result in thickening of the airway wall^{2,3,8,9}. CT imaging of the airways is being developed as a technique to study airway remodeling *in vivo*. Multiple studies have documented increased airway wall thickness in asthma using CT. Most of these studies^{5,13-15} employed manual tracing methods, with either manual or digital measurement of airway dimensions. These previous studies using manual tracing methods have demonstrated significant

differences in comparing asthmatics to normals though these differences may be related to selection bias. Kasahara et al. found that the radiographic measurement of WT and WA were: increased in asthmatics, correlated with LR, and inversely related to FEV₁¹³. A pediatric study found similar, although less robust results²⁹. To improve objectivity, reproducibility, and efficiency, automated airway segmentation and analysis methods have been implemented³⁰. However, automated assessments previously have been restricted to those airways that are nearly round in transaxial images, so that the long axis is roughly perpendicular to the scan plane. Consequently, quantitative measurements were obtained only on (nearly) round airways in a limited number of slices, which may lead to potential selection bias as our data demonstrates significant regional heterogeneity in segmental airway remodeling. The automated technique we used eliminated selection bias by segmenting, labeling and measuring all of the proximal airways and allowing comparison of those airways that may have been excluded using previous methods.

In this study, we used an automated, quantitative software program to analyze and measure the differences in airway WT between severe asthmatics versus milder disease. We found that when using MDCT indices of airway WT that account for TA, specifically WT% and WA%, that severe asthmatics have on average slightly more thickened airway walls compared to mild-moderate asthma and normals. Interestingly, there was no significant difference when comparing airway WT% or WA% in mild-moderate asthmatics with normals. Previous studies normalized airway measurements to the total airway diameter/area or body surface area^{13,30}. Our data demonstrates that there is substantial variability in airway diameter and lumen between airways in the same subject and between subjects and that this must be taken into consideration when averaging data. Our measurements were normalized for segmental total thickness or area which accounts for inter-airway variability.

Furthermore, we found that the MDCT indices WT% and WA% correlated with physiologic measures of airflow obstruction across subjects. Similarly, Kasahara et al. also found that WT, WA, and LR were all inversely correlated with post-bronchodilator FEV₁¹³. Increased segmental airway thickness may correlate with more distal, small airway narrowing³¹. Gono et al. compared expiratory and inspiratory (E/I) lung density measurements to assess air trapping as a measure of small airways disease. Asthmatics with irreversible airflow obstruction had significantly higher E/I ratios than asthmatics whose expiratory flows normalized after bronchodilation⁵. Hasegawa et al. in a recent study using 3-D measurements of airway dimensions in chronic obstructive pulmonary disease focused their analysis on two bronchi (the right upper lobe and right lower lobe) and found statistically significant correlations between lumen area, WA% and FEV₁ (% predicted). They also found a stronger correlation when distal smaller airways (up to 6th generation) were analyzed³². These findings suggest that airway remodeling in more proximal airways reflects similar changes occurring in more distal airways, resulting in measurable airflow limitation and air trapping.

A current limitation of MDCT measures of airway thickness is the inability to be more specific about which component of the airway has truly changed. In our study we are unable to discern if the MDCT findings of increased WT% and WA% in severe asthma truly reflects increases in epithelial and LR changes or some other feature of airway remodeling such as increased smooth muscle mass^{1,3}. This particular aspect of airway remodeling has not been well characterized due to the limited sample of smooth muscle available with an endobronchial approach. Future longitudinal studies are needed to evaluate temporal changes in airway wall thickness within individual patients and to evaluate the effects of different treatments.

There are limitations to our ability to measure airway remodeling and accurately obtain airway biopsies from the same segment measured by MDCT. The biopsy sites were obtained from the upper lobes only and therefore we are not able to generalize our remodeling measures to other lung segments. Accurate histologic measurement of the epithelial and LR layers requires that the biopsies have an intact epithelium²⁸, therefore not all biopsies were included in our analysis.

The natural history of airway remodeling in asthma, its rate of progression and its response to treatment are questions that remain unanswered. Non-invasive measures of airway remodeling using MDCT would allow us to longitudinally monitor the effects of various stimuli and treatments on remodeling. Eventually, this technique may help identify individuals with asthma who are likely to develop severe disease and who may benefit from early targeted, aggressive therapy.

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ABBREVIATION LIST

ANOVA	Analysis of variance
ATS	American Thoracic Society
CT	Computed tomography
DSMB	Data Safety and Monitoring Board
ED	Emergency Department
E/I	Expiratory/inspiratory
Epi	Epithelium
FEV ₁	Forced expiratory volume in one second
FEV ₁ % _{Pred}	Percent predicted of Forced expiratory volume in one second
H&E	Hematoxylin-eosin
HRCT	High resolution computed tomography
Ig E	Immunoglobulin E
ICC	Intraclass correlation
ICS	Inhaled corticosteroids
LR	Lamina reticularis
LA	Luminal area
LA%	Luminal area percent
MDCT	Multidetector-row computed tomography
NAEPP	National Asthma Education and Prevention Program
NIH	National Institutes of Health
ns	Not significant
PC ₂₀	Provocative concentration of methacholine to cause a 20% decline in FEV ₁

SARP	Severe Asthma Research Program
SD	Standard deviation
TA	Total area
WA	Wall area
WA%	Wall area percent
WT	Wall thickness
WT%	Wall thickness percent

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Wall Thickness = Average Outer Diameter - Average Inner Diameter

$$\text{Wall Thickness \%} = \frac{\text{Wall Thickness}}{\text{Average Outer Diameter}} \times 100$$

Figure 1. Airway measurements by MDCT

Multiple airway measurements can be performed by the Pulmonary Workstation program. Depicted are the two primary measurements used in the current study. *Wall thickness* is measured over the middle one-third of each segment at each centerline voxel. This value is averaged, resulting in a single wall thickness value for each segment. The average outer diameter for the segment is calculated in a similar fashion. *Wall thickness %* for each segment is the calculated by dividing the wall thickness by the average outer diameter. Total airway area and lumen area are similarly calculated at each centerline voxel and averaged over the middle one-third of the segment. *Wall area* was calculated by subtracting the lumen

area from the total area. *Wall area %* was calculated by dividing the wall area by the total airway area.

Figure 2. Pulmonary Workstation MDCT images and bronchial biopsy from normal and severe asthma subjects

Representative images from matching Pulmonary Workstation MDCT analysis and hematoxylin-eosin (H&E) sections from an endobronchial biopsy from a normal control subject (Panel A & C) and a severe asthma subject (Panel B & D) are demonstrated. The MDCT analysis was performed using the Pulmonary Workstation software (VIDA) and a screen capture of the cross-sectional MDCT image is demonstrated. The H&E sections were obtained from endobronchial biopsies that were processed as described in Methods. The epithelial layer (Epi), lamina reticularis (LR) and the basement membrane (dashed line) are indicated.

Figure 3. MDCT wall thickness % and wall area % are correlated with airway remodeling

In a subset of patients ($n = 32$), endobronchial biopsies were performed. Epithelial thickness was measured in μm and normalized for the length of basement membrane, resulting in an epithelial ratio. These morphometric measurements were then correlated with the radiographic indices WT% and WA%. (a) Wall thickness % is correlated with epithelial thickness ($r = 0.47, p = 0.007$). (b) Wall area % is correlated with epithelial thickness ($r = 0.52, p = 0.003$ respectively).

Table 1

Group characteristics

Characteristic	Normal (N=25)	Mild-Moderate Asthma (N=35)	Severe Asthma (N=63)	P value *
Age – mean yr (SD)	30.2 (8)	34.4 (10.6)	37.8 (13.3)	0.023
Female sex – no (%)	16 (64)	21 (60)	37 (59)	0.9
Age at diagnosis of asthma – mean yr (SD)	--	13.6 (13.8)	13.4 (14.9)	0.9
Duration of Asthma – mean yr (SD)	--	20.8 (13.2)	24.4 (13.2)	0.2
Baseline FEV ₁ - liters (% predicted)	3.64 (101)	2.82 (81)	1.98 (61)	<0.001
FEV ₁ PC ₂₀ - mg/ml (SD)	--	1.66 (1.67)	1.20 (1.80)	0.051
Atopic % [†]	33.3	100	100	<0.001
Ig E – mean IU (SD)	97 (174)	226 (291)	456 (697)	<0.001
Medication Use (%)				
Any β -agonist	--	88.2	98.3	<0.001
Long-acting β -agonist	--	41.2	91.7	<0.001
Inhaled corticosteroid	--	52.9	98.3	<0.001
Oral corticosteroid	--	2.9	60	<0.001
ED visits or hosp - past 12 months (%)	--	19.2	42.9	<0.001
Hospitalizations - past 12 months (%)	--	0	25.9	0.002
History of Intubation (%)	--	0	20.3	0.001

SD = standard deviation, FEV₁ = forced expiratory volume in one second, ED = Emergency department

Nonparametric Wilcoxon test was used for PC₂₀ comparison.

* comparing groups by χ -square or analysis of variance (ANOVA) after IgE was log transformed.

[†] Percent of subjects with one or more positive allergy skin tests

Table 2

MDCT airway measurements by group

MDCT Measurement	Normal (N=25)	Mild-Moderate Asthma (N=35)	Severe Asthma (N=63)	P value (N v. S) *	P value (M v. S) *
Wall Thickness <i>Mean (SD) mm</i>	1.59 (0.13)	1.66 (0.14)	1.66 (0.2)	ns	ns
Wall Thickness % <i>Mean (SD)</i>	16.3 (1.2)	16.5 (1.6)	17.2 (1.5)	0.031	0.014
Wall Area <i>Mean (SD) - mm²</i>	41.2 (5.5)	44.1 (6.4)	42.2 (7.4)	ns	ns
Wall Area % <i>Mean (SD)</i>	54.6 (2.4)	54.7 (3.3)	56.6 (2.9)	0.003	0.005
Lumen Area <i>Mean (SD) mm</i>	42.5 (7)	45.9 (9.3)	42 (9.1)	ns	ns
Lumen Area % <i>Mean (SD) mm</i>	45.4 (2.4)	45.3 (3.3)	43.4(2.9)	0.005	0.003
Total Area <i>Mean (SD) - mm²</i>	83.7 (12.2)	90 (15)	84.1 (16.1)	ns	ns

SD = standard deviation, ns = not significant

* comparing groups by *t*-test