Quantitative assessment of cross-sectional area of small pulmonary vessels in patients with COPD using inspiratory and expiratory MDCT

(慢性閉塞性肺疾患における吸気呼気 CT を用いた肺末梢血管面積の定量的評価)

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ABSTRACT

Objectives: Structural and functional changes in pulmonary vessels are prevalent at the initial stages of chronic obstructive pulmonary disease (COPD). These vascular alterations can be assessed using cross-sectional area (CSA) of small pulmonary vessels. However, neither in non-COPD smokers nor in COPD patients it has been defined whether the structural changes of pulmonary vessels detected by paired inspiratory and expiratory CT scans are associated with emphysematous changes. We quantified the CSA and low attenuation area (LAA) and evaluated the changes in these parameters in the inspiratory and expiratory phases.

Materials and Methods: Fifty consecutive non-COPD smokers and COPD patients were subjected to multi detector-row CT and the percentage of vessels with a CSA less than 5 mm$^2$ as well as the percentage LAA for total lung area (%CSA < 5, %LAA, respectively) were calculated.

Results: The %CSA < 5 correlated negatively with %LAA. The %CSA < 5 was lower in COPD patients with emphysema as compared with non-COPD smokers and COPD patients with or without mild emphysema. In addition, the %CSA < 5 was lower in the no / mild emphysema subgroup as compared with non-COPD smokers. The respiratory phase change of %CSA < 5 in COPD patients was greater than that in non-COPD smokers.

Conclusion: The percentage of small pulmonary vessels decreased as emphysematous changes increase, and this decrease was observed even in patients with no / mild emphysema. Furthermore, respiratory phase changes in CSA were higher in COPD patients than in non-COPD smokers.
INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterized by persistent airflow limitation associated with an enhanced chronic inflammatory response of the lungs to noxious particles or gases, primarily caused by cigarette smoking (1, 2). Airflow limitation is caused by a combination of parenchymal destruction (emphysema)-induced loss of elastic coil and small airway remodeling. The pathophysiology of COPD depends on these factors, although their relative contributions vary from person to person.

Although major COPD abnormalities occur in the alveolar structures, including peripheral airways, changes in pulmonary vessels are also an important component of this disease (3, 4). In severe COPD, emphysematous destruction accompanied with vascular changes may result in pulmonary hypertension. Pulmonary vessel alterations in COPD are characterized by wall thickening and endothelial dysfunction (5, 6). Recent studies have shown that these changes are observed in the early stages of COPD as well as in smokers with normal pulmonary function (7).

The technological progress of high resolution computed tomography (HRCT) has made it possible to detect small units of emphysema and subsegmental bronchus as well as peripheral pulmonary arteries (8, 9). Many quantitative assessments of emphysema or small airways have been performed. However, few studies have focused on pulmonary vessels. Recently, Matsuoka et al. proposed the cross-sectional area (CSA) of small pulmonary vessels as a parameter of pulmonary vessel alterations in patients with COPD (10-12). They reported that in case of severe emphysema the total CSA of
subsegmental levels correlated with the mean pulmonary arterial pressure. These authors also reported a good correlation of total CSA with forced expiratory volume in one second / forced vital capacity (FEV$_1$ / FVC) and FEV$_1$ %predicted in patients with severe COPD (11). However, whether these correlations are also observed in smokers with normal lung function and patients with early-stage COPD has not been defined.

Emphysema volume or mean lung density in expiratory CT images has been reported to be a superior predictor of pulmonary function tests (PFTs) abnormalities compared to those in inspiratory CT images (13-15). Yet, there has been no study comparing paired inspiratory and expiratory CT images with regard to CSA in patients with COPD. Whether CSA or the respiratory phase change of CSA differs between emphysema and non-emphysema phenotypes of COPD has not been established. In this study, we measured CSA and low attenuation area (LAA) in paired inspiratory and expiratory CT scans, to see whether lung vessel involvement was associated with lung destruction or obstructive impairment.
MATERIALS AND METHODS

Subjects

Fifty patients diagnosed with or suspected of having COPD were recruited at Chiba University Hospital from July 2009 to December 2010. COPD was diagnosed on the basis of past history, physical examination and spirometric data according to the Japanese Respiratory Society (JRS) guidelines. Spirometric measurements were performed using Fudac-60 (Fukuda Denshi; Tokyo, Japan); as recommended by the American Thoracic Society (ATS). This study was approved by the ethics committee of Chiba University School of Medicine and all patients gave their informed consent in writing.

MDCT scanning

Multi detector-row CT (MDCT) was performed in the supine position with 1mm collimation. All patients underwent 64-multi detector CT (Aquillion ONE, Toshiba Medical systems; Tokyo, Japan) at full inspiration and full expiration. Images were obtained using 120 kV and 200 mA at 0.35 sec/rotation. CT images were reconstructed with 0.5mm slice thickness using standard and bone algorithms.

CT measurement of small pulmonary vessels

For CSA measurements, three HRCT images were selected; (1) the level at 1cm above the upper margin of the aortic arch (upper lung fields), (2) 1cm below the carina (middle lung fields), and (3) 1cm below the right inferior pulmonary vein (lower lung fields). HRCT images were analyzed using an image processing program (ImageJ Version 1.44, available on the Web at imagej.nih.gov/ij/download/).
The CSA measurements were performed according to the following steps (Figure 1).

1. The threshold technique was adopted with attenuation between -500 and -1024 Hounsfield units (HU).
2. These images were converted into binary images at a window level of -720 HU.
3. The range of circularity was set from 0.9 to 1.0 using the "Analyze particles" function of ImageJ software.
4. CSA was measured separately by the size of each vessel (less than 5 mm$^2$ and 5-10 mm$^2$), and the CSAs on the three selected CT slices were summed up.

LAA measurements were performed according to the following steps.

1. The threshold technique was adopted with attenuation between -500 and -1024 HU.
2. These images were converted into binary images at a window level of -950 HU.
3. The range of circularity was set from 0 to infinity, and the LAA was summed using the "Analyze particles" function of ImageJ software on each slice. The total lung area was obtained using threshold values between -500 to -1024 HU.

The percentage of CSA < 5 (%CSA < 5), CSA 5-10 (%CSA 5-10), and LAA (%LAA) in the total lung area were calculated. For the evaluation of the difference in %CSA among COPD phenotypes and smokers with normal lung function (non-COPD smokers), COPD patients were divided into two groups according to the extent of LAA as follows: emphysema phenotype (%LAA ≥ 12.5%) and no / mild emphysema phenotype (%LAA < 12.5%) (16).

**Statistical analysis**
Data are expressed as mean (range). Univariate analysis used $\chi^2$ tests for categorical variables and one-way analysis of variance for quantitative variables with Sheffe’s test as a post hoc test for multiple comparisons. Correlations of %CSA (%CSA < 5, %CSA 5-10) with %LAA and airflow obstruction (FEV$_1$/FVC and FEV$_1$ %predicted) were evaluated by Spearman’s rank correlation analysis. The differences in CSA among the three groups, and in change of %CSA < 5 between inspiration and expiration were assessed by two-way analysis of variance and Tukey-Kramer test. For all statistical analyses, the level of significance was set at $p < 0.05$. All statistical analyses were performed using JMP 10.0 software (SAS institute, Cary, NC).
RESULTS

Patient characteristics and pulmonary function tests

The characteristics and the results of PFTs of the 50 patients are summarized in Table 1. The number of patients with COPD in each Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage was as follows: stage 1, n = 10; stage 2, n = 12; stage 3, n = 13; stage 4, n = 3. Twelve smokers with normal pulmonary function tests (FEV₁/FVC ≥ 0.7) were included in this study. Non-COPD smokers and COPD patients with mild to moderate (stage 1 and 2) degrees of airflow limitation, accounted for 70% of the whole study population.

Difference in %CSA < 5 among COPD phenotypes and smokers

Because there was a wide variation of %CSA < 5 among patients with COPD, the %CSA < 5 was compared among COPD phenotypes and non-COPD smokers. The %CSA < 5 was significantly lower in patients with the emphysema phenotype as compared with non-COPD smokers and patients with the no / mild emphysema phenotype. In addition, the %CSA < 5 was significantly lower in patients with the no / mild emphysema phenotype of COPD as compared with that in non-COPD smokers (Figure 2). A wide variation was observed regarding %CSA < 5 in the no / mild emphysema phenotype subgroup. However, a significant correlation was observed between %CSA < 5 and %LAA on inspiratory images in non-COPD smokers and in the no / mild emphysema phenotype subgroup.

Difference in %CSA 5-10 among COPD phenotypes and non-COPD smokers

The %CSA 5-10 was significantly lower in patients with the emphysema phenotype as
compared with non-COPD smokers (Figure 3). The %CSA 5-10 gradually decreased in relation to the severity of emphysema, however, there were no significant differences between patients with the no / mild emphysema phenotype and those with the emphysema phenotype, or between patients with the no / mild emphysema phenotype and non-COPD smokers.

**Change in %CSA < 5 from the inspiratory to the expiratory phase on CT images**

To evaluate the change in %CSA < 5 from the inspiratory to the expiratory phase, we calculated $\Delta$%CSA < 5 ($100 \times \left[\text{expiratory } %\text{CSA } < 5 - \text{inspiratory } %\text{CSA } < 5\right] / \text{inspiratory } %\text{CSA } < 5$). The $\Delta$%CSA < 5 in COPD patients, including both phenotypes, was greater compared with that in non-COPD smokers (Figure 4). $\Delta$%CSA < 5 did not differ significantly between the two COPD phenotypes. However, when COPD patients were distributed according to obstructive impairment, the $\Delta$%CSA < 5 in patients with stages 1 and 2 COPD was larger than in patients with stages 3 and 4 COPD or in non-COPD smokers. The $\Delta$%CSA < 5 in patients with stages 3 and 4 COPD was similar to that in non-COPD smokers (Figure 5).

We also evaluated the change in %LAA ($\Delta$LAA) from the inspiratory to the expiratory phase ($100 \times \left[\text{expiratory } %\text{LAA} - \text{inspiratory } %\text{LAA}\right] / \text{inspiratory } %\text{LAA}$). The $\Delta$LAA was greater in patients with the no / mild emphysema phenotype than in those with the emphysema phenotype, but in patients with the no / mild emphysema phenotype it was similar to that in non-COPD smokers (Figure 6).
Correlation among %CSA < 5, %LAA and lung function

Percentage CSA < 5, %CSA 5-10 and %LAA determined based on paired inspiratory and expiratory CT images are presented in Table 1. Percentage CSA < 5 in expiration (0.93 ± 0.22) was significantly larger than that in inspiration (0.77 ± 0.21) (p < 0.001). Correlation coefficients between %CSA and %LAA or obstructive impairment are shown in Table 2.

Percentage CSA < 5 showed a significant negative correlation with %LAA both in the inspiratory (r = -0.68) and expiratory phases (r = -0.59) (Figure 7), while %CSA 5-10 showed a weak correlation (inspiratory phase; r = -0.50, expiratory phase; r = -0.41). Percentage CSA < 5 showed a significant correlation with FEV₁/FVC and FEV₁ %predicted both in the inspiratory and expiratory phases. In addition, %CSA < 5 showed a significant correlation with V₅₀/V₂₅, especially in the expiratory phase (table 2).
DISCUSSION

In the present study, %CSA < 5 was lower in patients with emphysema COPD phenotype than in those with no / mild emphysema phenotype, and lower in these than in non-COPD smokers. This suggests that the total number of small pulmonary vessels in lung fields decreases with the worsening of emphysematous changes, and that these pulmonary vessel changes may occur even in patients with mild COPD. On the other hands, the percentage of small pulmonary vessels of 5-10 mm$^2$ were not clearly associated with %LAA. Percentage CSA < 5 may include both elastic and muscular vessels, but would mostly reflect elastic vessels. No pulmonary imaging instrument can distinguish between these two types of vessels, although secondary pulmonary lobular arteries with a diameter around 1 mm are easily observed on HRCT. Narrowing and disappearance of small airways (< 2 mm in diameter) are one of the characteristic findings in COPD patients (17). The secondary lobular arteries that accompany small airways are included in %CSA < 5, as these vessels travel mostly vertically in CT slices. Percentage CSA < 5 could serve as an index to detect changes in small pulmonary vessels associated with emphysematous changes or initial COPD changes; that is, small airway changes.

This study showed that %CSA < 5 correlated negatively with the extent of emphysema. This finding is compatible with the results of a previous study, supporting the concept that vascular alteration in COPD is influenced by emphysematous changes (11). Early studies suggested that the pulmonary vascular bed was destroyed by emphysematous changes in COPD patients (18, 19). A decrease of %CSA < 5 in emphysematous lungs might reflect these histological changes, which
could be detected by HRCT. Furthermore, a decrease in %CSA < 5 might reflect passive vascular compression by emphysema (air trapping in lung fields) (11). On CT images obtained during the expiratory phase, %CSA < 5 was higher than that found in the inspiratory phase. Passive vascular compression may be partly released by expiration. In the present study, ∆%LAA was lower in patients with emphysema phenotype than that in patients with the no / mild emphysema phenotype and in non-COPD smokers. Trapped air may decrease in parallel with the decrement in total lung volume in patients with COPD emphysema phenotype.

Percentage CSA < 5 correlated with %LAA and obstructive impairment expressed as FEV₁ / FVC, FEV₁ %predicted and V₅₀ / V₂₅, in the present study. Our study confirmed previous findings and in addition we assessed %CSA and %LAA in non-COPD smokers and especially mild to moderate COPD based on paired inspiratory and expiratory CT images. In both inspiratory and expiratory phases, CSA was similarly associated with %LAA, extent of emphysema and obstructive impairment. It remains controversial whether inspiratory or expiratory CT indices are better predictors of COPD (14, 20). However, some studies reported that expiratory CT images were superior for determining the extent of emphysema and showed better correlation with PFTs than inspiratory images (15, 21, 22).

In this study, ∆%CSA < 5 was defined as the percentage change from the inspiratory to the expiratory phase, and this index was higher in patients with early-stage (stages 1 and 2) COPD than that in non-COPD smokers. This suggested that there might be some difference in the behavior of small pulmonary vessels between early-stage COPD
and non-COPD smokers regarding respiratory phases. Basic science research revealed a role for endothelial dysfunction in COPD (23, 24), although published studies assessing in vivo endothelial dysfunction are few (25-27). Barr and co-workers (27) reported that flow-mediated dilation of the brachial artery is a noninvasive procedure and measures endothelium-dependent, NO-mediated vasodilation. The larger $\Delta%\text{CSA} < 5$ found in early-stage COPD may indicate that the effects of impaired endothelial function are greater in patients with early-stage COPD. Interestingly, $\Delta%\text{CSA} < 5$ was lower in patients with stages 3 and 4 COPD than in those with stages 1 and 2 COPD, although the baseline $%\text{CSA} < 5$ differed between the two groups. Progression of obstructive impairment can decrease respiratory phase-induced changes in small pulmonary vessels. The anatomical destruction or functional disturbance of pulmonary vessels may partly explain the decrement of $\Delta%\text{CSA} < 5$ in patients with severe COPD.

Percentage $\text{CSA} < 5$ showed a positive correlation with the degree of peripheral airway obstruction ($V_{50}/V_{25}$). Within the lung parenchyma, the bronchi and pulmonary artery branches are closely associated. Hasegawa et al. demonstrated that in COPD patients the dimension of distal airways was more closely related to airflow limitation than that of proximal airways (28). The positive correlation between $%\text{CSA} < 5$ and one of the indexes of peripheral airway obstruction ($V_{50}/V_{25}$), suggests that small pulmonary vessels may be affected by the inflammation of these distal or peripheral airways.

There are some limitations to this study. First, the number of patients was relatively
Moreover, our study focused on patients with early-stage COPD and non-COPD smokers, since 70% of our patients were non-COPD smokers and COPD with mild and moderate (stages 1 and 2) degree of airflow limitation. Second, we used the same thresholds for inspiratory and expiratory CT images for LAA quantification and CSA measurement. There are some studies using different thresholds for quantification of emphysema (21). However, this threshold issue has been undefined, since other authors have used the same setting for both measurements (22). Third, inspiration and expiration depend on patients’ efforts. The patients were instructed to expire air as much as possible and hold it at deep expiration, but the effort in inspiration and expiration probably differed among them. Finally, we did not analyze the airway dimension in the current study, thus the relationship between airway disease and pulmonary vessels was not clarified. Therefore, we distributed the COPD patients into no / mild emphysema phenotype and emphysema phenotype. Further studies are needed to clarify the relationship between airway disease and pulmonary vessels.

In conclusion, CSA measured using paired inspiratory and expiratory MDCT revealed that CT images are influenced in different ways by the degree of LAA and obstructive impairment in non-COPD smokers and even in patients with mild to moderate COPD.
REFERENCE LIST


Figure 1

Method used to measure the cross-sectional area of small pulmonary vessels (CSA) employing ImageJ software. (a) Computed tomography (CT) image of lung fields segmented within the threshold between -500 and -1024 Hounsfield units (HU). (b) These images were converted into binary images at a window level of -720 HU. The range of circularity was set from 0.9 to 1.0 using the "Analyze particles" function of the ImageJ software. (c) The CSA of vessels less than 5 mm$^2$ and 5-10 mm$^2$ were measured separately on inspiratory and expiratory CT images (left: CSA < 5 on an inspiratory image, %CSA < 5 = 0.64; right: CSA < 5 on an expiratory image, %CSA < 5 = 0.84 in a patient with COPD).
Figure 2

Cross-sectional area (CSA) of small pulmonary vessels less than 5 mm² (%CSA < 5) in non-COPD patients, COPD patients with no / mild emphysema phenotype (%LAA < 12.5) and COPD patients with emphysema phenotype (%LAA ≥ 12.5%).
Cross-sectional area (CSA) of small pulmonary vessels 5 to 10 mm$^2$ ($\%$CSA 5-10) in non-COPD subjects and COPD phenotypes classified by the severity of emphysema.
Figure 4

Comparison of $\Delta$%CSA < 5 (% change in CSA < 5 from inspiration to the expiration phase) between non-COPD smokers and COPD patients.
Figure 5

Comparison of Δ%CSA < 5 (% change in CSA < 5 from inspiration to the expiration phase) among non-COPD smokers and COPD patients distributed according to the severity of obstructive impairment (stages 1 and 2 vs. stages 3 and 4).
Figure 6

Comparison of ∆%LAA (% change in LAA from inspiration to the expiration phase) among non-COPD smokers and two COPD phenotypes.
Figure 7

Relationship between %CSA < 5 and %LAA measured on (a) inspiratory and (b) expiratory phases.
Table 1  Characteristics of the 50 patients.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Non-COPD smoker</th>
<th>No/mild emphysema phenotype</th>
<th>Emphysema phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>63.3 (44–82)</td>
<td>71.1 (56–84)</td>
<td>70.7 (47–83)</td>
</tr>
<tr>
<td><strong>Sex (male/female)</strong></td>
<td>11/1</td>
<td>24/1</td>
<td>13/0</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td>23.7 (20.1–32.7)</td>
<td>23.1 (16.4–33.4)</td>
<td>20.4 (16.5–23.5)</td>
</tr>
<tr>
<td><strong>Smoking (pack-year)</strong></td>
<td>46.2 (7.3–105)</td>
<td>46.1 (11–106)</td>
<td>46.7 (26.5–60)</td>
</tr>
<tr>
<td><strong>Pulmonary function tests</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>VC % predicted (%)</td>
<td>99.5 (68.1–135.9)</td>
<td>98.7 (49.1–141.3)</td>
<td>89.9 (70.2–110.1)</td>
</tr>
<tr>
<td>FVC (L)</td>
<td>3.37 (1.73–5.51)</td>
<td>3.05 (1.34–4.23)</td>
<td>2.88 (2.02–4.69)</td>
</tr>
<tr>
<td>FEV1 (L)</td>
<td>2.49 (1.36–4.31)</td>
<td>1.81 (0.55–2.92)</td>
<td>1.23 (0.51–3.26)</td>
</tr>
<tr>
<td>FEV1/FVC (%)</td>
<td>75.5 (70.6–85.3)</td>
<td>57.1 (28.2–69.9)</td>
<td>40.4(26.5–69.5)</td>
</tr>
<tr>
<td>FEV1% predicted (%)</td>
<td>85.0 (56.1–121.2)</td>
<td>69.1 (25.5–107.1)</td>
<td>46.4(25.2–83.4)</td>
</tr>
<tr>
<td>V50/V25</td>
<td>4.18 (2.1–7.04)</td>
<td>3.38 (1.45–6.81)</td>
<td>2.06(0.77–3.36)</td>
</tr>
<tr>
<td><strong>Measurements of CT parameters</strong></td>
<td></td>
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<tr>
<td>%CSA &lt; 5</td>
<td></td>
<td></td>
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<tr>
<td>inspiration</td>
<td>0.94 (0.62–1.17)</td>
<td>0.78 (0.53–1.32)</td>
<td>0.59(0.39–0.76)</td>
</tr>
<tr>
<td>expiration</td>
<td>1.04 (0.52–1.33)</td>
<td>0.98 (0.67–1.28)</td>
<td>0.73(0.34–1.18)</td>
</tr>
<tr>
<td>%CSA5–10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>inspiration</td>
<td>0.47 (0.31–0.70)</td>
<td>0.39 (0.21–0.78)</td>
<td>0.30(0.15–0.40)</td>
</tr>
<tr>
<td>expiration</td>
<td>0.51 (0.24–0.85)</td>
<td>0.46 (0.13–0.81)</td>
<td>0.34(0.19–0.52)</td>
</tr>
<tr>
<td>%LAA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>inspiration</td>
<td>1.76 (0.10–9.34)</td>
<td>1.57 (0.21–7.8)</td>
<td>27.1(13.4–46.5)</td>
</tr>
<tr>
<td>expiration</td>
<td>1.03 (0–6.59)</td>
<td>0.48 (0.003–2.30)</td>
<td>22.5(7.36–52.5)</td>
</tr>
</tbody>
</table>

BMI, body mass index; VC, vital capacity; FVC, forced vital capacity, FEV1, forced expiratory volume in 1 s. Data shown as mean (range).

a p < 0.05 vs non-COPD.
b p < 0.05 vs no/mild emphysema phenotype.
Table 2

Spearman's correlation coefficients for comparison between CT measurements and pulmonary function tests.

<table>
<thead>
<tr>
<th></th>
<th>%LAA</th>
<th>FEV₁/FVC</th>
<th>FEV₁ % predicted</th>
<th>V₅₀/V₂₅</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>p</td>
<td>r</td>
<td>p</td>
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<tr>
<td><strong>Insp.</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>%CSA &lt; 5</td>
<td>-0.68</td>
<td>&lt; 0.001</td>
<td>0.53</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>%CSA 5-10</td>
<td>-0.50</td>
<td>&lt; 0.001</td>
<td>0.31</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td><strong>Exp.</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>%CSA &lt; 5</td>
<td>-0.59</td>
<td>&lt; 0.001</td>
<td>0.55</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>%CSA 5-10</td>
<td>-0.41</td>
<td>&lt; 0.01</td>
<td>0.41</td>
<td>&lt; 0.01</td>
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</table>

Note: NS = not significant.
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