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Tracheal collapsibility in adults is dynamic over time.

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\textbf{Declarations of interest: None}

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**Introduction:**

Tracheal collapse is increasingly seen due to the rapidly rising number of computed tomography (CT) scans of the chest performed in hospitals [1]. Since 1993 [2], the CT modality with both inspiratory and expiratory scans has identified numerous patients with excess tracheal collapse during expiration. The patients report symptoms such as dyspnea, cough, and recurrent infections [3] and often they have comorbid lung diseases as well, especially chronic obstructive pulmonary disease (COPD) [4]. The similarity in symptom patterns complicates the distinction between excessive tracheal collapse and other more common lung diseases. Today, tracheal collapse is divided into categories dependent on the morphology of the trachea in expiration. The most commonly recognized type is affection of the posterior membranous wall [5]. When the posterior wall is bulging into the lumen during expiration, resulting in a reduction of the lumen with more than 50% compared to the lumen during inspiration [6], the condition is known as EDAC (excessive dynamic airway collapse). The cut-off value is adapted directly from the diagnostics through bronchoscopy [7], probably leading to the false positive diagnosis of EDAC [8][9]. When the cartilage is affected the disease is denoted tracheomalacia, although the term tracheomalacia was indistinct from the excess tracheal collapse in previous literature [7]. The description of the natural history of tracheal collapse is based on 40-year-old studies. In these studies, evaluation of the tracheal collapse was based on bronchoscopy and the evaluation was repeated with an average follow-up period of 5.2 years[10][11]. The conclusion was that no patients improved, the majority progressed and in a few patients the collapse was stable. The potential pathways of the different disease trajectories were not established. Whether the morphology of the trachea is related to the changes in collapsibility is unknown. However, CT images are able to visualise the existence of different shapes of the trachea during expiration. Furthermore, the CT software options can facilitate exact measurements of the tracheal dimensions making it feasible to investigate both morphology and tracheal collapsibility. The potential risk factors for progression or regression of the tracheal collapse during expiration have not yet been clarified. A previous study suggests that the increasing use of inhaled corticosteroids (ICSs) may play a role [12]. In the present study, we examined the tracheal collapse in 20 patients at two time points with a two-year interval on average. Furthermore, we investigated whether the change in collapsibility depended on the morphology of the trachea during forced expiration, use of corticosteroids or recurrent infections. In addition, we examined the correlation between the changes in tracheal collapse and changes in the pulmonary function tests and the symptoms.
METHOD:

Patients:
We identified 20 outpatients with excessive tracheal collapse identified by a multi-detector CT. The indications for CT varied from examination for suspected bronchiectasis to potential progression in known interstitial lung disease. Patient records were scrutinized for demographic data, symptoms, body mass index (BMI), smoking history, use of ICSs, use of oral corticosteroids, use of antibiotics and pulmonary function tests.

CT scan:
Subsequently, we performed a repeat CT scan to see if collapsibility persisted. Before the repeat scan, patients were trained in maximal inspiration, expiration and in holding the breath. The patients were also instructed by MN during CT acquisition. HRCT was performed on a multi-row detector scanner and included a scan range of the whole chest in full inspiration and at end-expiration. The CT acquisition parameters were 64 x 0.625 mm or 126 x 0.625 mm collimation, kV 120, mAs/slice 150-200, rotation time 0.5 s, pitch 0.59, reconstruction thickness 0.9 mm, increment 0.45 mm. A high-resolution kernel was used. Images were transferred to a picture archiving communication system (PACS).

Image interpretation:
Image assessment was performed on a dedicated CT workstation (Philips, Extended Brilliance workspace version 4.5.2.) using standard lung window display settings (level: -500HU, width: 1500HU). The cross-sectional area of the trachea was determined in each 10 mm slice from the carina to the thoracic outlet in both the inspiratory and the expiratory images. The sum of these volumes was multiplied and the difference between the inspiratory and expiratory scan was calculated [13].

In tracheomalacia, the primary diagnostic criterion is a reduction of more than 50% in the cross-sectional diameter of the trachea in expiration compared to inspiration. The shape of the trachea alters during expiration in different ways:
1. Reduction in the sagittal diameter of the trachea and at the same time elongation of the coronal diameter is called crescent type tracheomalacia. Index: Coronal/Sagittal ratio > one,
2. Reduction in the coronal diameter leading to an index of < 0.667 is called saber sheath type and
3. Combined reduction in both the sagittal and coronal diameter is called circumferential type [14][15][16].
The morphology of the trachea in both inspiration and expiration was evaluated and the dimensions of the trachea were measured.

**Statistics:**

First, the normal distribution of the continuous variables was checked by the QQplot. The continuous variables are reported as means and standard deviations (SDs). The categorical data are presented as counts and proportions. The chi-square test was used to test if there was a significant relationship between the categorical variables. The T-test was used for continuous variables. Analyses were performed using STATA, version 13.

The study was approved by the Danish Data Protection Agency and the The Central Denmark Region Committee on Health Research Ethics. Patients were only included after informed signed consent.
RESULTS:

Study population:

The study population included 20 patients. Patient demographics are provided in Table 1. Repeat CT scans were performed after 24.5 months ± 7.4 (mean ±SD).

Changes in tracheal collapse:

We divided the patients into three groups depending on the changes in tracheal collapse (Fig.1).

Demographic indices at baseline were similar in the three groups (Table 1).

1. **No changes** in tracheal collapse: We defined patients as stable when the change in tracheal collapse was less than 10% between the two scans. Four patients (20%) met this criterion. In the same period, their pulmonary function parameters and Medical Research Council (MRC) dyspnea score were also unchanged.

2. **Progression** in tracheal collapse: Defined as an increase in the tracheal collapse of more than 10% from the baseline scan to the second scan. In this group of seven patients (35%), dyspnea did not deteriorate by progression of the tracheal collapse when measured by changes in the MRC score. FEV1 was stable in six out of seven patients and FVC was stable in four out of seven patients.

3. **Regression** in tracheal collapse: 9/20 patients (45%) demonstrated less collapse (≥10% reduction) in the second scan compared to baseline. The improvements lead to tracheal collapse of less than 50% during expiration at the time of the second scan and the patients could no longer be diagnosed with EDAC/TM based on this scan. Their MRC score did not improve in the same period. The FEV1 was stable over time, but the FVC actually decreased in 5/9 patients; FVC improved in only one patient.

The clinical diagnosis (Table 1) and the indications for the CT scan were evenly distributed in the three groups.

Morphology:

The mean sagittal and coronal diameters at maximal collapse in both scans are depicted in Fig. 3. A corresponding list of the distribution of the different types of tracheal collapse on expiratory CT images is listed in Table 3. The morphology was evaluated at maximal collapse of the trachea during expiration and based on the previously described criteria (cf. METHOD: Image interpretation). EDAC was most common at baseline (55%) and DAC at follow-up (50%). In nine of 20 patients, the shape of the trachea changed over time. There was no significant correlation between the
morphology and the change in tracheal collapse over time. The group of patients who had less collapse of the trachea in the second scan improved to such an extent that they only had dynamic airway collapse (collapse <50% i.e. normal variation) at the time of the second scan.

**Flow-volume curves:**

Flow-volume loops were present in 19/20 patients. Notching was seen in one patient (5%) and biphasic expiratory limb in three patients (16%). The typical changes in the flow-volume curves were not correlated to the degree of collapse or symptoms.

**Use of corticosteroids:**

The patients in our cohort had a limited use of corticosteroids both inhaled and orally administered. 60% never used steroid inhalation. Only 30% used inhaled steroid both at baseline and at follow-up CT scans. In this small group of patients, three out of six (50%) had EDAC at baseline (p=0.80) and four out of five (67%) at the time of the second scan (p=0.44). For oral corticosteroids, the numbers were comparable; 60% never used prednisolone and only 15% had a constant small daily dose of prednisolone. The latter was owing to connective tissue disease and sarcoidosis. Four patients had steroid courses due to COPD exacerbations. One patient was receiving prednisolone at the time of the follow-up CT scan. This patient had worsened his tracheal collapse from 70% at baseline to 90% at follow-up. See Table 4.

**Infection as a risk factor?**

In our small cohort, two patients were in prophylactic antibiotic treatment at baseline. They were both treated with azithromycin 250 mg three times a week. At follow-up, the two patients were still treated with azithromycin and yet another patient was added to the list. These three patients did all have less tracheal collapse in the follow-up scan than at baseline (p=0.12). None of the patients were getting antibiotics for an ongoing infection at the time of scanning.
In this pilot study of patients suffering from a variety of lung diseases, we found that the collapsibility of the trachea is dynamic over time. In almost half of the patients, the tracheal collapse regressed over a time period of two years. Earlier studies based on bronchoscopy have only reported progression or stable disease [10,17]. Our results suggest that in case of clinical indices for excess tracheal collapse, investigations should be carried out despite previously normal CT scans.

The discrepancy between our study and earlier studies may be a result of the application of different diagnostic tools. Previous studies were based on bronchoscopic evaluation whereas our study was based on CT. On CT images, the diagnosis of excess tracheal collapse is based on measurements of the cross-sectional areas of the trachea in inspiratory and expiratory images. The earlier studies were based on a more subjective method - individual endoscopic evaluations. In our study, the first CT scans were performed conventionally with an automatic instruction during the acquisition. In relation to the second scans, we tried to optimize the procedure with training prior to execution and with personal instruction during acquisition [18]. Therefore, we expect the second scans to be superior in quality compared to the baseline scans and the improvement in the tracheal collapse is therefore unlikely to be a result of insufficient CT scans. However, the changes might be a result of measurement uncertainty, as the changes do not correlate with any other parameters measured in this study. Nevertheless, a previous study by Boiselle et al found a high reproducibility of tracheal collapse in healthy volunteers over time (1 year follow-up period) [19].

Another potential reason for the improvement in tracheal collapses could be the indication for performing a scan. Normally, when performing a CT scan the patients experience progression in their primary disease or from new symptoms. This was also the case with the first scans in our cohort whereas the second scans were performed exclusively for the purpose of this study. At the time of the second scan the patients were all stable and without aggravating complaints. This could indicate that the collapse is related to fluctuation in the severity of the primary lung disease. However, the changes in collapsibility did not correlate to changes in the MRC score or lung function parameters. The MRC score provide information on disabilities associated with breathlessness and is not a quantification of the breathlessness itself such as the Borg scale or the Saint Georg Respiratory Questionnaire, which would probably be more appropriate for this correlation[20].

In patients with excessive tracheal collapse the most common abnormal morphologies of the flow-volume curves are notching, oscillation, and biphasic expiratory limb. In our study, these changes
were only seen in 21% (4/19) of the patients which is in accordance with previous findings [21][22].

None of our patients’ curves had oscillations. The patients with biphasic expiratory limb were all suffering from emphysema, which might be the explanation for the morphology.

The shape of the trachea after expiration is important, as the classification of tracheal collapse is based on the morphology. In accordance with our findings, previous studies of the morphology of the trachea report a very low incidence of the Saber sheath type TM[23][24]. Earlier studies report a high incidence of crescent type TM. These studies were performed before the term EDAC was launched. The lunate shape of the trachea was denoted crescent type TM even though no data support the concurrent increase in coronal diameter with the excess tracheal collapse. This may explain why we find very few patients with crescent type TM compared to earlier studies. EDAC and DAC are nearly the only configurations found in our patients. The morphology changed in our cohort from the first CT scan to the second. This may be due to active inflammation or infection which supposedly influence DAC and EDAC [7]. However, only one of our patients received oral corticosteroids treatment at the time of the follow-up scan. The tracheal morphology did not change in the patient who had EDAC in both scans. Yet a progression in the tracheal collapse of 20 percentage points was noticed.

We found no relation between the use of ICSs and progression in tracheal collapse over time. Moreover, we did not find any correlation between use of corticosteroids and the different tracheal morphologies. We would expect the ICSs to reduce the smooth muscle thickness in the trachea but also weaken the cartilage due to alteration in the blood supply[12] resulting in both EDAC and TM. The lacking correlation is probably due to limited use of ICS in our cohort.

The most important limitation to the study is the cohort size. The standard deviations are high making the differences between the three groups undetectable. A larger sample size is necessary to find a statistically significant difference between the groups and to make it possible to find characteristics predicting the natural history and risk factors of excess tracheal collapse.

Secondly, the analyses of the images were done unblinded and by only one reader. However, the measurements of the trachea are semi-automatic, and it is thereby unlikely that introduction of a second reader would have influenced the findings.

Finally, the scanning procedure differed between the first and the second CT scan. The first scans were done traditionally whereas the patients in the second scan were trained and coached to improve quality of the images, which may have led to discrepancies in tracheal collapse due to the technique [25].
Conclusion: Excess tracheal collapse is a potentially reversible condition. In our study, the collapsibility was not related to the active infection or inflammation (shown by the prescribed courses of oral corticosteroids). Furthermore, there was no correlation to pulmonary function parameters or symptoms. The lack of correlation is probably due to the small sample size [26] making generalisation uncertain. In this pilot study, the different morphologies of the trachea do not correlate to the changes in tracheal collapse. The majority of our patients suffered from Excessive Dynamic Airway Collapse. However, more prospective studies are needed to identify the factors of importance for the improvement or progression of the expiratory tracheal collapse.
References:


Fig. 1. Development in tracheal collapse in 20 patients evaluated by MDCT (multidetector computed tomography) scanning.

20 patients with tracheal collapse >50% on MDCT at baseline.
Repeat CT after approx. 2 years.

9 patients improved (collapse reduced by ≥10%)
4 patients were stable (Change in collapse: 0-10%)
7 patients progressed (Collapse increased by ≥10%)
Table 1. Patient characteristics at baseline divided into groups based on changes in tracheal collapse.

<table>
<thead>
<tr>
<th></th>
<th>Improved (9/20)</th>
<th>Stable (4/20)</th>
<th>progressed (7/20)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (yrs)</strong></td>
<td>66 (12.8)</td>
<td>70 (24.3)</td>
<td>67 (24.9)</td>
</tr>
<tr>
<td><strong>Gender (F/M)</strong></td>
<td>8/1</td>
<td>3/1</td>
<td>3/4</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td>25 (6.8)</td>
<td>26 (4.8)</td>
<td>27 (6.0)</td>
</tr>
<tr>
<td><strong>Diagnoses</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TM: 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COPD: 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma: 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchiectasis: 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ILD: 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sarcoidosis: 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>TM: 1</td>
<td>COPD: 1</td>
<td>TM: 1</td>
</tr>
<tr>
<td></td>
<td>Asthma: 0</td>
<td></td>
<td>Asthma: 3</td>
</tr>
<tr>
<td></td>
<td>Bronchiectasis: 2</td>
<td>ILD: 0</td>
<td>Bronchiectasis: 1</td>
</tr>
<tr>
<td></td>
<td>ILD: 2</td>
<td>Sarcoidosis: 0</td>
<td>ILD: 1</td>
</tr>
<tr>
<td></td>
<td>Sarcoidosis: 0</td>
<td></td>
<td>Sarcoidosis: 0</td>
</tr>
<tr>
<td><strong>FEV1 predicted (%)</strong></td>
<td>74 (30)</td>
<td>95 (34)</td>
<td>81 (44)</td>
</tr>
<tr>
<td><strong>FEV1/FVC</strong></td>
<td>67 (15)</td>
<td>73 (11)</td>
<td>70 (25)</td>
</tr>
</tbody>
</table>

Data are presented as mean (Standard Deviation). FEV1 = Forced Expiratory Volume in 1 second, FVC = Forced Vital Capacity, TM: Tracheomalacia, COPD: chronic obstructive pulmonary disease, ILD: interstitial lung disease.
Table 2. Collapse of the trachea (mean ± standard deviation) divided into groups based on the changes.

<table>
<thead>
<tr>
<th></th>
<th>Improved (9/20)</th>
<th>Stable (4/20)</th>
<th>Progression (7/20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tracheal collapse (%)</td>
<td>61 (± 10.9)</td>
<td>58 (± 22.0)</td>
<td>61 (± 20.5)</td>
</tr>
<tr>
<td>on the first CT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tracheal collapse (%)</td>
<td>29 (± 15.2)</td>
<td>57 (± 34.4)</td>
<td>81 (± 15.2)</td>
</tr>
<tr>
<td>on the second CT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difference in collapse</td>
<td>-31.9 (± 15.3)</td>
<td>0.2 (± 14.8)</td>
<td>20.6 (± 9.1)</td>
</tr>
<tr>
<td>(% points)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Fig 2. Axial CT Images of the trachea at end-expiration at the first (left) and second (right) scanning.

A. Regression: 77-year-old female suffering from NSIP.

B. Progression: 47-year-old female suffering from asthma

C. Unchanged: 77-year-old female suffering from bronchiectasis.
Table 3. Distribution of the different types of tracheal collapse during expiratory CT imaging

<table>
<thead>
<tr>
<th>Type of Collapse</th>
<th>Baseline CT scan (n = 20)</th>
<th>Follow-up CT scan (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crescent type, n (%)</td>
<td>2 (10%)</td>
<td>2 (10%)</td>
</tr>
<tr>
<td>Saber-Sheath type, n (%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>EDAC, n (%)</td>
<td>11 (55%)</td>
<td>8 (40%)</td>
</tr>
<tr>
<td>DAC, n (%)</td>
<td>7 (35%)</td>
<td>10 (50%)</td>
</tr>
</tbody>
</table>

EDAC = Excessive Dynamic Airway Collapse, DAC = Dynamic Airway Collapse.
Table 4. Use of corticosteroids in the cohort.

<table>
<thead>
<tr>
<th></th>
<th>Inhaled corticosteroids.</th>
<th>Oral corticosteroids.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number (%)</td>
<td>Number (%)</td>
</tr>
<tr>
<td>Only at baseline</td>
<td>1 (5%)</td>
<td>0</td>
</tr>
<tr>
<td>Only at the second scan</td>
<td>1 (5%)</td>
<td>0</td>
</tr>
<tr>
<td>Continuously</td>
<td>6 (30%)</td>
<td>3 (15%)</td>
</tr>
<tr>
<td>Never</td>
<td>12 (60%)</td>
<td>12 (60%)</td>
</tr>
</tbody>
</table>
**Fig. 3.** Bar graph of the dimensions of the trachea in the first (A) and the second (B) scan.

A: Mean inspiratory and expiratory tracheal measurements at baseline.

B: Mean inspiratory and expiratory tracheal measurements at the second scan.
Highlights:

- Excessive tracheal collapse do improve over time
- Improvement in collapse is not related to improvement in pulmonary function tests
- The changes in collapse over time are not related to the morphology of the trachea
Declarations of interest: None