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FMUP FACULDADE DE MEDICINA UNIVERSIDADE DO PORTO

MESTRADO INTEGRADO EM MEDICINA

2019/2020

Bruno Filipe de Sá Chambel

# Avaliação não invasiva da Estenose Traqueal Benigna

# Non-invasive assessment of Benign Tracheal Stenosis

abril, 2020

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**Mestrado Integrado em Medicina**

**Área:** Medicina Clínica – Pneumologia e Broncologia de Intervenção

**Tipologia:** Dissertação

**Trabalho efetuado sob a Orientação de:**

Doutor Hélder Novais e Bastos

**Trabalho organizado de acordo com as normas da revista:**

Respiration

**abril, 2020**

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DESIGNAÇÃO DA ÁREA DO PROJECTO

Pneumologia e Broncologia de Intervenção

TÍTULO DISSERTAÇÃO

Non-invasive assessment of Benign Tracheal Stenosis.

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COORIENTADOR (se aplicável)

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hoje

de portada livre para quem sou

decorada d'ornatos plurais de brisa e sol

decreto a suspensão do tempo

para perfundir o mundo c'o aroma que versa em seus corpos…

é de ti que se acerca o amor que cercou meu berço com teus braços

é seguindo-te que aprendo em matilha através do exemplo e de teus traços

é vindo de ti que sinto força com teu próprio jeito de ser mulher

é contigo que a coragem s'emproa e dobro os cabos que o mar fizer

é em cantorias nossas que levo abrigo e paz nas algibeiras

é em vossos anéis de vida que crescem todos estes baobás e oliveiras

é à tua imagem que visto academismo e traje de estudante

é nas nossas viagens de *passarola* que resgato uma infância já distante

é em ti que sigo a candeia de brilho mais inteiro que a noite escura

é com meus rebentos de humildade e flor que encontro sidéreo em gente pura;

foi por memórias coletivas que arredámos a tristeza da folia

foi girgo a semente de caibro os companheiros de saudade em melodia

foi no mapa de um mundo novo que descobrimos cinco continentes de amizade

foi com declamação que deixámos o solo para projetar a arte e a verdade

foi enquanto amantes do sol que terminámos esta jornada com astro inteiro

foi com vossa orientação que transformámos o nada em derradeiro

foi na anatomia do teu ensino que provei conflagrante chama intelectual

foi no teu corpo que senti o mistério da Invicta capital;

será por apreço a todos vós que vai além desta imagem

que agradeço poesia vida e universo com que escreveram em meu capítulo de viagem

… com calma e saber

deixo o sonho comandar

para convosco vir abraçar

a mestria de cuidar de um futuro

# *Research Article*

# *Non-invasive assessment of Benign Tracheal Stenosis*

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Keywords: Benign Tracheal Stenosis; Spirometry; Computed Tomography; Bronchoscopy; Quality of Life.

## Abstract

Background: Benign tracheal stenosis (BTS) management is challenging. Although bronchoscopy is the gold standard for diagnosis, its inherent risks makes it a less than ideal follow-up method. This study aims to assess the impact of BTS-related symptoms on quality of life and to correlate BTS severity with non-invasive measures, in order to optimize the follow-up and management.

Methods: Patients with BTS were recruited. Data was collected from clinical files and by patient interview. Respiratory function tests and cervicothoracic imaging were performed within 6 months of clinical assessment. Stenosis Index (SI) was objectively measured using image analysis software (*ImageJ*) applied to radiological images. We analysed the correlation between lung function values and stenosis features.

Results: Of 28 patients enrolled (mean age 55.1±15.9 years, 53.6% female), 89.3% had complex stenosis. The most common etiology was post-intubation (67.8%) and the most common location was subglottic (71.4%). The majority (81%) presented <50% of airway narrowing. A SI ≥50% was associated with higher FEV1/PEF ratio and lower PEF value (p=0.042 and p=0.045, respectively). FEV1/PEF ratio accurately classified those cases with SI ≥50% (AUC=0.80; 95%CI 0.53-1.00). Overall, patients were symptomatic, which had impact in quality of life (QoL). Remarkably, the number of total endoscopic procedures during follow-up was inversely correlated with QoL (r=-0.427, p=0.023).

Conclusions: Spirometry is a potential method to predict BTS severity, and with potential utility at monitoring these patients, thus reducing the need of diagnostic bronchoscopies during follow-up.

## Introduction

Benign tracheal stenosis (BTS) is a pathological tracheal narrowing with an underlying non-malignant process (1). It is a rare and diverse clinical condition with numerous etiologies, being the iatrogenic post intubation tracheal stenosis (PITS) and the post tracheostomy tracheal stenosis (PTTS) the most frequent (1–3). There are symptoms that patients may experience regardless the etiology of their stenosis: stridor, shortness of breath under exercise and inability to clear secretions caused by an inefficient cough mechanism (1,3–5). Evidence seems to show a negative physical and mental burden on patients with BTS that severely impairs their quality of life (QoL) (6), but there is lack of studies regarding this topic.

BTS management is challenging and require a multidisciplinary approach for the better benefit of patients (4,7–9). On the assessment, the essential characteristics that directly impacts management are: symptomatology, overall functional impairment, etiology, stenosis structural characteristics (severity of airway narrowing, anatomic location, vertical extent and morphology), voice features, swallowing capability and presence or absence of tracheomalacia (10). BTS are usually classified as simple or complex. A simple stenosis has <1 cm extension with absence of tracheomalacia or loss of cartilaginous support. Conversely, a complex stenosis has >1 cm extension and/or with involvement of the tracheal wall (10–12).

Bronchoscopy enables direct visualization of the stenosis and is considered the gold standard for its diagnosis and assessment (5,10). Nevertheless, this is an invasive procedure, carrying risks of potential iatrogeny, which makes it a less than ideal follow-up method (13). The analysis of flow-volume loops given by spirometry seem to be useful to monitor disease progression, particularly in more severe stenoses (3), and to monitor physiologic changes following interventions (10). Previous studies from the 70s proposed spirometry as a quantitative tool for evaluating BTS (14,15), but scarce research was conducted since then.

Subjective assessment using still bronchoscopic images seems to misclassify airway narrowing in tracheal stenosis (16), therefore it should be objectively assessed (17). Although computed tomography (CT) is inferior to bronchoscopy in evaluating mucosal disease, central airways can be evaluated with CT as an intervention guide for the purpose of characterizing airway wall thickening and narrowing, as well as the stenosis location and extent (18). Moreover, there are efforts to create an automated software system that objectively calculates in real-time the severity of airway narrowing (19).

This cross-sectional study aims to (i) assess the impact of BTS-related symptoms on QoL and (ii) to correlate BTS severity with non-invasive measures, in order to optimize the follow-up and management of these patients.

## Materials and Methods

### 1. Setting and study design

This cross-sectional study included participants with diagnosed BTS under follow-up on the Bronchoscopic Unit at the Pulmonology Department of Centro Hospitalar Universitário de São João (CHUSJ) – between January 2019 and January 2020. Study design is presented as **Fig. 1**. The ethics committee of CHUSJ approved this study (approval number 290-19).

### 2. Participants screening and selection criteria

Patients with diagnosis of BTS under follow-up at our institution were screened. The following exclusion criteria were applied: (i) age <18 years; (ii) presence of bronchial stenosis; (iii) tracheal stenosis of malignant etiology; (iv) unable to provide informed consent or to comply with the protocol; (v) deceased before data collection. After providing all the required information and obtaining their informed consent, the remaining patients were included in the study.

### 3. Data collection and interventions

We invited all subjects to participate in one of two structured group sessions at the Pulmonology Department, that took place on 13th September 2019 (**Attachment 1**). The presence of caregivers was allowed. The session consisted on a brief explanation of the study and information about BTS, followed by a time for patients' questions. Under supervision of a specialist physician, patients also filed in a form (**Attachment 2**), answered the EQ-5D QoL form (**Attachment 3**) and did 3 peak flow meter measurements (highest value recorded), as well as anthropometric determinations. The following clinical data was extracted from clinical records and the available forms (**Attachment 2 and 3**): age, gender, past medical history, smoking status, environmental exposure history, comorbidities, severity of signals/symptoms, vital signs, anthropometric measures, modified Borg dyspnea scale, mMRC, EQ-5D values, results of peak flow meter tests, recent spirometry tests, recent cervicothoracic CT tests, bronchoscopic and etiologic characteristics of the stenosis, implemented treatment and subsequent follow-up, including additional bronchoscopic/surgical interventions and long-term complications/recurrence.

Spirometry and cervicothoracic CT performed within 6 months of the clinical assessment were accepted for analysis (between March 2019 and January 2020). No bronchoscopic treatment took place between clinical assessment and these two examinations. Patients underwent bronchoscopy only if clinically relevant.

Spirometric values of forced expiratory volume in one second (FEV1), forced vital capacity (FVC) and peak expiratory flow (PEF), percentage of predicted FEV1 (FEV1%), FVC (FVC%) and PEF (PEF%) and FEV1/FVC and FEV1/PEF ratios were registered.

Stenosis severity was objectively assessed using *ImageJ* (image analysis software available free of charge at http://rsb.info.nih.gov/ij/) applied to cervicothoracic CT images, similar to Murgu and Colt's work (16). This software, through the Polygon Selections Tool, enabled us to manually select the contours that limit the stenotic and normal airway cross-sectional areas (CSA) and measure them in pixels by selecting Analyse->Measure. For sectional selection we established the most stricted section of the stenosis ($CSA_{abnormal}$) and the section of the first normal cartilaginous tracheal ring distal to the stenosis ($CSA_{normal}$). Then we calculated the Stenosis Index (SI) [SI = ($CSA_{normal} - CSA_{abnormal}$/ $CSA_{normal}$) × 100%] (20). From a flow dynamic standpoint, the degree of narrowing based on the percentage reduction in luminal CSA matters most compared to the absolute airway diameter (21). Having this in consideration, the stenosis was classified as mild (<50% narrowing), moderate (50%-70% narrowing) or severe (>70% narrowing) (22). The measurement error was considered of ±3% as pointed out by the original authors (16).

## 4. Statistical analysis

Kolmogorov-Smirnov test was used to determine the normality of distribution of all continuous variables, and Levene's test used to assess the equality of variance. Differences between means were analyzed using t tests for normally distributed variables and Mann-Whitney U tests for non-normally distributed variables. Chi-squared test was used to compare frequencies and proportions between groups. The correlations were evaluated with Pearson correlation test when both continuous variables followed a normal distribution, otherwise with Spearman correlation test. All statistical analysis was performed using SPSS® software v. 26. A p value $<0.05$ was considered statistically significant.

## Results

From 46 patients screened, 2 patients were deceased, 2 had bronchial stenosis, 9 rejected their inclusion and 5 were not reachable, therefore excluded. The remaining 28 patients were enrolled in this study with a mean (±SD) age of 55.1 ± 15.9 years, 15 females (53.6%) and 13 males (46.4%). There were no active smokers, 16 patients never smoked (57.1%) and 12 were former smokers (42.9%). A relevant inhalation occupational exposure was found in 8 cases (28.6%). Patients' median (min-max) body mass index (BMI) was 26.2 Kg/m² (18.4-39.1). The most frequent comorbidities were arterial hypertension (64.3%), dyslipidaemia (53.6%), obesity (42.9%), arrhythmia (39.3%), obstructive sleep apnoea (28.6%), cardiopathy (25.0%) and diabetes type 2 (21.4%). All patients' characteristics are presented in Table 1.

There were 25 BTS classified as complex (89.3%), which included 12 cases with concomitant tracheomalacia, and 3 as simple (10.7%). The most common etiology was PITS (67.8%) followed by idiopathic (17.9%), PTTS (10.7%) and Wegener's granulomatosis (3.6%). Causes for tracheal intubation in PITS subjects were respiratory or multiorganic failure (42.1%), surgery (36.8%) or trauma (21.1%). Mean tracheal intubation time was 17.5 ± 12.6 days. Longer intubation duration was associated with complex stenosis (21.5 ± 11.3 days in complex PITS vs 4.0 ± 5.2 days in simple PITS, p=0.027). Tracheostomy in PTTS participants were due to an unsuccessful extubation (66.7%) or a bilateral vocal cord paralysis (BVCP) (33.3%). The most affected location with stenosis was subglottic (71.4%), followed by the upper third of the trachea (25.0%) and the middle third of the trachea (10.7%). All tracheal stenosis features are presented in Table 2.

Regarding treatment details, the median number of endoscopic interventions was 4 (1-11). The most frequent first endoscopic approach was mechanical dilation with rigid bronchoscope (75%) followed by tracheal stent implantation (14.3%), laser endoscopic treatment (7.1%) and dilation with balloon (3.6%). Besides PTTS etiology, 7 patients underwent tracheostomy during BTS management (25.0%). The reasons for tracheostomy were unsuccessful extubation (28.6%), BVCP (28.6%), BTS refractory to treatment (28.6%) and excessive dynamic airway collapse (EDAC) (14.3%). The median tracheostomy duration was 57.3 months (0.4-212.4). Currently there are 5 patients with tracheostoma (17.9%), 3 of them is due to BVCP (60.0%), 1 due to BTS refractory to treatment (20.0%) and 1 due to EDAC (20.0%).

There were 5 patients with complex stenosis that previously had tracheal stent treatment (17.9%), which were all removed afterwards, with a median tracheal stent treatment duration of 24 months (1-75). Only 3 patients underwent surgery (10.7%) and 2 of them had post-surgical recurrence (1 case of tracheoplasty and 1 of tracheoesophageal fistula surgery). All tracheal stenosis management details are presented in Table 3.

Clinical vignettes examples are shown in Table 4.

### Severity of BTS and correlation with non-invasive parameters

There were 21 patients that underwent CT evaluation and further SI calculation (were excluded from this evaluation 5 patients with tracheostomy and 2 patients that were unable to comply with the protocol). The grade of patients' stenosis was mild in 17 patients (81.0%), moderate in 2 (9.5%) and severe in 2 (9.5%). The mean SI was 38.5 ± 19.6 % (min 3.7 - max 82.7), the median stenosis vertical extension was 12 mm (5-42), the mean stenosis proximal distance to vocal cords (VC) was 30.4 ± 16.3 mm and the mean stenosis distal distance to carina was 85.2 ± 16.2 mm. Of all patients enrolled, 17 patients completed the study protocol with spirometry (were excluded from this evaluation 5 patients with tracheostomy and 6 patients that were unable to comply with the protocol). The mean spirometric value for FEV1 was 2.6 ± 0.7 L, for PEF was 5.0 ± 1.7 L/s and for FEV1/PEF ratio was 8.8 ± 2.1 mL/L/min. 22 patients were tested with peak flow meter (were excluded

from this evaluation 5 patients with tracheostomy and 1 patient that was unable to comply with the protocol). The peak flow meter maximum PEF mean value was 278.6 ± 129.3 L/min. All peak flow meter, spirometry and cervicothoracic CT measures are shown in Table 2.

There were 16 patients that performed both spirometry and a cervicothoracic CT. SI had a statistically significant inverse correlation with spirometry-measured PEF (r=-0.51, p=0.042). Although spirometry-measured PEF and peak flow meter measured maximum PEF were highly correlated (r=0.76, p=0.001), peak flow meter measured maximum PEF failed to correlate significantly with SI (r=-0.14, p=0.553). Similarly, correlation was poor between SI and spirometry-measured FEV1 (r=-0.43, p=0.095) or FEV1/PEF ratio (r=0.39, p=0.139). Nevertheless, when analysing as a categorical variable, tracheal narrowing ≥50% was significantly associated with higher FEV1/PEF mean values (8.3 mL/L/min for SI<50% and 11.0 mL/L/min for SI≥50%, p=0.042) and with lower spirometry-measured PEF mean values (5.4 L/s for SI<50% and 3.3 L/s for SI≥50%, p=0.045). When using a pre-specified cut-off value of FEV1/PEF >8 mL/L/min, referred in the literature as a promisor indicator of stablished central airway obstruction (CAO) (23,24), we found that it was the only spirometric parameter that accurately classified those with SI ≥50% (AUC=0.80; 95%CI 0.53-1.00).

SI had no statistical correlation with: age, sex, stenosis etiology, stenosis localization, stenosis classification as simple or complex, PITS' tracheal intubation time, number of total endoscopic procedures, stenosis vertical extension, stenosis distance to VC, peak flow meter measurements or other spirometry-measured parameters/ratios. Relevant results on this topic are shown in Fig. 2.

## Symptoms and quality of life analysis

The most common symptoms were dyspnea (71.4%), sputum (64.3%), cough (57.1%), stridor (46.4%), hoarseness (46.4%), dysphagia (32.1%) and wheezing (28.6%). The median Borg dyspnea scale value was 3 (0-9) and the median mMRC value was 1 (0-4). All information regarding symptoms is presented in Table 1.

Symptoms had no association with stenosis complexity, vertical extension, distance to VC, grade of stenosis and QoL. Heartburn had also no association with BTS idiopathic etiology.

All patients answered EQ-5D QoL questionnaire. Mean QoL was 63.2 ± 20.1 %. For each of the 5 dimensions we detach the following impairments: in *Mobility* was moderate in 13 (46.4%), in *Self-care* was moderate in 5 (17.9%) and severe in 2 (7.1%), in *Usual Activities* was moderate in 12 (42.9%) and severe in 1 (3.6%), in *Pain/Discomfort* was moderate in 8 (28.6%) and in *Anxiety/Depression* was moderate in 11 (39.3%) and severe in 2 (7.1%). All frequencies reported by dimension and level are shown in Table 5.

QoL had a significant inverse correlation with age and with the number of total endoscopic procedures during follow-up (r=-0.40 p=0,033 and r=-0.43 p=0.023, respectively). QoL was marginally significantly correlated with SI (r=-0.41, p=0.063). No statistical differences were found between QoL values and BTS etiologies or spirometric lung functional parameters, but a discrepancy between QoL in PTTS or non-PTTS etiologies was noted (PTTS 45.0 ± 22.9 % and non-PPTS 65.4 ± 19.0 %, p=0.096) and QoL had a marginally significant correlation with peak flow meter maximum PEF (r=0.41, p=0.057). Relevant results on this topic are shown in Fig. 3.

## Discussion/Conclusion

Bronchoscopy enables direct visualization of the stricture and is considered the gold standard for diagnosis and evaluation of BTS (5,10). Nevertheless, non-invasive assessment through CT scan and functional measurements became appealing follow-up tools in cases of BTS. Additionally, data is scarce regarding the impact that BTS has on patients' QoL (6). In the present study we analysed the impact of BTS-related symptoms on QoL and correlated stenosis severity with non-invasive measures.

Our statistical analysis was limited by the small sample size, with subsequent aggravation by cases lacking spirometry and cervicothoracic CT. Some of these patients, after clinical stabilization, are being followed up at smaller centres closer to their residential area. Moreover, most participants were clinically stable, which we correlate to the fact that they were being regularly monitored for the need of bronchoscopic treatment, lessening their impairment in QoL and lung functional parameters. At our centre, the need for intervention is decided mainly whether patients are symptomatic or with an obstruction >50% (25) and in our sample only 19% had a SI ≥50%. Although CT scans cannot provide information about the dynamic behaviour of the narrowing and may be affected by the presence of secretions (17), we chose this method to estimate the grade of stenosis due to its non-invasive nature and because measurements are less likely to be affected by subjectivity. It has been shown previously that CT images may be used to accurately measure the stenosis grade, length and distance from VC, also correlating well with the preoperative and intraoperative findings of the gold standard bronchoscopy (26–28).

The most frequent etiology of BTS was PITS and mean distance to VC was small. Longer tracheal intubation time was associated with greater proportion of complex PITS, which is explained by a longer damage stimulus against the tracheal wall. It has been proposed that PITS results from tracheal wall hypoxia exerted by the cuff followed by inflammation and further scar formation (29).

Empey et al. was the first to report that an increase of the index FEV1/PEF would be expected in case of CAO, as opposed to asthma, COPD and lung fibrosis (15). In fact, during a forced expiration, increased airway resistance caused by BTS reduces particularly maximal flow rates. This way, when CAO is present, it is expected a greater reduction in PEF compared to FEV1 and, therefore, higher values of FEV1/PEF ratio. They also proposed that CAO was characteristically associated with FEV1/PEF > 10 mL/L/min. In our study, comparing with the expected values, PEF was the only spirometric measurement that was particularly decreased. Also, the FEV1/PEF ratio was relatively high in our sample, registering mean values over 8 mL/L/min. These two findings are characteristic of CAO when present (23,24). The only spirometric parameter that correlated with statistical significance with the SI was spirometry-measured PEF, in an inverse correlation. When analysing as a categorical variable, a SI ≥50% was significantly associated with lower spirometry-measured PEF and with higher FEV1/PEF ratio, the later over 10 mL/L/min such as in Empey et al. work (15). Rotman et al. also showed that, when included on the routine indices, FEV1/PEF ≥ 10 mL/L/min can help to distinguish CAO from healthy patients and patients with obstructive pathology (30). Miller et al. demonstrated that FEV1/PEF > 8 mL/L/min had a specificity of 94% and a sensitivity of 64% in detecting CAO (24). By using this cut-off value in our sample, we could accurately classify those with SI ≥50%, with an AUC score of 0.80. We expect that a larger sample size would provide a more robust statistical strength to this analysis. However, we believe that these results support the role of spirometry at predicting BTS severity and its utility as a non-invasive monitoring tool, potentially reducing the need for diagnostic bronchoscopies during follow-up. On a more recent study with larger sample size, Nouraei et al. used a similar approach by calculating a variation of FEV1/PEF ratio, the expiratory disproportion index (EDI) (EDI = FEV1/PEF x 100) (L/L/s) (31). This method showed an AUC score of 0.98 (95%CI 0.968-0.992) and for a threshold of EDI > 50 L/L/s it had a sensitivity of 95.9% and a specificity of 94.2% in differentiating between stenotic and nonstenotic cases. Also, a consensus paper of the European Laryngological Society highlighted the importance of performing

lung function tests before and after therapy (8). This assessment should include flow-volume loops (32), which with the stenosis development results on a simultaneous decrease of both the inspiratory and the expiratory loops (14,33). However, the interpretation of this method is not always clear and the determination of PEF and PIF values is relevant and has shown higher sensitivity to detect CAO (32,34). Moreover, a recent study by Linhas et al. also pointed PEF as a potential predictor of more challenging surgical approach, with lower PEF values correlating with increased vertical extent of the stricture (13), which we did not found in our study. Nonetheless, the exact extent, location and morphology of the airway stenosis cannot be accurately assessed with spirometry (17).

On the other hand, there are authors that do not agree with the potential role of spirometry as monitoring tool for BTS (17,35), reporting low sensitivity of this method on detecting mild to moderate reduction in airway patency (14) and a non-linear behaviour between the stenosis anatomic severity and airflow impairment (36). Still, as far as we know, there are no recent studies correlating spirometry parameters with the objective anatomical grading of BTS.

Given the strong statistical correlation between spirometry-measured PEF and peak flow meter measurement, this portable device could be helpful as a quick ambulatory or self-monitoring test. A previous work by Vössing et al. emphasised the reproducibility and easy-to-perform features of peak flow meter evaluation and that it's a reliable parameter to detect extrathoracic stenosis (37).

Although most cases had mild stenosis, most patients were symptomatic and we still found a marginally significant inverse correlation between QoL and SI and a marginally positive correlation between QoL and peak flow meter measured PEF. This early QoL and functional deterioration reinforces the relevance of non-invasively monitoring BTS. A considerable impairment of QoL was found on the 0-100% scale value and on all 5 disability dimensions. A moderate to severe disability was present in half of our sample on *Mobility, Usual Activities* and *Anxiety/Depression*, as well as in a quarter of our sample on *Self-care* and *Pain/Discomfort* fields. During clinical assessment, even though we found no statistical correlation between symptoms and QoL, a high proportion of patients related their EQ-5D field disabilities with their symptoms. Dyspnea was the most common symptom in our sample and Nouraei et al. work considered it as the primary cause of disability in BTS (38). Evaluating symptoms along with functional evaluation can give additional and relevant information to the physician about the severity of CAO. A reduction in airway diameter to about 8mm generally causes symptoms on exercise (39) and to 5 mm produces the characteristic finding of stridor (40).

Increased age and higher number of total endoscopic interventions during follow-up were associated with impaired QoL, which is probably related with more complicated stenosis, increased disability, and higher recurrence rate. Despite non-statistically significant, we highlight the lower QoL in PTTS etiology. Normally, the tracheostomy canula constitutes a longer damage stimulus than the ventilation tube in PITS patients. Also, the tube attachment at the stoma site may cause additional cartilaginous damage (41). Studies showed that PTTS patients had more complicated stenosis and poorer general condition than PITS one's (42), that complications regarding tracheostomy bear a significant physical burden (43) and that a disfigured neck leads to depression and anxiety (44).

In conclusion, the invasive nature of bronchoscopy creates the need to find another evaluation method for BTS. This study shows the role that spirometry can have in predicting BTS severity and in monitoring these patients, thus potentially reducing the need for diagnostic bronchoscopies during follow-up. Also, peak flow meter seems to be helpful as an additional functional monitoring tool as it strongly correlates with spirometry-measured PEF. In our sample, the symptomatic burden was evident and QoL was significantly impaired. Moreover, the number of endoscopic procedures seems to negatively impact QoL, giving strength to the need of seeking less invasive procedures to monitor these patients. We encourage further studies on this topic, with larger samples and possibly in a multicentre setting.

# Statements

## Acknowledgement

None.

## Statement of Ethics

The current study was conducted in accordance with the World Medical Association Declaration of Helsinki and approved by the Ethics Committee of CHUSJ (approval number 290-19).

## Disclosure Statement

The authors have no conflicts of interest to declare.

## Funding Sources

None.

## Author Contributions

**B. Chambel:** Conceptualization, Data curation, Software, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing - original draft, Writing - review & editing. **J. Pinto:** Data curation, Software, Formal analysis, Investigation, Resources, Visualization, Writing - review & editing. **C. Freitas:** Conceptualization, Investigation, Methodology, Resources, Visualization, Writing - review & editing. **M. Conceição:** Data Curation, Software, Formal analysis, Investigation, Visualization, Writing – review & editing. **H. Novais-Bastos:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Validation, Visualization, Writing – review & editing.

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## Figure Legends

**Fig. 1**. Study Design.

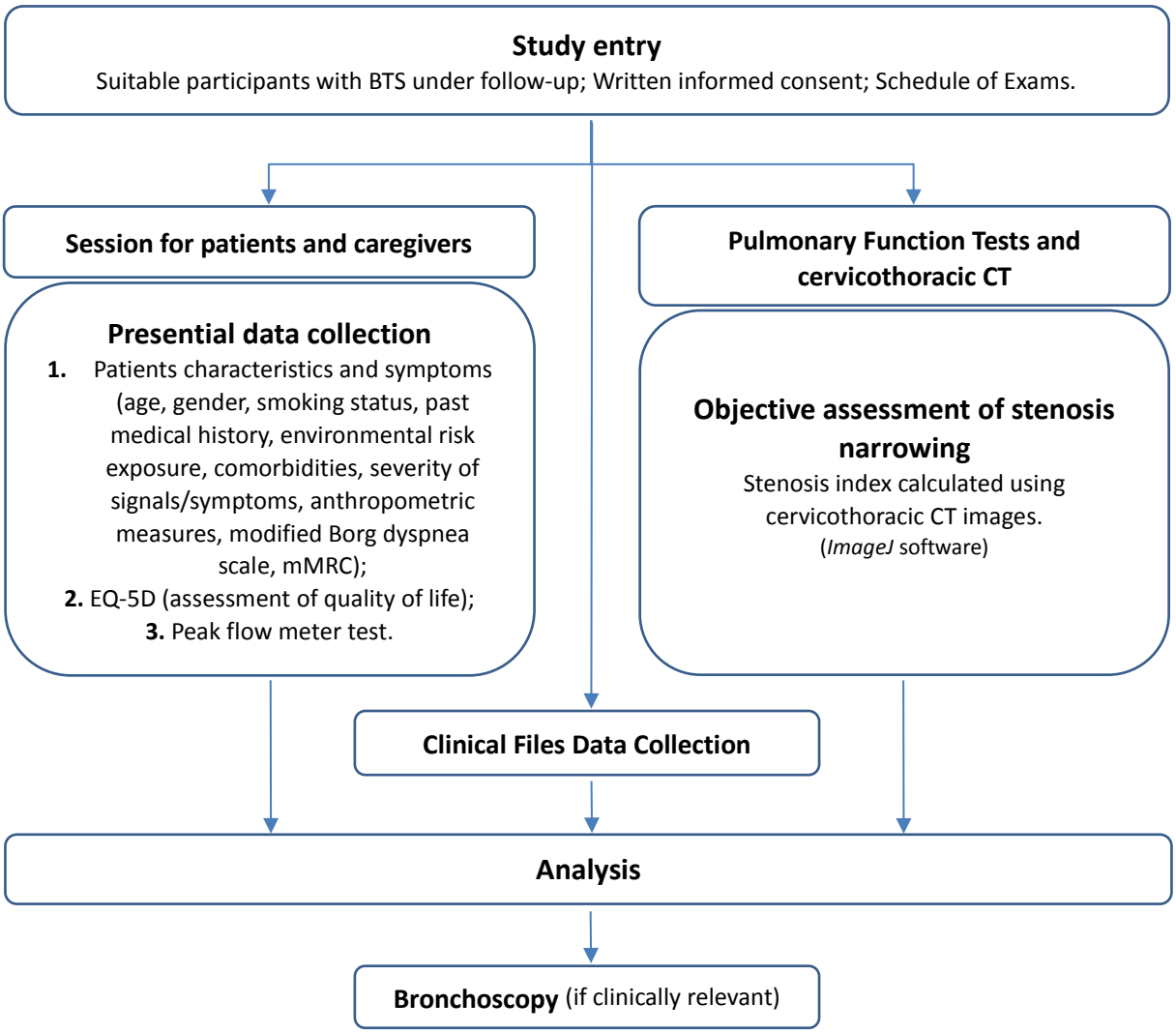
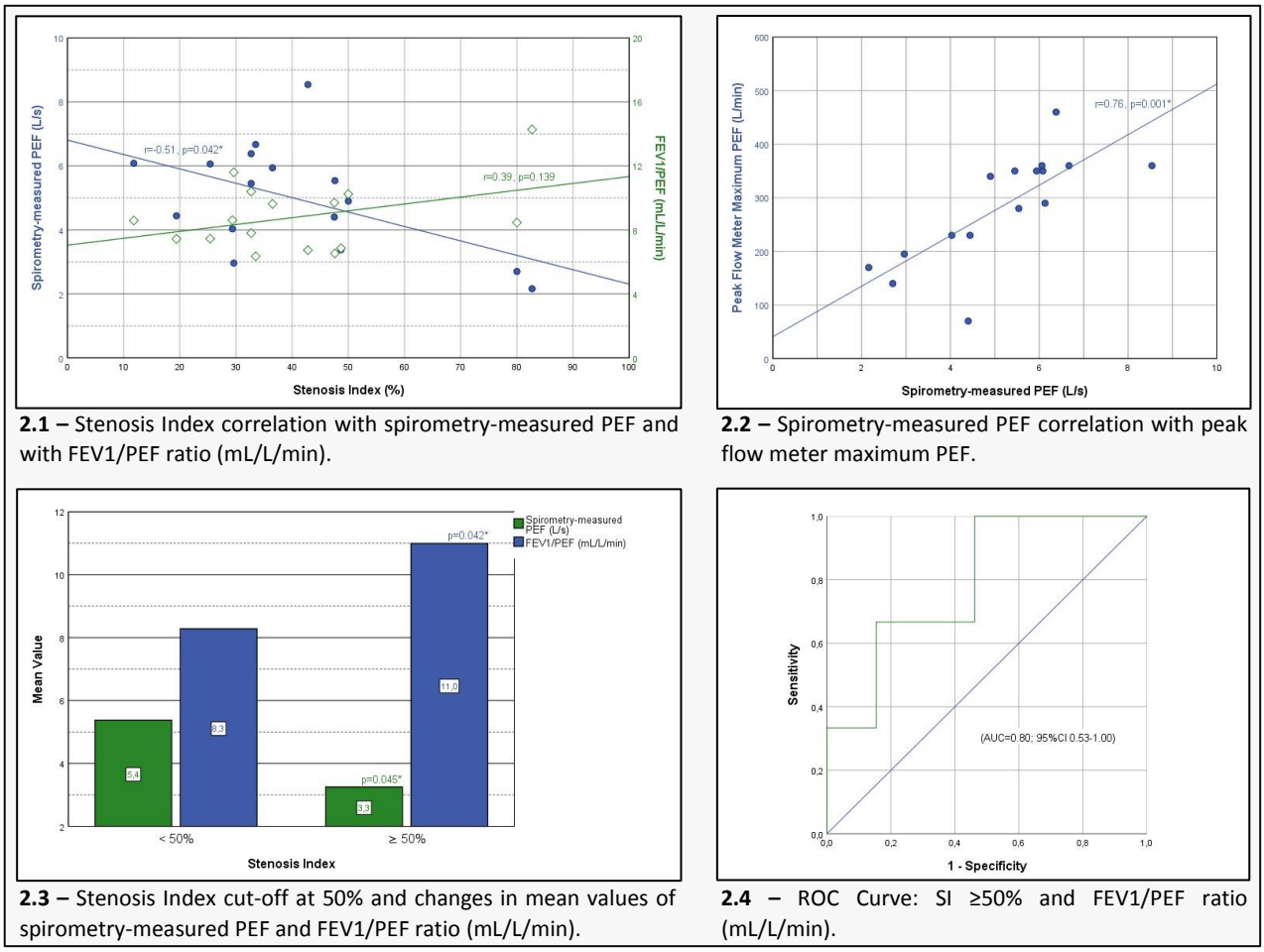


**Fig. 2**. Severity of BTS and correlation with non-invasive parameters.



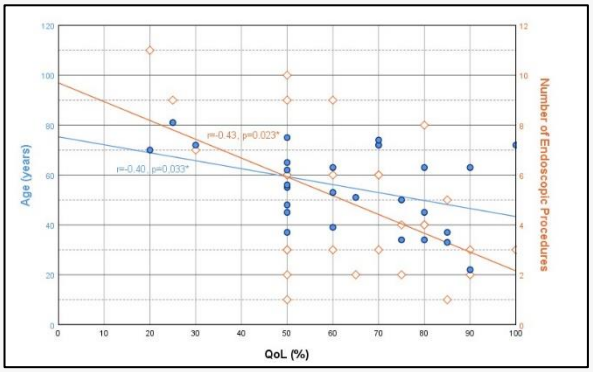

**2.1 –** Stenosis Index correlation with spirometry-measured PEF and with FEV1/PEF ratio (mL/L/min).

**2.2 –** Spirometry-measured PEF correlation with peak flow meter maximum PEF.

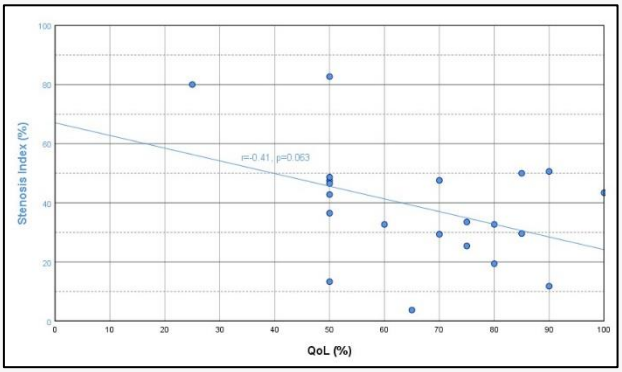
**2.3 –** Stenosis Index cut-off at 50% and changes in mean values of spirometry-measured PEF and FEV1/PEF ratio (mL/L/min).

**2.4 –** ROC Curve: SI ≥50% and FEV1/PEF ratio (mL/L/min).

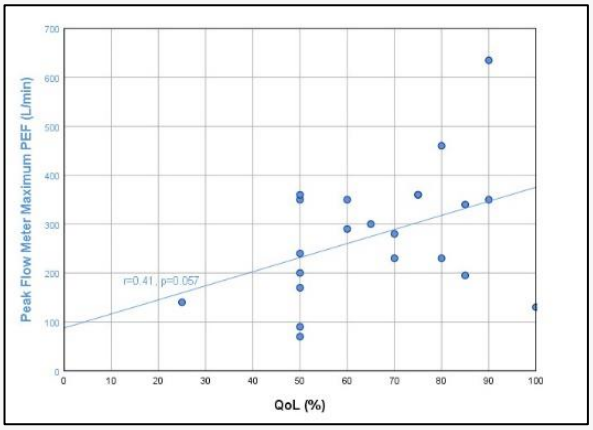
**Fig. 3**. Quality of life analysis.



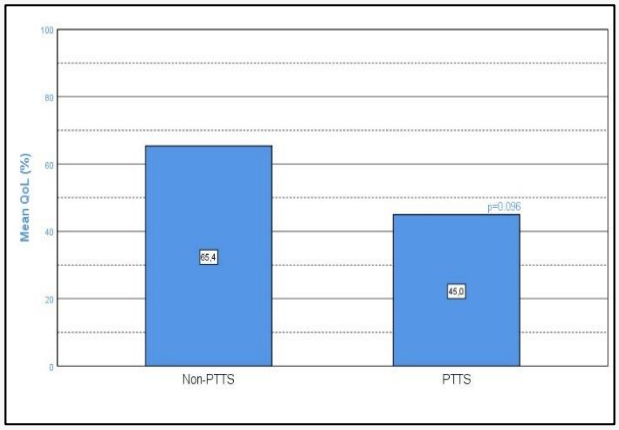

**3.1 –** QoL correlation with age and with number of endoscopic procedures.




**3.2 –** QoL correlation with Stenosis Index.




**3.3 –** QoL correlation with peak flow meter maximum PEF.




**3.4 –** PTTS or non-PTTS etiologies and changes in mean values of QoL.

**Table 1**. Patients' characteristics.

| **Table 1** Patients' characteristics. | |
|---|---|
| Characteristics | Total (n=28) |
| Age (years, mean ± SD) | 55.1 ± 15.9 |
| Gender, n (%) | |
| Female | 15 (53.6) |
| Male | 13 (46.4) |
| Smoking status, n (%) | |
| Never smoked | 16 (57.1) |
| Former smoker | 12 (42.9) |
| Relevant inhalation occupational exposure | 8 (28.6) |
| BMI, Kg/m$^2$ (median, min-max) | 26.2 (18.4-39.1) |
| Comorbidities, n (%) | |
| Arterial hypertension | 18 (64.3) |
| Dyslipidaemia | 15 (53.6) |
| Obesity | 12 (42.9) |
| Arrhythmia | 11 (39.3) |
| OSA | 8 (28.6) |
| Cardiopathy | 7 (25.0) |
| Diabetes type 2 | 6 (21.4) |
| Previous stroke | 5 (17.9) |
| COPD | 5 (17.9) |
| Depression | 4 (14.3) |
| Chronic renal disease | 3 (10.7) |
| Osteoarticular disease | 3 (10.7) |
| Neoplasia* | 2 (7.1) |
| Chronic hepatic disease | 2 (7.1) |
| Asthma | 2 (7.1) |
| Vasculitis | 1 (3.6) |
| Tuberculosis | 1 (3.6) |
| DRGE | 1 (3.6) |
| Symptoms, n (%) | |
| Dyspnea | 20 (71.4) |
| Sputum | 18 (64.3) |
| Cough | 16 (57.1) |
| Stridor | 13 (46.4) |
| Hoarseness | 13 (46.4) |
| Dysphagia | 9 (32.1) |
| Wheezing | 8 (28.6) |
| Heartburn | 4 (14.3) |
| Haemoptysis | 2 (7.1) |
| Borg dyspnea scale (median, min-max) | 3 (0-9) |
| mMRC (median, min-max) | 1 (0-4) |
| QoL (EQ-5D) (%, mean ± SD) | 63.2 ± 20.1 |

BMI, body mass index; COPD, chronic obstructive pulmonary disease; GERD, gastroesophageal reflux disease; QoL, quality of life; OSA, obstructive sleep apnoea.
*1 case of skin basal cell carcinoma and 1 case of papillary thyroid carcinoma.

**Table 2**. Tracheal stenosis features.

| **Table 2** Tracheal Stenosis Features. | |
|---|---|
| Features | Total (n=28) |
| Stenosis Etiology, n (%) | |
| PITS | 19 (67.8) |
| . Respiratory or multiorganic failure | . 8 (42.1) |
| . Surgery | . 7 (36.8) |
| . Trauma | . 4 (21.1) |
| Idiopathic | 5 (17.9) |
| PTTS | 3 (10.7) |
| . Unsuccessful extubation | . 2 (66.7) |
| . Bilateral VC paralysis | . 1 (33.3) |
| Wegener's granulomatosis | 1 (3.6) |
| PITS' tracheal intubation time (days, mean ± SD) | 17.5 ± 12.6[a] |
| Stenotic affected locations, n (%) | |
| Subglottic | 20 (71.4) |
| Upper third of the trachea | 7 (25.0) |
| Middle third of the trachea | 3 (10.7) |
| BTS classification, n (%) | |
| Complex stenosis | 25 (89.3) |
| Simple stenosis | 3 (10.7) |
| Stenosis with concomitant tracheomalacia, n (%) | 12 (42.9) |
| Peak Flow Meter | Subtotal (n=22) |
| Maximum PEF (L/min, mean ± SD) | 278.6 ± 129.3 |
| Spirometry | Subtotal (n=17) |
| FEV1 (L, mean ± SD) | 2.6 ± 0.7 |
| FVC (L, mean ± SD) | 3.1 ± 0.8 |
| PEF (L/s, mean ± SD) | 5.0 ± 1.7 |
| FEV1%, % (median, min-max) | 96.3 (53.0-111.0) |
| FVC% (%, mean ± SD) | 92.7 ± 18.2 |
| PEF% (%, mean ± SD) | 72.9 ± 18.8 |
| FEV1/FVC (mean ± SD) | 80.7 ± 7.5 |
| FEV1/PEF (mL/L/min, mean ± SD) | 8.8 ± 2.1 |
| Cervicothoracic CT | Subtotal (n=21) |
| Grade of stenosis, n (%) | |
| Mild (SI < 50%) | 17* (81.0) |
| Moderate (SI 50-70%) | 2 (9.5) |
| Severe (SI > 70%) | 2 (9.5) |
| SI (%, mean ± SD) | 38.5 ± 19.6 |
| Stenosis vertical extension, mm (median, min-max) | 12 (5-42) |
| Stenosis proximal distance to VC (mm, mean ± SD) | 30.4 ± 16.3 |
| Stenosis distal distance to carina (mm, mean ± SD) | 85.2 ± 16.2 |

BTS, benign tracheal stenosis; CT, computed tomography; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; PEF, peak expiratory flow; PITS, post intubation tracheal stenosis; PTTS, post tracheostomy tracheal stenosis; SI, stenosis index; VC, vocal cords.

*4 borderline cases with SI>47% (within the 3% estimated margin of error inherent to this method)

[a]data from 13 cases out of 19.

**Table 3**. Tracheal stenosis management details.

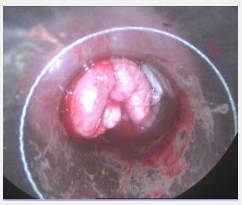
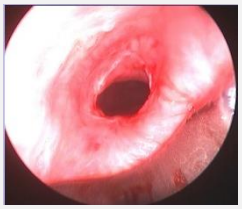
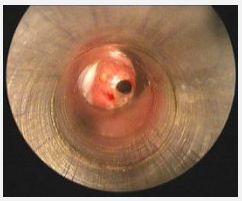
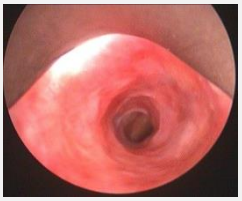
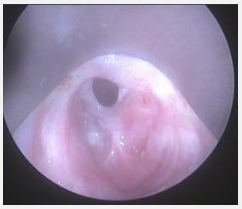
| **Table 3** Tracheal stenosis management details. | |
|---|---|
| Features | Total (n=28) |
| First endoscopic approach, n (%) | |
| Mechanical dilation with rigid bronchoscope | 21 (75.0) |
| Tracheal stent | 4 (14.3) |
| Laser | 2 (7.1) |
| Dilation with balloon | 1 (3.6) |
| Number of endoscopic interventions (median, min-max) | 4 (1-11) |
| Non-PTTS with history of tracheostomy, n (%) | 7 (25.0) |
| . Unsuccessful extubation | . 2 (28.6) |
| . Bilateral VC paralysis | . 2 (28.6) |
| . BTS refractory to treatment | . 2 (28.6) |
| . EDAC | . 1 (14.3) |
| Tracheostomy duration, months (median, min-max) | 57.3 (0.4-212.4)[a] |
| Current tracheostoma, n (%) | 5 (17.9) |
| . Bilateral VC paralysis | . 3 (60.0) |
| . BTS refractory to treatment | . 1 (20.0) |
| . EDAC | . 1 (20.0) |
| History of tracheal stent, n (%) | 5 (17.9) |
| . Complex stenosis, n (%) | . 5 (100) |
| Tracheal stent duration, months (median, min-max) | 24 (1-75) |
| Surgery, n (%) | 3 (10.7) |
| . Tracheoplasty | . 2 (66.7) |
| . Tracheoesophageal fistula surgery | . 1 (33.3) |
| - Post-surgery recurrence | - 2[b] (66.7) |

BTS, benign tracheal stenosis; EDAC, excessive dynamic airway collapse; PTTS, post tracheostomy tracheal stenosis; VC, vocal cords.

[a]data from 7 cases out of 10.

[b]1 case of tracheoplasty and 1 case of tracheoesophageal fistula surgery.

**Table 4**. Clinical Vignettes.

| Patient Data | BTS Features | Functional Parameters | CT Measures | Bronchoscopic image (acute phase) |
|---|---|---|---|---|
| . Male<br>. 70 years<br>. Tracheostomized for BVCP caused by a stroke (214 months duration)<br>. Borg 9 and mMRC 4<br>. QoL: 20 % | . PTTS<br>. Complex stenosis with granulation tissue formation<br>. Upper third of trachea<br>. Tracheomalacia | - | - |  |
| . Female<br>. 62 years<br>. Previous tracheal stent treatment (31 months)<br>. Surgery for TEF with recurrence<br>. Borg 5 and mMRC 3<br>. QoL: 50 % | . PITS - 31 days TI<br>. Complex stenosis<br>. Upper third of trachea<br>. Tracheomalacia | . PFM max PEF: 90 L/min<br><br>Spirometry-measured:<br>. PEF: (no data)<br>. FEV1: (no data)<br>. FVC: (no data)<br>. FEV1/FVC: (no data)<br>. FEV1/PEF: (no data) | . SI: 13.3 %<br><br>. Stenosis proximal distance to VC: 59 mm<br><br>. Stenosis vertical extension: 11 mm |  |
| . Female<br>. 33 years<br>. Borg 0.5 and mMRC 0<br>. QoL: 85 % | . Idiopathic BTS<br>. Simple stenosis<br>. Subglottic | . PFM max PEF: 340 L/min<br><br>Spirometry-measured:<br>. PEF: 4.9 L/s<br>. FEV1: 3.0 L<br>. FVC: 3.4 L<br>. FEV1/FVC: 88.0<br>. FEV1/PEF: 10.2 mL/L/min | . SI: 50.0 %<br><br>. Stenosis proximal distance to VC: 21 mm<br><br>. Stenosis vertical extension: 5 mm |  |
| . Female<br>. 81 years<br>. Borg 5 and mMRC 2<br>. QoL: 25 % | . Idiopathic BTS<br>. Complex stenosis<br>. Upper third of trachea<br>. Tracheomalacia | . PFM max PEF: 140 L/min<br><br>Spirometry-measured:<br>. PEF: 2.7 L/s<br>. FEV1: 1.4 L<br>. FVC: 1.8 L<br>. FEV1/FVC: 74.0<br>. FEV1/PEF: 8.5 mL/L/min | . SI: 80 %<br><br>. Stenosis proximal distance to VC: 45 mm<br><br>. Stenosis vertical extension: 12 mm |  |
| . Female<br>. 45 years<br>. Borg 7 and mMRC 1<br>. QoL: 50 % | . PITS - 13 days TI<br>. Complex stenosis<br>. Upper and middle third of trachea | . PFM max PEF: 70 L/min<br><br>Spirometry-measured:<br>. PEF: 4.4 L/s<br>. FEV1: 2.6 L<br>. FVC: 3.1 L<br>. FEV1/FVC: 82.3<br>. FEV1/PEF: 9.7 mL/L/min | . SI: 47.5 %<br><br>. Stenosis proximal distance to VC: 67 mm<br><br>. Stenosis vertical extension: 17 mm |  |

BTS, benign tracheal stenosis; BVCP, bilateral vocal cord paralysis; CT, computed tomography; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; PEF, peak expiratory flow; PFM, peak flow meter; PITS, post intubation tracheal stenosis; PTTS, post tracheostomy tracheal stenosis; QoL, quality of life; SI, stenosis index; TEF, tracheoesophageal fistula; TI, tracheal intubation; VC, vocal cords.

**Table 5**. EQ-5D QoL questionnaire: frequencies reported by dimension and level.

| **Level**[a] | **Mobility** N (%) | **Self-care** N (%) | **Usual Activities** N (%) | **Pain / Discomfort** N (%) | **Anxiety / Depression** N (%) |
|---|---|---|---|---|---|
| Level 1 | 15 (53.6) | 21 (75.0) | 15 (53.6) | 20 (71.4) | 15 (53.6) |
| Level 2 | 13 (46.4) | 5 (17.9) | 12 (42.9) | 8 (28.6) | 11 (39.3) |
| Level 3 | 0 (0) | 2 (7.1) | 1 (3.6) | 0 (0) | 2 (7.1) |

[a]Higher levels report more impairment.

# Attachments

**Attachment 1**. Group Sessions.

**Attachment 2**. Patient Form.

# FORMULÁRIO - ESTENOSES BENIGNAS DA TRAQUEIA

SÃO JOÃO HOSPITAL

## A. IDENTIFICAÇÃO

| | | | | |
|---|---|---|---|---|
| **Nº PROCESSO** | | | **DATA** | 13-09-2019 |
| **SEXO** | ☐ MASCULINO | ☐ FEMININO | **IDADE** | |
| **CONTEXTO** | ☒ PROGRAMADO | | | |
| **HOSPITAL DE ORIGEM** | ☒ HOSPITAL S. JOÃO | ☐ OUTRO: | | |
| ☐ **CONSENTIMENTO INFORMADO** | Contacto do Doente ou Familiar: | | | |

## B. ANTECEDENTES

| **HISTÓRIA LABORAL DE EXPOSIÇÃO CONTINUADA DE RISCO** | **TABAGISMO** | | |
|---|---|---|---|
| ☐ ASBESTOS; CRIAÇÃO DE POMBOS; MINA; CARPINTARIA, etc. | ☐ NÃO FUMADOR | ☐ EX-FUMADOR | ☐ FUMADOR |

| **COMORBILIDADES** | | |
|---|---|---|
| ☐ Hipertensão Arterial | ☐ Dislipidemia/Colesterol Alto | ☐ Cardiopatia Valvular/Isquémica/Outra |
| ☐ Fibrilação Auricular | ☐ Hipertensão Pulmonar | ☐ Doença Autoimune. Qual? |
| ☐ Doença do refluxo gastroesofágico | ☐ AVC Prévio | ☐ Patologia Osteoarticular. Qual? |
| ☐ VIH | ☐ Doença Hepática Crónica | ☐ Doença Degenerativa. Qual? |
| ☐ Síndrome de Apneia Obstrutiva do Sono | ☐ Asma | ☐ Doença Pulmonar Idiopática. Qual? |
| ☐ Granulomatose de Wegener | ☐ Tuberculose | ☐ Neoplasia/Cancro. Qual? |
| ☐ Enfisema | ☐ Traqueomalácia | ☐ Doença Respiratória Crónica. Qual? |
| ☐ Diabetes | ☐ Doença Pulmonar Obstrutiva Crónica | |
| ☐ OUTRA: | | |

## C. AVALIAÇÃO DO DOENTE

| **SINTOMAS (assinale uma ou mais)** | | | | |
|---|---|---|---|---|
| ☐ Falta de ar | ☐ Tosse | ☐ Tosse com sangue | ☐ Dificuldade a engolir | ☐ Expetoração. Cor: |
| ☐ Rouquidão | ☐ Estridor | ☐ Sibilos | ☐ OUTROS: | |

| **1. ESCALA DE BORG MODIFICADA** | | **2. mMRC** | |
|---|---|---|---|
| ☐ 0 | NENHUMA | ☐ 0 | TENHO FALTA DE AR AO REALIZAR EXERCÍCIO INTENSO |
| ☐ 0,5 | MUITO, MUITO LEVE | | |
| ☐ 1 | MUITO LEVE | ☐ 1 | TENHO FALTA DE AR QUANDO ACELERO O PASSO OU SUBO ESCADAS OU LADEIRAS |
| ☐ 2 | LEVE | | |
| ☐ 3 | MODERADA | ☐ 2 | PRECISO PARA ALGUMAS VEZES QUANDO ANDO NO MEU PASSO OU ANDO MAIS DEVAGAR QUE OUTRAS PESSOAS DA MINHA IDADE |
| ☐ 4 | POUCO INTENSA | | |
| ☐ 5 | INTENSA | | |
| ☐ 6 | MUITO INTENSA | ☐ 3 | PRECISO PARAR MUITAS VEZES DEVIDO ÀFALTA DE AR QUANDO ANDO CERCA DE 100 METROS OU APÓS POUCOS MINUTOS DE CAMINHADA EM TERRENO PLANO |
| ☐ 7 | | | |
| ☐ 8 | | | |
| ☐ 9 | MUITO, MUITO INTENSA | ☐ 4 | SINTO TANTA FALTA DE AR QUE NÃO SAIO DE CASA OU PRECISO DE AJUDA PARA ME VESTIR OU TOMAR BANHO |
| ☐ 10 | MÁXIMA | | |

| **VOZ** | | **DEGLUTIÇÃO** | |
|---|---|---|---|
| ☐ 1 | SEM PROBLEMAS COM A VOZ | ☐ 1 | COME E BEBE |
| ☐ 2 | ALGUNS PROBLEMAS COM A VOZ | ☐ 2 | DIETA NORMAL, MAS COM ALGUMA DIFICULDADE NA DEGLUTIÇÃO |
| ☐ 3 | PRODUZIR VOZ REQUER ESFORÇO E DIFICULDADES SIGNIFICATIVAS EM SER OUVIDO/COMPREENDIDO | ☐ 3 | DIFICULDADES SIGNIFICATIVAS A DEGLUTIR |
| ☐ 4 | APENAS CONSIGO PRODUZIR UMA VOZ FRACA/SUSSURO | ☐ 4 | PROBLEMAS SÉRIOS A DEGLUTIR (DIETA CONSISTE QUASE TOTALMENTE EM COMIDAS LIQUEFEITAS) |
| ☐ 5 | SEM VOZ | ☐ 5 | INCAPAZ DE DEGLUTIR |

## D. NOTAS

**Attachment 3**. EQ-5D Form.

EQ-5D

## AVALIAÇÃO DE GANHOS EM SAÚDE
## QUESTIONÁRIO EQ-5D

Assinale com uma cruz (assim X), um quadrado de cada um dos seguintes grupos, indicando qual das afirmações melhor descreve o seu estado de saúde hoje.

**Mobilidade**
- Não tenho problemas em andar ..... ❑1
- Tenho alguns problemas em andar ..... ❑2
- Tenho de estar na cama ..... ❑3

**Cuidados Pessoais**
- Não tenho problemas com os meus cuidados pessoais ..... ❑1
- Tenho alguns problemas em lavar-me ou vestir-me..... ❑2
- Sou incapaz de me lavar ou vestir sozinho/a ..... ❑3

**Actividades Habituais** *(ex. trabalho, estudos, actividades domésticas, actividades em família ou de lazer)*
- Não tenho problemas em desempenhar as minhas atividades habituais ..... ❑1
- Tenho alguns problemas em desempenhar as minhas atividades habituais ..... ❑2
- Sou incapaz de desempenhar as minhas atividades habituais ..... ❑3

**Dor / Mal-estar**
- Não tenho dores ou mal-estar..... ❑1
- Tenho dores ou mal-estar moderados ..... ❑2
- Tenho dores ou mal-estar extremos ..... ❑3

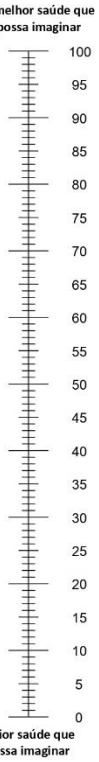
**Ansiedade / Depressão**
- Não estou ansioso/a ou deprimido/a ..... ❑1
- Estou moderadamente ansioso/a ou deprimido/a ..... ❑2
- Estou extremamente ansioso/a ou deprimido/a ..... ❑3



Gostaríamos de saber o quanto a sua saúde está boa ou má HOJE

- A escala está numerada de 0 a 100.
- 100 significa a melhor saúde que possa imaginar. O significa a pior saúde que possa imaginar.
- Coloque um X na escala de forma a demonstrar como a sua saúde se encontra HOJE.
- Agora, por favor, escreva o número que assinalou na escala no quadrado abaixo.

A SUA SAÚDE HOJE = ☐




**Muito obrigado por ter preenchido este questionário.**

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**Attachment 4**. Editorial and Journal Policy - *Respiration*.

## *Respiration*

### Aims and Scope

Respiration brings together the results of both clinical and experimental investigations on all aspects of the respiratory system in health and disease. Clinical improvements in the diagnosis and treatment of chest and lung diseases are covered, as are the latest findings in physiology, biochemistry, pathology, immunology and pharmacology. The journal includes classic features such as editorials that accompany original articles in clinical and basic science research, reviews and letters to the editor. Further sections are: The Eye Catcher, What's Your Diagnosis?, New Insights from Clinical Practice and Guidelines. Respiration is the official journal of the Swiss Respiratory Society (SGP) and also home to the European Association for Bronchology and Interventional Pulmonology (EABIP), which occupies a dedicated section on Interventional Pulmonology in the journal. This modern mix of different features and a stringent peer-review process by a dedicated editorial board make Respiration a complete guide to progress in thoracic medicine.

### Journal Sections

. Clinical Investigations: Clinical improvements in the diagnosis and treatment of chest and lung diseases. Including the latest findings in physiology, biochemistry, pathology, immunology and pharmacology.

. Interventional Pulmonology: Articles reporting the use of endoscopy and other tools to diagnose and treat conditions in the lungs and chest.

### Article Types

Research Articles report on primary research. They must describe significant and original observations. Consideration for publication is based on the article's originality, novelty, and scientific soundness, and the appropriateness of its analysis. Research Articles are reports of original work. Authors are asked to follow the EQUATOR Network for Research Articles. Prior approval from an Institutional Review Board (IRB) or an Ethics Review Committee is required for all investigations involving human subjects. Research articles should contain a 250-word abstract.

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