

Title: Sniff nasal inspiratory pressure in patients with moderate to severe chronic obstructive pulmonary disease; learning effect and short-term between session repeatability.

Short Title: SNIP between-session repeatability in COPD

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Abstract

Background: Sniff nasal inspiratory pressure (SNIP) is a non-invasive measure of inspiratory muscle function often used as an outcome measure in clinical studies. An initial period of familiarisation with the test is recommended to minimise the learning effect. The repeatability of SNIP in patients with chronic obstructive pulmonary disease (COPD) is currently unknown.

Objectives: The aim of this study was to assess the between-session repeatability of SNIP over a three-week period, in moderate to severe COPD patients and compare it with that of maximal inspiratory and expiratory pressure (P_Imax and P_Emax respectively).

Methods: Twenty one patients (13M) with mean FEV₁ 38% predicted (SD:15), FEV₁/FVC%: 34.3 (SD:10.4), performed SNIP and P_Imax and P_Emax manouevres on three different sessions (S1, S2 and S3), 3-7 days apart. SNIP was performed at functional residual capacity (FRC), P_Imax was performed at FRC and at residual volume (RV) to explore volume-dependent differences in the learning effect between sessions and P_Emax from total lung capacity (TLC).

Results: The intra-class correlation coefficient (ICC) for SNIP was the highest of the three measures (S1-S3 ICC (95% CI) SNIP: 0.96 (0.88 to 0.94); P_Imax at FRC 0.82 (0.63 to 0.92); P_Imax at RV: 0.89 (0.78 to 0.95); P_Emax: 0.96 (0.92 to 0.98) and had the lowest mean change between sessions [mean (p value) S2-S1: 2.1(0.4) and S3-S2: -0.3(0.9)].

Conclusions: SNIP is repeatable over a period of 3 weeks in medically stable, moderate to severe COPD patients. In our study, two sessions were adequate to learn how to perform the test.

Introduction

Respiratory muscle function tests are often used in clinical practice to assess respiratory muscle weakness or to monitor change in respiratory muscle strength over time. The most common tests are maximal inspiratory and expiratory pressure (P_Imax and P_Emax) and sniff nasal inspiratory pressure (SNIP) [1]. These tests are relatively easy to perform and the development of portable devices has allowed their assessment in a variety of clinical settings. SNIP is a more natural manoeuvre than the P_Imax or P_Emax manoeuvres [2] and is used as an outcome measure in clinical studies, such as in patients with degenerative neuromuscular disease [3, 4] or chronic obstructive pulmonary disease (COPD) [5]. Due to its volitional nature, the SNIP, just like P_Imax and P_Emax, requires a period of familiarization before baseline measurements are accepted. In COPD, although values for SNIP have been reported [6], there is limited information about the repeatability of the measure.

The repeatability of SNIP has been studied in healthy subjects [4, 7]. Maillard and colleagues [7] showed that the SNIP values obtained after one day were maintained after a period of one month and Terzi and colleagues [4] showed that SNIP had good reproducibility over two sessions a few days apart. The optimal number of sniffs per session has also been established in healthy subjects and a variety of patient groups [8] contributing to the standardisation of baseline assessments prior to clinical studies. However, there are currently no data on the between-session repeatability of SNIP in COPD patients.

The aim of this study was to explore the between-session repeatability of SNIP over a period of three weeks in COPD patients and compare it with that of P_Imax and P_Emax pressures. We also wished to establish how many practice sessions COPD patients need prior to entering an interventional study and to obtain information that would allow us to make sample size calculations for a longer repeatability study.

Methods

Subjects

The study was conducted as part of a larger rehabilitation study and participants were the first twenty one patients (13M: 8F) who were recruited in that study. Patients had moderate to severe COPD ($FEV_1/FVC < 70\%$, $FEV_1 < 60\%$ predicted) and were recruited from outpatient clinics at King's College Hospital, London and from South London British Lung Foundation Breathe Easy groups. Data was collected in March 2000- March 2002 in the context of a larger rehabilitation study that was ongoing and registered in January 2004 (ISRCTN: 19258620), before the 13th September 2005 deadline set by the International Committee of Medical Journal Editors (ICMJE) for clinical trials registration.

The inclusion criteria for the study were: positive smoking history, absence of exacerbations of COPD for at least 4 weeks prior to the initial session, and no change in medication for the same period. The exclusion criteria were: co-existing severe heart disease, hypertension or cor pulmonale and long term oral corticosteroid treatment due to its effect on inspiratory muscle function that could potentially influence our measurements [9]. The protocol was accepted by the local ethics committee and patients gave their informed consent.

Study design and measurements

Our COPD patients attended three laboratory-based sessions (S1, S2 and S3) three to seven days apart. On each session, patients performed SNIP, P_Imax and P_Emax manoeuvres. Pressures were measured using Validyne MP45 differential pressure transducers (Validyne Corp, Northridge, CA, USA). The pressure signal from the pressure transducer was amplified by a carrier amplifier (Validyne Co., Northridge, CA, USA) and acquired on a Macintosh

PowerMac computer running Labview 4.1 software (National Instruments, Texas, USA). The same investigator performed the measurements on all sessions. In each session, the highest value for each measure was accepted for analysis as long as it was within 5% of the previous two highest values.

Participants were naive to the investigations and performed the following tests:

Lung function

Lung function testing was performed on the first session only by senior clinical physiologists in the lung function department of King's College Hospital. Measurements of forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) were obtained using a dry bellows spirometer (S Model, Vitalograph, Buckinghamshire, UK) while total lung capacity (TLC) and residual volume (RV) were measured by constant whole body plethysmography (Auto-link, Morgan Medical, Gillingham, Kent, UK). Blood gases were measured from arterialised ear lobe capillary samples (Rapidlab 248, Chiron, MA, USA).

Sniff nasal pressure (SNIP)

SNIP manoeuvres were performed from functional residual capacity (FRC) with patients in the sitting position. Each patient had custom-made nasal plugs made from dental putty and hand-fitted around the tip of an 80cm catheter connected to a pressure transducer (Validyne MP45, Validyne Corp., Northridge, CA, USA). Each nasal plug was kept in a named envelope for use in subsequent sessions. Patients were asked to perform a strong, sharp, maximal sniff. Pressure tracings were accepted for analysis if they had a smooth downstroke, a sharp peak and took a maximum of 400ms from baseline to peak. A minimum of 10 efforts were made with rest intervals of 30secs and the peak value was recorded. Visual feedback and strong verbal encouragement was given throughout.

Maximum inspiratory pressure (P_{Imax})

Maximum inspiratory pressure was assessed from two lung volumes, functional residual capacity (FRC) and residual volume (RV), using a flanged mouthpiece (PK Morgan Ltd, Rainham, UK) connected to a metal tube. A valve in the tube allowed normal breathing before maximal efforts were made and a separate hole in the tube ensured maintenance of an open glottis. The metal tube was connected to a differential pressure transducer (Validyne MP45, Validyne Corp., Northridge, CA, USA) and P_Imax tracings were recorded in real time. All patients were seated upright and encouraged to make maximal inspiratory efforts sustained for one second. Nose clips were worn at all times and patients performed a minimum of 10 efforts with rest intervals of 30-60 seconds between efforts. The peak value was recorded. Visual feedback and strong verbal encouragement was given throughout.

Maximum expiratory pressure (P_Emax)

P_Emax was assessed from total lung capacity (TLC) using the same equipment as for the P_Imax measurements. Patients wore nose clips, had visual feedback and were given strong verbal encouragement throughout. A minimum of 10 manoeuvres were performed and the peak pressure was recorded on each session.

Statistical analysis

Data were analysed under the null hypothesis that there were no differences in SNIP, P_Imax and P_Emax between the 3 sessions. Differences between sessions (S2-S1, S3-S2 and S3-S1) were analysed using a paired t-test and the intra-class correlation coefficient (ICC) was calculated for all 3 sessions. The significance level was set at 5%. Data were analysed using SPSS (17.0) and graphs were created in Graph Pad Prism (version 3.03).

Results

All patients tolerated the tests well. There were no complaints of pain or discomfort during the tests. The baseline characteristics of study participants are presented in Table 1.

Table 1: *Anthropometric and spirometric characteristics of the study participants*

Gender (M/F)	13/8
Age (years)	71.9 (10)
MRC scale	3 (0.8)
BMI (kg/m²)	26.4 (2.3)
Pack years	69 (51)
FEV₁ (L)	0.9 (0.3)
FEV₁ (%pred.)	38 (15)
FEV₁/FVC (%)	34.3 (10.4)
TLC(L)	6.5 (1.3)
RV(L)	4.1 (1.2)
TLC(%pred.)	117.2 (13.2)
RV(%pred.)	180.5 (40.5)

SNIP values were repeatable between sessions. SNIP showed greater repeatability than P_Imax, especially following the second session (S₂). The mean SNIP value was consistently higher than P_Imax in each session, regardless of the lung volume the P_Imax measurements were assessed from (Figure 1). When the best value of all three sessions was considered, SNIP was (mean (SD) 72.21 (18.14) cmH₂O while P_Imax at FRC was 64.60 (12.75) cmH₂O and P_Imax at RV was 64.92 (13.88) cmH₂O. Therefore the SNIP value was 11.8% higher than P_Imax at FRC and 11.2% higher than P_Imax at RV.

PI_{max} at RV was more repeatable than PI_{max} at FRC and tended to plateau after the second session (ICC 0.89 and 0.82 respectively). The intra-class correlation coefficient (ICC) for sessions 1 to 3 for PE_{max} was 0.96 and 0.94 respectively.

A summary of the results is shown in Table 2.

Table 2: *Between-session repeatability of SNIP, PI_{max} and PE_{max}*

Tests (cmH ₂ O)	Sessions mean(SD)			Differences mean (p value)			Intra-class Correlation Coefficient (ICC) (95% CI)
	1	2	3	S2-S1	S3-S2	S3-S1	
SNIP	65.69 (15.65)	67.78 (18.06)	67.49 (20.25)	2.1 (0.4)	-0.3 (0.9)	1.8 (0.6)	0.94 (0.88 to 0.98)
PI_{max}/at FRC	58.60 (12.83)	55.04 (13.18)	56.24 (15.62)	-3.6 (0.2)	1.2 (0.7)	-2.4 (0.4)	0.82 (0.63 to 0.92)
PI_{max}/at RV	57.60 (11.72)	60.04 (16.13)	58.95 (13.50)	2.4 (0.4)	-1.1 (0.6)	1.4 (0.5)	0.89 (0.78 to 0.95)
PE_{max}	90.41 (28.47)	91.73 (28.81)	92.96 (31.30)	1.3 (0.7)	1.2 (0.7)	2.6 (0.3)	0.96 (0.92 to 0.98)

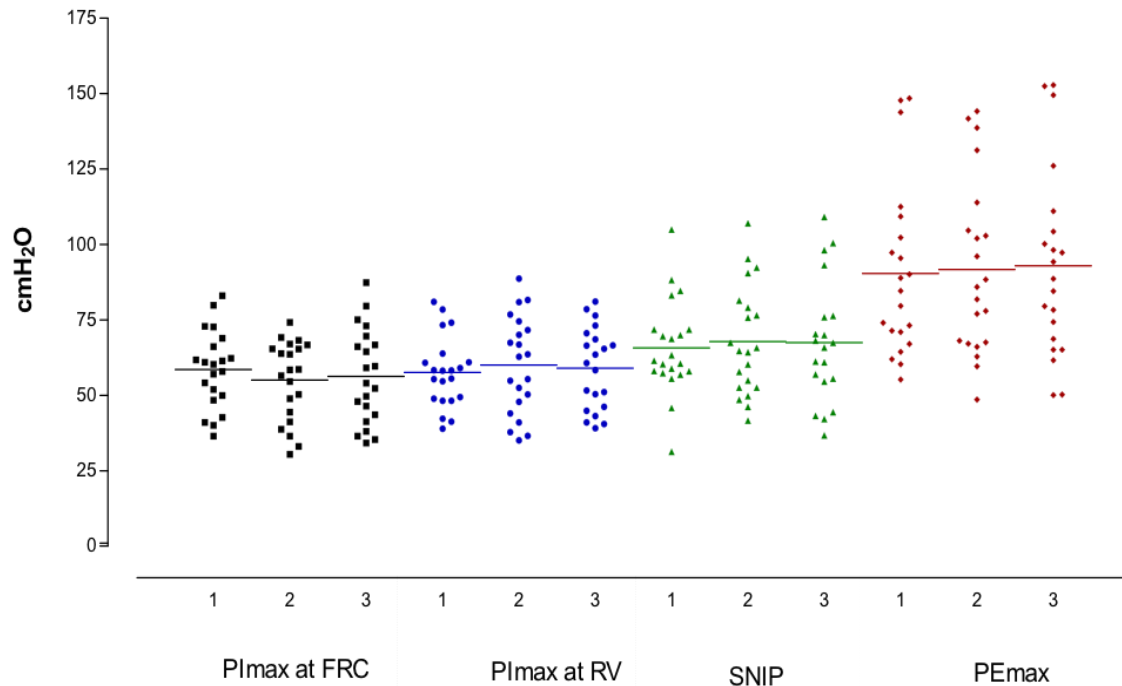


Figure 1: Repeated measures per test in COPD patients. Each data point represents the maximal value for each patient during the sessions. The horizontal lines represent the mean value of the group per session.

DISCUSSION

Volitional measures of respiratory muscle function are often used in clinical rehabilitation studies for sequential assessment of changes in muscle strength. The main advantage over their non-volitional equivalent is that they are easier to perform in a variety of clinical settings, such as in community studies, and avoid the need for insertion of balloon catheters [1] and possible patient discomfort. However, they are influenced by motivation and patients may learn how to do the test better on each session. The exploration of the between-session repeatability of these measures allows us to estimate how much of the change observed after a clinical study is due to the intervention under investigation or due to the learning effect.

The between-session reproducibility of SNIP has been studied in healthy subjects [4, 7]. Terzi and colleagues [4] found the measure repeatable over a period of 2 weeks and more reproducible than P_Imax. Similarly, Mailard and colleagues [7] studied the SNIP over a period of a month and showed that it had good repeatability in healthy subjects. The number of sniffs required to eliminate the learning effect on the same session has also been investigated by Lofaso and colleagues [8] who studied SNIP in patients with a variety of neuromuscular and respiratory diseases. The authors showed that more than 10 sniffs were required per session to achieve accurate SNIP measurements. To the best of our knowledge, the between-session repeatability of SNIP has not yet been investigated in COPD patients. This patient group is often reported to have functional inspiratory muscle weakness and the outcome of rehabilitation interventions that may affect the degree of dynamic hyperinflation, or respiratory muscle function can be evaluated by the non-invasive SNIP.

Our study showed that the SNIP was a repeatable measure in COPD patients who were free of exacerbations over a three week period. The test had better repeatability than P_Imax, regardless of the lung volume at which P_Imax was measured, and generated a higher group mean value (Figure 1).

The better repeatability of SNIP could be attributed to the fact that the sniff is a more natural manoeuvre than the static P_Imax manoeuvre and is therefore rarely underperformed [2]. In COPD patients, SNIP has a disadvantage as a measure in that it underestimates slightly the more invasive sniff oesophageal pressure [6] but its non-invasive nature makes it an ideal test in non-laboratory based clinical studies. In addition, SNIP improves diagnostic precision when used in tandem with P_Imax [12] or diaphragm twitch mouth pressure [13] and it is therefore important for the non-invasive assessment of respiratory muscle function. In our study, SNIP group values were consistently higher than the P_Imax values in each session. A similar result was observed when we identified the best value from all three sessions. In

particular, SNIP values were 12% greater than P_Imax at FRC and 11% greater than P_Imax at RV. The consistency in higher values of SNIP in our group suggests that this test is a valuable outcome measure for repeated measures in COPD patients who are participating in interventional studies or rehabilitation programmes.

Our COPD patients performed a minimum of 10 SNIP manoeuvres per session and we recorded the maximum value from each session. Our results showed that the maximum value plateaued after the second session. This suggests that two sessions, three to seven days apart, are adequate to minimise the learning effect from SNIP in COPD patients as long as more than 10 sniffs are performed per session.

In contrast to previous studies, we did not observe a significant learning effect associated with the P_Imax and P_Emax pressures. P_Imax measurements have been reported to be sensitive to the learning effect due to the nature of the manoeuvre. In COPD patients, the learning effect of P_Imax and P_Emax has been evaluated in a study by Larson and colleagues [10] over a period of 4 weeks. The authors suggested that a substantial amount of practice was required to learn to do the test but the number of manoeuvres per session were not specified. In addition, two researchers were used for the data collection although instructions were standardised. In our study, one experienced investigator performed the measurements in all three sessions. It is possible that P_Imax measurements show greater repeatability between sessions if the same investigator is involved throughout the sessions. Future studies need to investigate the variation of results when experienced and novel researchers take the measurements.

Equally, repeatability of the measure is influenced by the lung volume at which it is measured. P_Imax is conventionally measured at residual volume (RV) [1] as measurements are expected to be more repeatable from this minimal volume. Pressures generated at RV are

more negative than those measured at functional residual capacity (FRC) as the pressure reflects the contribution of the elastic recoil of the respiratory system as well as the optimal length and configuration of the inspiratory muscles [1]. Our results confirmed that the P_Imax value at RV was more negative than the pressure from FRC in most sessions but we found that both were repeatable, especially after the second session. When the best value of all three visits was considered, P_Imax at FRC was close to the P_Imax value at RV. This result could be attributed in part to the large number of practice manoeuvres each patient had to perform throughout the three sessions and the fact that only one investigator was performing the test.

P_Emax was also a repeatable measure in our study. The P_Emax manoeuvre requires recruitment of the abdominal muscles that are usually activated during a cough. Therefore, this manoeuvre is perhaps more natural than the P_Imax manoeuvre. It is also well standardised as it is always performed from total lung capacity (TLC) [1]. Some studies, however, have shown less good repeatability, as in a study in non-CF bronchiectasis patients [14]. Moran and colleagues [14] found that P_Emax increased significantly on their second session which was 10-14 days after the first one. In healthy subjects [11] and COPD patients [10] the repeatability and reproducibility of P_Emax has been more consistent between sessions. The results of our study are in agreement with these studies and suggest that P_Emax is highly repeatable in COPD patients over a period of three weeks and that two practice sessions are adequate for baseline measurements prior to clinical studies.

Limitations of the study

This study examined the repeatability of SNIP over a period of 3 weeks, aiming to determine the minimum number of practice sessions needed to minimise the learning effect prior to clinical studies. Clinical studies or rehabilitation programmes often take longer to complete,

usually 7-8 weeks. Therefore, results of this study may not be generalisable to longer periods of time. In addition, the sample size could not be determined in advance in our study, as there was limited information about the between session standard deviation for SNIP in COPD patients. However, based on the largest standard deviation of SNIP between sessions in our cohort (S3-S1, SD=17.14), we estimated that a future study, would need 21 patients to explore the repeatability of SNIP over a longer period, with a 5% significance level and 80% power.

Furthermore, the results of our study provide information about the repeatability but not the reproducibility of SNIP. In our study, the same investigator performed all assessments as we aimed to exclude between-investigator bias. However, clinical studies are often conducted in different sites and more than one investigator takes measurements of respiratory muscle function. Therefore, future studies need to establish the reproducibility of these measures over repeat sessions using more than one investigator and more than one setting.

Finally, this study examined the repeatability of SNIP in patients with moderate to severe disease who were optimally managed and stable. The results may not apply to COPD patients in, for example, the early period of recovery after an exacerbation.

CONCLUSION

Sniff nasal pressure is a highly repeatable test over a period of three weeks in patients with moderate to severe COPD. Two repeat practice sessions are adequate to minimise the learning effect associated with SNIP prior to interventional studies, as long as more than ten attempts are performed in each session. In contrast to previous studies, we did not observe a significant learning effect for P_Imax and P_Emax.

References

American Thoracic Society/ European respiratory society. ATS/ERS statement on respiratory muscle testing. *Am J Resp Crit Care Med* 2002; 166: 518-624.

Heritier F, Rahm F, Pasche P, et al. Sniff nasal inspiratory pressure; a noninvasive assessment of inspiratory muscle strength. *Am J Respir Crit Care Med* 1994; 150: 1678-1683.

Chaudri MB, Liu C, Watson L, Jefferson D, Kinnear WJ: Sniff nasal inspiratory pressure as a marker of respiratory function in motor neuron disease. *Eur Respir J* 2000; 15: 539-542.

Terzi N, Corne F, Mouadil A, Lofaso F and Normand H: Mouth and Nasal inspiratory pressure: learning effect and reproducibility in healthy adults. *Respiration* 2010; 80: 379-386.

Hopkinson N.S, Man W. D-C, Dayer M.J., Ross E.T, Nickol A.H, Hart N, Moxham J, Polkey M.I.: Acute effect of oral steroids on muscle function in chronic obstructive pulmonary disease. *Eur Respir J* 2004; 24: 134-142.

Uldry C, Janssens B, de Muralt B, et al. Sniff nasal inspiratory pressure in patients with chronic obstructive pulmonary disease. *Eur Resp J* 1997;10: 1292-1296.

Maillard et al. Reproducibility of twitch mouth pressure, sniff nasal inspiratory pressure and maximal inspiratory pressure. *Eur Resp J* 1998;

Lofaso et al. Sniff nasal inspiratory pressure: what is the optimal number of sniffs? *Eur Resp J* 2006;

Nava S, Gayan-Ramirez G, Rollier H, et al: Effects of acute steroid administration on ventilatory and peripheral muscles in rats. *Am J Respir Crit Care Med* 1996; 153: 1888-1896.

Larson J L, Covey M K, Vitalo C A, et al. Maximal inspiratory pressure; learning effect and test-retest reliability in patients with chronic obstructive pulmonary disease. *Chest* 1993; 104: 448-453.

Morrison N J, Richardson J, Dunn L, et al. Respiratory muscle performance in normal elderly subjects and patients with COPD. *Chest* 1989; 95: 90-94.

Steier J, Kaul S, Seymour J, et al. The value of multiple tests of respiratory muscle strength. *Thorax* 2007; 62: 975-980.

Hughes P D et al. Measurement of sniff nasal and diaphragm twitch mouth pressure in patients. *Thorax* 1998; 53:96-100.

Moran F, Piper A, Elborn JS, et al. Respiratory muscle pressures in non-CF bronchiectasis: repeatability and reliability. *Chronic Respir Dis* 2010; 7; 165-171.