

Inspiratory muscle maximum relaxation rate measured from submaximal sniff nasal pressure in patients with severe COPD

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Background: Slowing of the inspiratory muscle maximum relaxation rate (MRR) is a useful index of severe inspiratory muscle loading and potential fatigue and has been measured from the oesophageal pressure during sniffs in patients with chronic obstructive pulmonary disease (COPD). The purpose of this study was to investigate whether it is possible to measure MRR and detect slowing using sniff nasal pressure in patients with COPD and to investigate the relationship between sniff oesophageal and sniff nasal MRR.

Methods: Eight patients with severe COPD (mean FEV₁ 0.7 l; 26% predicted) were studied. Each subject performed submaximal sniff manoeuvres before and after walking to a state of severe dyspnoea on a treadmill. Oesophageal and gastric pressures were measured using balloon tipped catheters and nasal pressure was measured using an individually modelled nasal cast. MRR (% pressure fall/10 ms) was determined for each sniff and any change following exercise was reported as percentage of baseline to allow comparison of sniff nasal and oesophageal MRR.

Results: At rest the mean (SE) sniff Poes MRR was 7.1 (0.3) and the mean Pnasal MRR was 8.6 (0.1). At 1 minute following exercise there was a mean decrease in sniff Poes MRR of 33.7% (range 20.7–53.4%) and a mean decrease in sniff Pnasal MRR of 28.2% (range 8.1–52.8%). The degree of slowing and time course of recovery was similar, with both returning to baseline values within 5–10 minutes. A separate analysis of the sniff pressures using only the nasal pressure traces demonstrated a similar pattern of slowing and recovery.

Conclusions: It is possible to detect slowing of the inspiratory muscles non-invasively using sniff nasal pressures in patients with COPD. This could be a useful technique with which to measure severe and potentially fatiguing inspiratory muscle loading, both in clinical settings and during exercise studies.

Slowing of the maximum relaxation rate (MRR) of skeletal muscle signifies excessive loading¹ and precedes failure of force generation. Slowing of the inspiratory muscles during a sniff is a useful measure of inspiratory muscle loading and fatigue.²

We have previously shown that it is possible to measure the onset and recovery of slowing of inspiratory muscle MRR in healthy subjects^{3,4} and patients with severe chronic obstructive pulmonary disease (COPD)⁵ using the MRR of the sniff oesophageal pressure (Poes MRR). However, this requires placement of an oesophageal catheter. Sniff nasal pressure (Pnasal) provides an accurate reflection of oesophageal pressure in subjects with no underlying respiratory disease, and we have shown that there is good agreement between Pnasal MRR measured at the nose and Poes MRR.⁶

In patients with severe COPD there is an acceptable level of agreement between nasal and oesophageal pressure amplitude measured from maximal sniffs although the nasal pressure is consistently less negative.⁷ However, a poor level of agreement has been reported between sniff Poes and Pnasal MRR measured from maximal sniffs⁸ which is thought to be due to impaired transmission of pleural pressures to the upper airways. Moreover, maximal sniffs are less likely than submaximal sniffs specifically to reflect inspiratory muscle activity in patients with COPD⁵ due to recruitment of additional muscle groups which may influence the MRR.

Excessive inspiratory muscle loading occurs during exercise in patients with COPD⁵ and chronic heart failure⁹ as well as in patients attempting to wean from mechanical ventilation.¹⁰ A non-invasive measure of inspiratory muscle MRR may be a useful clinical research tool in patients with COPD. To investi-

gate whether this is possible we measured sniff MRR during submaximal sniffs from pressures sampled simultaneously at the nose (Pnasal MRR) and from an oesophageal balloon catheter (Poes MRR) before and after exhaustive exercise in patients with severe COPD.

METHODS

The patients had severe COPD (mean (SE) forced expiratory volume in 1 second (FEV₁) 25.7 (2.1)% predicted) and minimal reversibility (less than 10%). The study was approved by the King's College Hospital ethics committee and all patients gave written informed consent.

Spirometric tests were performed with a wedge bellows spirometer (Vitalograph, Buckinghamshire, UK) and lung volumes were determined by body plethysmography (P K Morgan, Rainham, Kent, UK). Normal values were taken from the official statement of the European Respiratory Society.¹¹

Sniff nasal pressure was measured using an individually modelled nasal cast to minimise leakage, as previously described.⁶ A cast was made for each patient using pliable silicon based elastomeric material (Optosil, Bayer Dental, Germany) and an activator liquid (Optosil-Xantopren activator, Bayer Dental). The putty was gently pressed around a small obturator which was inserted into the nostril. Once the cast had hardened it was removed from the nostril and a pressure catheter was inserted through the channel created by the obturator. Oesophageal and gastric pressures were measured using 110 cm balloon tipped catheters (P K Morgan) positioned and tested in the standard manner.¹² Each catheter was connected to a Validyne MP45-1 differential pressure

Table 1 Anthropometric and pulmonary function data of study subjects

No	Age (years)	Sex	Height (m)	Weight (kg)	FEV ₁ (l)	FEV ₁ (% pred)	FEV ₁ /VC (%)	VC (l)	VC (% pred)
1	68	M	1.68	63.1	0.8	28.6	31	2.6	72.2
2	61	F	1.54	52.6	0.7	35.0	29	2.4	79.0
3	74	M	1.76	74	1.0	33.0	29	3.4	87.2
4	67	F	1.58	66.1	0.5	25.0	26	1.9	79.2
5	70	M	1.69	90.8	0.5	19.2	16	3.1	83.8
6	53	M	1.66	51.8	0.6	20.0	23	2.6	66.7
7	65	M	1.73	92	0.6	21.4	32	1.9	48.7
8	76	M	1.69	62.1	0.6	23.0	19	3.2	94.0
Mean	66.8		1.7	69.1	0.7	25.7	25.6	2.6	76.4
SE	2.6		0.03	5.5	0.1	2.1	2.1	0.2	5.0

FEV₁=forced expiratory volume in 1 second; VC=vital capacity.

transducer, range ± 200 cm H₂O (Validyne Corporation, Northridge, California, USA) which was calibrated before each study with a Universal Pressure Meter (Bio-Tek Instruments Inc, USA). The signals were digitised via a 12 bit NB-M10-16 analogue to digital convertor (National Instruments, Austin, TX, USA) and acquired into a Macintosh Quadra 700 computer (Apple Computer, Cupertino, CA, USA) running LabView software (National Instruments).

Poes MRR and Pnasal MRR were measured by a semi-automated LabView program modification which identifies the 50 ms period of greatest pressure drop. MRR was derived as the maximal rate of pressure decay divided by the peak pressure and expressed in units of percentage pressure loss/10 ms. This normalisation of MRR allows the comparison of MRR values taken from pressure traces with different peak pressure amplitudes. As described previously, sniff pressure amplitude was measured from the end expiratory oesophageal pressure measured during quiet breathing before the treadmill walk and sniffs were accepted for analysis on the basis of previously identified and described criteria.⁵ The exercise protocol used has been described in full in our previous study⁵; an identical protocol was used for this study.

Sniff Poes MRR and sniff Pnasal MRR were measured from submaximal sniffs before and for 10 minutes after exhaustive constant rate treadmill exercise to a condition of severe intolerable dyspnoea. Breathlessness was measured before and at the end of exercise using the Borg breathlessness score¹³; arterial oxygen saturation (Sao₂) and heart rate were monitored continuously throughout each exercise and recovery period by a pulse oximeter (Ohmeda, Boulder, CO, USA).

All patients attended at least one preliminary session for modelling of the nasal plug and to allow familiarisation with the sniff technique and use of the treadmill. They were encouraged to perform short sharp submaximal sniffs and abdominal muscle contraction was discouraged; they received visual feedback from the computer.

Data analysis

Sniffs were analysed in two ways: (1) using the criteria described previously which allowed a direct comparison of nasal and oesophageal MRR, and (2) the same data were analysed using the nasal pressure trace with all other traces deleted. Criteria for isolated analysis of the nasal trace were: duration of peak pressure less than 50 ms; total sniff duration less than 600 ms in the fresh state and 800 ms after the exhaustive walk; pressure waveform displaying a smooth downstroke and decay curve; and similar amplitude sniffs (± 5 cm H₂O) throughout the protocol to allow comparison with baseline.

The individual mean number of sniffs performed at baseline was 97 (range 72–147) and the mean acceptance rate applying conventional criteria to sniff Poes MRR was 51% (range 36–68%); 69% (range 44–91%) of baseline sniffs were acceptable using the nasal trace alone. Following exercise 470 sniffs were collected and 57% were acceptable for further analysis

using the conventional method and 66% using the nasal trace. This acceptance rate is comparable with our previous studies.^{5,9} Within occasion reproducibility was assessed for baseline Poes MRR and Pnasal MRR using an analysis of variance model taking the pooled within subject standard deviation. Comparisons between sniff Pnasal and sniff Poes and between sniff Pnasal MRR and Poes MRR were made using a Student's paired *t* test.

To compare Pnasal MRR and Poes MRR following exercise, changes in MRR were expressed as a percentage of baseline. Baseline values were derived from the mean of a group of fresh sniffs performed on the same day. Data were compared using the Student's paired *t* test and presented by plotting the percentage change from baseline against time.

The ratios of sniff Pnasal to sniff Poes and sniff Pnasal MRR to sniff Poes MRR were calculated to compare the values for the two methods immediately following exercise and during recovery. The relationships between the ratios of sniff Pnasal to sniff Poes and sniff Pnasal MRR to Poes MRR and FEV₁ (% predicted) were assessed by linear regression analysis. A *p* value of <0.05 was considered significant. Data are presented as mean (SE) values.

RESULTS

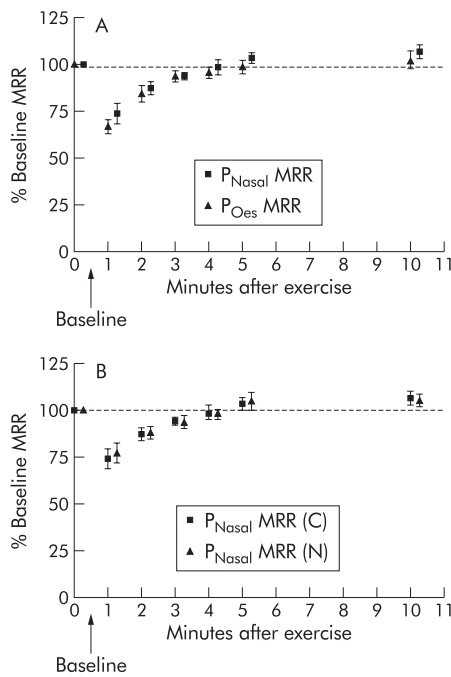
Anthropometric and pulmonary function data of the patients are shown in table 1. At baseline the mean Poes MRR was 7.1 (0.3) and the mean Pnasal MRR was 8.6 (0.1) and these data followed a normal distribution. Mean within occasion coefficient of variation for baseline Poes MRR was 8.8% and for Pnasal MRR was 9.4%. All patients stopped exercise due to severe breathlessness, rating their breathlessness between 4 "somewhat severe" and 7 "very severe". The mean Sao₂ at the end of exercise was 85% (range 77–93%).

The mean difference between sniff Pnasal and Poes amplitude was -11.6 (2.1) which was significant ($p<0.0001$). There was also a significant mean difference ($p<0.001$) of 1.44 (0.26) between sniff Pnasal MRR and Poes MRR. The mean nasal and oesophageal pressures and maximum relaxation rates (with respective ratios) during the recovery period following exercise are shown in table 2. The relaxation rates are presented as absolute values and as a percentage of baseline. The mean baseline sniff Pnasal to sniff Poes ratio was 0.68 (0.05) and varied very little during recovery. The mean baseline sniff Pnasal MRR to sniff Poes MRR ratio was 1.22 (0.06) and was slightly increased at 1 minute.

The time course of slowing and recovery in Pnasal MRR and Poes MRR was similar (fig 1A). In the first minute after exercise there was significant slowing of sniff Pnasal MRR ($p<0.005$) and Poes MRR ($p<0.001$). Sniff Pnasal and Poes MRR were reduced from baseline by 28.2% (range 8.1–52.8%) and 33.7% (range 20.7–53.4%), respectively. There was no significant difference between the degree of slowing at 1 minute. By the 4th minute MRR had returned to within 10% of baseline and there was no significant difference between sniff Pnasal MRR and sniff Poes MRR. The time course of slowing

Table 2 Nasal (Pnasal) and oesophageal (Poes) pressures and maximum relaxation rate (MRR) before (baseline) and after exercise

Time course of recovery (min)	Pnasal	Pnasal MRR	% baseline	Poes	Poes MRR	% baseline	Pnasal/Poes	Pnasal MRR/Poes MRR
Baseline	24.9	8.6	100	36.5	7.1	100	0.68	1.22
1	25.7	6.3	71.8	37.4	4.7	66.3	0.69	1.34
2	26.6	7.5	85.3	36.6	6.2	84.3	0.73	1.20
3	25.9	8.0	91.5	36.9	6.6	93.7	0.70	1.21
4	28.0	8.5	96.5	39.7	6.8	96.0	0.70	1.25
5	25.9	8.9	101.3	37.9	7.0	99.2	0.68	1.27
10	23.6	9.2	104.5	34.7	7.2	102.7	0.68	1.27
Mean	25.8			37.1			0.70	1.25
SE	0.5	–	–	0.6	–	–	0.01	0.02

**Figure 1** (A) Degree of slowing and time course of recovery of Pnasal and Poes MRR as a percentage of baseline (offset for clarity). (B) Slowing of sniff Pnasal MRR analysed using conventional criteria (C) compared with sniff Pnasal MRR analysed using only the nasal (N) trace (offset for clarity).

and recovery of sniff Pnasal MRR analysed in the conventional manner was compared with sniff Pnasal MRR analysed using the nasal pressure trace alone (fig 1B). At 1 minute the slowing of sniff Pnasal MRR analysed from the nasal trace alone was 25.2% compared with 28.2% using conventional analysis; this difference was not significant.

There was no significant relationship between the sniff Pnasal/Poes ratio and severity of airflow obstruction (FEV_1 % predicted) ($p=0.058$) or between the sniff Pnasal MRR/Poes MRR ratio and severity of airflow obstruction ($p=0.059$).

DISCUSSION

This study shows that it is possible to detect severe inspiratory muscle loading as indicated by slowing of inspiratory muscle MRR non-invasively in patients with advanced COPD. The degree of slowing and the time course of recovery for sniff Poes MRR and sniff Pnasal MRR were similar.

Critique of methods

We have previously addressed methodological issues relevant to the measurement of inspiratory muscle MRR in patients with COPD¹⁴ but specific issues concerning sniff Pnasal MRR

deserve discussion. Sniff Pnasal underestimated oesophageal pressure with a mean sniff Pnasal to Poes ratio of 0.68 (0.05). This finding is consistent with other studies,^{7,8} although previous investigations have focused on maximal sniffs. This relatively poor level of agreement reflects the increased time constant for pressure equilibration (a product of airway resistance and upper extrathoracic airway compliance) which is a feature in COPD.¹⁵ A significant correlation between pressure transmission impairment (sniff Pnasal/Poes ratio) and the severity of airflow obstruction has been reported⁸ but we were unable to confirm this.

At baseline, sniff Pnasal MRR was faster than Poes MRR with a mean Pnasal/Poes MRR ratio of 1.22 (0.06) and there was a poor level of agreement between them. A faster Pnasal MRR has also been noted in normal subjects to a lesser degree.⁶ Pharyngeal muscle contraction occurs during a short inspiratory manoeuvre to maintain patency of the upper airways.^{16,17} Upper airway muscles have a greater preponderance of fast twitch fibres,^{18,19} and it has been suggested that relaxation of these upper airway muscles during the relaxation phase of the sniff may contribute to a faster sniff nasal relaxation rate.⁶ It is possible that upper airway muscles are better developed in patients with COPD and could make a more important contribution to the faster sniff nasal MRR.

The poor level of agreement between nasal and oesophageal MRR in patients with COPD has been previously reported⁸ from studies using maximal sniffs and has deterred researchers from further investigation of this technique. Maximal sniffs are more likely to recruit upper airway and neck muscles, perhaps resulting in a faster MRR. In addition, there is likely to be greater abdominal recruitment with expiratory muscle contraction during the relaxation phase of the sniff manoeuvre. This may produce an abnormally fast MRR as the rate of rise of abdominal tension may exceed the rate of decline of inspiratory muscle tension.⁸

We therefore chose to measure MRR from submaximal sniffs and, in order to compare changes in Pnasal MRR and Poes MRR following exercise, all values were expressed as a percentage of baseline. There was a good level of agreement between the two measures. There were significant decreases in both sniff Pnasal MRR and Poes MRR at 1 minute and the slowing and time course of recovery were similar for both nasal and oesophageal sniff MRR (fig 1A). The slowing of Poes MRR was very similar to that previously reported from our laboratory,^{5,20} confirming severe inspiratory muscle loading in patients with COPD during exercise.

A potential problem of the non-invasive sniff Pnasal technique is that one of the selection criteria conventionally used for selecting good quality pressure traces for analysis of MRR requires the examination of the oesophageal and gastric pressure traces to detect expiratory muscle contraction during the relaxation phase of the sniff manoeuvre. Abdominal recruitment is easily detected from overshoot of the oesophageal trace and from an asymmetrical gastric trace, but this is not

possible if sniff nasal MRR is measured in isolation. Abdominal recruitment is quite common during the sniff manoeuvre in patients with COPD⁸ and failure to detect it will produce a falsely high MRR, leading to an underestimation of the degree of slowing. We therefore analysed all sniffs using the nasal trace only and 18% more sniffs were included. Nevertheless, at 1 minute into recovery the slowing of sniff nasal MRR analysed in the conventional manner was 28.2% compared with 25.2% from sniffs analysed using the nasal trace alone. There was no significant difference between the two measurements. This suggests that measurement of sniff P_{nasal} MRR can accurately detect slowing of the inspiratory muscles.

Significance of the findings

Excessive loading precedes failure of force generation and sniff nasal MRR could be a valuable non-invasive technique for monitoring potential fatigue in a variety of clinical and experimental settings. Inspiratory muscle loading plays an important role in exercise limitation in COPD and studies of MRR could be used to investigate the impact of interventions, including pulmonary rehabilitation. It may also prove a valuable tool with which to explore further the relationship between respiratory muscle loading and dyspnoea. Development of a portable pressure meter to measure MRR would allow domiciliary monitoring of MRR during disease exacerbations and could provide useful information about the onset of significant loading which may precipitate ventilatory failure. Monitoring of nasal MRR might also facilitate optimal weaning of patients from ventilatory support.

We conclude that it is possible accurately to measure slowing of inspiratory muscle MRR non-invasively in patients with severe COPD exercised to a state of severe breathlessness. Being able to measure MRR without an oesophageal balloon makes it an easier and more acceptable test for patients, and this may facilitate further investigation of inspiratory loading and its role in exercise limitation and ventilatory failure.

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