ORIGINAL ARTICLE

# A simple noninvasive pressure–time index at the mouth to measure respiratory load during acute exacerbation of COPD A comparison with normal volunteers

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**Abstract**

We assessed the validity of the pressure–time index (PTI) measured at the mouth as a noninvasive and simplified alternative to conventional tension–time index for assessing respiratory load and inspiratory muscle force reserve. PTI was measured within 48 h of hospital admission and at 24 h before discharge in 37 consecutive patients with acute exacerbation of chronic obstructive pulmonary disease(COPD) using the equation PTI = ($P_{awo}$/MIP)($T_I/T_T$)100, where $P_{awo}$ is the mean airway pressure measured at the mouth, MIP the maximal inspiratory pressure, and $T_I/T_T$ the inspiratory time ($T_I$) to total cycle length ($T_T$) ratio. Controls were 30 normal volunteers with similar anthropometric features. Mean (± SD) PTI values were significantly higher in COPD patients (0.29 ± 0.10) than in controls (0.11 ± 0.04) ($P<0.001$) primarily because MIP and $T_I/T_T$were significantly lower and $P_{awo}$ was higher in the COPD population than in controls. As a result of improvement of the respiratory condition, PTI values were significantly lower at discharge (0.20±0.10 *vs.* 0.29±0.10, $P<0.001$) due to a drop in $P_{awo}$ and an increase in MIP. The accuracy of different PTI cutpoints was assessed by comparison of the receiver operating characteristics curves. Best cutpoint values for differentiating COPD patients on admission and at hospital discharge from controls were 0.13 (positive predictive value 76%) and 0.17 (positive predictive value 92%), respectively. Noninvasive PTI measured at the mouth provides a valid and easy method for assessing respiratory muscle load and reserve. Changes in PTI values reflect functional improvement following treatment of acute exacerbation of COPD. 

doi:10.1053/rmed.2002.1464, available online at http://www.sciencedirect.com

**Keywords** chronic obstructive pulmonary disease; respiratory muscle fatigue; respiratory load; pressure–time index

## INTRODUCTION

Respiratory muscle fatigue, especially that of the diaphragm, is defined as the inability of a muscle to continue to generate a given tension. In healthy persons, inspiratory muscle fatigue occurs only under extreme conditions, such as experimental respiratory loading (1) or highly demanding strenuous exercise. By contrast, inspiratory muscles of patients with chronic obstructive pulmonary disease (COPD) may be functioning close to the tension threshold of fatigue, so that small departures from the spontaneous breathing pattern (e.g., episodes of acute exacerbation) can lead to respiratory failure (2–4). During an acute exacerbation, the COPD patients are at risk of developing respiratory fatigue because their inspiratory muscle force reserve is smaller than in normal subjects. Therefore, accurate and prompt detection of increased load to the inspiratory muscles could be very useful in the identification and control of subclinical respiratory failure.

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Received 20 December 2001, accepted in revised form 9 September 2002

It has been shown that respiratory muscles reach a fatiguing level when the product of the effort they generate and the duration of their contraction exceed a critical threshold. The tension–time index of the diaphragm ($TT_{di}$) proposed by Bellemare and Grassino (5,6) can be used to predict the onset of diaphragmatic fatigue. It is calculated as the product of the pressure generated by the diaphragm during tidal breathing ($P_{di}$) expressed as a fraction of the maximal force that the diaphragm can generate ($P_{di_{max}}$), and the duration of the muscle contraction expressed as the ratio of inspiratory time ($T_I$) to total cycle duration ($T_T$), with the following equation: $TT_{di} = (P_{di}/P_{di_{max}})(T_I/T_T)$.

Measurement of $TT_{di}$, however, has mostly been used for research protocols in the laboratory setting because the requirement of a balloon catheter system to measure esophageal and gastric pressures has limited its application in clinical practice. In the studies of Bellemare and Grassino (5,6), $TT_{di}$ was established using the transdiaphragmatic pressure ($P_{di}$) as an expression of the effort for each ventilatory cycle and $P_{di_{max}}$ as an expression of the maximal effort capacity. However, a simplified noninvasive index can be obtained with the use of the pressure measured at the mouth with the open airway ($P_{awo}$) as an alternative to $P_{di}$ and the maximal inspiratory pressure (MIP) instead of $P_{di_{max}}$. Thus, the pressure–time index (PTI) is derived from the equation, $PTI = (P_{awo}/MIP)(T_I/T_T)$. As the mouth pressure that can be developed against an occluded airway at conditions of contraction in healthy subjects is much greater than the pressure that can be developed under conditions of shortening against the elastic and resistive forces seen during acute exacerbation of the COPD, to overcome this difficulty the pressure is best referenced to the maximum pressure (MIP) that can be generated under the same conditions of contraction. In a previous study of noninvasive nasal mask ventilation in the treatment of 15 patients with exacerbation of chronic respiratory insufficiency (7), clinical and blood gas exchange improvements were associated with statistically significant decreases of PTI in a subgroup of six patients in whom parameters of ventilatory muscle function and respiratory drive were measured. In accordance with these preliminary results, another study carried out in a small group of COPD patients showed that PTI measured at the mouth adequately reflected diaphragmatic $TT_{di}$ and its electromyographic signal analysis at rest and during a $CO_2$ rebreathing (8).

To validate the feasibility of PTI in clinical practice, a prospective study was designed with the following purposes: (a) to assess PTI values in patients admitted to the hospital for an episode of acute exacerbation of COPD, (b) to compare PTI values obtained within 48 h of admission and at 24 h before discharge from the hospital, and (c) to determine PTI values in a group of normal volunteers with similar age and anthropometric characteristics than patients with COPD.

## METHODS

The study population included 37 patients admitted consecutively to the respiratory ward of our hospital for treatment of an acute exacerbation episode of COPD. All patients had COPD confirmed by medical history, clinical and functional examinations and fulfilled the criteria of the American Thoracic Society for acute exacerbation (9). The control group consisted of 30 volunteers seen at the respiratory function laboratory for routine preoperative assessment. They had no history of pulmonary disease or respiratory symptoms, and had normal spirometry. In order to study homogeneous samples of both COPD patients and controls, only subjects older than 60 years of age were included. The study protocol was approved by the institutional review board and all participants gave their written informed consent.

### Physiologic measurements

Patients with COPD were studied on two separate occasions, that is, within 48 h of admission to the hospital and at 24 h before discharge. In each case, decisions regarding hospital admission and discharge were taken by the physician in charge of the patient who was unaware of the purpose and results of the study. All patients were treated according to the same conventional treatment for COPD patients not requiring ICU admission. Subjects in the control group were studied once. Forced vital capacity (FVC), forced expiratory volume in 1 s ($FEV_1$), and flow–volume curves were obtained using a calibrated pneumotachograph (Micro S-2000, C. Schatzman, Madrid, Spain). A minimum of three airflow and volume tracings was obtained and the highest value for FVC and $FEV_1$ as percent predicted normal were used for calculations.

Ventilatory parameters were obtained using a Lilly-type pneumotachograph connected to a Mingograf recorder (Siemens, Elema, Germany). Inspiratory time ($T_I$) and total duration of breathing cycle ($T_T$) ($T_I/T_T$) were measured, separating the inspiratory line from the expiratory one by return of the volume signal to resting levels at point zero airflow. The mean airway pressure measured at the mouth ($P_{awo}$) was assessed on the pressure signal curve, during spontaneous breathing and after regular ventilation pattern was obtained. The pressure signal was recorded for 15 min at a paper speed of 6 cm/min. The mean airway pressure was then calculated by summing the pressure values of sequential milliseconds intervals and expressed as the mean value of all breaths taken over the whole interval. MIP was determined using an electromanometer with a transducer

(Siebelmed 163, Siebeld, Barcelona, Spain) (range, $\pm$ 300 cm $H_2O$; resolution, 1 cm $H_2O$) (10). The subject was asked to do a maximal inspiratory effort against a partially occluded airway and to maintain maximal pressure for $\geq$ 1 s. MIP was determined at near-residual volume as the best of three maximum inspiratory maneuvers in which intratesting differences were less than 10%. Results were compared with predicted values reported by Black and Hyatt (11). Both pressures were calculated with sign as negative.

PTI was derived from the following equation: PTI = ($P_{awo}$/MIP)($T_I/T_T$). The result was multiplied by 100 to simplify calculations.

Arterial blood gases were measured at rest while breathing room air (Radiometer ABL 500, Radiometer, Copenhagen, Denmark). Blood samples were analyzed for arterial carbon dioxide tension ($PaCO_2$), arterial oxygen tension ($PaO_2$), and pH.

### Statistical analysis

Data are expressed as mean ($\pm$ SD). Results obtained in COPD patients and in controls were compared with the Student's *t*-test for independent samples, whereas results at different times in patients with COPD were compared with the *t*-test for paired samples. Statistical significance was set at $P < 0.05$. The discriminatory ability of PTI scores for differentiating COPD patients from controls was evaluated using the receiver operating characteristics (ROC) curves (12).

## RESULTS

As shown in Table 1, there were no differences in anthropometric characteristics between COPD patients and the controls. However, results of pulmonary function tests were significantly different between both groups and revealed severe airflow limitation with hypoxemia and hypercapnia in patients with COPD.

Breathing cycle parameters in COPD patients and controls are detailed in Table 2. Measurements taken within 48 h of admission to the hospital showed for patients with COPD numerically greater values for $P_{awo}$ and reduced magnitude of MIP, which were significantly different than those found in controls ($P < 0.001$). The $T_I/T_T$ ratio was significantly lower in patients than in controls ($0.37 \pm 0.05$ *vs.* $0.41 \pm 0.05$, $P < 0.001$). Accordingly, COPD patients had a significantly higher PTI values than controls ($0.29 \pm 0.10$ *vs* $0.11 \pm 0.04$, $P < 0.001$). Appropriate treatment of the acute exacerbation episode of COPD resulted in a statistically significant decrease of the initial mean PTI value to $0.20 \pm 0.10$ ($P < 0.001$), although this value was still significantly higher than in controls. Table 3 shows the values of PTI within the group of the patients.

To determine if the relative value of the PTI measured on admission would predict anything with regard to clinically course while hospitalized we have done a logistic regression with the value of the PTI at admission and another variables as $FEV_1$, $PaCO_2$ and $PaO_2$ but the results were negative.

Differences of PTI values between COPD patients on admission and controls showed that a PTI threshold value of 0.17 had a 90% sensitivity and specificity and a 92% positive predictive value for differentiating acutely decompensated COPD patients from controls. The threshold value at which PTI differentiated patients at hospital discharge with improved respiratory condition from controls was 0.13. This cutpoint showed a sensitivity of 78%, specificity of 70%, and positive predictive value of 76%.

The threshold value at which PTI differentiated within COPD patients from admission to discharge was 0.22.

**Table 1.** Anthropometric data, pulmonary function tests, and blood gases in the study population.

| | COPD patients, (*n*=37) | | CONTROLS, n=30 |
|---|---|---|---|
| | At admission | At discharge | |
| Age (years) | 70.6 ± 7.7 | 70.3 ± 7.6 | 66.4 ± 7.4 |
| Weight (kg) | 73.2 ± 12.2 | 73.6 ± 12.6 | 70.0 ± 12.7 |
| Height (cm) | 164 ± 6 | 164 ± 6 | 161 ± 7 |
| $FEV_1$ (% predicted normal) | 31.9 ± 8.6 | 41.2 ± 15.5** | 112.1 ± 20.7* |
| FVC (% predicted normal) | 50.3 ± 13.7 | 62.07 ± 13.6** | 111.4 ± 16.1* |
| $FEV_1$/FVC | 0.49 ± 0.09 | 50.6 ± 11.0 | 0.83 ± 0.05* |
| $PaO_2$ (mmHg) | 50.6 ± 9.2 | 60.6 ± 11.4** | 85.1 ± 8.5* |
| $PaCO_2$ (mmHg) | 52.8 ± 11.7 | 50.34 ± 9.3 | 39.4 ± 5.0 |
| PH | 7.40 ± 0.03 | 7.42 ± 0.03** | 7.42 ± 0.05 |

Data as mean ± SD.

*$P < 0.001$ between COPD at admission and controls.

**$P < 0.001$ between COPD at admission and at discharge.

**Table 2.** Breathing cycle parameters in COPD patients and controls

| | COPD patients, ($n$=37) | | CONTROLS, $n$=30 |
|---|---|---|---|
| Parameters | On admission | Before discharge | |
| $P_{awo}$ (cm $H_2O$) | -0.41 ± 0.09 | -0.34 ± 0.10** | -0.21 ± 0.05* |
| MIP (cm $H_2O$) | -55.1 ± 15.8 | -70.2 ± 24.4** | -84.5 ± 21.7* |
| $P_{awo}$/MIP | 0.009 ± 0.01 | 0.008 ± 0.01 | 0.002 ± 0.001* |
| $T_I/T_T$ | 0.37 ± 0.05 | 0.38 ± 0.05 | 0.41 ± 0.05* |
| PTI | 0.29 ± 0.10 | 0.20 ± 0.10** | 0.11 ± 0.04* |

$P_{awo}$, mouth pressure with open airway during tidal breathing; MIP, maximal inspiratory pressure; $T_I/T_T$, inspiratory time ($T_I$) to total duration of breathing cycle ($T_T$) ratio; PTI, pressure–time index. Data as mean ± SD

*$P < 0.001$ between COPD at admission and normal subjects.

**$P < 0.001$ between COPD at admission and before discharge.

**Table 3.** PTI values within the group of the patients.

| | PTI | |
|---|---|---|
| COPD | At admission | At discharge |
| 1 | 0.19 | 0.14 |
| 2 | 0.38 | 0.14 |
| 3 | 0.32 | 0.14 |
| 4 | 0.36 | 0.34 |
| 5 | 0.40 | 0.27 |
| 6 | 0.30 | 0.26 |
| 7 | 0.28 | 0.16 |
| 8 | 0.25 | 0.16 |
| 9 | 0.12 | 0.44 |
| 10 | 0.28 | 0.19 |
| 11 | 0.20 | 0.14 |
| 12 | 0.25 | 0.14 |
| 13 | 0.26 | 0.23 |
| 14 | 0.58 | 0.20 |
| 15 | 0.15 | 0.13 |
| 16 | 0.26 | 0.30 |
| 17 | 0.36 | 0.24 |
| 18 | 0.19 | 0.12 |
| 19 | 0.33 | 0.16 |
| 20 | 0.39 | 0.26 |
| 21 | 0.21 | 0.17 |
| 22 | 0.13 | 0.09 |
| 23 | 0.38 | 0.11 |
| 24 | 0.18 | 0.23 |
| 25 | 0.50 | 0.50 |
| 26 | 0.34 | 0.17 |
| 27 | 0.22 | 0.19 |
| 28 | 0.27 | 0.21 |
| 29 | 0.21 | 0.18 |
| 30 | 0.16 | 0.10 |
| 31 | 0.45 | 0.11 |
| 32 | 0.25 | 0.12 |
| 33 | 0.24 | 0.18 |
| 34 | 0.18 | 0.15 |
| 35 | 0.46 | 0.36 |
| 36 | 0.36 | 0.30 |
| 37 | 0.28 | 0.07 |

This cutpoint showed a sensitivity of 65%, specificity of 70% and positive predictive value of 71%.

The findings obtained with the current method have been compared with those of more traditional examinations such as $FEV_1$, $PaCO_2$ and $PaO_2$—both with regard to difference and differentiation between patients and controls and for improvement from admission to discharge. Comparisons have been made with the ROC curves and the results are depicted in Figs. 1–3.

## DISCUSSION

Important findings of the present study are as follows: firstly, that a simple noninvasive PTI measured at the mouth is significantly higher in patients with COPD than in controls, and secondly, that improvement of the patient's condition as a result of treatment of acute exacerbation was associated with decreases in PTI values. However, PTI levels in COPD patients with improved clinical condition, that is, at hospital discharge, remained significantly higher than the corresponding values in normal volunteers.

Assessing the magnitude of the fatiguing process of the respiratory muscles or their response to mechanical load has been an important but difficult goal in clinical practice. Several indices have been used to provide such information. The best characterized of these diagnostic tools is the $TT_{di}$, although it is relatively specific for the functional assessment of the diaphragm. Normal value for adults is 0.02 ± 0.01. Under experimental conditions, if the index increases beyond a critical value of 0.15–0.20 (threshold zone of fatigue), contraction of the diaphragm can only be sustained for approximately 1 h (time limit or $T_{lim}$) (5). The $TT_{di}$ has not gained widespread clinical acceptance because it is relatively invasive and its thresholds can only be determined under strict experimental conditions.

In other studies in which noninvasive assessment of respiratory muscles load was determined, the mean age of the study groups were different, so that results may be

influenced by this circumstance (13). By contrast, the design of the present study included recruitment of two matched groups in terms of age and anthropometric characteristics. We sought homogeneity in the groups because it is well known that there is a loss of pulmonary function as well as of muscle strength and muscle mass with aging (11).

The simple and noninvasive PTI measured at the mouth, as here reported, aims to be a practical and comprehensive measurement of the effort to breathe and may be an overall measure of the load placed on the respiratory muscles. The index is measured while the subject breathes spontaneously, requires minimal cooperation on the part of the subject, and is highly reproducible. The information provided by the PTI is different from that offered by the $TT_{di}$, because not only diaphragmatic effort is measured, but also the contribution of inspiratory muscles acting in concert (8). In this way, the major determining factors to induce muscle fatigue are the magnitude of the pressure used to breathe (here measured as the $P_{awo}$) and its relationship with MIP. This relationship shows the balance between the magnitude of the respiratory load and the muscle strength available to confront it (4). In most patients, PTI increases (or the onset of fatigue would be accelerated) in situations in which the $P_{awo}$ increases (e.g., with an increase in the resistance of the airway or a decrease in compliance) or conversely, in patients whose MIP decreases (e.g., muscle weakness or mechanical deterioration), which occurs as the obstruction to airflow worsens (14).

On admission to the hospital, COPD patients had a mean $T_I/T_T$ value of $0.37 \pm 0.05$. This was significantly lower than that found in normal volunteers ($0.41 \pm 0.05$) and in agreement with the values reported by Tobin *et al*. (15) but substantially lower than $0.49 \pm 0.10$ described by Bellemare and Grassino (6) in the experimental conditions of their study. Our findings suggest that changes in $T_I/T_T$ are relatively small and occur in the direction of decreasing the PTI. In addition, $TT_{di}$ depends on the $P_{di}/P_{di_{max}}$ and $T_I/T_T$, while the spontaneous PTI is less influenced by the $T_I/T_T$. Indeed, the correlation between $P_{awo}$/MIP and $T_I/T_T$ was poor ($r = 0.2$).

As shown in our preliminary results, PTI decreases after mechanical improvement in patients with an exacerbation of chronic respiratory insufficiency (7). In the present study, higher PTI values at the time of patient's admission to the hospital were found to have decreased significantly at the time of discharge. PTI improved as the magnitude of the load decreased (mainly seen as a fall in $P_{awo}$) in a similar degree than in our previous study, 0.7 *vs*. 0.8. Simultaneously, as functional parameters of the COPD acute exacerbation episode improved, there was an increase in MIP probably as a consequence of a decrease in dynamic hyperinflation. The combination of both changes would account for the significant improvement in PTI.

When we showed the changes of PTI within the patients (Table 3), we observed that there were three patients for whom the value of the index between admission and discharge rose; they are the patients 9, 16 and 24. Of these, patient 9 admitted again to the hospital 10 days after the discharge while patient 16 was admitted to the ICU 14 days after the discharge.

When comparing the results obtained with the current method with those of more traditional examinations such as $FEV_1$, $PaCO_2$ and $PaO2$—both with regard to difference and differentiation between patients and controls and for improvement from admission to discharge, the results showed that for differences within patients, the PTI was close to $PaO_2$, with an area under the curve of $0.75 \pm 0.05$ and presented better discriminatory power than $FEV_1$ and $PaCO_2$ (Fig. 1).

With respect to the differentiation between patients and controls, the PTI did at discharge show a greater area under the ROC curve ($0.80 \pm 0.06$) than $PaO_2$ and $PaCO_2$ ($0.54 \pm 0.06$ and $0.77 \pm 0.05$, respectively) while on admission it showed a smaller area than $FEV_1$ and $PaO_2$ (Figs. 2 and 3).

In summary, PTI measured at the mouth during spontaneous breathing is a useful, noninvasive, and reproducible measurement of overall respiratory load, which provides important information regarding mechanical load and functional reserve of the respiratory muscles. Variations in PTI values reflect clinical changes experienced by COPD patients during episodes of acute exacerbation and can be used as a complementary tool to clinical and laboratory data for establishing the degree of respiratory impairment.

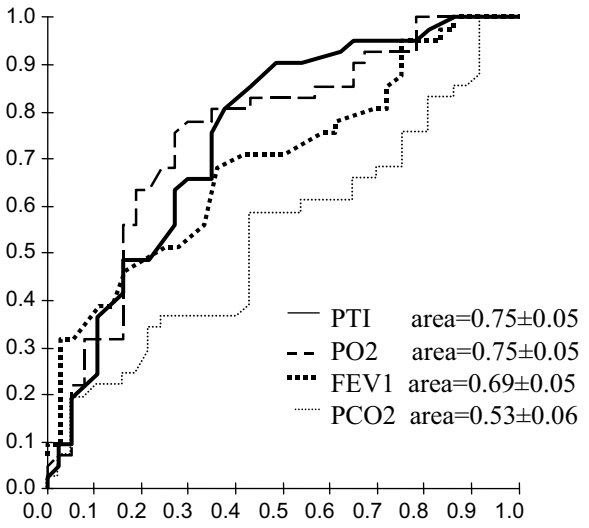


**Fig. 1** Receiver operating characteristics (ROC) curves for PTI measured at the mouth, $FEV_1$, $PaO_2$ and $PaCO_2$ within patients from admission to discharge. Areas under the curve $\pm$ SD of each index are given.

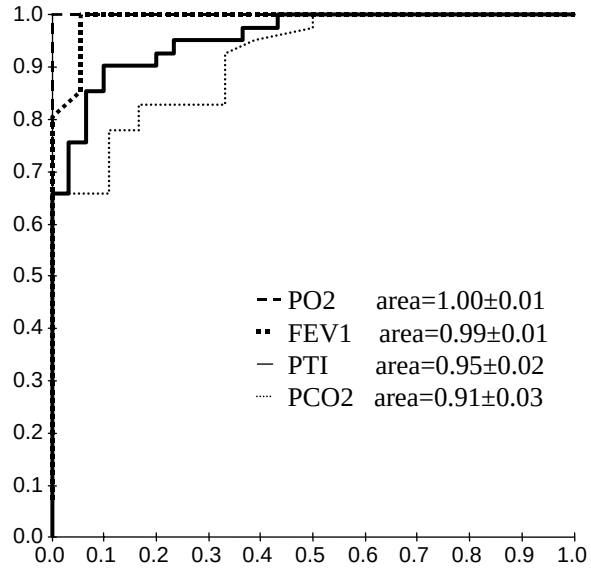


**FIG. 2** ROC curves for PTI measured at the mouth, $FEV_1$, $PaO_2$ and $PaCO_2$ between patients at admission and controls. Areas under the curve ± SD of each index are given

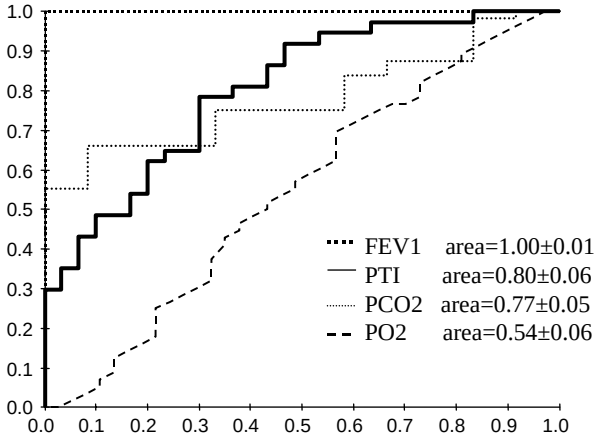


**FIG. 3.** ROC curves for PTI measured at the mouth, $FEV_1$, $PaO_2$ and $PaCO_2$ between patients at discharge and controls. Areas under the curve ± SD of each index are given.

## Acknowledgements

We thank María Luisa Blasco, MD, Carmen Muñoz, MD, Rafael Sanjuan, MD, and Cristina Zaragoza, PhD, for valuable co-operation in the study and Marta Pulido, MD, for editing the manuscript and editorial assistance. The experiments of this study comply with the current laws of Spain.

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