Can maximal inspiratory and expiratory pressures during exercise predict complications in patients submitted to major lung resections? A prospective cohort study†

Majed Refai*, Cecilia Pompili, Michele Salati, Francesco Xiumè, Armando Sabbatini and Alessandro Brunelli

Division of Thoracic Surgery, Ospedali Riuniti, Ancona, Italy

* Corresponding author. Division of Thoracic Surgery, Ospedali Riuniti, Via Conca 1, Ancona 60122, Italy. Tel: +39-071-5964439; fax: +39-071-5964481; e-mail: majedit@yahoo.com (M. Refai).

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Abstract

OBJECTIVES: The measurement of maximal inspiratory pressure (PImax) and maximal expiratory pressure (PEmax) generated at the mouth is an accepted non-invasive clinical method for evaluating the strength of respiratory muscles. The aim of our study was to verify whether PImax and PEmax measured before and after a symptom-limited stair-climbing test are associated with complications in patients submitted to major lung resections.

METHODS: In a prospective cohort study of 283 consecutive patients submitted to lobectomy (231) or pneumonectomy (52) with a pre-operative symptom-limited stair-climbing test, PImax and PEmax were measured before and immediately after the exercise. PImax and PEmax values were expressed as percentages of predicted values. ΔPImax and ΔPEmax were defined as the percentage difference between the pre- and postexercise values. Logistic regression analysis and the bootstrap resampling technique were performed to identify predictors of cardiopulmonary complications.

RESULTS: On average, PImax dropped by 3.6% and PEmax increased by 0.8% after the exercise. In total, 173 patients (61%) experienced a reduction in their PImax after exercise, while 150 (53%) had their PEmax reduced. Postoperative cardiopulmonary complications occurred in 74 patients (26%). Complicated patients had a greater reduction in their PImax compared with non-complicated patients (8.7% vs 2.1%, P = 0.03), whereas ΔPEmax was similar in complicated and non-complicated patients (0.7% vs 1.3%, P = 0.5). Receiver operating characteristic analysis indicated that the best cut-off for predicting complications was a ΔPImax of 10%. Stepwise logistic regression analysis and bootstrap confirmed that ΔPImax of >10 was associated with cardiopulmonary complications after adjusting for baseline and surgical factors (ΔPImax regression coefficient −0.02, P = 0.09, bootstrap frequency 51%). A progressive increase in complications was observed in patients with greater reduction in ΔPImax after exercise, particularly for values >10% reduction.

CONCLUSION: The measurement of PImax at the mouth during exercise represents an additional parameter that can be used to refine risk stratification of lung resection candidates and to identify patients who may benefit from inspiratory muscle training.

Keywords: maximal inspiratory pressure • Maximal expiratory pressures • Stair-climbing test • Major lung resections • Cardiopulmonary complication

INTRODUCTION

The measurement of maximal inspiratory and expiratory pressures (PImax and PEmax) generated at the mouth is an accepted non-invasive clinical method for evaluating the strength of respiratory muscles [1, 2]. Respiratory muscle weakness increases the relative load for breathing, leading to clinical consequences such as dyspnoea and impaired exercise performance [3], and may be present in patients with dyspnoea and chronic obstructive pulmonary disease (COPD) [4].

Although patients with some muscle weakness may have their basal PImax and PEmax in the normal range, they may develop abnormal fatigue on exercise [5]. For this reason, we measured PImax and PEmax before and immediately after a stair-climbing test in a series of patients submitted to major lung resection with the objective to verify whether these parameters or their changes after exercise were associated with postoperative cardiopulmonary complications.

METHODS

This is a prospective cohort study of 283 consecutive patients submitted to lobectomy (231) or pneumonectomy (52) for lung cancer in a single centre, during a 5-year period. The study was approved by the local Institutional Review Board, and all patients

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gave their consent to participate in the trial. All patients enrolled, performed a preoperative stair-climbing test including the measurement of PImax and PEmax before and immediately after the exercise.

The following exclusion criteria were applied: inability to perform a stair-climbing test; patients submitted to chest wall resection, diaphragm resection and minor resections (wedge or segmentectomy); patients with known coronary symptomatic cardiac valve disease or arrhythmia prior to surgery.

**Stair-climbing test**

Our hospital has 16 flights of stairs of 11 steps each. Each step is 0.155 m in height. The patients were asked to climb, at a pace of their own choice, the maximum number of steps and to stop only for exhaustion, limiting dyspnoea, leg fatigue or chest pain. All patients were accompanied by a physician during the exercise and their pulse rate and capillary oxygen saturation were monitored by means of a portable pulse oximeter with a finger probe. All tests were performed on room air. No complications related to the stair-climbing test were observed in this series.

**PImax and PEmax measurements**

The measurements of PEmax were performed using the Micro Medical Limited mouth pressure meter. The method adopted was similar to that described by Black and Hyatt [2]. The patients were seated and asked to breathe through a falanged mouthpiece with a nose clip. This is the preferred technique recommended by the American Thoracic Society/European Respiratory Society (ATS/ERS) statement on respiratory muscle testing [6]. For the measurement of PImax, each patient was instructed to exhale to the residual volume followed by a maximal inspiration effort through the mouthpiece. The manoeuvre was repeated until 2–3 reproducible measurements were taken; the highest pressure measured was used for analysis. For the measurement of PEmax, each patient was instructed to inhale to total lung capacity followed by a maximal expiratory effort through the mouthpiece [2, 7]. Values of PImax and PEmax were expressed as the percentage of pre-scale from 0 to 10) during the

**Perioperative management**

Besides stair-climbing test and PImax and PEmax measurements, all patients underwent preoperative functional cardiological and pulmonary function studies.

Contraindications for major lung resection were according to the ESTS/ERS guidelines [9]. All patients were operated on by qualified thoracic surgeons through a muscle-sparing and nerve-sparing lateral thoracotomy [10].

Postoperative management was standardized and included chest physiotherapy, early mobilization, physical rehabilitation and adequate paravertebral or systemic analgesic therapy, which was titrated to keep the visual analogue pain score of <4 (on a scale from 0 to 10) during the first 48–72 h.

For the purposes of this study and according to previous studies [11, 12] and the European Society of Thoracic Surgeons’ definitions [13], the following complications were included: respiratory failure requiring mechanical ventilation for >48 h, pneumonia (chest roentgenograms, infiltrates, increased white blood cell count and fever), atelectasis requiring bronchoscopy, adult respiratory distress syndrome, pulmonary oedema, pulmonary embolism, myocardial infarction (suggestive electrocardiogram findings and increased levels of myocardial enzymes), haemodynamically unstable arrhythmia requiring medical treatment, cardiac failure (suggestive chest roentgenograms, physical examination and symptoms), acute renal failure (change in serum creatinine >2 mg/dl compared with preoperative values) and stroke. Postoperative morbidity was defined as those complications occurring within 30 days postoperatively or a longer period if the patient was still in the hospital.

**Statistical analysis**

ΔPImax and ΔPEmax were defined as the percentage difference between the pre- and postexercise values.

Several preoperative and operative variables, including age, body mass index, forced expiratory volume in 1 s (FEV1), carbon monoxide lung diffusion capacity (DLCO), comitant cardiac comorbidity, extent of resection (lobectomy vs pneumonectomy), ΔPImax and ΔPEmax were tested for possible association with postoperative cardiopulmonary morbidity. Cardiac comorbidity included one or more of the following conditions: history of coronary artery disease, current treatment for hypertension, chronic heart failure (CHF) or arrhythmia. Variables were initially screened by univariate analysis. The univariate comparisons of outcomes were performed by means of the unpaired Student’s t-test for numeric variables with a normal distribution and by means of the Mann–Whitney U-test for those without a normal distribution. The Shapiro–Wilk normality test was used to assess normal distribution. Categorical variables were compared by means of the χ² test or Fisher’s exact test, as appropriate.

Variables with P < 0.10 at univariate analysis were used as independent variables in the stepwise logistic regression analysis, while the occurrence of cardiopulmonary morbidity was the dependent variable.

Backward stepwise logistic regression analysis was performed with P < 0.1 for final retention in the model. The final model was then validated by bootstrap analyses with 1000 samples. In the bootstrap procedure, repeated samples of the same number of observations as the original database were selected with replacement from the original set of observations. The stability of the final model was assessed by identifying those variables that entered most frequently in the repeated bootstrap models and comparing those variables with the variables in the final model. If the final stepwise model variables occurred in the majority (>50%) of the bootstrap models, they were judged to be stable [14–16].

Receiver operating characteristic (ROC) analysis was used to identify the best cut-off of ΔPImax associated with the occurrence of postoperative complications. Different values of ΔPImax were tested with ROC analysis and the one with the best area under ROC curve was selected as the best cut-off.

All statistical tests were two-tailed, with a significance level of 0.05, and were performed on the statistical software Stata 9.0 (Stata Corp., College Station, TX, USA).

**RESULTS**

The characteristics of the patients analysed in this study are reported in Table 1. Cardiopulmonary complications occurred in
74 patients (26%). The average pre- and postexercise PImax values were 66.9% and 63.1%, respectively, and the average pre- and postexercise PEmax values were 54.2% and 53.7%, respectively.

Compared with baseline values, PImax dropped by 3.6% and PEmax increased by 0.8% after the exercise. In total, 173 patients (61%) experienced a reduction in their PImax after exercise, while 150 (53%) had a reduction in their PEmax.

The results of the univariate comparison between patients with and those without complications are summarized in Tables 2 and 3. In particular, when compared with patients without complications, those with complications had a lower PImax measured before exercise ($P = 0.06$) and lower PImax measured after exercise ($P = 0.03$). Complicated patients had a 4-fold greater reduction in their $\Delta$PImax compared with non-complicated ones (8.7% vs 2.1%, $P = 0.03$), whereas $\Delta$PEmax was similar in complicated and non-complicated patients (0.7% vs 1.3%, $P = 0.5$).

ROC analysis indicated that the best cut-off for predicting complications was a $\Delta$PImax of 10%. One hundred and sixteen patients showed a reduction in PImax of >10%. Of these, 38 (33%) developed complications. Of the remaining 167 patients, 35 (20%) showed a reduction in PImax of ≤10% ($P = 0.03$).

Table 4 summarizes the results of the logistic regression analysis. In particular, a postexercise reduction in PImax with respect to the baseline value was associated with cardiopulmonary complications ($\Delta$PImax regression coefficient $-0.02$, $P = 0.09$, bootstrap frequency 51%). Figure 1 shows an increased incidence of complications in patients with greater reduction in their PImax after exercise, particularly for values >10% reduction.

**DISCUSSION**

**Physiological background and definitions**

The measurement of the maximum static inspiratory pressure (PImax) or the maximum static expiratory pressure (PEmax) that a subject can generate at the mouth is a simple way to assess inspiratory and expiratory muscle strength. The pressure measured during these manoeuvres reflects the pressure developed by the respiratory muscles [6]. They are tests assessing the global neuromuscular function of combined diaphragm, abdominal, intercostal and accessory muscles [5]. Although the precise assessment of the respiratory muscle function is complicated and may need more sophisticated and invasive tests, PImax and PEmax measured at the mouth represent practical indicators of muscle weakness [5].
It is known that respiratory muscle fatigue may play a major role in limiting the exercise capacity even in normal subjects [17, 18]. The stair-climbing test is a form of symptom-limited, maximal exercise that is widely used in the clinical practice to screen candidates for lung resections and has been shown to be highly predictive of postoperative complications [9, 19–21].

Clinical background

Several studies have been published on respiratory muscle performance during maximal exercise in COPD and CHF patients by using the cardiopulmonary exercise test [22]. Generally, they have shown a decrease in PImax after exercise mainly in patients with reduced endurance [22].

However, there is scant information about the measurement of PImax and PEmax before and after exercise in candidates for lung resection and the possible association of these values with the occurrence of postoperative complications.

Main findings

ΔPImax (the percentage difference between the pre- and postexercise values) was higher in complicated patients with respect to non-complicated patients after major lung resection. Stepwise logistic regression analysis and bootstrap confirmed that a reduction in ΔPImax after exercise is independently associated with postoperative complications.

Limitations

(i) We included only major anatomical lung resections and generalization of our results to minor resections (wedge or segmentectomy) needs independent confirmation.

(ii) In this series, patients were operated on through a muscle-sparing thoracotomy. Generalization of these findings to patients operated on through a minimally invasive access (video assisted thoracoscopic surgery) needs to be verified, owing to the lower impact of this latter approach to the chest wall.

(iii) A potential limitation of the method adopted is, that a higher PEmax can be reached through a ‘learning effect’.

(iv) The lower limit of normal values used to calculate the percentage of predicted PImax and PEmax are not securely based and should be regarded as rough guidelines [5].

Clinical and research implications

A large ΔPImax after exercise may be used to select patients who may benefit from respiratory muscle training before the operation. In fact, several authors have demonstrated that specific inspiratory muscle training programmes have a general impact in terms of exercise capacity and endurance [23–25]. Future research is needed to verify whether specific inspiratory muscle training in this subset of patients may lead to an improved postoperative course.

CONCLUSIONS

The measurement of PImax at the mouth during the symptom-limited stair-climbing test is a simple, safe, economical and valid parameter that may be implemented to refine risk stratification of lung resection candidates and to identify patients who may benefit from inspiratory muscle training before lung resection in order to reduce the risk of postoperative complications.

Conflict of interest: none declared.

REFERENCES


APPENDIX. CONFERENCE DISCUSSION

Dr M. Morgan (Leicester, UK): I have no disclosures to make. I have a declaration of interest to make, and that is that I am a physician and not a surgeon and therefore privileged to be here.

This study involves a large number of patients who have undergone a prospective examination but with a volitional test of respiratory muscle function following their stair-climbing task, and I assume that the physician following behind the stair-climbing task is something like that on the picture.

The questions that I would like to ask you are that, firstly, it is difficult for me to see how a slight reduction in respiratory muscle strength might relate to the complications of thoracic surgery. The ones that you list, anoxic and therefore grouped together, include things like atelectasis or pneumonia, which might be related to respiratory muscle strength, but also things like pulmonary embolus or acute renal failure or myocardial infarction, which are difficult to link to a change in respiratory muscle function.

The second question is that I would like you just to explore what the mechanism would be. You didn’t find a reduction in respiratory muscle strength, only in inspiratory muscle strength. The point there is that inspiratory muscle strength has to be measured at residual volume. Some of these patients will have had hyperinflation because of their severe air flow obstruction and therefore at the end of the exercise task you will be measuring at end expiratory lung volume and not true residual volume, and this might simply have accounted for the change.

You have done some complicated statistics, and the next question is that I wonder what you think the clinical significance of a 10% change in your Pmax would be, because actually the values are all in the normal range and there is a very large element of excess respiratory muscle strength over and above what is needed to develop ventilation or preserve vital capacity, and the coefficient of variation of a Pmax measurement is about 10%. So you may be seeing natural variation.

Fourthly, I would like you to tell us how this compared to the predictive value of other measurements like airway function, gas transfer or standardized exercise tests, because they perhaps might do just as well.

Lastly, you are recommending that inspiratory muscle training might be helpful. I have to say it has been very disappointing in other circumstances. It doesn’t improve exercise capacity in COPD; it simply improves respiratory muscle strength. Perhaps full-blown pulmonary rehabilitation might be more effective, because the limitation to most people’s exercise is their skeletal muscle function and not their respiratory muscle function.

Dr Refai: Concerning the role of Pmax after exercise in relation to the different complications, we didn’t separate our complications, the cardiac from the pulmonary, because of the small number of complications that we had. A good proportion of these patients had both cardiac and pulmonary complications.

For the second question about the significance of the 10% of APmax, the clinical significance is that it may help us to screen those patients that may benefit from specific rehabilitation. It may help us also to select those patients needing a different extent of lung resection or a different approach. Instead of doing open surgery, VATS surgery may help them due to the reduction in chest wall injury that may happen with open surgery. And also doing an aggressive postoperative treatment may help us to reduce these complications.

With respect to the correlation with other parameters, the variables that remained significant at the stepwise logistic regression as independent variables were age, cardiac comorbidity, and only the Pmax. At the univariate analysis, FEV1 and DLCO also were significantly associated with the cardiopulmonary complications.

I missed the second question about the mechanism of reduction of Pmax. We think that the reduction of Pmax was more evident than the one of PEmax, because expiratory muscles are not strictly related to respiration but most of them are correlated to other functions.

For Pmax we know that we have different extrinsic and intrinsic factors that may influence this reduction. For the extrinsic situation, as you have mentioned, patients who are hyperinflated may have their diaphragm shortened and they have difficulty also in producing a higher pressure. The same for patients who may have a stiff lung, so we may have reduction in the recoil of the chest wall of these patients, and again they cannot generate normal Pmax pressures and on exercise it is more evident. For intrinsic factors, it may be that these chronic patients may have their sarcomeres shorter and sometimes they may experience deleterious oxidation on exercise, especially in COPD patients.

With respect to normal patients, the recovery is longer and they need more time to return to their normal status to have normal inspiratory pressures.

Dr E. Lim (London, UK): I enjoyed your presentation a lot, and I think that in the literature there are a lot of presentations about physiological estimation and how low physiological parameters predict complications. There are hundreds of papers like this. But they all suffer with the same problem, we can’t use the data, and the reason why we can’t use the data, and I made this little acronym, is because they are ‘clumped,’ C-L-U-M-P.

One is that it’s always Composite. You include many end points, some of which we don’t even know are related, outcomes are so small, like renal failure. The L is you use composite end points because the numbers tend to be Low. The numbers tend to be low so you have to compensate by increasing power if
you include outcomes, which leads to the problem of U, you can’t adjust for it (Unadjusted). So you don’t know if it’s mortality. If you want to look at mortality, adjust using Thoracoscore so we understand it is independent. The M stands for Meaningful. Are the outcomes meaningful to the patients? If you say I have got a high predictive test, it predicts with 100% certainty you develop atelectasis postop, are you going to go for the operation? Yes, in which case, why would you use it?

And finally the P for CLUMP stands for Predictive certainty. Everybody says above a threshold no complications, below a threshold you have complications, but with what predictive certainty like an AUC/ROC or some estimate of ability can you use it to make a prediction? Your paper and all of the same papers fall into that category.

Dr Refai: Please, can you repeat the question loudly because I didn’t hear it.

Dr Lim: It is just the last part. Do you think the outcomes are meaningful so that patients will change their opinion about surgery even though you can predict the high risk of complications when you include complications like atelectasis? Do you think that will influence a patient’s decision?

Dr Refai: This parameter may add to the different parameters that we already have to identify those patients at higher risk of cardiopulmonary complications. The aim of our study was to identify a new parameter that we can try in inspiratory muscle rehabilitation and obtain some results that can help them survive these complications.

Dr P. Van Schil (Antwerp, Belgium): Just to echo Dr. Lim, last week at the ESMO conference in Lugano, we had a tough discussion about which parameters to use in those patients, and specific guidelines also established by this Society and published in the European Respiratory Journal, state that in patients with a compromised pulmonary function we should determine VO2 max. So the question is, in your study did you see a correlation between VO2 max and the number of pulmonary complications, and related to that, do you think you have to change those guidelines?

Dr Refai: In this subset of patients we didn’t check the correlation between VO2 max and PImax, but this may be a good idea for future investigations.