PNEUMOLAB PROCEEDINGS
CONTENTS

PNEUMOLAB PROCEEDINGS

1
Clinical applications of diaphragm ultrasound: moving forward
Zanforlin A., Bezzi M., Carlucci A., Di Marco F.

7
Pulmonary endarterectomy: the lancet first, tears for pills
Morsolini M., Boffini M., Paciocco G., Corsico A. G., Solidoro P.

17
Smoking cessation, anxiety, mood and quality of life: reassuring evidences
Baiardini I., Sorino C., Di Marco F., Facchini F.
Clinical applications of diaphragm ultrasound: moving forward

A. ZANFORLIN 1, M. BEZZI 2, A. CARLUCCI 3, F. DI MARCO 4

Establishing the correct time of weaning from mechanical ventilation is a crucial issue in the clinical practice. The difficult process of weaning can be due to pathological conditions that result in an imbalance between respiratory-muscle strength and respiratory load. Recently it has been suggested that ultrasound measurements of diaphragm muscle thickening in inspiration during weaning could provide an estimation of extubation success. Bedside ultrasonography, particularly sonographic evaluation of the diaphragm by measuring the percentage variation of diaphragm thickness (tdi) between end-inspiration and end-expiration (Δtdi%), has become a valuable tool in the management of intensive care unit patients. This non-invasive, low-cost and fast to perform technique seems to predict with a good accuracy the extubation failure. Some limitations derive from the difficulty to determine the maximum (end inspiratory) and minimum (end expiratory) tdi observing a dynamic image in B-mode, in particular in non-collaborating patients. In addition, some dynamic situations causing extubation failure could not be predicted by an ultrasound measure performed at the beginning of the weaning trial. Nowadays the technique proposed remains a useful tool for helping the prediction of extubation failure. It would be useful in the future to set up multicentric studies with a standardised description of the procedure and serial measurements in different timing during the weaning trial. Furthermore, randomized controlled trials to evaluate the efficiency of Δtdi% versus other indexes in predicting extubation failure are needed.

Key words: Diaphragm - Airway extubation - Respiration, artificial - Ultrasonography.

DiNino et al. have recently investigated whether ultrasound measurements of diaphragm muscle thickening during inspiration could provide an estimation of extubation success. In their recent paper they described the rationale for using ultrasound measures of diaphragm muscle thickening to predict extubation outcomes. The authors also make clear how these measures differ from ultrasound evaluations of diaphragm dome motion and how diaphragm thickening in the zone of apposition is related with other measures used to predict extubation success. The purpose of this research is to sort out a practical, useful parameter that
could predict the right timing for extubation by measuring diaphragm thickness (tdi) with ultrasound at end-inspiration and end-expiration during weaning trials in patients spontaneously breathing (SB) or ventilated in pressure support mode (PS).

The correct time of weaning from mechanical ventilation is crucial in the clinical practice. It is well known that subjective decisions and clinical prediction of extubation success are often incorrect mostly leading to mechanical ventilation dependency. Both premature discontinuation of mechanical ventilation and unnecessary delays in weaning may be deleterious with up to 25% of patients requiring reinstitution of ventilator support. If a prolonged time of mechanical ventilation can result in longer stay, higher costs, excessive sedation, longer exposure to lung “biotrauma” due to positive pressure, and increased infection risk, also a premature ventilator withdrawal can be dangerous, with airway loss, compromised gas exchange, aspiration, and inspiratory muscle fatigue. Extubation failure is also associated with an increased risk of death, ranging between 40 and 50%, that is correlated with the etiology of extubation failure and the delay in re-intubation. A high incidence of pneumonia and clinical deterioration before re-intubation are considered to play a predominant role in worsening outcome.

This is why many efforts have been made to provide tools aimed at predicting the right time for a successful discontinuation of mechanical ventilation. The difficult process of weaning can be due to pathological conditions that result in an imbalance between respiratory-muscle strength and respiratory load. Lung disease, cardiovascular dysfunction and chest-wall disease are responsible of increased respiratory load, whilst inspiratory muscle weakness (either pre-existing or acquired in ICU) and diminished respiratory drive, affect respiratory capacity.

Several measured variables as minute ventilation, maximal inspiratory pressure, airway-occlusion pressure 0.1 s after the start of inspiratory flow (P0.1), respiratory rate, tidal volume, or calculated indexes, such as the rapid shallow breathing index (RSBI, the ratio between breathing frequency and tidal volume), and the CROP index (compliance, rate, oxygenation, and pressure) have been proposed.

Breathing frequency, minute ventilation, and maximal inspiratory pressure, have had little success as well in selecting the perfect timing of successful extubation. The RSBI is the most extensively investigated and used index to predict weaning success. Unfortunately, variation in the way the RSBI has been used since its original description (during SBT, CPAP or PSV) precludes a simple summary statement regarding its value and role.

The diaphragm strength and ability to contract has also been evaluated with similar purposes through magnetic stimulation of the phrenic nerves. Cervical (CMS) and anterior (AMS) magnetic stimulation of the phrenic nerves can be performed using double circular stimulating coils. For CMS, one coil is placed over the cervical spine to bilaterally stimulate the phrenic nerve roots, whereas for AMS the coils are placed on the anterolateral aspect of the neck to allow unilateral and bilateral stimulation. Diaphragm contractility is assessed as transdiaphragmatic pressure (Pdi) measured with balloon catheters positioned in the midesophagus and stomach. Stimulus supramaximality is normally assured by reporting diaphragm twitch Pdi (TwPdi) across a range of stimulator outputs: 85, 90, 95, and 100% of maximum. Patients are normally studied supine to minimize abdominal influence on diaphragm motion. However this technique is invasive, requires specific equipment and a well trained and specialized team. It also takes a long time for a correct and reproducible evaluation.

Bedside ultrasonography, particularly sonographic evaluation of the diaphragm, has become a valuable tool in the management of intensive care unit patients. The evaluation of the motion of the diaphragm dome has shown to be useful in predicting extubation outcomes; however, factors such as tidal volume, proximity of rib cage and abdominal organs may affect diaphragm motion.
The measurement of diaphragm thickness (tdi) by placing a linear ultrasound probe in the zone of apposition of the diaphragm to the ribcage has been used for the diagnosis of paralysis of the diaphragm. This measurement, however, may also significantly vary with the weight and the height of the patient.

DiNino E et al. recently proposed some parameters, such as percent change in tdi between end-inspiration and end-expiration (Δtdi%), the product between tidal volume (VT) and Δtdi% and the ratio between Δtdi% and respiratory frequency (f) and compared the respective predictive values on extubation success. Author’s purpose is to introduce a technique that is non invasive, fast and easy to learn. This measure of diaphragm function can be performed at the bedside, requires standard ultrasound equipment largely available in most intensive care units without additional costs. Ultrasonography is easy and quick to perform. It is painless and doesn’t require any special effort by the patient himself.

What is innovative, is the idea to use the variation of diaphragm thickness as a performance index that could predict extubation success: a patient with a poor diaphragm contraction is likely to fail extubation trial because his muscle could not provide a sufficient respiratory drive.

Focusing on the ultrasound technique, the authors used B-mode for determining end-inspiratory and end expiratory tdi confirming the respiratory phase by using a flow meter.

In COPD patients, the medium tdi at end-inspiration (total lung capacity) and end expiration (residual volume) are respectively 6 mm and 3.3 mm as recently reported by Smargiassi et al. and the medium Δtdi is 2.7 mm. A Δtdi% cutoff equal to 30% measures about 0.9 mm: consequently it is crucial a maximum precision in measuring diaphragm thicknesses. Technically it could be difficult to determine the maximum (end-inspiratory) and minimum (end-expiratory) tdi observing a dynamic image in B-mode, in particular in non collaborating patients. Moreover, for mechanical reasons, diaphragm contraction may anticipate flow modifications, so tdi and flow modifications may not be synchronous, in particular in obstructed and hyperinflated patients.

Another useful technique to measure tdi variations is provided by M-mode (the analysis of the variation of a selected vertical line of ultrasound scan in function of time), that could enhance the tdi variations allowing to correctly identify minimum and maximum tdi. In the “methods” section, the authors state they followed the protocol described by Cohn et al., where M-mode is indicated as a possible confounding factor of tdi, for example in presence of little liquid structures (effusions). However this study, conducted on only 9 subjects, refers to technical problems that so far could be avoided thanks to the technological evolution of ultrasound machines that often allow to examine M-mode and B-mode images together in real time, avoiding the discussed confounding factors and providing a more precise tdi measurement (Figure 1).

Actually, the measurement procedure is not clear because it is not specified if the measures are taken during tidal or forced breathe and the authors affirm to prefer right hemidiaphragm because the better acoustic window provided by the liver makes easier to acquire the measure of tdi. However, the analysis of tdi in the apposition zone is technically possible both right and left, because the acoustic window is the same (between ultrasound probe and diaphragm there is only the thoracic wall), so maybe it would have been useful to measure tdi also in the left zone of apposition to exclude cases of hemidiaphragm paralysis (Figure 2).

Generally, abdominal organs influence acoustic window during the study of diaphragm kinetic performed analyzing the diaphragmatic dome: this approach in effect is almost always possible on the right, thanks to the acoustic window provided by the liver, but often it is not possible on the left hemidiaphragm, because of the interposition of bowel or stomach. However, this approach is not considered by the authors because, as themselves affirm, there could be confounding factors on dome kinetics.
Actually all patients were enrolled when they were ready to undergo a low-level PS weaning trial or a SB trial, but there is no mention to the outcome of the trial: all patients succeeded the weaning trial and were extubated. Moreover the ultrasonographic measurements were performed during the first 5 minutes of the weaning trial. However failure can occur later in the course of the trial. Sometimes an inspiratory load that is tolerable at the beginning of the trial increases throughout the SBT. This is generally due to an unrecognized or latent cardiac dysfunction which can become evident when interrupting the ventilator support to resume spontaneous breathing negative intrathoracic pressure swings leads to a rise in both cardiac preload (i.e., venous return) and afterload (i.e., left ventricular transmural pressure), which may worsen pulmonary mechanics and increase the magnitude of the load imposed on the respiratory muscles.

Finally, there is another important bias, that is very frequent in more other studies: the inability to consider, in the definition of the outcome to predict, an important difference between failure to discontinue mechanical ventilation and failure to wean from the endotracheal tube. The latter can be consequent to the incapacity to maintain the spontaneous unassisted breathing after removal of the endotracheal tube, suggesting an increase of the load imposed on the respiratory muscles (upper airways obstructions or incapacity to adequately clear secretions) “after” extubation. All these situations could not be predicted by an ultrasound measure performed during the weaning trial, leading to underpowered negative predictive value and specificity of the proposed method.

Nevertheless, the technique proposed by the authors remains a useful tool for determining extubation success. It would be useful in the future to set up multicentric studies with a precise description of the procedure and serial measurements in different moments during the extubation process. Furthermore, the planning of randomized controlled trial to evaluate the efficiency of Δtdi% versus other indexes in predicting extubation success is needed.

Research on diaphragm ultrasound is constantly evolving, with latest study indicating its possible applications also in diseases such as COPD, previously not accessible to ultrasound evaluation. Chest ultrasound has been often centered on evaluation of artifacts whose origin is still debated and not demonstrated unambiguously. Hopefully the future direction of research could be the global evaluation of respiratory muscles: such elements are
clearly visible with ultrasound and compose the ventilatory pump. The evaluation of their contractility in normal and pathological conditions could give precious information on pathophysiology of the respiratory system and help us in the management of complex diseases determining a ventilatory failure.

References


Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Received on August 1, 2014. Accepted for publication on September 17, 2014.
Chronic thromboembolic pulmonary hypertension (CTEPH) is a progressive disease due to the incomplete resolution of pulmonary emboli, leading to right heart failure, with a poor survival. Pulmonary endarterectomy (PEA) is the operation of choice for CTEPH. As there are no well-defined criteria to discriminate surgically accessible from inaccessible obstructive lesions, the operability assessment relies on the surgeon’s experience. The recommended algorithms to perform a correct diagnosis of CTEPH still suggest the lung ventilation/perfusion scan, despite advances in computed tomography with 3-D reconstruction and magnetic resonance imaging. Selective pulmonary angiography is the gold standard to assess operability in CTEPH. Medical therapy should not be considered an alternative to PEA, as it should be reserved to patients with either peripheral disease, deemed inoperable by an experienced PEA surgeon, or persistent/recurrent pulmonary hypertension after PEA. Lung transplantation, when indicated, still represents a viable option for patients with either inoperable CTEPH or CTEPH with concomitant severe parenchymal lung disease that contraindicates PEA. The outcome of operable CTEPH is still best predicted after surgery. Remarkably, the recovery of exercise capacity is not as immediate as hemodynamic improvement, underlining the importance of early identification of surgical candidates before physical deconditioning.

Key words: Thoracic surgery - Cardiac surgical procedures - Hypertension, pulmonary - Transplantation.

Corresponding author: M. Morsolini, Department of Clinical-Surgical, Diagnostic and Pediatric Sciences, Division of Cardiac Surgery, Heart and Lung Transplantation and Pulmonary Endarterectomy Unit, University of Pavia School of Medicine, Pavia, Italy. E-mail: m.morsolini@smatteo.pv.it

In a recent article, Skoro-Sajer et al. try to point out the effects of PEA on pulmonary vascular resistance (PVR) and compliance, and the prognostic impact of these effects in the first prospective longitudinal study,
confirming a correlation between surgical specimens, hemodynamics, and long-term right ventricular recovery.\textsuperscript{5}

PEA is the only curative option for CTEPH, but it requires a complex clinical, radiological, and functional assessment to be performed in an experienced center. The first step is the correct diagnosis and the correct operability assessment, following an algorithm integrating different imaging diagnostic approaches.

**Patient selection: imaging**

The recommended algorithms to perform a correct diagnosis of CTEPH suggest the use as first step of lung ventilation/perfusion (V/Q) scan. Despite advances in computed tomography pulmonary angiogram (CTPA) with 3-D reconstruction and magnetic resonance imaging (MRI), the V/Q scan remains the gold standard.\textsuperscript{4} There are, in fact, some limitations for using CTPA for detecting chronic thromboembolic disease. CTPA showed a low sensitivity (51\%) compared with lung V/Q scan (96\%).\textsuperscript{5} An additional concern regarding reliance on CTPA for diagnosing CTEPH includes false-positive cases resulting from conditions mimicking chronic thromboembolic disease, like proximal thrombi associated with pulmonary arterial hypertension or congenital heart defects.\textsuperscript{6} Another important concern is related to operability assessment. Even with the latest 320-slice CT technology, disease confined to very distal segmental or sub-segmental pulmonary arteries may be missed with sensitivity that reduces from 97\% in main or lobar branches to 86\% for the segmental vessels.\textsuperscript{7} However, in a complete diagnostic workup, CTPA provides helpful information when performed after lung V/Q scan, showing additional details including vascular wall thickness, mediastinal structures, and indirect signs of pulmonary hypertension, as bronchial artery collaterals and mosaic perfusion pattern.\textsuperscript{8, 9} New promising modalities as dual-energy CTPA and lung perfusion MRI could emerge in the next future to improve pulmonary vascular imaging.\textsuperscript{10, 11} Despite advances in CTPA and MRI techniques, selective pulmonary angiography remains the gold standard for the operability assessment of CTEPH. A major advantage of pulmonary angiogram is the possibility to combine the imaging with the assessment of hemodynamic parameters by using right heart catheterization.\textsuperscript{12} Moreover, pulmonary angiography provides a direct dynamic view of the pulmonary arterial circulation, detecting any delay in the blood flow due to obstructions at very distal level that are not directly shown but play a key role in determining the increase in PVR.

**Surgery**

As there are no well-defined criteria to discriminate surgically accessible from inaccessible obstructive lesions, the operability assessment relies only on the surgeon's experience. Despite growing experience worldwide, and although currently available tools are adequate in identifying the presence of pulmonary arterial obstruction at very distal level, the criteria for operability remain variable and center-dependent.\textsuperscript{13}

The aim of the operation is the clearance of all the chronic thromboembolic arterial obstructions to reduce PVR immediately. Surgery is performed by median sternotomy incision for approach to both lungs, using cardiopulmonary bypass to divert blood flow from the pulmonary artery and sustain function of heart and lungs. After arteriotomy incisions within the pericardium, a true endarterectomy with meticulous full distal dissection to segmental and sub-segmental vessels is achieved. Despite full cardiopulmonary bypass, in many cases pathological collateral blood flow from bronchial circulation obscures the operative field. The standard operative technique pioneered at the University of California at San Diego, USA, to overcome this situation is complete circulatory arrest during deep hypothermia to 20 °C to reduce metabolic activity and to protect vital organ functions.\textsuperscript{14}

A different technique has recently been proposed by the University of Pavia, Italy.\textsuperscript{15}
Hemodynamic data

After PEA the cardiac output is generally high, due to the remarkable unloading of the hypertrophic right ventricle, and may lead to lung reperfusion edema. Hence, inotropes and inhaled nitric oxide are discontinued rapidly, vasopressors agents are continued for a few days, and a vigorous diuresis is achieved to obtain negative fluid balance. A protective ventilation (high positive end-expiratory pressure and low tidal volume) is preferred, to prevent both lung reperfusion edema and ventilation-induced lung injury. Extubation is performed as soon as possible, switching to helmet continuous positive airways pressure ventilation usually for a few days.

All hemodynamic parameters normalize after surgery and the improvement is steadily maintained over time. As a direct consequence, a reverse right ventricle remodeling generally occurs after surgery. Immediately after PEA right ventricle volume decreases significantly, and tricuspid regurgitation radically improves, as well as right ventricular ejection fraction. Also right ventricular hypertrophy reverses, but over a longer time. Failure to remodel of the right ventricle affects prognosis. Higher ventricular volume and lower ejection fraction of the right ventricle are associated with poor functional status at any time postoperatively, and persistence of pulmonary hypertension (PVR greater than 509 dyn*s*cm\(^{-5}\)) and right ventricular ejection fraction below 24% predict clinical failure at 12-month follow-up.

Long-term survival after PEA is excellent and cardiopulmonary function can be almost normalized in most patients. The only absolute contraindication to PEA is underlying severe parenchymal lung disease. Severe pulmonary hypertension above 1,200 dyn*s*cm\(^{-5}\), particularly when associated with small and peripheral arterial obstructions, worsens surgical candidacy and affect surgical outcome. Current techniques of operation lead this complex procedure to a very low risk of death, despite the increasing number of PEA performed in extremely distal disease. The expertise of the surgeon and the center is fundamental to achieve good short and long-term results, and the referral to experienced centers is important to normalize selection and follow-up. In Italy, from April 1994 to April 2014, 546 consecutive patients diagnosed with CTEPH underwent PEA at the University of Pavia, Italy. A dedicated database, approved by the institutional review board, was created since the beginning to record prospectively patients’ information. All patients provided written informed consent. All CTEPH patients referred for a surgical evaluation underwent a complete diagnostic workup according to the published standardized protocol and the current guidelines. Postoperative follow-up visits are scheduled 3 months after surgery, yearly for the following 5 years, and after 7, 10, 15, and 20 years after PEA. Follow-up after discharge is complete for about 95% of the patients.

Vol. 105 - Suppl 1 to No. 5  MINERVA MEDICA  9
events. After successful PEA, reduced pulmonary arterial compliance is an important determinant of exercise capacity, in association with the age and sex of the patient and the extent of recovery of both cardiac and respiratory function. However, exercise capacity does not explain a large proportion of the effect of surgery on subsequent survival.

**Functional tests**

After PEA, most of the improvement in clinical and hemodynamic recovery is achieved within the first 3 months as a result of the relief of central mechanical obstruction. The article by Skoro-Sajer shows that PEA immediately decreased PVR and increased pulmonary arterial compliance. At variance, the recovery of restrictive lung function is known to be delayed as usual after major cardiothoracic surgery, while patients with CTEPH often have TLCO in the normal range. This is postulated to be because of back-perfusion of the capillary bed by the extensive bronchial arterial collateral flow that plays a role in the maintenance of pulmonary parenchymal viability and in carbon monoxide exchange, although it does not improve the oxygen exchange. The preoperative overestimation of TLCO masks the effect of PEA on the time trend of this parameter. The persistence of a significant impairment of TLCO at the end of follow-up is probably due to the remodeling before surgery on vessels in the non-obstructed segments of the lungs.

Remarkably, there is a discrepancy in the time course of recovery between hemodynamic and exercise data. In many patients, a reduced exercise tolerance persists at 4 years. Likely, the recovery of exercise capacity is not only an immediate result of hemodynamic improvement. The peripheral adaptation and the recovery from the physical deconditioning might delay or need a longer time recover. This underlines the importance of an early identification of candidates for surgery before physical deconditioning. Given the progressive nature of the disease, with hypertensive vascular remodeling of the patent arteries due to flow overload, the development of capillary plexiform lesions, and the calcification of the chronic obstructive material, even patients with CTEPH presenting with WHO class II symptoms might benefit from early surgery, with lower operative risk.

In the study of Skoro-Sajer, immediate postoperative PVR is the only predictor of long-term survival/freedom of lung transplantation and patients from whom more and longer thrombus tails were removed had better postoperative hemodynamics and were less likely to develop persistent/recurrent PH. In another recent study, pulmonary arterial compliance was strongly associated with exercise tolerance but the exercise capacity, as assessed 3 months after surgery by the Bruce test, does not appear to explain a large proportion of the effects of PEA on subsequent survival. This is probably due to the multifactorial etiology of exercise tolerance.

**Medical treatment**

As described in PH guidelines, medical therapy in CTEPH should not be considered an alternative to PEA. Medical therapy should be reserved to patients with either peripheral disease, deemed inoperable by an experienced surgeon, or persistent/recurrent PH after PEA. Recognizing that the treatment of choice and the only potential for complete cure remains PEA, there are 2 largest RCTs to date showing a specific role of PH drugs in inoperable patients. The first was the BENEFIT study with bosentan. The 16 weeks study observed doubtful results in the 2 co-primary endpoints: 6-minute walk distance was unchanged (treatment effect: +2 m), whereas PVR reduction was significant with treatment effect of -24%. In the more recent CHEST-1 study with riociguat, a placebo-controlled trial including 261 patients (73% with inoperable CTEPH and 27% with persistent/recurrent PH after PEA), the treatment group walked 46 meters more compared to the control group (p<0.001).
16 weeks after randomization. Several secondary end-points (PVR, N-terminal pro-B-type natriuretic peptide and WHO function class) showed statistically significant differences. However, the CHEST-1 trial and its long-term open-label extension (CHEST-2) described six serious hemoptysis events, one requiring bronchial artery embolization. All patients were receiving anticoagulants and none of these events was considered related to the study drug. An increased incidence of hemoptysis was observed also in short and long-term trials in PAH (PATENT-1 and PATENT-2). Riociguat-related bleeding resolved in most cases, and even if non dose-dependent, some further clarification on the possible mechanism is needed. Several open-label non-randomized trials have been published in literature using different specific treatments (epoprostenol, treprostinil, iloprost, and sildenafil) with positive results on 6-minute walk distance and PVR changes after a 3 to 6-month period, but their role remains uncertain due to lack of robust data.

Transplantation

Lung transplantation (LTx) remains the only effective therapy for end stage lung disease in selected patients. Regardless its origin, pulmonary hypertension has been demonstrated to be a significant early risk factor that jeopardizes immediate outcomes after transplant. However LTx for idiopathic pulmonary hypertension provides good results in terms of survival (5-year survival about 50%) and excellent quality of life in the long term.

LTx, when indicated, still represents a viable option for patients with either inoperable CTEPH or CTEPH with concomitant severe parenchymal lung disease that contraindicates PEA.

Intra- and post-operative management of patients with pulmonary hypertension undergoing LTx may be highly demanding and can explain the higher early mortality (1-year mortality about 10%) compared to other indications. Historically, heart-lung, single lung, and double lung transplants were indicated for those patients. In the recent era, single lung transplantation has been abandoned and the procedures of choice are double lung and heart-lung transplantation. The choice between the two strategies is mainly based on cardiac function. Heart function evaluation is crucial. Right ventricle dilation and dysfunction is very often present but very rarely it represents a contraindication to double lung transplantation. In fact, the replacement of both lungs leads to a significant reduction of the right ventricular afterload, allowing a progressive reverse remodeling of the right ventricle, as it happens after PEA. The “reverse right ventricle remodeling lesson” learned from PEA allows to allocate hearts to other patients. The only contraindication to double LTx is represented by a left ventricle diastolic dysfunction, which is difficult to be assessed preoperatively. In this case, heart-lung transplantation is indicated.

LTx poses some technical issues related with the extreme dilation of the pulmonary artery requiring an accurate arterial anastomosis due to the severe dimensional mismatch between donor and recipient pulmonary artery. Although there is some evidence that is not always mandatory, pulmonary hypertension is generally considered an indication to use the cardiopulmonary by-pass during the lung transplant procedure. This increases the risk of bleeding and the need for blood product transfusion. Intraoperative transfusions, the use of cardiopulmonary by-pass and the presence of pulmonary hypertension itself are well-known risk factors for primary graft dysfunction occurrence. As a consequence, patients with pulmonary hypertension undergoing LTx have higher risk of primary graft dysfunction, requiring an extracorporeal membrane oxygenation support in the most severe cases. Veno-arterial configuration is usually preferred, because the support warrants optimal oxygenation and reduction of right ventricle afterload, and the use of a protective and ultra-protective ventilation leads to a progressive recovery of the graft function.
logical side, pulmonary artery vasodilation should be avoided to reduce the augmented blood flow in the low resistance pulmonary vascular bed occurring after transplant. This is a critical point, well studied in PEA intensive care unit management too, with important consequences: the strategies to counteract the pulmonary hyper-afflux reduce 1) the risk of ischemia-reperfusion injury and 2) the development of hemodynamic edema due to the increased flow in the presence of a small and hypo-diastolic LV. Inotropes should be used very carefully, limiting to support a failing ventricle. Eventually an intra-aortic balloon pump can be inserted to reduce LV afterload and to increase LV contractility. Volume restriction is also mandatory and renal replacement strategy can be useful in case of poor response to pharmacological diuretic therapy.14

Discussion

Patients with sub-massive pulmonary embolism are likely to survive when treated with heparin alone, and the associated right ventricle dilation is likely to resolve spontaneously in the majority. The current literature cannot help in determining which proportion of patients will progress to CTEPH. The main issue is the lack of reliable and accurate tools for the identification of these patients.

PEA is the operation of choice for CTEPH because it is considered curative and therefore greatly superior to medical treatment or transplantation for this condition. Indications for conservative surgery changed over time and nowadays also more distal lesions can be successfully treated.17, 18 Despite growing experience worldwide, and although currently available tools are adequate in identifying the presence of pulmonary arterial obstructions at very distal level, the criteria for operability remain variable and center-dependent.13 The referral to an experienced surgeon as second opinion has to be performed before starting any specific medical therapy, which is less effective and related to a lower survival, and before referring to a transplant center, as LTx is followed by higher mortality and more comorbidities related to immunosuppression.15, 16

The postoperative outcome of CTEPH is still best predicted after surgery, mainly based on PVR and the correlation between PVR and the surgical specimens. To date a scoring system is not available as the most important risk factor for postoperative outcome is the surgeon’s experience. Defining and following a correct and complete diagnostic algorithm seems to be fundamental to reduce single centre bias in selection and data interpretation. In fact, the outcome can be deeply influenced by patient selection.

Postoperative hemodynamic assessment is fundamental to identify patients at risk for complicated outcome, and to start promptly the most appropriate treatment. In case of persistent/recurrent pulmonary hypertension following PEA, specific medical therapy is indicated.

References


Smoking cessation, anxiety, mood and quality of life: reassuring evidences

I. BAIARDINI 1, C. SORINO 2,3, F. DI MARCO 4, F. FACCHINI 5

A close and complex relationship between smoking and mental health problems was found. Different hypotheses have been proposed to explain these associations: 1) smoking and poor mental health may share common causes (genetic factors or environmental mechanisms); 2) for people with poor mental health smoking is a coping strategy to regulate psychiatric symptoms; 3) smokers worsen mental health. Moreover, smokers with psychiatric disorders may have more difficulty quitting and patients with mental diseases who received mental health treatment within the previous year were more likely to stop smoking than those not receiving treatment. Taylor et al. hypothesized that quitting smoking might improve rather than exacerbate mental health, because it allows to avoid multiple episodes of negative affect induced by withdrawal. With the aim to verify this hypothesis, they conducted a systematic review and meta-analysis on longitudinal studies (randomized controlled trials and cohort studies) in which the difference in change in mental health between subjects who stop smoking and subjects who continue to smoke has been explored. A total of 26 longitudinal studies evaluating anxiety, depression, mixed anxiety and depression, positive effect, psychological quality of life, and stress have been included. The study results provided enough evidence to assure that quitting smoking is associated with a reduction of depression, anxiety, and stress, with an improvement of psychological quality of life and positive affect compared with continuing to smoke. The strength of association was similar for both the general population and study enrolled populations, including those with mental health disorders. The results of this meta-analysis have direct clinical implications: the benefits for mental health could motivate physicians and patients to take into account the possibility of smoking cessation.

**Key words:** Smoking cessation - Mental health - Mood disorders - Stress, psychological - Quality of life.

Tobacco smoking represents a global epidemic of public health concern. It is the leading preventable cause of disability, morbidity and death worldwide. Despite detrimental effects from smoking on health are well known, a substantial portion of the population smokes cigarettes regularly. In

---

Corresponding author: I. Baiardini, Allergy and Respiratory Diseases Clinic, DMI - University of Genoa, IRCCS AOU San Martino-IST, Genoa, Italy. E-mail: ilaria.baiardini@libero.it
particular, it has been shown that tobacco dependence is more frequent in people suffering from mental diseases and these patients find quitting more difficult than other smokers. For this reason, the close and complex relationship between smoking and mental health problems is increasingly explored and recognized. Smoking cigarette has been described as a coping strategy that aims to regulate negative affects and to reduce feelings of anxiety, depression and distress. This cognitive process is common to smokers with and without mental disorders and has a negatively reinforcing effect, leading to think that smoking allows to guarantee mental health benefits. Smokers consider smoking as a way to feel comfortable in social situations, stabilize mood, maintain a better concentration, enhance stimulation and reduce anxiety and distress.

Nevertheless, an association between smoke and poor mental health has been found in recent epidemiological studies. People suffering from a psychiatric disease are twice as likely to be current smokers compared to the general population and represent more than a half of nicotine-dependent smokers. Moreover, they are heavier consumers of cigarettes and have poorer cessation outcomes.

The bidirectional association between smoking and mental disorders is supported by the fact that smokers have an increased probability to meet current diagnostic criteria for psychiatric disorders than non-smokers. Several clinical and population-based studies have found an association between smoking or nicotine dependence and various mental illnesses including depression, suicidal behavior, anxiety, bipolar disorder, personality disorders, schizophrenia, attention-deficit/hyperactivity disorders, alcohol abuse and dependence. As a consequence, tobacco-related morbidity and mortality result higher among subject with mental health diseases. Moreover, the experience of stressful events and the resulting emotional or psychological distress play a critical role in cigarette use: a substantial amount of research has documented that smoking is more common among subjects who report high levels of strain in different life domains (work, family, social relationship, financial condition) or that have experienced stressful life events or childhood adversity. Mental diseases not only represent an independent risk factor for smoking, but are associated with smoking-related risk factors such as lower income, lower education and unemployment.

Different hypotheses have been proposed to explain these complex associations: 1) smoking and poor mental health may share common causes (genetic factors or environmental mechanisms); 2) people with poor mental health smoke to self-medicate their psychiatric symptoms and to manage the affective dysregulation; 3) or smoking might bring to the development of secondary mental disorders or worsen mental health. Moreover, literature data also suggest that smokers with psychiatric disorders may have more difficulty quitting, providing at least a partial explanation for why smoking rates are higher in this population. The effects on mental health often represent an impediment to successful quitting and may constitute the cause of smoking relapse. When tobacco use is stopped, nicotine withdrawal syndrome emerges in the first 24-48 hours. It is characterized by somatic and affective symptoms such as irritability, anger, frustration, restlessness, sleep disturbances, anxiety, depressed mood, difficulty concentrating, increased appetite, and craving for tobacco which may interfere with social relationships and daily life functioning. This syndrome constitutes an important obstruction to successful quitting and may lead to smoking relapse. Smokers may be less likely to stop because they fear they will experience mental health problems and professionals often do not encourage some patients to quit because they believe that quitting might exacerbate psychiatric symptoms.

The role of concomitant psychiatric diseases in smoking cessation has been underlined in a recent meta-analysis: individuals with mental diseases who received mental health treatment within the previous year were more likely to stop smoking than those not receiving treatment.
Taylor et al. hypothesized that smoking quitting might improve rather than exacerbate mental health, because it helps avoiding multiple episodes of negative affect induced by withdrawal. With the aim to test this hypothesis, they conducted a systematic review and meta-analysis on longitudinal studies (randomized controlled studies and cohort studies) in which the difference in change in mental health between subjects who stop smoking and subjects who continue has been explored.

Authors using a broad eligibility criteria selected 26 longitudinal studies in general population and in clinical selected populations including smokers with current psychiatric diseases, with the aim to capture all potentially relevant data. What emerges from the analysis conducted by Taylor et al. provides useful suggestions for clinical practice. Health professionals and patients must be aware about the links among smoking cessation, mental health and psychological well-being. In fact, both the physician’s decision to intervene and the patient’s motivation to quit may be influenced by incorrect beliefs and negative expectations regarding the detrimental effects of smoking cessation on mental health.

The effect measured by the meta-analysis has been calculated from a difference in standardized change in symptom scores from baseline. They compared those who were able to quit smoking to those who continued or restarted smoking after quitting. Findings are clinically very relevant as they show improvement in those who were able to quit smoking ranging from 0.37 of the standardized mean deviation (SMD) for anxiety, 0.31 for mixed anxiety/depression, 0.25 for depression, 0.27 for stress, 0.22 for psychological quality of life, 0.40 for positive affect; i.e., the change in mental health is similar to the effect expected with the use of antidepressant drugs as it has been remarked by the authors in their conclusion of the abstract and discussion of possible mechanisms and by comments to the article published in the BMJ. It is noteworthy that the effect on mild to severe depression of selective serotonin reuptake inhibitors is between 0.11 and 0.17, smaller than the 0.25 seen with smoking cessation. Similarly the effect on anxiety disorder of all type of antidepressant drugs ranges from 0.25 to 0.50; this is comparable to the improvement seen with smoking cessation: 0.31 for mixed anxiety/depression and 0.37 for anxiety. Moreover, the results of the meta-analysis have implications for research: starting from the available evidence, future studies are suggested to allow drawing causal inferences of the determinants of mental health after smoking cessation.

Smoking cessation in people with mental disorders has always been a source of concern for both the healthcare providers and the patients. The idea that smoking alleviate stress and anxiety provide a major obstacle for smokers to quit, and for physicians to recommend quitting. Many health professionals also believe that smoking is anxiolytic and that smoking cessation usually worsens mood. The belief about the relationship between smoking and mental health is particularly damaging for subjects with psychiatric disorders, who are less likely than other smokers to be offered cessation advice and support. It is no coincidence that in many countries, smoking is allowed in the psychiatric hospital wards. Nevertheless, smokers with mental disorders have a life expectancy around 20 years lower than people without such a problem, and much of the excess mortality is attributed to cigarette smoking, which is highly prevalent in this group.

It is known that nicotine absorbed by smoking stimulates the release of various neurotransmitters involved in feelings of pleasure and relaxation, such as dopamine, norepinephrine, serotonin, β-endorphin, and GABA. Eventually, smoking can affect pharmacokinetics of psychotropic medications in part by interfering with cytochrome CYP 450 system. On the other hand, the abrupt discontinuation of nicotine causes withdrawal symptoms including irritability, anxiety, difficulty concentrating, and depressed mood. It has been recently reported that about half the smokers in England cite stress relief as one
of the main reasons for smoking. McDemott et al. recently observed that people who quit smoking experience a marked reduction in anxiety, whereas those who fail to achieve abstinence experience a modest long-term increase of anxiety. These data contradict the assumption that smoking is a stress reliever, but suggest that failure of a quit attempt may generate anxiety.

Smoking does not seem to decrease stress in smokers who are not nicotine deprived; on the other hand, the intensity of stress in smokers after smoking is similar to those of non-smokers. It has been suggested, therefore, that the perceived beneficial effects of smoking upon stress are actually a misattribution of withdrawal relief. Withdrawal symptoms are usually experienced most acutely in the first 24-48 hours after quitting smoking and resolve within two to four weeks after cessation, when the neurological functioning of quitters returns to the same level as non-smokers. There is further research suggesting that smoking may actually cause stress and is a risk factor for the development of anxiety-related disorders.

Nicotine’s ability to quickly reverse the symptoms of withdrawal induces in smokers the feeling that it alleviates stress. Though depression is one of the less common symptoms of nicotine withdrawal, one of the biggest concerns about smoking cessation regards the fear of worsening mood or triggering a full-blown depression. This often leads to discourage smokers from trying to quit and physicians from intervening, particularly when smokers have current or past mental illness. However, many studies failed to show mood enhancing effects of nicotine.

The main studies which analyzed the relationship between cigarette smoking and mental health, were focused on six mind disorders: anxiety, depression, mixed anxiety and depression, positive affect, psychological quality of life, and stress. Several studies have differences in methodology, analyzed population and length of follow-up, but with appropriate adjustments Taylor and coworkers have obtained interesting global information. The study provided enough evidence to assure that quitting smoking is associated with a reduction of depression, anxiety, and stress, with an improvement of psychological quality of life and positive affect compared with continuing to smoke. The strength of association was similar for both the general population and clinical populations, including patients with mental health disorders.

The possible interpretations of this association are basically three: 1) smoking cessation may be the real cause of the improvement of mental health; 2) an improvement in mental health can facilitate attempts to smoking cessation; 3) a common factor (e.g., a positive life event) may cause both the improvement of mental health and the facilitation of smoking cessation. Even if these observational data cannot prove causality, they can at least reassure doctors and patients, even in the case of individuals with mental illness, that quitting smoking is likely to improve mental health.

As general rule, meta-analysis reflect the limitations of the included studies. For the meta-analysis of Taylor et al. the first limitation is the heterogeneity of the studies evaluated, i.e. study design (cohort studies, secondary analyzes, randomized trials), evaluated sample (general population, patients suffering from a chronic physical disease, post-operative patients, pregnant women, people suffering from physical and/or psychiatric chronic diseases), age of patients, number of cigarettes smoked, degree of dependence, number of cigarettes smoked a day, smoking cessation interventions (psychological and/or pharmacological), duration of follow-up (from 7 weeks to 6 years). Moreover, depending on the studies, several outcomes were analyzed (anxiety and/or depression, health related quality of life, health status, stress) with different tools, some of which are not validated. For example, the study of Hajek et al. evaluated the presence of perceived stress by two simple questions that explore the use of smoking as a coping strategy and the level of stress, with two different response Likert scales. The absence of proved psychomet-
It is noteworthy that other studies support the relationship between mental health status and successful quitting, but authors fail to recognize this difference. Other authors remarked this forced interpretation of causality and suggest the possibility that change in lifestyle rather than smoking cessation itself might have played a role in mental health improvement in successful quitters.

Authors also do not take into account the possible beneficial effect of smoking cessation drugs as varenicline or bupropion on mental health as this was beyond the clinical question explored by the meta-analysis. Benefit seen on mental health in successful quitters might well be related to the modality of the smoking cessation process rather than to the cessation itself. This acquires even more clinical relevance in the view of the recent data on the use of varenicline in patients with stable depression and schizophrenia.

Finally, gender is not considered in this meta-analysis despite suggesting evidence support the correlation between gender and different abstinence behavior, mental health and response to cessation program. Many questions remain open, and it is necessary to have more available data to answer them. First of all, studies that investigate the personal factors that influence the risk of developing a mental disorder after the cessation of smoking - coping strategies, distress tolerance, alexithymia, temperament traits, self-efficacy - are needed. This would help to develop targeted interventions and to evaluate their effectiveness in improving the success of cessation programs.

In addition, as recently pointed out by Leventhal, depression, as well as anxiety, stress, psychological well-being, include cognitive, behavioral, affective and autonomic symptoms. It is possible that some symptomatic expressions may be associated more than others both to smoking habits and smoking cessation. Considering a single descriptive label could make it harder to understand the complex variability of subjective reactions to smoking cessation.
Moreover, data on populations at increased risk of depression and anxiety, such as adolescents and the elderly are missing.

The link between smoking cessation and improved mental health condition brings up the question if smoking surrogates, like e-cigarettes with or without nicotine supplementation, have an impact on Taylor and co-workers findings. The topic is likely to gain more clinical relevance with an expanding market for these products, and enforces the need to understand the causality relation between gesture, life style, nicotine and mental health.

References

29. Sugahara H, Maeba C, Ohtani H, Hanada M, Ando K, Mine K et al. Effect of smoking and CYP2D6 poly-
34. Parrott A. Stress modulation over the day in cigarette smokers. Addiction 1995;90:233-44.
47. Sanderson SC, Taylor A, Munafo M. Article does not prove that smoking cessation has an “effect” on mental health. BMJ 2014;348:g2018.

Received on August 1, 2014.
Accepted for publication on September 17, 2014.