Ventilatory efficiency slope as a predictor of suitability for surgery in chronic obstructive pulmonary disease patients with lung cancer

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Lung cancer is one of the leading cancers with an estimated 1.8 million new cases in 2012 as per WHO estimates. Tobacco smoking is considered to be the key driver causing 70% or more of total lung cancer-related deaths worldwide (1). Lung cancer and chronic obstructive pulmonary disease (COPD) commonly coexist in smokers, and the presence of COPD increases the risk of developing lung cancer by 4–5 folds, even when the smoking history is controlled for (2). Lung cancer may consist of small cell carcinoma and non-small cell carcinomas encompassing squamous cell carcinoma, adenocarcinoma and large cell carcinoma (3). In a recent very comprehensive study by Shafiek and colleagues published in *European Journal of Cardio-Thoracic Surgery*, highlighted the lethal association between COPD and lung cancer and the risk of postoperative complications in these patients considered fit for surgery (4). This publication is a very timely reminder highlighting the importance of this association between COPD/lung cancer and warrants further experimental studies exploring the link between the two and complications associated. Unfortunately, the research effort directed into this has been disproportionately weak compared to its clinical and scientific importance, and indeed, COPD itself is the least researched of all common chronic conditions compared to its social significance (5,6). It is of interest and relevance in this context that up to 70% of lung cancer occurs in the context of mild-to-moderate (not severe) COPD (1,5,7-9).

In COPD patients with lung cancer, lung resection is the preferred method of cure. However, surgery involves increasing postoperative risks and long-term disability such as pneumonia, pulmonary embolism, acute pulmonary oedema, chronic respiratory failure, etc. (4,10). COPD patients undergoing resections also suffer from other co-morbidities such as atherosclerotic cardiovascular disease which further enhances the risk. However, the post-operative risk associated with surgical resection can be mitigated to some degree with the use of preoperative physiological measurements.

Pulmonary functional test (PFT) such as spirometric evaluation of predicted postoperative (PPO) FEV1 capacity along with PPO diffused capacity for carbon monoxide (DLCO) are commonly used as postoperative predictors for surgical complications. However, some evidence questions their independent capacity in predicting postoperative complications (10). One major disadvantage with PFTs is that evaluation of patients is carried out at rest, and best provide pulmonary baseline performance. Cardiopulmonary exercise testing (CPET) is now used extensively to enhance or potentially alternative for PFT as the preferred postoperative predictor. CPET were primarily employed in sports physiology to analyse endurance capacity in elite athletes. They are sophisticated physiologic testing technique capable of measuring multiple physiological parameters in an exercise environment. The instruments measure maximal or peak oxygen consumption (VO_2max), respiratory exchange ratio (RER), minute ventilation (VE) and anaerobic threshold (AT) which is calculated from data collected from CPET gas analysis. VO_2max is the widely used physiological measurement used in exercise tests and are recommended in patients with FEV1 and DLCO <80%

predicted (10). A low peak VO2max is indicative of high risk of postoperative pulmonary complication and death in patients with lung cancer undergoing lung resection.

According to the current guidelines, all patients with VO_2max consumption less than 10 mL/kg/min is considered as at high risk to surgical intervention while those with greater than 10 mL/kg/min and less than 20 mL/kg/min are considered as a moderate risk. Shafiek et al. (4) in their recent publication observed that reliance on VO_2max as an independent predictor of postoperative complication can be counter-indicative for moderate risk lung cancer patients with COPD. They show that the parameters especially VE/VCO_2 as a stronger and better predictor to VO_2max in postoperative complication.

VE is modulated by the metabolic production of CO_2 and a close linear relationship exists between them. Ventilatory efficiency index are determined by calculating the slope derived from their ratio. VE/VCO_2 slope is independent of gender and although it increases with age, normal results are below 30 even into old age. The authors observed that in patients with VE/VCO_2 with slope >35 was increased postoperative complication events in COPD patients. They further reported a significant association of mortality in these patients with a calculated hazard ratio of 2.6. The authors provide parameters that impact ventilatory inefficiency such as percent VE at AT (VT/AT) and VO_2/kg (%) and VO_2 (L/min) which again is associated with the number of overall postoperative complication events. This is interestingly the first study that provides valuable prognostic solutions by relating postoperative complications events after lung resection to that of ventilator efficiency. However, the study was not clear on the number of patients that died of lung cancer recurrence and other co-morbidities after the first year of follow-up. Patients in this study met the GOLD criteria for moderate to severe airflow obstruction, but there is little information on the relationship between severity of COPD and postoperative complications. As major percentage of lung cancer is in the early disease, it is important to know whether severity relates to postoperative complications or if the patient is mild-moderate then the complications are low.

COPD patients are usually on certain pharmacological treatments especially the severe ones and these treatments focus on alleviating symptoms and reducing "infective" exacerbation rates, which are a complex mix of viral and bacterial aetiology. These are mainly long-acting bronchodilators and inhaled corticosteroids (ICS). However, there is a high risk of pneumonia in COPD patients with the use of ICS, which is also a major postoperative complication (11-13). There is substantial evidence in the literature supporting this fact. However, hardly any evidence explaining why exactly ICS increase the risk of pneumonia in COPD patients. In this study, it would be highly beneficial to go back and see how many COPD patients were on ICS and if that is related to the development of postoperative pneumonia. It is not very clear from the current study.

Torchio et al. (14) first reported that a high VE/VCO_2 slope increased the risk of postoperative complication and mortality in COPD patient with non-small cell carcinoma, and no deaths were reported among patients in the normal range. Although, they further observed that peak VO_2 was also important in predicting the severe postoperative occurrence of cardiopulmonary complication (14). Brunelli et al. (15) confirmed these findings in 225 patients that underwent anatomical resections and observed that VE/VCO_2 was again an independently strong predictor of respiratory complication in comparison to VO_2max.

Similarly, high VE/VCO_2 slope has been earlier demonstrated as an independent predictor of disease such as heart failure (HF) (16) idiopathic pulmonary fibrosis (IPF) (17) and in pulmonary hypertension patients with COPD (18). A meta-analysis of 491 published papers found increase in VE/VCO_2 slope equally powerful as peak VO_2 in predicting events in systolic HF and further was suggested to be used in combination with VO_2 peak (19). However, in HF patients with VE/VCO_2 >35 showed increased risk of mortality and was found to be independently a better predictor than VO_2max (20). One of the major advantages of employing resting ventilatory efficiency measurements over maximal oxygen consumption is that it overcomes the challenging condition for patients that need them to achieve peak exercise performance. VE/VCO_2 is determined by two variables: dead space ventilation relative to tidal volume (VD/VT) and arterial $PaCO_2$. The major finding in this study that a VE/VCO_2 >35 at maximal exercise is a better predictor of adverse events such as postoperative complications or mortality than VO_2max is interesting and merits further investigation. However, from a practical point of view it does not remove the need for a maximal exercise test and the associated clinical risk to the patient. The finding that high baseline VE/VCO_2 is also an independent predictor is more relevant from a workload and clinical risk point of view although it must be noted that VD/VT may increase due to hyperventilation during periods of stress or anticipation such as prior to or during

a new test procedure and therefore the obtained result may be less reliable than VE/VCO$_2$ taken during exercise. An alternative may be to gather reliable information from a submaximal exercise workload. This reduces the potential issues associated with resting measurements while reducing clinical risk and stress for the patient, and helps the clinician to strategise other treatment options that would improve their exercise performance (fitness) before undergoing surgical intervention.

Finally, the current study discussed here and previous observation are indicative that ventilatory efficiency parameters especially VE/VCO$_2$ slope are important in predicting postoperative complication in lung cancer patients with COPD undergoing resection. Thus, it becomes imperative that this exercise physiology parameter be considered in future guidelines along with VO$_2$max as a perioperative measurement in lung cancer surgical resections.

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Footnote

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Page 4 of 4

Eapen et al. Postoperative complications in chronic lung disease

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