Original Article

The utility of gradient of end-tidal carbon dioxide between two lungs in lateral decubitus position in predicting a drop in oxygenation during one-lung ventilation in elective thoracic surgery- A prospective observational study

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ABSTRACT

Background and Aims: Baseline difference in the perfusion of two lungs is the cause of intra-operative shunt during one-lung ventilation (OLV). This study aimed to test the hypothesis that the gradient of end-tidal carbon dioxide ($EtCO_2$) between two lungs in lateral position (D-$EtCO_{2lateral}$) would predict the quantity of shunt and hence the drop in the oxygenation during OLV. **Methods:** An observational study was conducted to include consecutive 70 patients undergoing thoracic surgery using a double-lumen tube in a lateral position. D-$EtCO_{2lateral}$ was calculated by subtracting $EtCO_2$ from the non-dependent lung from that of the dependent lung when ventilation parameters are the same for each lung. Oxygenation was assessed by measuring PaO_2/FiO_2 ratios (P/F ratio) at 10, 20 and 40 min after OLV. Correlations between D-$EtCO_{2lateral}$ and P/F ratios were calculated. Receiver operating curves were analysed to test the ability of D-$EtCO_{2lateral}$ to identify patients with a P/F ratio of <100 during OLV. **Results:** A moderate correlation was found between D-$EtCO_{2lateral}$ and P/F ratios at 10 and 20 min of OLV. Among lung resection cases (n = 61), correlation was moderate at 10 (r = 0.64), and 20 min (r = 0.65) (P < 0.001) and became weak at 40 min (r = 0.489, P < 0.001). Areas under curve for D-$EtCO_{2lateral}$ to predict the drop in P/F ratio <100 at 10, 20 and 40 min after OLV were 0.90 (cut-off: 2.5), 0.78 (cut-off: 3.5) and 0.78 (cut-off: 4.5), respectively. **Conclusion:** D-$EtCO_{2lateral}$ could predict the drop in oxygenation in the early part of OLV in lung resection surgeries.

Key words: End-tidal carbon dioxide, one-lung ventilation, oxygenation, thoracic surgery

INTRODUCTION

A primary concern during one-lung ventilation (OLV) is hypoxaemia, defined as the partial pressure of oxygen in the arterial blood (PaO_2) less than 60 mm Hg.[1] An obligatory shunt in the non-ventilated lung is the leading cause of hypoxaemia during OLV.[2,3] Baseline difference in the perfusion of two lungs affects the quantity of intra-operative shunt. Lung cancers, by exerting pressure on the airways, create an area of regional hypoxia within the lung. It initiates hypoxic pulmonary vasoconstriction (HPV), which diverts the pulmonary blood flow to the opposite lung.

A perfusion scan helps assess the baseline difference in perfusion of two lungs and can predict intra-operative hypoxaemia.[4]

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End-tidal carbon dioxide ($EtCO_2$) is the partial pressure of carbon dioxide in expired gas. It is a surrogate marker of perfusion and ventilation of the lung.[5] When the lungs are isolated using a double-lumen tube (DLT), the $EtCO_2$ from the exhaled gases of the lung would indicate the perfusion of that lung, if minute ventilation, anatomical dead space and cardiac output to a lung are constant. Thus, the gradient between $EtCO_2$ values of the two lungs ($D-EtCO_2$) in lateral decubitus (LD) position would indicate the difference in the perfusion of the two lungs. The larger the gradient, the lesser would be the perfusion to the non-dependent lung and the lesser would be the drop in oxygenation during OLV. To test this hypothesis, we conducted a study with the primary objective to find the correlation between $D-EtCO_{2lateral}$ and PaO_2/FiO_2 ratios (P/F ratios) during OLV. Secondary outcomes were the cut-off values of $D-EtCO_{2lateral}$ to identify the patients with severe oxygenation disorder during OLV.

METHODS

A prospective observational study was conducted after the institutional ethics committee's approval and registration with the Clinical Trial Registry of India. The study included consecutive 70 adult patients undergoing elective thoracic surgery with OLV using a DLT in LD position from June 2015 to January 2017 at a tertiary care cancer hospital. Insertion of an arterial cannula was mandatory for inclusion in the study. Use of airway devices other than a DLT, non-insertion of an arterial cannula, surgical position other than LD position and emergency surgeries were considered as exclusion criteria. Written consents were sought from all eligible patients.

In the operation theatre (OT), clinical management of the patient was done by the OT anaesthesiologist, who was not a part of the study team. Readings were noted by the investigator from the study team. Standard monitors (electrocardiogram, pulse-oximeter and non-invasive blood pressure manometer) were applied to the patient. Anaesthesia induction was done using intravenous induction agents and muscle relaxants by the OT anaesthesiologist. Insertion and confirmation of a DLT were performed by the OT anaesthesiologist using a paediatric bronchoscope. Lungs were isolated by adequate inflation of the bronchial cuff of DLT. An artery (radial or dorsalis pedis) was cannulated by the OT anaesthesiologist.

Dräger Primus® anaesthesia workstation (Drägerwerk AG and Co. KGaA, Germany) was used to deliver the gases to the patient. Ventilator settings were as follows:

- For two-lung ventilation (TLV): tidal volume 8 ml/kg ideal body weight (IBW), respiratory rate of 14 per min, the fraction of oxygen in inspired gas (FiO_2) of 0.5 with air and oxygen mixture, and application of positive end-expiratory pressure (PEEP) of 5 cm of water on volume control mode.
- For OLV: tidal volume was 6 ml/kg IBW with PEEP of 5 cm of water, volume control mode. Respiratory rate and FiO_2 settings were managed by the OT anaesthesiologist.

Sufficient depth of anaesthesia was maintained with sevoflurane (minimum alveolar concentration: 0.8–1) and intermittent doses of vecuronium and fentanyl as titrated by the OT anaesthesiologist. Local anaesthetic infusion via an epidural catheter and intravenous fluids were titrated by the OT anaesthesiologist according to the haemodynamic parameters.

The connectors and sample lines were assembled in such a way that the exhaled gas from the individual lung would be directed to the side-stream capnometer, incorporated in the Dräger Primus®Workstation (sampling rate: 50 ml/min) [Figure 1]. Expired tidal volume (ETV) from each lung was measured by the flow sensor of the workstation. Considering the lag time of a capnometer and flow sensor, readings of $EtCO_2$ and ETV were recorded after the completion of six breaths following the switching from one lung to the other. Time gap between the readings from the two lungs was fewer than 40 s. We assumed that the cardiac output would remain same over this short period of time.

In the supine position, both lungs were ventilated with ventilator settings as mentioned above. $EtCO_2$ from each lung was measured alternately and the
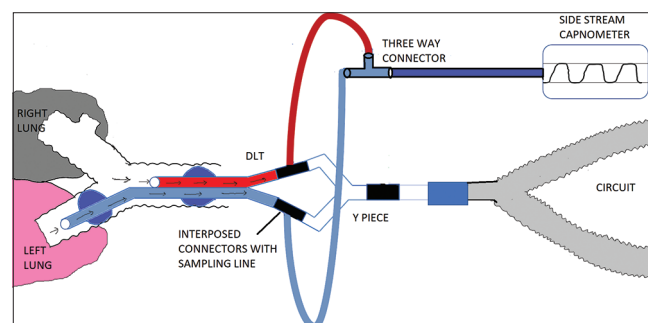
Figure 1: Assembly to measure $EtCO_2$ from two lungs

gradient between $EtCO_2$ values in supine position was measured as

$D\text{-}EtCO_{2supine}$ = $EtCO_2$ from the normal lung − $EtCO_2$ from the diseased lung or lung to be collapsed.

After recording $EtCO_2$ from both lungs, arterial blood was analysed using a standard arterial blood gas (ABG) analyser to calculate the ratio of PaO_2 to set FiO_2 (P/F ratio$_{supine}$).

Ten minutes after turning the patient lateral, the dependent and non-dependent lungs were ventilated with OLV settings alternately and $D\text{-}EtCO_{2lateral}$ was measured as

$D\text{-}EtCO_{2lateral}$ = $EtCO_2$ from dependent lung − $EtCO_2$ from non-dependent lung.

An arterial blood sample was analysed to calculate the P/F ratio$_{lateral}$.

Following this data collection, OLV to the dependent lung began.

During the surgery, arterial blood samples were analysed at 10, 20 and 40-min intervals from the start of OLV to calculate the P/F ratio$_{10}$, P/F ratio$_{20}$ and P/F ratio$_{40}$, respectively.

In case of a drop in oxygenation during OLV (defined as a drop in oxygen saturation less than 96% for more than 1 min), ABG was repeated to note the P/F ratio. Oxygenation was restored by using standard rescue manoeuvres as per the discretion of the OT anaesthesiologist.

To reject the null hypothesis of no correlation with a power of 0.8 and an alpha error of 0.05, a sample size of 13 patients is required if a moderate correlation is expected, that is, r = 0.70. Yamamoto *et al*.[6] found a moderate correlation (r = 0.69, *P* < 0.01) between $D\text{-}EtCO_2$ and P/F ratio at 15 min after OLV in 18 patients undergoing lung surgery. Hence, considering the non-interventional design of the study and to test correlation in the later part of OLV, we chose the sample size as 70 patients. We performed a post-hoc subgroup analysis of the patients who underwent lung resection surgeries for lung cancers (n = 61).

Data were analysed using Statistical Package for the Social Sciences software (International Business Machines Corporation, Version 21.0. Armonk, United States of America). The normality of the data was tested using the Shapiro–Wilk test. Bivariate correlation analysis between $D\text{-}EtCO_{2lateral}$ and P/F ratios at various time points during OLV was performed. Spearman's rank correlation coefficients were calculated if data were not normally distributed. For normally distributed data, Pearson correlation coefficients were computed. Interpretation of correlation coefficient was done as follows: negligible (0.00 < r < 0.10), weak (0.10 < r < 0.39), moderate (0.40 < r < 0.69), strong (0.70 < r < 0.89) and very strong (r > 0.90).[7] Correlation was considered as significant if the two-tailed test of significance demonstrated *P* < 0.05. Receiver operating characteristic (ROC) curves were plotted for testing the ability of $D\text{-}EtCO_{2lateral}$ to identify the patients with a drop in the P/F ratio below 100, at 10, 20 and 40 min after the start of OLV. The optimal cut-off values of $D\text{-}EtCO_{2lateral}$ were determined by considering the values that maximised sensitivity and specificity.

RESULTS

Data of 70 American Society of Anesthesiologists (ASA) physical status I-III patients undergoing elective thoracic surgery using right- or left-sided DLT were considered for the analysis [Figure 2 and Table 1].

When considered for all 70 cases, we found a moderate and significant correlation between $D\text{-}EtCO_{2lateral}$ and P/F ratios at 10 (r = 0.52, *P* < 0.001) and 20 min (r = 0.52, *P* < 0.001) from the start of OLV. However, at 40 min, the correlation became weaker (r = 0.40, *P* = 0.01) [Table 2]. Correlation coefficients between
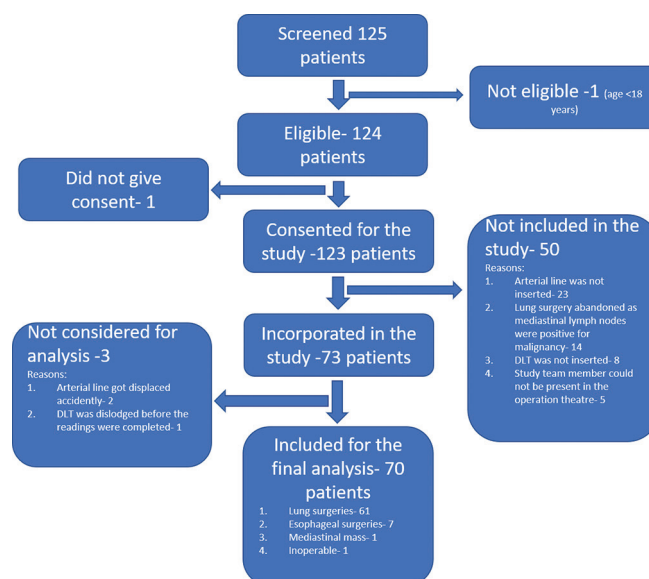
Figure 2: CONSORT diagram for recruitment of patients

D-EtCO$_{2lateral}$ and P/F ratios were significantly better when left lung was ventilated (n = 47) as compared to when right lung was ventilated (n = 23) (0.71, 0.72 and 0.56 versus 0.46, 0.49 and 0.30 at 10, 20 and 40 min of OLV respectively; $P < 0.001$).

In a subgroup analysis of 61 cases undergoing lung resection surgery, the correlations between D-EtCO$_{2lateral}$ and P/F ratios at 10 (r = 0.64, $P < 0.001$) and 20 min (r = 0.65, $P < 0.001$) were moderate and significant but became weaker at 40 min after the start of OLV (r = 0.489, $P < 0.001$) [Figure 3]. In oesophageal surgeries (n = 7), the correlations between D-EtCO$_{2lateral}$ and P/F ratios at 10, 20 and 40 min after the start of OLV were inverse and non-significant (r = −0.664, $P = 0.104$; r = −0.290, $P = 0.528$; and r = −0.110, $P = 0.814$, respectively).

Among patients undergoing lung resection surgery (n = 61), the ability of D-EtCO$_{2lateral}$ to identify the patients who had a drop in the P/F ratios below 100 at 10, 20 and 40 min after OLV was tested using the ROC curve analysis. Areas under curve for D-EtCO$_{2lateral}$ were 0.90 ($P = 0.004$), 0.78 ($P = 0.007$) and 0.78 ($P = 0.01$) at 10, 20 and 40 min after the start of OLV, respectively. The optimal cut-off values for D-EtCO$_{2lateral}$ were 2.5 (sensitivity: 100%, specificity: 84%), 3.5 (sensitivity: 89%, specificity: 65%) and 4.5 (sensitivity: 100%, specificity: 55%) at 10, 20 and 40 min after the start of OLV, respectively [Figure 4].

Nine patients suffered desaturation, which occurred after 40 min of OLV. They received interventions, such as an increase in the FiO$_2$ (9 patients), recruitment and increase in the PEEP (6 patients), and application of continuous positive airway pressure (CPAP) to non-ventilated lung (1 patient), to restore the oxygenation. Mean D-EtCO$_{2lateral}$ in these patients was 2.7 ± 1.7. Mean P/F ratio at the time of the event was 71.1 ± 9.8. Weak correlation was found between D-EtCO$_{2lateral}$ and P/F ratio in these patients (r = 0.39, $P = 0.03$). None of the patients had any other intraoperative complications. We found no post-operative mortality among the study patients.

DISCUSSION

We found that D-EtCO$_{2lateral}$ had a moderate and significant correlation with the P/F ratios during the early part of OLV in lung resection surgeries. In addition, D-EtCO$_{2lateral}$ identified the patients who had a drop in P/F ratio below 100 in the early part of OLV. However, the strength of the correlation and the

Table 1: Baseline demographics of sample population	
Variable	**Values**
Age (mean±SD) in years	52.35±12.3
Male:Female	55:15
ASA status 1:2:3	32:30:8
Lung resection surgery:oesophageal surgery: thymoma resection:inoperable	61:7:1:1
Baseline lung function tests (all values in % predicted) (mean±SD)	
FEV1 in all patients (*n*=70)	67.41±8.4%
FEV1 in patients undergoing lung resections (*n*=61)	66.77±8.3%
FVC in all patients (*n*=70)	77.15±8.4%
FVC in patients undergoing lung resections (*n*=61)	77.16±8.2%
Extent of lung resections (*n*=61)	
Pneumonectomy (Right:Left)	6:5
Upper Lobectomy (Right:Left)	10:10
Middle Lobectomy (Right:Left)	3:0
Lower Lobectomy (Right:Left)	9:8
Bi-lobectomy (Right:Left)	9:0
Metastatectomy (Right:Left)	1:0
Histology of tumours	
Lung resection surgeries-Adenocarcinoma: Squamous cell carcinoma: Neuroendocrine tumours: mesothelioma: others	36:11:6:4:4
Oesophageal surgeries-Squamous carcinoma: Adenocarcinoma	6:1
Open thoracotomy: VATS: Robotic surgery	48:17:5
Left side DLT: Right side DLT	55:15
Right lung ventilated: left lung ventilated	23:47

ASA - American Society of Anesthesiologists, FEV1 - Forced expiratory volume in 1 second, FVC - Forced vital capacity, VATS - Video-Assisted Thoracoscopic Surgery, DLT - Double Lumen Tube, SD - Standard deviation
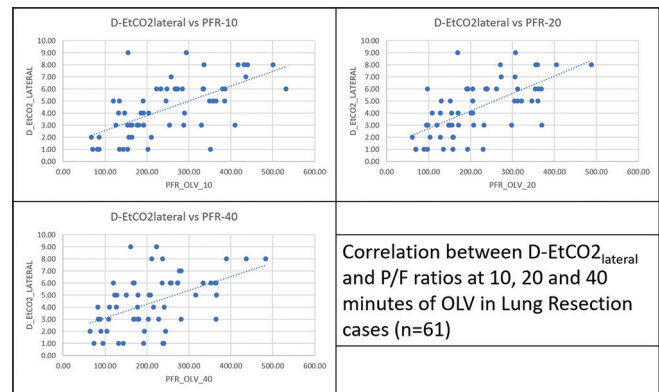
Figure 3: Scatter graph for correlation between D-EtCO$_{2lateral}$ and P/F ratios during OLV in lung resection cases

predictive ability of D-EtCO$_{2lateral}$ became weaker in the latter part of OLV. Yamamoto *et al.*[6] found a moderate correlation between D-EtCO$_{2lateral}$ and oxygenation at 15 min during OLV in 18 patients undergoing lung surgeries. Our study tested the correlation over a longer period of time during OLV by involving a larger sample population and tested the predictive ability of D-EtCO$_2$.

Various predictors of hypoxaemia during OLV are side of the surgery, the position of the patient during surgery, preoperative pulmonary function tests and difference

Table 2: Timeline of the study, ventilation and oxygenation parameters				
Order	Steps	Variable	Mean±SD	Median
1	TLV in supine position	Tidal volume- right lung	458.2±50.1 ml	452.2 ml
		Tidal volume- left lung	448.7±32.3 ml	445.1 ml
		$EtCO_2$ from normal lung	38.2±1.3 mm Hg	37.8 mm Hg
		$EtCO_2$ from diseased lung	36.5±1.2 mm Hg	36.0 mm Hg
		$D\text{-}EtCO_{2supine}$	1.7±1.7 mm Hg	1.0 mm Hg
2	ABG in supine position on TLV	$P/F\ ratio_{supine}$	354.7±132.6	384.4
3	Change of position from supine to lateral decubitus			
4	Alternate OLV in lateral decubitus position	Tidal volume - right lung	330.3±35.1 ml	330.0 ml
		Tidal volume- left lung	329.9±35.6 ml	333.0 ml
		$EtCO_2$ from dependent lung	41.4±7.0 mm Hg	40.0 mm Hg
		$EtCO_2$ from non-dependent lung	37.2±7.2 mm Hg	35.5 mm Hg
		$D\text{-}EtCO_{2lateral}$	4.2±2.4 mm Hg	4.0 mm Hg
5	ABG in lateral position on OLV	$P/F\ ratio_{lateral}$	376.2±109.8	392.3
6	Commencement of OLV to dependent lung			
7	ABG at 10 min after start of OLV	$P/F\ ratio_{10}$	240.2±111.5	207.5
8	ABG at 20 min after start of OLV	$P/F\ ratio_{20}$	203.3±100.6	180.4
9	ABG at 40 min after start of OLV	$P/F\ ratio_{40}$	205.1±93.8	193.0
10	ABG at the time of interventions to correct drop in oxygenation			

TLV - Two lung ventilation, OLV - One lung ventilation, $EtCO_2$ - End-tidal carbon dioxide, P/F ratio - ratio of partial pressure of oxygen in arterial blood to fraction of oxygen in the inspired gas, $D\text{-}EtCO_2$ - difference between EtCO2 values of two lungs, ABG - Arterial blood gases
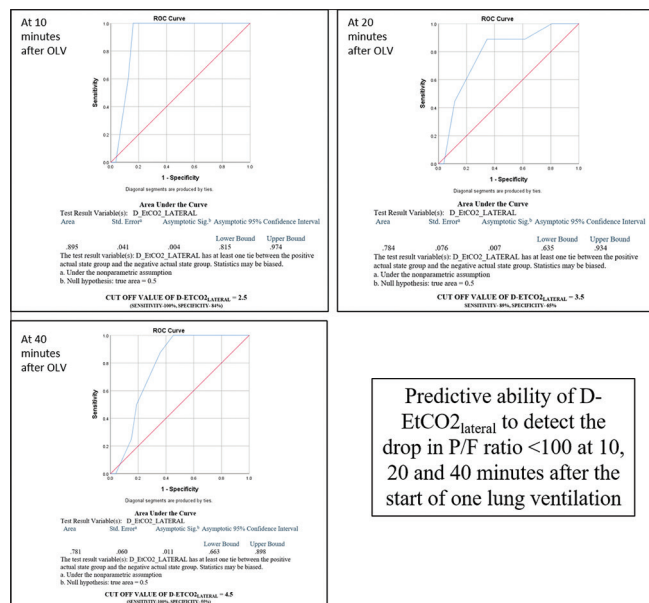

Figure 4: ROC curve analysis for predictive ability of $D\text{-}EtCO_{2lateral}$

in perfusion of the two lungs.[3] These predictors help anaesthesiologists to prepare for likely hypoxaemia during OLV. Although the use of minimal FiO_2 is an accepted principle of protective one-lung ventilation, a low value of $D\text{-}EtCO_{2lateral}$ can identify the patients in whom high FiO_2 may be required in the early part of OLV.[8,9] In addition, the necessary equipment to counteract hypoxaemia (e.g., CPAP device) can be arranged. Prediction of hypoxaemia is important in patients with cardiovascular co-morbidities where hypoxaemia is poorly tolerated.[10] In principle, $D\text{-}EtCO_{2lateral}$ identifies the difference in baseline

perfusion of two lungs, similar to perfusion scan.[11] Hence, $D\text{-}EtCO_{2lateral}$ may be helpful in those institutes where the facility of perfusion scan is not available. However, $D\text{-}EtCO_{2lateral}$ neither measures the regional lung function nor predicts the postoperative lung function. However, $D\text{-}EtCO_{2lateral}$ takes into account the effect of gravitational distribution of pulmonary blood flow. We noted a rise in $D\text{-}EtCO_2$ gradient when the patients were turned from supine to lateral. This is the reason why we chose $D\text{-}EtCO_{2lateral}$ over $D\text{-}EtCO_{2supine}$ to correlate with the P/F ratios.

We found that $D\text{-}EtCO_{2lateral}$ correlated better with P/F ratios in lung resection surgeries but not in oesophageal surgeries. The reason for this difference could be the fact that the lungs in oesophageal cancer surgeries are essentially normal and tumour-related diversion of pulmonary blood flow does not occur in these patients. Moreover, the numbers of oesophageal surgeries (n = 7) were too low to draw any inference.

Another interesting finding was that the correlation between $D\text{-}EtCO_{2lateral}$ and P/F ratio was significantly stronger when the left lung was ventilated as compared to the cases when the right lung was ventilated. It could be because the right lung receives more blood flow than the left. Hence, the shunt fraction is high when the left lung is ventilated and the right is collapsed. We found that the correlation between $D\text{-}EtCO_{2lateral}$ and intra-operative P/F ratios became weak at 40 min after OLV. HPV could be a possible reason for this finding. Complete effect of HPV sets in at approximately 30–

40 min after OLV.[12] As HPV modifies the perfusion in the latter part of OLV, the predictive ability of D-EtCO$_{2\text{lateral}}$ becomes weak. However, we cannot ascertain this cause as we did not measure the shunt during OLV. In addition, the cause of hypoxaemia during the early part of OLV is the obligatory shunt in the non-ventilated lung, but in the latter part, hypoxia can occur due to additional reasons like- atelectasis in the ventilated lung, displacement of DLT, etc. These findings limit the clinical utility of D-EtCO$_{2\text{lateral}}$ to the early part of OLV.

Ideally, the difference in the EtCO$_2$ values between the two lungs should be measured when both the lungs are ventilated using two different ventilators delivering the same tidal volume simultaneously. However, the arrangement of such an assembly would be practically impossible. In addition, cardiac output may vary at the time of recording two readings of EtCO$_2$. These limitations weaken the internal validity of the study. Although the study is powered to reject the null hypothesis of no correlation between D-EtCO$_{2\text{lateral}}$ and P/F ratios during OLV, it is grossly underpowered to find the correlation between D-EtCO$_{2\text{lateral}}$ and the incidence of hypoxaemia during OLV (PaO2 < 60 mm Hg). A low P/F ratio does not necessarily mean clinical desaturation.[13] As the incidence of hypoxaemia during OLV dropped below 4%, a larger sample size (nearly 450 cases) would be required to find the correlation between D-EtCO$_{2\text{lateral}}$ and hypoxaemia during OLV.[2] The inherent limitations of post-hoc sub-group analysis (e.g., false positives due to multiple comparisons, false negatives due to inadequate power, etc.) apply to this study as well. Hence, the sub-group analysis of lung cancer patients is severely underpowered (estimated power = 20%) to find the correlation with the incidence of hypoxaemia. Lastly, the use of protective one-lung ventilation, and pressure control mode would have improved oxygenation parameters during OLV.[9,14] We acknowledge these limitations of our study.

CONCLUSION

We found that D-EtCO$_{2\text{lateral}}$ had a moderate correlation with the P/F ratios, and predicted the drop in P/F ratio in the early part of OLV in patients of lung resection surgeries. However, the strength of correlation and predictive ability of D-EtCO$_{2\text{lateral}}$ became weak in latter part of OLV.

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Conflicts of interest
There are no conflicts of interest.

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