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Patterns of changes and diagnostic values of FEF50%, FEF25%-75% and FEF50%/FEF25%-75% ratio in patients with varying control of bronchial asthma

Mohamed Faisal Lutfi

Department of Physiology, College of Medicine, Qassim University, KSA
Faculty of Medicine and Health Sciences, Al-Neelain University, Khartoum, Sudan

Abstract

Background: The pattern of change in FEF50%, FEF25%-75% and FEF50%/FEF25%-75% ratio depends on mechanics of forceful expiration, provided that non-homogenous lung emptying is faithfully recorded in the expiratory flow-volume loops.

Objective: To assess the potential clinical value of FEF50%, FEF25%-75% and FEF50%/FEF25%-75% ratio as an indicator of bronchial asthma (BA) control.

Methodology: The study involved 75 patients with BA matched for age and gender with 45 non-asthmatic subjects. Based on asthma control test (ACT) and spirometry, asthmatic patients were subdivided into controlled and poorly controlled/uncontrolled. The relationship between FEF50% and FEF25%-75% as well as FEF50%/FEF25%-75% ratio and ACT score were assessed using linear regression. ROC curves were used to assess reliability of FEF25%-75% and FEF50% to diagnose BA in patients with different degree of asthma control.

Results: FEF50% correlated strongly with FEF25%-75% (r = 0.989, P < 0.001) and the relationship between the two indices is governed by the formula FEF50% = 1.132* FEF25%-75% – 0.003. There was no significant correlation (r = - 0.159, P = 0.083) between FEF50%/FEF25-75% ratio and ACT score. The diagnostic capability of FEF25%-75% for spirometric diagnosis of BA is only marginally better compared to FEF50% (area under ROC curves were 0.88 and 0.89 respectively, P < 0.001); however, diagnostic power of both spirometric indices deceased with poor BA control.

Conclusion: FEF50%/FEF25%-75% has no clinical value as an indicator for BA control. Role of FEF25%-75% in evaluation of BA is marginally better than FEF50%; however, efficiency of both indices declined substantially as BA control worsened.

Keywords: Asthma control test, Bronchial Asthma, flow volume loop, FEF50%, FEF25%-75%.

Correspondence:

Mohamed Faisal Lutfi
Department of Physiology,
College of Medicine, Qassim University, KSA
Faculty of Medicine and Health Sciences, Al-Neelain University,
Khartoum, Sudan
Mailbox: 12702 – code: 11121
Tel: +249912257731 - +966507675335
Fax: +2499183797836
Email: mohamedfaisallutfi@gmail.com

Introduction

Expiratory flow-volume loops (EFVL) are exceptionally useful for evaluation of bronchial asthma (BA). [1-3] Imaging studies demonstrated strong correlations between EFVL-derived spirometric indices and some measures of airways obstructions like air trapping. [4] To the trained eye, the pattern of lung ventilatory defect is easy predictable from the configuration of EFVL. [5] In depth review of EFVL-derived spirometric indices will not only reflect severity of obstructive ventilatory defects, but also the size of airways involved. [6] In cases of BA, forced expiratory flows (FEFs) measured at mid-portion of EFVL, namely FEF50% and FEF25%-75%, are efficient in assessing airways narrowing. [7] However, there are considerable debates in the literature on whether FEF50% or FEF25%-75% is more effective to reflect ventilatory function in patients with BA. [6-10]

Mathematically, whether FEF50% is an average of FEF25%-75% or they are just correlated depends on the downslope of EFVL and consequently pattern of lung emptying during forceful expiration. Physiologically, forceful lung emptying depends on its time constant (TC), which is determined by airways resistance (AR) and pulmonary compliance (PC) as follows: TC = AR*PC. [11] The rate of change in TC determines curvilinearity of EFVL downslope, which in turn determine the relationship between FEF50% and FEF25%-75%. [12,13] If the lungs empty mono exponentially with a single time constant, FEF50% and FEF25%-75% are expected to correlate linearly and to have almost constant FEF50%/FEF25%-75% ratio. Alternatively, increased TC in patients with BA is expected to induce non-homogenous lungs emptying and enhance curvilinearity of EFVL downslope. [14] At least two separate studies were able to prove steeper slope of EFVL between 25%-50% than between 50%-75% in patients with BA or other obstructive pulmonary diseases. [14, 15] It follows that FEF50%/ FEF25%-75% ratio is expected to increase with the increase in TC, provided that non-homogenous lung emptying is faithfully recorded in EFVL. However, several studies claimed that configuration of EFVL may underestimate non-homogeneous regional lung emptying, [16-18] which make the role of FEF50%/FEF25%-75% ratio questionable if used for evaluation of BA.

The aims of this study are to assess the relationship between FEF50% and FEF25%-75% and their role in assessment of BA control. In addition the potential clinical value of FEF50%/FEF25%-75% ratio as an indicator of asthma control was evaluated.

Methods

The study received ethical clearance from the ethics review committee at the faculty of medicine – University of Khartoum – Sudan. Informed written consents were signed by all volunteers before being involved in the study.

The study involved a test group of 75 patients with BA (AP) but no or other chronic respiratory diseases (38 males and 37 females), matched for age, gender and body mass index (BMI) with a control group of 45 apparently healthy subjects (HS) (22 males and 23 females). Asthmatic patients were mostly recruited from the outpatient clinics of the teaching hospitals in Khartoum state – Sudan. Alternatively, subjects of the control group were recruited from staff members of Al-Neelain University - Khartoum – Sudan. Absence of current or past history of smoking was ensured in both groups.

Studied subjects were evaluated in the morning between 09.00 and 12.00 am to avoid possible influences of circadian rhythm on the spirometric measurements. Asthma control test (ACT) was used to assess asthma severity at the time of examination. [19,20] Asthmatic patients whose ACT score > 19 were labeled as controlled AP (CAP) while those who scored ≤ 19 were considered poorly/uncontrolled AP (UAP). Weight and height were measured by GIMA scale (Professional Medical Products - Italy). Body mass index (BMI) was calculated using the formula: BMI (Kg/m^2) = Weight (Kg) / Height (m^2). Spirometry was performed using Allflow Spirometer (Version 5.18 - Clement Clarke International Limited – U. K). Special care was given for End of Test (EOT) criteria and other ATS/ERS standards while performing spirometry for the studied subjects. [5, 21]

Statistical evaluation was performed using the SPSS for windows (version 16; Chicago, IL). Skewed variables were further assessed by Shapiro-Wilk test to evaluate distribution curves of the studied variables. Unpaired T-test was used to assess statistical difference of the mean for normally distributed scaled variables; and the results were expressed in tables that compares means and standard deviations (mean (SD)) of the corresponding variable. Alternatively, significant statistical differences of abnormally distributed scaled variables were assessed by comparing median and 25–75 inter quartile (Q1 – Q3) using Mann-Whitney U test. Logarithmic scale was used to normalize distribution of FEF50% and FEF25%-75%. Using one sample T test, synchrony of Log FEF50% and Log FEF25%-75% readings was evaluated by assessing if the means of their algebraic difference is significantly above zero. The relationship between Log FEF50% and Log FEF25%-75% were assessed using linear regression model. Efficiency of FEF50%/FEF25%-75% ratio as an indicator of asthma control was evaluated by assessing Spearman's bivariate correlation between this ratio and ACT score. Receiver Operating Characteristic (ROC) curves were used to assess reliability of FEV1%, FEF50%, FEF25%-75% and FEF50%/FEF25%-75% ratio to diagnose BA in different ACT groups. $P < 0.05$ was considered significant.

Results

Males constitute 48.9% (95% CI = 35.0-63.0%) and 50.7% (95% CI = 39.6-61.7%) of the control and test groups respectively. Gender distribution was not significantly different among studied groups ($chi^2 = 0.36$, $P = 0.850$). Age, weight, height and body mass indices were comparable in asthmatic and non-asthmatic subjects (table 1).

Table 1: Age, weight, height and BMI of the studied groups

	HS N=45 Mean (SD) Median (Q1-Q3)	**AP N=75 Mean (SD) Median (Q1-Q3)**	**Significance**
Age (Years)	25.0 (23.0 - 29.0)	27.0 (24.0 - 30.0)	0.071
Weight (Kg)	63.2 (55.9 - 74.3)	63.3 (54.5 - 75.0)	0.803
Height (Cm)	165.8 (7.41)	166.1 (10.1)	0.848
BMI (Kg/m2)	23.6 (20.4 - 26.7)	22.7 (19.7 - 27.1)	0.605

Comparison between means (SD) (or median (Q1 – Q3)) confirms that distribution spirometric measurements is well aligned with asthma severity (table 2). The differences between Log FEF50% and Log FEF25%-75% indices (M (SD) = 0.05(0.04) L/Sec) were significantly above zero (P < 0.001). FEF50% correlated strongly with FEF25%-75% ($r = 0.99$, $P < 0.001$) and the relationship between the two indices is governed by the formula Log FEF50% (L/Sec) = 0.98*Log FEF25%-75% (L/Sec) + 0.06 (figure 1) or FEF50% = 1.132* FEF25%-75% – 0.003 in non-logarithmic scale. As shown in table 3, there was no significant correlation between FEF50%/FEF25-75% ratio and ACT score ($r = -0.080$, P = 0.494). In contrast, FEF50% ($r = 0.417$, P < 0.001) and FEF25%-75% ($r = -0.433$, P < 0.001) correlated significantly with ACT score. Based on ROC curves analysis, the diagnostic capability of FEF25%-75% for spirometric diagnosis of BA is only marginally better compared to FEF50% (figure 2). ROC curves of FEF50% and FEF25%-75% were comparable in different categories of BA severity; however, diagnostic power of both spirometric indices increased in UAP (figure 2). Alternatively, FEF50%/FEF25%-75% ratio had poor performance in identifying BA.

Table 2: ACT Scores and spirometric measurements of the studied groups

	HS Mean (SD) Median (Q1-Q3)	CAP Mean (SD) Median (Q1-Q3)	UAP Mean (SD) Median (Q1-Q3)	Significance
ACT Score		22.0 (20.5 -23.0)	14.0 (11.8 - 17.0)	CA vs. UA P < 0.001*
FEV1	3.2 (0.7)	2.7 (0.9)	2.2 (0.8)	HS vs. CA P = 0.039* HS vs. UA P < 0.001* CA vs. UA P = 0.053
FVC	3.6 (0.8)	3.2 (0.8)	3.1 (1.0)	HS vs. CA P = 0.185 HS vs. UA P = 0.021* CA vs. UA P = 0.903
FEV1%	90.5 (5.6)	83.9 (10.9)	77.4 (14.7)	HS vs. CA P = 0.077 HS vs. UA P < 0.001* CA vs. UA P = 0.001*
PEFR (L/sec)	7.4 (1.7)	6.2 (2.1)	4.9 (1.5)	HS vs. CA P = 0.041* HS vs. UA P < 0.001* CA vs. UA P = 0.004*
FEF25% (L/Sec)	6.8 (1.6)	5.4 (2.1)	4.5 (1.8)	HS vs. CA P = 0.15* HS vs. UA P < 0.001* CA vs. UA P = 0.004*
FEF50% (L/Sec)	4.7 (3.7 - 6.0)	3.2 (2.2 -4.7)	2.1 (1.1 - 3.2)	HS vs. CA P = 0.006* HS vs. UA P < 0.001* CA vs. UA P = 0.032*
FEF25%-75% (L/Sec)	4.1 (3.3 - 5.1)	3.0 (1.9 -3.9)	1.8 (0.9 - 2.8)	HS vs. CA P = 0.004* HS vs. UA P < 0.001* CA vs. UA P = 0.015*
FEF75% (L/Sec)	2.1 (1.7 - 2.6)	1.6 (0.7 -2.1)	0.8 (0.4 - 1.3)	HS vs. CA P = 0.026* HS vs. UA P < 0.001* CA vs. UA P = 0.010*
FEF50%/FEF25%-75%	1.1 2 (1.09 - 1.15)	1.10 (1.06 -1.17)	1.1 7 (1.10 -1.19)	HS vs. CA P = 0.758 HS vs. UA P = 0.036* CA vs. UA P = 0.135

Figure 1: Relationship between FEF50% and FEF25-75%

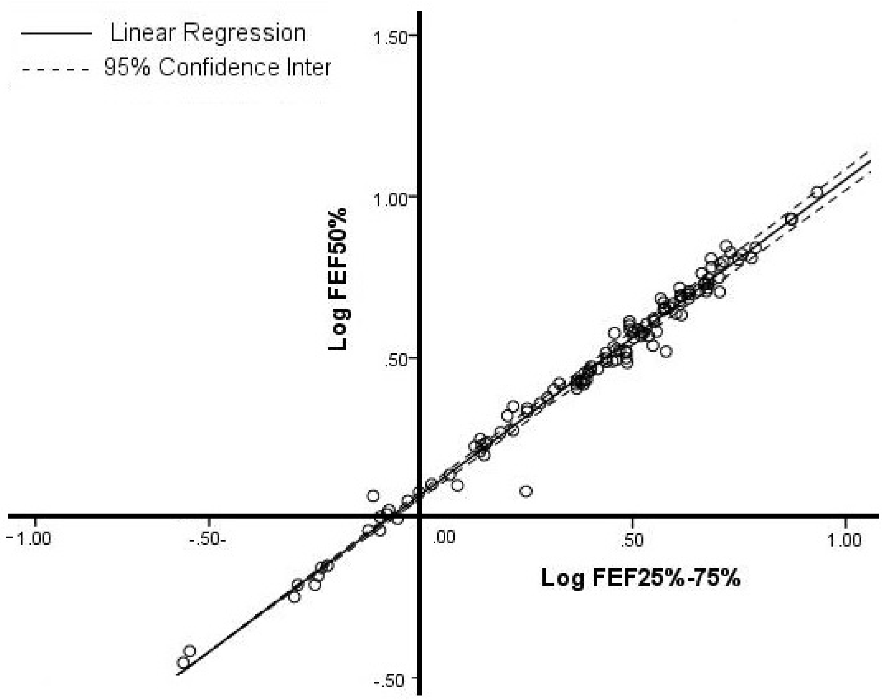
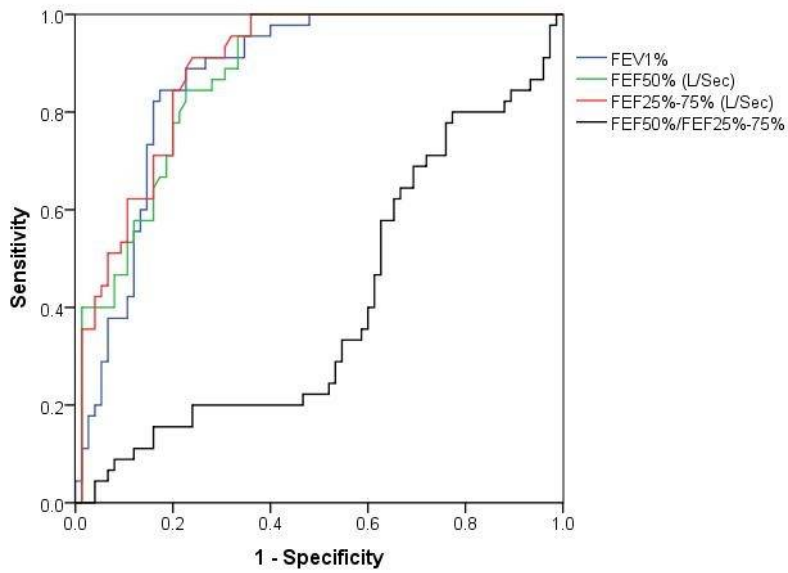


Table 3: Coreelation between spirometric measurements and ACT score in AP

	r	P
FEV1 (L)	0.306	0.008*
FVC (L)	0.096	0.414
FEV1%	0.450	<0.001*
PEFR (L/sec)	0.290	0.012*
FEF25% (L/Sec)	0.377	0.001*
FEF50% (L/Sec)	0.417	< 0.001*
FEF25%-75% (L/Sec)	0.433	< 0.001*
FEF75% (L/Sec)	0.432	< 0.001*
FEF50%/FEF25%-75%	-0.080	0.494

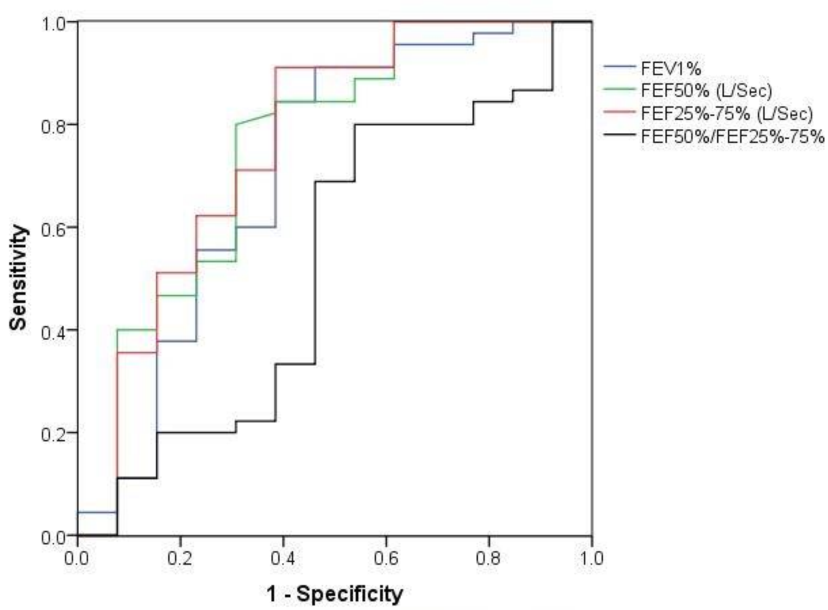
Figure 2: ROC curve analysis of FEV1%, FEF50%, FEF25%-75% and FEF50%/FEF25%-75% in different studied groups

A. Non-Asthmatic VS. Asthmatic Subjects



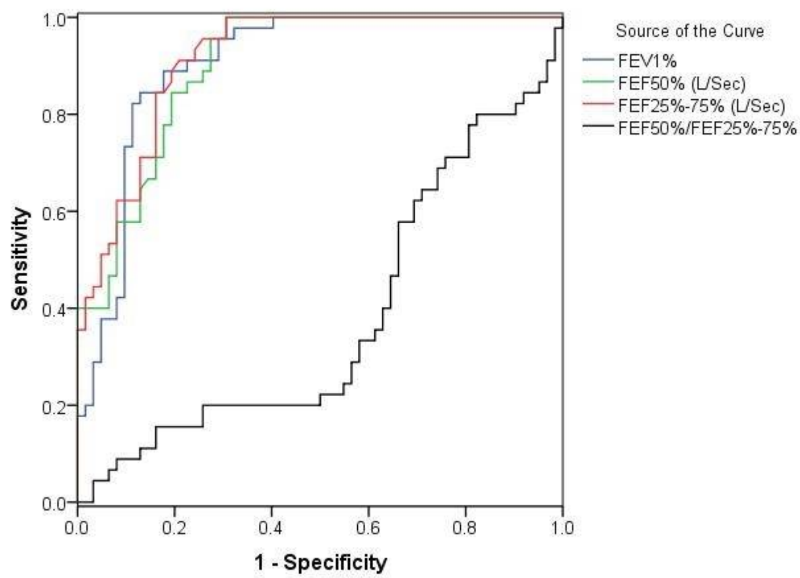
s	Area	95% CI	P
FEV1%	0.871	0.807 - 0.934	< 0.001
FEF 50% (L/Sec)	0.875	0.815 - 0.935	< 0.001
FEF 25% -75% (L/Sec)	0.890	0.834 - 0.946	< 0.001
FEF 50% /FEF 25% -75%	0.406	0.301 – 0.512	0.086

B. Non-Asthmatic VS. Controlled Asthmatic Subjects



	Area	95% CI	P
FEV1%	0.711	0.523 - 0.899	0.021
FEF 50% (L/Sec)	0.753	0.581 - 0.925	0.006
FEF 25% -75% (L/Sec)	0.764	0.592 - 0.936	0.004
FEF 50% /FEF 25% -75%	0.528	0.329 - 0.727	0.758

C. Non-Asthmatic VS. Poorly/Uncontrolled Asthmatic Subjects



	Area	95% CI	P
FEV1%	0.904	0.846 - 0.962	< 0.001
FEF 50% (L/Sec)	0.901	0.845 - 0.956	< 0.001
FEF 25% -75% (L/Sec)	0.916	0.866 - 0.966	< 0.001
FEF 50% /FEF 25% -75%	0.381	0.271 - 0.490	0.036

Discussion

The current results revealed three main findings: firstly, FEF50% and FEF25%-75% are strongly correlated. Secondly, the diagnostic value of FEF25%-75% for evaluation of asthma control was only marginally better compared to FEF50%; however, efficiency of both indices increases as asthma control worsened. Lastly, no significant clinical value was noted for FEF50%/FEF25%-75% ratio as an indicator of asthma control. It is worth mentioning that the present findings are reinforced by the well-established study design, where age, gender and anthropometric measurements were matched between studied groups to guard against their confounding effects on spirometry. [5, 21] In addition, evaluation of asthma severity was based on a clinically sound measure [19, 20] and was further validated by spirometric measurements. [6, 7]

In the late seventies of the last century, the intimate relationship between FEF50% and FEF25%-75% was demonstrated by Ligas *et al* in a small sample of 22 patients with cystic fibrosis. [22] By the beginning of the current century, Bar-Yishay *et al* were able to reproduce findings of Ligas *et al* after studying 1.350 forced expiratory maneuvers. [23] According to Bar-Yishay *et al*, FEF50% correlated with FEF25%-75% as follows: FEF50% (L/Sec) = 1.136*FEF25%-75% (L/Sec) + 0.041, r = 0.956, P < 0.001. In comparison, the present study demonstrated that relationship between the two spirometric indices is governed by the formula: FEF50% (L/Sec) = 1.132* FEF25%-75% (L/Sec) – 0.003, r =0.990, P < 0.001. Given these two formulae, it is evident that the absolute values of FEF50% and FEF25%-75% are proportional with a more or less constant FEF50/FEF25–75 ratio. This assumption is further supported by Douglas who considered FEF50/FEF25–75 ratio equal to 1.10. [24] The constant FEF50%/FEF25%-75% ratio points to two important implications: firstly, FEF50% and FEF25%-75% are linearly correlated, but their absolute values were marginally different. Based on the present findings, Bar-Yishay *et al* and Douglas, FEF50% is only 10%-15% higher than FEF25%-75%. The minor differences between FEF50% and FEF25%-75% readings are further supported by the current results which demonstrate that the means of (FEF50% - FEF25%-75%) are slightly above zero, nonetheless statistically significant. Secondly, constancy of FEF50%/FEF25%-75% ratios in asthmatic patients precludes this parameter as an indicator of BA control and probably obstructive ventilatory diseases in general. This conclusion is reinforced by failure of our result to demonstrate significant correlation between FEF50%/FEF25-75% ratios and ACT scores.

Absence of significant correlation between FEF50%/FEF25-75% ratio and indicators of BA control does not necessarily means that the lungs of BA patients empty monoexponentially with a single TC. Alternatively, it suggested FEF50%/FEF25-75% ratio is an inappropriate indicator of non-homogeneous lung emptying, probably due to compensatory mechanisms at the alveolar level. [16-18] ROC curve analysis of FEF50% and FEF25%-75% in patients with varying degree of asthma control demonstrate that reliability of FEF25%-75% for evaluation of asthma severity is highly comparable with FEF50%. Noteworthy, some previous reports, [6-8] but not others, [9] suggest that FEF25%-75% is more sensitive than FEF50% for evaluation of BA control. According to Valletta *et al*, FEV1 and PEFR were, respectively, normal in 69% and 92% subjects with abnormally reduced FEF25%-75%. [10] FEF25%-75% was the only reduced spirometric measurement in 12% of the asthmatic children studied by Lebecque *et al* [8] In a separate study, FEF25%-75% was more efficient than FEF50% in discriminating uncontrolled from poorly controlled asthmatic patients. [7] Alternatively, Murray *et al* reported that FEF50% was more sensitive than FEF25%-75% in detection of early and late onset asthma; nonetheless it was the only spirometric index which demonstrated false positive BA diagnosis. [9]

Accordingto the present results, the capability of FEF25%-75% for spirometric evaluation of BA is almost as effective as FEF50%; however, diagnostic power of both spirometric indices increased with poor BA control. In contrast, several reports demonstrated insensitivity of maximum expiratory flow-volume curve configuration to reflect non-homogeneous lung emptying in patients with obstructive ventilatory defects. [16-18] Using an alveolar capsule technique, McNamara *et al* studied the evolution of alveolar pressure heterogeneity during the course of forced expiration. [17] Changes in the flow-volume loops obtained by McNamara *et al* from six anesthetized open-chest dogs failed to reflect heterogeneity of alveolar pressure after provocation of airways narrowing. Improved air flow in well ventilated lung zones seemed to compensate for the weak flow in poorly ventilated zones and therefore nullifies upstream non-uniformities. What was observed by McNamara *et al* explained why differential regional lung emptying in advanced obstructive pulmonary diseases might be invisible in the maximum expiratory flow-volume curves and consequently FEF25%-75% and FEF50%. [18] This interdependent compensatory readjustment of alveolar pressures and flow is expected to increase in advanced airways narrowing; which in turn explain why diagnostic powers of FEF25%-75% and FEF50 were deceased in UAP we studied.

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