Diagnostic value of oscillation technique for chronic obstructive pulmonary disease: a meta-analysis

Cai-Shuang Pang[1,2], Mei Chen[1,2], Jun Hu[1,2] and Fu-Qiang Wen[2,*]

[1]West China School of Medicine, and
[2]Department of Respiratory Medicine, West China Hospital of Sichuan University, 37 GuoXue Street, 610041 Chengdu, China

Many studies have investigated the usefulness of oscillation technique, including forced oscillation technique (FOT) and impulse oscillation technique (IOS), for the diagnosis of chronic obstructive pulmonary disease (COPD). However, the overall diagnostic accuracy of oscillation technique for COPD remains unclear. The aim of the present meta-analysis was to determine the overall accuracy of oscillation techniques for diagnosis of COPD. We performed a systematic search in PubMed and Embase. Data on sensitivity, specificity, positive/negative likelihood ratio (PLR/NLR), and diagnostic odds ratio (DOR) were pooled. Summary receiver operating characteristic (SROC) curves and area under the curve (AUC) were used to summarize overall test performance. Six studies met our inclusion criteria. Summary estimates for oscillation technique in the diagnosis of COPD are as follows: sensitivity – 0.77 (95%CI 0.70–0.83; I^2 = 87.6%); specificity – 0.85 (95%CI 0.81–0.88; I^2 = 58.4%); PLR – 5.99 (95%CI 2.91–12.34); NLR – 0.16 (95%CI 0.005–0.47); DOR – 47.95 (95%CI 9.99–230.17) and AUC – 0.96. Pooled estimates for FOT were as follows: sensitivity 0.94 (95% CI 0.86–0.98), specificity 0.94 (95% CI 0.86–0.98), PLR 11.48 (95% CI 5.17–25.48), NLR 0.08 (95% CI 0.03–0.17), DOR 221.8 (95% CI 58.39–842.5), and AUC 0.98. Given its easy to perform and subject-independent nature, our meta-analysis suggests a potential role for oscillation technique in diagnosis of COPD, especially FOT.

Keywords: Chronic obstructive pulmonary disease, diagnosis, forced oscillation technique, impulse oscillation technique, meta-analysis.

CHRONIC obstructive pulmonary disease (COPD) is an increasing health problem, especially in the developed countries, and is the fourth cause of overall mortality[1]. The chronic airflow limitation characteristic of COPD is caused by a combination of small airway disease (obstructive bronchiolitis) and parenchymal destruction (emphysema)[2]. Currently, diagnosis of COPD depends on conventional pulmonary function test (CPFT) of spirometry, which requires maximal individual effort through forced expiratory manoeuvre and good cooperation. Thus, these may be variable and subject-dependent. There is need for a reliable, easy to perform screen test for the disorders.

Oscillation technique has been introduced to resolve previous problems, and suggested as an alternative for CPFT of spirometry[3–5]. This includes forced oscillation technique (FOT) and impulse oscillation technique (IOS). The basic indices obtained by oscillation technique are the two components of respiratory impedance: total respiratory resistance (Rrs) and reactance (Xrs)[6,7]. Rrs is determined mainly by the calibre of central airways, whereas Xrs is determined by elastic and mass-inertial properties of airways, lung tissue and thorax. FOT has been modified and computerized in such a way that it allows measurement of respiratory impedance, Rrs and Xrs components over a range of oscillating frequencies within seconds, with simple tidal breathing, a method called IOS[8,9]. Oscillation technique is simple and requires only passive cooperation and no forced expiratory manoeuvres. Thus, a growing number of studies have focused on extending the use of oscillation technique to the diagnosis of COPD[10]. Therefore, the present meta-analysis was undertaken to comprehensively assess the overall accuracy of oscillation technique for diagnosis of COPD.

PubMed and Embase were searched for suitable articles in English language before 31 December 2014. No starting data limit was applied. Articles were also identified using the related-articles function in PubMed. Reference lists of the included studies were checked to identify additional studies. The following search terms were used: 'impulse oscillation technique or IOS or forced oscillatory technique or forced oscillation technique or FOT' and 'chronic obstructive pulmonary disease or COPD'.

Inclusion criteria were set as follows: (1) original English publications; (2) human studies provided sufficient data to allow calculation of true positive, false positive, false negative, true negative of IOS or FOT for the diagnosis of COPD and (3) there were at least 20 participants (10 patients and 10 controls). Accordingly, the following exclusion criteria were also used: (1) abstracts and reviews and (2) repeat or overlapping publications.

Two reviewers independently checked all potentially relevant studies and reached a consensus on all items. The following data from each study were collected: first author, year of publication, country, number of patients, test method, sensitivity, specificity and methodological quality. The methodological quality of the studies was assessed using the guidelines published by the STARD (standards for reporting diagnostic accuracy, maximum score 25)[11] initiative, and QUADAS (quality assessment for studies of diagnostic accuracy, maximum score 14)[12] tool.

Standard methods recommended for meta-analysis of diagnostic test evaluations were used[13]. Stata 12.0 and Meta-DiSc 1.4 were used for statistical analysis. The following accuracy measures were calculated for each study:

*For correspondence. (e-mail: wenfuqiang.scu@gmail.com)

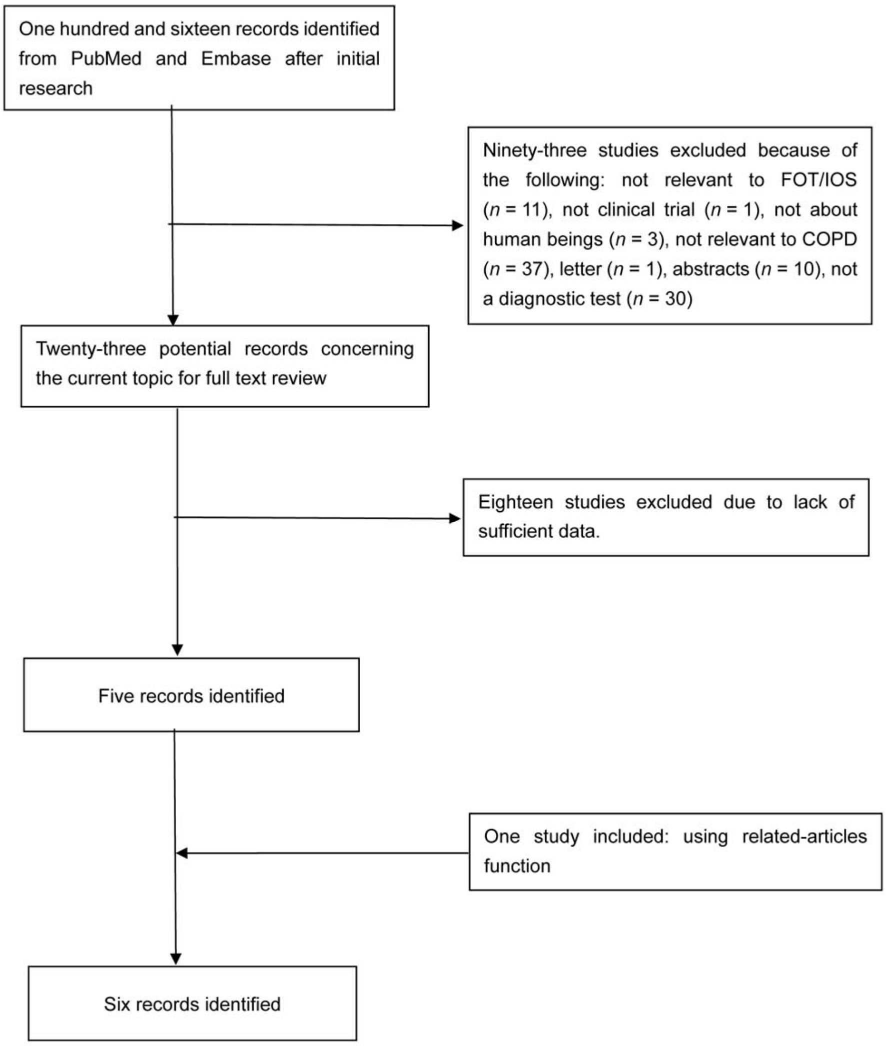

Figure 1. Flow diagram of included and excluded studies.

sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR) and summary receiver operating characteristic (SROC) curves[14–16].

Heterogeneity across studies was detected using chi-squared and Fisher's exact tests. We planned to use a random-effects model to synthesize data if heterogeneity was present ($P < 0.05$ and $I^2 > 50\%$)[17], which was then analysed in the meta-regression analysis to assess the effect of study quality on the relative DOR (RDOR) of oscillation technique for the diagnosis of COPD. The following covariates were analysed as possible sources of heterogeneity: QUADAS score (<9 versus ≥9), STARD (<13 versus ≥13), method (FOT versus IOS), sample size (<100 versus ≥100), publication year (before 2010 versus after 2010), design (cross-sectional versus non-cross-sectional), blinding (yes versus no or not reported), sampling method (consecutive/random versus non-consecutive/non-random/not reported), data collection (prospective versus retrospective). Based on this rule, pooled sensitivity, specificity and other diagnostic parameters were calculated using, a random-effects model and a fixed-effects model respectively[15,16]. Potential presence of publication bias was tested using Deeks' funnel plots[18]. All statistical tests were two-sided, and the threshold of significance was set at $P < 0.05$. Except for meta-regression, in case of missing factors influencing the heterogeneity, threshold of significance was set at $P < 0.1$ (ref. 19).

After searching electronic databases and manually searching reference lists in relevant studies, six studies of IOS or FOT to diagnose patients with COPD were judged eligible for inclusion[20–25]. The major reasons for excluding other studies were as follows: they were not diagnostic studies or cannot get sufficient data to construct 2 × 2 tables. Figure 1 shows the process of study identification and selection.

The average sample size of six included studies was 90 (30–230), involving 151 patients with COPD and 386

Table 1. Summary of studies included in the meta-analysis

First author	Year	Country	No. of patients	Method	Test results TP (%)	FP (%)	FN (%)	TN (%)	Quality scores STARD	QUADAS
Franqoise Zerah	1995	France	42	FOT	19 (45.2)	3 (7.2)	1 (2.4)	19 (45.2)	10	9
S. S. Al-Mutairi	2007	Kuwait	146	IOS	14 (9.6)	19 (13)	22 (15.1)	91 (62.3)	16	11
Jorge L. M. Amaral	2010	Argentina	30	FOT	14 (46.7)	0 (0)	1 (3.3)	15 (50)	12	8
Karla Kristine Dames Silva	2011	Brazil	39	FOT	18 (46.1)	1 (2.6)	1 (2.6)	19 (48.7)	17	9
Mehdi Nikkhah	2011	Iran	230	IOS	43 (18.7)	32 (13.9)	13 (5.7)	142 (61.7)	11	8
Jorge L. M. Amaral	2012	Brazil	50	FOT	23 (46)	1 (2)	2 (4)	24 (48)	11	8

FOT, Forced oscillation technique; IOS, Impulse oscillation technique; TP, True positive; FP, False positive; FN, False negative; TN, True negative; STARD, Standards for reporting diagnostic accuracy; QUADAS, Quality assessment for studies of diagnostic accuracy.

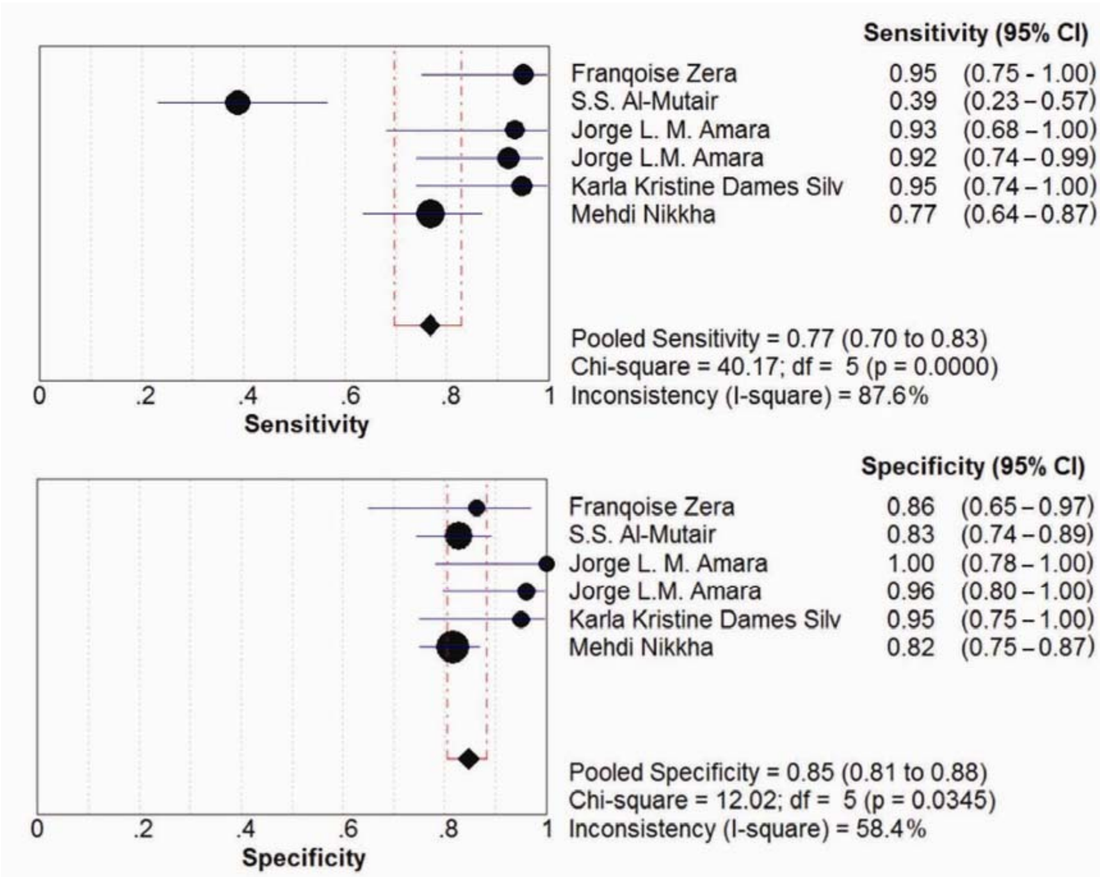

Figure 2. Forest plot of estimates of sensitivity and specificity of forced oscillation technique (FOT) and impulse oscillation technique (IOS) for diagnosis of chronic obstructive pulmonary disease (COPD). The point estimates of sensitivity and specificity from each study are shown as solid circles. Error bars indicate 95% CI.

controls. For all of the included studies, the diagnosis of COPD was based on positive history (dyspnea, cough, chronic sputum), global initiative for chronic obstructive lung disease (GOLD) guidelines[2], and confirmed by CPFT of spirometry when FEV1/FVC was less than 70% after using a bronchodilator. Using STARD and QUADAS, quality score was compiled for every study on the basis of title, introduction, methods, results and discussion. A score of 1 was given when a criterion was fulfilled, 0 if a criterion was unclear, and –1 if a criterion was not achieved. Overall, three studies had a higher QUADAS score (≥9) and two studies had higher STARD (≥13). Table 1 summarizes the clinical characteristics of patients as well as quality scores for each study.

Figure 2 shows a forest plot of sensitivity and specificity for six studies in the diagnosis of COPD; diagnostic sensitivity ranged from 0.39 to 0.95, and specificity ranged from 0.82 to 1.0. Pooled estimates of the other

Table 2. Pooled diagnostic accuracy of FOT/IOS in chronic obstructive pulmonary disease (COPD)

	Total	FOT	IOS
Number of studies	6	4	2
Sensitivity (95% CI)	0.77 (0.70–0.83)	0.94 (0.86–0.98)	0.62 (0.51–0.72)
Heterogeneity* (P)	40.71 (<0.001)	0.23 (0.97)	13.43 (<0.001)
Specificity (95% CI)	0.85 (0.81–0.88)	0.94 (0.86–0.98)	0.82 (0.77–0.86)
Heterogeneity (P)	12.02 (0.03)	3.8 (0.28)	0.06 (0.8)
PLR (95% CI)	5.99 (2.91–12.34)	11.48 (5.17–25.48)	3.21 (1.76–5.86)
Heterogeneity (P)	16.18 (0.006)	2.33 (0.51)	3.27 (0.07)
NLR (95% CI)	0.16 (0.005–0.47)	0.08 (0.03–0.17)	0.47 (0.16–1.36)
Heterogeneity (P)	51.39 (<0.001)	0.36 (0.95)	15.06 (<0.001)
DOR (95% CI)	47.95 (9.99–230.17)	221.80 (58.39–842.50)	6.78 (1.45–31.64)
Heterogeneity (P)	30.13 (<0.001)	0.40 (0.94)	7.74 (0.005)
AUC (SEM)	0.96 (0.03)	0.98 (0.01)	–

*Q value.

AUC, Area under the curve; DOR, Diagnostic odds ratio; NLR, Negative likelihood ratio; PLR, Positive likelihood ratio.

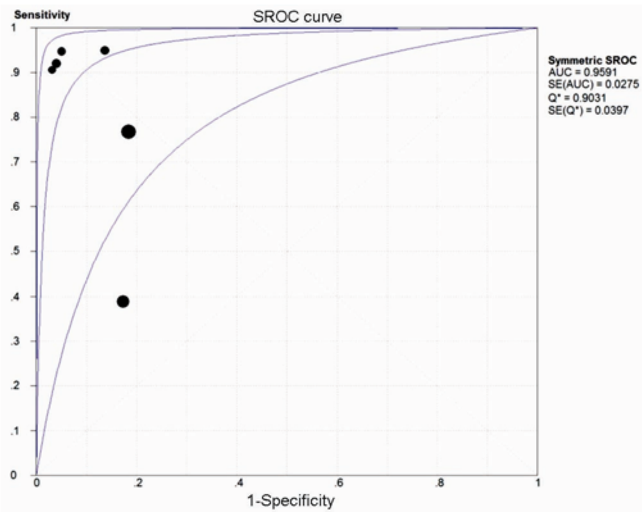

Figure 3. Summary receiver operating characteristic (SROC) curve of FOT/IOS for diagnosis of COPD. Solid circles represent each study included in the meta-analysis. The size of each study is indicated by the size of the solid circle. The regression SROC curves summarize the overall diagnostic accuracy.

diagnostic parameters were as follows: sensitivity – 0.77 (95% CI 0.70–0.83; I^2 = 87.6%); specificity – 0.85 (95% CI 0.81–0.88; I^2 = 58.4%); PLR – 5.99 (95%CI 2.91–12.34); NLR – 0.16 (95% CI 0.005–0.47); and DOR – 47.95 (95% CI 9.99–230.17). Chi-squared values for sensitivity, specificity, PLR, NLR and DOR were 40.71, 12.02, 16.18, 51.39 and 30.13 respectively ($P < 0.05$ for all), indicating significant heterogeneity between studies (Table 2).

Pooled sensitivity for FOT was 0.94 (95% CI 0.86–0.98), while pooled specificity was 0.94 (95% CI 0.86–0.98). PLR was 11.48 (95% CI 5.17–25.48), NLR was 0.08 (95% CI 0.03–0.17), and DOR was 221.8 (95% CI 58.39–842.5). Chi-square values for sensitivity, specificity, PLR, NLR, PPV, NPV and DOR were 0.23, 3.8, 2.33, 0.36 and 0.4 respectively ($P > 0.05$ for all), indicating no significant heterogeneity between studies (Table 2). Table 2 also provides summary estimates for IOS.

Two types of oscillation technique were used in the studies included in the meta-analysis. One was FOT, whose basic principle is to measure the relationship between pressure waves applied externally to the respiratory system, and the resulting respiratory airflow. FOT consists of applying small sinusoidal pressure variations to stimulate the respiratory system at frequencies higher than the normal breathing frequency and measuring the flow response[6,26]. IOS is a modified version of FOT. IOS is computerized in such a way that it allows measurement of respiratory impedance, Rrs and Xrs components over a range of oscillating frequencies within seconds, with simple tidal breathing[7,8,27]. Table 2 provides a comparison of overall diagnostic values from IOS and FOT. The sensitivity, specificity, PLR, DOR and area under the curve (AUC) for FOT are higher than those for IOS. It can be concluded that the overall accuracy of FOT for diagnosis of COPD is superior to that of IOS.

We assessed the overall diagnostic performance by calculating SROC curves and the corresponding AUC, and the point where sensitivity equals specificity (Q) was 0.90; the optimum AUC was 0.96 (Figure 3), suggesting high overall accuracy.

Significant heterogeneity was identified among included studies the threshold of significance was set at $P < 0.1$. Table 3 summarizes the influence of certain covariates to investigate the possible sources of this heterogeneity. Sample size significantly affected RDOR of IOS and FOT for the diagnosis of COPD ($P = 0.06$); other covariates showed no significant difference. Two out of six studies had higher STARD (≥13), and three studies had higher QUADAS (≥9) scores, both of them indicating no significant difference.

Publication bias was evaluated by Deeks' funnel plot (Figure 4). This plot showed asymmetry; statistically significant value ($P = 0.04$) for the slope coefficient

Table 3. Meta-regression of the effects of study quality on the relative DOR (RDOR) of oscillation technique for diagnosis of COPD

Covariate	Number of studies	Coefficient	RDOR (95% CI)	*P* value
STARD score				
≥13	2	0.172	1.19 (0.4–3.49)	0.647
<13	4			
QUADAS score				
≥9	3	–1.182	0.31 (0.00–22.39)	0.445
<9	3			
Method				
FOT	4	–2.716	0.07 (0.01–0.82)	0.417
IOS	2			
Sample size				
≥100	2	–0.012	0.99 (0.98–1.00)	0.06
<100	4			
Publication year				
Before 2010	3	0.616	1.85 (0.01–628.81)	0.76
After 2010	3			
Design				
Cross-sectional	2	–0.675	0.51 (0.00–232.97)	0.75
Non-cross-sectional	4			
Blinding				
Yes	1	–3.905	0.02 (0.00–120.61)	0.25
No or not reported	5			
Sampling method				
Consecutive/random	1	–3.905	0.02 (0.00–120.61)	0.25
Non-consecutive/non-random/not reported	5			
Data collection				
Prospective	3	–0.958	0.38 (0.00–108.12)	0.63
Retrospective	3			

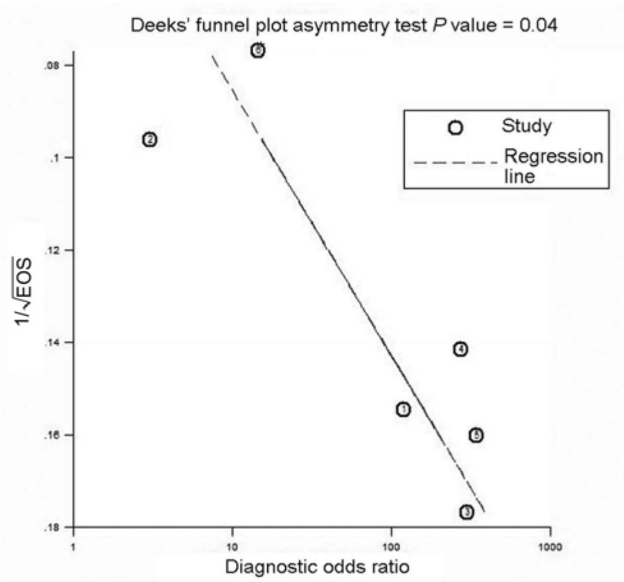

Figure 4. Deeks' funnel plot to assess the likelihood of publication bias of six included studies. The funnel graph plots the log of the diagnostic odds ratio (DOR) against the standard error of log DOR (an indicator of sample size). Solid circles represent each study in the meta-analysis. The line indicates the regression line.

suggested asymmetry in the data and likelihood of publication bias.

Oscillation technique has been introduced as an alternative to CPFT of spirometry to test pulmonary function. Several studies have suggested that it may be a good alternative to CPFT for diagnosis of COPD. However, further studies in large groups of patients and subjects are needed[21,24]. So we conducted this meta-analysis to assess diagnostic accuracy of oscillation technique in COPD. To the best of our knowledge, there have been no previous meta-analyses to assess the overall accuracy of oscillation technique for diagnosis of COPD.

We found that the pooled estimate sensitivity and specificity of FOT and IOS were 0.94, 0.62 and 0.94, 0.82 respectively. These data suggest that FOT plays a valuable role in the diagnosis of COPD; however, the relatively low sensitivity of IOS indicates that it would not be possible to exclude COPD from other obstructive lung diseases.

The SROC curve has been recommended to represent the overall performance of a diagnostic study, which shows the trade-off between sensitivity and specificity, based on data from meta-analysis[28,29]. The AUC and index *Q* are recognized as potentially useful summaries of the curve. *Q* value, the intersection point of the SROC curve with a diagonal line from the left upper corner to the right lower corner of the ROC space, which corresponds to the highest common value of sensitivity and specificity for the test, represents an overall measure of the discriminatory power of a test. In the present study, the *Q* value was 0.9, and the maximum joint sensitivity and specificity of oscillation technique for COPD was

0.9. The AUC also represents the overall accuracy of the diagnostic study. It represents an analytical summary of test performance and displays the trade-off between specificity and sensitivity. If the AUC is 1, it means the oscillation technique differentiates perfectly between COPD and non-COPD patients. An AUC value greater than 0.9 indicates high diagnostic accuracy. In the present meta-analysis the AUC was 0.96, suggesting that the level of overall accuracy of oscillation technique for COPD is high.

DOR is a single indicator of diagnostic accuracy that combines data from sensitivity and specificity into a single number[30]. It is defined as the ratio of the odds of positive test results in the diseased relative to the odds of positive test results in the non-diseased. The value of DOR ranges from zero to infinity, with higher values indicating better discriminatory test performance. In the present meta-analysis, the pooled DOR was 47.95, suggesting that oscillation technique may be helpful in the diagnosis of COPD. DOR was 221.80 for FOT and 6.78 for IOS, the difference indicating that FOT is more useful in practice because it has test properties that complement those of CPFT. Since the SROC curve and DOR are not easy to interpret and use in clinical practice, likelihood ratios are considered more clinically meaningful[31]. PLR was 5.99, indicating that COPD patients have about six-fold higher chance of being oscillation technique-positive compared with non-COPD subjects. NLR was 0.16, indicating that if the oscillation technique result is negative, the probability that this subject has COPD is 16%, which is not low enough to exclude COPD.

FOT measures the relationship between pressure waves applied externally to the respiratory system, and the resulting respiratory airflow. The ratio of the amplitude of pressure wave to that of the resulting flow wave constitutes the impedance of the respiratory system[21]. IOS uses brief pulses of pressure generated by a loudspeaker instantaneously moving back and forth, superimposed on the spontaneous breathing of the subject[8]. Both of them are noninvasive, easy to perform, subject-independent and their operation is similar. Thus, we combined them together in this meta-analysis. As shown in Table 2, the sensitivity, specificity, PLR, DOR and AUC for FOT were higher than those for IOS. NLR was lower for FOT than for IOS. We found that the overall accuracy of FOT for diagnosis of COPD was superior to that of IOS. Also IOS is not as yet accepted as an alternative, or even as an adjunct to spirometry in general pulmonary function laboratories worldwide [27]. Only two studies used IOS for the diagnosis of COPD[21,24], and the sample size of four FOT studies[20,22,23,25] was limited. Thus large, well-designed, multi-centre diagnostic studies should be carried out in the future.

While meta-analysis is well-suited for generating summary outcomes, the pooled results can mask heterogeneity that should be understood in detail[32]. The reasons for heterogeneity were explored. STARD score, QUADAS score, method, sample size, publication year, design, blinding, sampling method and data collection were used in the meta-regression analysis. The sample size substantially affected diagnostic accuracy, while the others did not. Future studies should aim for expanding the sample size and greater rigour in order to decrease the risk of bias. Deeks' funnel plot suggested that asymmetry was statistically significant. Although we used the related-articles function in PubMed, and references lists of the included studies were checked to identified additional studies, only six publications were included according to our inclusion criteria. Owing to the limited number (below 10) of studies included in this meta-analysis, an updated meta-analysis needs to be conducted in the future.

Our meta-analysis has several limitations. First, although we used a comprehensive search strategy, and the screening, study selection, data extraction and quality assessment were done independently and reproducibly by two reviewers, there were only six publications included, and the limited number of patients may have influenced the outcomes; so it is still hard to arrive at a definitive conclusion about the diagnostic accuracy of the oscillation technique. Thus, further studies on a large scale may be needed to confirm the diagnostic value of oscillation technique in COPD. Second, due to limited studies and sample size, we did not use QUADAS-2 to assess methodological quality, which is more detailed, and more rigorous on literature screening[33]. Third, due to limited studies, we combined FOT and IOS together; they are similar, but not quite the same. When there are new studies, we may need to analyse them separately.

The meta-analysis suggests a potential role for oscillation technique in diagnosis of COPD, especially FOT, given its easy-to-perform and subject-independent nature. Further studies are required to confirm our findings.

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ACKNOWLEDGEMENTS. We thank the authors of the primary studies included in this meta-analysis, without whose contributions this work would not have been possible. This work was supported by grant 2014BAI08B04 from the National Key Technology Research and Development Program of Ministry of Science and Technology of China, and grant 2015SZ0151 Projects in the Science and Technology Pillar Program from Department of Science and Technology of Sichuan Province, China. The funding agencies had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Received 3 March 2015; revised accepted 28 June 2015

doi: 10.18520/v109/i9/1697-1703