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### What can we learn about COPD from impulse oscillometry?

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Abstract: Impulse oscillometry (IOS) is the most commonly used type of forced oscillation technique in clinical practice, although relatively little is known about its application in COPD. Resistance at 20Hz (R20) is unrelated to COPD severity and does not improve with bronchodilatation or bronchoconstriction, inferring a lack of large airway involvement in COPD. Peripheral airway resistance expressed as frequency dependent heterogeneity between 5Hz and 20Hz (R5-R20), and peripheral airway compliance as area under the reactance curve (AX), are both closely related to COPD severity and exacerbations. Both R5-R20 and AX markedly improve in response to long acting bronchodilators, while AX appears to be more sensitive than R5-R20 in response to bronchoconstriction. Future studies may be directed to assess if IOS in combination with spirometry is more sensitive at predicting future exacerbations. Perhaps AX might also be useful as a screening tool in early stage disease or to monitor long term decline in COPD.

## Highlights

- Impulse oscillometry (IOS) is the most commonly used forced oscillation technique
- Relatively little is known about its application in COPD
- lung resistance (R) and reactance (X) reflect airway geometry and compliance
- IOS indices relate to disease severity, bronchodilatation and bronchoconstriction
- Trials are required for the predictive value of IOS in relation to COPD exacerbations

1 **What can we learn about COPD from impulse oscillometry?**

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Abstract

Impulse oscillometry (IOS) is the most commonly used type of forced oscillation technique in clinical practice, although relatively little is known about its application in COPD. Resistance at 20Hz (R20) is unrelated to COPD severity and does not improve with bronchodilatation or bronchoconstriction, inferring a lack of large airway involvement in COPD. Peripheral airway resistance expressed as frequency dependent heterogeneity between 5Hz and 20Hz (R5-R20), and peripheral airway compliance as area under the reactance curve (AX), are both closely related to COPD severity and exacerbations. Both R5-R20 and AX markedly improve in response to long acting bronchodilators, while AX appears to be more sensitive than R5-R20 in response to bronchoconstriction. Future studies may be directed to assess if IOS in combination with spirometry is more sensitive at predicting future exacerbations. Perhaps AX might also be useful as a screening tool in early stage disease or to monitor long term decline in COPD.

75 Abbreviations:  
76  
77 AX: Area Under reactance curve between 5Hz and resonant frequency  
78 COPD: Chronic obstructive pulmonary disease  
79 FEF25-75: Forced expiratory flow between 25 and 75%  
80 FEV1: Forced expiratory volume in 1 second  
81 FVC: Forced vital capacity  
82 FOT: Forced oscillation technique  
83 Fres: Resonant Frequency  
84 GOLD: Global Initiative for Chronic Obstructive Lung Disease  
85 HRCT: High resolution CT scanning  
86 IOS: Impulse oscillometry  
87 R: Resistance  
88 R5: Resistance at 5Hz  
89 R20: Resistance at 20Hz  
90 R5-R20: Heterogeneity of resistance  
91 SRM: Standardised response mean  
92 X: Reactance  
93 X5: Reactance at 5Hz  
94 Z: Impedance  
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113 Background:

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115 Current COPD guidelines advocate using spirometry to assess airflow limitation in  
116 conjunction with symptoms and exacerbation history [1]. Spirometry involves a forced  
117 expiratory manoeuvre to measure dynamic lung volumes and expiratory flow. It has  
118 no comparable manoeuvre in real life, and hence is an artificial action. Cooperation  
119 may be difficult especially in patients who are breathless or susceptible to coughing.  
120 The forced expiratory flow between 25 and 75% (FEF<sub>25-75</sub>) of forced vital capacity  
121 (FVC) is thought to represent dynamic volume dependent small airway closure, but  
122 has marked inherent variability. Hence there is an unmet need for an alternative  
123 more patient friendly method to assess lung function in patients with COPD.

124 The forced mono-frequency oscillation technique (FOT) was first described in 1956  
125 by Dubois [2]. Since then several FOT methods have been developed of which  
126 impulse oscillometry (IOS) is most commonly used in every day clinical practice. The  
127 application of IOS has been extensively described in asthma [3]. The purpose of this  
128 article is to critically appraise the potential role of IOS in COPD, where much less is  
129 known. It will focus on the more clinical applications of IOS, as this appertains to the  
130 general pulmonologist. This review will therefore not detail the physics of IOS or  
131 other FOT methods which have been covered elsewhere [4-6].

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133 Basic principles of impulse oscillometry:

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135 The currently used method of IOS was originally detailed in 1976 by Michaelson [7]  
136 and was then commercialised in 1998 [8], available as the Jaeger Masterscreen IOS  
137 (Hoechberg, Germany). It has been widely adopted in paediatric pulmonology, but  
138 less so for adults, aside as a research tool. IOS propagates a train of bi-directional,  
139 harmonic sound waves along the bronchial tree, from a source such as a  
140 loudspeaker. The oscillations are applied at a fixed square wave frequency of 5Hz,  
141 from which all other frequencies of interest are derived, typically multiples of 5Hz  
142 (between 5 and 35Hz) [9], each impulse lasting between 30 to 40ms. Measurements  
143 are made via a conducting tube to a mouthpiece with the cheeks held to obviate  
144 upper airway shunting. Forced oscillations are superimposed on top of tidal breathing  
145 to assess the frequency (Hz) dependence of the pressure/flow (as kPa/L/s or  
146 cmH<sub>2</sub>O/L/s) relationship of respiratory impedance (Z), as in phase resistance (R) and  
147 out of phase reactance (X) components. A transducer attached to a  
148 pneumotachograph measures inspiratory and expiratory flow and pressure with

149 signal filtering used to separate breathing patterns from pressure and flow. It is  
150 performed using normal tidal breathing over a period of around 30 to 40s, and being  
151 effort independent is more physiological than spirometry. Conventionally the mean of  
152 whole breath values are used rather than separate inspiratory and expiratory  
153 moieties. As in spirometry three technically acceptable IOS manoeuvres are used.  
154 In essence, IOS can be considered as bronchial sonar. Higher frequency waves  
155 travel shorter distances typically reflecting larger airways. Thus the resistance at  
156 20Hz (R20) represents proximal resistance. Lower frequency waves travel further  
157 reaching the smaller airways <2mm in diameter after the eighth generation .Hence  
158 the resistance at 5Hz (R5) represents the total lung resistance. COPD and asthma  
159 will increase total resistance (R5) to a relatively greater degree than proximal  
160 resistance (R20). This is known as a frequency dependent change or heterogeneity  
161 of resistance evident as raised peripheral resistance (R5-R20). Nonetheless further  
162 validation is required to characterise heterogeneity of resistance and its relationship  
163 to the calibre of small and large airways.

164 Reactance can be considered as the out of phase component of respiratory  
165 impedance (with flow, but not volume), reflecting the balance between inertial and  
166 elastic properties of distensible airways. Typically this is measured at 5Hz (X5) or as  
167 the area under the reactance curve (AX) between 5Hz and the resonant frequency  
168 (RF),the latter representing the point at which opposing inertial and capacitive  
169 components cancel each other out . Conventionally AX is reported as a positive  
170 value for the area under the curve, even though in reality reactance per se becomes  
171 more negative (figure). AX represents low frequency reactance in smaller airways  
172 where elastance exceeds inertance, with increased values reflecting reduced lung  
173 compliance and stiffer lungs (Table). In asthma resistance and reactance tend to  
174 change in proportionate fashion, while in COPD reactance usually alters to a  
175 relatively greater degree than resistance.

176 IOS therefore provides more detailed information than spirometry on regional lung  
177 function and should be considered as being complementary to spirometry to  
178 comprehensively assess lung function in COPD. For example in patients with  
179 persistent asthma who had a preserved FEV<sub>1</sub>, the combined use of R5-R20 with  
180 FEF<sub>25-75</sub> results in more predictive of impaired long term asthma control than either  
181 parameter used alone [10]. Although there are no defined reference values for  
182 COPD, we would propose pragmatic IOS cut offs for R5 > 0.5 kPa/L/s (>5.1  
183 cmH<sub>2</sub>O/L/s), R5-20 > 0.10 kPa/L/s (1.02 cmH<sub>2</sub>O/L/s), AX > 1.0 kPa/L  
184 (>10.2cmH<sub>2</sub>O/L) as being abnormal [11, 12]. Further cohort based studies are  
185 required to define proper reference values for COPD and asthma.



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188 Relationship of IOS to disease severity:

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190 The largest database involving IOS was the ECLIPSE cohort comprising 2054  
191 patients with COPD (GOLD stage 2-4) and 233 healthy controls , in whom high  
192 resolution CT scanning (HRCT) was also performed [11]. R20 values were similar  
193 across GOLD stages 2-4 (0.29, 0.31, 0.31 kPa/L/s), but higher than controls (0.26  
194 kPa/L/s). In contrast R5-R20 increased proportionately from GOLD stage 2 -4 (0.15,  
195 0.20, 0.24 kPa/L/s), compared to controls (0.07kPa/L/s) .This in turn suggests that  
196 smaller rather than larger airways are the main determinant of increased lung  
197 resistance.

198 For AX there were increasing values across GOLD stages 2-4 (1.37, 2.25, 3.23  
199 kPa/L) which were also higher than controls (0.38 kPa/L) along with a similar pattern  
200 for X5. Comparing GOLD 2 versus 4, equated to a 136% difference in AX and 60% in  
201 R5-20. Hence increased reactance (i.e. reduced compliance) predominates over  
202 increased resistance in relation to increasing COPD severity. There was a poor  
203 degree of correlation between R5-R20 or AX and HRCT low attenuation, inferring  
204 that the degree of emphysema is not closely related to either resistance or  
205 compliance.

206 In a cohort of 215 patients GOLD stages 1-4 ,values for AX (0.66 ,1.43 ,2.07, 2.5  
207 kPa/L) mirrored the ratio of residual volume to total lung capacity (RV/TLC)  
208 (45.7,51.2,58.1,66.0 %) ,inferring the degree of air trapping is related to reduced lung  
209 compliance [12]. Studies have also shown a relationship between increasing AX and  
210 exacerbation frequency in COPD [11, 12]. A cross sectional evaluation of 94 COPD  
211 patients with moderate COPD revealed the strongest relationships for X5 in relation  
212 to FEV1 and specific airway conductance [13]. Multiple regression analysis of 75  
213 patients with moderate COPD found that R5-R20 and X5 but not R20 were more  
214 closely related to health status and symptoms than either FEV1 or HRCT low  
215 attenuation [14] .In a screening study to detect early COPD , among 124 subjects  
216 who had positive spirometry criteria ,the presence of self reported symptoms was  
217 associated with higher values of R5-R20 ,X5 and AX [15].

218 A comparison of 36 asthma patients ,24 COPD patients and 24 healthy subjects  
219 showed values for R5-R20 and X5 in severe asthma were 0.13 kPa/L/s and -0.18  
220 kPa/L/s respectively ; in moderate COPD 0.22 kPa/L/s and X5 -0.27 kPa/L ; and in  
221 controls 0.01 kPa/L/s and -0.12 kPa/L/s [16]. Thus, patients with COPD have a  
222 relatively higher level of peripheral airway dysfunction compared to those with

223 asthma in respect of both resistance and reactance. This is in keeping with  
224 pathological and radiological changes seen in small airways associated with disease  
225 progression in COPD [17, 18] .

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227 Bronchodilator response and IOS:

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229 Significantly greater changes were observed for R5 and RF, but not R20 or X5, when  
230 comparing responses to tiotropium 18ug and salmeterol 100ug in 32 patients with  
231 moderate COPD [19] . A trial in 16 patients with moderate COPD evaluated the  
232 effects of 4 weeks with open label tiotropium alone or with the addition of tulobuterol .  
233 Tiotropium alone produced significant improvements versus baseline in AX, R5 and  
234 R5-20, both drugs were better than tiotropium ,while R20 was unchanged [20] . For  
235 example with both drugs there were 56% ,46% and 38% changes in AX ,X5 and  
236 R5-R20 respectively, as compared to a 16% change in FEV1.

237 In an open label study 20 patients with moderate COPD received either tiotropium or  
238 glycopyrronium/indacaterol with IOS measured at baseline and 52 weeks [21] .

239 Compared to baseline there were significant changes in R5, X5 but not R20 with  
240 glycopyrronium /indacaterol, while tiotropium afforded no improvements.

241 A double blind randomised cross-over trial involved 19 patients with severe COPD  
242 who received tiotropium or placebo for 2 weeks as add on to budesonide/formoterol  
243 combination taken during the preceding 4 weeks[22] . Compared to placebo the first  
244 but not last dose of tiotropium as triple therapy conferred significant improvements in  
245 X5, AX and RF, but not R5 or R20. Specific airways resistance but not RV/TLC also  
246 improved after single but not chronic dosing with tiotropium.

247 Taken together these data suggest that muscarinic and beta-2 receptors located in  
248 small airways (R5-R20, X5, AX) are relatively more important than large airways  
249 (R20) for mediating bronchodilator responses in COPD. Alternatively one might  
250 speculate that large airways disease per se is less important than small airway  
251 disease in COPD. Moreover increased lung compliance (as reduced AX values) in  
252 response to bronchodilators may reflect lung deflation, perhaps allowing the patient  
253 to breathe at a better mechanical advantage at a lower RV.

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255 Bronchoconstrictor response with IOS:

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257 Methacholine challenge was performed in 10 asthma and 25 moderate to severe  
258 COPD patients to achieve a 20% fall in FEV1. In asthma there was concordance  
259 between effects on resistance and reactance ,as a significant fall in X5 along with a

260 significant rise in R5 , while in COPD there was discordance in terms of a significant  
261 change in X5 but not R5 [23] .  
262 12 moderate to severe COPD patients receiving beclometasone/formoterol  
263 combination at baseline were given the non selective beta-blocker carvedilol  
264 ,followed by formoterol withdrawal while continuing on carvedilol and belcometasone  
265 [24]. Compared to baseline, carvedilol produced a 1% change in R20, 21% in R5,  
266 59% in X5, and 135% in AX. After formoterol cessation, only AX was associated with  
267 a further significant change amounting to a 210% increase from baseline. Hence  
268 large airways are not involved in beta-2 receptor mediated effects since R20 did not  
269 significantly alter in response to either addition of beta-2 antagonist or removal of  
270 beta-2 agonist. Furthermore the signal to noise ratio for bronchoconstriction with IOS  
271 was calculated as the standardised response mean, which is the ratio of the mean  
272 divided by the standard deviation, with a value of  $\geq 0.8$  indicating a sensitive test. The  
273 highest value was observed with AX at 1.74 versus R5 at 0.72, as compared to a  
274 value of 2.08 for FEV1. Thus measuring peripheral lung compliance as AX might be  
275 useful at detecting subtle changes in lung function in COPD, perhaps as a screening  
276 tool in early stage disease or to monitor long term decline. Nonetheless we would  
277 advocate that IOS should be used in conjunction with spirometry in order to make a  
278 comprehensive assessment of a given patient.

279

280 Future directions for IOS research:

281

282 There are fundamental gaps in the literature which warrant further investigation.  
283 Large prospective data sets are required to look at the possible predictive value of  
284 IOS for future moderate to severe exacerbations in high risk patients in GOLD  
285 groups C/D. Such studies should evaluate if lung stiffness (as AX) is more predictive  
286 than FEV1 or FVC.

287 Given the apparent lack of involvement of large airways (as R20) in mediating  
288 bronchodilator responses in COPD, it would seem logical to perform randomised  
289 controlled trials to investigate the impact of extra fine particle (ie<2um) inhaler  
290 formulations to see if putative improvements in small airway indices such as AX and  
291 R5-R20 might translate into superior longer term reductions in exacerbations, as  
292 compared to larger particle formulations.

293 Since there is a relatively poor signal with spirometry in COPD, IOS might prove to  
294 be more sensitive at detecting subtle differences in response to either bronchodilator  
295 or anti-inflammatory therapy, in order to explain commensurate reductions in  
296 exacerbations, improved symptoms and health status.

297 It also remains to be seen if IOS might be more suitable than spirometry for detecting  
298 early stage lung damage in COPD. Reference values and minimal important  
299 differences for IOS in COPD are required for use in clinical practice and  
300 interventional trials.

301 We believe the so called airway oscillometry (AOS) Tremoflo system (Thorasys,  
302 Montreal ,Canada) which uses a novel vibrating mesh, may fulfil the requirement for  
303 a more portable less expensive user friendly device. In turn this may make it more  
304 widely adopted in everyday clinical practice among adult pulmonologists.

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**Figure Legend:**

67 year old female, ex-smoker; COPD; BMI 23, FEV1 0.56L (31% predicted). IOS values are as follows: Resistance at 5Hz (R5) 0.85 kPa/l/s; Resistance at 20Hz (R20) 0.47 kPa/l/s; Heterogeneity of resistance between 5 and 20Hz (R5-R20) 0.38 kPa/l/s; Reactance at 5Hz (X5) -1.00 kPa/l/s; Area under the curve reactance (AX) 11.71 kPa/l; Resonant frequency (Fres).

1 **What can we learn about COPD from impulse oscillometry?**

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Abstract

Impulse oscillometry (IOS) is the most commonly used type of forced oscillation technique in clinical practice, although relatively little is known about its application in COPD. Resistance at 20Hz (R20) is unrelated to COPD severity and does not improve with bronchodilatation or bronchoconstriction, inferring a lack of large airway involvement in COPD. Peripheral airway resistance expressed as frequency dependent heterogeneity between 5Hz and 20Hz (R5-R20), and peripheral airway compliance as area under the reactance curve (AX), are both closely related to COPD severity and exacerbations. Both R5-R20 and AX markedly improve in response to long acting bronchodilators, while AX appears to be more sensitive than R5-R20 in response to bronchoconstriction.

Future studies may be directed to assess if IOS in combination with spirometry is more sensitive at predicting future exacerbations ~~is superior to spirometry in predicting future exacerbations~~. -Perhaps AX might also be useful as a screening tool in early stage disease or to monitor long term decline in COPD.

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76 Abbreviations:  
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78 AX: Area Under reactance curve between 5Hz and resonant frequency  
79 COPD: Chronic obstructive pulmonary disease  
80 FEF25-75: Forced expiratory flow between 25 and 75%  
81 FEV1: Forced expiratory volume in 1 second  
82 FVC: Forced vital capacity  
83 FOT: Forced oscillation technique  
84 Fres: Resonant Frequency  
85 GOLD: Global Initiative for Chronic Obstructive Lung Disease  
86 HRCT: High resolution CT scanning  
87 IOS: Impulse oscillometry  
88 R: Resistance  
89 R5: Resistance at 5Hz  
90 R20: Resistance at 20Hz  
91 R5-R20: Heterogeneity of resistance  
92 SRM: Standardised response mean  
93 X: Reactance  
94 X5: Reactance at 5Hz  
95 Z: Impedance  
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114 Background:

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116 Current COPD guidelines advocate using spirometry to assess airflow limitation in  
117 conjunction with symptoms and exacerbation history [1]. Spirometry involves a forced  
118 expiratory manoeuvre to measure dynamic lung volumes and expiratory flow. It has  
119 no comparable manoeuvre in real life, and hence is an artificial action. Cooperation  
120 may be difficult especially in patients who are breathless or susceptible to coughing.  
121 The forced expiratory flow between 25 and 75% (FEF25-75) of forced vital capacity  
122 (FVC) is thought to represent dynamic volume dependent small airway closure, but  
123 has marked inherent variability. Hence there is an unmet need for an alternative  
124 more patient friendly method to assess lung function in patients with COPD.

125 The forced mono-frequency oscillation technique (FOT) was first described in 1956  
126 by Dubois [2] . Since then several FOT methods have been developed of which  
127 impulse oscillometry (IOS) is most commonly used in every day clinical practice. The  
128 application of IOS has been extensively described in asthma [3] .The purpose of this  
129 article is to critically appraise the potential role of IOS in COPD, where much less is  
130 known. It will focus on the more clinical applications of IOS, as this appertains to the  
131 general pulmonologist. This review will therefore not detail the physics of IOS or  
132 other FOT methods which have been covered elsewhere [4-6].

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134 Basic principles of impulse oscillometry:

135

136 The currently used method of IOS was originally detailed in 1976 by Michaelson [7]  
137 and was then commercialised in 1998 [8] , available as the Jaeger Masterscreen IOS  
138 (Hoechberg ,Germany) .It has been widely adopted in paediatric pulmonology, but  
139 less so for adults ,aside as a research tool . IOS propagates a train of bi-directional,  
140 harmonic sound waves along the bronchial tree, from a source such as a  
141 loudspeaker. The oscillations are applied at a fixed square wave frequency of 5Hz,  
142 from which all other frequencies of interest are derived, typically multiples of 5Hz  
143 (between 5 and 35Hz) [9], each impulse lasting between 30 to 40ms . Measurements  
144 are made via a conducting tube to a mouthpiece with the cheeks held to obviate  
145 upper airway shunting. Forced oscillations are superimposed on top of tidal breathing  
146 to assess the frequency (Hz) dependence of the pressure/flow (as kPa/L/s or  
147 cmH<sub>2</sub>O/L/s) relationship of respiratory impedance (Z), as in phase resistance (R) and  
148 out of phase reactance (X) components. A transducer attached to a

149 pneumotachograph measures inspiratory and expiratory flow and pressure with  
150 signal filtering used to separate breathing patterns from pressure and flow. It is  
151 performed using normal tidal breathing over a period of around 30 to 40s, and being  
152 effort independent is more physiological than spirometry. Conventionally the mean of  
153 whole breath values are used rather than separate inspiratory and expiratory  
154 moieties. As in spirometry three technically acceptable IOS manoeuvres are used.  
155 In essence, IOS can be considered as bronchial sonar. Higher frequency waves  
156 travel shorter distances typically reflecting larger airways. Thus the resistance at  
157 20Hz (R20) represents proximal resistance. Lower frequency waves travel further  
158 reaching the smaller airways <2mm in diameter after the eighth generation .Hence  
159 the resistance at 5Hz (R5) represents the total lung resistance. COPD and asthma  
160 will increase total resistance (R5) to a relatively greater degree than proximal  
161 resistance (R20). This is known as a frequency dependent change or heterogeneity  
162 of resistance evident as raised peripheral resistance (R5-R20). Nonetheless further  
163 validation is required to characterise heterogeneity of resistance and its relationship  
164 to the calibre of small and large airways.

165 Reactance can be considered as the out of phase component of respiratory  
166 impedance (with flow, but not volume), reflecting the balance between inertial and  
167 elastic properties of distensible airways. Typically this is measured at 5Hz (X5) or as  
168 the area under the reactance curve (AX) between 5Hz and the resonant frequency  
169 (RF),the latter representing the point at which opposing inertial and capacitive  
170 components cancel each other out . Conventionally AX is reported as a positive  
171 value for the area under the curve, even though in reality reactance per se becomes  
172 more negative (figure). AX represents low frequency reactance in smaller airways  
173 where elastance exceeds inertance, with increased values reflecting reduced lung  
174 compliance and stiffer lungs (Table). In asthma resistance and reactance tend to  
175 change in proportionate fashion, while in COPD reactance usually alters to a  
176 relatively greater degree than resistance.

177 IOS therefore provides more detailed information than spirometry on regional lung  
178 function and should be considered as being complementary to spirometry to  
179 comprehensively assess lung function in COPD. For example in patients with  
180 persistent asthma who had a preserved FEV1, the combined use of R5-R20 with  
181 FEF25-75 results in more predictive of impaired long term asthma control than either  
182 parameter used alone [10]. Although there are no defined reference values for  
183 COPD, we would propose pragmatic IOS cut offs for R5 > 0.5 kPa/L/s (>5.1  
184 cmH<sub>2</sub>O/L/s), R5-20 > 0.10 kPa/L/s (1.02 cmH<sub>2</sub>O/L/s), AX > 1.0 kPa/L

185 (>10.2cmH<sub>2</sub>O/L) as being abnormal [11, 12]. Further cohort based studies are  
186 required to define proper reference values for COPD and asthma.

187

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189 Relationship of IOS to disease severity:

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191 The largest database involving IOS was the ECLIPSE cohort comprising 2054  
192 patients with COPD (GOLD stage 2-4) and 233 healthy controls , in whom high  
193 resolution CT scanning (HRCT) was also performed [11]. R20 values were similar  
194 across GOLD stages 2-4 (0.29, 0.31, 0.31 kPa/L/s), but higher than controls (0.26  
195 kPa/L/s). In contrast R5-R20 increased proportionately from GOLD stage 2 -4 (0.15,  
196 0.20, 0.24 kPa/L/s), compared to controls (0.07kPa/L/s) .This in turn suggests that  
197 smaller rather than larger airways are the main determinant of increased lung  
198 resistance.

199 For AX there were increasing values across GOLD stages 2-4 (1.37, 2.25, 3.23  
200 kPa/L) which were also higher than controls (0.38 kPa/L) along with a similar pattern  
201 for X5. Comparing GOLD 2 versus 4, equated to a 136% difference in AX and 60% in  
202 R5-20. Hence increased reactance (i.e. reduced compliance) predominates over  
203 increased resistance in relation to increasing COPD severity. There was a poor  
204 degree of correlation between R5-R20 or AX and HRCT low attenuation, inferring  
205 that the degree of emphysema is not closely related to either resistance or  
206 compliance.

207 In a cohort of 215 patients GOLD stages 1-4 ,values for AX (0.66 ,1.43 ,2.07, 2.5  
208 kPa/L) mirrored the ratio of residual volume to total lung capacity (RV/TLC)  
209 (45.7,51.2,58.1,66.0 %) ,inferring the degree of air trapping is related to reduced lung  
210 compliance [12]. Studies have also shown a relationship between increasing AX and  
211 exacerbation frequency in COPD [11, 12]. A cross sectional evaluation of 94 COPD  
212 patients with moderate COPD revealed the strongest relationships for X5 in relation  
213 to FEV1 and specific airway conductance [13]. Multiple regression analysis of 75  
214 patients with moderate COPD found that R5-R20 and X5 but not R20 were more  
215 closely related to health status and symptoms than either FEV1 or HRCT low  
216 attenuation [14] .In a screening study to detect early COPD , among 124 subjects  
217 who had positive spirometry criteria ,the presence of self reported symptoms was  
218 associated with higher values of R5-R20 ,X5 and AX [15].

219 A comparison of 36 asthma patients ,24 COPD patients and 24 healthy subjects  
220 showed values for R5-R20 and X5 in severe asthma were 0.13 kPa/L/s and -0.18  
221 kPa/L/s respectively ; in moderate COPD 0.22 kPa/L/s and X5 -0.27 kPa/L ; and in

222 controls 0.01 kPa/L/s and -0.12 kPa/L/s [16]. Thus, patients with COPD have a  
223 relatively higher level of peripheral airway dysfunction compared to those with  
224 asthma in respect of both resistance and reactance. This is in keeping with  
225 pathological and radiological changes seen in small airways associated with disease  
226 progression in COPD [17, 18] .

227

228 Bronchodilator response and IOS:

229

230 Significantly greater changes were observed for R5 and RF, but not R20 or X5, when  
231 comparing responses to tiotropium 18ug and salmeterol 100ug in 32 patients with  
232 moderate COPD [19] . A trial in 16 patients with moderate COPD evaluated the  
233 effects of 4 weeks with open label tiotropium alone or with the addition of tulobuterol .  
234 Tiotropium alone produced significant improvements versus baseline in AX, R5 and  
235 R5-20, both drugs were better than tiotropium ,while R20 was unchanged [20] . For  
236 example with both drugs there were 56% ,46% and 38% changes in AX ,X5 and  
237 R5-R20 respectively, as compared to a 16% change in FEV1.

238 In an open label study 20 patients with moderate COPD received either tiotropium or  
239 glycopyrronium/indacaterol with IOS measured at baseline and 52 weeks [21] .

240 Compared to baseline there were significant changes in R5, X5 but not R20 with  
241 glycopyrronium /indacaterol, while tiotropium afforded no improvements.

242 A double blind randomised cross-over trial involved 19 patients with severe COPD  
243 who received tiotropium or placebo for 2 weeks as add on to budesonide/formoterol  
244 combination taken during the preceding 4 weeks[22] . Compared to placebo the first  
245 but not last dose of tiotropium as triple therapy conferred significant improvements in  
246 X5, AX and RF, but not R5 or R20. Specific airways resistance but not RV/TLC also  
247 improved after single but not chronic dosing with tiotropium.

248 Taken together these data suggest that muscarinic and beta-2 receptors located in  
249 small airways (R5-R20, X5, AX) are relatively more important than large airways  
250 (R20) for mediating bronchodilator responses in COPD. Alternatively one might  
251 speculate that large airways disease per se is less important than small airway  
252 disease in COPD. Moreover increased lung compliance (as reduced AX values) in  
253 response to bronchodilators may reflect lung deflation, perhaps allowing the patient  
254 to breathe at a better mechanical advantage at a lower RV.

255

256 Bronchoconstrictor response with IOS:

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258 Methacholine challenge was performed in 10 asthma and 25 moderate to severe  
259 COPD patients to achieve a 20% fall in FEV1. In asthma there was concordance  
260 between effects on resistance and reactance ,as a significant fall in X5 along with a  
261 significant rise in R5 , while in COPD there was discordance in terms of a significant  
262 change in X5 but not R5 [23] .

263 12 moderate to severe COPD patients receiving beclometasone/formoterol  
264 combination at baseline were given the non selective beta-blocker carvedilol  
265 ,followed by formoterol withdrawal while continuing on carvedilol and belcometasone  
266 [24]. Compared to baseline, carvedilol produced a 1% change in R20, 21% in R5,  
267 59% in X5, and 135% in AX. After formoterol cessation, only AX was associated with  
268 a further significant change amounting to a 210% increase from baseline. Hence  
269 large airways are not involved in beta-2 receptor mediated effects since R20 did not  
270 significantly alter in response to either addition of beta-2 antagonist or removal of  
271 beta-2 agonist. Furthermore the ~~best~~ signal to noise ratio for bronchoconstriction with  
272 IOS was calculated expressed as the highest standardised response mean, which is  
273 the ratio of the mean divided by the standard deviation, with a value of  $\geq 0.8$   
274 indicating a sensitive test. -The highest value was observed with AX at 1.74 versus  
275 R5 at 0.72, as compared to a value of 2.08 for FEV1. Thus measuring peripheral  
276 lung compliance as AX might be useful at detecting subtle changes in lung function  
277 in COPD, perhaps as a screening tool in early stage disease or to monitor long term  
278 decline. Nonetheless we would advocate that IOS should be used in conjunction with  
279 spirometry in order to make a comprehensive assessment of a given patient.

280

281 Future directions for IOS research:

282

283 There are fundamental gaps in the literature which warrant further investigation.

284 Large prospective data sets are required to look at the possible predictive value of  
285 IOS for future moderate to severe exacerbations in high risk patients in GOLD  
286 groups C/D. Such studies should evaluate if lung stiffness (as AX) is more predictive  
287 than FEV1 or FVC.

288 Given the apparent lack of involvement of large airways (as R20) in mediating  
289 bronchodilator responses in COPD, it would seem logical to perform randomised  
290 controlled trials to investigate the impact of extra fine particle (ie<2um) inhaler  
291 formulations to see if putative improvements in small airway indices such as AX and  
292 R5-R20 might translate into superior longer term reductions in exacerbations, as  
293 compared to larger particle formulations.

294 Since there is a relatively poor signal with spirometry in COPD, IOS might prove to  
295 be more sensitive at detecting subtle differences in response to either bronchodilator  
296 or anti-inflammatory therapy, in order to explain commensurate reductions in  
297 exacerbations, improved symptoms and health status.

298 It also remains to be seen if IOS might be more suitable than spirometry for detecting  
299 early stage lung damage in COPD. Reference values and minimal important  
300 differences for IOS in COPD are required for use in clinical practice and  
301 interventional trials.

302 We believe the so called airway oscillometry (AOS) Tremoflo system (Thorasys,  
303 Montreal ,Canada) which uses a novel vibrating mesh, may fulfil the requirement for  
304 a more portable less expensive user friendly device. In turn this may make it more  
305 widely adopted in everyday clinical practice among adult pulmonologists.

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436 **Figure Legend:**

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441 kPa/l; Resonant frequency (Fres).  
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**Table.****Comparison of spirometry and IOS in COPD**

	Spirometry	IOS
Outputs	FEV1,FVC ,FEF25-75	R5, R20, X5, AX, RF
Signal to noise ratio	+	+
Patient friendly	-	+
Breathing pattern	Forced expiratory	Tidal
Reference values for COPD	+	-
Large/small airways	+/-	+
Cost	+	-
Portability	+	-
FDA approved	+	+

FEV1 :forced expiratory volume in 1s ,FVC :forced vital capacity ,FEF25-75:forced expiratory flow between 25 and 75% of FVC , R5 :resistance at 5Hz ,resistance at 20Hz ,X5 :reactance at 5Hz ,AX :area under reactance curve , RF :resonant frequency .Both methods should be used in complimentary fashion to fully assess lung function .

Figure

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