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Double blind, placebo controlled crossover study in COPD patients to assess the acute effect of budesonide/formoterol using multi-slice CT and lung function tests

Lieve De Backer, Wim Vos, Jan De Backer, Cedric Van Holsbeke, Samir Vinchurkar, Wilfried De Backer

De Backer Lieve (1)
Vos Wim (2)
De Backer Jan (2)
Van Holsbeke Cedric (2)
Vinchurkar Samir (2)
De Backer Wilfried (1)

(1) Antwerp University Hospital, Department of Respiratory Medicine
(2) FluidDA, Antwerp, Belgium

The GOLD classification of COPD does not always matches with other clinical disease descriptors such as exacerbation frequency and quality of life indicating that FEV1 is not a perfect descriptor of the disease. The aim of this study was to see whether changes in airway geometry after inhalation of the most commonly used inhalation therapy in severe COPD can more adequately be described with an imaged based approach then with spirometry. A total of 10 COPD GOLD III patients was assessed in a double blind cross over study. Airway volumes were analysed using segmentation of the MSCT images, airway resistance was determined using computational fluid dynamics (CFD). Results showed that distal airway volume significantly increased (p=0.011) in patients four hours after receiving budesonide/formoterol combination from 9.6 ± 4.67cm3 to 10.14 ± 4.81cm3. Also CFD-based airway resistance significantly decreased (p=0.047) from 0.051 ± 0.021 kPas/l to 0.043 ± 0.019 kPas/l. None of the lung function parameters showed a significant change. Only FRC showed a trend to decline (p=0.056). Only the image-based parameters were able to predict the visit at which the combination product was administered. This study showed that imaging is a sensitive, complementary tool to describe changes in airway structure.

Introduction

Chronic obstructive pulmonary disease or COPD is characterised by chronic airway inflammation (bronchitis) and the destruction of lung parenchyma in combination with the loss of vascular structures (emphysema). A hallmark of COPD is the relatively irreversible nature of the airway constriction. In clinical practice, patients are diagnosed with COPD if the decrease in forced expiratory volume in one-second (FEV1) is not fully reversible after the administration of bronchodilating products and when the ratio between the FEV1 and the forced vital capacity (FVC) remains below 70%. It is, however, possible that a substantial degree of reversibility of bronchoconstriction in COPD can be detected. This reversibility of bronchoconstriction tends to vary over time and with disease severity as well as with the method and product of treatment[1 2]. It would be interesting to predict this response and

categorize patients according to bronchodilating capacity. FEV1 represents the whole of the bronchial tree, so cannot show local bronchodilation, which can be as important for the patient to have an effect of the medication. As COPD is such a heterogeneous disease, bronchodilating capacity is only part of the patient assessment. The severity of COPD is defined by the GOLD guidelines[3] consisting of four categories. Patients are subdivided into these groups based on their postbronchodilator FEV1 value. Even though FEV1 remains the primary outcome parameter to describe respiratory diseases in clinical studies and practice, only weak correlations have been found between this parameter and patient reported outcomes such as the Saint George respiratory questionnaire (SGRQ)[4-7]. The FEV1 based categorisation can still be improved[8]. Today, the standard treatment of COPD includes inhaled corticosteroids (ICS) and short (SABA) and long (LABA) acting beta 2 agonist. However, the inherent black box approach of the spirometry parameters in combination with the above-mentioned weak clinical correlations often causes difficult and very costly development and registration processes for new compounds targeted at treating COPD[9]. Even in very large clinical trials the beneficial effect of therapies on FEV1 or even survival is difficult to demonstrate[10-12] . With an increasing prevalence of COPD[13] , the need for new outcome parameters that more adequately describe the influence of inhalation medication on the airway geometry becomes apparent. These outcome parameters should ideally facilitate development of novel effective therapies that relieve the burden primarily on the patient but also on the social healthcare structure. Within the field of COPD, imaging and in particular multi-slice computed tomography (MSCT), has emerged as a complementary tool to spirometry and body plethysmography, predominantly to assess the extent of emphysema[14-16]. The severity of emphysema is typically correlated with a decrease in local Hounsfield units (HU) indicating a destruction of pulmonary lung tissue. Recent developments have extended the use of MSCT scans by adding more functionality to the static images by means of airway segmentation and computational fluid dynamics (CFD)[17]. Patient-specific assessments of the airway volume and airflow in the respiratory system can be obtained by solving mathematical flow equations within the segmented airway structures[18]. Several studies have indicated the possible applications of this method and have validated the approach through comparison with in-vitro and in-vivo data[19;20]. The current study used the same approach where patient specific computer models are constructed based on MSCT images using segmentation principles and flow parameters are derived using CFD. The aim of the present study was to see whether in GOLD III COPD patients, treated with inhalation of routinely used inhalation therapy or placebo, changes in airway structure and function are more adequately described

with this new imaging technology than with spirometric data. Fixed combinations were chosen as the study medication to reflect real life situation. We also performed a sample size calculation to calculate the number of patients in clinical trials needed when using more sensitive, image-based outcome parameters.

Materials and methods

Ethics

The study was conducted according to all ethical principles. Approval from the ethical committee was obtained and patients all gave their informed consent (EudraCT 2009-016502-16, PML_DOC_0905_/_ISSSYMB0020).

Patient population

In this study a total of 10 COPD patients (6M/4F) was included. All patients were categorised by the GOLD guidelines as GOLD III with an average FEV1 of 34.8 ± 7.7 %p. The average age of the patients was 65.1 ± 3.3 years with an average height of 170 ± 7 cm and weighing on average 93 ± 15 kg.

Study design

The study was designed to investigate a number of topics. A first aim was to demonstrate how functional imaging parameters such as changes in airway volumes and CFD-based resistance can assess changes induced by a combination product compared to placebo. Subsequently these changes could be compared to other lung function parameters. Furthermore a comparison could be made between the combination product and placebo. A final aim of the study was to analyse whether the different outcome parameters could distinguish between placebo and active product. The latter was possible considering the double blind design of the study.

At the baseline visit (V1) patients received full lung function testing and a low dose inspiratory-expiratory MSCT scan. A low dose CT scan reduces the radiation by lowering the current and increasing the pitch compared to a normal CT thorax. Due to the natural contrast between air and the surrounding airway tissue a significant reduction, up to six-fold, in the radiation dose can be obtained (21). The lung function tests yielded following parameters: FEV1, FEV1/FVC, peak expiratory flow (PEF) from the spirometry and airway resistance (Raw), specific airway resistance (sRaw), functional residual capacity (FRC) and total lung capacity (TLC) from bodyplethysmography. After the initial tests and scans the patients were randomised to receive either placebo or budesonide/formoterol combination (Symbicort®, AstraZeneca, Sweden). In this study a combination product (ICS/LABA) was used as suggested by the GOLD guidelines for the treatment of COPD GOLD stage III patients. The lung function and imaging tests were repeated four hours after the administration of the product or placebo (V2). One week later patients returned to the hospital where the lung

function tests were repeated pre-dose (V3). To limit radiation dose, no baseline MSCT scan was taken at this point. Subsequently patients received either the combination product or placebo. Again four hours after the administration of the formulation both lung function and imaging tests were performed (V4). To limit the radiation dose to the patient as much as possible a dose reduction protocol was applied. The natural contrast between the intraluminal air and the surrounding tissue allows for a significant reduction in dose without compromising image quality. The scanner that was used was a General Electic VCT lightspeed scanner with 64 detector rows. The MSCT settings were as follows: tube voltage, 120 kV; tube current,10 (low weight patients) –100 (high weight patients) mAs; noise factor, 28; collimation, 0.625 mm ; rotation time, 0.6 sec; and pitch factor, 1.375. The field of view was indicated by the CT technician based on the scout image and was positioned closely around the thorax to optimize in-plane image resolution which was approximately 0.5mm. The resulting radiation dose was in the order of 1-2 mSv per scan. Images were reconstructed to a slice thickness of 0.6mm to attain near cubic voxels. Respiratory gating was used to ensure the proper lung volume. CT examinations were performed blindly.

Image post-processing

Post-processing of the MSCT images included segmentation of the airway tree structure and CFD flow simulations. Segmentation can be defined as the grouping of voxels that belong to an anatomical structure (eg tracheobronchial tree, lung,...). This group of voxels or mask can subsequently be used to create a patient-specific three-dimensional model of the anatomical structure under consideration. For this study the focus was placed on the tracheobronchial tree, with Hounsfield Units ranging from -1024 to -824 (20), and in particular the smaller airways starting from the segmental level (generation 2-4). Using state of the art imaging equipment it is possible to distinguish, in the MSCT images, airways with a diameter down to 1mm. Smaller airways cannot be further detected since the in-plane resolution of the scanner (512 x 512) is typically not sufficient to distinguish between the intraluminal and the alveolar air. Consequently the analysis was performed on all airways starting from generation 2-4 down to the smallest detectable airways. The DICOM images obtained in this clinical study at the different measurement instances were assessed using the commercially available, FDA approved software package MIMICS (Materialise, Belgium). The tracheobronchial tree was subsequently segmented using a semi-automatic approach where the central airways up to around generation 4-5 are automatically generated and the smaller branches are added manually. A total of three airway tree models were obtained per patient: the model from V1

was based on pre-bronchodilation images, the airway constructed at V2 was either after administration of placebo or the combination and the model based on V4 was again either after adminstration of placebo or the combination depending on what was used in V2. After segmentation, all models of the same patient were superimposed using a least squares method. Subsequently all models were trimmed such that the branches extended equally far and a comparison could be made between the different geometries excluding the variability induced by the manual segmentation. The main outcome parameter of the segmentation procedures is the distal airway volume (iVaw) (Figure 1). In addition to the changes in volume also the changes in airway resistance (iRaw) were determined using CFD. CFD is a computer method that provides flow characteristcs throughout the entire reconstructed airway model. Flow simulations were performed using Fluent v6.3 (Ansys Inc, Lebanon, NH) that solved the Reynolds-averaged Navier-Stokes (RANS) equations. Steady flow was considered at 30 l/min. More details on the flow simulation principles can be found in De Backer et al[19]. The CT and CFD analysts were blinded with respect to the randomisation to avoid any biass.

Statistics

Differences were assessed using Wilcoxon matched pairs test. Sample size calculations were performed using a power analyses. A p-value < 0.05 was considered to be statistically significant.

Results

Results (Table 1) showed that iVaw significantly increased (p=0.011) in patients four hours after receiving budesonide/formoterol combination. The distal airway volumes increased from 9.6 ± 4.67cm3 to 10.14 ± 4.81cm3. The airway resistance decreased from 0.051 ± 0.021 kPas/l to 0.043 ± 0.019 kPas/l. Figure 2 illustrates changes in distal airway volumes after the administration of the placebo and the combination product. No lung function parameter showed a significant change. The FEV1 did increase slightly from 34.8 ± 7.69%p to 35.9 ± 7.89%p but not significantly (p = 0.34). The sRaw decreased from 5 ± 2.87 kPas to 4,65 ± 2.29 kPas but again not significantly (p=0.14). Although both iRaw and sRaw declined, there was no correlation between both parameters (r=0.45, NS). A decreasing trend in FRC was observed after administration of budesonide/formoterol indicating a reduction in hyperinflation.
The bronchodilating effect, defined as an increase in iVaw and a decrease in iRaw, seems higher in a limited number of patients (n=7), it seems to be no systematic effect. This appears more clearly in the functional imaging parameters. (table 3)

A sample size calculation revealed that in order to have a well-powered study with iVaw as primary outcome parameters a total of 16 patients would be required. When using iRaw, 34 patients were needed. When the FEV1 would be used as primary end point the number of required patients would go up to 93. The most insensitive parameter in this regard is the PEF with a total of 217 patients required to attain statistically significant results.

When considering the effect of placebo a significant decline in iVaw (p = 0.025) and PEF (p = 0.025) was observed. A downward trend was depicted by FEV1 (p = 0.09). CFD-based resistance increased significantly (p=0.005) and also the bodyplethysmography showed a significant increase in sRaw (p=0.026) and an upward trend in Raw (p = 0.07). Figure 3 illustrates the individual changes in iVaw and iRaw after the administration of the combination product and placebo.

A significant difference between placebo and the budesonide/formoterol combination was observed in two lung function parameters: PEF (p = 0.027) and FEV1 (p = 0.037). Also the sRaw indicated a significant difference (p = 0.036) as well as TLC and FRC volumes. The

image based airway volumes, again, showed the most significant difference between placebo and the active combination with p-value of 0.0005 (Table 2).

Before unblinding, a prediction was made regarding the visit at which the active product was administered. The hypothesis was that after this visit the values must improve where an improvement is defined as an increase in iVaw, FEV1, FEV1/FVC, PEF and a decline in sRaw and Raw. Results showed that the FEV1 correctly predicted in 7 out of 10 cases (

Table 4). The FEV1/FVC was correct in only 5 out of 10 patients. Both PEF and Raw predicted 8 out of 10 correctly and the sRaw 9 out of 10. The only parameter that in all cases adequately predicted the visit, at which the active compound was administered, was the iVaw (Table 5).

Discussion

In this study we could demonstrate that in severe COPD patients after inhalation of fixed combinations, changes in imaged based three dimensional airway geometry can be detected that are not reflected in the spirometric data. The thee-dimensional images clearly provide the possibility to assess the airway tree and the susbequent changes comprehensively. The traditional 2D approach is typically limited to a slice-by-slice assessment.

The severity of the disease is predominantly defined by FEV1, which is judged to be not completely reversible and in fact very little reversible in a stable stage III COPD patients[21-23].Demonstrating an improvement is therefore almost inherently impossible and a product is then assessed based on its ability to slow down this decline[10]. The current study results confirmed this hypothesis as only a minor, insignificant change in FEV1 is observed when patients are treated with the combination product. At least a trend towards decline in FEV1 is seen in the placebo group. Airway volumes obtained using body plethysmography appear to be more sensitive and depict a declining trend in FRC in line with recent studies. The only parameters that describe a small but nonetheless significant improvement in the treated group and a significant decline in the placebo group are the iVaw and the iRaw.

The decline in iRaw goes along with a decline (although not statistically significant) in the Raw measured with the body plethysmography. The absolute value of the Raw is much higher than the iRaw because iRaw does not take into account the resistance of the upper airway and the equipment and illustrates the relative importance of the upper airway resistance.

Furthermore, from this study it can be seen that when a COPD GOLD III patient doesn't receive active bronchodilating medication a relatively rapid decline in airway diameter and function is occuring even after some hours, indicating also the role of the fixed combinations to maintain airway patency in daily life situations. Therefore a highly significant difference is observed when comparing the treated and placebo groups.

The clinical relevance of these changes is the topic of ongoing research. In the current study the main question was to assess how different outcome parameters would describe changes induced by the inhalation product. It would appear valuable to first have outcome parameters that accurately describe changes in airway structure and function induced by a product. In a second phase one could investigate the clinical relevance of these changes by correlating them to, for example, patient reported outcome parameters (PRO). After all, one might ask the question, if a parameter is not sensitive enough to reliably pick up changes in the system following a treatment, what would be the value of correlating this parameter with PRO's? Should a correlation exist, this would still not mean that the product caused this change in

PRO. Of course it is important to asses these PRO ‘s, as diminishing respiratory symptoms should be one of the goals of treating COPD. As we can see that some patients have a more pronounced effect of budesonide/formoterol than others, it is interesting to know if they also report less dyspnoea.

The double blind protocol in this study offered an interesting possibility to assess how well the different parameters could distinguish between the placebo visit and the visit where the active product was administered. The image-based parameters appeared to be the only parameters that correctly identified the respective visits for all patients. The FEV1/FVC ratio performed the worst followed by the FEV1.

Even though this trial was performed in a limited number of patients, the placebo controlled, crossover design ensured a good power of this pilot study. Based on these results one could hypothesise that imaging, or at least a combination of lung function tests and imaging, is better suited to describe the mode of action of a product. The sample size calculations that were based on these data and performed post-hoc indicated that imaging parameters could significantly reduce the number of patients in clinical trials by providing more sensitive information on the mode of action of a product. This opens the possibility to use this method in an early clinical stage to compare different compounds to each other or to placebo. Also dose-response based on imaging parameters in a limited number of patients could yield a more compeling picture versus the FEV1 response to different doses in very large clinical trials where results are often ambiguous.

In previous large scaled studies using FEV1 as an end-point, one could observe that inhaled therapy with the recommended fixed combinations do improve FEV1 in absolute terms only to a limited extent and that the decline in FEV1 was not altered. But at the same time other end points like quality of life or even, in larger populations, mortality did show at least a trend to improvement[10;24-26]. This suggests that FEV1 may underscore real changes in airway structure induced by inhalation of combination therapies.

At present fixed combinations are most frequently and often uniquely used in severe stage III COPD patients and are considered to be mainly symptomatic treatments with the aim to improve daily life symtoms and exacerbations, but not or at a limited extent the progression of the disease. We therefore did choose a combination product in this study to see whether the widely and mainly for the symptomatic improvement used fixed combination do have an influence on the airway geometry in severe stage III COPD patients with the aim not only to understand and to see the sensitivity of the FEV1 but also to better understand the discrepencies between some PRO’s and FEV1 with the fixed combinations. Therefore both

insight in the mode of action but also in the clinical relevance of fixed combination inhalation therapy that is mostly used and recommended could be obtained. For this aim, a small scale study seemed to be indicated given that the mentioned discrepencies between PRO's and FEV1 were already demonstrated in previous large scaled and long term studies [Tristan, Torch, Euroscope, Uplift].

In COPD patients the treatment is mainly targeted at reducing the work of breathing in the patients. From physiological and anatomical studies[27;28] it is known that the majority of the airway resistance is situated in the first 4-6 generations. It is therefore not unreasonable to assume that airway dilation in this region results in a clinical improvement in the patient's condition. It would be worthwhile to assess the respiratory structure and function in a broader range of disease severity levels in a larger set of patients. One could for instance take lung function tests and MSCT images during an episode of exacerbation and after recovery. This would allow for a correlation between imaging parameters, lung function and patient reported outcome parameters.

Even though the functional imaging method appears to provide sensitive and valuable information, the technique also has its limitations. Segmentation still involves some manual processing of the images potentially introducing a level of variability. The airways smaller than 1-2mm are not visible with the current state-of-the-art CT scanners and therefore cannot be segmented. The cost and the use of ionizing radiation currently prevents the implementation of the method in very large phase III trials and as a standard test in clinical routine for all patients. It appears that this method is best suited to determine product efficacy in early clinical phases and to assess treatment of the more severe patients in a clinical routine setting. As such the method could complement other novel pulmonary function tests such as multi-breath nitrogen washout and forced oscillation that are targeted at obtaining more information about the smaller airways. These methods are in general less expensive and provide information about the tissue and the smaller airways. However they do not provide regional information and are sometimes labour intensive. Therefore a proper combination of imaging and lung function tests could result in an efficient, comprehensive set of tools treat patient with respiratory diseases.

References

Tables

Table 1 Comparison of lung function and imaging parameters before and after the administration of the combination product and the placebo

	symbicort			placebo		
	pre	post	p	pre	post	p
iVaw (cm3)	9.60±4.67	10.14±4.81	**0.011**	9.60±4.67	9.16±4.37	**0.025**
iRaw (kPs/L)	0.05±0.02	0.04±0.02	**0.047**	0.05±0.02	0.06±0.03	**0.047**
FEV1 (L)	0.95±0.33	0.98±0.33	0.34	0.96±0.31	0.93±0.33	**0.07**
FEV1 (%p)	34.80±7.69	35.90±7.89	0.34	34.90±6.71	33.70±7.24	**0.09**
FEV1/VC	34.32±6.99	34.72±6.67	0.51	33.68±7.36	33.89±6.8	0.74
PEF (L/s)	3.00±1.26	3.12±1.22	0.71	3.07±0.95	2.77±1.03	**0.025**
Raw (kPas/L)	1.00±0.5	0.92±0.45	0.20	0.94±0.46	1.01±0.43	**0.07**
sRaw (kPas)	5.00±2.87	4.65±2.29	0.14	4.89±2.72	5.33±2.48	**0.026**
FRC (%p)	155.90±35.6	151.00±32.44	**0.056**	151.30±32.46	155.10±30.95	0.15
TLC (%p)	115.80±21.64	114.20±19.03	0.13	114.10±19.3	116.00±18.25	**0.058**

Table 2 Comparison between the changes in lung function and imaging parameters induced by the combination product and placebo

Change (%)	symbicort	placebo	p
iVaw	+6.48±7.46	-4.29±4.45	**0.0005**
iRaw	-13.13±17.73	15.15±16.88	**0.005**
FEV1	+3.56±10.49	-3.63±6.1	**0.037**
FEV1/VC	+1.53±5.81	+1.02±6.45	0.87
PEF	+4.47±20.2	-10.26±12.89	**0.027**
Raw	-7.17±23.62	+10.42±14.75	**0.09**
sRaw	-9.03±25.01	+12.84±14.24	**0.036**
FRC (%p)	-4.9±7.06	3.8±7.67	**0.017**
TLC (%p)	-1.6±3.03	1.9±2.77	**0.015**

Table 3 Average changes and standard deviations in iVaw and iRaw for all patients after administration of combination product indicating the level of inhomogeneity in bronchodilation

	ΔiVaw		ΔiRaw	
patient	average (%)	stdev (%)	average (%)	stdev (%)
01	14.11	9.07	-27.09	21.74
02	2.79	7.89	8.24	49.17
03	-4.55	3.88	24.83	53.04
04	6.21	5.03	-11.67	36.77
05	-2.53	14.82	51.02	118.36
06	19.52	27.85	-34.71	43.05
07	17.40	26.14	-19.57	40.66
08	5.36	10.87	-9.21	37.27
09	35.38	134.81	-6.48	39.89
10	13.24	10.82	-38.45	20.81

Table 4 Predictive value of the change in FEV1 to determine the visit where combination product was administered

ΔFEV1 V2	ΔFEV1 V3	product	unblind
-0.069	0.081	V3	V3
-0.02	0	V3	V2
-0.02	0.041	V3	V3
0.029	-0.1	V2	V2
-0.099	-0.11	V2	V2
-0.041	0.19	V3	V3
0.02	0.01	V2	V2
-0.041	-0.05	V2	V3
-0.021	0.03	V3	V2
0.09	0.02	V2	V2

Table 5 Predictive value of the change in iVaw (top) and iRaw (bottom) to determine the visit where combination product was administered

ΔiVaw V2	ΔiVaw V3	product	unblind
-0.25	14.45	V3	V3
2.19	-7.32	V2	V2
-6.87	-3.11	V3	V3
5.16	-7.87	V2	V2
-4.59	-6.88	V2	V2
-7.27	17.23	V3	V3
11.87	-3.34	V2	V2
-1.56	6.09	V3	V3
2.55	-7.25	V2	V2
12.97	5.74	V2	V2

ΔiRaw V2	ΔiRaw V3	product	unblind
-0.98	-19.46	V3	V3
-0.86	23.10	V2	V2
59.41	12.47	V3	V3
-18.94	34.23	V2	V2
35.18	41.80	V2	V2
49.05	-43.74	V3	V3
-32.42	29.69	V2	V2
9.95	-16.25	V3	V3
-14.94	11.34	V2	V2
-42.81	-18.93	V2	V2

Figures

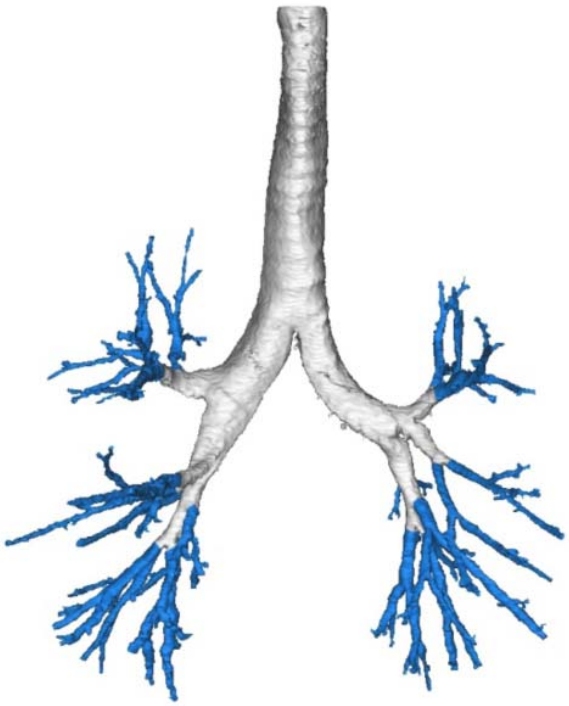

Figure 1 MSCT-based airway models indicating distal airway branches (iVaw) at baseline

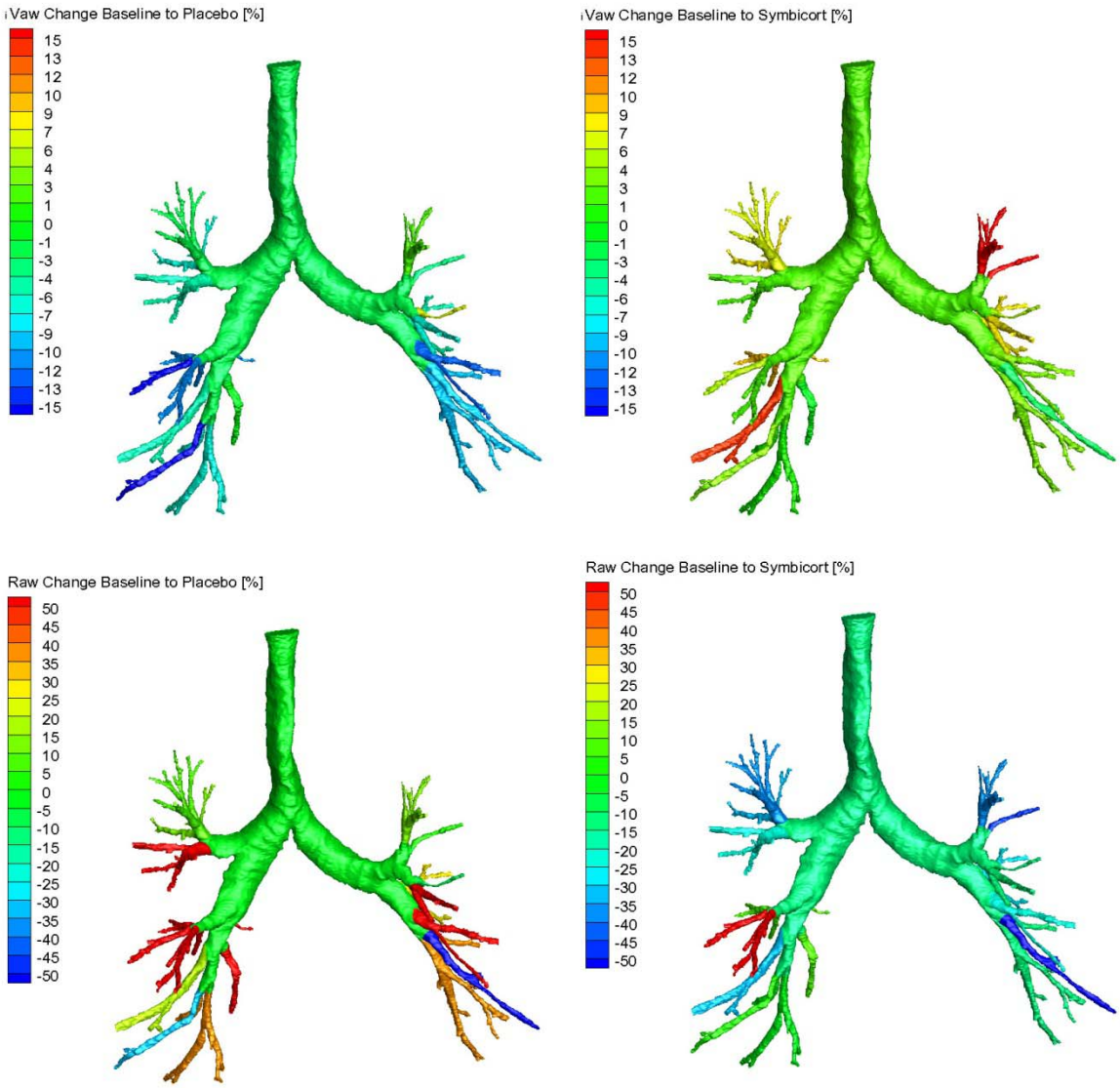

Figure 2 Illustration of distal airway volume (top) and resistance (bottom) changes [%] after administration of placebo (left) or combination product (right)

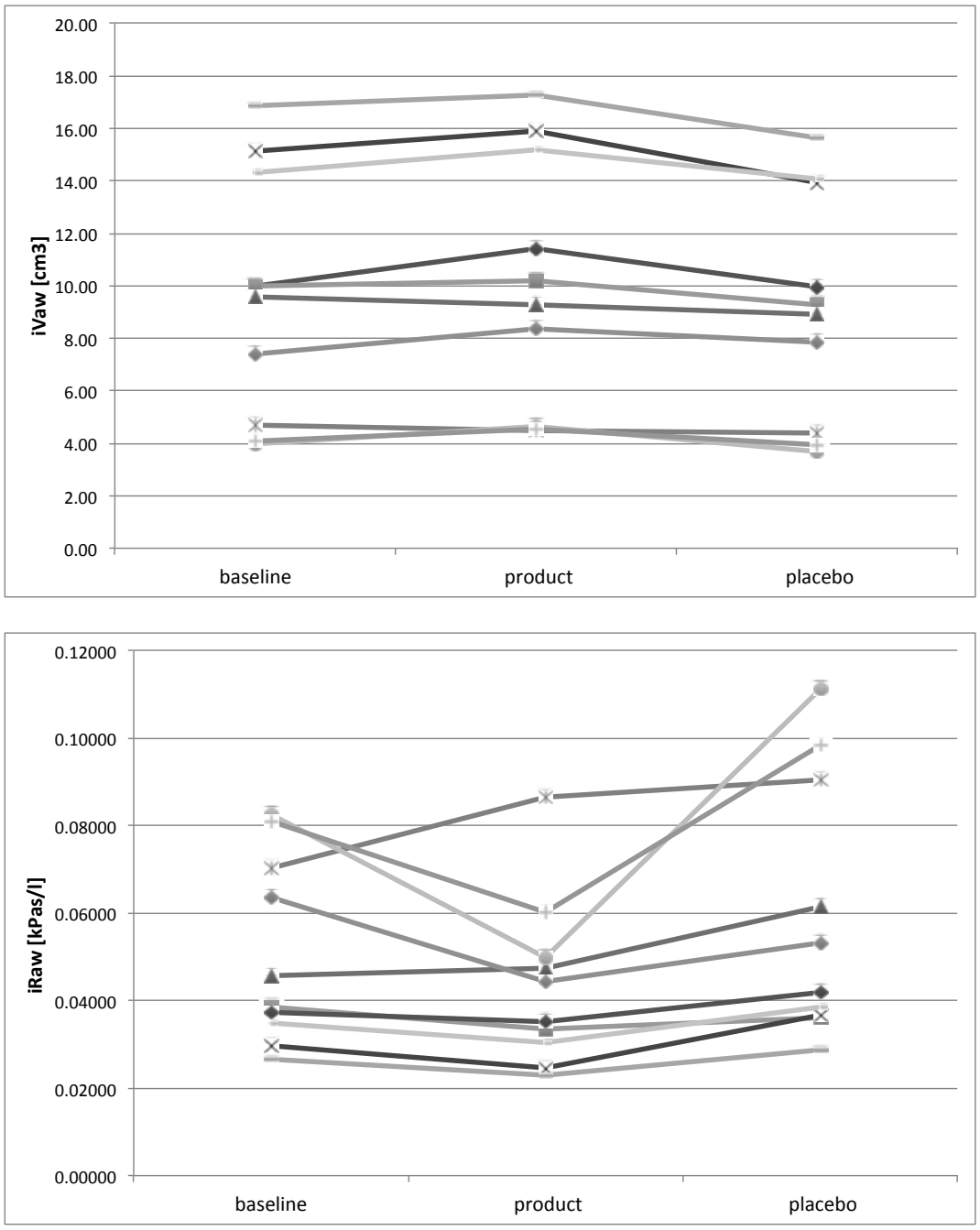

Figure 3 Individual changes in iVaw (top) and iRaw (bottom) after administration of combination product and placebo

Reference List

1. **Tashkin, D. P., B. Celli, M. Decramer, D. Liu, D. Burkhart, C. Cassino, and S. Kesten. 2008. Bronchodilator responsiveness in patients with COPD. *Eur Respir J* 31:742-750.**

2. **Calverley, P. M., P. S. Burge, S. Spencer, J. A. Anderson, and P. W. Jones. 2003. Bronchodilator reversibility testing in chronic obstructive pulmonary disease. *Thorax* 58:659-664.**

3. **Pauwels, R. A., A. S. Buist, P. M. Calverley, C. R. Jenkins, and S. S. Hurd. 2001. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. *Am.J Respir Crit Care Med.* 163:1256-1276.**

4. **Jones, P. W., F. H. Quirk, and C. M. Baveystock. 1991. The St George's Respiratory Questionnaire. *Respir Med.* 85 Suppl B:25-31.**

5. **Jones, P. W. and T. K. Bosh. 1997. Quality of life changes in COPD patients treated with salmeterol. *Am.J Respir Crit Care Med.* 155:1283-1289.**

6. **Jones, P. W. 2011. COPD: functional status, health status and primary care. *Prim.Care Respir J* 20:227-228.**

7. **Jones, P. W., J. A. Anderson, P. M. Calverley, B. R. Celli, G. T. Ferguson, C. Jenkins, J. C. Yates, J. Vestbo, and M. D. Spencer. 2011. Health status in the TORCH study of COPD: treatment efficacy and other determinants of change. *Respir Res.* 12:71.**

8. **Hurst, J. R., J. Vestbo, A. Anzueto, N. Locantore, H. Mullerova, R. Tal-Singer, B. Miller, D. A. Lomas, A. Agusti, W. Macnee, et al. 2010. Susceptibility to exacerbation in chronic obstructive pulmonary disease. *N.Engl.J Med.* 363:1128-1138.**

9. **Adams, C. P. and V. V. Brantner. 2010. Spending on new drug development1. *Health Econ.* 19:130-141.**

10. **Calverley, P. M., J. A. Anderson, B. Celli, G. T. Ferguson, C. Jenkins, P. W. Jones, J. C. Yates, and J. Vestbo. 2007. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N.Engl.J Med.* 356:775-789.**

11. **Calverley, P., R. Pauwels, J. Vestbo, P. Jones, N. Pride, A. Gulsvik, J. Anderson, and C. Maden. 2003. Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet* 361:449-456.**

12. **Burge, P. S., P. M. Calverley, P. W. Jones, S. Spencer, J. A. Anderson, and T. K. Maslen. 2000. Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. *BMJ* 320:1297-1303.**

13. **Mannino, D. M. 2002. COPD: epidemiology, prevalence, morbidity and mortality, and disease heterogeneity. *Chest* 121:121S-126S.**

14. **Haruna, A., S. Muro, Y. Nakano, T. Ohara, Y. Hoshino, E. Ogawa, T. Hirai, A. Niimi, K. Nishimura, K. Chin, et al. 2010. CT scan findings of emphysema predict mortality in COPD. *Chest* 138:635-640.**

15. **Mair, G., J. Maclay, J. J. Miller, D. McAllister, M. Connell, J. T. Murchison, and W. Macnee. 2010. Airway dimensions in COPD: relationships with clinical variables. *Respir Med.* 104:1683-1690.**

16. **Diaz, A. A., C. Valim, T. Yamashiro, R. S. Estepar, J. C. Ross, S. Matsuoka, B. Bartholmai, H. Hatabu, E. K. Silverman, and G. R. Washko. 2010. Airway count and emphysema assessed by chest CT imaging predicts clinical outcome in smokers. *Chest* 138:880-887.**

17. **Lin, C. L., M. H. Tawhai, G. McLennan, and E. A. Hoffman. 2009. Computational fluid dynamics. *IEEE Eng Med.Biol.Mag.* 28:25-33.**

18. **De Backer, J. W., W. G. Vos, C. D. Gorle, P. Germonpre, B. Partoens, F. L. Wuyts, P. M. Parizel, and W. De Backer. 2007. Flow analyses in the lower airways: Patient-specific model and boundary conditions. *Med.Eng Phys.***

19. De Backer, J. W., W. G. Vos, S. C. Vinchurkar, R. Claes, A. Drollmann, D. Wulfrank, P. M. Parizel, P. Germonpre, and B. W. De. 2010. Validation of computational fluid dynamics in CT-based airway models with SPECT/CT. *Radiology* 257:854-862.

20. De Backer, J. W., W. G. Vos, A. Devolder, S. L. Verhulst, P. Germonpre, F. L. Wuyts, P. M. Parizel, and W. De Backer. 2008. Computational fluid dynamics can detect changes in airway resistance in asthmatics after acute bronchodilation. *J.Biomech.* 41:106-113.

21. Appleton, S., P. Poole, B. Smith, A. Veale, T. J. Lasserson, and M. M. Chan. 2006. Long-acting beta2-agonists for poorly reversible chronic obstructive pulmonary disease. *Cochrane.Database.Syst.Rev.* 3:CD001104.

22. Sin, B. A., O. Akkoca, S. Saryal, F. Oner, and Z. Misirligil. 2006. Differences between asthma and COPD in the elderly. *J Investig.Allergol.Clin.Immunol.* 16:44-50.

23. Donohue, J. F. 2005. Minimal clinically important differences in COPD lung function. *COPD.* 2:111-124.

24. Calverley, P. M., K. F. Rabe, U. M. Goehring, S. Kristiansen, L. M. Fabbri, and F. J. Martinez. 2009. Roflumilast in symptomatic chronic obstructive pulmonary disease: two randomised clinical trials. *Lancet* 374:685-694.

25. Tashkin, D. P., B. Celli, S. Senn, D. Burkhart, S. Kesten, S. Menjoge, and M. Decramer. 2008. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N.Engl.J Med.* 359:1543-1554.

26. Bale, G., P. Martinez-Camblor, P. S. Burge, and J. B. Soriano. 2008. Long-term mortality follow-up of the ISOLDE participants: causes of death during 13 years after trial completion. *Respir Med.* 102:1468-1472.

27. Calverley, P. M. and N. G. Koulouris. 2005. Flow limitation and dynamic hyperinflation: key concepts in modern respiratory physiology. *Eur Respir J* 25:186-199.

28. Yang, X. L., Y. Liu, and H. Y. Luo. 2006. Respiratory flow in obstructed airways. *J Biomech.* 39:2743-2751.