

## The Minimal Important Difference for Residual Volume in patients with severe emphysema

**Running head:** Minimal Important Difference for Residual Volume

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## **Abstract**

Residual Volume measured by body plethysmography is a routine measurement in clinical pulmonary practice and is often an important outcome variable in clinical trials. However, it is not known which size of improvement can be regarded as being important in severe emphysema patients. Therefore, the aim of the study is to establish the Minimal Important Difference (MID) for Residual Volume in severe emphysema patients undergoing bronchoscopic lung volume reduction.

Ninety-one severe emphysema patients were included. Residual Volume and Total Lung Capacity were measured by body plethysmography. MID estimates were calculated with anchor-based and distribution-based methods. FEV<sub>1</sub>, Six-Minute-Walk-Distance and SGRQ total score were used as anchors and Cohen's effect size was used as distribution-based method.

The calculated MID estimates according to the different anchors and methods ranged between -0.31;-0.43L for Residual Volume, -6.1;-8.6% for percentage change in Residual Volume from baseline and -2.8;-4.0% for RV% TLC.

These MID estimates are useful for sample size determination of new studies on interventions aimed at reducing Residual Volume and for interpreting the results from clinical trials in severe emphysema patients.

## **Keywords**

Chronic Obstructive Pulmonary Disease

Hyperinflation

Lung volume reduction

## **Introduction**

Lung hyperinflation is an important feature in patients with Chronic Obstructive Pulmonary Disease (COPD) and is the result of increased airway resistance, reduced lung recoil and shortened available expiratory time [1]. Lung hyperinflation is strongly associated with important patient-centered outcomes like dyspnea, exercise tolerance and daily physical activity [1,2]. As a consequence it negatively affects patients' daily functioning and their quality of life.

In the past decade, reducing lung hyperinflation has become an important treatment goal in the management of severe emphysema. Several treatment methods have shown to improve lung hyperinflation temporarily, like pursed lip breathing, exercise training and oxygen use, while bronchodilators or lung volume reduction surgery have shown to improve lung hyperinflation in patients with COPD more definitively [1,3]. Lung volume reduction surgery has shown to improve lung function, quality of life and exercise capacity [4]. Lung volume reduction techniques by bronchoscope are less invasive, and show promising results in improving lung hyperinflation, quality of life and exercise capacity [5-8].

Residual Volume assessed by body plethysmography is commonly used to measure (changes in) lung hyperinflation. Body plethysmography is a routine measurement in clinical pulmonary practice based on Boyle's law, with reproducible measurements of absolute lung volumes. In studies on methods that aim to improve hyperinflation, increased Residual Volume constitutes an important inclusion criterion as well as outcome variable. Unfortunately, at this moment it is not known which size of improvement can be regarded as being clinically important for the severe emphysema patient.

The concept of Minimal Important Difference (MID) can be used to establish which size of effect in Residual Volume measurements after a treatment adequately reflects the perceived improvements by patients. MID can be defined as ‘a threshold value for a change that would be meaningful and worthwhile by the patients such that he/she would consider repeating the intervention if it were his/her choice to make again’ [9]. Any treatment effect above the MID is considered to be relevant. The MID for Residual Volume could therefore be useful when interpreting the significance of the results of clinical trials for patients, besides the statistical significance of the changes. Additionally, the MID could be used to establish the minimal numbers of subjects to be included in a study to be able to infer meaningful conclusions in future trials (i.e. power calculations). To our knowledge, the MID for Residual Volume in patients with severe emphysema has not been established yet.

The aim of this study is to establish the MID for Residual Volume in patients with severe emphysema who are being treated by bronchoscopic lung volume reduction.

## **Methods**

### *Study population*

A total of 91 patients with severe emphysema were included in this study. All patients participated in one out of three different bronchoscopic lung volume reduction studies, performed in one hospital in the Netherlands (University Medical Center Groningen). Patients were included in this study on MID if they had performed body plethysmography measurements both at baseline and 1 month after completing the specific bronchoscopic lung volume reduction treatment. Twenty-nine patients with severe homogeneous emphysema (10 controls) were included from a randomized, double-blind, sham controlled trial on bronchoscopic transbronchial airway bypass treatment (NCT00391612)[10], 33 patients with severe upper- or lower lobe heterogeneous emphysema (0 controls) were included from a bronchoscopic lung volume reduction treatment study using self expandable nitinol coils (NCT01220908)[6], and 29 patients with severe upper- or lower lobe heterogeneous emphysema (9 controls) were included from a bronchoscopic lung volume reduction treatment study using one-way endobronchial valves (NCT01101958) [7]. All studies were approved by the local Medical Ethics Committee and all patients gave written informed consent.

### *Measurements*

Residual Volume and Total Lung Capacity were measured by body plethysmography (PFT; Viasys) according to the ERS/ATS guidelines [11]. Furthermore, all patients performed spirometry (PFT, Masterscreen, Masterscope; Viasys) [12], a Six Minute Walk Distance test (6MWD) [13] and completed the St. George's Respiratory Questionnaire (SGRQ) [14]. All

measurements were performed at baseline and 1 month after the bronchoscopic lung volume reduction treatment.

#### *Minimal Important Difference calculation methods & statistical analysis*

Selected outcome variables for the statistical analyses were Residual Volume, percentage change in Residual Volume from baseline and the Residual Volume - Total Lung Capacity ratio (RV%TLC). To estimate a MID, various methods have been described in the literature [15,16]. Because the combination of multiple methods is generally recommended, our current study included both anchor-based and distribution-based methods to calculate the MID.

Anchor-based methods compare the change in outcome measure with the change in another measure with an established MID ('the anchor') [9]. The anchors chosen in this study were Forced Expiratory Volume in 1 second (FEV<sub>1</sub>) (MID: 100 ml [17]), 6MWD (MID: 26 meter [18]) and SGRQ total score (MID: 4 units [19]). An anchor is suitable to use if there is an appreciable association between the outcome variable and the anchor. Therefore, first the correlation coefficient between the change in Residual Volume, percentage change in Residual Volume from baseline or change in RV%TLC versus change in the anchor was assessed. In general, there is no consensus on when a correlation coefficient is considered to be an appreciable association. One review recommends statistically significant ( $p < 0.05$ ) Pearson correlation coefficients of 0.3 or higher as appreciable [16], and 2 studies in COPD patients performed the analyses when correlation coefficients were 0.3 or 0.5 [18,20]. Therefore, it is an arbitrary decision, and for the current study, Pearson correlation coefficients of 0.4 or higher were accepted. Afterwards, linear regression analyses were performed with respectively change in Residual Volume, percentage change in Residual Volume from baseline or change in RV%TLC as dependent variables and one of the above described anchors as the independent variable.

Subsequently, the MID value of the anchor is put into the equation derived from the linear regression analysis and the MID was calculated from the established equation.

Distribution-based methods compare the change in outcome measure with some measure of variability [9]. In this study, the Cohen's effect size was used. A moderate effect size was calculated of the change score of the outcome measure from baseline to 1 month after the bronchoscopic lung volume treatment.

All statistical analyses were performed using PASW statistics 18.

## Results

Ninety-one patients with severe emphysema, who had undergone body plethysmography measurements at baseline and 1 month later, were included in this study (63% female, mean age 60 years). Population characteristics at baseline as well as the 1 month follow up change scores from baseline are shown in table 1.

### *MID estimates according to Anchor-based method*

Scatter plots and Pearson correlation coefficients between change in Residual Volume, percentage change in Residual Volume from baseline, and RV%TLC respectively, versus change in FEV<sub>1</sub>, 6MWD and SGRQ (total score) are depicted in figure 1. Pearson correlation coefficients ranged from 0.43 to 0.58. The highest correlations were present with FEV<sub>1</sub> (range 0.47- 0.58) and the lowest with SGRQ total score (range 0.43- 0.47).

The MID estimates derived from the linear regression equations with use of the anchor MID showed that the MID estimates for the absolute change in Residual Volume according to the different anchors were: -0.43L (FEV<sub>1</sub>), -0.41L (6MWD) and -0.35L (SGRQ total score) (table 2). The MID estimates for percentage change in Residual Volume from baseline according to the different anchors were: -8.62% (FEV<sub>1</sub>), -8.41% (6MWD), and -6.86% (SGRQ total score). The MID estimates for RV%TLC according to the different anchors were: -4.0% (FEV<sub>1</sub>), -3.9% (6MWD), and -3.2% (SGRQ total score).

*MID estimates according to the Distribution-based method*

The MID estimates calculated with the distribution-based method (Cohen's effect size) were: -0.31L for Residual Volume, -6.1% for percentage change in Residual Volume from baseline and -2.8% for RV%TLC (table 2).

## Discussion

This is the first study describing Minimal Important Difference (MID) estimates for lung hyperinflation measurements. Our results indicate a MID estimate for Residual Volume of -0.31; -0.43 liter, for percentage change in Residual Volume from baseline of -6.1; -8.6% and for RV%TLC of -2.8; -4.0%, in patients with severe emphysema undergoing bronchoscopic lung volume reduction. MID estimates were determined using both anchor-based and distribution-based methods. High correlations were found between changes in lung hyperinflation measurements and changes in patient-centered outcomes like exercise capacity and health related quality of life, emphasizing the importance of this clinical feature for patients with severe emphysema.

Anchor-based and distribution-based methods were used to determine the MID, and for the anchor-based method three anchors were chosen. Therefore, four MID estimates of each outcome variable were generated. These ranges of MID estimates can be used for power calculations in future trials. For this specific intervention and study population, in the next paragraphs, the used methods and anchors will be critically evaluated.

For the anchor-based method, it is important that the used anchor is suitable for the analysis. A number of criteria can be used to establish the quality of the anchor; firstly if the MID of the anchor is derived from multiple high quality studies, including many well characterized COPD patients, using multiple methods to establish the MID, and agreeing about the final MID estimate. Secondly, if the anchor is derived from a comparable COPD population, thus for the current study patients with severe emphysema. Thirdly, if the anchor somehow reflects the perception of

improved lung hyperinflation. And, finally, if the anchor is highly correlated with changes in Residual Volume variables. The anchors used in the current study will be discussed below.

The Forced Expiratory Volume in 1 second (FEV<sub>1</sub>) seems to be attractive as it is a highly reproducible measurement and strongly associated with Residual Volume outcomes. The MID calculation for FEV<sub>1</sub> is based on multiple studies, but establishing the MID was never the primary aim of these studies [17]. Also, the MID of FEV<sub>1</sub> was based on a broad variety of COPD patients, including different treatment modalities and therefore might not be applicable to our population. In addition, the improvement in FEV<sub>1</sub> is largely dependent of improvement in Vital Capacity, which is mainly dependent on a change in Residual Volume, so Residual Volume and FEV<sub>1</sub> are indirectly related. However, the major disadvantage of this anchor is that it does not reflect the perceived improvement by patients [1] and is not a patient-reported outcome.

The Six-Minute-Walking-Distance (6MWD) highly correlated with Residual Volume measurements. Another advantage of this anchor is that the 6MWD MID estimate was calculated from a study investigating the effect of lung volume reduction surgery in severe COPD patients [18], and thus is derived from a comparable COPD study population that underwent a comparable, although more invasive intervention. Furthermore, another study investigated the 6MWD MID using another treatment method and demonstrated a similar MID estimate for lung rehabilitation [20]. Also, the perceived improvement in 6MWD is thought to be a good reflection of the perceived improvement in lung hyperinflation after bronchoscopic lung volume reduction treatment.

The St. George's Respiratory Questionnaire (SGRQ) total score seems more attractive because this instrument is excellently validated for patient-reported outcomes in COPD. However, when using the SGRQ total score as anchor the Pearson correlation coefficients demonstrated the lowest values of the three anchors in this study. Another disadvantage is that the MID estimate for SGRQ total score (4 units) is based on multiple studies, using different populations and different MID estimation techniques [19].

A recent study showed that different interventions in different groups of COPD patients may produce different MID estimates [21]. The results in SGRQ total score from three different lung volume reduction treatment studies were plotted against the change in 6MWD and compared with the effects after pulmonary rehabilitation. A different response pattern between 6MWD and a larger result in health-related quality of life was found, between the different treatment modalities. This could indicate that a higher MID estimate for the SGRQ total score for studies using lung volume reduction techniques would be more appropriate. Furthermore, it is important to acknowledge that unblinded interventions can lead to larger improvements in health related quality of life (HRQL), due to the fact that patients are aware that they have been treated. Therefore, we advocate that the MID of the SGRQ should subsequently be established in a similar COPD population after a similar treatment, preferably, with a placebo-controlled design before using it as an anchor.

Distribution-based methods do not comply with the primary aim of the MID concept, namely identifying an effect size that is meaningful in the perception of the patient. Therefore, we agree with the consensus that the distribution-based method should only be used to support estimates derived from anchor-based methods [9,16].

In summary, out of the used methods and anchors in the current analyses, the anchor method is the best method to calculate the MID and the 6MWD appears to be the anchor with the highest quality for this specific patient group and intervention.

For the current study, the percentage change in Residual Volume from baseline and RV%TLC were chosen as outcome variables besides absolute change in Residual Volume. Percentage change in Residual Volume from baseline was chosen because this adjusts for baseline scores, e.g. it takes gender differences into account. RV%TLC was chosen because it takes one's individual lung capacity into account, and has shown to be an important determinant of improvement in FVC after LVRS [22]. Unfortunately, most MID estimates are only expressed in absolute numbers. One study that did measure the MID estimate of percentage change from baseline for 6MWD, found a MID estimate of 14% [20]. However, this MID estimate was based on the effects after a rehabilitation program and therefore was not chosen as anchor in our current study. We recommend that besides MID estimates for absolute variables, also the percentage change from baseline and percentage predicted should be calculated.

A first limitation of the current study is the relative small sample size. However, all study measurements were performed in one specialized research hospital in the Netherlands, always in the same setting, using the same equipment. This has led to highly standardized measurements with low variation, possibly explaining the rather high correlations between changes in lung hyperinflation and the chosen anchors. A second limitation is the measurement of only static lung hyperinflation and not dynamic lung hyperinflation. We anticipate that improved dynamic lung hyperinflation is at least as important for perceived dyspnea and exercise tolerance as improved static lung volume. Future lung volume reduction studies might therefore also investigate

correlations between improved dyspnea scores and improved inspiratory capacities during exercise. A final limitation of the current study is the potentially low generalizability of the MID estimates to other COPD populations or other treatment methods. Our study population is rather homogenous (predominantly female, severe emphysema patients) and based on short term results, this strengthens the MID estimate for this population, but might limit the usefulness for other COPD populations, treatment methods and long term effects. It is indeed known, at least for SGRQ, that different interventions can lead to different MID estimates in different COPD populations [21]. Therefore, to be able to apply the MID estimates to a more heterogenic COPD population, further research in a larger, more gender balanced population is needed to investigate if other interventions that reduce lung hyperinflation, like treatment with bronchodilators, and other COPD populations provide the same MID estimates for Residual Volume measurements.

In conclusion, this is the first study that estimated the MID for change in emphysema-related static lung hyperinflation. The calculated MID estimates according to the different anchors and methods ranged between -0.31;-0.43L for Residual Volume, -6.1;-8.6% for percentage change in Residual Volume from baseline and -2.8;-4.0% for RV%TLC. These MID estimates are useful for sample size determination of new studies on interventions aimed at reducing Residual Volume and for interpreting the results from clinical trials in patients with severe emphysema.

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## Tables

Table 1: Baseline characteristics and change scores at 1 month follow up (n=91)

<i>Variable</i>	<b>Baseline</b>		<b>Change scores 1 month - baseline<sup>#</sup></b>		
	absolute	% predicted	absolute	% change from baseline	% > MID
<b>Female/ Male.</b> number	57/34	na	na	na	na
<b>Age,</b> year	60.1 ± 8.3	na	na	na	na
<b>BMI,</b> kg/m <sup>2</sup>	24.2 ± 3.3	na	0.3 ± 0.8	1.2 ± 3.3	na
<b>FEV<sub>1</sub>,</b> L	0.73 ± 0.3	26.7 ± 9.8	0.10 ± 0.17	13.1 ± 21.2	35.2
<b>6MWD,</b> m	319.2 ± 97.5	48.8 ± 14.7	29.7 ± 58.6	11.3 ± 23.2	52.2
<b>SGRQ,</b> total score	62.5 ± 11.2	na	-7.8 ± 12.9	-13.0 ± 21.5	64.0
<b>RV,</b> L	5.0 ± 1.1	241.0 ± 46.6	-0.43 ± 0.61	-8.7 ± 12.2	?
<b>TLC,</b> L	7.8 ± 1.4	136.5 ± 14.2	-0.23 ± 0.43	-2.8 ± 5.5	?
<b>RV%TLC,</b> %	64.3 ± 8.3	166.8 ± 23.5	-4.1 ± 5.7	-6.3 ± 8.8	?

Data presented as number or mean ± standard deviation, FEV<sub>1</sub>: Forced Expiratory Volume in 1 second, RV: Residual Volume, TLC: Total Lung Capacity, 6MWD: 6 Minute Walk Distance, SGRQ: St. George's Respiratory Questionnaire, MID: Minimal Important Difference, na: not applicable, <sup>#</sup> Placebo/control group included

Table 2: MID estimates for Residual Volume

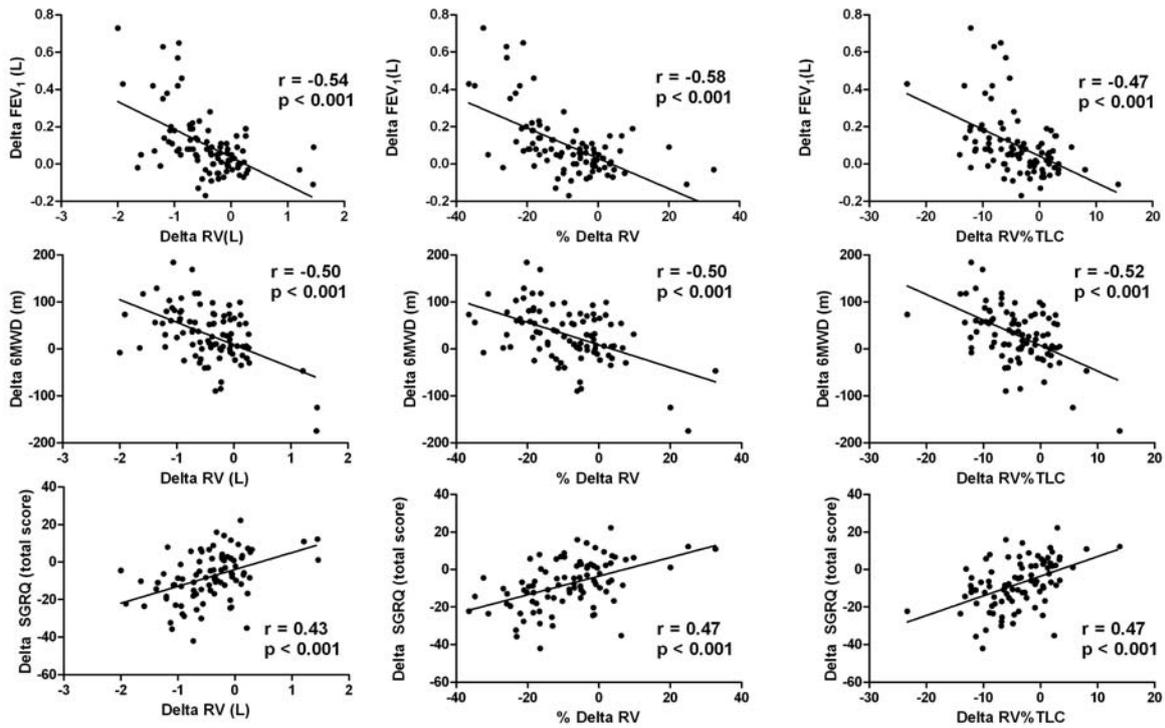
<b>Anchor-based method</b>						
	<b>change in RV</b>		<b>% change in RV</b>		<b>change in RV%TLC</b>	
<b>FEV<sub>1</sub>, L</b>	-0.43	(-0.62; -0.24)	-8.62	(-5.71; -9.53)	-4.0	(-5.9; -2.2)
<b>6MWD, m</b>	-0.41	(-0.59; -0.23)	-8.41	(-4.92; -11.91)	-3.9	(-5.5; -2.3)
<b>SGRQ, total score</b>	-0.35	(-0.45; -0.24)	-6.86	(-4.90; -8.82)	-3.2	(-4.2; -2.3)
<b>Distribution-based method</b>						
Cohen's effect size	-0.31		-6.1		-2.8	

Data presented as MID (95% Confidence Interval), RV: Residual Volume, TLC: Total Lung Capacity, 6MWD: 6 Minute Walk Distance, FEV<sub>1</sub>: Forced Expiratory Volume in 1 second, SGRQ: St. George's Respiratory Questionnaire

**Legend to the figure.**

Figure 1: Scatter plots of change in lung hyperinflation measurement versus change in anchor variable.

Figure 1: Scatter plots of change in lung hyperinflation measurement versus change in anchor variable.



**Legend:**

FEV<sub>1</sub>= Forced Expiratory Volume in 1 second, 6MWD= Six Minute Walk Distance, SGRQ= St. George's Respiratory Questionnaire, RV= Residual Volume, TLC= Total Lung Capacity, r= Pearson's correlation coefficient