

Methacholine Bronchial Provocation Measured by Spirometry versus Wheeze Detection in Preschool Children

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Abstract

Background: Determination of PC₂₀-FEV₁ during Methacholine bronchial provocation (MCH) is considered to be unfeasible in preschool children, as it requires repetitive spirometry sets.

Aim: Assess the feasibility of determining PC₂₀-FEV₁ in preschool age children and compare the results to the wheeze detection (PCW) method.

Subjects and Methods: 55 preschool children (ages 2.8-6.4years) with recurrent respiratory symptoms were recruited. Baseline spirometry was performed according to ATS/ERS guidelines MCH was performed and the following parameters were determined at baseline and after each inhalation: spirometry-indices, lung auscultation at tidal breathing, oxygen saturation, respiratory and heart rate.

Analysis: Comparison between PCW and PC₂₀-FEV₁ and clinical parameters at these end-points was done by paired Student's t-tests.

Results: Thirty-six of 55 children successfully performed spirometry-sets up to the point of PCW. PC₂₀-FEV₁ occurred at a mean concentration of 1.70±2.01mg/ml while PCW occurred at a mean concentration of 4.37±3.40mg/ml (p<0.05). At PCW, all spirometry-parameters were markedly reduced: FVC by 41.3±16.4% (mean ±SD); FEV₁ by 44.7 ±14.5%; PEF_R by 40.5±14.5 and FEF₂₅₋₇₅ by 54.7±14.4 (P<0.01 for all parameters). This reduction was accompanied by de-saturation, hyperpnoea, tachycardia and a response to bronchodilators.

Conclusions: Determination of PC₂₀-FEV₁ by spirometry is feasible in many preschool children. PC₂₀-FEV₁ often appears at lower provocation dose than PCW. The lower dose may shorten the test and encourage participation. Significant decrease in spirometry indices at PCW suggests that PC₂₀-FEV₁ determination may be safer.

Key words: Preschool, Airway reactivity, Methacholine challenge, PCwheeze, PC₂₀-FEV₁.

Running title: PC₂₀-FEV₁ compared with PCW in preschool children.

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Background

Measurements of bronchial hyper-reactivity (BHR) have provided insight into the physiological basis of asthma, and provide a tool for asthma diagnosis, assessment of asthma severity and response to treatment. [1,2]. The bronchial provocation tests require an objective outcome measurement that reflects airway function. Forced expiratory volume in 1 second (FEV₁) has been standardized to measure changes in airway caliber that occur with bronchial provocation [3]. In the Methacholine challenge test (MCT), the provocative concentration reducing FEV₁ by 20% from baseline (PC20-FEV₁) is considered the end point of the test. Traditionally, spirometry in young children has been difficult to achieve. Therefore, techniques that do not require cooperation (i.e., detection of wheeze during normal breathing, a fall of 5% in O₂-saturation (SaO₂), or an increase of 50% in respiratory rate and/or heart rate) have been used as alternative end points in bronchial provocation tests in the preschool age [4-7]. Recently it has been shown that young children can be taught to perform reliable forced expiratory maneuvers [8-11]. Yet, it is unclear whether these young children have the drive to perform and tolerate repetitive reproducible spirometry-sets that are measured during the interval between inhalations. Concentration of methacholine (MCH) causing wheeze, a fall of 5% in O₂- Saturation, an increase of 50% in respiratory rate and/or heart rate (PCW) and PC20-FEV₁ were compared in school children and a good correlation was found between the two methods [7,12-14].

This study assesses the ability of young asthmatic preschool children to cooperate with repetitive spirometry-sets during MCT, and thereby allow determination of PC20-FEV₁ in comparison with PCW.

Subjects and Methods:

Subjects: Consecutive preschool children referred to the Pediatric Pulmonary Clinic, Meyer Children's Hospital, Rambam Medical Center, Haifa, over a 6-month period were recruited. None of the children had experienced spirometry previously. *Inclusion criteria were:* 2.5-6.5 year-old children who were asthmatic according to GINA guidelines [15] with recurrent episodes of wheeze, cough and/or shortness of breath with clinical response to bronchodilator; normal chest auscultation and FEV₁ >75% of predicted for healthy preschool children [9] after saline inhalation. *Exclusion criteria were:* presence of other chronic respiratory conditions; emergency room visit in the past three months; respiratory infection in the past month; oral or inhaled steroids or other anti-inflammatory medication taken in the last week; bronchodilator taken within 24 hours prior to the test.

The Rambam Medical Center Ethics Board approved the study. Parental consent was obtained for each child.

Methods:

Methacholine Challenge: Tests were performed in a designated room at the Pediatric Pulmonary Unit, Meyer Children's Hospital, Haifa, Israel. A parent and the investigating team (a pediatric pulmonary physician, respiratory physiologist and technician) were present throughout the test. MCT was performed according to published guidelines, [3], with doubling doses of fresh Methacholine solutions (0.06 to 8.00 mg/ml) dissolved in saline. Solutions were driven by compressed air of 5 l/min flow (giving a mean output of 0.4 ml/min), and nebulized using a Hudson nebulizer (Hudson RCI, Temecula, CA, USA). Inhalations were performed using a facemask while the child was sitting up straight and breathing normally. Nebulized Methacholine was inhaled for 2 minutes, with 5-minute

intervals between doses, until the maximal concentration or the end point was reached. To ensure safety, the MCH increment was only half the usual amount when transient wheeze or cough was noted. Oxygen saturation and heart rate were monitored continuously by pulse oximetry (Biox 3700e; Ohmeda). A single observer (LB) performed auscultation for 20 seconds over the trachea and two zones of both lungs (upper front and lower back) according to Springer et al. [7]

The following indices were considered "end of test": appearance of audible wheeze, a fall of $\geq 5\%$ in O₂-saturation, or an increase of $\geq 50\%$ in respiratory rate and/or heart rate [7]. At the "end of test", spirometric measurements were performed, followed by administration of nebulized Albuterol (2.5 mgr).

Spirometry: Forced expiratory flow volume (FEFV) curves were measured with a ZAN100 commercial spirometer (ZAN Messgeraete GmbH, Oberthulba, Germany). Calibration was performed before the testing sessions. The curves were monitored on the computer screen to ensure best effort. Results were corrected to BTPS conditions. The software included an interactive animated computer game set by targets of the FEFV maneuver, combining forced inhalation preceding forced expiration, peak expiratory flow rate (PEFR) and forced vital capacity (FVC) with emphasis on prolonged expiration. [8] The targets were the extrapolated values derived from comparative data from older children, corrected for height. [16] An experienced pulmonary technician instructed each child how to operate the game. On-line rejection of curves was based on visual inspection for "non-cooperation" errors and included: poor effort; incomplete expiration; cough; glottis closure. Curves had to show a rapid rise to peak flow, and gradual, smooth decline of flow. Baseline maneuvers were repeated to visually obtain best possible efforts on at least 3 technically acceptable FEFV curves. After

obtaining baseline spirometry, MCT was performed. A duplicate spirometry set was performed immediately after auscultation. PC20-FEV₁ was determined off line by the provocative concentration that reduced FEV₁ by 20% from baseline. Spirometry indices included FVC, FEV₁, PEF, forced expiratory flow at 50% FVC (FEF₅₀), FEV₁/FVC ratio.

Analysis and Statistics:

Three baseline spirometry curves were analyzed for acceptability criteria according to ATS/ERS guidelines [17,18] and in comparison with similar data for preschool children [11,19]. These included: a) "Start of test" criteria: time to peak expiratory flow and backward extrapolated volume (V_{be}) b) "End of test criteria": described by "total expiratory time" and the ratio of "no change in expiratory volume" to "total expiratory time" c) reproducibility of the three baseline curves, calculated as SD/mean*100.

After inhalations, the curves were inspected visually online, and were analyzed offline in relation to baseline using paired t-test. Pearson's correlation coefficient was used to compare PCW and PC20-FEV₁. Differences were considered significant when $p < 0.05$.

Results

A total of 55 children (28F/27M, age range 2.8-6.4 years) were recruited. Eleven children failed spirometry and underwent MCT by auscultation only. Failure to perform spirometry was due to lack of comprehension (4 children) or failure to repeat spirometry after baseline measurements (7 children). Failure was not age dependent. Eight children refused to cooperate with either test. Thirty-six of 55 (65.5%) children performed the MCT with spirometry tests and with auscultation. Of these 36 children, eleven were 2.5-3.9 years old, 15 were 4-5 years old, and 10 were >5 years old. Three children failed to produce FEV₁ on the baseline measurements but were able to produce it after saline administration. In these

children, post saline FEV₁ measurements were considered as baseline. FEV₁ at that point was >75% predicted. The anthropometric data and baseline lung function of the 36 patients are presented in Table-1a and clinical characteristics in Table-1b.

All children participating in the study had a previous clinical response to bronchodilators. The average duration of respiratory symptoms was 18±14 weeks. Five children were not receiving any medication for a period of weeks. Nine children were receiving bronchodilators as needed, and 22 were using both inhaled steroids and bronchodilators as needed.

Quality of baseline maneuvers:

Start of test: Peak expiratory flow rates were reached within 98±7ms and mean V_{be} was 3.4±1.5% of FVC. *Intra-subject reproducibility* for the baseline triplicate maneuvers was: for FVC, 4.1±2.3%; for FEV₁, 3.8±2.3%; for PEF_R, 4.4±2.8% and for FEF₂₅₋₇₅, 7.9±3.5%.

End of test: Mean expiratory time was 1.48±0.47 seconds and the ratio of "no change in expiratory-volume" to "total expiration time" was 0.20±0.06.

MCT test: Children's response to MCT (n=36) is summarized in Figure 1 and Table 2. Average test time to reach PC₂₀-FEV₁ was 29±11 minutes, while for PCW it was 41±10 minutes (not including bronchodilator administration) (p<0.001). The end point of the challenge was determined by the pediatric pulmonologist as positive in 35/36 children. One child did not display any of the determined criteria for PCW up to 8mg/ml and was considered to have no BHR. The mean (±SD) concentration at PCW for the 36 children was 4.26±3.31mg/ml. Wheezing at the end point was observed in 26/36 children and in 9/36 the test was ended before the appearance of wheeze due to either oxygen desaturation or

tachypnea accompanied by audible long expiration. Mean increase in heart rate at PCW was $25.5 \pm 11\%$; respiratory rate increased by $30.0 \pm 21.1\%$ and SaO_2 decreased by $6.3 \pm 2.7\%$.

PC20-FEV₁ occurred at a mean concentration value of 1.96 ± 1.83 mg/ml. The one child who did not respond to MCH of up to 8mg/ml by PCW (negative BHR) did not show a fall of 20% from baseline FEV₁ value either. The other 35 children exhibited a fall of 20% in FEV₁ from baseline values in response to MCH ≤ 8 mg/ml (Figure 1 and Table 2). A representative set of FEFV curves from a single patient that includes the predicted curve, baseline, PC20-FEV₁ and end of test curves is shown in Figure 2.

At PC20-FEV₁ there was a mean increase in heart rate of $13.5 \pm 11.0\%$, respiratory rate increased by $15.4 \pm 15.8\%$ and SaO_2 decreased by $2.4 \pm 2.1\%$ from baseline level. These changes were significantly lower than those found at PCW ($p < 0.01$ for three parameters). The appearance of PC20-FEV₁ occurred 2 concentrations earlier than PCW in 5 children, 1.5- concentrations earlier in 3 children, one concentration earlier in 17 children, 0.5 concentrations earlier in 3 children and at the same concentration as PCW in 7 children (Figure 1). There was a high degree of correlation between PCW and PC₂₀-FEV₁ ($\text{PCW} = 1.2195 * \text{PC}_{20}\text{-FEV}_1 + 0.0288$; $R^2 = 0.9733$; $p < 0.005$). The effects of MCH on the spirometry parameters are presented in Table 3.

At PC₂₀-FEV₁, parameters were moderately decreased, while at end point, test parameters were markedly reduced. The severity of FEV₁ reduction at PCW was variable, ranging from 30.8 to 68.2% of baseline.

Bronchodilators improved FEV₁ by 43±29% from PCW values and all respiratory symptoms disappeared shortly after bronchodilator administration. A representative set of FEFV curves from a different patient, including predicted curve, baseline, end of test and post bronchodilator curves is presented in Figure 3. It can be seen that the shape of the FEFV curve and values returned to baseline 15 minutes after bronchodilator administration.

Discussion:

In this study we assessed the feasibility of determining PC₂₀-FEV₁ during Methacholine bronchial provocation testing in asthmatic preschool children. We found MCT was feasible in 65% of our preschool children. Children as young as 3 years old complied and cooperated with what seems to be a most fatiguing procedure. Baseline measurements met most of the ATS criteria for older children and adults [17,18] and quality control studies on spirometry in preschool children [11,19]. We found that PC₂₀-FEV₁ correlates with PCW. However, PC₂₀-FEV₁ frequently precedes PCW. All spirometry parameters at PC₂₀-FEV₁ were significantly higher than those measured at PCW.

In this study, we used interactive spirometry games [8] with multiple spirometry targets, since single targeted games (usually peak expiratory flow targeted) have not fulfilled expectations [20,21]. Our teaching method is supported by the findings that 65% of the children fully cooperated not only with baseline measurements but also with spirometry sets. Of note, 26 of the 36 children were younger than 5 years. Conforming quality control was necessary to proceed with the test. The quality control of baseline spirometry in our study met

most ATS/ERS criteria concerning reproducibility and start of test criteria [17,18] and matched those reported for preschool children [11,19], encouraging us to continue with the MCT test. It should be noted that our work did not compare verbal coaching [9] or other spirometry games [11,22] as the preferable methodology for keeping the child going and performing repetitive spirometry sets.

The mean PC₂₀-FEV₁ of 1.70±2.01mg/ml found in our group reflects a mild degree of BHR, as we recruited children with mild asthmatic symptoms. Our findings for PC₂₀-FEV₁ are comparable to those of Hayden et al [13], who found a mean PC₂₀-FEV₁ at FEV_{0.5} of 2.49±2.55 mg/ml in infants. Adinoff et al [23] reported a mean provocative dose of 3.0mg/ml Methacholine in their preschool children and infants. Tepper [24] et al. reported that infants with asthma-like respiratory symptoms might respond to MCH concentrations as low as 1.25 mg/ml. These studies included infants who were studied under sedation with the raised volume compression technique. Although differences may reflect different disease severity, it can also reflect differences in methodologies.

PCW: We found that PCW occurred in our group at a mean concentration of 4.26±3.31mg/ml. PCW values in our study were much higher than the PCW (0.4 mg/ml) reported by Springer [7]. The difference may be attributed to inclusion of more severe asthmatics in their study group.

Spirometry at PCW: We found that PC₂₀-FEV₁ occurred at a lower concentration than PCW in most subjects. This finding is in agreement with several other studies comparing PCW detection to PC₂₀-FEV₁ in school age children. [4-7,14] There was a significant correlation between the two tests (PCW vs. PC₂₀-FEV₁; p<0.005). However, in none of these studies were spirometry measurements carried out to the point of wheeze. We found that at PCW, FEFV curves visually seemed to be smaller and all parameters were reduced simultaneously

(Figure 2), with a highly significant reduction in flows and volume parameters. The reduction in curve was gradual in most children, was accompanied by an increase in respiratory symptoms (Table 2), and responded to bronchodilators, and hence was not considered to reflect fatigue. To further strengthen this point a representative curve of one child illustrating, a poor effort performed at teaching process vs. end of test curve is shown in figure 4. The poor-effort curve did not fulfill start of test criteria and is round while the "end of test curve" has an obstructed shape.

The reduced FVC and flows are most likely due to a severe degree of airway narrowing involving small to medium airways that may be accompanied by air trapping and elevation in FRC. Alternatively, it may be due to partial closure of airways, or increased negative intra-thoracic pressure due to increased airway resistance [6] or increased glottic narrowing due to MCH irritation [25,26]. This pattern occurred in some cases before appearance of wheeze or other clinical end-points. Indeed, in 9/36 subjects, the test was terminated due to oxygen desaturation or tachypnea rather than wheeze. Similar to our results, Sprickelman et al [26] reported that wheeze was detected in only 33% of 15 school-age asthmatic children at PC₂₀-FEV₁, and Springer et al [7] terminated the test without the presence of wheeze in 19.2% of young children. Novitzki et al (4) found in 5-8 year-old children that FEV₁ is decreased by 33.3±7.4% at PCW. Spence et al [27] reported a mean fall of 51±14% from baseline FEV₁ when wheeze appeared in their asthmatic older subjects. Our results strengthen these prior findings, and suggest that spirometric PC₂₀-FEV₁ may result in inhalation of lower MCH concentrations than those used to achieve wheeze.

Measuring PCW during tidal volume breathing has the advantage that no active cooperation on the child's part is needed. Therefore the success rate of PCW is higher than spirometry (44/55 children). However, there was significant shortening of test time in determining PC₂₀-

FEV₁ relative to PCW, and avoidance of inhalation of higher concentrations of MCH used to achieve wheeze. Furthermore, our findings of significant diminished flows at PCW suggest that PC20-FEV₁ is a safer endpoint of test.

We conclude that PC20-FEV₁ is feasible in preschool asthmatic children using respiratory games techniques and that the children tolerate repetitive duplicate sets of spirometry maneuvers. PC₂₀-FEV₁ in preschool children appears to be as sensitive as in adults and school children. Further studies are needed for standardization and definition of methodological criteria.

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Figures legend

Figure 1: Number of children responding to each MCH concentration (mg/ml) at PCW and at PC₂₀-FEV₁

Figure 2: A representative example of forced expiratory flow-volume curves from one child. Predicted, Baseline, PC₂₀-FEV₁ and PCW curves are presented

Figure 3: A representative example of forced expiratory flow-volume curves from one child. Predicted, Baseline, Post challenge and 15 minutes post bronchodilator administration are presented.

Figure 4: A representative example of poor-effort forced expiratory flow-volume curves from one child. Baseline, Post challenge and poor effort during teaching process are presented.

Table 1: Anthropometric and clinical data and spirometry baseline values of the 36 children who performed both auscultation and spirometry. The results are expressed as mean \pm SD.

Table 1a: Anthropometric data and lung function

Anthropometric data				Baseline lung function %predicted [16]				
N	Height (cm)	Weight (kg)	Sex (M/F)	FVC	FEV1	FEV1/FVC	PEFR	FEF50
36	104 \pm 7	18 \pm 3	20/16	95 \pm 15	91 \pm 14	96 \pm 3	99 \pm 14	101 \pm 16

Table 1b: Clinical Characteristics

N =	Recurrent cough	Recurrent lung infiltrates	Shortness of breath	Wheezing	Atopy	Family history of allergy	GINA [15]
36							
N	35	24	24	16	16	23	1-2

Table 2: Appearance of respiratory distress signs at PCW and PC20-FEV1

Symptom	Cough	Wheeze	Rhonchi	Prolonged Audible Expiration	Decrease SaO ₂	Increased HR	Increased RR
# Children at PCW	32	26	29	24	33	28	25
# Children at PC20-FEV1	28	2	7	7	15	3	7

Table 3: Changes in respiratory indices at PCW and PC₂₀-FEV₁. The results are expressed as mean \pm SD. (n=35/36, as one child did not respond to MCH and his spirometry did not change throughout the test).

Parameter	End of test	PC ₂₀ -FEV ₁
FVC	- 41.3 \pm 15.5	- 18.4 \pm 10.0 *
FEV ₁	- 44.7 \pm 14.5	- 24.6 \pm 6.4 *
FEV ₁ /FVC	- 6.09 \pm 6.8	- 4.1 \pm 3.8 *
PEFR	- 44.2 \pm 13.2	- 21.4 \pm 10.6 *
FEF ₅₀	- 61.2 \pm 14.2	- 38.6 \pm 16.9 *
Expiratory time (sec)	+2.8 \pm 0.4	+2.2 \pm 0.4 *

* Changes at PC₂₀-FEV₁ are significantly lower than at "end of test", p<0.05

Figure 1

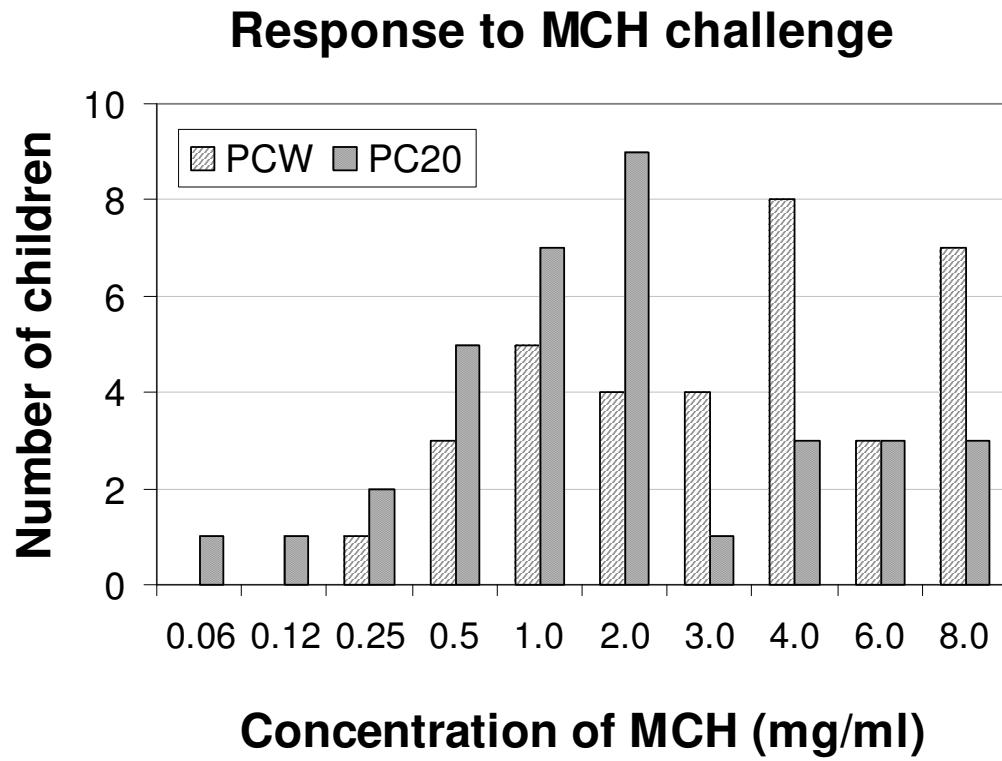


Figure 2:

The effect of MCT on FEFV curve

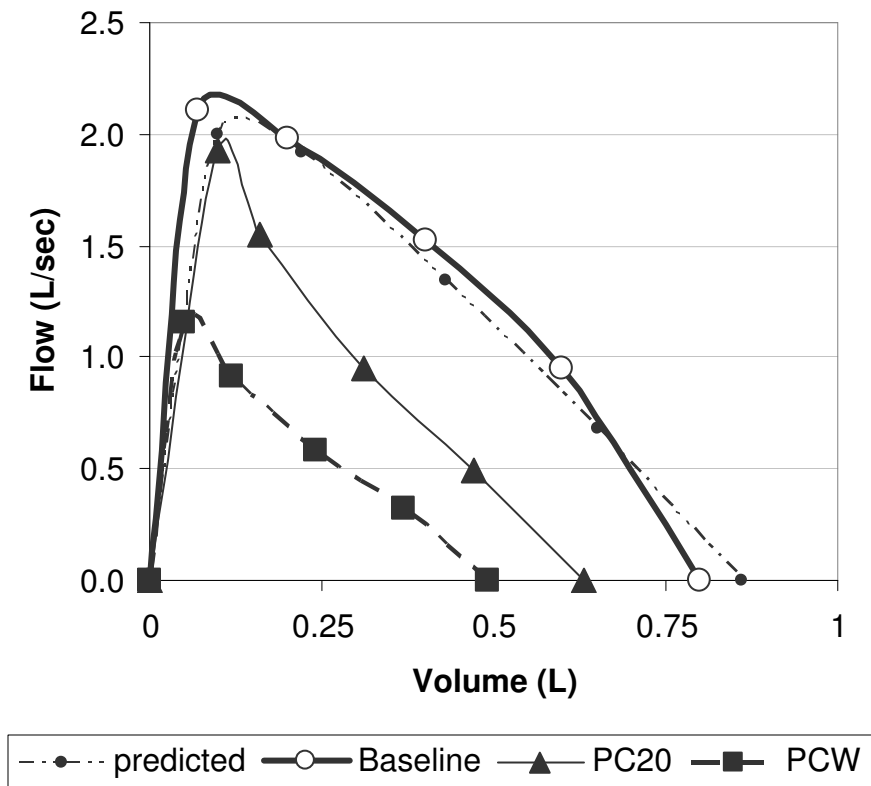
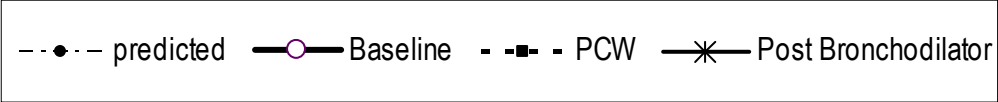
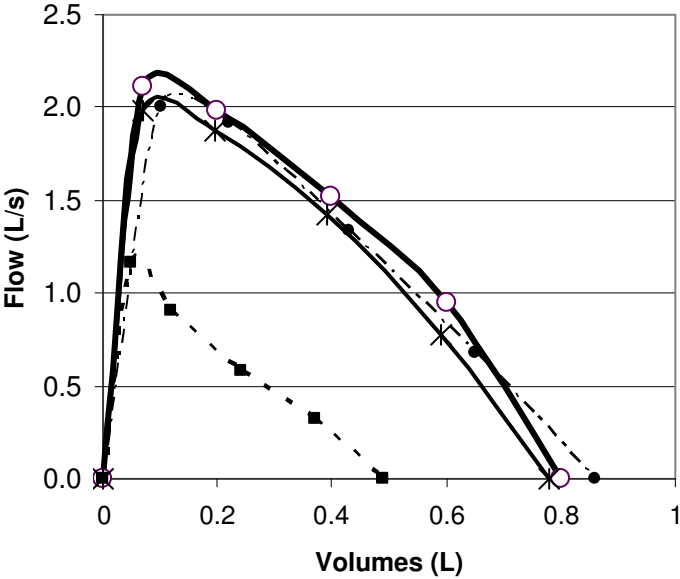


Figure 3:

The effect of Bronchodilator after PCW



FEFV at PCW vs. Poor-effort

