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Volumetric capnography as a tool to detect early peripheric lung obstruction in cystic fibrosis patients

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Abstract

Objective: To compare spirometry and volumetric capnography (VCap) to determine if the capnographic values add more information about early lung disease in cystic fibrosis (CF) patients.

Methods: This was a cross-sectional study involving CF patients: Group I (42 patients, 6-12 years of age); and Group II (22 patients, 13-20 years of age). The corresponding control groups were comprised of 30 and 50 healthy subjects, respectively. Forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), and the FEV_1/FVC ratio was determined by spirometry. Using VCap, we measured peripheral oxygen saturation (SpO_2), respiratory rate (RR), inspiratory time (IT), expiratory time (ET), and the phase III slope normalized by expiratory volume (phase III slope/Ve).

Results: In comparison with control groups, all CF patients presented higher phase III slope/Ve values ($p < 0.001$) independent of the pulmonary disease stage. The phase III slope/Ve was significantly higher in the 24 patients who presented normal spirometry results ($p = 0.018$). The Group II patients showed lower FVC, FEV_1, FEV_1/FVC ($p < 0.05$), and also lower SpO_2 values ($p < 0.001$) when compared with Group I patients. In comparison with Control Group II, the Group II patients presented higher RR ($p < 0.001$), and lower IT and ET values ($p < 0.001$).

Conclusions: Compared to the controls, all studied CF patients showed an increase in phase III slope/Ve values. VCap identified the heterogeneity of the ventilation distribution in the peripheral airways of CF patients who presented normal spirometry.

J Pediatr (Rio J). 2012;88(6):509-17: Volumetric capnography, cystic fibrosis, spirometry.

Introduction

There is evidence that pulmonary function begins to decrease quite early in patients with cystic fibrosis (CF), even in those considered asymptomatic.[1] Forced expiratory volume in one second (FEV_1) is traditionally regarded as good predictor of prognosis in the moderate and severe forms of the disease. Notwithstanding, FEV_1 as the sole factor for deciding for or against intervention, such as possible lung transplantation, has been questioned.[2]

In lung disease, heterogeneity of gas distribution results from different structural lesions, including permanent

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reduction of the caliber of the small airways. These results can be determined early on by means of multiple-breath washout (MBW) of gases such as helium (He), nitrogen (N_2), and sulfur hexafluoride (SF_6). The lung clearance index (LCI), derived from the MBW findings, is considered a highly sensitive marker of small aiway involvment in CF.[2-13]

Heterogeneity of gas distribution can also be identified by an increase in the slope of the alveolar plateau of the exhalation curve of gases, such as carbon dioxide (CO_2) measured during tidal volume breathing through volumetric capnography (VCap).[14]

Studies evaluating uneven gas distribution as an early indicator of lung disease have shown that the methods used can be more sensitive than spirometry for detecting and measuring functional changes in lung disease in children who present with normal FEV_1 values – including those with CF or asthma.[11-13]

The pattern of CO_2 elimination in VCap, and the pattern of elimination of gases used in MBW, provides information regarding gas distribution, especially those in the distal air spaces.[14-19]

However, few studies have evaluated the use of VCap in children and adolescents, or the association between VCap and spirometry in patients with CF.

The purpose of the present study was to compare spirometry values and VCap measurements in patients with CF and normal control groups to determine if the capnographic values add more information about possible early lung function compromise in CF patients.

Methods

This was an analytical, observational, cross-sectional, and nonrandomized study involving children and adolescents treated at the Hospital da Universidade Estadual de Campinas, in Campinas, Brazil. We included male and female patients, ranging in age from 6 to 20 years, who had been diagnosed with CF, based on pilocarpine iontophoresis sweat test results (two or more determinations of chloride concentrations above 60 mEq/L), whether or not the diagnosis had been confirmed by molecular genetic studies. All invited patients were included, and none had any difficulties in performing spirometry or capnography. None of them were experiencing an exacerbation of the disease at the time of the evaluation.

We also included healthy, nonsmoking control individuals who had no previous or current respiratory disease and were not using any medication.

Those patients with CF were divided into two groups according to age: Group I was comprised of 42 patients ranging in age from 6 to 12 years; and Group II was comprised of 22 patients ranging in age from 13 to 20 years. The control subjects were divided into two corresponding groups: Control Group I made up of 30 individuals ranging in age from 6 to 12 years, who underwent spirometry and VCap; and Control Group II consisting of 50 individuals ranging in age from 13 to 30 years, who underwent VCap only.

For the patients with CF, the Shwachman-Kulczycki score was used to determine the severity of the disease and was applied by three physicians, all of whom were blinded to the severity of lung function diagnosis of each patient.

Spirometry was used to determine forced vital capacity (FVC), FEV_1, FEV_1/FVC and forced expiratory flow between 25 and 75% of FVC ($FEF_{25-75\%}$). The following were determined by VCap: peripheral oxygen saturation (SpO_2), measured through pulse oximetry; peak expiratory flow; respiratory rate (RR); inspiratory time (IT); expiratory time (ET); and the phase III slope normalized by expiratory volume (phase III slope/Ve).

The subjects were submitted to VCap using a CO_2SMO Plus Analyzer® (Respironics, Murrysville, PA, USA). The sensors of the device were connected to the subject by means of a mouthpiece with a fitted nose clip to avoid air leaks through the nose. They were instructed to breathe normally for 1 min so as to adjust themselves to the equipment, after which the monitoring began and the data were recorded on a computer using the Analysis Plus program (Respironics, Murrysville, PA, USA). The subjects remained breathing at tidal volume for a period of 4 min, during which time the variables were measured and the data were stored in the computer. At the end of data collection, an offline sequence of the respiratory cycles of the subjects was selected to accommodate a variation of < 25% for expiratory tidal volume and of < 10% for end-tidal arterial CO_2 tension. The respiratory cycles, those presenting phase III slope values of zero, were excluded. When comparing slopes of patients of different ages, it was necessary to normalize the values of the phase III slopes. It is well known that the greater the expired volume, the smaller is the phase III slope. Thus, all phase III slope values were divided by the mean expired volume measured for all the breaths that were analyzed for each patient during VCap, and the results were then expressed as mm of Hg per liter per mL of expired volume.[20]

Spirometry was performed, using a CPFS/D spirometer (Medical Graphics Corporation, St. Paul, MN, USA), in accordance with the guidelines of the European Respiratory Society and the American Thoracic Society.[21] Results were based on predicted values for children, adolescents,[22] and adults.[23] The low limit of normality for FVC, FEV_1, FEV_1/FVC was considered to be 80%, and 70% for $FEF_{25-75\%}$.

Comparisons between independent variables without normal distribution were made using the Mann-Whitney test (Statistical Package for the Social Sciences, version 16.0; SPSS Inc., Chicago, IL, USA). Values of $p \leq 0.05$ were considered statistically significant.

The present study was approved by the local research ethics committee (protocol no. 430/2008). All adult patients, controls, and the caretakers of patients and controls younger than 18 years-old, provided informed consent by signing the appropriate forms.

Results

Of the 42 Group I patients, 19 (45.2%) were male. The median z scores in Group I were as follows: for height, -0.45 (range, -3.91 to 1.46); for weight, -0.77 (range, -3.39 to 1.33); for body mass index, -0.65 (range, -2.73 to 1.26).

The median Shwachman-Kulczycki score in Group I was 80 (35-90). Of the 42 Group I patients, 27 (64.3%) were chronically infected with *Pseudomonas aeruginosa*, 38 (90.5%) were ΔF508 homozygotes or heterozygotes, 32 (76.2%) presented normal FVC, and 10 (23%) presented an obstruction on the spirometry test.

As can be seen in Table 1, the FVC, FEV_1, FEV/FVC, $FEF_{25-75\%}$ and SpO2 values were significantly lower in Group I than in Control Group I ($p < 0.05$), whereas the values for the phase III slope/Ve were significantly higher in Group I ($p = 0.001$).

Of the 42 Group I patients, 24 (57.1%) presented normal spirometry results. However, as shown in Table 2, phase III slope/Ve values were significantly higher in this subgroup than in Control Group I ($p = 0.018$).

Of the 22 Group II patients, 10 (45.5%) were male. The median z scores in Group II were as follows: for height, -0.24 (range, -3.22 to 1.35); for weight, -0.91 (range, -3.85 to 0.95); and for body mass index, -1.20 (range, -3.19 to 0.90).

The median Shwachman-Kulczycki score in Group II was 68 (40-90). Of the 22 Group II patients, 18 (81.8%) were chronically infected with *Pseudomonas aeruginosa*, 19 (86.5%) were ΔF508 homozygotes or heterozygotes, 9 (40.9%) presented normal FVC, and 15 (68%) presented an obstruction.

The Shwachman score was lower in Group II patients than in Group I ($p < 0.008$).

Table 1 shows that the values for SpO_2, IT, and ET were lower in Group II than in Control Group II ($p < 0.001$), whereas the values for the phase III slope/Ve and RR were significantly higher in Group II ($p < 0.001$).

The values for FVC, FEV_1, and $FEF_{25-75\%}$ were significantly higher in Group I than in Group II ($p = 0.008$, $p < 0.001$, and $p < 0.001$, respectively), as were the phase III slope/Ve values ($p < 0.006$). The FEV_1/FVC ratio was significantly lower in Group II ($p < 0.001$).

As can be seen in Table 1, the comparison between Group I patients and Group II patients, as well as between Control Group I individuals and Control Group II individuals (in terms of VCap data), showed that phase III slope/Ve values were significantly higher in the younger groups of individuals ($p < 0.05$).

Discussion

Spirometry continues to be included in the battery of mandatory routine tests for the evaluation of pulmonary function in patients with CF. However, it has become increasingly difficult to use FEV_1 to document and interpret early alterations and the progression of lung disease, principally in preschool and school-age children.[1-12]

The use of spirometry in CF has two limitations: the first results from the difficulty in performing the test in children younger than 5 years of age; the second is related to the fact that many children and adolescents with CF present normal spirometry test results, even in the presence of confirmed lung disease. Consequently, there has been support for research aimed at developing noninvasive methods that are more sensitive than spirometry for monitoring pulmonary function in patients with CF.

Various studies, using washout of inert gases such as N_2 and SF_6 to evaluate pulmonary function in obstructive pulmonary diseases, have yielded promising results. The plateau of phase III elimination of such gases is considered to be an important variable in evaluating peripheral airway function.[24] More recently, the gas elimination measure (known as the LCI) has been employed in evaluating early respiratory disease in patients with CF. A study exploring the differences between the curves of exhaling gases, used in the LCI test (SF_6 and He), showed early peripheral airway involvement in CF.[25]

Because it measures endogenous CO_2, VCap is easier to use and less expensive than the LCI. It is a technique that analyzes the pattern of CO_2 elimination as a function of expired volume. The capnogram represents the total amount of CO_2 eliminated by the lungs during each breath. Expired gas receives CO_2 from three sequential compartments forming three recognizible phases on the expired capnogram. Phase I contains gas from apparatus dead space and proximal conducting airways. Phase II represents the transitional region characterized by an increasing CO_2 concentration resulting from progressive CO_2 emptying from more proximal alveoli to central airways. Further, phase III represents essentially alveolar gas and is known as the alveolar plateau. Most of the CO_2 from each respiratory cycle is expelled in the last phase, which presents a slight ascending inclination, even in healthy individuals.

VCap measurements allow the calculation of many indices that can reflect pulmonary function disturbances, and may be useful as a noninvasive method of estimating

pulmonary involvement in many diseases. Heterogeneity of gas distribution is also evaluated by VCap, and its severity can be used to gather information regarding the anatomy and function of distal air spaces. In asthma and emphysema, the phase III slope of VCap increases, thereby demonstrating the presence of functional and structural alterations that lead to heterogeneity of gas distribution.[14]

Studies involving children have suggested that capnographic measurements are useful in predicting the success of ventilator weaning/extubation,[26,27] are useful

Table 1 - Comparison of capnographic and spirometric variables among cystic fibrosis patients and their respective healthy controls, and between cystic fibrosis patients of different ages

Variables	Group I (n = 42)	Control Group I (n = 30)	p
FVC (% predicted)	90.50 (55-128)	97 (82-116)	0.002
FEV_1 (% predicted)	85.50 (46-125)	104 (83-128)	< 0.001
FEV_1/FVC	85.50 (61-98)	92 (78-100)	0.001
$FEF_{25-75\%}$ (%)	74.50 (22-136)	116 (62-159)	< 0.001
SpO_2 (%)	96.84 (94-98.45)	97.78 (96.45-98.97)	< 0.001
IT (s)	1.16 (0.76-2.38)	1.27 (0.87-2.05)	0.163
ET (s)	1.65 (1.11-4.49)	1.49 (0.90-2.65)	0.180
RR (bpm)	20.96 (10.46-31.72)	20.37 (13.52-34.97)	0.416
Phase III slope/Ve (mmHg/L/mL of Ve)	0.09 (0.012-0.42)	0.04 (0.01-0.27)	0.001
	Group II (n = 22)	**Control Group II (n = 50)**	
FVC (% predicted)	77 (44-125)	-	
FEV_1 (% predicted)	57.50 (27-117)	-	
FEV_1/FVC	72 (52-95)	-	
$FEF_{25-75\%}$ (%)	37.50 (10-137)	-	
SpO_2 (%)	95.93 (90.19-98.19)	97.61 (95.57-99.19)	< 0.001
IT (s)	1.38 (0.88-2.80)	2.00 (1.19-3.37)	< 0.001
ET (s)	1.85 (1.08-3.26)	2.80 (0.00-5.24)	< 0.001
RR (bpm)	18.09 (11.1-31.66)	12.56 (7.03-20.36)	< 0.001
Phase III slope/Ve (mmHg/L/mL of Ve)	0.06 (0.01-0.36)	0.01 (0.00-0.03)	< 0.001
	Group I (n = 42)	**Group II (n = 22)**	
FVC (% predicted)	90.50 (55-128)	77 (44-125)	0.008
FEV_1 (% predicted)	85.50 (46-125)	57.50 (27-117)	< 0.001
FEV_1/FVC	85.50 (61-98)	72 (52-95)	< 0.001
$FEF_{25-75\%}$ (%)	74.50 (22-136)	37.50 (10-137)	0.001
SpO_2 (%)	96.84 (95-98.54)	97.61 (95.57-99.19)	0.005
IT (s)	1.16 (0.76-2.38)	1.38 (0.88-2.80)	0.008
ET (s)	1.65 (1.11-4.49)	1.85 (1.08-3.26)	0.006
RR (bpm)	20.96 (10.46-31.72)	18.08 (11.1-31.66)	0.021
Phase III slope/Ve (mmHg/L/mL of Ve)	0.09 (0.01-0.42)	0.06 (0.01-0.36)	0.006
	Control Group I (n = 30)	**Control Group II (n = 50)**	
SpO_2 (%)	97.78 (96.45-98.97)	97.61 (95.57-99.19)	0.363
IT (s)	1.27 (0.87-2.05)	2.00 (1.19-3.37)	< 0.001
ET (s)	1.49 (0.90-2.65)	2.80 (0.00-3.52)	< 0.001
RR (bpm)	20.37 (13.52-34.97)	13.32 (7.03-20.36)	< 0.001
Phase III slope/Ve (mmHg/L/mL of Ve)	0.04 (0.01-0.27)	0.01 (0.00-0.03)	< 0.001

ET = expiratory time; $FEF_{25-75\%}$ = forced expiratory flow between 25 and 75% of FVC; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; IT = inspiratory time; phase III slope/Ve = value of the normalized slope of curve III divided by expired volume; RR = respiratory rate; SpO_2 = peripheral oxygen saturation.
Group I: cystic fibrosis patients, 6-12 years of age; Group II: cystic fibrosis patients, 13-20 years of age; Control Group I: healthy subjects, 6-12 years of age; Control Group II: healthy subjects, 13-20 years of age.
Statistical significance set at $p < 0.05$.
All variables are expressed as median values (minimum and maximum values).

Table 2 - Comparison between cystic fibrosis patients with normal spirometry (Group I, 6-12 years old) and their controls

Variables	CF patients with normal spirometry (n = 24)	Control group (n = 30)	p
FVC (% predicted)	93 (82-128)	97 (82-116)	0.333
FEV_1 (% predicted)	96.50 (80-125)	104 (83-128)	0.085
FEV_1/FVC	90.50 (81-98)	92 (78-100)	0.332
$FEF_{25-75\%}$	99.50 (66-138)	116 (62-159)	0.075
SpO_2 (%)	96.97 (94-98.45)	97.72 (96.45-98.97)	0.025
IT (s)	1.18 (0.78-2.38)	1.27 (0.87-2.05)	0.120
ET (s)	1.73 (1.18-4.49)	1.49 (0.90-2.65)	0.437
RR (bpm)	18.51 (10.46-28.97)	20.72 (13.52-34.97)	0.814
Phase III slope/Ve (mmHg/L/mL of Ve)	0.09 (0.012-0.326)	0.04 (0.01-0.268)	0.018

CF = cystic fibrosis; ET = expiratory time; $FEF_{25-75\%}$ = forced expiratory flow between 25 and 75% of FVC; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; IT = inspiratory time; phase III slope/Ve = value of the normalized slope of curve III divided by expired volume; RR = respiratory rate; SpO_2 = peripheral oxygen saturation.
Statistical significance was set at $p < 0.05$.
All variables are expressed as median values (minimum and maximum values).

in detecting the presence of pulmonary shunts in patients with congenital heart disease,[28] to determine the survival probability in patients with diaphragmatic hernia,[29] and to evaluate pulmonary function after extracorporeal oxygenation.[30]

In adult patients, VCap has been used to diagnose pulmonary embolisms,[17,18,31-33] to monitor the infusion of fluids in those with asthma,[34] to measure the effect of bronchodilator use in those with chronic obstructive pulmonary disease,[35] and to evaluate the breathing pattern and gas distribution inhomeogeneitis in patients with CF and non-CF bronchiectasis.[19]

The phase III slope of capnography follows the same evaluation principles as do the slopes resulting from other gas washout studies.

One of the important findings of the present study is that the phase III slope/Ve for the Control Group I (younger) individuals was significantly greater than that for Control Group II (older) individuals. These data confirm the findings of Ream et al.,[36] who evaluated the VCap results of children ranging in age from 5 months to 18 years demonstrating that the steepness of the slope decreases in parallel with increasing age (Figure 1).

Postnatally, the gas exchange membranes (of alveoli and of vessels) seem to reach their maximum size (that seen in adults) by 5-8 years of age. During the development of an individual, the exact point at which the lungs begin to behave like the lungs of an adult remains unknown. The behavior of the phase III slope, which decreases progressively from childhood to adulthood, seems to indicate that, during the maturation process, some event (most likely an increase in both the number of alveoli and in their total volume) interferes with gas exchange.[37]

The comparison between the slopes of healthy individuals and those of individuals with diseases should take this interference into consideration; thus, the reason we segmented our study population by age.

In the present study, patients older than 13 years of age (Group II patients) presented spirometry values that were significantly lower than those observed in Group I patients. In comparison with individuals in Control Group II, Group II patients presented higher RR, lower IT, lower ET, and normal peak expiratory flow, all features suggestive of a restrictive ventilatory pattern. The same breathing pattern during VCap, suggesting a restrictive disease, was observed in a previous study.[19] Phase III slope/Ve was significantly greater in Group II patients than in Control Group II individuals, perhaps indicating the presence of diffuse disease of the small airways in Group II patients (Table 1 and Figure 2).

The results of our study are in accordance with the data from the literature,[5,38] in regard to the observation that, in most patients under 13 years of age, spirometry will not reveal obstruction. Our patients presented conditions of pulmonary function similar to those of patients of the same age listed in the Annual Registry of the Cystic Fibrosis Foundation, thereby demonstrating the well-known age-dependent progression of lung disease in CF patients.

Although the spirometry values observed in Group I patients were better than those observed in Group II patients, the phase III slope/Ve values observed in Group I were significantly higher than those observed in Control

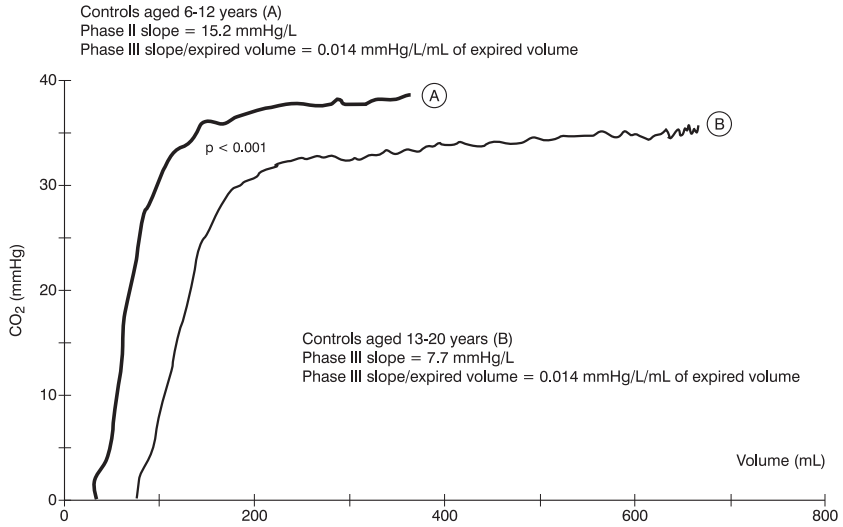

Figure 1 - Examples of carbon dioxide elimination curves, by volumetric capnography, in 30 healthy controls aged 6 to 12 years old (A), compared to 50 healthy controls aged 13 to 20 years old (B). Volumetric capnography values are representative of median values found for each group

Group I, indicating the presence of structural lung damage in the patients (Figure 2).

In fact, because of the very small convective velocities in the lung periphery, gas transport by diffusion is the dominant mechanism in acinar air spaces before the alveolar-capillary membrane is reached. Steepened phase 3 slopes may represent increased diffusional resistance in the peripheral lung. These steepened slopes occur when breathing involves a smaller than normal maximum interfacial area between the tidal volume and the functional residual capacity (FRC) during a breathing interval.[19] Smaller interfacial areas may result from diffuse obliteration of small airways.

Despite the fact that the younger patients had milder lung disease, when evaluated by spirometry, the phase III slope/Ve values were higher in Group I than in Group II. This finding may have two interpretations that are not mutually exclusive: the phase III slope is more sensitive than spirometry to detect lung disease in CF young patients, and (or) the influence of age and of lung development is as important as the severity of lung disease in determining the steepness of phase III slope.

Of the 42 Group I patients, 24 (57%) presented normal spirometry results. However, the phase III slope/Ve values observed in Group I patients were significantly higher than those observed in Control Group I subjects. This finding clearly shows that VCap can reveal lung impairment undetectable by spirometry.

Similar results were reported by a group of authors who demonstrated, through gas washout studies, lung disease in the peripheral region of the airways before spirometry testing of smokers,[39] in patients with post-transplant bronchiolitis obliterans,[40] in children with CF,[2-6,9,11,12] and in patients with asthma.[41]

The present study is the first to have used VCap as a tool for the evaluation of respiratory function in children and adolescents with CF and different degrees of lung disease severity. Further research is required in order to establish cut-off points for the phase III slope, as well as to compare VCap with high-resolution computed tomography as a means of identifying structural alterations in small and central airways.

In our estimation, the main limitation of this study is that spirometric evaluation was not realized in Group II individuals, thereby making it infeasible to compare spirometry variables between older CF patients and their controls.

Future perspectives: the techniques to measure heterogeneity of gas distribution in the periphery of the lungs have a great potential application for early detection of pulmonary dysfunction; and VCap seems to be a sound tool for evaluating these abnormalities. VCap is an easy-to-perform technique with no complex respiratory effort required, and it can be accomplished either by school age children or severely disabled patients. In this study,

VCap was able to detect abnormal gas distribution in CF patients with normal spirometric results, and the test also demonstrated that all patients studied presented phase III slope/Ve values higher than their control groups, thereby suggesting that VCap can be a routine part of pulmonary assessment for CF patients.

Conclusions

VCap identified increased diffusional resistance in the peripheral lungs of CF patients who presented normal spirometry. Thus, this technique seems to represent, when age is taken into account, a suitable alternative for detecting early impairment of lung function in patients with CF.

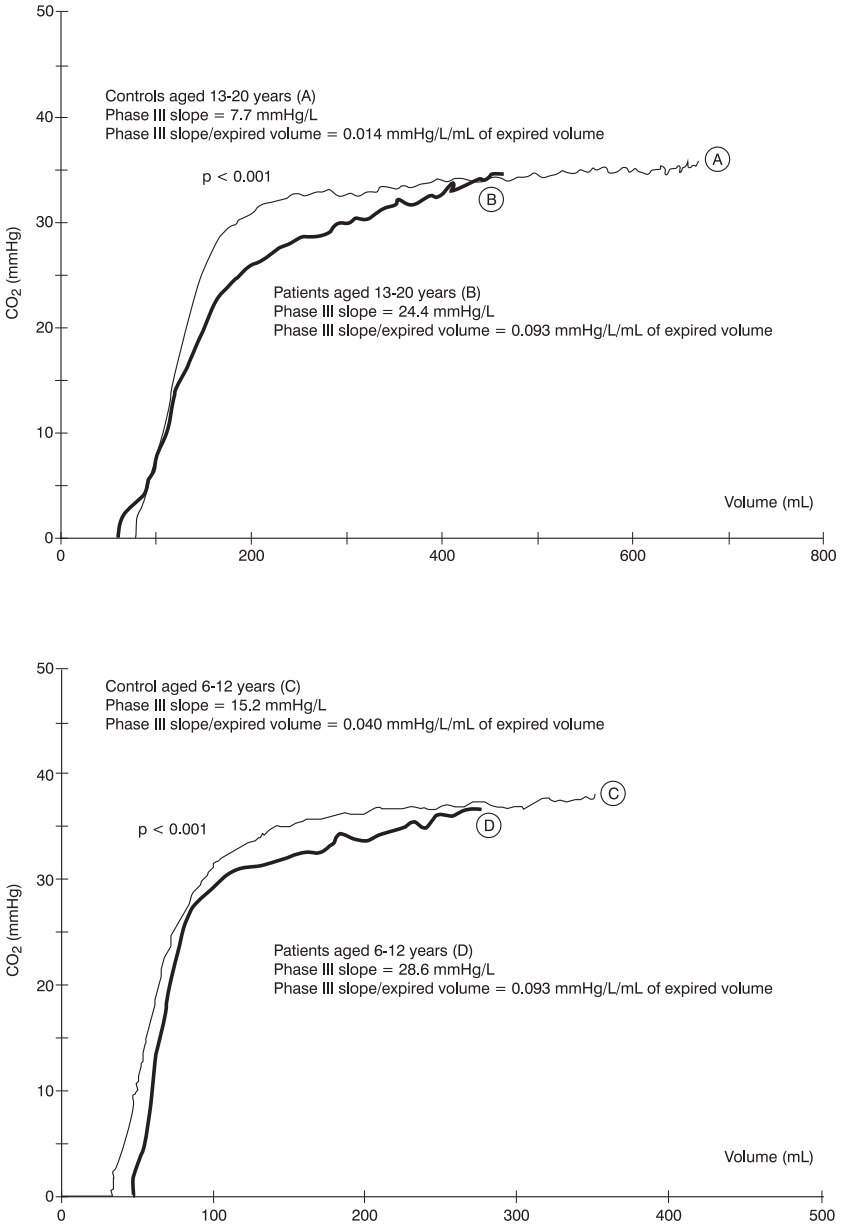

Figure 2 - Examples of carbon dioxide elimination curves, by volume capnography, in 50 healthy controls aged 13 to 20 years old (A), compared to 22 aged-matched cystic fibrosis patients (B); and 30 healthy controls aged 6 to 12 years old (C), compared to 42 aged-matched cystic fibrosis patients (D). Volumetric capnography values are representative of median values found for each group

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