Ability of single-breath nitrogen closing volume to detect early airway obstruction

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Funahashi, A., Melville, G. N., and Hamilton, L. H. (1975). *Thorax*, 30, 220–224. Ability of single-breath nitrogen closing volume to detect early airway obstruction. In order to determine the ability of single-breath nitrogen closing volume (CV) to detect early airway obstruction, the CV was measured in patients with either minimal obstruction on spirometry or with increased residual volume (RV). A total of 39 subjects was included in this study. The mean CV was largest in patients who had reduced maximum mid-expiratory flow rates (MMF). There was no difference in mean CV between smokers and the patients who had large RV but no airway obstruction, although both groups had higher mean CV than ex-smokers. Normal CV was seen in four of 11 patients who had reduced MMF and in four of seven who had large RV but no airway obstruction. All ex-smokers had normal CV while five of 12 smokers had abnormal CV. The results indicate that the closing volume should be used to complement spirometry, rather than to replace it, for screening of early airway obstruction.

Much attention has been recently directed toward the measurement of closing volume (CV) as a sensitive measurement of early pathological changes in small airways (Macklem, 1972; McCarthy *et al.*, 1972; Buist, 1973; Buist, van Fleet, and Ross, 1973). The CV is defined as that lung volume at which dependent lung regions cease to be ventilated. There are two basically different methods which are widely used to measure the CV. The first method is termed the bolus technique. It was originally described by Dolfuss, Milic-Emili, and Bates (1967), utilizing radioactive xenon (^{133}Xe) as a marker gas; subsequently, the use of nonradioactive gases such as argon or helium was described (Dolfuss *et al.*, 1967; McCarthy *et al.*, 1972).

The second method has been termed the resident gas technique or single-breath nitrogen method (Buist and Ross, 1973). Because the latter method requires less expensive equipment and is simple to perform, it has been recommended for screening a large number of people for chronic obstructive pulmonary disease (Buist *et al.*, 1973; Buist, 1973; Buist and Ross, 1973). Recently, Travis, Green, and Don (1973) suggested that the

single-breath nitrogen method may lose sensitivity when there is a disturbance of residual gas distribution.

The single-breath nitrogen method for measuring CV has been compared with conventional spirometry in a large group of subjects in an emphysema screening clinic (Buist and Ross, 1973). It was concluded that the CV was more sensitive in detecting abnormality than was spirometry, but the conclusion was based only on the frequency of detecting abnormalities, and no direct comparison was made between the measurements on the same subjects.

Reduction of the maximum mid-expiratory flow rate (MMF) and the ratio of forced expired volume in one second (FEV₁) to forced vital capacity (FVC) have been considered to be sensitive spirometric measurements for detecting early airway obstruction (Leuallen and Fowler, 1955; McFadden and Linden, 1972; Higgins and Keller, 1973), whereas lung volume measurements have traditionally been considered much less sensitive for this purpose. However, the increased residual volume (RV) in subjects who have normal spirometry, termed nonobstructive pulmonary

overinflation (NOPO), has been suggested also to reflect early small airway disease (Kory, Banaszak, and Viernes, 1973).

If the CV measurement is more sensitive than spirometry in detecting early small airway disease, the CV should be abnormal in most subjects who have minimal but measurable abnormalities in spirometry, ordinarily suggesting obstructive airway disease. In addition, if NOPO is a manifestation of small airway disease, these subjects should also demonstrate abnormal CV. The purpose of this study was to measure CV in a group of NOPO patients and patients with minimal signs of chronic obstructive airway disease and to compare the results with measurements from smokers, ex-smokers, and non-smokers of the same age.

MATERIALS AND METHODS

The subjects were selected from patients who have been studied in the Pulmonary Function Laboratory of the Veterans Administration Center, Wood (Milwaukee), Wisconsin. Spirometry, lung volume, and CV measurements were obtained from all subjects. Spirometry was done with a Stead-Wells spirometer, and lung volume was measured by the helium dilution method using clinical methods employed in our

laboratory. The predicted values for spirometry and lung volume were those of the Veterans Administration Army Cooperative Study (Kory *et al.*, 1961; Boren, Kory, and Syner, 1966). The CV was measured by the single-breath nitrogen method, similar to that described by Buist and Ross (1973), with a slight modification in the recording system. After discarding tracings which displayed a vital capacity less than 95% of the vital capacity recorded with spirometry, the mean of two values was obtained and CV was expressed as percent of vital capacity. Predicted normal values for CV were calculated according to the formula reported by Buist and Ross (1973).

All subjects were men between 40 and 59 years of age. A total of 39 subjects were included in the study. There were 12 smokers, seven subjects whose lung volume showed NOPO, and 11 subjects who had reduced MMF in spirometry. It was difficult to obtain nonsmokers in this age group; thus, eight ex-smokers who were free of respiratory symptoms and one nonsmoker were selected as a control group.

RESULTS

All smokers, ex-smokers, and the nonsmoker had normal spirometry and lung volumes. The physical characteristics of patients comprising the NOPO group and subjects with decreased MMF are shown in Tables I and II, respectively.

TABLE I
PULMONARY FUNCTION RESULTS OF PATIENTS WITH NO OBSTRUCTION BUT WITH LARGE RESIDUAL VOLUMES

Age	Cigarettes (pack-years)	FEV ₁ (l/s)	FEV ₁ /FVC	MMF ¹ (l/s)	VC (ml)	RV (ml)	TLC (ml)
56	30	3.05(80)	67	1.81	4.71(92)	3.60(170)	8.31(110)
50	52	3.43(105)	77	2.82	4.57(108)	2.50(150)	7.07(118)
51	28	3.52(101)	73	2.42	4.80(105)	3.44(191)	8.24(127)
46	30	2.98(95)	68	1.79	4.39(111)	2.90(196)	7.29(134)
49	0	3.65(96)	68	2.73	5.33(107)	3.21(167)	8.54(121)
54	34	3.23(105)	78	2.73	4.21(105)	2.78(166)	6.99(119)
50	54	3.20(98)	70	2.44	4.30(103)	3.04(184)	7.34(123)

Age, history of smoking, and routine pulmonary function data in patients with increased residual volume but with normal FEV₁ and MMF (NOPO). Numbers in parentheses represent percent predicted.

¹Predicted value is > 1.8 l/s.

TABLE II
PULMONARY FUNCTION RESULTS OF PATIENTS WITH NORMAL OR NEAR NORMAL FEV₁ BUT REDUCED MMF

Age	Cigarettes (pack-years)	FEV ₁ (l/s)	FEV ₁ /FVC	MMF ¹ (l/s)	VC (ml)	RV (ml)	TLC (ml)
44	30	2.78(86)	69	1.68	4.31(107)	1.80(124)	6.11(121)
58	48	2.64(82)	71	1.70	3.94(92)	2.11(114)	6.05(95)
56	62	2.33(79)	69	1.43	3.45(89)	3.00(180)	6.45(113)
45	31	3.00(95)	62	1.52	4.93(117)	2.95(190)	7.88(135)
52	35	2.82(88)	66	1.70	4.98(120)	2.23(133)	7.21(121)
52	60	2.82(84)	67	1.52	4.55(104)	2.50(143)	7.05(113)
54	90	2.62(84)	67	1.70	4.17(107)	2.95(174)	7.12(121)
47	25	2.69(85)	66	1.68	4.21(106)	2.75(182)	6.96(126)
48	93	3.00(88)	65	1.66	4.71(108)	1.92(116)	6.63(109)
48	45	3.27(93)	65	1.72	5.04(112)	2.15(124)	7.19(113)
59	43	2.56(98)	66	1.79	3.86(111)	1.79(114)	5.65(110)

Age, history of smoking, and routine pulmonary function data in patients with normal or near normal FEV₁ but decreased MMF and FEV₁/FVC ratios. Numbers in parentheses represent percent predicted.

¹Predicted value is ± 1.8 l/s.

FIGURE The individual CV and predicted normal values in each group: A, ex-smokers; B, smokers; C, NOPO; and D, decreased MMF. Shaded area represents the predicted normals by Buist *et al.* (1973) (see text).

The Figure shows individual CV in each group and the normal predicted value of Buist and Ross (1973). The CV was normal or low for all nine subjects in the control group. In the group of 12 smokers, seven had normal CV and five had abnormal CV. Four of seven NOPO subjects had normal or low CV and three had abnormal CV. Of the subjects who had decreased MMF, four had normal CV and seven had abnormal CV.

The mean values for the CV in each group are shown in Table III. Smokers and subjects who had a decreased MMF had a significantly higher mean CV than ex-smokers. The NOPO group had a mean CV which was higher than the values for ex-smokers, but the difference did not achieve statistical significance.

TABLE III
MEAN CLOSING VOLUME OF EACH GROUP

Group	No. of Subjects	Mean Age	CV ± SE
A Non- and ex-smokers	9	51.6	16.7 ± 1.6
B Smokers	12	52.7	22.5 ± 2.0
C NOPO	7	50.8	21.8 ± 2.4
D Decreased MMF	11	51.2	26.7 ± 2.8

CV = closing volume.

SE = standard error.

NOPO = nonobstructive pulmonary overinflation, see text.

MMF = maximum mid-expiratory flow rate.

DISCUSSION

It has been well demonstrated that a high percentage of smokers demonstrate an abnormal CV (Leblanc, Ruff, and Milic-Emili, 1970; Buist *et al.*, 1973). Buist (1973) recently published a study of CV in a large number of smokers who had a normal FEV₁, in which 41% of the men and 33% of the women had abnormal CV.

Although the total number of subjects in our series is small, 40% of the smokers showed an abnormal CV, which was in close agreement with Buist's series. The actual mechanism of early airway closure (large CV) is not known, but it has been postulated that the loss of lung elastic recoil produces an early airway closure (Holland *et al.*, 1968; Anthonisen *et al.*, 1969).

The fact that NOPO is primarily observed in smokers of middle age or older and is rarely found in young smokers strongly suggests that this condition is a result of a long-standing history of smoking and suggests that there is more tissue destruction than in smokers who have normal spirometry and lung volumes. One might expect to find larger CV in NOPO patients as a result of the loss of elastic tissue leading to the development of airway obstruction. However this study failed to show any difference in mean CV or

percent of subjects who had abnormal CV between smokers and NOPO subjects. We cannot yet explain why more than half the NOPO subjects showed a normal CV. Perhaps the larger residual volume increases the elasticity of the lung tissue and returns transpulmonary pressure to the normal range. It is conceivable, as pointed out by Travis *et al.* (1973), that when the disease process advances to the point of causing an abnormal distribution of residual volume, the single-breath nitrogen CV may become less sensitive. If the increased residual volume found in NOPO patients involved the lower parts of the lung more than the upper parts, the single-breath nitrogen method for CV might not demonstrate an increased CV even if it were present. The bolus method, on the other hand, might be expected to measure the increased CV under these conditions. Further study is necessary to clarify this point by measuring CV with the bolus method and the single-breath nitrogen method on the same subjects who have normal spirometry but abnormal lung volumes.

The subjects who showed a lowered MMF showed a significantly higher mean CV than all other groups, indicating that, in general, CV increases as the obstructive process becomes apparent. However, four of the 11 patients still showed a normal CV. This high percentage of normal values was surprising and may support the contention of Travis *et al.* (1973) that advanced lung disease attenuates the sensitivity of the measurement of CV by the single-breath nitrogen method. It casts doubt on the advisability of depending on the single-breath nitrogen method for CV as a single screening procedure for chronic obstructive airway disease. Perez-Guerra (1973) recently reported normal values for single-breath nitrogen CV in six 'asymptomatic subjects' who had a reduced MMF on spirometry. He concluded that the measurement offered no advantage over carefully performed spirometry. However, his subjects were young (17 to 24 years old), and it would be surprising if they had chronic irreversible obstructive airway disease.

We do not want to underrate the value of measuring CV. There is little doubt that it indicates an abnormality in a higher percentage of smokers of all age groups than in those tested with spirometry. However, as stated by Buist (1973), our present knowledge is insufficient to provide prognostic value from CV measurements among smokers. It is of interest that all the ex-smokers in our study had a normal CV. They had

an average smoking history of 35.3 pack-years of cigarettes and had stopped smoking for a mean period of 8.5 years. This suggests, therefore, that the elevated CV observed among smokers may be reversible.

This study has suggested that the single-breath nitrogen method for measuring CV may be useful for detecting early changes in lung disease which may not be seen by conventional pulmonary function tests. However, because of the relative frequency of normal CV in subjects who have a measurable abnormality in spirometry or lung volume, the CV measurement should be considered to complement spirometry rather than to replace it, especially when it is used for screening purposes.

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