Fractional carbon monoxide uptake in an employed population

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Stebbings, J. H. (1974). *Thorax*, **29**, 505–510. **Fractional carbon monoxide uptake in an employed population.** The fractional carbon monoxide uptake in 913 New York City transit workers was studied. A prediction equation for white males, based on nonsmokers, was obtained: fractional CO uptake $= 0.58032 - 0.00204 \times$ age $+ 0.0004 \times$ weight (kilograms). Weight was the index of body size most strongly correlated with the fractional CO uptake. Decline in function with age by amount of tobacco smoked is described. A correction factor for respiration, based on results from 581 workers with two or more tests, was calculated: $-0.123654 \times$ (standard tidal volume $-$ observed tidal volume). Tidal volume was the most important contributor to individual variability of the fractional CO uptake, and minute volume or respiration rate do not add significantly to it. For epidemiological or screening uses, prediction equations are given for the fractional CO uptake corrected to 0.5 l. tidal volume. Respiration variables explain only 1.5 % of individual variability, and individual variability over a mean period of 16.6 months was much larger (an individual standard error of 0.07) than the unexplained population variability (a population standard error of 0.01–0.02); thus the usefulness of the fractional CO uptake as a test of respiratory function is in doubt.

The fractional carbon monoxide uptake has been suggested as a useful index of pulmonary diffusing capacity in clinical evaluations, in respiratory screening programmes, and in epidemiological studies (Bates, Macklem, and Christie, 1971; Lacoste, 1971, 1972). The study reported on here was designed to evaluate this, to establish normal values, and to determine the effects of cigarette smoking.

SUBJECTS

A survey of the prevalence of chronic respiratory disease was carried out in New York City Transit Authority workers between November 1961 and August 1963. A total of 7,974 workers with job titles of motorman, surface line operator, and surface line dispatcher were studied. Details of the survey and results are given by Densen, Jones, Bass, and Breuer (1967), Densen *et al.* (1969), and Stebbings (1972; 1973).

From the workers surveyed approximately 2,000 were selected for a five-year follow-up study which was carried out between June 1964 and June 1969. Criteria for selection for the follow-up study were complex and depended upon the smoking histories, ages, one-second forced expiratory volumes, and symptoms of the indivi-

duals (Densen, Jones, and Bass, 1965). The majority of individuals in the follow-up study may be considered as a random sample of the surveyed transit workers; among the remainder there was an excess of both nonsmokers and heavy smokers, and among smokers there was an excess of individuals with either high or low one-second forced expiratory volumes or severe or absent respiratory symptoms. An analysis of the effect of lack of random selection of the follow-up population upon the results of this paper will be presented below.

The fractional carbon monoxide uptake was measured at only one of the three clinic sites in Brooklyn and Manhattan utilized in the follow-up study. A total of 913 individuals had at least one fractional CO uptake test, but it is not known what fraction of the respondents attending the one clinic this represents. For all three clinics combined, 89.8 % of the defined follow-up population received at least one examination. The analyses presented in this paper are based on these 913 individuals, or upon a subset of 581 of the 913 who had two or more tests of their fractional CO uptake during the five-year study period.

METHODS Respondents were interviewed and examined in most cases immediately following their annual (if over 50 years of age) or biannual (if younger) Transit Authority physical examination. An intensive effort was made to induce retirees, ex-employees, and those not scheduled

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for a routine physical examination in that year to make a special appointment for their follow-up examination. The questionnaire covered respiratory symptoms and smoking habits. Routine spirometry was done.

For determination of the fractional CO uptake (FUco) the subject was seated and allowed to breathe room air for two minutes with mouthpiece and noseclips in place. Then for three minutes the subject breathed a mixture of air and approximately 0·1% carbon monoxide. Expired air was collected for the following two minutes, while the technician counted and recorded respirations per minute. The collected air was immediately analysed in a N.V. Godart infrared CO analyser; the volume used in analysis was recorded and added to the volume remaining in the collection bag, which was measured in a Parkinson Cowan type CD1 portable spirometer. The volume measured was corrected to BTPS. The infrared meter was calibrated daily with known gas mixtures. The minute ventilation ($\dot{V}E$) was calculated, and divided by the respiration rate to give the tidal volume (VT).

The fractional CO uptake was calculated as:

$$FUco = \frac{Finco - Fexco}{Finco}$$

No allowance was made for the small difference between inspired and expired volumes.

CHARACTERISTICS OF SUBJECTS   The age range of subjects was from 25 to 70 years of age, the mean age 49·0 years. Of the 913 subjects, 30·12% were Negroes; the mean age of these was 43·7 years. The mean standing height of the subjects was 176·72 cm, the mean weight 82·36 kg. The mean value for the fractional CO uptake was 0·486, for the tidal volume 0·420 l., for the minute volume 7·47 l., and for the respiratory rate 17·7 per minute.

RESULTS

EFFECT OF VENTILATION   Minute ventilation ($\dot{V}E$), tidal volume (VT), and respiratory rate (RR) affect the diffusing capacity of the lung (Anderson and Shephard, 1968). These factors, within the range of values found in normal individuals at rest, were studied among the 581 respondents tested on two or more occasions. Since all three ventilation variables were significantly correlated with age and weight within this population, the preferred procedure for estimating their effect on the FUco was to regress the difference between the first and second FUco (dFUco) on the corresponding differences (dVE, dVT, dRR) in the ventilation variables. A multiple regression technique was used. The effect of change over time was removed by incorporation of a variable dt, the time between the first and second measurements of the FUco. The mean time difference was 16·6 months, the minimum and maximum possible differences were 6 months and 5 years, and the modal difference 12 months.

Of the three ventilation variables dVT was most highly correlated with dFUco after correction for dt;

neither dVE nor dRR contributed significantly when added to the regression of dFUco on dt and dVT. While the addition of dVT to the regression was highly significant ($p < 0·01$), it explained only 1·5% of the variance of dFUco. As the variance of dFUco is related to the variability of repeated measurements on the same subjects, rather than to the variability of the FUco among individuals, this implies that very little of the individual variability in FUco measurements is due to individual variability in resting ventilation.

The FUco declines with increasing tidal volume; the estimated regression coefficient of dFUco on dVT may be used to correct a measured FUco to a constant tidal volume. The remainder of these analyses are based on the FUco corrected to a tidal volume of 0·5 l. BTPS by addition of the term $-0·123654 \times (0·5 - VT)$. The correction is minor: as the mean tidal volume is 0·42 l., the mean correction is approximately $-0·01$.

VARIABLES AFFECTING FUco IN THE POPULATION   Age, standing height, weight, race, and smoking habit variables were tested for their effect on the FUco, again using multiple regression techniques. Age was, of course, highly significant ($p < 0·001$) and accounted for 17·5% of the total sums of squares. Standing height, while significantly correlated with the FUco in a simple regression ($p < 0·05$), was found to account for only one-third as much of the variance as weight; after correction for weight, standing height was no longer significantly correlated with the FUco. Weight, on the other hand, contributes significantly ($p < 0·05$) to the prediction of the FUco even after the effects of age, race, and smoking habits (which are correlated with weight) are removed; its importance is minor, however, as it accounts for only 0·35% of the sums of squares.

The effect of race, a higher FUco in Negroes by 0·0023, was marginal ($0·05 < p < 0·10$) but has been retained in this analysis. The interaction term race × age did not approach significance, indicating no racial difference in the decline of the FUco with age.

Seven smoking categories were defined: three of cigarette smokers, less than 15, 15 to 24, and 25 plus cigarettes per day; nonsmokers; exsmokers; current pipe and/or cigar smokers; and mixed smokers (both cigarettes and pipes and/or cigars). A dummy variable (taking the value 1 if the respondent belonged to that smoking category, 0 otherwise) was assigned to each of these categories except the nonsmokers. These six dummy variables were added to the equation and as a group were very highly significant ($p < 0·001$). Then the set of interaction terms of each with age was added and also found to be significant. These two

TABLE I
PREDICTION EQUATION FOR FRACTIONAL CARBON MONOXIDE UPTAKE

Independent Variables	Bx	Bx_{xAge}
Age	−0·00204	—
Weight (kg)	+0·00040	—
Race Negro	+0·00230	—
Ex-smoker	+0·02413	−0·00097
Pipe/cigar smoker	+0·11588	−0·00265
Cigarette smoker <15/day	+0·09130	−0·00236
15–24/day	+0·03466	−0·00125
25+/day	+0·06053	−0·00233
Pipe/cigar and cigarette smoker	−0·02686	−0·00034
Intercept	0·57046	—

Bx=regression coefficient; Bx_{xAge}=regression coefficient on independent variable times age. Race and smoking variables equal 1 if respondent belongs in that category, 0 otherwise. N=913. Statistical significance discussed in text.

TABLE II
PREDICTED VALUES FOR FRACTIONAL CARBON MONOXIDE UPTAKE IN NON-SMOKERS AND ADDITIVE EFFECTS OF TOBACCO SMOKING

Smoking Category	N	Predicted FUco at Age	
		30 yr	60 yr
Non-smokers	121	0·537	0·476
Ex-smokers	171	−0·005	−0·034
Pipe/cigar smokers	121	+0·036	−0·043
Cigarette smokers <15/day	65	+0·021	−0·050
15–24/day	194	−0·003	−0·040
25+/day	208	−0·009	−0·079
Pipe/cigar and cigarette smokers	33	−0·037	−0·047

For Caucasians, weight 71 kg, tidal volume 0·5 l.; add +0·010 to correct predicted values to population mean tidal volume.

TABLE III
DISTRIBUTION OF STANDARDIZED RESIDUALS FROM REGRESSION OF FRACTIONAL CARBON MONOXIDE UPTAKE

Standard Errors of Estimate	Residuals	
	No. Expected	No. Observed
< −2·00	20·8	19
−2·00 − −1·50	40·2	29
−1·50 − −1·00	83·9	79
−1·00 − −0·50	136·8	134
−0·50 − −0·00	174·8	224
+0·00 − +0·50	174·8	178
+0·50 − +1·00	136·8	123
+1·00 − +1·50	83·9	58
+1·50 − +2·00	40·2	36
> +2·00	20·8	33

Residuals are differences between observed FUco and those expected according to regression equation given in Table I, divided by 0·0693, the standard error of estimate. Expected distribution is Normal, with mean 0 and SD 1. χ^2 test of goodness of fit significant at the 0·001 level. N=913.

sets of variables together account for 5·4% of the total sums of squares; due to their interdependence their contributions should not be separated.

The final regression coefficients may be seen in Table I. The smoking effects are more readily apparent, however, in Table II which gives the expected FUco at ages 30 and 60 for nonsmokers and the additive effects of smoking at those two ages. Clearly, there is little difference between smokers and nonsmokers at age 30 and there is even a tendency for light smokers to have higher values than nonsmokers at that age. Rates of decline with age are greater, even doubled, among smokers, however, and by age 60 their FUcos are distinctly lower, by approximately 10%, than those of nonsmokers.

VARIABILITY OF FUco The standard deviation of the FUco in this population was 0·0786, the coefficient of variation 16·5%. Of more interest, the standard error of estimate about the regression was 0·0693. Assuming that individual variability was equal on the first two tests, and that the 581 individuals with two tests were reasonably representative of the entire tested population of 913, the standard deviation of an individual's measurement could be estimated at 0·0690. This, of course, refers to individual variability over a period of one to two years.

It was only in the writing of this report that the close similarity between the population standard error of estimate and the individual variability was noted. The implication was that there was almost no variability among individuals remaining to be accounted for; a population standard error of ~0·01 is implied. Reanalysis of existing results on the 581 respondents with two measurements yielded an estimated population standard error of 0·035; removal of the effect of age reduced this to 0·023; assuming that the effect of race, weight, and smoking habits were equally important relative to the age effect in these 581 persons as in the total population of 913, the population standard error can be reduced to approximately 0·018. These values are still extremely small relative to the mean.

A test of the normality of the distribution of the residuals about the regression was carried out. A χ^2 value of 43·62 (15 df, P<0·001) indicated that the residuals are not normally distributed. A somewhat collapsed distribution is shown in Table III; a large excess of small negative deviates is seen. In view of the small population standard error this distribution is primarily determined by the shape of the distribution of values about the individual means.

The deviation from normality in the distribution is statistically significant, but not extreme, and should not affect the estimates here of means and regression coefficients; significance levels and variance estimates might be slightly affected.

EFFECTS OF POPULATION SAMPLING SCHEME ON RESULTS
As described above, this sample had been stratified in a very complex manner (Densen *et al.*, 1965). Numerous multiple regression equations, including as

independent variables all factors and all the inter-
actions of those factors utilized in the sampling
procedure, were carried out. The predicted values
for nonsmokers in Table II were found to be changed
by less than ±0·002, and no significant changes in the
estimated smoking effects were found. What might
be somewhat inflated, are the proportions of the
variance accounted for by the age and smoking
history variables in the regression analysis.

DISCUSSION

Bates (1952) reported measurements of the fractional
CO uptake in normal subjects and in patients with
emphysema. Since that time a number of authors
have reported on the use of the FUco in the evalua-
tion of respiratory patients (Marks, Cugell, Cadigan,
and Gaensler, 1957; MacNamara, Prime, and
Sinclair, 1959; Bates, Woolf, and Paul, 1962;
Kreukniet and Visser, 1962; Woolf, 1964; Woolf,
1965; Bates et al., 1966; James and Rumble, 1967;
Rasmussen and Nelson, 1971; Bates, 1973).

Mean values of the FUco for small numbers of
normal subjects have been published by several
authors (Bates, 1952; Marks et al., 1957; Shephard,
Carey, and Phair, 1958; MacNamara et al., 1959;
Woolf, 1964; Woolf, 1965). Mean values of the
FUco during exercise for 298 normal women have
been published by Woolf and Suero (1971). Aguzzi,
Woolf, and Paterson (1966) have reported on the
FUco in very old people.

Predicted normal values for the FUco as a function
of age and height have been published by Bates et al.
(1971). A prediction equation for white males has
been published by Bates et al. (1962): it is FUco =
0·82085 − 0·00341 × age − 0·00322 × height (inches).
The prediction equation for white males, based on
nonsmokers, from this study is FUco = 0·58032 −
0·00204 × age + 0·0004 × weight (kilograms) without
correction for tidal volume.

In this study weight correlated much more strongly
with the FUco than did height, and the effect of
standing height was not significant after correction
for weight. The effects of weight and height in this
study were positive, rather than negative, as in the
equation above of Bates et al. (1962). Anderson and
Shephard (1969) found weight to be the most useful
anthropometric predictor of single-breath diffusing
capacity, and theirs appears to be the only study of
diffusing capacity in which the optimum index of
body size has been arrived at statistically rather than
chosen arbitrarily. The effect of weight on the FUco,
although statistically significant, is certainly not
strong (Table I).

The effect of race, although again statistically
significant, is both minor (Table I) and constant; no

indication of a racial difference in decline of the
FUco with age comparable to that observed for
the FEV₁ in this population (Stebbings, 1973) was
seen, but the analysis of the FUco data may have
been too unsophisticated to detect such an effect.

That the FUco should decline with age is not
surprising; nor is it surprising that the rate of decline
with age increases with increasing tobacco con-
sumption. The effect of these variables on the decline
of the pulmonary diffusing capacity in population
studies has been thoroughly reviewed by Van Ganse,
Ferris, and Cotes (1972). Reduction of the FUco
during exercise among smokers has been reported for
both men (Rasmussen and Nelson, 1971) and women
(Woolf and Suero, 1971).

Bates et al. (1971) emphasize the sensitivity of the
FUco to differences in minute volume; Lacoste
and Rouch (1965) emphasize the effect of respiratory
frequency. In this study of normal subjects at rest,
minute volume, tidal volume, and respiratory
frequency explained only 1·5% of the individual
variability in the FUco, and this contribution may in
practice be ascribed to the tidal volume alone.
(Obviously, if individual variability over much
shorter time periods is studied, the percentage con-
tribution of these variables would be higher.)
Correction of the FUco to any constant tidal
volume within the normal testing range is simple; the
correction is small but should be used in epidemio-
logical studies or when observed values are on the
borderline of abnormality.

One of the most interesting findings of this study
was that the individual variability of a subject's FUco
(over a period of one to two years) was much greater
than the unexplained variability in the population.
This is the opposite of the situation with lung volumes
and flow rates (Stebbings, 1971). Here the standard
error of the individual measurement was estimated as
approximately 0·07; the population standard error
was estimated to be in the range 0·01 to 0·02.

The standard deviation of the FUco in this
population was generally comparable to that reported
by others (MacNamara et al., 1959; Woolf, 1964).
However, Bates (1973) has estimated the standard
error of the individual FUco determination to be in
the range 0·025–0·04. These estimates refer, though,
to monthly measurements within a year so the time
periods between measurements are much less than the
mean 16·6 months in this study.

If the results of this study are valid for measurement
of the FUco in large populations, they imply that the
FUco is essentially worthless as a screening test for
chronic respiratory disease. The purpose of screening
is to detect individuals at high risk of ultimate
disability or mortality from chronic respiratory

disease; a measurement which changes drastically over a period of months, or two or three years, is of little use. What is required is a test which varies among individuals in the population much more than from time to time in the individual, and not the other way around.

However, if changes in an individual's FUco over time truly reflect changes in the state of his lungs then the test might be a sensitive tool for the measurement of short-term effects of environmental factors on the lung.

Bates *et al.* (1971) express the opinion that the FUco is 'a most useful index of normality'. They claim the major advantage of simplicity of measurement and calculation for the FUco, point out as its main disadvantage sensitivity to minute volume, and suggest that it would be useful in screening for chronic respiratory disease. The simplicity of the procedure is evident, but these data do not fully support their other generalizations. Extrapolation of these findings concerning the fractional carbon monoxide uptake to more sophisticated methods of measuring carbon monoxide exchange I shall leave to others.

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