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Original Research

LUNG FUNCTION TESTING

A New Breath-Holding Test May Noninvasively Reveal Early Lung Abnormalities Caused by Smoking and/or Obesity

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Background: **Smoking and obesity are leading global causes of death. The aim of the present study was to develop a test to detect early lung abnormalities caused by smoking and/or obesity and to elucidate the underlying mechanisms and major contributory factors.**

Methods: **One hundred twenty-nine healthy adults, 20 to 40 years of age, with normal spirometry findings, were divided into the following five groups: 38 healthy subjects (15 female subjects); 46 smokers (5 female smokers); 18 overweight nonsmokers (2 female nonsmokers; normal body mass index [BMI], ≥ 25 kg/m^2; range, 25.0 to 37.2 kg/m^2); 19 overweight smokers (1 female smoker; BMI range, 25.2 to 33.5 kg/m^2); and 8 ex-smokers (BMI range, 20.8 to 24.1 kg/m^2). A modified pulse oximeter was employed for measuring the fall in pulse oximetric saturation caused by 20-s breath-holding ($dSpO_2$) at resting end expiration in the sitting posture.**

Results: **In healthy subjects, $dSpO_2$ had no significant correlation with age ($r^2 = 0.009$; $p = 0.66$). In smokers, $dSpO_2$ correlated with both the number of pack-years ($r^2 = 0.590$; $p < 0.001$) and closing volume (CV)/vital capacity (VC) ratio ($r^2 = 0.573$; $p < 0.001$). In overweight nonsmokers, $dSpO_2$ increased significantly with BMI alone ($r^2 = 0.667$; $p < 0.001$). In overweight smokers, the largest increase in the mean $dSpO_2$ was observed. Multiple linear regression analysis suggested that BMI and CV/VC are the two major contributing factors determining $dSpO_2$ during breath-holding. In young former smokers, no significant increase in the mean $dSpO_2$ was observed ($p = 0.77$) a mean (± SD) duration of 5.2 ± 2.9 years after the cessation of smoking. No significant difference in $dSpO_2$ was observed between men and women.**

Conclusions: **A new test that measures oxygen saturation during breath-holding reveals early lung abnormalities in subjects who either smoke or are overweight, especially if these factors are combined. Peripheral airway abnormalities and/or lung volume reduction may play roles in the greater desaturation.** ***(CHEST 2009; 136:545–553)***

Abbreviations: BMI = body mass index; CC = closing capacity; COHb = carboxyhemoglobin; CV = closing volume; $dSpO_2$ = fall in pulse oximetric saturation caused by 20-s breath-holding; $FEF_{50\%}$ = forced expiratory flow at 50% of FVC; $FEF_{75\%}$ = forced expiratory flow at 75% of FVC; FRC = functional residual capacity; RV = residual volume; SaO_2 = arterial oxygen saturation; SpO_2 = pulse oximetric saturation; SpO_2b = baseline oxygen saturation at start of breath-holding; TLC = total lung capacity; TT = lung-to-finger transport time; VC = vital capacity

Smoking and obesity are leading preventable causes of death,[1,2] and their prevalence is increasing worldwide.[3] At present, pulmonary physicians confront a difficult situation when trying to reveal early lung abnormalities caused by smoking and/or obesity because no simple and convenient tools are available that can easily be applied in clinical practice.[4–6] With respect to gas-exchange abnormalities of the lung, measurement of alveolar gas and arterial blood oxygen tension difference can detect early lung abnormalities,[7] although such a test is invasive. Noninvasive pulse oximetry would be preferable,

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although it is unreliable for detecting small differences in oxygen saturation in ranges where the oxyhemoglobin dissociation curve is nearly flat. Thus, an additional loading test, such as exercise, breathing a hypoxic mixture, or breath-holding, may be required to magnify any changes of arterial oxygen saturation (Sa_{O_2}). To our knowledge, pulse oximetry has not been used in conjunction with a voluntary breath-holding for evaluating early lung abnormalities in smokers and/or obese subjects. The aim of the present study was to develop a new test that simply and noninvasively detects gas-exchange abnormalities of the lung caused by smoking or obesity and to elucidate the underlying mechanisms and major contributing factors that determine arterial oxygen desaturation in these subjects.

Materials and Methods

One hundred twenty-nine healthy subjects, 20 to 40 years of age with normal spirometry findings were divided into the following five groups: group N, healthy subjects (mean body mass index [BMI], 22.0 kg/m^2; range, 18.1 to 24.6; n = 38; 15 women) who were asymptomatic nonoverweight nonsmokers with no small airway abnormalities; group S, nonoverweight smokers (mean BMI, 21.7 kg/m^2; range, 17.9 to 24.6 kg/m^2; n = 46; 5 women); group O, overweight nonsmokers with BMI $\geq$ 25 kg/m^2 (mean BMI, 29.2 kg/m^2; range, 25.0 to 37.2 kg/m^2; n = 18; 2 women); group OS, overweight smokers (mean BMI, 29.1 kg/m^2; range, 25.2 to 33.5 kg/m^2; n = 19; 1 woman); and group FS, nonoverweight ex-smokers (mean BMI, 22.5 kg/m^2; range, 20.8 to 24.1 kg/m^2; n = 8). In this report, the term *overweight* was defined as a BMI $>$ 25 kg/m^2 but $<$ 40 kg/m^2. All subjects were free from current or past serious respiratory diseases, and none had experienced airway infections within the previous 2 months. Eleven subjects out of the total 140 subjects were excluded prior to assignment to a group (1 subject, common cold; 4 subjects, history of pulmonary diseases [2 subjects, childhood asthma; 1 subject, pneumonia; 1 subject, pneumothorax], and 6 subjects (4 women) who were identified as passive smokers, in whom abnormal closing volume was observed).[6]

After obtaining anthropometric data and smoking status, the blood carboxyhemoglobin (COHb) level was estimated by using a carbon monoxide analyzer (Micro CO meter; Micro Medical Ltd; Rochester, UK) to confirm the declared status.[8,9] Spirometric tests using a flow-sensing spirometer (HI-801; Chest Co; Tokyo, Japan) were performed according to standardized procedures,[10,11] and closing volumes were obtained by a single-breath nitrogen test[12] by using a semiautomatic machine (Chestac-8800; Chest Co). Lung volumes were measured based on a single-breath method in subjects who agreed with our proposal to the measurement in group N (n = 8), group S (n = 8), and group O (n = 8) to elucidate the underlying mechanisms of the fall in pulse oximetric saturation caused by 20-s breath-holding (dSp_{O_2}) abnormalities (Table 2).

Pulse waves and fall of pulse oximetric saturation (Sp_{O_2}) during a period of apnea were obtained by a modified pulse oximeter (8000AA; Nonin Medical Inc; Plymouth, MN). The moving average circuit was excluded so that the recorded data were sampled at a rate of $\times$ 3/s for a faster response and more precise fall of Sp_{O_2}. The Sp_{O_2} probe was mounted on the right middle fingertip and held at the level of the neck to avoid possible effects of motion or circulatory congestion. The oximeter was calibrated by a test system (Fingersim; BC Group International Inc; St. Louis, MO). Mouth flow and lung volume were detected using a pneumotachograph and a flow integrator (3700A and 1110A PA-1; Hans Rudolph Inc; Shawnee, KS). Partial pressure of end-tidal carbon dioxide was monitored by a carbon dioxide analyzer (OGS-2002; Nihon Kohden Inc; Tokyo, Japan). All measured outputs were displayed in real time on a portable computer (Compaq nx9040; Hewlett-Packard Japan; Tokyo, Japan).

To establish functional residual capacity (FRC), seated subjects first voluntarily breathed at relaxed resting tidal levels for at least 1 to 2 min through a heated pneumotachograph supported at the mouth level. The mean ($\pm$ SD) breathing rate was paced with a metronome (SP-100; Seiko Co; Tokyo, Japan) at 20 $\pm$ 2 breaths/min. Then, subjects made a deep inspiratory maneuver, followed by the resumption of tidal breathing for 2 min. The deep inspiration was repeated, followed by another 4 to 5 min of tidal breathing. After ensuring that the resting end-expiratory level was the constant and that baseline Sp_{O_2} and end-tidal Pc_{O_2} were stable and at normal levels, the subjects were asked to interrupt tidal breathing at the end of a normal expiration (*ie*, at FRC). Simultaneously, the circuit was closed at the distal end of the pneumotachograph by inflating a balloon (9340 Series; Hans Rudolph Inc) for 20 s. The end of breath-holding was signaled by one audible click per second during the last 5 s. Immediately after deflating the balloon, the subjects were asked to make two deep inspiratory maneuvers to inhale fresh air followed by tidal breathing for 1 min. This protocol was repeated until more than three consecutive repeatable measurements were obtained.

The lung-to-finger transport time (Tt) was calculated from the Sp_{O_2} tracings as the interval between the abrupt inhalation after breath-holding up to the point at which Sp_{O_2} started a sharp recovery. The Sp_{O_2} at Tt s after starting breath-holding was taken as the baseline ($Sp_{O_2}b$).

Predicted values for pulmonary function tests were obtained from published data.[12,13] The entire study was approved by the Iwate Medical University Ethics Committee, and written consent was obtained from each subject.

Statistical Analysis

Comparisons among more than two independent means were made by using one-way analysis of variance followed by Tukey-Kramer or Games-Howell tests for normally or nonnormally distributed data, respectively. Linear correlations between the

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two indexes were tested by the Pearson correlation coefficient. The Chow test was employed to determine whether the set of linear regression parameters of the slopes was equal across groups. Multiple linear regression analysis was performed by using a stepwise forward procedure to build a regression model in which independent variables were included as only statistically related to the dependent variable. Data were analyzed by a statistical software package (SPSS, version 16.0J for Windows; SPSS Inc; Chicago, IL), were expressed as the mean ± SD, and were considered to be significant if the p value was < 0.05. Overweight and/or smoking female subjects in our population were relatively scarce, so the data analysis was mainly confined to male subjects unless stated otherwise.

Results

Table 1 presents the mean values of the anthropometrics, lung function, Sa_{O_2}, and circulation data of the five groups of subjects. The mean ages and heights of the five groups of subjects did not show any significant differences among the groups. In addition, no significant differences in weight and BMI were observed among the three nonoverweight groups (groups N, S, and FS) or between the two overweight groups (groups O and OS).

Polygraph tracings of four sample subjects in the four groups are shown in Figure 1, *A–D*, in which variable reductions, in the four examples shown, began during the 20-s breath-hold and continued after breathing recommenced. In Figure 2, *A*, significantly higher mean dSp_{O_2} values were observed in smokers (group S), overweight subjects (group O), and especially combined subjects (group OS) compared with healthy control subjects (group N). However, the mean dSp_{O_2} of former smokers (group FS) at 5.25 ± 2.92 years after the cessation of smoking who had a similar pack-year smoking history to that of the current smokers showed no significant difference from that of control subjects (group N) [$p = 0.58$] (Fig 2, *A*). Paralleling the changes in dSp_{O_2}, a significantly higher mean closing volume (CV)/vital capacity (VC) ratio (percent predicted) was observed only in groups S and OS (Fig 2, *B*), and significantly lower mean forced expiratory flow at 75% of FVC ($FEF_{75\%}$ [percent predicted]) was observed only in group OS (Fig 2, *C*).

Contributing factors associated with increased dSp_{O_2} did not show a significant correlation with age in the healthy male subjects ($r^2 = 0.009$; $p = 0.66$) [Fig 3, *A*] and female subjects ($r^2 = 0.003$; $p = 0.86$; data not shown), whereas significant inverse correlations were observed with $Sp_{O_2}b$ ($r^2 = 0.453$; $p < 0.001$) [Fig 3, *B*] and Tt ($r^2 = 0.450$; $p < 0.001$) [Fig 3, *C*], indicating that the baseline arterial oxygen desaturation and the increase in cardiac output were the basic contributing factors for dSp_{O_2} in healthy subjects (group N).

In smokers (group S), dSp_{O_2} was strongly correlated with the number of pack-years ($r^2 = 0.590$; $p < 0.001$) [Fig 3, *D*] and CV/VC ($r^2 = 0.573$; $p < 0.001$) [Fig 3, *E*], whereas a significant inverse, weak correlation was observed with $FEF_{75\%}$ ($r^2 = 0.123$; $p = 0.03$; data not shown), suggesting that peripheral airway abnormalities caused by smoking were a factor of the increase in dSp_{O_2}. Indeed, a fairly high correlation between the number of pack-years and CV/VC ($r^2 = 0.489$; $p < 0.001$) or a correlation between the number of pack-years and $FEF_{75\%}$ ($r^2 = 0.274$; $p < 0.001$) may support this hypothesis.

In overweight subjects (group O), dSp_{O_2} was strongly correlated only with weight ($r^2 = 0.598$; $p < 0.001$) and BMI ($r^2 = 0.667$; $p < 0.001$) [Fig 3, *F*]. If combined with smoking (group OS), a strong correlation was observed between dSp_{O_2} and BMI ($r^2 = 0.640$; $p < 0.001$) [Fig 3, *G*], and CV/VC ($r^2 = 0.415$; $p < 0.001$) [Fig 3, *H*], in which significantly steeper slopes of dSp_{O_2} vs BMI ($p = 0.003$) and dSp_{O_2} vs CV/VC ($p = 0.032$) were observed compared with those of group O ($p = 0.003$) [Fig 3, *F*] and group S ($p = 0.032$) [Fig 3, *E*], respectively. An additional correlation was observed with weight ($r^2 = 0.392$; $p = 0.005$), CV/VC (percent predicted) [$r^2 = 0.520$; $p = 0.001$], closing capacity (CC)/total lung capacity (TLC) ratio ($r^2 = 0.272$; $p = 0.03$), and CC/TLC (percent predicted) [$r^2 = 0.252$; $p = 0.03$; data not shown].

In these groups of subjects (groups N, S, O, and OS), the multiple linear regression analysis model showed the following: $dSp_{O_2} = -7.203 + 0.272 \times BMI + 0.336 \times CV/VC$ ($r^2 = 0.756$; $p < 0.001$; *R* adjusted for degrees of freedom), in which BMI and CV/VC were significant, independent variables among the nine possible independent variables (age, BMI, pack-years, FEV_1, forced expiratory flow at 50% of FVC [$FEF_{50\%}$], $FEF_{75\%}$, CV/VC, CC/TLC, and Tt). Weight, forced expiratory flow at 1% of FVC (percent predicted), $FEF_{50\%}$ (percent predicted), $FEF_{75\%}$ (percent predicted), CV/VC (percent predicted), and CC/TLC (percent predicted) were excluded as having multicollinearity with at least one of the nine factors just mentioned. Therefore, BMI and CV/VC are the statistically major contributing factors for dSp_{O_2} in the present subjects as a whole. A strong correlation of CV/VC with the number of pack-years ($r^2 = 0.524$; $p \leq 0.001$) again suggests a greater contribution of cigarette smoking to the increase in CV/VC. In women, the mean dSp_{O_2} was not significantly different from that of men (2.22% ± 0.34% vs 2.57% ± 0.55%, respectively; $p = 0.13$) in group N, and comparable changes were observed with those of men in the corresponding groups.

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Table 1—*Anthropometrics and Lung Function, Arterial Oxygen Saturation, and Cardiovascular Parameters in the Five Groups of Study Subjects*

Variables	F Value	p Value*	Group N (n = 23)	Group S (n = 41)	p Value* (Group N vs S)	Group O (n = 16)	p Value* Group N vs O	p Value* Group S vs O	Group OS (n = 18)	p Value* Group N vs OS	p Value* Group S vs OS	Group FS (n = 8)	p Value* Group N vs FS	p Value* Group S vs FS	p Value* Group O vs FS	p Value* Group OS vs FS
Age, yr	2.451	0.051	27.9 ± 4.9	31.1 ± 5.2	NS	30.4 ± 5.0	NS	NS	31.6 ± 5.5	NS	NS	33.5 ± 4.5	NS	NS	NS	NS
Height, cm	1.03	0.4	171.1 ± 6.0	173.2 ± 4.8	NS	173.3 ± 5.5	NS	NS	172.3 ± 4.3	NS	NS	170.3 ± 6.6	NS	NS	NS	NS
Weight, kg	47.832	< 0.001	64.5 ± 7.0	64.9 ± 5.8	1	87.9 ± 11.5	< 0.001	< 0.001	85.5 ± 8.1	< 0.001	< 0.001	65.3 ± 6.8	1	1	< 0.001	< 0.001
BMI, kg/m^2	69.398	< 0.001	22.0 ± 1.7	21.7 ± 1.7	0.96	29.2 ± 3.2	< 0.001	< 0.001	29.1 ± 2.4	< 0.001	< 0.001	22.5 ± 1.2	0.94	0.62	< 0.001	< 0.001
Cigarettes smoked, No./d	97.289	< 0.001	0	17.5 ± 4.5	< 0.001	0	NA	< 0.001	20.8 ± 7.5	< 0.001	0.45	17.9 ± 8.1	0.03	1	0.003	0.91
Smoking history, pack-yr	37.565	< 0.001	0	9.7 ± 5.0	< 0.001	0	NA	< 0.001	12.4 ± 6.3	< 0.001	0.49	8.5 ± 4.8	0.01	0.97	0.01	0.44
COHb, %	34.292	< 0.001	0.34 ± 0.13	2.82 ± 1.44	< 0.001	0.45 ± 0.22	0.48	< 0.001	2.61 ± 1.04	< 0.001	0.97	0.52 ± 0.29	0.5	< 0.001	0.96	< 0.001
FVC, % predicted	0.839	0.503	101.9 ± 9.4	98.6 ± 19.4	NS	106.3 ± 18.7	NS	NS	103.6 ± 13.5	NS	NS	103.9 ± 6.9	NS	NS	NS	NS
FEV_1, % predicted	0.175	0.95	97.0 ± 8.6	97.0 ± 11.5	NS	98.9 ± 18.3	NS	NS	95.4 ± 15.5	NS	NS	98.1 ± 8.8	NS	NS	NS	NS
FEV_1/FVC, %	2.511	0.046	85.7 ± 5.0	85.9 ± 5.9	1	83.2 ± 4.1	0.64	0.48	82.0 ± 6.5	0.23	0.11	81.7 ± 5.8	0.41	0.31	0.97	1
$FEF_{25–75\%}$, % predicted	0.58	0.68	101.5 ± 15.7	106.0 ± 23.5	NS	104.1 ± 24.8	NS	NS	96.9 ± 25.1	NS	NS	101.8 ± 17.5	NS	NS	NS	NS
$FEF_{50\%}$,% predicted	0.441	0.78	100.3 ± 18.4	99.7 ± 19.7	NS	105.4 ± 23.6	NS	NS	96.2 ± 24.3	NS	NS	102.3 ± 20.4	NS	NS	NS	NS
$FEF_{75\%}$, L/s	3.918	0.005	2.33 ± 0.41	2.29 ± 0.73	1	2.12 ± 0.60	0.83	0.88	1.72 ± 0.52	0.01	0.01	1.85 ± 0.42	0.3	0.32	0.83	0.99
$FEF_{75\%}$, % predicted	3.864	0.006	100.6 ± 19.8	97.1 ± 26.5	0.98	90.1 ± 25.9	0.66	0.85	74.5 ± 20.2	0.006	0.009	85.1 ± 21.7	0.51	0.69	0.99	0.83
CV/VC, %	16.995	< 0.001	11.0 ± 1.8	14.7 ± 2.4	< 0.001	12.3 ± 2.2	0.31	0.009	17.6 ± 4.6	< 0.001	0.11	15.6 ± 2.6	0.007	0.89	0.06	0.59
CV/VC, % predicted	18.182	< 0.001	103.2 ± 9.5	124.9 ± 18.6	< 0.001	103.2 ± 10.0	1	< 0.001	150.1 ± 36.4	< 0.001	0.08	108.4 ± 11.9	0.79	0.04	0.82	0.002
CC/TLC, %	2.371	0.057	34.1 ± 3.8	36.9 ± 8.4	NS	31.7 ± 4.9	NS	NS	34.5 ± 4.9	NS	NS	37.0 ± 4.1	NS	NS	NS	
CC/TLC, % predicted	3.293	0.014	112.3 ± 15.2	117.9 ± 23.5	0.79	99.4 ± 16.6	0.22	0.01	107.5 ± 13.7	0.92	0.3	104.8 ± 11.8	0.87	0.38	0.96	1
Spo_2b, %	6.612	< 0.001	97.7 ± 0.8	96.7 ± 0.9	0.001	96.6 ± 0.9	0.002	0.99	96.7 ± 0.9	0.012	1	97.6 ± 0.7	1	0.9	0.08	0.22
$dSpo_2$, %	21.371	< 0.001	2.57 ± 0.55	3.70 ± 0.88	< 0.001	4.63 ± 1.54	0.001	0.19	6.70 ± 3.09	< 0.001	0.006	2.78 ± 0.25	0.62	< 0.001	0.002	< 0.001
Tr, s	6.862	< 0.001	22.4 ± 3.9	18.0 ± 3.3	< 0.001	21.8 ± 3.4	0.98	0.016	21.0 ± 3.6	0.75	0.08	23.4 ± 7.6	0.98	0.007	0.89	0.61

The data were obtained in 106 male subjects. Comparisons among mean data of the five groups were made using one-way analysis of variance (F values and p values in the left-hand side of the table), followed by Tukey-Kramer or Games-Howell for normally or nonnormally distributed data. The p values among groups are also shown. No significant differences were observed in pack-years between the two smoker groups (groups S and OS) and in body weight or BMI between the two overweight groups (groups O and OS). NA = no analyzable comparison; NS = no significant difference; $FEF_{25–75\%}$ = forced expiratory flow, midexpiratory phase.

*The p values of the significant differences among corresponding groups are presented.

Table 2—*Separately Measured Lung Volumes in Group N, Group S, and Group O*

Variables	F Value	p Value	Group N (n = 8)	Group S (n = 8)	p Value (Group N vs S)	Group O (n = 8)	p Value: Group N vs O	p Value: Group S vs O
Age, yr	1.810	0.19	29.3 ± 5.8	33.8 ± 4.8	NS	33.8 ± 5.7	NS	NS
Height, cm	1.465	0.25	170.9 ± 6.9	174.6 ± 2.7	NS	170.9 ± 4.6	NS	NS
Weight, kg	14.899	< 0.001	64.9 ± 11.8	64.5 ± 6.3	1.00	91.3 ± 14.1	< 0.001	< 0.001
BMI, kg/m^2	15.384	< 0.001	22.4 ± 3.3	21.8 ± 1.8	0.95	31.4 ± 5.6	< 0.001	< 0.001
Cigarettes smoked, No./d	361.000	< 0.001	0	19.0 ± 2.8	< 0.001	0	NA	< 0.001
Smoking history, pack-yr	79.025	< 0.001	0	12.4 ± 3.9	< 0.001	0	NA	< 0.001
TLC, L	0.013	0.99	6.18 ± 1.02	6.19 ± 0.68	NS	6.24 ± 0.58	NS	NS
FRC, L	5.591	0.01	2.91 ± 0.57	3.36 ± 0.52	0.20	2.51 ± 0.42	0.28	0.008
FRC/TLC, %	14.695	< 0.001	47.0 ± 4.1	54.4 ± 6.9	0.03	40.1 ± 4.3	0.04	< 0.001
ERV, L	6.749	0.005	1.59 ± 0.37	1.63 ± 0.38	0.97	1.04 ± 0.34	0.02	0.009
ERV/TLC, %	11.397	< 0.001	26.4 ± 4.9	26.3 ± 4.7	1.00	16.5 ± 4.7	0.001	0.001
RV, L	5.728	0.01	1.32 ± 0.28	1.73 ± 0.21	0.008	1.48 ± 0.23	0.43	0.12
RV/TLC, %	8.046	0.003	21.9 ± 2.0	28.2 ± 4.2	0.002	23.7 ± 3.1	0.53	0.03

Mean lung volumes in the present subjects are presented in liters, body temperature, pressure, saturated (with water vapor) [BTPS]. Comparisons among mean data of the three groups were made as noted in Table 1. The mean data of anthropometrics and lung function of the three groups of subjects were not significantly different among the groups except for the mean weight and BMI. In addition, no significant difference in the anthropometrics between the corresponding groups in Table 1 and Table 2 was observed. ERV = expiratory reserve volume. See Table 1 for abbreviations not used in the text.

Importantly, an additional study of lung volume measurements in corresponding groups from consented subjects (Table 2) showed a significant mean decrease of FRC/TLC in overweight subjects (group O) [p = 0.04], and a significant mean increase of residual volume (RV)/TLC in smokers (group S) [p = 0.002] were observed compared with healthy subjects (group N). The former indicates lung vol-

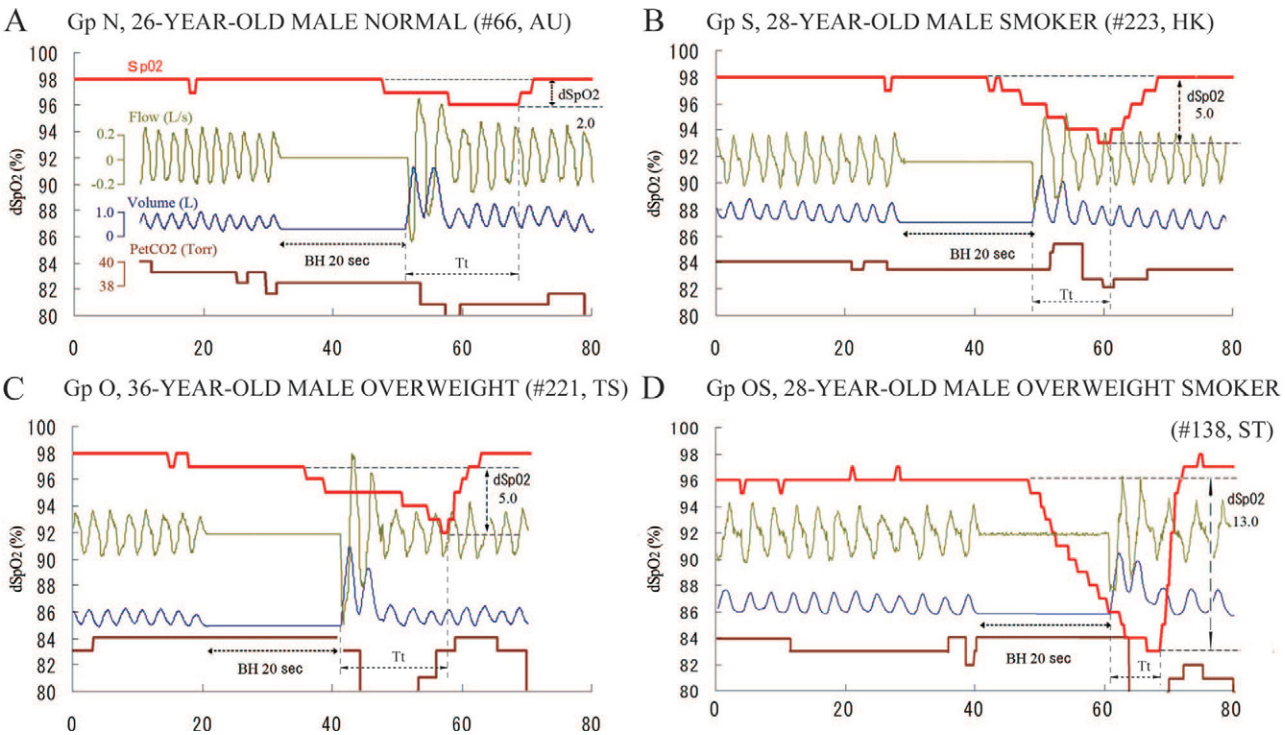

FIGURE 1. Polygraph tracings of four sample subjects in the four groups (N, S, O, and OS). *A*: group N, 26-year-old healthy man (BMI, 22.5 kg/m^2; CV/VC 11.5%; Tt, 17.4 s). *B*: group S, 28-year-old male smoker (BMI, 24.6 kg/m^2; 8.0 pack-years; CV/VC, 16.1%; Tt, 11.9 s). *C*: group O, 36-year-old overweight man (BMI, 26.7 kg/m^2; CV/VC, 13.2%; Tt, 16.7 s). *D*: group OS, 28-year-old male overweight smoker (BMI, 30.4 kg/m^2; CV/VC, 18.6%; Tt, 8.4 s). Note that the last subject (*D*) had one of the highest $dSpO_2$ values in the present study. Gp = group.

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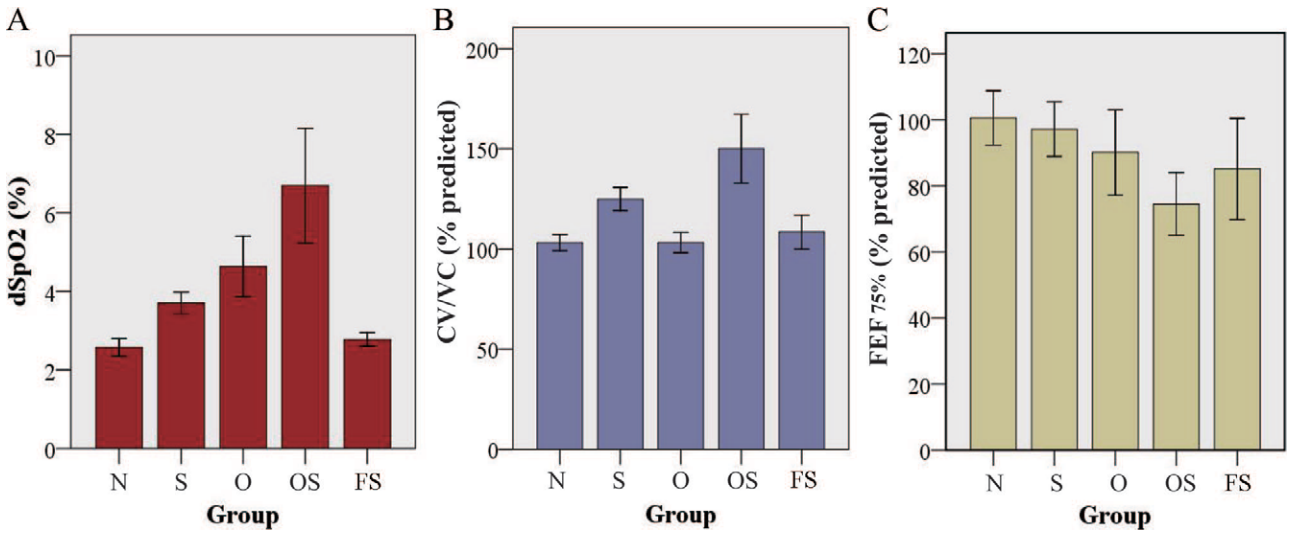

FIGURE 2. Comparison of the mean $dSpO_2$, CV/VC (percent predicted), and $FEF_{75\%}$ (percent predicted) values of the five groups of subjects N, S, O, OS, and FS. CV/VC (percent predicted) represents percent predicted CV/VC value and $FEF_{75\%}$ (percent predicted) represents percent predicted $FEF_{75\%}$ value. The data suggest that these indexes show different characteristics for detecting early lung abnormalities caused by smoking and/or overweight (see text).

ume reduction at FRC in obese subjects, and the latter indicates increase in premature airway closures at their RV in smokers.

DISCUSSION

Our data show that breath-holding induces higher than normal transient oxygen desaturation in smokers and/or overweight subjects in a dose-related manner, even when their individual spirometry data were within normal ranges. The data also suggested that smoking cessation for a period of about half a decade can largely reverse the changes in young smokers. The phenomenon of arterial desaturation is well recognized after the induction of anesthesia in smokers[14,15] or during apnea in obese subjects.[16,17] Although two studies[18,19] have reported the effect of voluntary breath-holding on arterial oxygen desaturation in the obese, the aims of their studies were not to evaluate early lung abnormalities caused by obesity.

Arterial oxygen desaturation would likely be one of the main consequences of lung function abnormalities. The main factors influencing arterial oxygen desaturation during apnea[17,20] would be as follows: (1) ventilation perfusion ratio unevenness at apnea onset; (2) thoracic gas volume at apnea; (3) cardiac output; (4) duration of apnea; (5) baseline inspired oxygen concentration; (6) resting oxygen consumption; and (7) mixed venous oxygen desaturation, some of which may overlap.

In smokers in the present study, the first possibility may be especially important because a strong correlation was observed between $dSpO_2$ and CV/VC. Increases in the latter usually indicate uneven ventilation because of the known peripheral airway abnormalities found in smokers.[4–7,21–24] A small but significant difference in mean baseline SpO_2 values between smokers (group S) and healthy subjects (group N) [97.7% and 96.7%; $p < 0.001$] (Table 1) also supports this possibility. However, a greater difference of SaO_2 could have been masked by an overestimation of SpO_2 in smokers because of the higher COHb level in their blood.[25,26] Because the mean difference of the estimated COHb between groups N and S was 2.48% (Table 1), the baseline SaO_2 would be close to 97.7% and 93.8%, respectively. In addition, abnormal pulmonary perfusion caused by endothelial injury because of cigarette smoke is another possible contributing mechanism. In contrast to the reported changes in the systemic circulation,[27–29] at present, direct evidence of a disturbance in the pulmonary circulation in smoker's lung is lacking except in an animal model[30] and human COPD.[31]

Concerning the contributing factors that enhanced the apneic oxygen desaturation in overweight subjects, the second possibility may be important because a strong correlation was observed between $dSpO_2$ and BMI in overweight subjects (group O). In addition, a significant mean decrease in lung volume (*ie*, FRC/TLC) was observed, which is comparable to that described in

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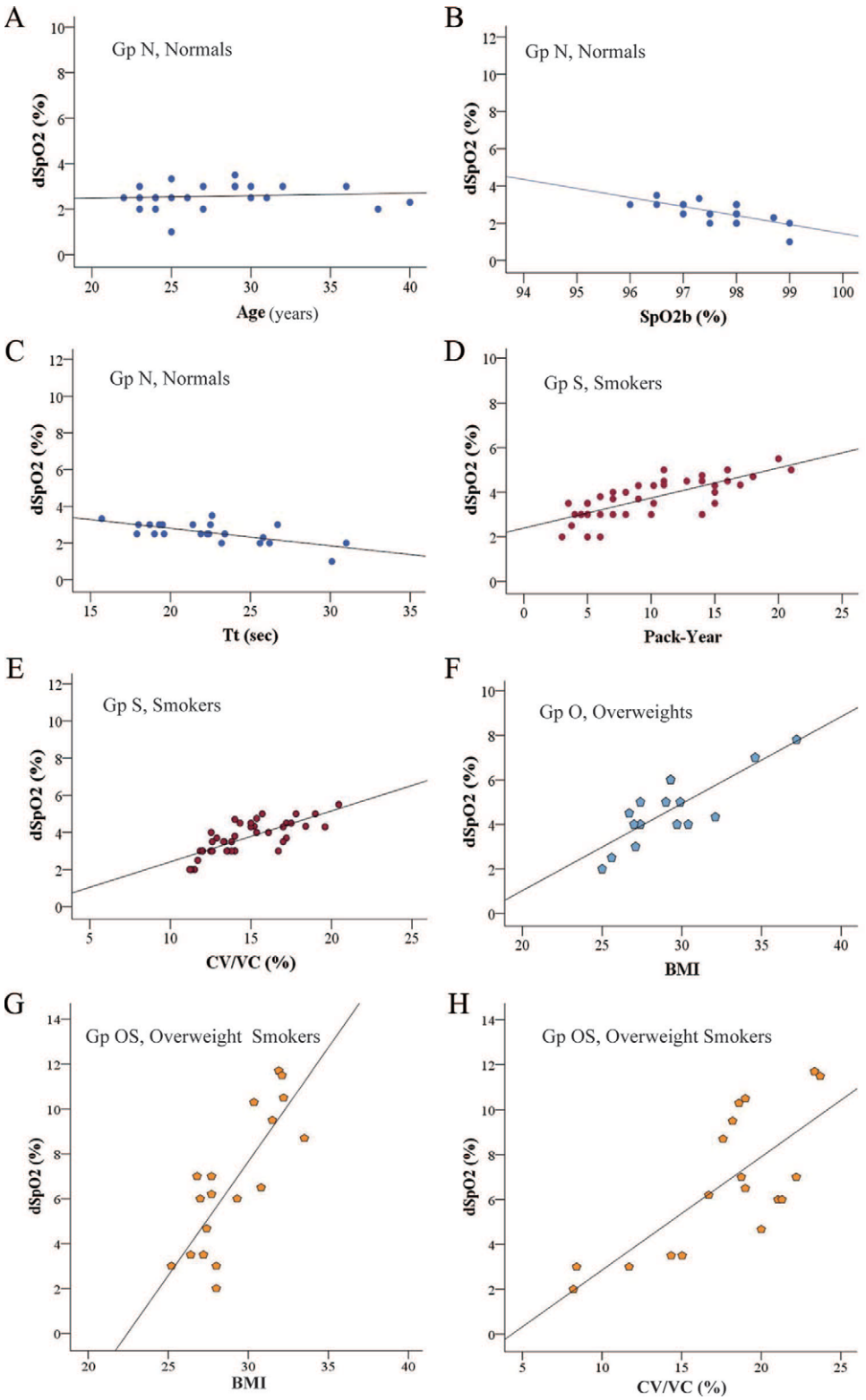

FIGURE 3. Linear regression analysis among measured variables. Note that some data points overlapped in each of these figures, so that the number of points visible may be less than the number in the group. Each data point shown is the mean of several measurements in the individual subject. See the legend of Figure 1 for abbreviation not used in the text.

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previous reports.[20,32] The reduced lung volumes may also induce mismatched ventilation and perfusion in obesity.[33] A significant mean decrease of Spo_2b in group O compared with that in group N ($p = 0.002$) [Table 1] may support this deduction. The reason why abnormal mean closing volumes could not have been detected in group O would be because of a preceding deep inspiratory maneuver of the method.[34] The role of other factors is minor or unknown in the present study.

Concerning the possible mechanisms for the greater enhancement of oxygen desaturation when smoking and obesity were combined, the present data demonstrated significant steeper slopes of $dSpo_2$ vs CV/VC or $dSpo_2$ vs BMI in group OS (Fig 3, *H* and *G*, respectively) compared with corresponding slopes in groups S or group O (Fig 3, *E* and *F*, respectively), which may suggest a concept that ventilation unevenness because of peripheral airways abnormalities caused by smoking could be exaggerated by the lung volume reduction because of obesity.

Pulse oximetry is now widely used clinically as a simple, convenient, and noninvasive monitor,[35] and it is regarded as a reliable tool, especially for detecting dynamic changes of oxygen desaturation.[36] Some of the possible limitations of pulse oximetry[25,26] were carefully resolved as described in the "Materials and Methods" section. First, the lack of decimal fractions in the measured values of the pulse oximeter would be mostly canceled by obtaining the mean values of more than three repeatable measurements. However, extrapolations based on the present data should be made with care because the ages and weights of the subjects were in only a small range (20 to 40 years of age; BMI, 17.9 to 37.2 kg/m^2). If the ages of the subjects ranged more widely, age may have been a more important factor in determining the $dSpo_2$.

Interestingly, apneic episodes of varying duration can be observed in common activities, such as swallowing, cough, face washing, swimming, diving, parturition,[37] sleep-disordered breathing, and the apnea reflex[38] (the latter two happen at FRC), so that the arterial oxygen desaturation during apnea is a relevant issue in the awake situation. Our data indicate that during apnea, cigarette smokers and/or overweight subjects may suffer greater risks of hypoxemia, especially if the subjects may have suffered ischemic heart diseases, cerebral arteriosclerosis, and/or lung diseases.

In conclusion, the new breath-holding test may reveal an early stage of gas-exchange abnormalities of the lung in smokers and/or overweight subjects in proportion to cigarette consumption or increase in body weight, especially if these factors are combined. The breath-holding test may also be useful to help subjects recognize potentially severe future lung abnormalities and to promote more effective behavioral intervention.

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