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Comparison of Three Carbon Monoxide Monitors for Determination of Smoking Status in Smokers and Nonsmokers with and without COPD

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ABSTRACT

In this (CAMOXI) study, three carbon monoxide (CO) monitors and salivary cotinine are assessed regarding their ability to distinguish smokers from nonsmokers, both in chronic obstructive pulmonary disease (COPD) and healthy people. Twenty-six healthy smokers, 25 healthy nonsmokers, 25 smoking, and 25 former smoking stable COPD patients (age 40–72 years) were included based on self-report ($N = 101$). All volunteers were measured following a 12-h abstinence period. Sensitivity, specificity, and predictive values of a positive and negative test result were assessed for a range of cutoff points for both CO and salivary cotinine. The prescribed 9-ppm cutoff point of the Breath CO® generates a sensitivity of 68% and 42% for COPD patients and healthy people, respectively. Using the prescribed cutoff point (10 ppm) the Smokelyzer® produces 56% sensitivity for COPD patients and 23% for healthy people. Both monitors generate 100% specificity in both groups. The cutoff point for the Micro CO meter® (5 ppm) generates 88% sensitivity and 92% specificity for COPD patients, and for healthy people 92% and 88%, respectively. The optimal cutoff points depend upon the goal of the test. Salivary cotinine has a 100% sensitivity, specificity, positive predictive value, and negative predictive value over the range of 15 ng/mL through 40 ng/mL for healthy participants and at 10 ng/mL for COPD patients. The prescribed cutoff points for all three CO monitors generate misleading results concerning the determination of the smoking status in both populations. Salivary cotinine measurement outperforms CO measurements and a combination of the two tools is recommended.

INTRODUCTION

SMOKING CESSATION is the most effective treatment for chronic obstructive pulmonary disease (COPD). Developing smoking cessation programs for COPD patients is therefore of high clinical importance. The effectiveness of a smoking cessation program is generally expressed in terms of point prevalence abstinence rates (at 12 months) or continuous abstinence rates (during the full 12 months follow-up period). Unfortunately, self-reported quit rates in smoking cessation programs are likely to be biased,[1] and tend to overestimate program effectiveness. Several studies specifically aimed at COPD patients also demonstrated high deceiving rates.[2,3] More detailed information about deception is available,[4–7] but reaches beyond the scope of this

manuscript. There are two obvious explanations for discrepancies between self-report and biochemical validation: (1) patients deny their smoking status because they tend to give a socially desirable answer or wish to report behavior consistent with a healthy life style, or (2) biochemical validation tools (e.g., CO monitors) are not valid.[8,9]

Various biochemical validation methods are available: (1) cotinine, typically measured in saliva, serum, or urine, is the major metabolite of nicotine and has a half-life of 15 to 40 h. Cotinine is considered to be the "gold standard" for biochemical validation because of its superior sensitivity and specificity,[3,10] and has the advantage of being almost specific to tobacco.[11] (2) Thiocyanate is a metabolic byproduct of hydrogen cyanide gas, and can be assessed from serum, plasma, or urine. Serum thiocyanate (SCN) has a half-life of 10–14 days, but its sensitivity and specificity is low.[3,12,13] (3) Carbon monoxide (CO) is typically measured in exhaled air, has a half-life of 4 to 5 h, and a high sensitivity and specificity.[3] Carboxyhemoglobin (COHb) can be measured in blood and has a half-life of 1 to 4 h.[12] Compared to the other techniques mentioned, exhaled CO has several advantages. The first is the possibility to provide immediate feedback to the user. Other techniques require more time-consuming chemical processing. Furthermore, exhaled CO is a noninvasive and relatively inexpensive method that is easy to apply. Unfortunately, CO in exhaled air can be confounded by many factors like variations in diet, physical exercise, exposure to atmospheric pollution, time of day, time since the last cigarette, and last but not least, environmental tobacco smoke exposure (ETS). Also, the level of CO seems to be higher in subjects with coronary heart disease and/or an inflammatory airway disease like COPD.[14] Nevertheless, despite these possible confounders, subjects can be successfully classified into broad categories of smoking activity by CO levels in exhaled air.[15]

There are only a few studies available concerning validation of exhaled CO in COPD patients. Murray et al.[4] compared CO measures, using either the MiniCO® (MSA, Pittsburgh, PA), or the Smokerlyzer®, with self-report as a "gold standard" in a large intervention study (Lung Health Study). The sample consisted of cigarette smokers with evidence of early stage chronic obstructive lung disease. They found a sensitivity of 93.7% and a specificity of 87.2% using the prescribed cutoff level of 10 ppm. Middleton et al.[16] assessed the use of exhaled CO with the Smokerlyzer® to determine the smoking status of 41 patients attending a respiratory outpatient clinic and of 24 healthy subjects, compared to self-report. They concluded that the Smokerlyzer® is a suitable instrument for assessing smoking status in a clinical setting: a breath CO level of > 6 ppm gave a sensitivity of 94% and a specificity of 96%. Sato et al.[17] assessed the optimal cutoff level of breath CO concentration, using the Smokerlyzer® to distinguish actual smokers from nonsmokers among patients with asthma and COPD by using serum cotinine concentrations as the "gold standard." They concluded that a cutoff level of 10 ppm (85% sensitivity; 86% specificity) was optimal in patients with stable asthma, and 11 ppm (73% sensitivity; 85% specificity) in patients with stable COPD. The higher cutoff level in these patients was explained by the potential influence of underlying airway inflammation. Recently, Low et al.[18] performed a study comparing breath CO levels with self-reported smoking status in smokers with nonsmokers among 195 military outpatients using the Smokerlyzer®. A cutoff level of 5 ppm (96% sensitivity; 98% specificity) was concluded to be the optimal cutoff level.

Neither in the literature nor in the manuals of the three different CO monitors has consensus been reached concerning the ideal cutoff point for exhaled CO in the general smoking population and certainly not for COPD patients. The exploration of the generated sensitivity, specificity, positive and negative predictive values may elucidate the range in which the optimal cutoff level may vary. Single optimal cutoff points, conditional upon the goal of the specific type of study or intervention and population, can be determined from the tables presented. This is essential because these three elements can influence the degree of deceiving and/or the CO value measured.

The aim of the CAMOXI (carbon monoxide investigation) study is to investigate the validity of three CO monitors in smokers and current nonsmokers in a healthy and COPD population. Moreover, all smoking participants were asked to remain abstinent during 12 h prior to the tests. This mimics real life or clinical study situations in which smoking subjects know that their smoking status will be checked and may be inclined to mislead the investigator or physician by remaining abstinent immediately prior to the visit. Ob-

viously, this procedure provides a more critical test, as it assumes that all smokers will try to conceal their smoking status. A 12-h abstinence period prior to the CO monitor test seems reasonable as this requires only a few cigarettes not to be smoked, especially if the test is administered in the morning.

MATERIALS AND METHODS

Study population

Four groups were included in the CAMOXI study: 26 "healthy" smokers, 25 healthy nonsmokers, 25 current smokers, and 24 ex-smokers with stable COPD, all aged between 40 and 75 years were included. Subjects reporting to be currently smoking were defined as smokers and subjects reporting a nonsmoking status AND having a salivary cotinine level below 20 ng/mL were defined as nonsmokers. One patient was excluded from the study because both the COHb value (3.60) as well as the cotinine value (348 ng/mL) incontestably indicated that this COPD patient was a smoker despite a self-reported nonsmoking status. The healthy population was defined as a population without COPD or other clinically diagnosed illness based on self-report. The COPD patients had a clinical diagnosis of stable COPD. The COPD patients had to have clinically diagnosed moderate COPD (% predicted FEV_1 = 50–69) or severe COPD (% predicted FEV1 $<$ 50) as defined by the American Thoracic Society (ATS) criteria.[19]

Study design

This study compared three different CO monitors (EC50 Micro III Smokerlyzer®, Bedfont Instruments, Kent, UK; Breath CO®, Vitalograph Inc, Lenexa, KS; Micro CO meter®, Micro Medical Ltd, Kent, UK.[20,21] Following a 12-h abstinence period, end tidal expired air CO concentrations (ppm) were measured, according to standard procedures as described in the three different instruction manuals: subjects were asked to exhale completely, inhale fully, and hold their breath for a minimum of 10 sec and a maximum of 20 sec (depending on the used CO monitor) and exhale slowly into the CO monitor. The sequence of the different CO monitors was randomized. The monitors were checked and calibrated daily before use. A cotton swab (Salivette®) was used to take salivary samples and specimens were frozen and subsequently assayed for cotinine (ng/mL) using a Gas Chromatography–Mass Spectrometry (GC-MS) technique.[22] The precision and accuracy of this method was checked by means of reference samples. A smoking related questionnaire[23] was administered to measure the participants' smoking characteristics and smoking status (self-reported).

All participants gave written informed consent for participation in the study. Medical ethical approval was granted by the medical ethical committee of Medisch Spectrum Twente at Enschede, The Netherlands.

Data analysis

All continuous variables were assessed for normality of their distribution. In case of normality, means were compared using Analysis of Variance with Tukey's Honestly Significant Difference tests in case of pairwise post hoc comparisons. In case of nonnormal distributions means were compared using a Kruskall-Wallis test. Wilcoxon's Rank Sum test with Holm's correction was used for pairwise post hoc comparisons. Sensitivity, specificity and the predicted outcome of a negative and positive test result of the three different CO monitors was assessed using the cutoff points for the CO value as described in the separate manuals with salivary cotinine validated smoking status as the "gold standard." Results are displayed in receiver operating characteristic (ROC) curves.[24]

RESULTS

The baseline characteristics of the healthy participants and the COPD patients are presented in Table 1. The term "smoking environment" means the number of smokers in the direct environment. This term has been introduced to measure the amount of passive smoking. Although the two groups are clearly different, we will not elaborate on this finding because the differences are not relevant to this study. Furthermore, all the participants performed according to the use standards of the different CO monitors. No preference of the participants concerning the usability of the three CO monitors was indicated in this study. Table 2 shows the mean (SD) of the values of the different CO monitors in all four groups.

Table 1. Baseline Characteristics of the Participating COPD Patients and Healthy Participants

	All healthy participants (n = *51*)	*All COPD patients* (n = *49*)
Male/Female, number (%)	27 (53)/24 (47)	39 (80)/10 (20)
Age in years (SD)	58 (5.6)	64 (6.0)
Smoking environment	(almost) no smokers 21 (41)	(almost) no smokers 17 (35)
	<50% smokers 20 (39)	<50% smokers 26 (53)
	≥50% smokers 9 (18)	≥50% smokers 7 (15)
	Healthy smokers (n = *26*)	*Smoking COPD patients* (n = *25*)
Number of cigarettes per day (SD)	17 (8.4)	21 (18.2)

COPD, chronic obstructive pulmonary disease.

Using the independent sample *t*-test, no difference between healthy nonsmokers and nonsmoking COPD patients on all three monitors was found. On the other hand, the "healthy" smokers show significant lower CO values on the Smokerlyzer® ($p = 0.03$; 95% CI: 0.27–6.14) and the Micro CO® ($p = 0.049$; 95% CI: 0.14–5.40) and a borderline significant difference on the Breath CO® ($p = 0.06$; 95% CI: −0.07–6.13), compared to the smoking COPD-patients. As expected, the CO values of the smokers differ significantly from the CO values of the nonsmokers on all three CO monitors (all $p < 0.001$). For smokers there is a correlation between exhaled CO and salivary cotinine (correlation coefficient = 0.5; $p < 0.001$, for all three CO monitors). For nonsmokers there is only a weak correlation between CO and cotinine. Moreover, there is no linear relationship between these two variables.

The sensitivity (% actual smokers detected as such), specificity (% actual nonsmokers detected as such) and the positive predictive values (% actual smokers among the subjects classified as smokers by the CO monitor) and negative predictive values (% actual nonsmokers among the subjects classified as nonsmokers by the CO monitor) shown in Table 3 are generated when the cutoff points, as described in the manuals of the three monitors, are used. Values above the cutoff point are considered to be of smokers and values below and equal to the cutoff point are considered to indicate nonsmokers.

The sensitivity of the Smokerlyzer® used in COPD patients and the sensitivity of the Breath CO® and the Smokerlyzer® in healthy participants differ significantly from the Micro CO®.

ROC curves were generated to be able to determine sensitivity, specificity, positive and negative predictive values at different cutoff levels. Because all three ROC curves look very similar, only the ROC curves of the Breath CO® are presented in this article (Fig. 1) for both healthy participants and COPD patients. The optimal cutoff range is also shown in these curves. The lower boundary of the cutoff range is the cutoff point generating 100% sensitivity and the upper boundary is presented by the cutoff point generating 100% specificity.

These ranges are presented for all monitors in Tables 4 through 6. These tables are presented to enable the reader to determine the optimal cutoff point, which belongs to their specific goals. In some instances 100% sensitivity was not reached.

The optimal range, in which an acceptable cut-

Table 2. Mean (SD) of the CO Values of the Four Different Groups by the Different CO Monitors at Baseline

	Nonsmokers		*Smokers*	
	Healthy (n = *25*)	*COPD* (n = *24*)	*Healthy* (n = *26*)	*COPD* (n = *25*)
Breath CO®	2.3 (1.4)	2.6 (1.3)	9.7 (4.8)	12.8 (6.2)
Smokerlyzer®	1.7 (1.4)	2.0 (2.0)	8.0 (4.5)	11.2 (5.9)
Micro CO®	4.0 (1.2)	3.4 (1.3)	9.6 (4.1)	12.3 (5.4)

COPD, chronic obstructive pulmonary disease.

TABLE 3. SENSITIVITY, SPECIFICITY, POSITIVE PREDICTIVE VALUE AND NEGATIVE PREDICTIVE VALUE OF THE THREE DIFFERENT CO MONITORS USING THE PRESCRIBED CUTOFF POINTS FOR HEALTHY PARTICIPANTS (N = 51) AND COPD PATIENTS (N = 49)

	Sensitivity % (95% CI)		*Specificity % (95% CI)*		*Positive PV % (95% CI)*		*Negative PV % (95% CI)*	
	COPD	*Healthy*	*COPD*	*Healthy*	*COPD*	*Healthy*	*COPD*	*Healthy*
Breath CO® Cutoff: 9 ppm	68.0 (49.8–86.2)	42.3 (23.3–61.3)	100	100	100	100	75.0 (57.8–92.2)	62.5 (43.5–81.5)
Smokerlyzer® Cutoff: 10 ppm	56.0 (36.6–74.5)	23.1 (6.8–39.4)	100	100	100	100	68.6 (50.0–87.2)	55.6 (36.2–75.0)
Micro CO® Cutoff: 5 ppm	88.0 (75.3–100)	92.3 (82.1–100)	91.7 (80.7–100)	88.0 (75.3–100)	91.7 (80.9–100)	88.9 (76.7–100)	88.0 (75.7–100)	91.7 (80.9–100)

Note. PV, predictive value; ppm, parts per million; chronic obstructive pulmonary disease.

off point can be chosen, ranges from 1–7 ppm for healthy participants and from 3–5 ppm for COPD patients using the Breath CO® (Table 4). Note that a sensitivity of 100% was not reached in patients with COPD.

For the Smokerlyzer® the optimal cutoff points range from 2–7 ppm for healthy participants and from 2–10 ppm for COPD patients, and a sensitivity of 100% was reached in neither group (Table 5).

The optimal cutoff range for the Micro CO® ranges from 2–6 ppm for healthy participants and from 1–6 ppm for COPD patients (Table 6).

As mentioned before, cotinine measurement is generally referred to as the "gold standard" for validating abstinence from smoking. To verify this for both the healthy and COPD population included in this study (N = 100), an additional analysis was performed, comparing salivary cotinine measurements with self-reported abstinence to determine the optimal cutoff range. The cotinine values 15–40 ng/mL generate a 100% sensitivity, specificity, positive predictive value and negative predictive value for healthy participants, while in patients with COPD this is the case for a cotinine value of 10 ng/mL.

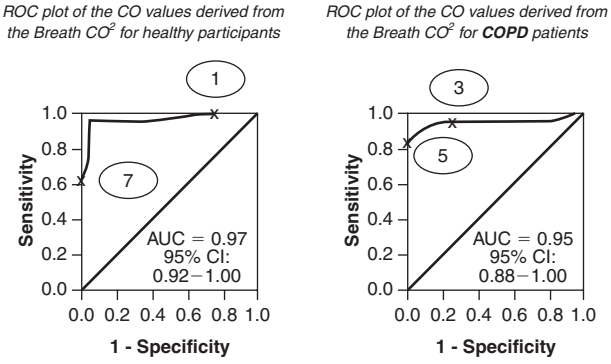

FIG. 1. Roc plots of the CO concentrations (ppm) to the self-reported smoking status of the Breath CO® for both healthy and COPD patients. AUC, area under the curve; 95% CI = 95% confidence interval.

DISCUSSION

In general, results from smoking cessation studies, in which abstinence is based on measurement of expired CO, lack validity because they are based on unsuitable cutoff points. The CAMOXI study shows that the cutoff points as described in the manuals lead to an underestimation of the number of smokers in both populations. If the prescribed cutoff points are adjusted properly, though, all three CO monitors are valid biochemical validation tools for the determination of the smoking status (within 12 h after the last cigarette). The optimal cutoff point depends on the target group, type of CO monitor, and the aim of the study.

Compared to existing studies, the CAMOXI study contains four vigorous elements. First, nonsmoking and smoking COPD patients were compared to nonsmoking and smoking healthy participants to determine whether the cutoff point of CO in exhaled air needed to be adjusted for COPD patients. Second, the validity of three different CO monitors was investigated in this study. Third, cotinine was measured to investigate the agreement with observed CO concentrations and optimal cutoff points for cotinine in the study population. Fourth, smoking participants were asked to abstain from smoking 12 h prior to the measurements. This abstinence period was chosen to mimic real life or clinical study situa-

Table 4. Sensitivity, Specificity, and Predictive Values of Positive and Negative Test Results for a Range of Cutoff Points (ppm) for the Breath CO® Expressed in Percentages

ppm	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*
Healthy participants										
Sensitivity	100	96.2	96.2	96.2	88.5	73.1	61.5	50.0	42.3	34.6
Specificity	28.0	56.0	92.0	96.0	96.0	96.0	100	100	100	100
+ PV	59.1	69.4	92.6	96.2	95.8	95.0	100	100	100	100
− PV	100	93.3	95.8	96.0	88.9	77.4	71.4	65.8	62.5	59.5
COPD patients										
Sensitivity	96.0	96.0	96.0	92.0	84.0	80.0	76.0	72.0	68.0	68.0
Specificity	16.7	50.0	75.0	91.7	100	100	100	100	100	100
+ PV	54.5	66.7	80.0	92.0	100	100	100	100	100	100
− PV	80.0	92.3	94.7	91.7	85.7	82.8	80.0	77.4	75.0	75.0

PV, predictive value; ppm, parts per million; COPD, chronic obstructive pulmonary disease.

tions in which smoking subjects know that their smoking status will be checked, and might try to mislead the investigator or physician by remaining abstinent immediately prior to the visit. This design enabled us to investigate whether or not "deceivers" would be detected by CO monitors. This approach leads to an artificial increase in the amount of deceiving which might be higher than the deceiving rate found in daily clinical practice. This might have resulted in a higher amount of smokers falsely labeled as nonsmokers. The sensitivity found in this study might therefore be lower than in daily clinical practice. However, it is also possible that some of the smoking participants failed to comply with the 12-h period of abstinence, which could not be validated. As a result, our design might be less conservative than originally intended. CO monitors can be used for different purposes, and each requires a specific cutoff point. For example, in smoking cessation studies the main aim is validation of self-reported abstinence. Consequently, a high sensitivity (when a smoker is detected as such) is the most important outcome measure. Taking this into account, the optimal cutoff point is 1 ppm (100% sensitivity) for COPD patients and 2 ppm (100% sensitivity) for healthy people using the Micro CO® monitor. Consequently, some nonsmokers will be wrongly classified as smokers (false positives). However, if the main aim of using CO monitors is to provide positive biofeedback to compliant subjects during counseling, the focus will be on high specificity (when a nonsmoker is detected as such). It is crucial in this case not to label a nonsmoker as a smoker, and therefore to strive for a low number of false positives. For example, with a cutoff level of 1 ppm for healthy participants using the Smokerlyzer®, 96% of all smokers will be detected. Unfortunately, only 56% of all nonsmokers will be regarded as nonsmokers, and as a consequence, the number of false positives is undesirably high.

The finding that different cutoff points need to be chosen depending on the type of CO monitor and kind of population next to the aim of the user has implications for the comparability of studies

Table 5. Sensitivity, Specificity, and Predictive Values of Positive and Negative Test Results for a Range of Cutoff Points (ppm) for the Smokerlyzer® Expressed in Percentages

ppm	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*
Healthy participants										
Sensitivity	96.2	96.2	84.6	84.6	73.1	53.8	42.3	34.6	26.9	23.1
Specificity	56.0	88.0	92.0	96.0	96.0	96.0	100	100	100	100
+ PV	69.4	89.3	91.7	95.7	95.0	93.3	100	100	100	100
− PV	93.3	95.7	85.2	85.7	77.4	66.7	62.5	59.5	56.8	55.6
COPD patients										
Sensitivity	96.0	96.0	92.0	84.0	80.0	76.0	68.0	64.0	64.0	56.0
Specificity	54.2	79.2	87.5	91.7	95.8	95.8	95.8	95.8	95.8	100
+ PV	68.6	82.8	88.5	91.3	95.2	95.0	94.4	94.1	94.1	100
− PV	92.9	95.0	91.3	84.6	82.1	79.3	74.2	71.9	71.9	68.6

PV, predictive value; ppm, parts per million; COPD, chronic obstructive pulmonary disease.

Table 6. Sensitivity, Specificity, and Predictive Values of Positive and Negative Test Results for a Range of Cutoff Points (ppm) for the Micro CO® Expressed in Percentages

ppm	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*
Healthy participants										
Sensitivity	100	100	96.2	92.3	92.3	84.6	69.2	50.0	38.5	30.8
Specificity	0	16.0	28.0	68.0	88.0	100	100	100	100	
+ PV	51.0	55.3	58.1	75.0	88.9	100	100	100	100	100
− PV	0	100	87.5	89.5	91.7	86.2	75.8	65.8	61.0	58.1
COPD patients										
Sensitivity	100	96.0	96.0	92.0	88.0	84.0	84.0	72.0	64.0	60.0
Specificity	4.2	20.8	66.7	79.2	91.7	100	100	100	100	
+ PV	52.1	55.8	75.0	82.1	91.7	100	100	100	100	100
− PV	100	83.3	94.1	90.5	88.0	85.7	85.7	77.4	72.7	70.6

PV, predictive value; ppm, parts per million; COPD, chronic obstructive pulmonary disease.

using a CO monitor as a validation tool. The outcomes of these studies cannot be compared unless the chosen cutoff is known.

All studies described in the introduction reported one specific value as the optimal cutoff point. This reduces the applicability of their findings because they are restricted to the specifics of these studies (e.g., investigated population, type of CO monitor, and aim of the study).

Sato et al.[17] concluded 11 ppm to be the optimal cutoff point for COPD patients. This exceeds the optimal range we found for the Smokerlyzer® in our study (range: 1–10 ppm for COPD patients). The trend in our results indicates that a cutoff point of 11 ppm might have generated a lower sensitivity and a higher specificity. This is probably caused by our design in which smoking participants were asked to remain abstinent 12 h before the start of the study. The distinction between smokers and nonsmokers will be less clear compared to a design without an abstinence period, which will result in a narrower optimal cutoff range with a higher sensitivity at similar cutoff points in which smokers did not refrain from smoking prior to the test. Specificity will not be influenced by the abstinence period because this only concerns the nonsmokers. Murray et al.[6] found a higher sensitivity and a lower specificity among COPD patients using the Smokerlyzer® or the Mini CO® with the prescribed cutoff point (10 ppm). This might have been due to the fact that their study was part of a larger intervention study in which self-reported abstinence, which was used as the "gold standard," might have been unreliable. The studies of Low and Middleton with the Smokerlyzer® were performed among target groups not fully comparable with our population. However, Middleton et al.[16] found 96% specificity and 94% sensitivity using a cutoff point of 6 ppm in patients of a respiratory outpatient clinic. The CAMOXI study found the same specificity, but a lower sensitivity (76%) using the same monitor and cutoff value. This might be explained by the fact that Middleton et al.[16] probably used a more heterogeneous respiratory patient group. Also, the target group included uninformed patients, unaware of the goal of the test, which decreases deceiving behavior and will lead to a higher sensitivity and the same specificity as mentioned earlier. Low et al.[18] tested "outpatients" among navy personnel and concluded that 5 ppm was the optimal cutoff point generating 96% sensitivity of and 98% specificity. Especially the sensitivity is higher than in our study for healthy participants using the same monitor and cutoff value. This might be caused by the forced abstinence period in our study. Unfortunately, Low et al.[18] did not present detailed information about the study population. It is plausible that this group did not consist of COPD patients, but it remains unclear whether it is comparable with the healthy participants in our study.

Comparing the three CO monitors, the Micro CO® shows the highest sensitivity, but unfortunately, this is also linked to a lower specificity. Again, because the optimal cutoff point is fully conditional upon the goal of the test, in specific cases a low specificity might be problematic.

In our research setting the used devices were checked and calibrated daily before use. Remarkably, the three CO monitors needed to be calibrated daily because a deviation of ±2 ppm (one day positive, the other day negative) was found. This occurrence is far more frequent than the occurrence described in the manuals (ranging

from once a month to once per year). Although the deviation seems small, if the chosen cutoff point is low this might have important implications for daily clinical practice. Because calibration with such frequency may not be feasible, this will increase the uncertainty of the test results.

By using self-reported abstinence corrected by salivary cotinine measurements in self-reported nonsmokers, only one COPD patient was excluded because the self-reported abstinence could not be confirmed by any biochemical validation measure. Among healthy nonsmokers self-reports appeared in full agreement with cotinine measurement. This suggests that self-reported smoking status is highly valid when subjects are in no way expected to quit, even in the case of COPD patients. In this case, subjects did not participate in a cessation program and were explicitly informed that smoking cessation was not the primary goal in this study. Belonging to a high-risk population, which is suggested as a third cause for biased self-reports of smoking abstinence,[3,4] seems to play only a minor role.

For smoking cessation research we recommend using CO monitors in a two-step approach. First, all participants claiming to be abstinent from smoking should be tested by CO monitors using a cutoff point with 100% specificity, and thus a 100% positive predictive value, which guarantees that identified smokers are actual smokers. Only the participants identified as nonsmokers by the CO monitor should then be subjected to a subsequent salivary cotinine test. This procedure will guarantee the most accurate and cost-effective validation of self-reported abstinence.

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