CHEST

Original Research

COPD

High Prevalence of Undiagnosed Airflow Limitation in Patients With Cardiovascular Disease

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Background: **The prevalence of airflow limitation (AL) in patients with cardiovascular disease (CVD) is unknown, and whether AL is adequately diagnosed and treated in these patients has not been investigated before, to our knowledge.**

Methods: **We compared clinical and spirometric data in three groups of individuals. Two of them were participants in the follow-up of an ongoing population-based study according to the presence or absence of CVD. The third group included patients with coronary artery disease (CAD) confirmed by coronariography regularly visited at a tertiary referral university hospital. AL was defined according to the Global Initiative for Obstructive Lung Disease guidelines.**

Results: **We studied 450 population participants without CVD, 52 population participants with CVD, and 119 hospital patients with CAD. The prevalence of AL in these three groups was 17.5% (95% CI, 14.0-21.0), 19.2% (95% CI, 8.1-30.7), and 33.6% (95% CI, 25.0-42.2), respectively ($P < .05$). Underdiagnosis of AL ranged from 60% in population participants with CVD up to 87.2% in hospital patients with CAD. Sixty percent of those with spirometrically confirmed AL (in all three groups) did not receive any respiratory treatment.**

Conclusions: **AL is frequent in individuals with CVD, particularly in those with CAD attended in the hospital, is largely underdiagnosed and therefore is highly undertreated.**

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Abbreviations: AL = airflow limitation; ATS = American Thoracic Society; CAD = coronary artery disease; CORSAIB = COR Sà Illes Balears; CVD = cardiovascular disease; ERS = European Respiratory Society; GOLD = Global initiative for Obstructive Lung Disease; MRC = Medical Research Council

COPD is the fourth most common cause of death in the world, and it is projected to become third by 2020 or earlier.[1,2] The prevalence of COPD in the general adult population depends on study methods and varies by country, but in those aged 40 years or older it ranges from 4% to >20%.[3,4] More than 80% of these patients are not diagnosed, and therefore they are not treated appropriately.[4]

Cigarette smoke is the major risk factor for COPD, albeit not all smokers develop the disease. Cigarette smoke is also a major contributor to the pathogenesis of cardiovascular disease (CVD), another major worldwide killer.[5] It has been suggested that the risk of CVD is further increased in those smokers who have developed COPD, and that COPD might be an independent risk factor for CVD.[6] Yet, the precise

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prevalence of COPD in patients with CVD is unknown.[7-9] Further, whether COPD is adequately diagnosed and treated in patients with CVD has not been investigated before, to our knowledge.

We hypothesized that the prevalence of airflow limitation (AL) compatible with COPD would be particularly high in patients with CVD, and that it would be undiagnosed (thus untreated) in a vast majority of them. To test this hypothesis, we quantified the prevalence and level of underdiagnosis and undertreatment of AL in 502 participants in an ongoing study investigating the distribution of CVD in the general population of the Balearic Islands (Spain),[10] as well as in 119 patients with coronariography confirmed coronary artery disease (CAD) regularly seen at a tertiary referral university hospital.

Materials and Methods

Design of the Study

Figure 1 shows the flowchart of participants. Participants in the follow-up of an ongoing population-based study, the COR Sà Illes Balears (CORSAIB), aimed at investigating the distribution of CVD and CVD risk factors in the general population of the Balearic Islands, Spain, were invited to participate also in our study. The design and full methodological details of the CORSAIB study have been published elsewhere.[10] Briefly, it started in 1999 and randomly selected a representative sample, stratified by age and gender bands, of the Balearic population living in any of the four inhabited islands in the Balearics.[10] Seven years later, this cohort was recontacted for the purposes of the present study (Fig 1). We also studied a group of patients with coronariography-confirmed CAD (coronary stenoses >70% at some of the major coronary vessels) regularly seen at the Cardiology Clinic of Hospital Universitari Son Dureta (Mallorca, Spain), the tertiary referral university hospital in our community. They were recruited sequentially from the daily scheduled list of visits when in the waiting room and invited to participate in this study irrespective of their respiratory history.

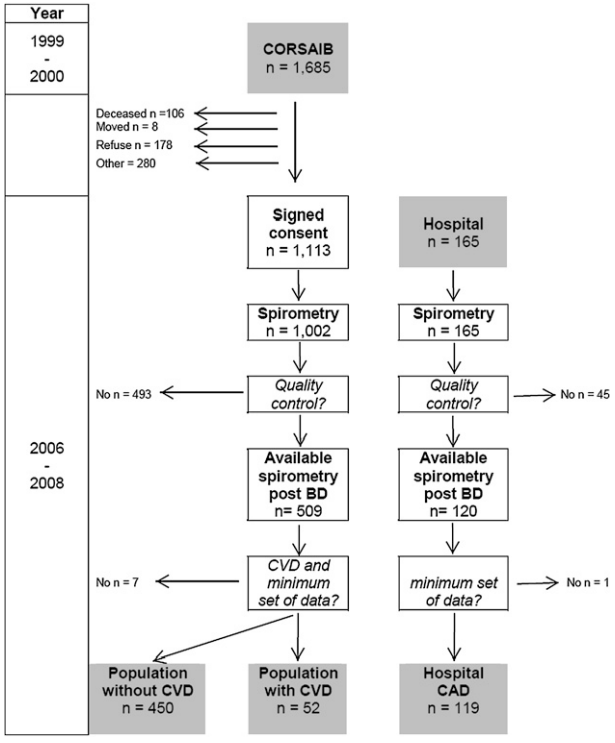

Figure 1. Consolidated Standards of Reporting Trials flowchart of participants. BD = bronchodilator; CAD = coronary artery disease; CVD = cardiovascular disease; CORSAIB = COR Sà Illes Balears.

Fieldwork was conducted from October 2006 to June 2008. Only participants whose spirometry fulfilled current quality control standards[11] and who had valid information on all clinically relevant variables (age, gender, BMI, smoking, and spirometry) were considered in the analysis.

Population and Ethics

We included in the study male and female individuals, aged 42 to 81 years, residents of the Balearic Islands. Participants recruited from the general population were grouped according to the presence or absence of diagnosed CVD by individual review of their primary care medical charts and hospital records. Apart from the inability to perform spirometry or of not signing the informed consent, there were no exclusion criteria in this research.

All participants were informed of the voluntary nature of this research and signed an informed written consent. This research protocol was approved by the corresponding Clinical Research Ethics Authority (www.ceicsalut.com) with references 9949 and IB 615/06 PI. This study is registered at www.clinicaltrials.gov with identifier NCT00787748.

Measurements

Dyspnea was quantified by the modified Medical Research Council (MRC) scale.[12] We used a standardized questionnaire of the American Thoracic Society (ATS) to assess the presence of chronic cough and sputum ("Have you had cough and sputum for at least 3 months for 2 consecutive years?"), previous COPD diagnosis ("Have you ever been diagnosed by a doctor with emphysema, chronic bronchitis, and/or emphysema?"), respiratory treatment ("During the last year has a doctor prescribed you with a drug for your respiratory problems?").[13] Comorbidities were assessed with the Charlson index.[14] The BMI was calculated by dividing weight in kilograms by the square of height in meters.

Spirometry was conducted according to current international guidelines[11] by means of portable spirometers (Easy One NDD; Medical Technologies; Zurich, Switzerland). Reported values correspond to those determined after inhalation of 200 μg of salbutamol. AL compatible with COPD was defined according to the Global initiative for Obstructive Lung Disease (GOLD) guidelines as a postbronchodilator $FEV_1/FVC < 0.7$.[15] The severity of AL was staged according also to the GOLD guidelines as mild, moderate, severe, or very severe if percent predicted FEV_1 was >80%, 50% to 80%, 30% to 50%, or <30%, respectively.[15] All spirometric measurements were individually reviewed and graded for quality control by an experienced pulmonologist (B.T.).

Statistical Analysis

Data are presented as mean and SD and 95% CI for continuous variables, or percentage with 95% CI for qualitative variables, as appropriate. Differences within groups were compared with analysis of variance for continuous variables, followed by *post hoc* contrast

of groups with t test if appropriate, and χ^2 for categorical variables. A P value $< .05$ was considered statistically significant.

Results

Sampling

As per Figure 1, we studied 1,113 participants from the original CORSAIB cohort plus a sample of 165 hospital patients with CAD, and spirometry was obtained in 1,002 and all 165, respectively. However, spirometry current quality control standards were only fulfilled by 509 (51%) and 120 (73%), respectively. A nonresponse study was conducted, comparing sociodemographic and clinical variables between the participants whose spirometry did/did not pass spirometry quality control (Table 1). Given the differences between the 493 population and 45 hospital participants whose spirometry did not pass the current ATS/European Respiratory Society (ERS) quality control, vs those 629 who did, we decided to exclude the former.

Clinical Data

We included for analysis the 621 individuals whose spirometry passed quality control and had a minimum set of data (see the "Materials and Methods" section), divided in three groups: 450 population participants without CVD, 52 population participants with CVD, and 119 hospital patients with CAD. There were significant differences in most sociodemographic and clinical characteristics among these three groups, as shown in Table 2. Compared with the population participants without CVD, participants with CVD were older, more frequently male, had a greater BMI, and were more frequently ex-smokers (all $P < .05$). When comparing patients with CVD recruited from the population with those with CAD selected from the hospital, they had similar age and BMI distribution, but the latter were more frequently male and had a greater smoking history ($P < .05$). Dyspnea and comorbidities were also more frequent in patients with CAD in the hospital than in the other two groups, but there were no significant differences in frequent cough and sputum between groups. Absolute values of postbronchodilator FEV_1 were lower in hospital patients with CAD and population participants with CVD than in population participants without CVD ($P < .05$), but the statistical significance of differences disappeared when expressed as percent of the reference value (Table 2). A previous medical diagnosis of COPD was rare, but was slightly more frequent in population participants with CVD (11.5%) than in hospital patients with CAD (7.6%) or in population participants without CVD (5.6%) ($P < .05$).

Prevalence and Severity of AL

The prevalence of AL was 17.5% (95% CI, 14.0-21.0) in population participants without CVD, 19.2% (95% CI, 8.1-30.7) in population participants with CVD, and 33.6% (95% CI, 25.0-42.2) in hospital patients with CAD ($P < .05$) (Fig 2). There were no

Table 1—*Comparison of Sociodemographic and Clinical Variables Between the Participants Whose Spirometry Did/Did Not Pass Spirometry Quality Control*

	Participants Who Did Pass Spirometry Quality Control (n = 629)	Participants Who Did Not Pass Spirometry Quality Control (n = 538)	*P* Value
Age, y, mean ± SD	60.4 ± 11.1	62.4 ± 11.6	.002
Male, %	54.5	45.9	.004
BMI, kg/m², mean ± SD	28.8 ± 5.2	28.2 ± 5.8	.085
Smoker, %			.000
Never	17.6	12.6	…
Ex	35.0	26.4	…
Current	46.1	52.6	…
Dyspnea MRC, mean ± SD	1.3 ± 0.7	1.5 ± 0.8	.000
Dyspnea MRC, %			.002
Grade 1	78.4	68.4	…
Grade 2	14.9	21.0	…
Grade 3	4.5	5.1	…
Grade 4	1.9	4.1	…
Grade 5	0.3	1.4	…
Cough and sputum, %	5.9	10.3	.008
Charlson index, mean ± SD	0.8 ± 1.2	0.7 ± 1.2	.081
FEV_1, L, mean ± SD	2.6 ± 0.8	2.5 ± 0.8	.078
FEV_1, % predicted, mean ± SD	96.7 ± 45.2	92.7 ± 25.7	.109
FEV_1/FVC, mean ± SD	0.76 ± 0.11	0.78 ± 0.11	.017
Previous COPD diagnosis, %	6.4	4.8	.155

MRC = Medical Research Council.

Table 2—*Sociodemographic, Clinical, and Functional Characteristics of Participants, According to Study Group*

	Population Participants Without CVD (n = 450)	Population Participants With CVD (n = 52)	Hospital Patients With CAD (n = 119)	Significant Differences Between Groups[a]
Age, y, mean ± SD	58.6 (10.9)	64.7 (10.4)	65.0 (10.2)	1-2, 1-3
Male, %	45.6	67.3	84.0	1-2, 1-3, 2-3
BMI, kg/m², mean ± SD	28.4 (5.4)	29.6 (4.5)	29.8 (4.5)	1-3
Smoker, %				1-3, 2-3
Never	52.4	42.3	26.9	…
Ex	27.6	42.3	62.2	…
Current	20.0	15.4	10.9	…
Dyspnea MRC, mean ± SD	0.2 (0.6)	0.3 (0.7)	0.6 (0.8)	1-3
Dyspnea MRC, %				1-3
Grade 1	83.3	77.6	61.9	…
Grade 2	12.3	14.3	24.6	…
Grade 3	2.7	6.1	10.2	…
Grade 4	1.4	2.0	2.5	…
Grade 5	0.2	0.0	0.8	…
Cough and sputum, %	4.8	12.0	6.7	…
Charlson index, mean ± SD	0.4 (0.7)	1.1 (1.2)	2.1 (1.7)	1-2, 1-3, 2-3
FEV_1, L, mean ± SD	2.6 (0.8)	2.2 (0.8)	2.3 (0.8)	1-2, 1-3
FEV_1, % predicted, mean ± SD	96.6 (50.5)	90.2 (26.1)	92.2 (24.0)	…
FEV_1/FVC, mean ± SD	0.77 (0.1)	0.76 (0.1)	0.71 (0.1)	1-3, 2-3
Previous COPD diagnosis, %	5.6	11.5	7.6	…
Prevalence of a restricted category[b], %	26.7	26.9	13.4	1-3, 2-3
Prevalence of AL, %	17.5	19.2	33.6	1-3, 2-3

AL = airflow limitation; CAD = coronary artery disease; CVD = cardiovascular disease. See Table 1 for expansion of other abbreviation.

[a]1-2: $P < .05$ when comparing population participants without CVD vs population participants with CVD. 1-3: $P < .05$ when comparing population participants without CVD vs hospital patients with CAD. 2-3: $P < .05$ when comparing population participants with CVD vs hospital patients with CAD.

[b]Restricted category is defined as $FEV_1/FVC > 0.70$ and $FVC < 80\%$ predicted.

significant differences in the distribution of AL severity within the three groups. Hence, in population participants without CVD, AL was mild in 48.8% of participants, moderate in 43.8%, severe in 6.3%, and very severe in 1.3%. In population participants with CVD these percentages were, respectively, 30.0%, 50.0%, and 20% severe (none had very severe AL). Likewise, 47.5% of hospital patients with CAD had mild AL, 42.5% moderate AL, and 10.0% severe disease ($P > .05$) (Fig 2).

Underdiagnosis and Undertreatment of AL

Underdiagnosis of AL was high in all three groups, ranging from 60.0% in population participants with CVD, to 81.0% in population participants without CVD, and up to 87.2% in hospital patients with CAD (Table 3). When we explored potential reasons to explain this high rate of underdiagnosis, we found that former smokers, less symptomatic individuals, and patients with mild AL tended to remain undiagnosed of AL across all three groups (Table 3), but differences failed to reach statistical significance.

Undertreatment of AL was also high, with 60% of those with spirometrically confirmed AL in all three groups not receiving any respiratory treatment (Table 3). The most frequently used respiratory medications were short-acting bronchodilators (42%), but all drug classes were rare (data not shown).

As an *a posteriori* analysis, our primary results were not statistically different and our conclusions unchanged if the entire population that performed spirometry is considered (Table 4). Therefore, although the application of stringent ATS/ERS quality control criteria disregarded information from many participants, we believe that information is more precise after quality control.

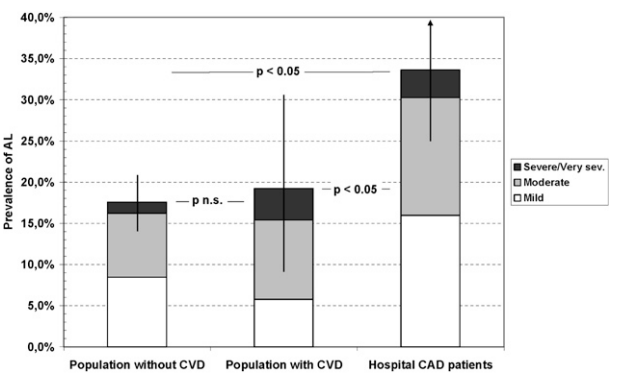

FIGURE 2. Distribution of prevalence of airflow limitation (AL) with 95% CI and severity according to the Global initiative for Obstructive Lung Disease (GOLD) criteria[10] by study group. See Figure 1 legend for expansion of abbreviations.

Table 3—*Underdiagnosis and Undertreatment of Airflow Limitation Among Those With Spirometrically Confirmed Airflow Limitation and Comparison of Those Not Diagnosed vs Those Diagnosed According to Study Group*

	Population Participants Without CVD (n = 79)	Population Participants With CVD (n = 10)	Hospital Patients with CAD (n = 40)
Underdiagnosis of AL, %	81.0	60.0	87.2
Undertreatment of AL, %	60.0	60.0	60.0
Age, y, mean[a]	58.3 vs 64.6	64.2 vs 69.5	64.7 vs 68.0
Male, %[a]	44.3 vs 68.0	65.2 vs 83.3	83.6 vs 87.5
BMI, kg/m^2, mean[a]	28.4 vs 29.3	29.4 vs 30.6	29.6 vs 33.2
Current smoker, %[a]	20.0 vs 16.0	15.2 vs 16.7	11.8 vs 0.0
Dyspnea MRC, mean[a]	0.2 vs 0.8	0.2 vs 1.2	0.5 vs 1.4
Cough and sputum, %[a]	3.3 vs 28.0	9.1 vs 33.3	4.5 vs 37.5
Charlson index, mean[a]	0.4 vs 0.5	1.1 vs 1.7	2.0 vs 2.5
FEV_1, % predicted, mean[a]	97.8 vs 78.2	91.8 vs 77.4	94.0 vs 72.6

See Tables 1 and 2 for expansion of abbreviations.
[a]Comparison of individuals not diagnosed with AL with those diagnosed.

Discussion

COPD is now considered a novel CV risk factor because the burden of CV disease is higher in smokers with COPD than in those without it.[6] Yet, the prevalence, level of diagnosis, and adequacy of treatment of COPD among patients with CVD has not been investigated before, to our knowledge. Our results show that one of every three patients with CAD recruited from the hospital clinic, and one of every five patients with CVD in the general population, suffer AL compatible with COPD, that the majority of them are not diagnosed, and, therefore, that they remain mostly untreated. These observations are clinically relevant because COPD is now considered a preventable and treatable disease.[15,16]

Previous Studies

Several previous studies have reported consistently that the burden of CVD is increased in patients with COPD. For instance, a large (n = 11,493) retrospective study in health-care databases of Saskatchewan, Canada reported increased risks for arrhythmia, angina, acute myocardial infarction, congestive heart failure, and stroke in patients with COPD.[17] Likewise, the Atherosclerosis Risk in Communities study cohort found that patients with severe COPD had a higher prevalence of hypertension and CVD.[18] Finally, cardiac failure has been found in about 20% of patients with COPD.[19] To our knowledge, however, our study is the first to investigate the prevalence, severity and treatment of COPD in patients with CVD.

Interpretation of Findings

Our study provides several novel observations. First, we found that the prevalence of AL in a population sample of adults of the Balearic Islands was 18%. This figure, which has never been estimated previously in this particular region of Spain, is twice the mean value of 9.1% reported by the Estudio Epidemiológico de EPOC en España study in our country.[20] Yet, this study also reported that the prevalence of COPD in Spain varied widely between different regions of the country and ranged from 4.9% (95% CI, 3.2-7.0) in Cáceres to 18.0% (95% CI, 14.8-21.2) in Manlleu (Catalunya). Our estimate of 18% is therefore in line with that reported in another nearby Mediterranean population (Catalunya). Further, it is similar to that reported in other parts of the world, such as Montevideo, Uruguay (19.7%), within the Proyecto Latinoamericano de Investigación en Obstrucción Pulmonar study[21] or even lower than the

Table 4—*Prevalence of AL in all Participants With Spirometry and in Those Whose Data Passed Spirometric Quality Control*

	Population Without CVD	Population With CVD	Hospital CAD	Total
AL in all participants with spirometry	126/886, (14.2%), [11.9-16.5]	19/108, (17.6%), [10.4-24.8]	58/165, (35.2%), [27.9-42.5]	203/1159, (17.5%), [11.7-23.3]
AL in participants whose data passed spirometric quality control	80/456, (17.5%), [14.0-21.0]	10/53, (18.9%), [8.3-29.5]	40/120, (33.3%), [24.8-41.8]	130/629, (20.7%), [17.5-23.9]

Data presented as No., (%), and [95% CI]. $P > .05$ for all comparisons of all participants with spirometry vs those whose data passed quality control.
See Table 2 for expansion of abbreviations.

Burden of Lung Disease investigators found in Salzburg, Austria (26.1%).[4]

Second, we found that the prevalence of AL in population participants with CVD (19.2%; 95% CI, 8.1-30.7) was only slightly higher than that of population participants without it (17.5%; 95% CI, 14.0-21.0) ($P > .05$). This observation is against our working hypothesis that predicted a higher prevalence of AL compatible with COPD in patients with CVD. However, the small size of this group (n = 52) limits the interpretation of this observation. In fact, when we studied a larger population of hospital patients with CAD (n = 119), we found that the prevalence of AL was indeed much higher (33.6%; 95% CI, 25.0-42.2; $P < .05$), as hypothesized (Fig 2). Apart from the small group size, other factors that may explain our results of a higher prevalence of AL in hospital patients with CAD than in population patients with CVD are that the former sample included more men, had an older age distribution, and had a greater history of tobacco smoking (Table 2), all factors associated with a higher COPD prevalence.[4] Irrespective of the factor(s) that can explain these observations, though, our study demonstrates that one in three patients in the hospital with CAD (and one in five population patients with CVD) had AL.

Third, and regrettably, we found that 60% to 87% of patients with CVD and AL identified here were undiagnosed and, therefore, untreated. Former smokers, less symptomatic patients, and those with milder lung function impairment tended to remain undiagnosed across all three groups (Table 3). These factors have been suggested as explanatory variables of COPD underdiagnosis in other population studies.[20,22] However, it is worth noting that in our study about half of undiagnosed patients with AL had moderate (42.3%) or severe (5.8%) AL and, nonetheless, they were untreated. It is likely that the similarity of symptoms (dyspnea, cough) and the fact that smoking is a shared risk factor for both CVD and COPD can explain this unfortunate clinical situation. To improve it, we propose here that a forced spirometry should be considered as an integral part of the routine clinical work-up package in any current or former smoker with CVD. Otherwise, these patients suffer an unnecessary disease burden because they are not offered treatments that improve many outcomes associated with COPD.[23]

Potential Limitations

Our study has some limitations that need to be addressed. First, it is a cross-sectional study and, therefore, causality of the observed association of AL with CVD cannot be assessed. Second, following up participants of a population cohort established 7 years earlier results in a sequential reduction of sample size (Fig 1). However, the comparison of the main anthropometric characteristics of the participants in our study and those of the original cohort did not identify any significant difference. Another limitation is the potential selection bias produced by analyzing only the 629 individuals whose data passed spirometric quality control, that is, 53.9% of those whose lungs were tested. There were indeed some baseline differences in those who did/did not pass spirometric quality control (Table 1), but as presented in Table 4, the comparison of prevalence of AL in all participants with spirometry (17.5%, 95% CI, 11.7-23.3) vs those whose data passed spirometric quality control (20.7%, 95% CI, 17.5-23.9) was not statistically significant. We can only speculate on the reasons that the current ATS/ERS quality standards[11] were not fulfilled by nearly half of participants whose lungs were tested. Spirometry was performed by auxiliary nurses who were trained in the referral hospital lung function unit, and approved by an expert (B.T.), who also graded each lung function individual result. Except for hospital patients with CAD, they conducted all spirometries of CORSAIB population participants in their respective primary care centers, located throughout the four inhabited islands of the Balearics. Therefore, a combination of these factors or others might explain the high rate of discarded lung function test results in this study. In a recent Proyecto Latinoamericano de Investigación en Obstrucción Pulmonar report,[24] factors significantly associated with failed spirometry, that is not being able to produce acceptable maneuvers, were: age 70 years or older, a higher GOLD stage, female gender, and zero education. All these factors should be taken into account to offset any future COPD epidemic. Perhaps, away from clinical trials or in the specialized setting, the consideration of tests of suboptimal quality might decrease the degree of uncertainty in clinical decision making. For a patient in search for a diagnosis, who conducted spirometry and blew in with maximal effort many times, is it better to have some information than no information at all? The best clinical pulmonary function laboratories disregard at least 20% of patient data, and this censored data can be greater than 40% in population studies, as found here. The implications of potential simplifications on the agreed data quality control remain to be investigated and are extensively discussed elsewhere.[25]

Finally, because the group of hospital patients with CAD was diagnosed and monitored by a hospital-based cardiologist, whereas CVD was identified in population participants by review of their primary care medical charts and hospital records, it is possible that some silent and undiagnosed CVD may exist in population participants. Likewise, although population participants without CVD were younger and had

a different distribution of gender and other characteristics than population participants with CVD, for the purposes of this study they merely serve as a reference from the source population to which both groups of participants with CVD, either selected from the population or from the hospital clinics, belong,[26] and therefore they do not influence our conclusions.

Conclusions

Our results show that the prevalence of AL in patients with CVD is substantial (one in three CAD patients seen in hospital clinics, and about one in five patients with CVD in the general population), that most of these patients are not diagnosed appropriately (60% in CVD patients from the community and up to 87% in patients with CAD in the hospital), and that the majority of them are not treated whatsoever (60% in all groups). Given that COPD is a preventable and treatable disease,[15,16] this unfortunate clinical situation should be corrected promptly.[25] We therefore propose here that screening of AL/COPD by forced spirometry must be considered routinely in the clinical management of smokers or former smokers with CVD.

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Dr Rigo: contributed to the design and protocol of the study, obtaining funding, and writing and approving the manuscript.
Ms Guerrero: contributed to statistical analysis and to writing and approving the manuscript.
Dr Yañez: contributed to writing and approving the manuscript.
Dr Forteza: contributed to conducting the hospital CAD arm of the study and writing and approving the manuscript.
Dr Frontera: contributed to writing and approving the manuscript.
Dr Togores: contributed to reviewing all spirometry quality control and to writing and approving the manuscript.
Dr Agustí: contributed to conceiving the original idea for the study, developing the protocol, obtaining funding, developing the plan of analysis, drafting the report, and writing and approving the manuscript.
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