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ORIGINAL ARTICLE

Screening for irreversible airflow obstruction in patients with coronary artery disease

Zohra KHELIFI, Hacène MEHDIOUI, Leila BELKADI, Mohamed BOUGRIDA

ABSTRACT

Chronic obstructive pulmonary disease (COPD), defined by irreversible airflow obstruction, and coronary artery disease (CAD) are both highly prevalent worldwide and frequently co-occur. However, the prevalence of COPD according to its severity in patients with coronary artery disease remains poorly characterized. The objective of this study was to assess the respiratory function of stable coronary artery disease patients. **Methods**. This descriptive, prospective, cross-sectional study included patients of both sexes, regardless of age, with coronary artery disease documented by positive coronary angiography and no previously known obstructive ventilatory disorder. Patients were recruited from private outpatient consultations in the city of Constantine between June 2016 and August 2017. They completed a questionnaire adapted from the American Thoracic Society (ATS) survey and underwent spirometric evaluation with a bronchodilator reversibility test. The diagnosis of COPD and the grading of bronchial obstruction were based on the GOLD (Global Initiative for Chronic Obstructive Lung Disease) criteria. All spirometric assessments were performed in accordance with ATS/ERS guidelines. **Results.** A total of 146 patients with coronary artery disease were enrolled; however, only 117 subjects were able to perform acceptable spirometry. The remaining patients were excluded due to poor cooperation. Among the 117 participants, 81.2% were male, with a mean age of 62 ± 9 years. Additionally, 78.7% were current or former smokers. Post-bronchodilator FEV1/FVC ratio below 70% — consistent with a diagnosis of COPD — was found in 17.1% of subjects. Among those with COPD, 25% were at GOLD stage 1, 70% at stage 2, and 5% at stage 3; no patients were classified at severity stage 4. Subjects with COPD were older, presented with greater comorbidity burden, and had more frequent multi-vessel coronary involvement. **Conclusion.** Patients with coronary artery disease carry a substantial risk of concurrent COPD. COPD in this population is frequently asymptomatic and therefore often goes undiagnosed. Systematic spirometric assessment of respiratory function in coronary artery disease patients appears warranted, as it enables the detection and staging of COPD and may contribute to improved monitoring and management of these patients.

Keywords: Coronary heart disease, chronic obstructive pulmonary disease (COPD), Obstructive Ventilatory Disorder, irreversible airflow obstruction.

Faculté de médecine, université Constantine 3 – Algérie.

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Correspondance to: Zohra KHELIFI
E-mail : khelifizohra@yahoo.fr

1. INTRODUCTION

Coronary heart disease is the most common manifestation of cardiovascular disease, which is the leading cause of death worldwide. Smoking is a major risk factor. Similarly, smoking, which continues to increase in importance in developing countries, is the main risk factor for chronic obstructive pulmonary disease (COPD), another major public health problem worldwide.

These two diseases are very widespread in the world and frequently associated; their incidence increases with the ageing of the population [1]. The relationship between COPD and coronary heart disease is much more complex than the mere coexistence of the two diseases in the same individual [2]. This association is characterized by systemic and inflammatory disorders under tension by interlocking pathophysiological mechanisms and processes. Indeed, a common background of low-grade systemic inflammation links the two pathologies. The increased inflammatory activity is most likely triggered by harmful environmental stimuli, such as cigarette smoke that damages both the pulmonary epithelium and the vascular endothelium [3].

The coexistence of COPD and coronary heart disease worsens the prognosis of these two diseases [4]. Indeed, for every 10% decrease in FEV1, cardiovascular mortality increases by 28%, and the frequency of non-fatal coronary events increases by 20% [4]. Similarly, studies suggest that cardiovascular disease is more severe in smokers with COPD than in those without [1].

Numerous epidemiological studies have linked the presence of COPD to coronary artery disease [5]. However, prevalence, pathological processes, clinical manifestations, and therapeutic management are still controversial, as progress towards discovering the link between these two disorders has been hampered by the complex nature of multimorbidity [3].

Worldwide, several studies have focused on the prevalence of COPD in patients with ischemic heart disease, however, their results were very heterogeneous, due on the one hand to the differences between the populations studied regarding age, duration of exposure to risk factors, including smoking, the nature of the ischemic heart disease considered, and on the other hand the diagnostic criteria considered, the measuring instruments and monitoring systems as well as the protocol instituted and the lack of spirometric tests. Indeed, the prevalence of irreversible airflow obstruction confirmed by spirometry in coronary patients has been little studied [6,7].

In Algeria, where already little epidemiological data concerning the prevalence of COPD in the general population have been published [8-10], the frequency of COPD, taking into account its severity in the coronary, is still poorly known. Hence the interest of our work, which aims to assess the frequency of COPD in patients with stable coronary disease in Constantine. To this end, we hypothesized that a significant proportion of stable coronaries would present an obstructive functional ventilatory disorder compatible with COPD and that they would be undiagnosed and therefore untreated.

2. MATERIALS AND METHODS

This is a descriptive cross-sectional study based on timely recruitment of patients with stable coronary artery disease documented by coronary angiography. Subjects who have given their informed consent to participate in the study are referred by the liberal cardiologists of the city of Constantine between June 2016 and August 2017 to the Department of Clinical Physiology and Functional Explorations at the Ibn Badis University Hospital of Constantine. Coronaries with known obstructive ventilatory disorder were not included. The anonymity of the patients was respected, and the study adhered to the principles of the Declaration of Helsinki.

All participants completed the questionnaire inspired by that of the American Thoracic Society (ATS). This questionnaire is composed of 28 questions written in French and explained, if necessary, in Arabic during the interview for certain patients. The questions are essentially closed-ended and most often dichotomous. It has several axes: a signage part, medical history, smoking clinical symptomatology (usual cough, sputum, the notion of sibilant, dyspnea quantified according to the *modified Medical Research Council* (mMRC) scale [11]).

All patients were provided with a recent frontal chest X-ray. Spirometry was performed according to ATS/ERS guidelines [12] using a ZAN 100 spirometer, calibrated daily using a 3L syringe. In case of imperfect performance of the maneuvers, the patient will make another test after one week before being excluded. The reversibility test was carried out according to the international recommendations of the ATS/ERS [12] for the detection of an irreversible airflow obstruction.

COPD was defined according to the diagnostic characteristics of GOLD [13], by a post-bronchodilator FEV1/FVC ratio of less than 70%. The classification of the severity of COPD bronchial obstruction is based on GOLD [13] on post-bronchodilator FEV1 expressed as a percentage of its predicted value. Reversibility is defined according to ATS/ERS [14] as an increase in FEV1 and/or FVC ≥ 200 ml and ≥ 12% from baseline.

Statistical analysis

All data was entered on SPSS software version 20. Data are presented as mean and standard deviation for continuous variables and totals and percentages for qualitative variables.

Parametric tests : Chi-squared test to compare qualitative variables ; the relationship between two continuous variables was tested using Pearson's correlation coefficient, and the association between two categorical or binary variables was assessed using the chi-square test or Fisher's exact test ; Student's t-test to compare quantitative variables. The relationships between the variables were determined for a significance level $p \leq 0.05$ for a 95% confidence interval.

3. RESULTS

A total of 146 subjects meeting the inclusion criteria gave their informed consent to participate in the study. Only 117 subjects were able to perform actionable spirometry. The others were excluded for poor cooperation (imperfect spirometric maneuvers). Excluded subjects were older (74.4 ± 7 years *vs* 61.2 ± 8 years), $p < 0.001$, had a higher smoking consumption (46.7 packets/year *vs* 34.3), $p = 0.02$. However, there was no significant difference in sex, body mass index, and ejection fraction as well as for comorbidities. It should be noted that the excluded subjects were more dyspneic (51.7% *vs* 14.5% were at stage 3 of mMRC), $p < 0.001$.

In this study, the overall frequency of COPD was 17.1% (Figure 1). 70% of patients had a respiratory functional profile that corresponded to grade 2. Patients with grade 3 accounted for only 5% of COPD subjects, and there were no patients with grade 4 severity (Figure 2). A decrease in inspiratory capacity was observed in 40% of COPD subjects classified as stage 1, in 71.4% of subjects at stage 2 as well as in all subjects classified as stage 3. The main characteristics of participants with or without a functional profile in favor of COPD are presented in Table 1.

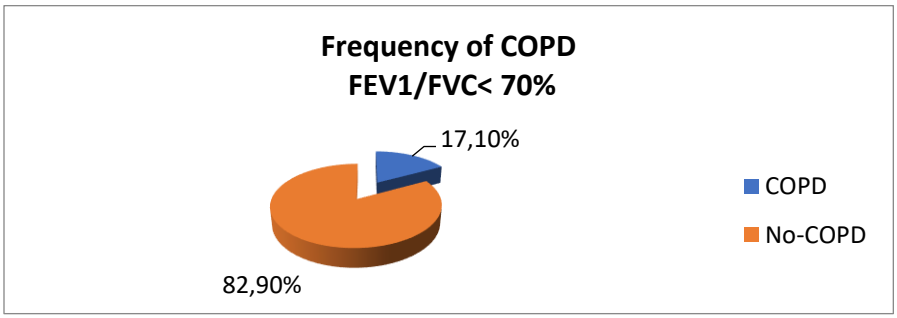

Figure 1. Frequency of COPD according to GOLD criteria.

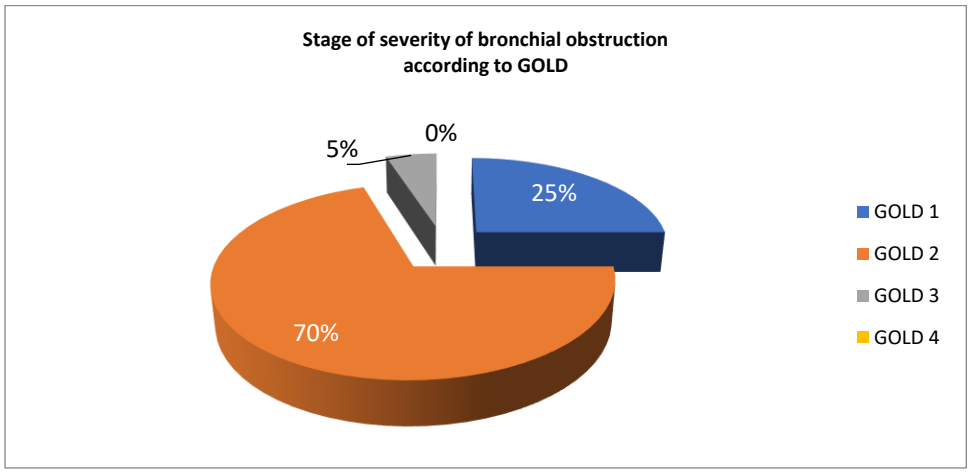

Figure 2. Classification of COPD subjects according to GOLD severity stages.

Table 1. Characteristics of COPD and no-COPD subjects.

	COPD	No-COPD	P
Age (year)	66.7 ± 7.32	61.12 ± 9.11	0.012
Smoking (packs/year)	54.16 ± 26.08	21.53 ± 20.82	<0.0001
Duration of smoking	47.95 ± 12.42	20.48 ± 16.05	<0.0001
BMI (kg/m2)	24.5 ± 6.2	27.2 ± 4.26	0.017
Ejection Fraction	44.6 ± 9	54.7 ± 8.75	<0.0001
Asymptomatic	5%	20. 2	0.026
Chronic Cough	55%	27.8%	0.018
Sputum	60%	25.8%	0.003
Cough and sputum	45%	20. 2	0.021
WHEEZING	15%	10.3%	n/s
Dyspnea			
No dyspnea			
Stage 1 mMRC	5%	24.7%	
Stage 2	5%	37.1%	<0.0001
Stage 3 mMRC	50%	34%	
Stage 4	40%	4.1%	
Comorbidities			
Several comorbidities	55%	32%	0.020
Diabetes	75%	5.	0.03
HYPERTENSION	60%	38.1	n/s
Dyslipidemia	20%	42.3%	n/s
Coronary heart disease	80%	26% 8	<0.0001
Multi-truncular	20%	73%2	
Single-truncular			

COPD subjects were significantly older, had a higher smoking rate, with a longer duration of exposure to this risk factor, as well as a lower BMI. The EF of subjects with COPD is around 44%, a value significantly lower than that of no-COPD. Subjects with irreversible airflow obstruction had significantly more comorbidities ($p = 0.02$). Mainly they had type 2 diabetes, dyslipidemia, and hypertension. Also, the frequency of multi-tronular involvement was 10.92 times higher in subjects diagnosed with COPD than in other coronaries.

4. DISCUSSION

Bias and limits

This study has some limitations: only patients with stable coronary artery disease documented by coronary angiography were included; as a result, our findings cannot be generalized to all patients with ischemic heart disease; a selection bias was identified due to the exclusion of a substantial proportion of patients because of non-interpretable spirometry related to poor cooperation. Excluded subjects were older and more dyspneic; advanced age and severe dyspnea are well-known barriers to performing acceptable spirometric maneuvers, leading to the preferential exclusion of the most symptomatic patients. These subjects also had a higher cumulative tobacco exposure. Given that smoking is the major risk factor for chronic obstructive pulmonary disease (COPD), the excluded patients were at high risk for COPD. Consequently, this methodological bias may have resulted in an underestimation of the true prevalence of COPD in the coronary population studied. Therefore, the findings cannot be generalized to all patients with coronary artery disease, particularly to older and more dyspneic individuals. Finally, given the descriptive and cross-sectional nature of the study, the data do not allow the identification of risk factors or causal relationships; the findings should be interpreted as associations only.

Comparison with the prevalence of COPD in the general Algerian population:

In the present study, the frequency of patients with coronary artery disease documented by coronary angiography, with COPD according to the GOLD diagnostic criteria, was 17.1%. Despite the burden of COPD on public health, and due to the difficulties of mass screening in the general population, little data exists on the prevalence of COPD in the Algerian population. Indeed, it was only in 2011 that the first assessment of COPD was published during a cross-sectional survey in the general population, based on a questionnaire

and a spirometry carried out among households in the wilaya of Algiers. The prevalence of COPD revealed by this study was 4.9% in the general population (aged 21 years and over) and 9.2% in subjects aged 40 years and over [8]. Another more recent study conducted by Dr.Awad Tageldin's team, as part of the Breathe study, found a prevalence of COPD of 3.7% [9]. Recently, a third, cross-sectional study conducted as part of the international *Burden Obstructive Lung Disease* (BOLD) study among households in the municipality of Elhadjar in Annaba reported a prevalence of 8.8% [10].

As expected, compared to these screening studies based on the general population, the frequency of COPD in coronary patients was higher. Indeed, current data suggest that COPD is more common in coronary patients than in the general population [3; 6; 15].

Comparison with COPD screening studies in coronary artery disease:

In Algeria, to date, no study has focused on estimating the prevalence of COPD in patients with ischemic heart disease. However, in Spain, Soriano et al. [16] published a study of COPD prevalence in 2010. This study included subjects of both sexes, aged between 42 and 81 years, residents of the Balearic Islands. Participants recruited from the general population were grouped according to the presence or absence of diagnosed cardiovascular disease by individually reviewing their medical and hospital records. The study showed that in 119 people with coronary artery disease confirmed by coronary angiography, 33.6% had COPD. The authors found that, despite its high prevalence, bronchial obstruction was underdiagnosed in 87% of patients with coronary artery disease.

This is a higher proportion than in the present study; this may have two explanations: probably due to a higher proportion of current smokers in the study by Soriano et al. [6] (46% *vs* 36.8%); but especially because in our study, and unlike the Spanish study, we did not include patients diagnosed and treated for COPD.

Another Spanish study published in 2015 by Almago et al. [6] was conducted in 133 subjects with ischemic heart disease, whose percutaneous coronary intervention (PCI) revealed stenosis greater than 50% in the main arteries. The authors reported a high prevalence of 24.8% of COPD patients, 81.8% of whom were unaware that they had COPD. This study, too, and unlike ours, included known COPD patients which explains the difference in proportion.

A third prospective study published in 2015 was carried out in China [15] in 475 coronary patients over 40 years of age with no known history of lung disease, who had undergone percutaneous coronary intervention. The prevalence revealed by this study was 10.7%, a lower prevalence compared to that found by the present study, probably due to a small proportion of smokers (current or former smokers), 58.5% against 78.6% identified in our study.

Recently in Pakistan, Razaullah et al. [17] performed spirometry with a reversibility test on 151 patients diagnosed with coronary artery disease; the diagnosis of coronary artery disease was made based solely on the results of ECG and echocardiography. The prevalence of COPD in these patients was estimated at 37.7%, with 31.57% of women with COPD. This high proportion found in Pakistan compared to our study can be explained on the one hand by the inclusion of known COPD patients and on the other hand by the existence of another risk factor not found in our study population, namely exposure to biomass combustion.

Severity of irreversible airflow obstruction

In this study there were no patients with obstructive ventilatory disorder corresponding to stage 4 of severity, and there was only 5% corresponding to stage 3. This can be explained by the fact that our study excluded subjects with a known airflow obstruction, and COPD is rarely undiagnosed at advanced stages. Indeed, these stages are punctuated by frequent periods of exacerbation during which the pathology is often diagnosed. It is also obvious that screening mainly concerns the early stages of the disease, during which symptoms are rare and trivialized by patients. Even dyspnea, which is the master symptom, is often put only on the account of coronary involvement.

These findings are like those of the Chinese study [15], which did not objectify subjects in stage 4 of COPD with only 2.9% in stage 3. This was also confirmed by the Spanish study conducted by P.Almagro et al. [6] showed that 12.1% of subjects had severe COPD but pointed out that all these patients had already been diagnosed.

COPD study

We found that the frequency of COPD in stable coronary patients increased with age, from 5% in subjects 40-49 years of age to 45% in subjects 70 years of age and older. This increase is already reported in the literature with regard to the general population. Indeed, the various COPD screening studies [18] have highlighted the increase in the prevalence of COPD with age and have explained it by the existence during life of a physiological decline in respiratory function, which begins at 30 to 40 years. And due to longer life expectancy, the proportion of elderly subjects with COPD is also increasing [19]. Similarly, all studies conducted on subjects with ischemic heart disease have reported this increase in frequency with age [7; 6; 8]. In this study all subjects identified as having COPD were male. This can be explained by the exclusively male smoking in our study population on the one hand, and on the other hand, all

of our patients were from the city of Constantine, a large city that has all the amenities of city life, and therefore they were not exposed to other environmental factors such as biomass smoke.

It should be noted that epidemiologically, men were classically at higher risk of developing COPD compared to women due to their smoking habits. This male predominance was found by all the studies mentioned above.

In this study population, we noted that three quarters of the subjects with irreversible airflow obstruction were active smokers. These results corroborate those of the different studies. Thus, the frequency of COPD among active smokers in the present study was 34.9%, a frequency that is consistent with the data in the literature since all COPD screening studies conducted in the general population in Algeria or worldwide have highlighted the high prevalence among smokers [18; 8]. This high frequency was predicted due to smoking, which is recognized as the main risk factor for COPD. In addition, the frequency of COPD increased with the number of packs/year smoked. It was also found that an average duration of smoking in COPD patients was twice that of non-COPD subjects (45.5 years *vs.* 20.4 years).

Numerous studies have linked COPD risk and severity in smokers to cumulative dose and current smoking status [20; 21; 22]. Other data [20] have indicated a highly significant quantitative relationship between decreased respiratory function and packs/year smoking consumption. Similarly, smoking duration and habitual smoking intensity appeared to be almost equal in weight to determine the observed decrease of approximately 3% in predicted FEV1 per 10 packs/year of cigarette consumption. However, it is difficult to completely separate the age-associating effect from the duration of smoking [20].

In addition, the frequency of COPD was 18.2% in ex-smokers. This relatively low frequency compared to that of active smokers can be explained by the beneficial effect of smoking cessation on respiratory function. Indeed, it is proven that after quitting smoking, the rate of decline of FEV1 becomes slower and parallel to that of non-smokers, thus reducing the risk of developing or worsening COPD [23].

COPD frequency and ejection fraction:

In the present study, a decrease in the ejection fraction of the left ventricle was observed in 70% of COPD subjects. This decrease was all the more significant as the stage of the pathology was advanced. These results are not consistent with those found by the Spanish Almagro team [7] as well as the Chinese team who did not objectify a significant difference between subjects with COPD and those free of this pathology in terms of ejection fraction.

However, Roversi et al. have suggested that patients with COPD and ischemic heart disease have an increased risk of developing heart failure (24).

COPD frequency and comorbidities:

In our study, the presence of comorbidities was more common in patients with COPD than in the rest of the coronary patients. Thus, 55% of COPD subjects had several significant comorbidities ($p = 0.04$). The main comorbidities were hypertension (60%), diabetes (75%), and dyslipidemia (20%). Such a finding has been reported by the majority of studies [90; 7; 6]. However, the proportion of different comorbidities in our population was significantly higher; this can be explained by the fact that we compared our results with those of other populations that would have different lifestyle habits.

Three quarters of COPD subjects in this population were diabetic. The relationship between these two pathologies has been reported by several studies. Type 2 diabetes is more common in patients with moderate to severe COPD than in the general population; its prevalence is around 12% [25]. However, the mechanism linking them remains unidentified. Studies have pointed out that the markers of systemic inflammation during diabetes are the same as those found during stable COPD, i.e. TNF-alpha, IL-6 and CRP [26]. Indeed, several epidemiological studies show an association between diabetes and markers of inflammation, particularly the C-reactive protein [27]. Many of these markers are produced and secreted by adipocytes [27]. Endocrinologists today emphasize the place of low-grade systemic inflammation during diabetes, without being able to assert its causal role in the condition or whether it is a simple marker of the metabolic activity of fatty tissue [26].

On the other hand, epidemiological studies have shown that smoking is an independent and modifiable determinant of type 2 diabetes [28]. This is how active smokers are twice as likely to develop diabetes compared to non-smokers. Similarly, cumulative smoking is directly correlated with the occurrence of diabetes. Cuvelier.A attributes to each level of 20 packs/year an increase of 0.12% in the HbA1c level [26]. It is therefore a common risk factor for both diseases (diabetes and COPD) [26].

Whatever the mechanism that links the two pathologies, it is known that diabetes impairs microcirculation and leads to non-enzymatic glycosylation of tissue proteins and results in a decrease in the elasticity of lung tissue [26]. This is why the existence of diabetes is a poor prognostic factor, causing an increase in mortality and hospitalizations.

Frequency of COPD and coronary artery involvement:

In the present study, 20% of subjects with irreversible airflow obstruction had single-truncular involvement, while 80% had multi-truncular involvement (25% bi-truncular and 55% tri-truncular). This data was only studied by the Spanish team, who found that COPD patients had a greater number of stenotic arteries [7]. It is accepted that the presence of multi-truncular involvement is associated with a poorer prognosis [29]. Indeed, studies have indicated that patients with both conditions have poor prognostic characteristics such as advanced age, a higher prevalence of anterior myocardial infarction, and a higher number of coronary artery vessels affected by atherosclerosis, compared to patients with isolated ischemic heart disease [24].

Recently, a Polish study published in 2018 by Rafał Januszek et al. [30] aimed to assess the impact of COPD on percutaneous coronary intervention (PCI) outcomes by clarifying its relationship with clinical status and type of coronary artery injury in a large group of patients.

This study analyzed 221,187 ICPs carried out between 1 January 2015 and 31 December 2016. COPD was defined on the basis of a previously established diagnosis. 2.5% of these patients had COPD; the highest incidence of COPD was reported in patients aged 70 and over. The authors specify that this result can be underestimated and attributed in part to the diagnosis of COPD, which was based solely on the interrogation of these patients referred for IPC. The latter seems to conceal signs of lung disease. Finally, the highest incidence was also noted in patients with multi-truncular disease compared to patients with single-truncular disease. The study therefore concluded that coronary atherosclerosis in COPD patients was more disseminated compared to patients without COPD and suggested that COPD-suspect patients who are hospitalized in invasive cardiology units should receive special care in terms of COPD diagnosis and treatment, which could improve their long-term outcomes.

5. CONCLUSION

The results of the present study made it possible to determine the frequency of COPD in patients with stable coronary artery disease on an outpatient basis in the city of Constantine. This frequency was 17.1%.

COPD, which is still underdiagnosed in the general population, is also diagnosed in stable coronaries. Indeed, all the subjects screened during this study were not previously diagnosed, and therefore not treated.

Spirometry is an effective, simple, reliable, and inexpensive means of diagnosis. However, mass screening in the general population using this exploration is difficult. However, early detection and treatment of COPD as a comorbidity with other diseases is easily achievable and could be important and beneficial not only for COPD itself but also for coronary artery disease to reduce mortality [31]. The systematic performance of spirometry in stable coronary patients could detect early any impairment in respiratory function in order to improve the quality of life of patients through adequate management.

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