UPDATE IN RADIOLOGY

Multidetector computed tomography assessment of cardiac comorbidity in patients with chronic obstructive pulmonary disease


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Received 13 November 2011; accepted 12 March 2012

KEYWORDS
Computed tomography; Chronic obstructive pulmonary disease; Comorbidity; Heart disease

Abstract Cardiac comorbidity is one of the most important prognostic factors in lung disease, especially in chronic obstructive pulmonary disease (COPD). The imaging techniques available for the study of this systemic manifestation concomitant with COPD include heart catheterization, transthoracic echocardiography, and magnetic resonance imaging. Multidetector computed tomography (MDCT) represents a significant advance in this field because it enables the acquisition of simultaneous studies of the cardiopulmonary anatomy that go beyond anatomic and morphologic analysis to include a functional approach to this condition. In this article, we review the practical aspects necessary to evaluate cardiac comorbidity in patients with COPD, both from the point of view of pulmonary hypertension and of the analysis of ventricular dysfunction and coronary heart disease.

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PALABRAS CLAVE
Tomografía computarizada; Enfermedad pulmonar obstructiva crónica; Comorbilidad; Enfermedad cardiaca

Resumen La comorbilidad cardiaca es uno de los factores pronósticos más importantes en las enfermedades pulmonares, particularmente en la enfermedad pulmonar obstructiva crónica (EPOC). Entre las distintas técnicas de imagen disponibles para estudiar dicha manifestación sistémica concomitante a la EPOC se incluyen el cateterismo cardíaco, la ecocardiografía transtorácica y la resonancia magnética. La tomografía computarizada multidetector (TCMD) ha supuesto un progreso significativo en este campo, al permitir obtener estudios simultáneos de la anatomía cardiopulmonar que van más allá del análisis anatómico-morfológico e incluyen una aproximación funcional a dicha afectación. En este trabajo se repasan aspectos prácticos necesarios para valorar la comorbilidad cardiaca en pacientes con EPOC, tanto desde el punto


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Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by a chronic obstruction little reversible to air flow, associated to an anomalous inflammatory reaction, mainly related with cigarette smoke.\(^1\) COPD has a 10.2\% prevalence among adult Spaniards and it represents the fourth cause of death in this population.\(^2\) Among the different factors that may affect these patients’ prognosis and survival are neoplasias, high blood pressure, diabetes mellitus and heart disease.\(^3\) The common denominator of these interrelations is still unknown, although it is postulated that chronic systemic inflammation present in COPD plays an important role in its development.\(^4\)

Among the systemic manifestations described, cardiovascular comorbidity is one of the most important determinants for the prognosis of COPD patients, which has been estimated as cause of mortality in up to 42\% of the cases.\(^5\) These patients present higher risk of deep vein thrombosis, pulmonary thromboembolism, ictus, cardiac arrhythmia, arteriosclerosis, myocardial infarction and heart failure.\(^6\) Cardiac comorbidity in the context of COPD may appear as Pulmonary Hypertension (PHT), right ventricular dysfunction, left ventricular dysfunction, coronary disease and arrhythmias. The most frequent arrhythmias in this group of patients are supraventricular tachyarrhythmias, such as auricular fibrillation and multifocal auricular tachycardia.\(^7\) Ischemic cardiopathy is an underestimated cause of death among COPD patients.

Cardiac comorbidity in COPD patients may be studied by means of several image techniques. Catheterization of right cavities and measurement of pulmonary pressure are the reference pattern to diagnose PHT. Echocardiography stands out among the non-invasive techniques, because of its rapidity and availability and magnetic resonance (MR), due to its accuracy and reproducibility. However, one of the techniques that has arisen the most interest to study cardiothoracic disease, and therefore, cardiac comorbidity in COPD patients, is multidetector computed tomography (MDCT). This interest is due particularly to 2 properties inherent to the technique. On one hand, it is the technique that makes it possible for air way and pulmonary parenchyma disease to be assessed with the greatest anatomical detail, and it has become the routine, standard reference technique to study pulmonary diseases. On the other hand, the breakthrough in this technology have permitted to synchronize the acquisition of the studies with the subject’s electrocardiographic rhythm (ECG), which implies a smaller number of artifacts devoted to the heart beat, but, above all, the possibility to assess additionally the heart and its vascularization. Therefore, in addition to studying pulmonary architecture, MDCT with ECG synchronicity contributes information about heart function and coronary disease in the same examination, which implies an improvement in COPD patient management (Fig. 1). Thus, MDCT offers diagnostic possibilities that surpass the mere anatomical or morphological study of the thorax, and goes into the functional assessment of cardiopulmonary interaction and COPD repercussion on pulmonary and heart function.

This paper revises the current usefulness of MDCT to establish cardiac comorbidity in COPD patients and its versatility is underscored, which makes it possible for an integral anatomical and function assessment of the cardiothoracic condition to be obtained.

Study protocol of multidetector computed tomography

The CT study protocol in COPD patients must be adapted to each subject and clinical suspicion. Perfecting CT technology has translated into development of multidetector (MDCT) equipment, with the subsequent increase of anatomical coverage, acquisition speed, and spatial and temporal resolution. Nowadays, the minimal standard for cardiothoracic MDCT are the MDCT-64 equipment Cortes,\(^8\) which with a spatial resolution of 0.4 mm (64 mm × 0.6 mm) and a temporal resolution of 165 ms (gantry rotation time of 0.33 s) make it possible for cardiothoracic studies to be acquired in just 15–18 s.\(^9\) Its greatest limitation is a temporal resolution that still results insufficient, which may make it necessary for drugs to be administered in order to reduce the patients’ heart rate before they are submitted to the examination. MDCT technology has evolved toward a greater anatomical coverage in state of the art volumetric equipment and toward a greater acquisition speed in dual second generation MDCT equipment, which are capable of obtaining cardiothoracic studies with greater diagnostic precision and accuracy, even in one single heart beat and in less than a second by means of the “high pitch” technique.\(^10\) The evolution seems to progress beyond the morphological study toward functional assessment, using to this end a simultaneous acquisition of low and high energy spectra with which to obtain attenuation contrast maps that allow us to characterize the tissues.\(^11,12\)

In COPD patients suspicious of cardiac comorbidity, MDCT-64 is a technology of great clinical usefulness. Their MDCT study protocol may be variable, ranging from routine thoracic examinations to more sophisticated, ECG-synchronized acquisitions, which, in turn, may include a directed cardiac study, or an integral cardiothoracic study, one of greater interest among this group of patients. In this sense, as a general rule, if the objective is to assess the heart exclusively, it is more recommendable to perform a directed cardiac study, since it is more rapid and it implies fewer artifacts, radiation dose and amount of iodate contrast.
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Figure 1  ECG-synchronized cardiothoracic study. Multidetector CT allows performing an integral study of cardiothoracic affection, including the large vessels (A–C), pulmonary parenchyma (D), tracheobronchial tree (E), heart and coronary vascularization (F).

Table 1  ECG-synchronized retrospective cardiothoracic MDCT-64 study protocol.

<table>
<thead>
<tr>
<th>Exploration</th>
<th>Range</th>
<th>Pulmonary apices – diaphragm</th>
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<tbody>
<tr>
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<td></td>
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</tr>
<tr>
<td>Current</td>
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<tr>
<td>Dose modulation</td>
<td>ECG – tube current modulation</td>
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</tr>
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<td>Acquisition</td>
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<td>Rotation Time: 330 ms</td>
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<tr>
<td>Pitch</td>
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<td>Beta Blockers: If HR &gt; 65 lpm and the coronary arteries are to be assessed</td>
<td></td>
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<tr>
<td></td>
<td>Nitroglycerin: 0.4 mg sublingual (tablet/spray) if the coronary arteries are to be assessed</td>
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</tr>
<tr>
<td>Contrast</td>
<td>Via: Right antecubital vein</td>
<td></td>
</tr>
<tr>
<td>Needle size</td>
<td>18–20 G</td>
<td></td>
</tr>
<tr>
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<td>Bolus</td>
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<tr>
<td>Flow</td>
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<tr>
<td>Technique</td>
<td>Bolus tracking</td>
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<tr>
<td>Region of interest</td>
<td>Pulmonary artery</td>
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<td>Threshold</td>
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<td>Delay</td>
<td>10 s</td>
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<tr>
<td>Reconstruction</td>
<td>Mediastinum (GC/IR): 1 mm/0.7 mm. Soft parts filter (B26f)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Coronary arteries (GC/IR): 0.75 mm/0.4 mm. Soft parts Filter (B26f)</td>
<td></td>
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<tr>
<td></td>
<td>Window of reconstruction: If HR &gt; 80 lpm, 40% of cardiac cycle</td>
<td></td>
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</tbody>
</table>

Source: modified from Bastarrika.72

FC: heart rate; G: gauge; CT/RI: cut thickness/reconstruction increase; kV: kilovolt; bpm: beats per minute; mAs: milliampere per second; mg: milligram; mgI: milligrams iodine; ml: milliliter; mm: millimeter; ms: millisecond; s: seconds; MDCT: multidetector computed tomography; UH: Hounsfield Units.
Contrariwise, if the objective is to study the thorax in an integral manner, including the tracheo-bronchial tree, pulmonary parenchyma, large vessels, the heart and coronary vessels, it is recommendable to perform an ECG-synchronized cardiothoracic protocol. Table 1 proposes an ECG-synchronized MDCT-64 cardiothoracic protocol.

If the decision is made to use ECG-synchronized protocols, as a rule, it is recommendable to use beta-blockers before the examination, due to the fact that high heart rate is usually the greatest limitation for diagnostic quality in this type of study. In our center we administer oral metoprolol one hour before the examination (50 mg if the patient weighs less than 80 kg; 100 mg if the patient weighs more than 80 kg). If the heart rate persists above 65 bpm, we administer the same medication intravenously (5–20 mg) until the desired heart rate is attained. Nevertheless, if the sole purpose is just to establish heart function and it is not deemed indispensable to study coronary arteries, the cardiothoracic protocol may be conducted without pre-medicating the patient. This way, we consider that ECG-synchronized cardiothoracic protocols may contribute clinically relevant information that goes beyond the mere cardiopulmonary morphological study. Said protocols ought to be carried out, for instance, if it is considered that knowing the ventricular function is of clinical interest or if it is desired to perform an integral cardiothoracic assessment in the same examination, for example, in patients with pulmonary hypertension.

Strategies to reduce radiation dose

ECG-synchronized cardiothoracic protocols require to use all the strategies available that allow reducing the radiation dose administered. Kilo voltage (kV) and milli amperage (mAs) must be adjusted according to the subjects’ bodily habits, either manually (consider the use of 100 kw in patients with body mass index below 25 kg/m²) or by means of software that regulate these parameters automatically. In addition, techniques that modulate tube current along the cardiac cycle should be used. This technology makes it possible for radiation dose to be reduced significantly by administering the maximum dose in the cycle phases in which it is considered that the coronary arteries will be better assessed (usually during diastole). If the equipment so allows it, it is recommendable to use techniques that minimize the radiation dose administered, as well as the prospective ECG synchronization. This option is useful if the only objective is to perform a morphological assessment of the cardiovascular structures, since only data from the selected cardiac cycle are acquired and, therefore, ventricular function parameters cannot be obtained, or to acquire the studies in a single heart beat. Comparatively, it is estimated that the radiation dose administered is 5–7 mSv for conventional MDCT-64 thoracic studies (without ECG synchronization), about 9 mSv for specific cardiac studies and about 16–18 mSv, for ECG-synchronized cardiothoracic studies.

Study of pulmonary hypertension

Estimated PHT prevalence in patients hospitalized for COPD at least once is 10–30%, and this figure rises to 90% in patients referred for pulmonary volume reduction surgery. In its multifactorial etiopathogenesis, factors such as chronic hypoxia, vascular remodeling of small-caliber pulmonary arteries and endothelial dysfunction are postulated. In COPD patients, PHT progresses slowly, it is usually mild or moderate (20–32.5 mmHg) at rest and it implies bad prognosis because it affects negatively these patients’ survival. Its severity depends on the extent of the air flow obstruction and the difficulty for gaseous exchange. In cases of serious PHT, or when there is a disproportion between PHT seriousness and COPD grade, concomitant diseases must be considered, such as oval foramen permeability (Fig. 2).

Although it is necessary to perform a right cavities catheterization to establish HTP diagnosis, an increasing number of non-invasive techniques make it possible to perform a suspicion diagnosis, and prevent morbimortality associated with the procedure. Among them echocardiography stands out, which, in spite of its well-known limitations, particularly in COPD patients, is used at present as an initial diagnostic technique. Echocardiography makes it possible, on one hand, to assess the right ventricle morphologically and establish chronic pressure overload signs or ventricular dysfunction. On the other hand, the Doppler study contributes parameters that make it possible to estimate pulmonary pressure by calculating the speed of the tricuspid insufficiency jet, the acceleration time in the right ventricle exit tract and the pulmonary flow proto- and telediastolic peak speed. Among the sectional techniques, the two that have shown the most promising results are TC and MR. In addition, the latter makes it possible to estimate pulmonary pressure in a non-invasive manner and it is considered to be a reference standard to quantify cardiac parameters. As it has been explained, in COPD patients, MDCT allows
knowing the disease’s anatomical or morphological repercussion and, according to what the most recent studies describe, obtaining functional information by analyzing parenchyma ventilation and vascularization/perfusion (Fig. 3). From the point of view of PHT assessment and cardiac comorbidity, the MDCT’s versatility lies in its capacity to add a thorough analysis of cardiopulmonary vascularization to the morphological study, to quantify ventricular function parameters, which are indicators of great interest for these patients.

PHT may be approached in MDCT studies from different perspectives. The simplest one is to measure the pulmonary artery’s main trunk diameter or the diameter of the left and right branches of the pulmonary artery in the routine MDCT studies. As a rule, it is assumed that if the pulmonary artery diameter in an MDCT angiography surpasses the aorta’s diameter, HTP must be suspected. In fact, a correlation between medium high pulmonary pressure and the relation between pulmonary artery diameter and aorta diameter > 1 has been observed, particularly in patients under 50 years of age. Thus, a diameter of the major pulmonary artery greater than or equal to 29 mm predicts PHT with a sensitivity of 86% and a specificity of 89%. Diameters surpassing 16.7 mm for the right pulmonary artery and 16.9 mm for the left pulmonary artery in a thorax radiography are considered augmented. Nevertheless, recent studies indicate that the actual accuracy and usefulness of measuring diameters is questionable, since vessel diameter may vary significantly depending on the cardiac cycle in which the study was acquired. In order to avoid this limitation, the recommendation is made to acquire the studies with ECG synchronization. This way, it is possible to estimate pulmonary artery distensibility, a parameter that depends on the elastic properties of the artery wall and it reflects the change in volume of the pulmonary artery between systole and diastole. Calculation of this parameter is performed in sectional multiplane reconstructions of the pulmonary artery’s right branch, on which the vascular outline in systole and diastole are drawn (Fig. 4). Its difference reflects pulmonary artery distensibility. A 20–25% reduction of the sectional area in diastole in front of systole is considered normal. In a recent study performed to establish MDCT-64 usefulness as opposed to right cardiac catheterization to diagnose PHT, distensibility has proved to be the parameter with the greatest diagnostic value. On the other hand, in spite of the fact that it is not possible to quantify pulmonary vascular resistances directly with MDCT, from the cardiac output data calculated by means of this technique complex formulas have been developed for its estimation.
Study of ventricular dysfunction

The 2 ventricles (left and right) are enclosed with the pericardium and they share the interventricular septum. Thus, the changes in pressure or volume that may occur in any of the two ventricles influence on the other ventricle’s function, which is known as ventricular interdependence. Therefore, in cases of right ventricle pressure overload, the interventricular septum’s bulging or displacement toward the left will affect the left ventricle’s filling up, and likewise, left ventricular dysfunction will have repercussions on the right ventricle’s function. ECG-synchronized MDCT is a useful technique to study said ventricular interdependence, without the limitations that other non-invasive techniques have.

Right ventricular function

PHT is the most frequent cause of right ventricle dysfunction in COPD patients. It is usually due to a chronic pressure overload that hypertrophies and dilates this ventricle. It is estimated that global prevalence of right ventricle systolic dysfunction (ejection fraction under 45%) in COPD patients is around 20%. In a study that analyzed ventricular dysfunction in a retrospective manner in patients with serious pulmonary disease, COPD, interstitial pulmonary diseases and PHT, a 66% prevalence of right ventricular dysfunction was observed. 12

Given its complex form, it is difficult to assess the right ventricle by means of non-sectional image techniques. Thus, in addition to MR, MDCT shapes up as an appropriate technique to study it. 43 Different morphological signs, such as right ventricle dilation (relation of the right ventricle/left ventricle diameter greater than 1) (sensitivity: 78–91.6%; specificity: 100%). 44,45 dilation of the right atrium, hepatic vein contrast reflux and vena cava, coronary sinus and hepatic vein system dilation, hint at right ventricular dysfunction. 46,47 In cases of pressure rise in the right cavities, in addition, it is possible to observe an interventricular septum flattening or inversion and bulging toward the left ventricle 48 (Fig. 5).

Left ventricular dysfunction

Given ventricular interdependence, in the case of COPD patients, right ventricular dysfunction influences significantly on left ventricular function. Thus, the extent of the left ventricular dysfunction secondary to right ventricular dysfunction acquires special importance in these patients. Right ventricle dilation, due to both increase in pulmonary arterial resistances present in COPD patients, and right cavity pressure chronic overload present in COPD and PHT, provokes displacement toward the left interventricular septum, which prevents adequate filling up of the left ventricle. Consequently, right ventricle dilation tends
Figure 5  ECG-synchronized cardiothoracic study of a 62-year-old male patient, with COPD and hypertension. (A) Axial image. (B) Oblique coronal image showing the entrance and exit trajectory of the right ventricle. (C) Axial image with maximum intensity projection (MIP). (D) Oblique sagittal image of the venas cavas. The study showed signs suggesting right ventricular dysfunction such as right ventricle (RV) and right auricle (RA) comparative dilation respecting the left ventricle (LV) and the left auricle (LA), interventricular septum paradoxic displacement (arrow), Hepatic veins (hv) contrast reflux and dilation of the superior and inferior venas cavas (SVC) and (IVC).

Figure 6  ECG-synchronized cardiothoracic study of a 58-year-old male patient, with COPD, pulmonary hypertension suspected of right ventricular dysfunction. TAPSE (tricuspid annular plane systolic excursion) calculation. (A) Volumetric image of the heart in 4-chamber plane obtained in diastole. (B) Volumetric image of the heart in 4-chamber plane obtained in systole. In MDCT the TAPSE is calculated by drawing a line through the tricuspid ring on a 4-chamber plane and measuring its anterior displacement (a <16 mm TAPSE indicates right ventricle systolic dysfunction). In this case, the TAPSE was 17 mm.
Figure 7  ECG-synchronized cardiothoracic study of a 69-year-old male patient, with COPD, pulmonary hypertension suspected of right ventricular dysfunction. Quantification of right ventricle parameters by means of Simpson’s method with a semiautomatic cardiac cavity segmentation program based on the attenuation thresholds.

to increase left ventricle telediastolic pressure and causes a drop of both this ventricle’s beat volume and the pulmonary venous return, with the subsequent left ventricular dysfunction. From the clinical point of view, these patients exhibit heart insufficiency and left ventricle diastolic dysfunction signs and symptoms with normal left ventricle or slightly depressed systolic function. These characteristics are known as heart failure with normal or preserved ejection fraction.51

In its evolution, patients with advanced COPD left ventricle diastolic dysfunction may progress to systolic dysfunction with a drop of ejection fraction.42 In addition, COPD patients exhibit left ventricle diastolic rigidity secondary inflammation and hypoxia, left ventricle hypertrophy and coronary disease, which contribute even further to left ventricular dysfunction.

Acquisition of ECG-synchronized MDCT studies allows us to quantify left ventricular function, although not exactly in an overlapping with respect of that of MR, given its lesser temporary resolution.52 In MDCT studies it is also possible to analyze regional heart function or left ventricle segmentary contractility, which have proved an acceptable concordance with respect of echocardiography and MR.53 As in the case of right ventricle, quantification of left ventricle parameters it requires delineating the heart’s endo- and epicardial outlines.54,55 From the point of view of the MDCT study protocols, it is important to underline that ventricular function assessment comes added to coronary vascularization analysis, so that the same examination acquired to study coronary arteries allows us to know ventricular volumes and their ejection fraction.56,57 It must be pointed out that performing MDCT examinations strictly aimed at studying ventricular function is limited to very concrete clinical circumstances, for example, to situations in which the diagnostic information contributed by conventional methods is considered insufficient.5 Therefore, nowadays it is not appropriate to use MDCT as a first-choice technique to study heart function.

Study of coronary disease

Numerous studies have proved that there is a direct association between COPD and coronary disease. The classically recognized causal mechanism of said association is smoking. However, current epidemiologic evidence suggests that, in addition to smoking, there are other risk factors that increase cardiovascular morbimortality.58 Thus, the role of chronic systemic inflammation in atheroma plaque pathogenesis and the development ischemic heart disease arouses growing interest.59-61 The fact is known that, in COPD
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Table 2  ECG-synchronized retrospective MDCT-64 coronary angiography study protocol.

<table>
<thead>
<tr>
<th>Exploration</th>
<th>Range</th>
<th>Carina – diaphragm</th>
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<td>ECG-tube current modulation</td>
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<td>Nitroglycerin</td>
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<td>Reconstruction window</td>
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<td>If HR &gt; 80 bpm, 40% of cardiac cycle</td>
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<td>Pulmonary parenchyma (GC/IR)</td>
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Source: modified from Bastarrika.72
FC: heart rate; G: gauge; CT/RI: cut thickness/reconstruction increase; kVp: kilovolt peak; bpm: beats per minute; mAs: milliampere per second; mg: milligram; ml: milliliters; mgI: milligrams iodine; mGy: milliGray; ml: milliliter; mm: millimeter; ms: millisecond; s: seconds; synch.: synchronization; MDCT: multidetector computed tomography; UH: Hounsfield Units.

patients, certain systemic inflammatory markers such as IL-6, IL1-β, TNF-α, MMP-9, MCP-1 and C-reactive protein are high.62 On the other hand, it has been described that the pharmacological agents used to treat COPD may also influence on the development of cardiac event.63

The current reference standard to diagnose coronary disease is conventional invasive coronary angiography. However, non-invasive diagnostic techniques are acquiring great relevance in population studies, since they make it possible for significant coronary disease to be ruled out with a

![Figure 8](image-url)  ECG-synchronized MDCT coronary angiography with retrospective of a 67-year-old male patient, with COPD and chest pain. Cardiac study performed to rule out coronary disease. (A–C) Curve multiplane reconstructions of the right coronary (A), anterior descending (B) and circumflex arteries (C). (D) Volumetric reconstruction of the heart. The study showed eccentric calcium plaques in the anterior descending coronary artery (arrows). The study ruled out significant coronary stenosis.
minimum morbility associated to the procedure. Nevertheless, in COPD patients, certain techniques to detect ischemia, such as the conventional stress testing or stress echocardiography, have a limited diagnostic performance because the physical condition of patients with advanced COPD and the physiopathological characteristics inherent to the disease make them difficult.

Numerous studies have proved that MDCT is a technique that exhibits great clinical usefulness to diagnose coronary disease. Table 2 proposes an MDCT-64 coronaryography study protocol with ECG-retrospective synchronization. MDCT makes it possible for coronary calcification "Agatston Score" to be quantified, an arteriosclerosis quantitative indicator and marker that reflects the total load of the atheroma plaque, for cardiovascular risk to be stratified, and it contributes prognostic value. On the other hand, respecting conventional coronaryography, the sensitivity and specificity values of coronaryography performed with double source MDCT-64 and TC equipment to detect coronary disease, range from 86–99% to 92–98%, with a negative prognostic value around 92–100%. In fact, the high negative prognostic value of MDCT coronaryography is the main reason why this technology may be used to rule out significant coronary disease in subjects suspected of having it and to avoid performing unnecessary complementary examinations or diagnostic catheterizations (Fig. 8). There are no data about the diagnostic performance of MDCT coronaryography in COPD patients, although it is possible that said figures are similar.

Conclusions

Cardiac comorbidity implies bad prognosis in COPD patients. The clinical manifestations of said comorbidity are variable, including PHT, ventricular dysfunction, coronary disease and arrhythmias. In addition to the classical risk factors, current scientific evidence suggests that chronic systemic inflammation contributes to the development of arteriosclerosis and coronary disease in COPD patients. Among the non-invasive diagnostic techniques available to establish cardiac comorbidity in these patients, MDCT stands out. Given its great versatility and potential to make an integral functional anatomical cardiorespiratory assessment, MDCT as a tool with great clinical relevance for diagnosing and following up COPD-associated cardiac comorbidity. Still, considering the radiation dose administered, it is necessary to individualize the acquisition protocols, establish the benefit/risk of the different types of examinations for each patient and carry out a profound research about the group of patients that would benefit the most from studies with these characteristics.

Ethical responsibilities

Protection of people and animals. The authors declare that no experiments on humans or animals were conducted for this research.

Data confidentiality. The authors declare that this article does not contain patient information.

Right to privacy and informed consent. The authors declare that this article does not contain patient information.

Authors

1. Person responsible for the study’s integrity: GB and ISY.
2. Conception of the study: GB and ISY.
3. Design of the study: GB, ISY and GV.
4. Data acquisition: GB, ISY and GV.
5. Data analysis and interpretation: GB, ISY, GV, JE and PJ.
6. Statistic treatment: not applicable.
7. Bibliographic search: GB and ISY.
8. Writing of paper: GB and ISY.
9. Critical revision of the manuscript with intellectually relevant contributions: GB, ISY, GV, JE and PJ.
10. Approval of final version: GB, ISY, GV, JE and PJ.

Conflict of interests

The authors declare to have no conflict of interests.

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Multidetector computed tomography assessment of cardiac comorbidity in patients


