The prognostic role of electrocardiography in chronic obstructive pulmonary disease

Raffaele Antonelli Incalzi, Leonello Fuso*

*Department of Geriatrics, *Department of Respiratory Physiology, Catholic University of the Sacred Heart, Rome, Italy*

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Address:

Dr. Raffaele Antonelli Incalzi

Dipartimento di Geriatria Università Cattolica del Sacro Cuore Policlinico A. Gemelli Largo A. Gemelli, 8 00168 Roma E-mail: raffaele_antonelli @rm.unicatt.it

In the next 20 years chronic obstructive pulmonary disease (COPD) is expected to become a leading cause of death and disability[1]. The course of COPD is complicated by the onset of hypoxemia and later, hypercarbia with which right ventricular pressure and, in a variable proportion of patients, volume overload usually coexist. Chronic cor pulmonale (CCP) represents the pathophysiological and clinical cardiac condition corresponding to this stage of COPD. However, a clear-cut definition of CCP is lacking. This is due to the wide interindividual variability in adaptation of the right ventricle to the loading conditions, to the partial reversibility of right ventricular dysfunction once hypoxemia and hypercarbia have been corrected, to the unpredictable changes in the left ventricular filling pattern and function[2]. The variable coexistence of anatomic and functional components in CCP accounts for the well-known wide fluctuations in its clinical expression. Furthermore, differences in the basic pathologic lung process likely contribute to increase variability in both the time to onset and in the degree of reversibility of CCP[3]. The recently reported high prevalence of thrombosis of the arterial pulmonary tree, even in the absence of severe pulmonary hypertension, qualifies as an additional factor contributing to increase variability in the loading conditions of the right ventricle and to render the relationship between blood gas derangement and hemodynamic impairment nonlinear[4].

The reported complexity and variability in the clinical expression of CCP represents the rationale for a diagnostic approach based upon simple and easily reproducible measures which should be directly related to heart dysfunction. Among these, electrocardiographic (ECG) signs of right ventricular hypertrophy or overload qualify as the most easily measurable. Their electrophysiologic significance has been clarified by classical vectorcardiographic studies, but only recently have their prognostic implications been appreciated.

Electrocardiographic signs of chronic cor pulmonale

Relationship to prognosis. Most of the observations on this topic date back to the era preceding the systematic use of oxygen therapy for chronic respiratory failure. In short, verticalization of the QRS axis and a P wave amplitude > 0.2 mV have been associated with reduced survival[5]. Pulmonary hypertension has been repeatedly reported to be the most negative prognostic marker in CCP, but it is associated with ECG signs of this condition in only 33% of patients[6]. More recent findings pertaining to COPD subjects on long-term oxygen therapy show that ECG signs of CCP add to the prognostic definition based upon comorbid diseases, mainly renal failure, ischemic heart disease and age[7]. An analysis of the contribution of individual signs in defining the long-term prognosis of COPD patients selected a P wave axis ≥ 90° (a sign of severe right atrial overload), and the S1S2S3 pattern as independent negative prognostic predictors[8]. Indeed, patients presenting with either one or both of these signs had a 3-year survival rate of 44 and 14% respectively versus 50 and 61% for patients having other or no ECG signs of CCP. An alveolar-arterial oxygen partial pressure difference > 48 mmHg, which reflects severely deranged gas exchange, further worsened the prognosis[8]. The remain-

ing signs of CCP (types A to C right ventricular hypertrophy, S1Q3 pattern, right bundle branch block, low voltage QRS) were less consistently associated with impaired survival. Interestingly, a P wave axis ≥ 70° qualifies as the ECG hallmark of, and thus, as a screening criterion for COPD[9,10]. A P wave axis ≥ 90° probably identifies the stage of lung hyperinflation corresponding to very severe or almost terminal illness. In the two studies assessing this sign[8,9], its prevalence was found to be 24% (64/263) and 15% (3/20) respectively. The vast majority of these patients had a P axis 90°. It cannot be excluded that in occasional cases a left atrial rhythm was responsible for a P wave axis ≥ 90°.

The definition of COPD encompasses a wide range of pathological conditions of the lung with a highly variable proportion of bronchitic and emphysematous changes[2,3]. Compared to emphysema, chronic obstructive bronchitis is characterized by a higher threshold for dyspnea and by an earlier increase in pulmonary artery pressure[3]. This apparent contradiction is explained by the major role dynamic hyperinflation plays as a determinant of dyspnea[11]. Dynamic hyperinflation, i.e. the exercise-related paradoxical increase in end-expiratory lung volume, is a key feature of COPD and is more commonly associated with the emphysematous than with the bronchitic type of this pathology; this accounts for dyspnea characterizing even the earliest stages of emphysematous, but not of bronchitic type COPD[11]. All this weakens the relationship between the clinical and the hemodynamic conditions. Nevertheless, the fact that two ECG signs probably associated with lung hyperinflation bear important prognostic implications seems theoretically sound: loss of pulmonary vessels is a well-known expression of severe emphysema. Given that no correlation has been found between right ventricular hypertrophy and total alveolar surface area, a decrease in the alveolar capillary bed could account for right ventricular dysfunction by promoting pulmonary arterial hypertension during exercise[12].

Unresolved issues. The following limitations in our knowledge regarding ECG markers of CCP deserve to be cited:

1. pathological correlates: removing the uncertainty about both pulmonary and cardiac pathological correlates of ECG patterns would allow identification of those COPD patients at greater risk for right ventricular dysfunction. Such information could help to identify those patients at high risk of cardiac decompensation and possibly, to improve criteria for selecting patients amenable to heart and lung transplantation;
2. functional correlates: given that ECG signs of CCP are frequently absent despite pulmonary hypertension, the possibility that the right atrial and ventricular volume overload observed in a variable proportion of patients also affects the ECG pattern should be assessed;
3. our observations refer to the COPD patient in stable conditions[8]. Uncertainty exists as to whether and to which extent the observed prevalence and prognostic implications of the ECG signs of CCP apply to the acutely decompensated patient. Comparing, in the same patient, ECG patterns during exacerbated and stable COPD might permit identification of those changes which characterize both conditions, thus representing the basic cardiovascular dysfunction;
4. coronary artery disease frequently coexists with COPD, mainly because smoking represents a risk factor for both conditions. It worsens both the long-term as well as the exacerbation-related prognosis of COPD patients, but its prevalence may be underestimated since physical limitations and dyspnea frequently prevent the patient from reaching the threshold for angina[13]. Furthermore, ECG signs of CCP could, to some extent, mask the expression of myocardial ischemia.

Noninvasive diagnosis of right ventricular overload: alternatives to electrocardiography

For the assessment of right ventricular kinetics in patients with COPD echocardiography has several limitations, particularly in cases of lung hyperinflation, i.e. in patients who are theoretically at the highest risk for CCP. Diagnosis may be improved by some recently developed refinements of the echocardiographic technique:

1. Doppler echocardiographic indexes of right ventricular function have been developed by Tei et al.[14] and have proved to be relatively insensitive to heart rate and loading conditions and to correlate both with functional status as well as with survival of patients with primary pulmonary hypertension. They are easily measurable and it seems worthwhile to test them in patients with CCP secondary to COPD;
2. color kinesis allows real-time encoding of endocardial motion throughout the cardiac cycle thus permitting quantitative analysis of regional wall motion. The available experience is mainly limited to the assessment of left ventricular kinetics whereas data regarding right ventricular kinetics are very preliminary[15].

Both these echocardiographic techniques, in particular the first one, seem promising as an alternative to electrocardiography for the diagnostic work-up of patients with CCP. However, a great deal of study is needed to explore their diagnostic potential. At present, they may be considered as investigative diagnostic methods;

3. analysis of heart rate variability at 24-hour electrocardiography: in hypertensive patients decreased heart rate variability is associated with left ventricular hypertrophy[16]. Analogously, abnormal cardiac autonomic modulation has been demonstrated in COPD secondary to $alpha_1$-antitrypsin deficiency[17]. It is not yet known whether and to which extent this finding also applies to other COPD patients. Had a well-defined relationship been established between right ventricular hy-

pertrophy and heart rate variability, the latter parameter, which is easily measurable, could be used to make an approximate estimate of the former;
4. nuclear magnetic resonance evaluation of the right ventricle: while the available information is very preliminary, the logistic problems raised by dyspnea and physical limitations are expected to exclude from this diagnostic technique precisely those patients who could benefit most;
5. radionuclide angiocardiography has proved to be a highly reliable diagnostic tool in COPD patients. It permits analysis of right ventricular systolic function and kinetics and of left ventricular function[18,19]. Myocardial scintigraphy may be employed in order to detect silent ischemia as well as to diagnose right ventricular hypertrophy[20]. However, several hospitals lack the facilities necessary for nuclear medicine studies. Furthermore, since such techniques necessitate the injection of a radioactive medium, they cannot be considered completely noninvasive.

Conclusions

At present it is not possible to clarify the pathophysiological bases of the relationship between the ECG signs of CCP and the prognosis of patients with COPD. On the other hand, no noninvasive diagnostic alternative may be proposed except for experimental studies. Thus, electrocardiography is expected to maintain an important diagnostic and prognostic role in COPD. However, research is needed to clarify the unresolved issues as well as to verify whether additional information may be obtained by refining electrocardiography. In this perspective the right thoracic leads might provide further information since they better reflect the right ventricular status. Analysis of the terminal phase of the P wave might help detect left atrial enlargement and thus, coexisting left ventricular dysfunction. Finally, the possibility that the ECG signs of CCP add to the prognostic information provided by ventricular arrhythmias and atrial fibrillation in the setting of acutely exacerbated COPD deserves to be assessed[13]. These considerations show that electrocardiography is expected to have a great diagnostic potential in the setting of COPD, provided attention is paid to its unexplored resources.

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