Electrocardiographic Signs of Chronic Cor Pulmonale
A Negative Prognostic Finding in Chronic Obstructive Pulmonary Disease

Raffaele Antonelli Incalzi, MD; Leonello Fusco, MD; Marino De Rosa, MD; Anteo Di Napoli, MD; Salvatore Basso, MD; Gabriella Pagliari, MD; Riccardo Pistelli, MD

Background—Chronic cor pulmonale (CCP) is a strong predictor of death in chronic obstructive pulmonary disease (COPD). The aims of this study were to assess the prognostic role of individual ECG signs of CCP and of the interaction between these signs and abnormal arterial blood gases.

Methods and Results—Two hundred sixty-three patients (217 men) with COPD, mean age 67±9 years, were grouped according to whether they had no ECG signs (group 1, n=100) or ≥1 ECG signs (group 2, n=163) of CCP and were followed up for 13 years after an exacerbation of respiratory failure. The median survival was significantly shorter in group 2 than in group 1 (2.58 versus 3.45 years, respectively; Mantel-Cox test, 9.58; P=0.002). The Cox regression analysis identified S1 S2 S3 pattern, right atrial overload (RAO), and alveolar-arterial oxygen gradient (PAdO2–PaO2) >48 mm Hg during oxygen therapy as the strongest predictors of death, with hazard rate (HR) 1.81 (95% CI, 1.22 to 2.69), HR=1.58 (95% CI, 1.15 to 2.18), and HR=1.96 (95% CI, 1.19 to 3.25), respectively. The median survivals of patients having both S1 S2 S3 pattern and RAO (n=14) and of patients having either S1 S2 S3 pattern or RAO (n=77) were 1.33 and 2.70 years, respectively (P=0.022). Group 2 patients had a 3-year survival of 18% or 53%, depending on whether their PAdO2–PaO2 during oxygen therapy was or was not >48 mm Hg.

Conclusions—Some ECG signs of CCP and PAdO2–PaO2 >48 mm Hg during oxygen therapy qualified as a simple and inexpensive tool for targeting subsets of COPD patients with severe or very severe short-term prognosis. (Circulation. 1999;99:1600-1605.)

Key Words: hypertension, pulmonary | pulmonary heart disease | electrocardiography | prognosis

Age, forced expiratory volume in 1 second (FEV1), and several respiratory function indices have been shown to be independent correlates of survival in chronic obstructive pulmonary disease (COPD). The prognostic role of variables reflecting the onset and progression of chronic cor pulmonale (CCP) has rarely been assessed. Kok-Jensen found that COPD patients with a QRS axis ranging between +90° and +180° and with a P-wave amplitude of ≥0.20 mV had a 4-year survival of 37% and 42%, respectively, whereas the corresponding figure for patients with normal ECG was 75%. Traver et al showed that the clinical diagnosis of cor pulmonale is associated with higher mortality. In a small series of COPD patients, ECG signs of CCP were found to be the hallmark of pulmonary hypertension, but only 33% of patients with high pulmonary vascular resistances had ECG signs of CCP. In the same study, 7-year survival was inversely related to pulmonary vascular resistances. In the Nocturnal Oxygen Therapy Trial (NOTT), a decrease in pulmonary hypertension after 6 months of oxygen therapy was associated with improved survival. The important prognostic role of pulmonary hypertension was further confirmed in COPD patients on long-term oxygen therapy. Recently, we found that ECG signs of CCP were the second strongest predictor of death in COPD patients discharged after an acute exacerbation of their respiratory failure. The aims of the present study were to clarify the prognostic role of individual ECG signs of CCP and to verify whether coexisting CCP signs have additive effects on the prognosis of COPD patients as well as whether hypoxemia and hypocapnia, which are the main determinants of pulmonary hypertension, may be independent predictors of death in a multivariate model including ECG signs of CCP.

Methods

Study Population and Design
We studied the relationships between ECG signs of CCP and mortality in 263 patients affected by COPD (217 men; mean age, 67±9 years) hospitalized in the years 1980 to 1990 in the Pneumology Unit of the Catholic University in Rome because of an acute exacerbation of their disease. The study design has been reported in detail elsewhere. The diagnosis of COPD was made according to the standards provided by the American Thoracic Society, and the acute exacerbation was defined as an increase in dyspnea and a reduction of physical function severe enough to require hospitalization. All patients were admitted through the Emergency Department, and the admission procedures were reevaluated by 2 of us (L.F. and...
R.P.). Once in stabilized condition according to standardized criteria, patients underwent a multidimensional assessment exploring nutritional status, comorbidity, respiratory function indices, arterial blood gases measured both with and without oxygen supplementation, and ECG signs of CCP. Continuous oxygen therapy was performed with a Venturi mask (Baxter) at a concentration ranging from 24% to 40%, according to individual needs. All patients were followed up every 6 months by telephone calls from the date of discharge up to June 30, 1994. If neither the patient nor his/her relatives could be contacted, the municipal register office was consulted. In the event of death, the death certificate was obtained.

The following ECG signs reflecting CCP were collected: (1) a P-wave axis of $90^\circ$ or more, a finding consistent with right atrial overload (RAO) and associated with lung overinflation; (2) an S$_1$S$_2$S$_3$ pattern, a relatively uncommon finding not highly specific for COPD but reflecting an anomalous wave front rightward and superiorly oriented and opposed to the electrical forces of the ventricular free wall; (3) an S$_Q$ pattern, a well-known ECG sign associated with acute cor pulmonale but occasionally seen in RBBB CCP; (4) right bundle-branch block, significantly associated with COPD but also present as a function of age in the healthy population; (5) right ventricular hypertrophy (RVH), as defined by one of the following patterns: type A, characterized by a dominant R wave in V$_1$-V$_2$ and by an rS pattern in V$_5$-V$_6$; type B, characterized by an Rs pattern in V$_1$ and by a R amplitude not at all or only slightly decreasing from V$_1$ to V$_6$; and type C, characterized by small R waves and deep S waves persistent throughout the precordial leads; and (6) low-voltage QRS, a finding frequently associated with CCP from COPD but not with CCP from other pulmonary diseases.

The diagnosis of coronary artery disease was made if ECG findings met the Minnesota criteria for previous acute myocardial infarction or for myocardial ischemia. To limit the confounding effect of RVH, criteria for myocardial ischemia were considered to lack validity if they coexisted with a pattern of RVH in precordial leads.

The ECGs were read by 2 independent observers unaware of the remaining clinical and laboratory information. In the event of disagreement, a third assessor was consulted, and his opinion prevailed.

The original design of the study aimed at assessing the prognostic implications of echocardiographic signs of pulmonary hypertension as well. However, a good-quality echocardiogram was obtained in only 61% of the patients. Furthermore, over an 11-year period, 4 operators performed the echocardiograms, and no measure of interobserver reproducibility of diagnoses of each ECG sign of CCP with $K$-values always $>0.80$.

We found a very high interobserver reproducibility in detecting the whole set of ECG signs of CCP with $K$-values always $>0.80$.

The survival curves of patients without any ECG signs of CCP (group 1) and with at least 1 ECG signs of CCP (group 2) are plotted in Figure 1. The median survivals were 3.45 years for group 1 and 2.58 years for group 2. The difference between the survival curves was significant by both the Mantel-Cox test (9.58, $P=0.002$) and the Breslow test (5.52, $P=0.019$).

As reported in Tables 1 and 2, many variables possibly associated with the length of survival were significantly

\begin{table}[ht]
\centering
\begin{tabular}{|c|c|c|c|}
\hline
\textbf{Variable} & \textbf{Group 1} & \textbf{Group 2} & \textbf{$P^*$} \\
\hline
\textbf{No. (men)} & 100 (84) & 163 (133) & \\
\hline
\textbf{Age, y (mean±SD)} & 69.10±9.36 & 65.69±9.39 & 0.005 \\
\hline
\textbf{Length of hospital stay, d (mean±SD)} & 22.90±11.58 & 30.68±23.01 & 0.003 \\
\hline
\textbf{Coma during hospital stay, %} & 5 & 11 & 0.092 \\
\hline
\textbf{Mechanical ventilation during hospital stay, %} & 7 & 22.1 & 0.001 \\
\hline
\textbf{Diabetes mellitus, %} & 16 & 13.5 & 0.575 \\
\hline
\textbf{Systemic hypertension, %} & 39 & 21.5 & 0.002 \\
\hline
\textbf{Chronic renal failure, %} & 7 & 6.1 & 0.782 \\
\hline
\textbf{Ischemic heart disease, %} & 14 & 8 & 0.118 \\
\hline
\textbf{History of myocardial infarction, %} & 3 & 3.1 & 0.975 \\
\hline
\end{tabular}
\caption{Baseline Characteristics and Comorbidity of the Patients Grouped According to Whether No ECG Signs (Group 1) or $\geq$1 ECG Signs (Group 2) of CCP Were Present}
\end{table}

*By $x^2$ test or unpaired t test or Mann-Whitney test, as appropriate.
different between the 2 groups of patients. Group 2 subjects were younger and had a lower prevalence of systemic hypertension; however, they had a longer length of hospital stay, a lower oxygen arterial tension during the hospital stay, a higher prevalence of a coma status associated with the respiratory exacerbation, a greater need for mechanical ventilation, and RAO.

Table 3 summarizes the results of the Cox regression analysis: 2 of the 6 ECG signs of CCP, ie, S1S2S3 pattern and RAO, were significant independent predictors of mortality. A PAO2–PaO2 value >48 mm Hg measured during oxygen therapy was a strong negative predictor of survival. On the contrary, none of the remaining arterial gas data with or without oxygen supplementation, tested separately, did reach statistical significance. Hypoxemia could not be normalized in 35% of patients by oxygen supplementation, tested separately, did not reach statistical significance. Hypoxemia could not be normalized in 35% of patients by oxygen supplementation, tested separately, did not reach statistical significance.

**Table 3. Relationship Between Individual ECG Sign of CCP, Arterial Blood Gases, and Mortality Evaluated by Multivariate Cox Regression Analysis**

<table>
<thead>
<tr>
<th>Variable</th>
<th>β-Coefficient</th>
<th>Hazard Rate (95% CI)</th>
<th>t Value</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1S2S3 pattern</td>
<td>0.593</td>
<td>1.81 (1.22–2.69)</td>
<td>2.936</td>
<td>0.004</td>
</tr>
<tr>
<td>RAO</td>
<td>0.459</td>
<td>1.58 (1.15–2.18)</td>
<td>2.817</td>
<td>0.005</td>
</tr>
<tr>
<td>RVH</td>
<td>0.289</td>
<td>1.33 (0.86–2.06)</td>
<td>1.303</td>
<td>0.194</td>
</tr>
<tr>
<td>RBBB</td>
<td>0.261</td>
<td>1.30 (0.86–1.95)</td>
<td>1.252</td>
<td>0.212</td>
</tr>
<tr>
<td>Low-voltage QRS</td>
<td>0.143</td>
<td>1.15 (0.80–1.66)</td>
<td>0.764</td>
<td>0.445</td>
</tr>
<tr>
<td>S1Q3 pattern</td>
<td>0.031</td>
<td>1.03 (0.65–1.63)</td>
<td>0.134</td>
<td>0.893</td>
</tr>
<tr>
<td>PAO2–PaO2 during oxygen therapy</td>
<td>0.675</td>
<td>1.96 (1.19–3.25)</td>
<td>2.621</td>
<td>0.009</td>
</tr>
</tbody>
</table>

*The model was adjusted for age, sex, severity of exacerbation, and comorbidity.† PAO2, PaCO2 with and without oxygen supplementation, and PAO2–PaO2 without oxygen supplementation, tested separately, did not reach statistical significance.

†Highest quartile versus other quartiles.

**Discussion**

The present study demonstrates that 2 of the 6 collected ECG signs of CCP were significantly associated with a collinearity and interaction between variables, had an independent prognostic significance.

In Figures 2 and 3, we plotted the survival curves of groups 1, 2a, 2b, and 2c and of subgroups 1y, 1n, 2y, and 2n, respectively. The median survivals of these groups and the results of the Mantel-Cox and Breslow tests are reported in Table 4. Subgroup 2y, including patients with at least 1 ECG sign of CCP and PAO2–PaO2 >48 mm Hg during oxygen therapy, had the shortest median survival (0.78 years). A very short survival was also observed in subgroup 2c (1.33 years), which was characterized by a coexisting S1S2S3 pattern and RAO.

Three-year and 5-year survivals of patients are shown in Table 5. Both classifications adopted could discriminate groups with very different prognoses. However, the classification based on both ECG signs of CCP and PAO2–PaO2 >48 mm Hg during oxygen therapy, had the strongest discrimination, as reflected by the 8-fold difference between 5-year survival of subgroups 1n (48%) and 2y (6%), whereas group 1 and subgroup 2c had 5-year survivals of 39% and 7%, respectively.

**Table 2. Respiratory Function Data and Arterial Gas Values Measured Both in Room Air and During Oxygen Therapy of the Patients Grouped According to Whether No ECG Signs (Group 1) and \( \geq 1 \) ECG Signs (Group 2) of CCP Were Present**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1</th>
<th>Group 2</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC, % predicted</td>
<td>65.97±17.63</td>
<td>63.60±17.26</td>
<td>0.566</td>
</tr>
<tr>
<td>FEV1, % predicted</td>
<td>37.00±16.85</td>
<td>31.81±14.93</td>
<td>0.055</td>
</tr>
<tr>
<td>FEV1/FVC, %</td>
<td>42.53±13.39</td>
<td>39.01±14.12</td>
<td>0.133</td>
</tr>
<tr>
<td>PaO2, mm Hg in room air</td>
<td>57.26±9.46</td>
<td>52.71±9.09</td>
<td>0.0003</td>
</tr>
<tr>
<td>PacO2, mm Hg in room air</td>
<td>44.55±7.23</td>
<td>47.85±8.44</td>
<td>0.001</td>
</tr>
<tr>
<td>PAO2–PaO2, mm Hg in room air</td>
<td>35.57±9.20</td>
<td>36.11±10.53</td>
<td>0.677</td>
</tr>
<tr>
<td>PAO2, mm Hg during oxygen therapy</td>
<td>68.57±7.24</td>
<td>66.37±8.35</td>
<td>0.044</td>
</tr>
<tr>
<td>PacO2, mm Hg during oxygen therapy</td>
<td>45.37±7.12</td>
<td>47.39±8.46</td>
<td>0.107</td>
</tr>
<tr>
<td>PAO2–PaO2, mm Hg during oxygen therapy</td>
<td>44.26±11.39</td>
<td>44.65±15.61</td>
<td>0.504</td>
</tr>
</tbody>
</table>

FVC indicates forced vital capacity. Values are mean±SD.

*By \( \chi^2 \) test or unpaired t test or Mann-Whitney test, as appropriate.

**Figure 2. Cumulative survival rate of patients without ECG signs of CCP (group 1), patients with \( \geq 1 \) ECG signs different S1S2S3 pattern and RAO (subgroup 2a), patients with either S1S2S3 pattern or RAO (subgroup 2b), and patients with both S1S2S3 pattern and RAO (subgroup 2c).**

**Figure 3. Cumulative survival rate of patients of groups 1 and 2 subgrouped according to whether they had (y) or did not have (n) a PAO2–PaO2 during oxygen therapy >48 mm Hg.**
shorter survival in COPD patients and that a PAO\textsubscript{2}−P\textsubscript{aO\textsubscript{2}} >48 mm Hg during oxygen therapy further worsened the prognosis. Among CCP signs, S\textsubscript{1}S\textsubscript{2}S\textsubscript{3}\textsubscript{p} pattern and RAO with \(\geq 1\) of the other ECG signs of CCP; subgroup 2b: patients with either S\textsubscript{1}S\textsubscript{2}S\textsubscript{3}\textsubscript{p} pattern and RAO; subgroup 2c: patients with both S\textsubscript{1}S\textsubscript{2}S\textsubscript{3}\textsubscript{p} pattern and RAO. Bottom: Subgroup 1n: patients without ECG signs of CCP and PAO\textsubscript{2}−P\textsubscript{aO\textsubscript{2}} \geq 48 mm Hg in oxygen therapy; subgroup 1y: patients without ECG signs of CCP and PAO\textsubscript{2}−P\textsubscript{aO\textsubscript{2}} \geq 48 mm Hg in oxygen therapy; subgroup 2n: patients with \(\geq 1\) ECG signs of CCP and PAO\textsubscript{2}−P\textsubscript{aO\textsubscript{2}} \geq 48 mm Hg in oxygen therapy; subgroup 2y: patients with \(\geq 1\) ECG signs of CCP and PAO\textsubscript{2}−P\textsubscript{aO\textsubscript{2}} >48 mm Hg in oxygen therapy.

The presence of both S\textsubscript{1}S\textsubscript{2}S\textsubscript{3}\textsubscript{p} pattern and RAO was a strong predictor of mortality, but even patients with only 1 of these signs and/or any other ECG sign of CCP survived for shorter periods than patients without ECG evidence of CCP. The analysis of survival curves shows that the impact of CCP on survival became more evident \(\approx 1\) year after discharge from the hospital. Indeed, all our COPD patients had a very high risk of death in the early period after the discharge whether ECG signs of CCP were present or not. The progressively declining fraction of surviving patients and the effect of age per se and of comorbidity on survival are likely to decrease the strength of the association between CCP and survival in the last phases of the study. Our findings agree with the results of a large multicenter trial assessing survival of hypercapnic COPD patients discharged from an acute-care hospital after an acute exacerbation: \(33\%\) of them died within 6 months, and CCP was an independent predictor of mortality.\textsuperscript{22} However, CCP was diagnosed according to 6 alternative criteria, only 1 of which took ECG findings into account.\textsuperscript{22} Indeed, our data focus on ECG signs of CCP and provide a standardized diagnosis for each of them.

Collaterally, in our study, ECG signs of CCP were also strong positive correlates of the length of hospital stay and of the use of mechanical ventilation. This finding should be interpreted with some caution, but if confirmed by prospective studies taking into account ECG features on admission, it would allow us to identify COPD patients requiring a heavier burden of care.

A high PAO\textsubscript{2}−P\textsubscript{aO\textsubscript{2}} value measured during oxygen therapy was the only index derived from the arterial gas analysis that was likely to improve the prognostic model on the basis of the ECG signs of CCP. This might be consistent with ECG signs of CCP reflecting pulmonary hypertension more closely than hypoxemia and hypercapnia or providing some additional information on the disease severity, eg, by reflecting the adaptation of the right heart to pulmonary hypertension. Indeed, in advanced COPD, structural changes in pulmonary vasculature, lung hyperinflation, and possibly thrombosis in the pulmonary arterial tree contribute to causing pulmonary hypertension, making pulmonary vascular resistances less dependent on hypoxemia and hypercapnia.\textsuperscript{23} Furthermore, whereas P\textsubscript{aO\textsubscript{2}} and P\textsubscript{aCO\textsubscript{2}} are differently affected by the relative proportions of high and low ventilation/perfusion units across the lungs, PAO\textsubscript{2}−P\textsubscript{aO\textsubscript{2}} can be considered a cumulative index of efficiency of pulmonary gas exchanges.\textsuperscript{24} This might provide a clue to understanding the prognostic role of PAO\textsubscript{2}−P\textsubscript{aO\textsubscript{2}}. The relationship between CCP and respiratory function data deserves some additional comment: in the last stages of COPD, the range of spirometric values is very narrow, which limits the possibility of further decline paralleling the worsening of the gas exchange function.\textsuperscript{25} This probably explains both the lack of differences in spirometric values between patients with and without ECG signs of CCP and the lack of prognostic implications of the respiratory function data. Moreover, oxygen supplementation frequently cannot completely correct hypoxemia and hypercapnia.\textsuperscript{26} However, increasing the inspired fraction of oxygen results in higher PAO\textsubscript{2}−P\textsubscript{ao} values according to the alveolar gas equation.\textsuperscript{27} Given that the inspired fraction of oxygen ranged between 24% and 40%, the ensuing increased disper-
sion of PAO\textsubscript{2}−PA\textsubscript{a}O\textsubscript{2} values could have contributed to strengthening the prognostic role of PAO\textsubscript{2}−PA\textsubscript{a}O\textsubscript{2} measured during oxygen supplementation.

None of the methods for a noninvasive diagnosis of pulmonary hypertension can be considered fully satisfactory. Indeed, radiological measurements achieve poor sensitivity and specificity, whereas catheter-measured and echo Doppler–assessed pulmonary artery pressures are significantly correlated.\textsuperscript{28,29} However, a good-quality echocardiogram cannot be obtained in a large fraction of COPD patients, mainly because a Doppler-detected tricuspid regurgitation jet is lacking.\textsuperscript{30} This and the high standard error of the estimated pressure limit the usefulness of echocardiographic measurements in the diagnosis of pulmonary hypertension and prevented us from testing their prognostic implications. ECG compares favorably with radiological methods in diagnosing pulmonary hypertension. Furthermore, ECG achieves better specificity but lower sensitivity than the echocardiogram and is easily measurable in every CCP patient.\textsuperscript{28} Thus, despite its low sensitivity, ECG seems worthy of being used in the assessment of CCP complicating COPD. The prognostic importance of ECG signs of CCP in our study further supports this conclusion.

Limitations of this study are the following: first, lack of right heart catheterization in most of our patients prevented us from assessing the relationship between ECG signs of CCP and pulmonary hypertension; second, ≥2 ECG signs of CCP coexisted in a large fraction of patients, which is expected to weaken the prognostic meaning of individual ECG signs; and third, the diagnosis of coronary artery disease based on ECG criteria might be unreliable in some CCP patients.\textsuperscript{31} Indeed, left ventricular systolic dysfunction is relatively uncommon in COPD, whereas left ventricular diastolic dysfunction has been reported to occur in a variable proportion of COPD patients and might to some extent reflect the effects of hypoxemia or silent myocardial ischemia as well as that of greater age itself on left ventricular relaxation.\textsuperscript{11} The lack of a stress test assessing coronary perfusion prevented us from making or excluding a diagnosis of coronary artery disease with a high degree of reliability.

Despite these limitations, the present study shows that ECG signs of CCP qualify as a simple and inexpensive tool for targeting COPD patients at risk of shorter survival and that a severely impaired gas exchange function has additional negative prognostic implications. Coexisting S\textsubscript{S},S\textsubscript{S}, pattern and RAO is a marker of a very high risk of death in the short term. Future studies should verify to what extent individual ECG signs of CCP reflect pulmonary hypertension. Collaterally, our findings confirm that hypoxemia with or without hypercapnia characterizes a consistent proportion of COPD patients despite continuous oxygen therapy. Any effort should be made to optimize arterial blood gases, whose derangement is the main determinant of increased pulmonary vascular resistances. Thus, properly defined programs aimed at improving oxygen delivery, mainly during physical exercise and sleep, and at realizing a comprehensive management of these patients could reverse the progression of pulmonary hypertension, although pulmonary artery pressure rarely normalizes.\textsuperscript{32} Finally, the present findings show that even in an era of rapidly developing and highly sophisticated technological, elementary diagnostic techniques maintain intrinsic validity provided that their meaning is carefully analyzed.

References


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