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

Raffaele Antonelli Incalzi, MD; Leonello Fuso, 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 S1S2S3 pattern, right atrial overload (RAO), and alveolar-arterial oxygen gradient (PAO2 − 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 S1S2S3 pattern and RAO (n = 14) and of patients having either S1S2S3 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 PAO2 − PaO2 during oxygen therapy was or was not > 48 mm Hg.

Conclusions—Some ECG signs of CCP and PAO2 − 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 hypercapnia, 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,11 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.8 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 overinflation12; (2) an R over Q3 pattern, a relatively uncommon finding not highly specific for COPD13 that reflects an anomalous wave front rightward and superiorly oriented and opposed to the electrical forces of the ventricular free wall14; (3) an S2Q3 pattern, a well-known ECG sign associated with acute cor pulmonale15 but occasionally seen in RBBB CCP16; (4) right bundle-branch block, significantly associated with COPD16 but also present as a function of age in the healthy population17; (5) right ventricular hypertrophy (RVH), as defined by 1 of the following patterns: type A, characterized by a dominant R wave in V1-V2 and by an rS pattern in V5-V618; type B, characterized by an Rs pattern in V1 and by a R amplitude not at all or only slightly decreasing from V1 to V219; and type C, characterized by small R waves and deep S waves persistent throughout the precordial leads18; (6) low-voltage QRS, a finding frequently associated with CCP from COPD but not with CCP from other pulmonary diseases.13

The diagnosis of coronary artery disease was made if ECG findings met the Minnesota criteria for previous acute myocardial infarction or for myocardial ischemia.13 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 interrater reliability of measurements was available. Accordingly, we excluded echocardiograms from the analysis. We judged that even repeating the analysis on patients having a good-quality echocardiogram would have been misleading because of an important selection bias; indeed, the best echocardiograms were obtained in patients having a relatively shorter history of respiratory disease and a predominately bronchitic rather than emphysematous type of COPD.

### Data Analysis

The statistical analysis was performed by use of BMDP Statistical Software. Interobserver reproducibility of diagnoses of each ECG sign of CCP was assessed by the K-test.20 Patients were grouped according to whether they had no ECG signs (group 1) or ≥1 ECG signs (group 2) of CCP. The Kaplan-Meier method was used to describe the survival curves of the 2 groups. The differences between curves were evaluated by the Mantel-Cox and Breslow tests, which explore mainly the early and the late phases of survival curves, respectively.21

![Figure 1. Cumulative survival rate of patients without (group 1) and with ≥1 (group 2) ECG signs of CCP.](image)

The significance of the association between each ECG sign of CCP and survival was assessed by the Cox regression analysis, adjusted for age, sex, severity of the episode of exacerbation, and comorbidity.8 Then, the prognostic importance of coexisting ECG signs was evaluated by splitting group 2 into 3 subgroups, as follows: subgroup 2a, 72 patients without S2S3 pattern and RAO; subgroup 2b, 77 patients having either S2S3 pattern or RAO; and subgroup 2c, 14 patients having both S2S3 pattern and RAO. The survival curves of these subgroups and of group 1 were compared by the Mantel-Cox and Breslow tests. An alternative partitioning of groups 1 and 2 into subgroups 1n, 1y, 2n, and 2y was also made according to whether the individual patients had (y, yes) or did not have (n, no) an alveolar-arterial oxygen gradient (PAO2–PAO2) measured during oxygen therapy >48 mm Hg, which corresponded to the 75th percentile of PAO2–PAO2 distribution. Survival curves of these subgroups were then compared. This procedure was made to test the prognostic relevance of the interaction between ECG signs of CCP and PAO2–PAO2, the latter being the only prognostically significant index derived from the arterial gas analysis.

### Results

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 ≥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

### Table 1. Baseline Characteristics and Comorbidity of the Patients Grouped According to Whether No ECG Signs (Group 1) or ≥1 ECG Signs (Group 2) of CCP Were Present

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>$P^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. (men)</td>
<td>100 (84)</td>
<td>163 (133)</td>
<td></td>
</tr>
<tr>
<td>Age, y (mean±SD)</td>
<td>69.10±9.36</td>
<td>65.69±9.39</td>
<td>0.005</td>
</tr>
<tr>
<td>Length of hospital stay, d (mean±SD)</td>
<td>22.90±11.58</td>
<td>30.68±23.01</td>
<td>0.003</td>
</tr>
<tr>
<td>Coma during hospital stay, %</td>
<td>5</td>
<td>11</td>
<td>0.092</td>
</tr>
<tr>
<td>Mechanical ventilation during hospital stay, %</td>
<td>7</td>
<td>22.1</td>
<td>0.001</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>16</td>
<td>13.5</td>
<td>0.575</td>
</tr>
<tr>
<td>Systemic hypertension, %</td>
<td>39</td>
<td>21.5</td>
<td>0.002</td>
</tr>
<tr>
<td>Chronic renal failure, %</td>
<td>7</td>
<td>6.1</td>
<td>0.782</td>
</tr>
<tr>
<td>Ischemic heart disease, %</td>
<td>14</td>
<td>8</td>
<td>0.118</td>
</tr>
<tr>
<td>History of myocardial infarction, %</td>
<td>3</td>
<td>3.1</td>
<td>0.975</td>
</tr>
</tbody>
</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 higher oxygen arterial tension (PaO2), and a higher carbon dioxide arterial tension (PaCO2). In addition, FEV1 was lower in group 2 patients, with a value close to statistical significance. Hypoxemia could not be normalized in 35% of patients by oxygen supplementation because of the frequently very severe impairment in pulmonary gas exchanges, as reflected by the high values of PaO2.

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 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 not reach statistical significance.

**Prognostic Role of ECG Signs of Cor Pulmonale**

**Discussion**

The present study demonstrates that 2 of the 6 collected ECG signs of CCP were significantly associated with a high risk of mortality in patients with chronic respiratory exacerbation, making these signs useful for risk stratification.
shorter survival in COPD patients and that a $P_{AO2-PaO2} > 48$ mm Hg during oxygen therapy further worsened the prognosis. Among CCP signs, $S1S2S3$ pattern and RAO with $\geq 1$ of the other ECG signs of CCP; subgroup 2b: patients with either $S1S2S3$ pattern or RAO; subgroup 2c: patients with both $S1S2S3$ pattern and RAO. Bottom: Subgroup 1n: patients without ECG signs of CCP and $PaO2-PaCO2 \leq 48$ mm Hg in oxygen therapy; subgroup 1y: patients without ECG signs of CCP and $PaO2-PaCO2 > 48$ mm Hg in oxygen therapy; subgroup 2n: patients with $\geq 1$ ECG signs of CCP and $PaO2-PaCO2 > 48$ mm Hg in oxygen therapy; subgroup 2y: patients with $\geq 1$ ECG signs of CCP and $PaO2-PaCO2 > 48$ mm Hg in oxygen therapy.

The presence of both $S1S2S3$ 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. However, CCP was diagnosed according to 6 alternative criteria, only 1 of which took ECG findings into account. 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 $P_{AO2-PaO2}$ 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. Furthermore, whereas $PaO2$ and $PaCO2$ are differently affected by the relative proportions of high and low ventilation/perfusion units across the lungs, $P_{AO2-PaO2}$ can be considered a cumulative index of efficiency of pulmonary gas exchanges. This might provide a clue to understanding the prognostic role of $P_{AO2-PaO2}$. 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. 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. However, increasing the inspired fraction of oxygen results in higher $P_{AO2-PaO2}$ values according to the alveolar gas equation. Given that the inspired fraction of oxygen ranged between 24% and 40%, the ensuing increased disper-

### TABLE 4. Comparison of Survival Curves of Patients Grouped According to 2 Alternative Methods*

<table>
<thead>
<tr>
<th>Group (Median Survival)</th>
<th>Mantel-Cox Test</th>
<th>P</th>
<th>Breslow Test</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (3.45 y) vs 2a (2.87 y)</td>
<td>3.03</td>
<td>0.082</td>
<td>2.42</td>
<td>0.120</td>
</tr>
<tr>
<td>1 vs 2b (2.70 y)</td>
<td>8.60</td>
<td>0.003</td>
<td>3.41</td>
<td>0.065</td>
</tr>
<tr>
<td>1 vs 2c (1.33 y)</td>
<td>10.83</td>
<td>0.001</td>
<td>9.54</td>
<td>0.002</td>
</tr>
<tr>
<td>2a vs 2b</td>
<td>1.08</td>
<td>0.298</td>
<td>0.01</td>
<td>0.922</td>
</tr>
<tr>
<td>2a vs 2c</td>
<td>4.63</td>
<td>0.031</td>
<td>3.75</td>
<td>0.052</td>
</tr>
<tr>
<td>2b vs 2c</td>
<td>5.26</td>
<td>0.022</td>
<td>5.60</td>
<td>0.018</td>
</tr>
<tr>
<td>1n (4.43 y) vs 1y (3.87 y)</td>
<td>0.290</td>
<td>0.590</td>
<td>0.163</td>
<td>0.687</td>
</tr>
<tr>
<td>1n vs 2n (3.31 y)</td>
<td>5.975</td>
<td>0.014</td>
<td>2.236</td>
<td>0.135</td>
</tr>
<tr>
<td>1n vs 2y (0.78 y)</td>
<td>21.732</td>
<td>0.00001</td>
<td>22.318</td>
<td>0.00001</td>
</tr>
<tr>
<td>1y vs 2n</td>
<td>1.104</td>
<td>0.293</td>
<td>0.414</td>
<td>0.519</td>
</tr>
<tr>
<td>1y vs 2y</td>
<td>6.426</td>
<td>0.011</td>
<td>5.569</td>
<td>0.018</td>
</tr>
<tr>
<td>2n vs 2y</td>
<td>13.484</td>
<td>0.0002</td>
<td>24.551</td>
<td>0.00001</td>
</tr>
</tbody>
</table>

*Top: Group 1: no ECG signs of CCP; subgroup 2a: patients without $S1S2S3$ pattern and RAO with $\geq 1$ of the other ECG signs of CCP; subgroup 2b: patients with either $S1S2S3$ pattern or RAO; subgroup 2c: patients with both $S1S2S3$ pattern and RAO. Bottom: Subgroup 1n: patients without ECG signs of CCP and $PaO2-PaCO2 \leq 48$ mm Hg in oxygen therapy; subgroup 1y: patients without ECG signs of CCP and $PaO2-PaCO2 > 48$ mm Hg in oxygen therapy; subgroup 2n: patients with $\geq 1$ ECG signs of CCP and $PaO2-PaCO2 \leq 48$ mm Hg in oxygen therapy; subgroup 2y: patients with $\geq 1$ ECG signs of CCP and $PaO2-PaCO2 > 48$ mm Hg in oxygen therapy.

### TABLE 5. Three-Year and 5-Year Survivals

<table>
<thead>
<tr>
<th>Groups and Subgroups*</th>
<th>3-Year Survival, %</th>
<th>5-Year Survival, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>61</td>
<td>39</td>
</tr>
<tr>
<td>Subgroup 2a</td>
<td>50</td>
<td>26</td>
</tr>
<tr>
<td>Subgroup 2b</td>
<td>44</td>
<td>22</td>
</tr>
<tr>
<td>Subgroup 2c</td>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td>$P$ by $\chi^2$ test</td>
<td>0.004</td>
<td>0.017</td>
</tr>
<tr>
<td>Subgroup 1n</td>
<td>65</td>
<td>48</td>
</tr>
<tr>
<td>Subgroup 1y</td>
<td>71</td>
<td>36</td>
</tr>
<tr>
<td>Subgroup 2n</td>
<td>53</td>
<td>28</td>
</tr>
<tr>
<td>Subgroup 2y</td>
<td>18</td>
<td>6</td>
</tr>
<tr>
<td>$P$ by $\chi^2$ test</td>
<td>0.0001</td>
<td>0.0009</td>
</tr>
</tbody>
</table>

*Groups and subgroups as in Table 4.
sion of $\text{PaO}_2 - \text{PaO}_2$ values could have contributed to strengthening the prognostic role of $\text{PaO}_2 - \text{PaO}_2$ 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, S, 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 cardiological technology, elementary diagnostic techniques maintain intrinsic validity provided that their meaning is carefully analyzed.

References


Electrocardiographic Signs of Chronic Cor Pulmonale: A Negative Prognostic Finding in Chronic Obstructive Pulmonary Disease
Raffaele Antonelli Incalzi, Leonello Fuso, Marino De Rosa, Anteo Di Napoli, Salvatore Basso, Gabriella Pagliari and Riccardo Pistelli

Circulation. 1999;99:1600-1605
doi: 10.1161/01.CIR.99.12.1600

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1999 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/99/12/1600

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/