Cardiac Complications in Patients With Community-Acquired Pneumonia
In Incidence, Timing, Risk Factors, and Association With Short-Term Mortality

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Background—Community-acquired pneumonia (CAP) affects >5 million adults each year in the United States. Although incident cardiac complications occur in patients with community-acquired pneumonia, their incidence, timing, risk factors, and associations with short-term mortality are not well understood.

Methods and Results—A total of 1343 inpatients and 944 outpatients with community-acquired pneumonia were followed up prospectively for 30 days after presentation. Incident cardiac complications (new or worsening heart failure, new or worsening arrhythmias, or myocardial infarction) were diagnosed in 358 inpatients (26.7%) and 20 outpatients (2.1%). Although most events (89.1% in inpatients, 75% in outpatients) were diagnosed within the first week, more than half of them were recognized in the first 24 hours. Factors associated with their diagnosis included older age (odds ratio [OR] 1.03; 95% confidence interval [CI] 1.02–1.04), nursing home residence (OR, 1.8; 95% CI, 1.2–2.9), history of heart failure (OR, 4.3; 95% CI, 3.0–6.3), prior cardiac arrhythmias (OR, 1.8; 95% CI, 1.2–2.7), previously diagnosed coronary artery disease (OR, 1.5; 95% CI, 1.04–2.0), arterial hypertension (OR, 1.5; 95% CI, 1.1–2.1), respiratory rate ≥30 breaths per minute (OR, 1.6; 95% CI, 1.1–2.3), blood pH <7.35 (OR, 3.2; 95% CI, 1.8–5.7), blood urea nitrogen ≥30 mg/dL (OR, 1.5; 95% CI, 1.1–2.2), serum sodium <130 mmol/L (OR, 1.8; 95% CI, 1.02–3.1), hematocrit <30% (OR, 2.0; 95% CI, 1.3–3.2), pleural effusion on presenting chest x-ray (OR, 1.6; 95% CI, 1.1–2.4), and inpatient care (OR, 4.8; 95% CI, 2.8–8.3). Incident cardiac complications were associated with increased risk of death at 30 days after adjustment for baseline Pneumonia Severity Index score (OR, 1.6; 95% CI, 1.04–2.5).

Conclusions—Incident cardiac complications are common in patients with community-acquired pneumonia and are associated with increased short-term mortality. Older age, nursing home residence, preexisting cardiovascular disease, and pneumonia severity are associated with their occurrence. Further studies are required to test risk stratification and prevention and treatment strategies for cardiac complications in this population. (Circulation. 2012;125:773-781.)

Key Words: pneumonia ■ complications ■ heart failure ■ arrhythmias, cardiac ■ myocardial infarction

Community-acquired pneumonia (CAP) affects >5 million adults, causes 1.1 million hospital admissions, and is responsible for >60 000 deaths each year in the United States.1-2 Cardiac diseases affect >30 million adult Americans and are responsible for 5 million hospital admissions and >300 000 deaths each year in this country.3,4 Both CAP and cardiac diseases occur more commonly in middle-aged and elderly individuals.4-5 It is estimated that more than half of the elderly patients with CAP who present to the hospital with this infection have a chronic cardiac condition.4-5

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Pneumonia contributes to the acute worsening of preexisting cardiac conditions and can trigger new cardiac events.6-9 Infection-induced changes in myocardial function, the conduction system of the heart, the stability of coronary plaques,
vascular tone, and blood coagulability may all account for this effect.9 Recent retrospective clinical observations suggest that incident (new or worsening) cardiac complications occur in a significant proportion of high-risk CAP patients (ie, elderly veterans and diabetics).10–14 However, the frequency of these complications in unselected CAP patients, the contribution of specific cardiac events to this burden, the timing of these complications in the course of CAP, the factors associated with their development, and their association with the short-term mortality of this infection remain unclear.

Using data from a multicenter, prospective cohort of patients presenting with clinical and radiological evidence of CAP, we specifically sought to determine: (1) the type, frequency, and timing of incident cardiac complications; (2) their risk factors; and (3) their associations with short-term mortality.

**Methods**

This study was approved by the Ottawa Hospital Research Ethics Board.

**Study Population**

Detailed methods of the Pneumonia Patient Outcomes Team (PORT) cohort study were reported previously.15 This cohort study recruited patients from October 1991 through March 1994 at 5 medical institutions: University of Pittsburgh Medical Center (UPMC) and St. Francis Medical Center (SFMC) in Pittsburgh, PA; Massachusetts General Hospital (MGH) and Harvard Community Health Plan–Kennmore Center (HCHP) in Boston, MA; and Victoria General Hospital (VGH) in Halifax, Nova Scotia, Canada. Inclusion criteria were age ≥18 years, the presence of ≥1 acute clinical symptoms suggestive of pneumonia, radiographic evidence of pneumonia within 24 hours of presentation, and appropriate informed consent for participation. Chest radiographs used for the diagnosis of pneumonia were independently reviewed by a 3-member panel of staff radiologists at UPMC who had no patient-specific clinical information. Patients were excluded if the radiographic findings were considered to represent a preexisting infiltrate or if they were consistent with an alternative diagnosis. Other exclusion criteria were discharge from an acute-care hospital within 10 days preceding presentation, HIV infection, the presence of an alternative diagnosis that likely explained the pulmonary symptoms and x-ray infiltrate (eg, lung carcinoma, pulmonary edema, or pulmonary embolus), or previous enrollment in the study. Patients initially treated in an ambulatory setting were classified as outpatients, and patients admitted to a hospital on presentation were classified as inpatients.

**Baseline Assessment**

Baseline sociodemographic characteristics and clinical data were obtained from all subjects by interviews and review of medical records. Clinical information included preexisting comorbidities, symptoms, and physical examination findings at presentation and pertinent laboratory findings within 48 hours of presentation. Severity of illness at presentation was quantified by means of the Pneumonia Severity Index (PSI), a validated prediction rule for 30-day mortality in patients with CAP.15 This rule calculates a score based on 3 demographic characteristics, 5 comorbid conditions, 5 physical examination findings, and 7 laboratory and radiographic findings from the time of presentation. On the basis of this score, CAP patients are classified into 1 of 5 risk classes, each with an increasing risk of 30-day mortality ranging from 0.1% for class I (lowest risk) to 27.0% for class V (highest risk).16 The PSI has been widely validated as a predictor of severity and short-term mortality risk in patients with CAP.16,17 Current guidelines recommend that patients with CAP in PSI risk classes IV and V should be hospitalized for the management of their infection, whereas those in classes I and II should be considered for treatment as outpatients or in short hospitalization units.18

**Assessment of Cardiac Complications**

Data regarding the incidence and timing of new or worsening morbid complications within 30 days of enrollment were prospectively ascertained for 96.1% of outpatients and 99.7% of inpatients.15 We focused on the development of 3 acute cardiac events: (1) new or worsening heart failure, ie, the simultaneous presence of clinical signs of new or worsening pulmonary edema or acute congestive heart failure (rales, increased jugular venous pressure, S3 gallop, peripheral edema) detected by the managing physician on physical examination and documented in the medical record, and a chest x-ray read by the local radiologist as showing pulmonary edema, cardiomegaly, vascular congestion, or congestive heart failure; (2) new or worsening arrhythmias, ie, documentation in the medical record, ECG, rhythm strips, ECG monitor, or Holter monitor of newly recognized or worsened atrial fibrillation, atrial flutter, supraventricular tachycardia, multifocal atrial tachycardia, ventricular tachycardia (≥3-beat run), or ventricular fibrillation; and (3) myocardial infarction (MI), ie, documentation in the medical record of myocardial ischemia or injury established by 2 of 3 criteria: chest pain, acute ECG changes (ST-segment and T-wave changes without the formation of Q waves, new Q waves, or a clear loss of R waves or sustained ventricular tachycardia or fibrillation), or elevated cardiac enzymes (creatinine phosphokinase-MB) determined from criteria provided by laboratories at participating clinical sites. These cardiac events were ascertained by means of detailed medical review by trained research assistants. We recorded only the index occurrence of each type of event and its date. Overall, incident cardiac complications were defined by the occurrence of any of the cardiac events above.

To explore the temporal relationships among specific cardiac events, we also classified them by their sequential occurrence. When a cardiac event occurred in the absence of other cardiac events during the observation period, it was classified as the only cardiac event; a cardiac event that preceded the development of other events in the same patient by at least 1 day was described as the first cardiac event; a primary cardiac event was said to be present when either a first or an only cardiac event occurred. Finally, a secondary cardiac event was any event that followed other cardiac events by at least 1 day or for which its precedence over the others could not be established (ie, occurred on the same day).

**Statistical Analysis**

Continuous variables are presented as mean±SD or medians (interquartile range) as appropriate. Categorical variables are presented as counts and percentages. For the univariable analysis of baseline factors and incident cardiac complications, we used unpaired t-tests or Wilcoxon rank-sum tests for continuous variables and χ² or Fisher exact tests for categorical variables as appropriate. Baseline factors associated with incident cardiac complications with a univariable significance level of P<0.1 in the univariable analysis were entered into a multivariable logistic model of this outcome. Because it is plausible that factors associated with the institution at which the patient was managed (UPMC, SFMC, MGH, HCHP, or VGH) and the site of care (outpatient versus inpatient) could have affected the occurrence and/or ascertainment of the outcomes of interest and to account for potential clustering, we performed these analyses using hierarchical models in which institution and site of care were entered as random and fixed factors, respectively. The purpose of these analyses was to identify and quantify the associations between discrete baseline factors and the development of cardiac complications. Accordingly, PSI score, a composite measure that includes 18 of the 28 baseline variables considered in these analyses, was not entered into the models to prevent problems of collinearity in the interpretations of our results. However, given that PSI is the most extensively validated and widely used tool for risk assessment of pneumonia patients in clinical practice,16–18 we also sought to explore its association with the risk of incident cardiac complications by using a multivariable model that incorporated PSI score and all baseline characteristics not used for its calculation as independent variables and the occurrence of incident cardiac complications as the dependent variable, generating a plot to illustrate this adjusted relationship. We also investigated the association between incident cardiac complications and 30-day mortality using a logistic regres-
A regression model that included the patient’s vital status at 30 days after enrollment as the dependent variable and the occurrence of cardiac complications and baseline PSI score as the independent variables. Hierarchical modeling (with institution and site of care as random and fixed factors, respectively) was also used in this model. Finally, we tested the robustness of the analyses of factors associated with the development of cardiac complications and of the association between cardiac complications and 30-day mortality by repeating these analyses after exclusion of those patients who had cardiac complications ascertained or who died the same day as presentation with CAP. This was done to remove the potential confounding from cardiac events that could have occurred before the pneumonia but that were ascertained only after presentation with the infection (and still accounted as CAP-related complications) and from patients with severe pneumonia who died soon after presentation in whom the significance of cardiac events would be less discernible. We conducted all statistical analyses using SAS (version 9.2, SAS Institute Inc, Cary, NC). The hierarchical models were estimated with the GLIMMIX procedure. We defined statistical significance as a 2-tailed value of \( P<0.05 \).

**Results**

Of 3964 eligible subjects, 2287 (57.7%) were enrolled. Characteristics of eligible individuals not enrolled in the study and the reasons for nonenrollment are detailed elsewhere. Of the enrolled patients, 1343 (58.7%) were treated as inpatients and 944 (41.3%) as outpatients. Baseline characteristics of inpatients and outpatients are presented in Table I in the online-only Data Supplement.

**Frequency, Type, and Timing of Cardiac Complications**

Overall, incident cardiac complications occurred in 358 inpatients (26.7%) and 20 outpatients (2.1%: Figure 1). New or worsening heart failure, new or worsening arrhythmias, and MI were the primary cardiac events in 239 (66.8%), 79 (22.1%), and 13 (3.6%) inpatients and 13 (65%), 7 (35%), and 0 outpatients, respectively. The specific incidence of each type of cardiac event and the temporal relations among them are depicted in Figure 2. New or worsening heart failure was the single most common cardiac event, occurring in 279 inpatients (20.8%) and 13 outpatients (1.4%). New or worsening heart failure was the only, first, and secondary cardiac event in 196 (70.3%), 43 (15.4%), and 40 (14.3%) inpatients who had this event and 11 (84.6%), 2 (15.4%), and 0 of the corresponding outpatients, respectively. New or worsening arrhythmias occurred less frequently in 137
blood urea nitrogen /H11350
laboratory or radiographic abnormalities (blood pH
hypertension), respiratory rate
previously diagnosed coronary artery disease, and arterial
tions (history of heart failure, prior cardiac arrhythmias,
nursing home residence, 4 preexisting cardiovascular condi-
tions (history of heart failure, prior coronary arrhythmias,
previously diagnosed coronary artery disease, and arterial
hypertension), respiratory rate ≥30 breaths per minute, 5
laboratory or radiographic abnormalities (blood pH <7.35,
blood urea nitrogen ≥30 mg/dL, sodium <130 mmol/L,
hematocrit <30%, and pleural effusion on chest x-ray), and
site of care (inpatient versus outpatient). The magnitude and
significance of these associations are presented in Table 2.
When the analysis was repeated excluding those patients who
had cardiac complications ascertained or who died the same
day of presentation (208 patients), the factors that remained
associated with cardiac complications were age (odds ratio
[OR], 1.03; 95% confidence interval [CI], 1.02–1.04), nurs-
ing home residence (OR, 2.2; 95% CI, 1.2–4.0), history of
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95% CI, 1.2–5.2), hematocrit <30% (OR, 2.4; 95% CI, 1.4–4.3),
and inpatient status (OR, 5.0; 95% CI, 2.4–10.2).

Association Between the PSI and Incident
Cardiac Complications
The baseline PSI score was significantly higher in patients
who developed incident cardiac complications compared with
those who did not (114±35 versus 63±37; P<0.01). There
was a significant increasing trend in the proportion of patients
developing incident cardiac complications across PSI risk
classes (P<0.01), ranging from 1.2% for class I to 47.7% for
class V. In a multivariable analysis, the association between
PSI risk score and cardiac complications was significant
(P<0.01) even after adjustment for baseline variables not
included in the calculation of the PSI (Figure 4).

Association Between Incident Cardiac
Complications and Short-Term Mortality
The 30-day mortality was significantly higher in patients with
CAP who developed incident cardiac complications compared with
those who did not (15.3% [58 patients] versus
2.8% [53 patients]; OR, 3.5; 95% CI, 2.3–5.2; P<0.01). This
association remained significant even after adjustment for
baseline PSI risk score. In this latter model, the development of
incident cardiac complications in patients with CAP was
associated with a 60% increase in the risk of death at 30 days
(OR, 1.6; 95% CI, 1.04–2.5; P=0.03; Figure 5). Repeating
these analyses after the exclusion of patients who had cardiac

Factors Associated With Incident
Cardiac Complications
Characteristics of patients who developed and did not
develop incident cardiac complications are presented in Table 1.
Although 22 of these factors had significant associations with
incident cardiac complications in univariable analysis, only
13 remained independently associated with the outcome in
our multivariable model. These factors consisted of older age,
nursing home residence, 4 preexisting cardiovascular condi-
tions (history of heart failure, prior coronary arrhythmias,
previously diagnosed coronary artery disease, and arterial
hypertension), respiratory rate ≥30 breaths per minute, 5
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blood urea nitrogen ≥30 mg/dL, sodium <130 mmol/L,
Table 1. Comparison of Patients With Community-Acquired Pneumonia With and Without Incident Cardiac Complications*

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Patients With Cardiac Complications (n=378), %</th>
<th>Patients Without Cardiac Complications (n=1909), %</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean±SD, yrs</td>
<td>72±14</td>
<td>53±21</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Male</td>
<td>51</td>
<td>50</td>
<td>0.52</td>
</tr>
<tr>
<td>Nursing home residence</td>
<td>18</td>
<td>7</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Race</td>
<td>White</td>
<td>90</td>
<td>84</td>
</tr>
<tr>
<td></td>
<td>Black</td>
<td>9</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Preexisting comorbid conditions</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>40</td>
<td>5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>43</td>
<td>13</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Cardiac arrhythmias</td>
<td>33</td>
<td>7</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Cardiac valvular disease</td>
<td>11</td>
<td>3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>48</td>
<td>21</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>22</td>
<td>8</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>22</td>
<td>7</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>39</td>
<td>23</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Chronic renal insufficiency</td>
<td>18</td>
<td>5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Smoking</td>
<td>20</td>
<td>28</td>
<td>&lt;0.01</td>
</tr>
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</table>

Physical examination findings

<table>
<thead>
<tr>
<th></th>
<th>Patients With Cardiac Complications (n=378), %</th>
<th>Patients Without Cardiac Complications (n=1909), %</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Altered mental status</td>
<td>23</td>
<td>8</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Respiratory rate ≥30 breaths/min</td>
<td>32</td>
<td>10</td>
<td>0.10</td>
</tr>
<tr>
<td>Pulse ≥125 bpm</td>
<td>15</td>
<td>8</td>
<td>0.11</td>
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<tr>
<td>Systolic blood pressure</td>
<td>15</td>
<td>9</td>
<td>0.10</td>
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<tr>
<td>Blood urea nitrogen ≥30 mg/dL</td>
<td>13</td>
<td>2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Sodium ≥130 mmol/L</td>
<td>8</td>
<td>3</td>
<td>0.08</td>
</tr>
<tr>
<td>Glucose ≥250 mg/dL (14 mmol/L)</td>
<td>10</td>
<td>3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hematocrit &lt;30%</td>
<td>14</td>
<td>5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>PO2 &lt;60 mm Hg or O2 sat &lt;90 mm Hg</td>
<td>41</td>
<td>16</td>
<td>0.01</td>
</tr>
<tr>
<td>Pleural effusion on chest x-ray</td>
<td>19</td>
<td>8</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>8</td>
<td>4</td>
<td>0.25</td>
</tr>
<tr>
<td>Site of care</td>
<td>Inpatient</td>
<td>95</td>
<td>52</td>
</tr>
<tr>
<td></td>
<td>Outpatient</td>
<td>5</td>
<td>48</td>
</tr>
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</table>

Pneumonia Severity Index score

<table>
<thead>
<tr>
<th></th>
<th>Total score, mean±SD†</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>114±35</td>
<td>63±37</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

*Incident cardiac complications included any of the following cardiac events: new or worsening heart failure, new or worsening arrhythmias, or myocardial infarction. †Mean ± SD.

Table 2. Factors Associated With the Development of Incident Cardiac Complications in Patients With Community-Acquired Pneumonia (Multivariable Model)*

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.03 (1.02–1.04)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Nursing home residence</td>
<td>1.8 (1.2–2.9)</td>
<td>0.01</td>
</tr>
<tr>
<td>Preexisting comorbidities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>4.3 (3.0–6.3)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>1.8 (1.2–2.7)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>1.5 (1.0–2.0)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

*Incident cardiac complications included any of the following cardiac events: new or worsening heart failure, new or worsening arrhythmias, or myocardial infarction. OR indicates odds ratio; CI, confidence interval.

Discussion

Using high-quality clinical outcomes data from the Pneumonia PORT cohort study, we demonstrate the following: (1) Incident cardiac complications occur in a substantial proportion of patients with CAP, affecting more than one quarter of those hospitalized for this infection; (2) the great majority of CAP patients who develop incident cardiac complications have their primary cardiac event within 7 days of presentation, with >50% occurring the same day of CAP diagnosis; (3) current tools for risk stratification of CAP patients underestimate the risk of incident cardiac complications in a large number of cases; and (4) the development of incident cardiac complications is independently associated with a 60% increase in the risk of short-term mortality in patients with CAP.

Given the burden of CAP in our population,1 2 our findings have important implications. First, clinicians need to realize the importance of incident cardiac complications in patients with CAP and exercise appropriate clinical alertness for their complications or died the same day of presentation with CAP yielded consistent results both before (OR, 4.4; 95% CI, 2.7–7.2; P<0.01) and after (OR, 2.4; 95% CI, 1.4–4; P<0.01) adjustment for PSI risk score.
timely recognition, mainly during the week after the diagnosis of CAP but especially in the first 24 hours of this period. Second, health officials need to increase efforts to optimize the rates of influenza and pneumococcal vaccination among the elderly and those with chronic cardiac conditions to reduce the incidence of pneumonia in these high-risk groups. Third, further research is required to test risk stratification, prevention, and treatment strategies for incident cardiac complications in patients with CAP. Finally, the prevention and optimal management of these events may significantly reduce the burden of death associated with this infection.

Several characteristics distinguish our analysis from previous studies dealing with cardiac complications in CAP. As summarized in Table 3, these retrospective studies involved heterogeneous populations, used diverse methodologies for ascertaining the exposure (CAP) and outcomes (cardiac events) of interest, and defined different lengths for their observation periods. It is likely that most of the variability in their reported rates of cardiac events is explained by these factors. In contrast, our study represents the first analysis of prospectively collected data on incident cardiac complications in patients with CAP. It involved a large multicenter cohort of unselected individuals enrolled only after careful evaluation of clinical and radiological evidence of pneumonia. The ascertainment of incident cardiac complications was based on prespecified clinically relevant definitions and was systematically carried out for all patients; accordingly, the rate of missing data for these outcomes was extremely low (≤2% for the entire cohort). Importantly, our study is also the first involving both inpatients and outpatients, capturing the burden of incident cardiac complications across the full spectrum of CAP severity, and the first in which a detailed account of the timing of these events is possible.

Several mechanisms, related largely to the systemic response to infection, can account for the development of incident cardiac complications in patients with CAP. Acute systemic inflammation can directly depress myocardial func-

Figure 4. Association of Pneumonia Severity Index (PSI) risk classes and score and incident cardiac complications in patients with community-acquired pneumonia (CAP). Incident cardiac complications included any of the following cardiac events: new or worsening heart failure, new or worsening arrhythmias, or myocardial infarction. †Association was adjusted for all baseline characteristics not included in the calculation of PSI score (ie, race, previously diagnosed coronary artery disease, cardiac arrhythmias, cardiac valvular disease, arterial hypertension, diabetes mellitus, chronic obstructive pulmonary disease, current smoking, and bacteremia). Dotted lines represent the 95% confidence interval.

Figure 5. The 30-day mortality risk in patients with community-acquired pneumonia who developed incident cardiac complications vs those who did not. Incident cardiac complications included any of the following cardiac events: new or worsening heart failure, new or worsening arrhythmias, or myocardial infarction. PSI indicates Pneumonia Severity Index; OR, odds ratio; and CI, confidence interval.
Hypoxemia decreases myocardial oxygen delivery and raises pulmonary arterial pressure and right ventricular afterload.\textsuperscript{20,21} Tachycardia increases myocardial oxygen needs and shortens diastole (when coronary perfusion occurs).\textsuperscript{22,23} The net effect is a negative shift of the cardiac metabolic supply-to-demand ratio and further myocardial dysfunction. Myocardial inflammation (myocarditis) may also play a role.\textsuperscript{24} Acute infections can promote inflammatory activity within coronary atherosclerotic plaques and induce prothrombotic changes in the blood and endothelium, resulting in plaque instability and facilitating coronary thrombosis.\textsuperscript{9} Preexisting coronary artery disease that is insufficient to produce myocardial ischemia under baseline conditions can also result in significant ischemia in the face of increased myocardial oxygen demand. The ability of pneumonia to cause acute abnormalities in the cardiac conduction system has been recognized since the early 20th century and consistently confirmed thereafter.\textsuperscript{25,26} In concordance with our findings, these effects would be more prominent when the influence of the pneumonia is stronger (ie, the first few days after CAP diagnosis). The concept of the systemic response to infection as a key element in the pathophysiology of cardiac complications in patients with CAP is further supported by the facts that 84\% of those who developed cardiac complications in our cohort had, by definition (at least two of the following: temperature $>$38.5°C or $<$35°C, heart rate $>$90 bpm, respiratory rate $>$20 breaths per minute, and white blood cell count $>$12,000 or $<$4,000 per 1 mm$^3$),\textsuperscript{27} signs of sepsis at presentation and that cardiac complications were more common in patients with sepsis than in those without it (Tables II and III in the online-only Data Supplement).

Previous studies have treated the different types of cardiac events that occur in CAP largely as unrelated clinical outcomes.\textsuperscript{11–14,19} However, given the likely mechanisms at play, it is expected that their development is interrelated. Musher et al\textsuperscript{10} were the first to document that many patients with pneumonia have $>$1 type of cardiac event during the course of their infection. In our cohort, this phenomenon was observed in one quarter of those who developed incident cardiac complications. Furthermore, about one sixth of the cases of new or worsening heart failures, one third of the cases of new or worsening arrhythmias, and more than two thirds of the cases of MIs were recognized the same day as or at least 1 day after another cardiac event was diagnosed. Together with the fact that the management of these events often involves common and/or interrelated strategies, these observations strongly favor an integrative approach to the evaluation of incident cardiac complications in the setting of CAP.

Our study identifies specific factors associated with the occurrence of incident cardiac complications in CAP patients. These factors are markers of higher baseline general risk (age and nursing home residence), increased cardiovascular risk (history of heart failure, prior cardiac arrhythmias, previously diagnosed coronary artery disease, and arterial hypertension), and more severe pneumonia at presentation (respiratory rate $\geq$30 breaths per minute, blood pH $<$7.35, blood urea nitrogen $\geq$30 mg/dL, sodium $<$130 mmol/L, hematocrit $<$30\%, pleural effusion on chest x-ray, and need for inpatient care), which is concordant with previous reports.\textsuperscript{12–14} The PSI, the most widely validated tool for disease severity assessment in CAP patients,\textsuperscript{16,17} incorporates most of these factors (except for history of prior cardiac arrhythmias, previously diagnosed coronary artery disease, and arterial hypertension). Ramirez et al\textsuperscript{12} showed a significant correlation between PSI score and the risk of MI in hospitalized veterans with pneumonia; our study now extends this association to other cardiac events and beyond that high-risk population. More important, however, is our finding that incident cardiac complications affect not only patients within high-risk PSI classes (IV–V) but also clinically meaningful proportions of patients otherwise considered to be at low risk by this parameter (PSI risk classes

---

Table 3. Previous Studies of Incident Cardiac Complications in Patients With Community-Acquired Pneumonia

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>n</th>
<th>Population</th>
<th>Design</th>
<th>Diagnosis of CAP</th>
<th>Method Used to Ascertain Cardiac Events</th>
<th>Follow-Up</th>
<th>Incidence of Cardiac Complications, %</th>
<th>Overall Cardiac Complications</th>
<th>Heart Failure</th>
<th>Arrhythmias</th>
<th>MI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Musher et al\textsuperscript{10}</td>
<td>2007</td>
<td>170</td>
<td>Inpatient veterans</td>
<td>Retrospective single center</td>
<td>Clinical symptoms and chest x-ray infiltrate</td>
<td>Chart review</td>
<td>In hospital</td>
<td>19.4</td>
<td>14.7</td>
<td>5.9</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Becker et al\textsuperscript{11}</td>
<td>2007</td>
<td>391</td>
<td>Inpatient diabetics</td>
<td>Retrospective multicenter</td>
<td>ICD-9 codes and chest x-ray infiltrate</td>
<td>Chart review</td>
<td>In hospital</td>
<td>17.4</td>
<td>12.3</td>
<td>2.8\textsuperscript{†}</td>
<td>7.9</td>
<td></td>
</tr>
<tr>
<td>Ramirez et al\textsuperscript{12}</td>
<td>2008</td>
<td>500</td>
<td>Inpatient veterans</td>
<td>Retrospective single center</td>
<td>Clinical symptoms and chest x-ray infiltrate</td>
<td>Chart review</td>
<td>In hospital</td>
<td>5.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corrales-Medina et al\textsuperscript{14†}</td>
<td>2009</td>
<td>206</td>
<td>Inpatient veterans</td>
<td>Retrospective single center</td>
<td>Clinical symptoms and chest x-ray infiltrate</td>
<td>Chart review</td>
<td>In hospital</td>
<td>15 d</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perry et al\textsuperscript{14}</td>
<td>2011</td>
<td>50 119</td>
<td>Inpatient veterans</td>
<td>Retrospective multicenter</td>
<td>ICD-9 codes</td>
<td>ICD-9 codes</td>
<td>30 d</td>
<td>9.1\textsuperscript{¶}</td>
<td>8.4\textsuperscript{¶}</td>
<td>1.2\textsuperscript{¶}</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mandal et al\textsuperscript{14}</td>
<td>2011</td>
<td>4408</td>
<td>Inpatient adults</td>
<td>Retrospective multicenter</td>
<td>ICD-10 codes and chest x-ray infiltrate</td>
<td>Chart review</td>
<td>In hospital</td>
<td>9.3\textsuperscript{¶}</td>
<td>3.2\textsuperscript{¶}</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CAP indicates community-acquired pneumonia; MI, myocardial infarction; ICD-9, International Classification of Disease, ninth revision; and ICD-10, International Classification of Disease, 10th revision.

\textsuperscript{*}Limited to cases of pneumococcal pneumonia.

\textsuperscript{†}Included cases of pneumococcal pneumonia from Musher et al\textsuperscript{10} and cases of Haemophilus influenza pneumonia.

\textsuperscript{‡}Atrial fibrillation only.

\textsuperscript{¶}Included MI and unstable angina.

\textsuperscript{¶¶}Included only new cardiac events in patients without a previous history of these conditions.
I–III). Consequently, an adequate estimation of the risk of incident cardiac complications in CAP patients will likely require of new strategies that, in addition to currently available tools for risk estimation in this population (ie, PSI), adequately weigh other factors such as those associated with cardiac events in our analyses. Cardiac biomarkers with recently proved predictive value in CAP (eg, C-reactive protein, serum troponins, and natriuretic peptides) should also be considered.28,29 These strategies may be especially valuable in identifying those CAP patients who develop incident cardiac complications despite the absence of a history of cardiac disease at presentation (one third of CAP patients with incident cardiac complications in our cohort).

Although CAP is a leading cause of death, little consideration has been given to understanding the contributors to this mortality. Only 2 previous studies have suggested an increased mortality in CAP patients who develop cardiac complications, but those analyses did not adjust for baseline mortality risk.10,19 Initially validated in our cohort,16 the PSI is the most comprehensive and sensitive tool for predicting short-term mortality on presentation with CAP.30 In our analysis, the development of incident cardiac complications was associated with a substantial increase (60%) in the risk of death at 30 days, even after adjustment for patients’ PSI scores, opening the possibility of decreasing the mortality associated with CAP by preventing and optimally managing these events. It is important to note, however, that cardiac events are not the only medical complications that occur in patients with CAP and that our mortality analysis did not account for possible interactions between incident cardiac complications and other important acute medical events that also occur in this population (ie, acute renal failure and respiratory failure).31 Such complex competing-risk analyses are beyond the scope of this work and should be the center of future research.

Our study has limitations. Although the definition of incident heart failure used in our study required the concomitant presence of clinical and radiographic signs consistent with this diagnosis, it is likely that a degree of misclassification still occurred as a result of the overlapping manifestations of heart failure and pneumonia. In this setting, a more accurate characterization of CAP-associated incident heart failure and its pathophysiology (ie, systolic versus diastolic) will likely need prospective studies in which the diagnosis of heart failure is also assisted by cardiac biomarkers (ie, brain natriuretic peptide) and/or echocardiographic or other cardiac imaging–based measurements. Likewise, the diagnosis of MI was not aided by the measurement of troponins, biomarkers of myocardial injury currently used in clinical practice that are more sensitive than creatine phosphokinase-MB for the diagnosis of MI. Consequently, we may have underestimated the true incidence of this outcome. In addition, the management of chronic conditions that predispose to acute cardiac events (coronary artery disease, chronic heart failure, chronic arrhythmias, hypertension, among others) has improved since the time that the PORT study was conducted, and it is possible that some of the events that we observed could have been prevented under current circumstances. Likewise, the acute management of the cardiac events that are the focus of this analysis has advanced after the PORT study was completed, especially for MI, and the impact of these events on the short-term mortality associated with pneumonia could currently be less prominent. Finally, time to antibiotic administration and appropriate empirical antibiotic therapy, well-recognized factors affecting the outcomes of patients with CAP, were not available for our analyses. Nevertheless, the facts that the definitions used in this study are clinically valid, that the outcomes were systematically and carefully sought, and that the procedures and findings from the pneumonia PORT study have been and continue to be widely validated around the globe17 provide reassurance for the validity of our results.

Conclusions

Our study demonstrates that incident cardiac complications are common in the course of CAP and have an independent impact on its short-term mortality. Our findings provide further support of the importance of increasing efforts to reduce the incidence of pneumonia in high-risk populations through influenza and pneumococcal vaccination. They also present a potential opportunity for interventions that should be tested in future studies. Such interventions should stem from a better understanding of the mechanisms involved in the occurrence of these events in CAP patients. Drugs with known beneficial cardiovascular effects such statins and aspirin, recently linked to improved outcomes in patients with CAP,32,33 should be looked at more exhaustively in relation to their possible effects in preventing the occurrence of incident cardiac complications in this population. The development of tools for optimal identification of patients with CAP at risk for cardiac events should greatly facilitate these processes.

Sources of Funding

The PORT study was funded by the Agency for Healthcare Research and Quality. Dr Corrales-Medina is supported by a research priority grant from the Department of Medicine of the Ottawa Hospital and a Junior Investigator Award from the Ottawa Hospital Research Institute.

Disclosures

None.

References

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CLINICAL PERSPECTIVE

Community-acquired pneumonia (CAP) is a common infection and a leading cause of morbidity and mortality that tends to occur in patients at high cardiovascular risk (ie, the elderly, smokers, diabetics, patients with chronic cardiac conditions). Community-acquired pneumonia can trigger acute cardiac complications. This study analyzed a prospective cohort of 2287 patients with community-acquired pneumonia in whom the 30-day incidence of cardiac complications was investigated. New or worsening heart failure, new or worsening arrhythmias, and myocardial infarction occurred in 20.8%, 11%, and 3% of inpatients and in 1.4%, 1%, and 0.1% of outpatients, respectively. Several patients had more than one of these conditions. Overall, cardiac complications (1 or more of the cardiac events above) were diagnosed in 27% and 2% of inpatients and outpatients, respectively. A majority of cardiac complications in both groups (89% inpatients and 75% outpatients) were diagnosed within the first week, more than half of them in the first 24 hours. Risk factors for cardiac complications included older age, nursing home residence, preexisting cardiovascular disease, and pneumonia severity. The occurrence of cardiac complications was associated with an adjusted 60% increase in risk of death at 30 days. Clinicians must recognize the burden of cardiac complications in patients with community-acquired pneumonia and exercise appropriate clinical alertness for their timely recognition. Rates of influenza and pneumococcal vaccination in groups of high cardiac risk need to be optimized. Further research to test risk stratification, prevention, and treatment strategies for incident cardiac complications in patients with community-acquired pneumonia may reduce the burden of death associated with this infection.

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Cardiac Complications in Patients With Community-Acquired Pneumonia: Incidence, Timing, Risk Factors, and Association With Short-Term Mortality
Vicente F. Corrales-Medina, Daniel M. Musher, George A. Wells, Julio A. Chirinos, Li Chen and Michael J. Fine

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**SUPPLEMENTAL MATERIAL**

**Supplementary Table 1:** Baseline characteristics of inpatients and outpatients with community acquired pneumonia (CAP)

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Inpatients (n = 1343) %</th>
<th>Outpatients (n=944) %</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean years ± SD †</td>
<td>64±19</td>
<td>45±18</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Male</td>
<td>52</td>
<td>47</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Nursing home residence</td>
<td>14</td>
<td>1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>86</td>
<td>84</td>
<td>0.01</td>
</tr>
<tr>
<td>Black</td>
<td>12</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td><strong>Pre-existing comorbid conditions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>17</td>
<td>3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>26</td>
<td>6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Cardiac arrhythmias</td>
<td>17</td>
<td>2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Cardiac valvular disease</td>
<td>6</td>
<td>2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>35</td>
<td>13</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>15</td>
<td>4</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>14.</td>
<td>2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>34</td>
<td>14</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Chronic renal insufficiency</td>
<td>10</td>
<td>2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Smoking</td>
<td>26</td>
<td>29</td>
<td>0.14</td>
</tr>
<tr>
<td>Physical-examination findings</td>
<td></td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
<td>----</td>
<td>----</td>
<td>------</td>
</tr>
<tr>
<td>Altered mental status</td>
<td>17</td>
<td>1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Respiratory rate ≥30/min</td>
<td>23</td>
<td>1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Pulse ≥125/min</td>
<td>13</td>
<td>3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Systolic blood pressure &lt;90 mm Hg or diastolic blood pressure &lt;60 mm Hg</td>
<td>13</td>
<td>5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Temperature &lt;35 °C or ≥40°C</td>
<td>2</td>
<td>1</td>
<td>0.01</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Laboratory and radiographic findings</th>
<th></th>
<th></th>
<th>&lt;0.01</th>
</tr>
</thead>
<tbody>
<tr>
<td>PH &lt; 7.35</td>
<td>6</td>
<td>0.1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Blood urea nitrogen ≥30 mg/dl</td>
<td>24</td>
<td>1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Sodium &lt; 130 mmol/liter</td>
<td>6</td>
<td>1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Glucose ≥ 250 mg/dl (14 mmol/liter)</td>
<td>7</td>
<td>1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hematocrit &lt; 30%</td>
<td>10</td>
<td>1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>pO2 &lt; 60 mm Hg or O2sat &lt; 90 mm Hg</td>
<td>34</td>
<td>1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Pleural effusion on chest-X-ray</td>
<td>13</td>
<td>4</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pneumonia Severity Index Score</th>
<th></th>
<th></th>
<th>&lt;0.01</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total score mean ± SD †</td>
<td>92±39</td>
<td>43±23</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

† SD: Standard deviation
**Supplementary Table 2:** Prevalence of sepsis at presentation in patients with CAP who developed cardiac complications

<table>
<thead>
<tr>
<th>Sepsis status at admission</th>
<th>Overall cardiac complications (n= 378)</th>
<th>Incident heart failure (n= 292)</th>
<th>Cardiac arrhythmias (n= 146)</th>
<th>Myocardial infarction (n= 44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis at admission</td>
<td>319 (84%)</td>
<td>247 (85%)</td>
<td>126 (86%)</td>
<td>40 (91%)</td>
</tr>
<tr>
<td>No sepsis at admission</td>
<td>59 (16%)</td>
<td>45 (15%)</td>
<td>20 (14%)</td>
<td>3 (9%)</td>
</tr>
</tbody>
</table>

All differences in the prevalence of sepsis for each of the cardiac complications above were statistically significant (p <0.01).

Sepsis was defined as the presence of ≥2 of the following: temperature >38.5°C or <35°C, heart rate >90, respiratory rate >20, and WBC >12000 or < 4000)², signs of sepsis at presentation.
Supplementary Table 3: Incidence of cardiac complications in patients with CAP with and without sepsis at presentation

<table>
<thead>
<tr>
<th>CAP patients by sepsis status at admission</th>
<th>Overall cardiac complications</th>
<th>Incident heart failure</th>
<th>Cardiac arrhythmias</th>
<th>Myocardial infarction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis at admission (n=1449)</td>
<td>319 (22%)</td>
<td>247 (17%)</td>
<td>126 (9%)</td>
<td>40 (3%)</td>
</tr>
<tr>
<td>No sepsis at admission (n= 838)</td>
<td>59 (7%)</td>
<td>45 (5%)</td>
<td>20 (2%)</td>
<td>3 (0.4%)</td>
</tr>
</tbody>
</table>

All differences in the incidence of cardiac complications between those who had sepsis and those who did not, were statistically significant (p <0.01).

Sepsis was defined as the presence of ≥2 of the following: temperature >38.5°C or <35°C, heart rate >90, respiratory rate >20, and WBC >12000 or < 4000)², signs of sepsis at presentation.