Acute Pulmonary Embolism Is an Independent Predictor of Adverse Events in Severe Decompensated Heart Failure Patients*

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Background: **Congestive heart failure (CHF) is a well-recognized risk factor for venous thromboembolism (VTE) and is associated with higher mortality in patients with an acute pulmonary embolism (PE). There are very few data on how acute PE affects the clinical course of patients with heart failure. The purpose of this study was to determine the impact of an acute PE on the short-term prognosis of patients hospitalized for decompensated CHF.**

Methods: **This was a prospective cohort study of 198 patients admitted to a coronary care unit between July 2001 and March 2003 with severe decompensated CHF. The primary outcome measure was death or rehospitalization at 3 months.**

Results: **PE was confirmed in 18 of 198 patients enrolled (9.1%). The groups with and without PE were comparable with regards to demographics, the prevalence of comorbid conditions, and severity of CHF ($p > 0.05$). The prevalence of cancer ($p = 0.0001$), previous VTE ($p = 0.003$), and right ventricular overload ($p = 0.006$) was higher in the PE group. The presence of PE was also associated with a longer hospital stay (37.5 ± 71.6 days vs 15.4 ± 15.0 days, $p = 0.001$) [mean ± SD] and a higher incidence of death or rehospitalization at 3 months (72.2% vs 43.9%, $p = 0.02$). In a multiple logistic regression analysis, PE remained an independent predictor of death or rehospitalization at 3 months (odds ratio, 4.0; 95% confidence interval, 1.1 to 15.1; $p = 0.038$).**

Conclusions: **Acute PE commonly complicates the hospital course of patients with severe CHF, increasing the length of hospital stay and the chance of death or rehospitalization at 3 months.**

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Key words: congestive heart failure; ICU; mortality; pulmonary embolism

Abbreviations: CCU = coronary care unit; CHF = congestive heart failure; CI = confidence interval; NYHA = New York Heart Association; OR = odds ratio; PE = pulmonary embolism; VTE = venous thromboembolism

Venous thromboembolism (VTE) and congestive heart failure (CHF) are among the most commonly encountered conditions in hospitalized patients,[1,2] and each of them contribute to the significant morbidity and mortality observed in this population.[1,3,4] Heart failure is an important risk factor for VTE in ambulatory[5] and hospitalized[6] patients, and a particularly high incidence of VTE has been documented in patients with severe decompensated CHF.[7]

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In the largest pulmonary embolism (PE) registry[8] and in other cohort studies,[9] the presence of CHF has been consistently associated with a higher mortality. In the International Cooperative Pulmonary Embolism Registry,[8] the prevalence of CHF was 11%, and on multiple regression modeling it was found to be a significant prognostic factor, more than doubling the chance of death (hazard ratio, 2.4). The impact of PE, however, on the clinical course of CHF patients is not known. The goal of the current study was to address this issue in a population of hospitalized patients with severe heart failure.

Materials and Methods

Patient Population

We prospectively enrolled consecutive patients admitted to our coronary care unit (CCU) with the diagnosis of CHF between July 2001 and March 2003. After the evaluation of the on-call physician, two investigators reviewed the clinical data in order to ascertain the diagnosis of CHF in patients before entering the study. Patients were excluded if they had an acute ST-segment elevation myocardial infarction and if they had a different admitting diagnosis despite having a history of CHF. All clinical and demographic data were collected directly from the patient, family member, attending physician, or chart. The enrolled patients were followed on a daily basis until hospital discharge. Three months after enrollment, the patients were contacted by telephone in order to obtain information regarding the combined end-point of death or rehospitalization. This study complies with the Declaration of Helsinki, was approved by the research ethics committee, and written informed consent was obtained from all patients.

Definitions

Confirmed PE was defined as any level of clinical suspicion associated with the following: (1) high-probability lung scintigraphy[10] (two or more large segmental mismatches, or one large plus two or more moderate mismatches, or four or more moderate mismatches); or (2) positive spiral CT of the chest[11] (presence of a hypoattenuating intraluminal filling defect in a pulmonary artery); or (3) positive conventional pulmonary angiography. Investigation for PE was initiated at the discretion of the attending physician. A total of 36 patients were investigated, and 18 had the diagnosis of PE confirmed. The other 18 patients had non–high-probability lung scans or negative chest CT findings. The only other imaging modality used in these patients was Doppler ultrasonography, and none had confirmed deep vein thrombosis. These patients were included in the group without PE and were observed for 3 months.

Cancer was considered to be present only if it had been treated within the last 6 months, or the patient was receiving palliative care. Acute renal failure was defined as an elevation in the creatinine concentration during hospitalization to ≥ 1.5 mg/dL with previously normal creatinine levels, or a 25% increase compared to the baseline values. Anemia was defined according to the World Health Organization criteria: hemoglobin < 12.0 g/dL for female patients and < 13.0 g/dL for male patients, and hyponatremia defined as a sodium level < 136 mEq/L. The New York Heart Association (NYHA) functional class referred to the patient status 3 weeks prior to the index admission.

Statistical Analysis

The comparisons between the groups with and without PE were performed using the unpaired Student *t* test for continuous variables and χ^2 test for categorical variables. All values were expressed as mean ± SD or as frequency (%).

A multiple logistic regression analysis was conducted in order to identify independent predictors of the primary combined end point of death or rehospitalization at 3 months. The secondary end points were death at 3 months, rehospitalization at 3 months, and length of hospital stay. All clinical end points were defined prospectively. In case both end points or repeated rehospitalizations were present, only one end point was counted. Continuous variables were categorized at clinically relevant cut points. Variables with significant univariate associations with the combined end point ($p < 0.1$) or variables thought to be clinically important were included in a multivariate model. A p value < 0.05 was considered significant. Statistical analysis was performed using statistical software (SPSS for Windows version 10; SPSS; Chicago, IL).

Results

During the study period, 223 patients were admitted to the CCU with a diagnosis of CHF. A total of 25 patients were excluded for the following reasons: acute ST-segment elevation myocardial infarction (n = 14), and unconfirmed diagnosis of CHF (n = 11) The study population was comprised of 198 patients, and general characteristics of the population according to the presence of PE are presented on Table 1. Mean age (68.2 ± 14.1 years vs 69.6 ± 13.4 years, p = 0.67) and the prevalence of male gender (61.1% vs 55.0%, p = 0.62) were similar in the groups with and without PE, as was the prevalence of comorbid conditions. Overall, this was a population with severe CHF as demonstrated by a high prevalence of severe left ventricular dysfunction (38.9% vs 42.1%; p = 0.79), poor functional class at baseline (NYHA class III/IV, 55.6% vs 55.0%; p = 0.96), hyponatremia (33.3% vs 21.1%; p = 0.23), and prior hospitalizations for CHF (64.7% vs 71.2%; p = 0.56). The prevalence of risk factors for VTE such as cancer (p = 0.0001), previous VTE (p = 0.003), and immobilization (p = 0.018) was higher in the PE group. Right ventricular overload was also significantly more frequent in the PE group (p = 0.006).

The diagnosis of PE was confirmed in 18 of 198 patients (9.1%) during their hospitalization period. The diagnostic methods utilized were lung scintigraphy in 14 patients (78%) and spiral CT in 4 patients (22%). Doppler ultrasonography demonstrated deep vein thrombosis in 8 of 18 patients (44.4%) with PE: seven cases involving the lower extremities, and one subclavian vein thrombosis. The majority of PE patients had their diagnosis confirmed within 5 days of hospital admission (67%). After the diagnosis, all patients received anticoagulation with therapeutic

Table 1—*Patient Characteristics According to the Presence of PE

Characteristics	PE (n = 18)	No PE (n = 180)	p Value
Age, yr	68.2 (14.1)	69.6 (13.4)	0.67
Male gender	61.1	55.0	0.62
Comorbid conditions			
Diabetes	33.3	33.9	0.96
Hypertension	66.7	79.8	0.20
Chronic renal failure	33.3	31.1	0.85
Anemia†	61.1	50.6	0.39
Cerebrovascular disease	16.7	15.0	0.85
Atrial fibrillation	16.7	26.0	0.39
COPD	16.7	5.0	0.05
Smoking	38.9	28.8	0.37
CHF severity			
Ischemic etiology	55.6	53.9	0.89
Ejection fraction < 30%	38.9	42.1	0.79
Restrictive pattern on mitral inflow	33.3	28.7	0.68
NYHA functional class III-IV‡	55.6	55.0	0.96
Na < 136 mEq/L	33.3	21.1	0.23
Previous hospitalization for CHF	64.7	71.2	0.56
Right ventricular overload§	61.1	29.1	0.006
VTE risk factors			
Cancer‖	33.3	2.8	< 0.0001
Previous VTE	22.2	4.5	0.003
Obesity (body mass index > 30 kg/m^2)	5.6	13.6	0.33
Surgery within 1 mo	5.6	1.7	0.27
Immobilization¶	16.7	2.2	0.018
VTE prophylaxis (enoxaparin, 40 mg/d)	66.7	70.0	0.77
In-hospital clinical events			
Acute renal failure#	55.6	44.45	0.37
Hospital death	33.3	21.7	0.26
Length of hospitalization, d	37.5 (71.6)	15.4 (15.0)	0.001

*Data are presented as mean (SD) or %.
†Hemoglobin < 12.0 g/dL for female patients and < 13.0 g/dL for male patients.
‡Three weeks prior to hospital admission.
§Echocardiographically documented right ventricular dilatation and/or systolic dysfunction.
‖Treated within 6 months or receiving palliative care.
¶Not able to ambulate during the hospitalization period.
#Creatinine levels > 1.5 mg/dL or a 25% increase compared to the baseline values.

doses of heparin, and one patient received an inferior vena cava filter. No patients received thrombolytic therapy.

The rates of clinical events according to the presence of PE are shown in Table 1 and Figure 1. At 3 months, the PE group presented a higher mortality rate (50.0% [95% confidence interval (CI), 26.8 to73.2%] vs 30.6% [95% CI, 24.0 to 37.9%], p = 0.09) and rehospitalization rates (58.3% [95% CI, 28.6 to 83.5%] vs 24.1% [95% CI, 17.5 to 32.2%], p = 0.01). The incidence of the combined end point of death or rehospitalization at 3 months was significantly higher in the group with PE (72.2% [95% CI, 46.4 to 89.3%] vs 43.9% [95% CI, 36.6 to 51.5%], p = 0.02). The mean length of hospitalization was 37.5 ± 71.6 days in the PE group and 15.4 ± 15.0 days in the group without PE (p = 0.001).

Table 2 shows the results of the univariate analysis for potential predictors of the combined end point of death and rehospitalization at 3 months. The presence of PE was significantly associated with the combined end point, and remained an independent predictor in a multiple logistic regression analysis (odds ratio [OR], 4.0; 95% CI, 1.1 to 15.1; p = 0.038) [Table 3]. Other significant predictors of the combined end point were cerebrovascular disease (p = 0.004), prior hospitalization for CHF (p = 0.002), hyponatremia (p = 0.002), and acute renal failure (p = 0.003).

Discussion

To the best of our knowledge, this is the first study to demonstrate that acute PE adversely affects the short-term clinical course of hospitalized patients with CHF, increasing the length of hospital stay and the chance of the combined end point of death or rehospitalization at 3 months.

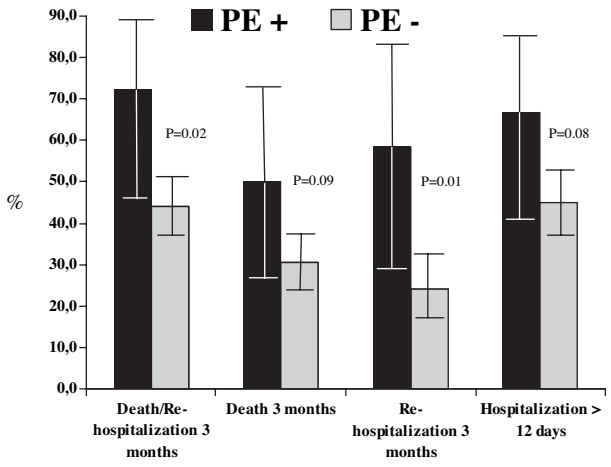

FIGURE 1. Clinical events according to the presence of PE.

The interaction between CHF and VTE is bidirectional and has multiple facets. With 550,000 new cases a year only in the United States, CHF is the most common admitting diagnosis in patients > 60 years old.[1] The disease process induces a number of rheologic alterations that lead to a chronic hypercoagulable state, which in association with venous stasis and reduced mobility places the patients at increased risk for VTE.[12] The elevated risk of VTE in CHF patients has been confirmed in clinical[7] and autopsy studies.[13] Additionally, it is also known that CHF is an independent predictor of mortality in patients with PE, as shown in large cohort studies.[8,9]

Table 2—*Univariate Predictors of Death or Rehospitalization at 3 Months*

Variables	OR (95% CI)	p Value
Age > 70 yr	1.62 (0.92–2.85)	0.097
Male gender	1.17 (0.67–2.05)	0.598
Aspirin use	0.43 (0.24–0.76)	0.0004
Comorbid conditions		
Hypertension	0.70 (0.35–1.37)	0.298
Diabetes	1.30 (0.72–2.34)	0.388
COPD	3.71 (0.98–14.15)	0.054
Anemia	1.87 (1.06–3.29)	0.031
Cerebrovascular disease	3.85 (1.62–9.15)	0.002
Chronic renal failure	1.80 (0.98–3.30)	0.058
Atrial fibrillation	1.37 (0.72–2.62)	0.341
Smoking	1.43 (0.80–2.73)	0.218
Cancer	1.40 (0.42–4.79)	0.580
CHF severity		
NYHA functional class III/IV	1.56 (0.88–2.74)	0.126
Ejection fraction < 30%	1.28 (0.72–2.26)	0.395
Restrictive pattern on mitral inflow	1.69 (0.90–3.19)	0.103
Ischemic etiology	1.21 (0.69–2.11)	0.514
Hyponatremia (Na < 136 mEq/L)	3.60 (1.76–7.49)	< 0.0001
Previous hospitalization	3.49 (1.77–6.88)	< 0.0001
In-hospital complications		
PE	3.32 (1.14–9.78)	0.028
Acute renal failure	3.02 (1.69–5.39)	< 0.0001
Length of hospitalization > 12 d	2.44 (1.38–4.33)	0.002

Table 3—*Multiple Logistic Regression Analysis**

Variables	OR	95% CI	p Value
Cerebrovascular disease	4.1	1.6–10.9	0.004
PE	4.0	1.1–15.1	0.038
Hyponatremia	3.7	1.6–8.5	0.002
Previous hospitalization	3.4	1.6–7.6	0.002
Acute renal failure	2.7	1.4–5.3	0.003
COPD	4.0	0.9–18.1	0.075

*Hosmer-Lemenshow, p = 0.593.

However, the impact of a pulmonary thromboembolic event on the clinical course of CHF patients is not known. Probably due to diagnostic difficulties and low incidence of PE, the large CHF series never addressed this issue. In a previous publication,[7] we documented a very high incidence of PE in patients with severe decompensated CHF, and the current study is the result of the 3-month clinical follow-up of the same population. The mean number of days spent at the hospital was two times greater in the patients with PE. Since 67% of PE patients had their diagnosis confirmed within 5 days of hospital admission, PE was probably the cause rather than a consequence of the longer hospitalization period. We have also shown that even after adjustment for known prognostic variables, PE remained an independent predictor of clinical outcome. Specifically, COPD was significantly associated with the presence of PE and clinical outcomes. Nonetheless, PE maintained its association with a worse clinical outcome even after adjustment for the presence of COPD.

The understanding of the pathophysiologic events following an acute PE helps us explain its negative impact on the clinical course of CHF patients. The sudden increase in pulmonary pressures has multiple effects on right ventricle and left ventricle physiology. Initially, it results in right ventricular dilatation and dysfunction, leading to a reduction in cardiac output.[14] Left ventricular filling is also decreased as a consequence of leftward shift of the interventricular septum and pericardial constrain.[15] Systemic hypotension ensues leading to impaired coronary perfusion, which in association with the increase in wall stress and oxygen demand results in right ventricular ischemia and infarction.[16,17] This vicious circle may ultimately lead to cardiogenic shock and death. The severity of this pathophysiologic sequence depends mainly on the degree of pulmonary vascular obstruction and the patient's cardiopulmonary reserve.[18] Thus, in patients with CHF, especially those with coronary disease, even small pulmo-

nary emboli may lead to important hemodynamic consequences,[19,20] potentially triggering episodes of acute decompensation and some cases of sudden cardiac death.

A retrospective analysis of the Studies of Left Ventricular Dysfunction[21] prevention and treatment database revealed that PE represented 16% of all thromboembolic events, 38% of which were fatal. This is a much higher mortality rate when compared to that observed in the largest international PE registry (17.8%).[8] In an interesting study[22] consisting of 119 CHF patients who died after having an implantable cardioverter defibrillator placed, PE was the cause of death in 5 patients (4.2%). It is worth noting that the final rhythms were most commonly electromechanical dissociation and bradyarrhythmias, rhythms compatible with PE. Thus, this probably represents an underestimation of the real incidence of fatal PE. In another study[23] involving 62 pediatric patients with end-stage dilated cardiomyopathy awaiting transplant, PE developed in 6 patients and 4 died within 6 weeks of anticoagulation therapy.

The demonstration of a higher mortality and rehospitalization rate in CHF patients with PE has important clinical implications. First, given its high incidence, physicians should maintain a high index of suspicion for PE in hospitalized CHF patients with an unexplained exacerbation because early diagnosis and treatment may improve clinical outcomes. In the current study, 50% of patients in whom PE was suspected had their diagnosis confirmed, which is a much higher proportion compared to other series,[10] and confirms the high thromboembolic risk in this population. In fact, a major problem with the diagnosis of PE is the relatively low sensitivity of its diagnostic modalities.[10] Therefore, it is possible that some of our CHF patients may have had undiagnosed PE, which only reinforces the conclusion of this study that PE is a common and dangerous complication in hospitalized CHF patients.

Second, although long-term anticoagulation has never been shown to benefit CHF patients in sinus rhythm, additional studies are needed to evaluate the effect of treatment in a specific population of CHF patients at high risk for PE. We have identified important predictors of PE in this population, such as right ventricular dilatation and/or dysfunction, cancer, and previous VTE.[7]

Two obvious limitations of this study should be emphasized. Recruitment was conducted at a single center, and the population studied included a specific group of patients with severe decompensated CHF admitted to a CCU. Both facts limit the generalization of our results to a wider-ranging CHF population. Additionally, as an observational study, we did not have control over which patients were selected for a PE workup or the interpretation of their diagnostic tests. The diagnosis of PE was made using well-established published criteria,[10,11] and almost half of our PE patients had associated deep vein thrombosis. Given the high positive predictive value of the criteria utilized,[10,11] the only potential diagnostic problem would be underdiagnosing PE. As discussed above, this would only serve to strengthen our conclusions. We also believe that the potential biased selection of patients for a PE workup did not affect our results in any meaningful way because the groups with and without PE were comparable (Table 1), and any potential confounding was accounted for in the multivariate analysis.

Our study adds to the literature by demonstrating that PE is frequently encountered and adversely affects the clinical course of patients with severe CHF. Further studies are necessary to assess the value of routine testing for PE in patients with CHF exacerbations, and to define the role of long-term anticoagulation for the prevention of thromboembolic events in this high-risk population.

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