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Clinical paper

Pulmonary embolism related sudden cardiac arrest admitted alive at hospital: Management and outcomes☆

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ABSTRACT

Aim: Pulmonary Embolism (PE) is a relatively common cardiovascular condition, occasionally and tragically manifesting as Sudden Cardiac Arrest (SCA). The natural history of SCA complicating PE has been poorly evaluated.In this study, we described the management and outcome of PE-related SCA.
Methods: In this prospective population--based study, we included all patients admitted at hospital alive after out of hospital SCA, in Paris and suburbs, France (6.6 million inhabits), from May 2011 to September 2015.
Results: Of 2926 patients hospitalized after SCA, 82 cases were diagnosed as PE-related SCA (2.8%, 95%CI = 2.2–3.4). Systemic thrombolysis was performed in 47 patients (57%), without significant increased risk of major bleeding among patients treated with thrombolysis. 12 patients (15%) were treated with ECLS, 29 patients (36%) had targeted temperature management, and 20 patients (24%) underwent coronary angiography. 94% of PE-related SCA had initial non-shockable rhythm, and were associated with better survival compared with other non-shockable SCA (crude OR = 3.0, 95%CI = 1.7–5.4, P < 0.001; adjusted OR = 4.1, 95%CI 2.0–8.3, P < 0.001). Among PE-related SCA, thrombolysis was independently associated with survival (OR = 12.5, 95%CI = 1.8–89.1, P = 0.01). Multiple sensitivity analysis was performed, with consistent results.
Conclusions: PE is responsible of approximately 3% of hospitalizations for SCA. Thrombolysis was associated with an increased survival in this population, reinforcing current guidelines advocating for such treatment in PE-related SCA.

Abbreviations: CPC, Cerebral Performance Categories; CPR, cardio-pulmonary resuscitation; CTPA, computed tomography pulmonary angiogram; ECLS, extracorporeal life support; PE, pulmonary embolism; ROSC, return of spontaneous circulation; RV, right ventricular; SCA, sudden cardiac arrest; SDEC, Sudden Death Expertise Center; TTM, targeted temperature management.

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Introduction

Pulmonary embolism (PE) is the third most frequent cardiovascular disease, with an incidence of 10 per 10,000 person-year in Europe [1,2]. Clinical presentation varies from completely asymptomatic or insidious disease, to sudden cardiac arrest (SCA) [1,3]. PE-related SCA has been traditionally considered to have a particularly poor prognosis [4], although this is based on very limited evidence. Epidemiologic data regarding PE-related SCA remain scarce, especially because the diagnosis of PE in the setting of resuscitated SCA is challenging.

The use of thrombolysis in patients with high-risk PE (defined by the presence of shock or arterial hypotension) [1] is associated with a significant decrease in the risk of death or recurrent disease [5,6]. Thrombolytic therapy has not been shown to decrease the risk of death in patients presenting with out-of-hospital SCA [7,8], but specific data in PE-related SCA are lacking. Considering these areas of uncertainty, guidelines suggest the consideration of thrombolytic therapy when PE-related SCA is suspected [4,9], despite the absence of evidence. Selection of patients as candidates for thrombolysis remains challenging. Contemporary data about management of PE-related SCA are lacking.

In the present study, we aim to describe the management and prognosis of PE-related SCA in the community.

Materials and methods

Population and study setting

The Sudden Death Expertise Center (SDEC) registry has been previously described [10,11]. Briefly, it is a population-based registry, concerning Paris and its suburbs, including a residential population of approximately 6.6 million. According to definitions from recent guidelines [12], every case of out-of-hospital SCA (defined as unexpected death without obvious extra-cardiac cause) occurring in the area of interest, with age over 18 years, was included in the SDEC registry. To ensure completeness of collection, the SDEC registry was derived from an intensive and prospective epidemiologic case-finding program. An individual review of each case, by two investigators, was performed to ensure accuracy of classification. Appropriate review boards approved the registry.

In this study, all consecutive patients admitted alive after successfully resuscitated SCA, between 15th, May 2011 and 15th, September 2015 were included. Exclusion criteria were obvious extra-cardiac cause of cardiac arrest (trauma, drowning, drug overdose, electrocution, asphyxia from external cause) [12].

Data collection

Utstein templates for patient data collection were followed [13]. General data were prospectively collected, and included demographic characteristics, and location of the SCA (residential or public place). Data recorded about pre-hospital care included presence of bystander, bystander cardio-pulmonary resuscitation (CPR) before Emergency Medical Service arrival, presence of initial shockable rhythm (ie. ventricular fibrillation or ventricular tachycardia) before advanced life support, delivery of epinephrine during resuscitation, return of spontaneous circulation (ROSC), and survival until admission. The following data were recorded during hospitalization: targeted temperature management, coronary angiogram, use of extracorporeal life support (ECLS), specific treatment (systemic thrombolysis, catheter-directed thrombolysis, surgical embolectomy) [14,15], date of death or discharge from hospital, and neurologic status at discharge (according to Cerebral Performance Categories (CPC) score [16], considering a CPC score of 1 or 2 as a favorable outcome).

The diagnosis of PE was considered as definite [1,17,18] when either (i) CTPA identified acute PE; CTPAs were centrally reviewed by two investigators (GM and BP) to confirm diagnosis; (ii) Echocardiography (transthoracic or transesophageal) identified right ventricular (RV) overload or mobile thrombi in the right heart [18]; or (iii) post-mortem autopsy confirmed PE. Considering the limited specificity of RV overload on echocardiography, we performed a sensitivity analysis excluding patients with isolated RV overload from definite PE.

The diagnosis of PE was considered as probable in haemodynamically unstable patients with a high clinical probability of PE (patients with both simplified Wells rule $\geq$2 and simplified Geneva score $\geq$3 [1,19]), but without objective confirmation by either CTPA, echocardiography or autopsy.

Diagnosis of PE-related SCA was defined as the association of the two following criteria i) SCA occuring in the setting of definite or probable PE, ii) SCA without other cause identified during the in-hospital course.

Bleeding complications were centrally adjudicated, by two investigators blinded to the use of thrombolysis or anticoagulation. Major bleeding was defined as: fatal bleeding, and/or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome, and/or bleeding causing a fall in hemoglobin level of 20 g L^{-1} or more, or leading to transfusion of two or more units of whole blood or red cells [20].

Statistical analysis

The methodology of this study is consistent with the STROBE checklist for observational studies [21].

Continuous data were expressed as mean (SD) or median (Interquartile). Categorical data were expressed as frequencies and percentages. Comparisons of categorical variables used the χ^2 test or Fisher's exact test, when appropriate. Comparisons of continuous variables used Student's *t*-test, Mann-Whitney or Kruskall-Wallis test, when appropriate. We assessed normality using the Shapiro-Wilk test. We checked the linearity of quantitative variables using fractional polynomial regression. In the case of absence of linearity, continuous variables were dichotomized according to the median. The main outcome variable was survival at hospital discharge.

Considering the high predominance of non-shockable rhythm among PE-related SCA, prognosis after SCA (survival at hospital discharge) was compared between PE and non-PE patients with non shockable rhythm, in univariate analysis, and multivariate logistic regression after adjustment for previously described prognostic factors in SCA (occurrence at home, bystander CPR, delay from collapse to CPR, delay from CPR to ROSC, TTM) [10–22].

Finally, factors associated with survival after SCA among PE-related SCA were determined on univariate and multivariate logistic regression (including factors with $P < 0.15$ on univariate analysis, among definite PE-related SCA).

A *P* value less than 0.05 was considered statistically significant. Sensitivity analyses were carried out, including only patients with definite PE (instead of definite and probable PE). Delay before diagnosis of PE could lead to immortal time bias (period of follow-up during which, by design, death or the study outcome cannot occur [23]), considering that patients need to survive until diagnostic strategy can be performed. To limit this risk of bias, we performed an additionnal analysis, excluding patients who died in the first 24 h after SCA (time necessary to confirm diagnosis in 99% of PE-related SCA). Missing data were handled using case-complete analysis, and sensitivity analyses with chained multiple imputation were performed. Imputation models included terms for age, sex, location,