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Original Contribution

# ECG abnormalities predict neurogenic pulmonary edema in patients with subarachnoid hemorrhage☆,☆☆

Wei-Lung Chen, MD, MS, PhD [a,b,*], Chi-Hung Huang, MD [b,c], Jiann-Hwa Chen, MD, MPH, PhD [a,b], Henry Chih-Hung Tai, MD [a,b], Su-Hen Chang, MD [a,b], Yung-Cheng Wang, MD [d,e]

[a] Department of Emergency Medicine, Cathay General Hospital, Taipei 106, Taiwan
[b] School of Medicine, Fu-Jen Catholic University, Taipei 242, Taiwan
[c] Department of Cardiology, Cathay General Hospital, Taipei 106, Taiwan
[d] Department of Radiology, Cathay General Hospital, Taipei 106, Taiwan
[e] School of Medicine, Taipei Medical University, Taipei 106, Taiwan

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ABSTRACT

*Objective:* The study aims to assess if electrocardiographic (ECG) abnormalities could predict the development of neurogenic pulmonary edema (NPE) within 24 hours in cases of spontaneous subarachnoid hemorrhage (SAH).
*Methods:* We studied prospectively a cohort of 269 adult patients with nontraumatic SAH in an emergency department of a university-affiliated medical center. A 12-lead ECG was taken for these patients. The patients were stratified into NPE and non-NPE based on serially clinical and radiologic findings. The ECG abnormalities were compared between these 2 groups of patients.
*Results:* Compared with the non-NPE (n = 229), the NPE (n = 40) had significantly higher World Federation of Neurological Surgeons class ($P < .001$), higher Hunt-Hess scale ($P < .001$), and higher prevalence of diabetes mellitus ($P = .033$). In addition, the percentage of ECG morphological abnormality was significantly higher in NPE, in which nonspecific ST- or T-wave changes (NSSTTCs) are significantly higher. Multiple logistic regression model identified World Federation of Neurological Surgeons class (95% confidence interval [CI], 2.6-13.3; $P < .001$), abnormal Q or QS wave (95% CI, 1.1-9.1; $P = .038$), and NSSTTCs (95% CI, 1.2-7.5; $P = .016$) as the significant variables associated with NPE.
*Conclusions:* Electrocardiographic abnormalities, especially abnormal Q or QS wave and NSSTTCs, may predict the development of NPE within 24 hours in adult patients with spontaneous SAH.


## 1. Introduction

Neurogenic pulmonary edema (NPE) is a well-recognized phenomenon in subarachnoid hemorrhage (SAH), especially in high-grade patients [1–3]. Neurogenic pulmonary edema often presents in the emergency department (ED), and the incidence of NPE is approximately 25% [2,4]. Neurogenic pulmonary edema can lead to an acute cardiopulmonary failure with consequent global hypoperfusion and hypoxia. These circumstances might cause severe secondary ischemic brain damage, and it has been reported to be associated with a worsened outcome [2,4]. Morbidity and mortality due to NPE might be reduced by early recognition and appropriate management with cardiac monitoring and fluid balance [1,4,5]; therefore, the awareness of development of NPE is essential for those potentially confronted with patients with SAH in the early stage.

Several mechanisms have been implicated in the pathogenesis of NPE, but the exact interactions remain unclear [2]. Increased permeability in the pulmonary capillary bed due to a disruption of the endothelial barrier by the transient increase in intravascular pressure seems to be one possible cause because patients who developed NPE have a protein concentration similar to that of plasma [2,4]. In addition, acute stunned myocardium, characterized by metabolic acidosis, cardiogenic shock, pulmonary edema, and electrocardiographic (ECG) abnormalities, due to a massive sympathetic discharge may also play an important role in the development of NPE [6]. Subarachnoid hemorrhage has been reported to be the most notorious intracranial event that manifests with ECG abnormalities which most often include morphologic changes and rhythm disturbances [7–9], and diverse ECG changes have been reported to occur in 25% to 90% of patients with SAH [10]. Previous studies have suggested that patients with more severe SAH are more likely to develop cardiac abnormalities and are further associated with poor

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* Corresponding author at: Department of Emergency Medicine, Cathay General Hospital, No. 280, Sec. 4, Jen-Ai Rd, Taipei, Taiwan.
*E-mail address:* weilung.chen@msa.hinet.net (W.-L. Chen).

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neurological outcome [10–13]. Because both occurrence of NPE and presence of ECG abnormalities have been suggested to be associated with poor outcome in these patients and acute stunned myocardium characterized by ECG abnormalities is believed to be a possible pathogenesis factor of NPE, we therefore speculated that ECG abnormalities may indicate the occurrence of NPE in patients with SAH.

Studies have suggested that the ECG abnormalities usually appeared early after brain injury and disappeared within 1 day [14]. Moreover, cardiac dysfunction in the context with NPE, presenting with pathologic findings in ECG during the acute stage, seems to be of transient and reversible nature [5]. Therefore, the aim of this study was to investigate if the ECG abnormalities assessed early in the ED could predict the development of NPE within 24 hours in patients with spontaneous SAH.

## 2. Materials and methods

### 2.1. Study design

This was a prospective cohort study that investigated whether the ECG abnormalities assessed in the ED are independently associated with the development of NPE within 24 hours in adult patients with spontaneous SAH. The study protocol was approved by the Institutional Review Board of the hospital. Written informed consent was obtained from the patients themselves or their next of kin before enrolling in the study.

### 2.2. Study setting and selection of participants

This study was conducted in a 700-bed university-affiliated medical center with a 40-bed ED staffed with board-certified emergency physicians that provide care for approximately 55,000 patients per year. From October 2004 to September 2014, adult patients who were admitted within 12 hours of the first clinical symptoms with nontraumatic SAH diagnosed by computed tomographic scans of brain, or xanthochromia of the cerebrospinal fluid if the computed tomographic scan was nondiagnostic, were eligibly enrolled. The exclusion criteria of this study included (1) tumor bleeding, (2) known arrhythmia (reviewing the past medical record or by the statements of the patients themselves), (3) cardiac pacing, (4) aged less than 18 years, or (5) referred from other hospital (the ECG abnormalities and NPE of the patient seen in our ED were not in the early stage any more).

### 2.3. Study protocol

After obtaining the written informed consent, a standard 12-lead ECG recording was performed immediately after the diagnosis was made. The patient's ECG was interpreted by the same cardiologist who was blinded to the outcome of the patient. The following measurements were made for each ECG: heart rate (ventricular rate) and heart rate–corrected QT interval (QTc) using the Bazett formula. The *morphological abnormalities* were defined as the presence of 1 or more of the following 7 variables, which are commonly noted after SAH [8,15,16], in at least 2 leads: (1) abnormal Q or QS wave (≥30 milliseconds or a pathological R wave in V1 to V2); (2) ST elevation (ST elevation ≥0.1 mV); (3) ST depression (ST depression ≥0.1 mV, 80 milliseconds post-J point); (4) peaked upright T wave (prominent peaked T wave); (5) T-wave inversions (pathologic T-wave inversion); (6) giant T-wave inversions (T-wave inversions >10 mV in depth); or (7) nonspecific ST- or T-wave changes (NSSTTCs) (ST- or T-wave abnormalities not meeting the above criteria).

The study period started at the time of diagnosis made and lasted 24 hours thereafter. The patients were divided into 2 groups: NPE and non-NPE. Neurogenic pulmonary edema was defined by both serially clinical and radiologic findings [4]. A standard chest radiograph (CXR) was taken after diagnosis made and 24 hours later. The patient's CXR was interpreted by the same radiologist who was blinded to the clinical symptoms and outcome of the patient. A radiologic diagnosis of NPE was made if bilateral, symmetric, smooth and diffuse, alveolar edema–like infiltrates were present in the CXR. Clinical criteria for NPE were one of presence of crackles by chest auscultation assessed at the same time of CXR taken by 2 emergency physicians and presence of frothy pink tracheal fluid.

The following demographic data and clinical variables were recorded at the same time for all patients: age, sex, vital signs, laboratory data, Hunt-Hess scale (class I, asymptomatic or mild headache; class II, moderate or severe headache, nuchal rigidity, can have oculomotor palsy; class III, confused, drowsiness, or mild focal signs; class IV, stupor or hemiparesis; class V, coma, moribund, and/or extensor posturing) [12], World Federation of Neurological Surgeons (WFNS) class (class I, Glasgow Coma Scale [GCS] = 15, no motor deficit; class II, GCS = 13-14, no motor deficit; class III, GCS = 13-14, presence of motor deficit; class IV: GCS = 7-12; class V: GCS = 3-6) [17], underlying diseases, and comedication that can affect the heart rate. To avoid misdiagnosis of actual ischemic heart disease, the serial ECGs, cardiac enzymes, and echocardiography were checked after admission in those patients with ischemic changes of ECG. Following hospital discharge, the inpatient medical record was reviewed to complete the data collection: length of hospital stay and outcome (in-hospital mortality). Patients discharged from the hospital in less than 28 days or who remained alive for more than 28 days were classified as "survivors" in this study; otherwise, the patients were referred to as "nonsurvivors" (in-hospital mortality).

### 2.4. Statistical analyses

$\chi^2$ test or Fisher exact test when appropriate was used for the statistical analysis of categorical variables. Continuous variables were presented as mean (SD) and compared using the independent-samples *t* test. For statistical purposes, the clinical scores used in this study were dichotomized into good and poor groups (WFNS 1-3 vs WFNS 4-5, Hunt-Hess 1-3 vs Hunt-Hess 4-5). The clinical variables and ECG abnormalities with univariate comparison $P < .2$ between 2 groups were eligible for inclusion in a forward selection multiple logistic regression model to identify the variables assessed early in the ED that were independently associated with NPE of the patients with spontaneous SAH. A $P < .05$ was considered statistically significant. Statistical analyses were performed using a common statistical package (SPSS 16.0 for Windows; SPSS Inc, Chicago, IL).

## 3. Results

During the 10-year study period, a total of 319 nontraumatic adult SAH patients were treated in the ED. Of them, 50 patients who did not meet the inclusion criteria were not included in the present study: 13 patients were tumor bleeding, 10 patients had known arrhythmia, 3 patients had cardiac pacing, 22 patients were already diagnosed with SAH at another hospital, and 2 patients died soon before CXR or ECG was taken. In all, 269 of 319 patients were included in the final analysis. Based on development of NPE, those 269 patients, aged 19 to 77 years, were stratified into NPE (n = 40) or non-NPE (n = 229).

The basic characteristics of both groups of patients are shown in Table 1. There were no significant differences in age, sex, mean arterial pressure (MAP), white blood cell, glucose, comedication, and underlying diseases except diabetes mellitus (DM) between these 2 groups of patients. However, the WFNS class, Hunt-Hess scale, DM, and the occurrence of ECG morphological abnormalities were significantly higher, whereas the length of hospital stay were significantly lower, in the NPE as compared with those in the non-NPE. In addition, the frequency of ECG morphological abnormalities for all enrolled patients was noted to be 39% (106/269).

Table 2 demonstrates the heart rate, QTc, and ECG morphological abnormalities for both groups of patients. We found that the NPE had significantly higher frequency of NSSTTC than the non-NPE.