Brain Natriuretic Peptide: A Relevant Marker to Rule Out Delayed Atrial Fibrillation in Stroke Patient

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Detection of new atrial fibrillation (AF) after ischemic stroke is challenging. The aim of the TARGET-AF study was to identify relevant markers for ruling out delayed AF in stroke patients. Early and prolonged Holter electrocardiography (ECG) monitoring during hospitalization was performed systematically in consecutive acute stroke patients naive to AF (no history of AF or no AF on baseline ECG). All clinical and paraclinical data for routine etiologic assessment were collected. The diagnostic value of all parameters significantly associated with AF was assessed by comparison of area under the receiver operating characteristic curve (AUC). Of the 300 stroke patients enrolled (mean age, 62.5 ± 15.5 years; sex ratio: 1.7; mean National Institutes of Health Stroke Scale score, 7.1 ± 7.9, median duration of Holter ECG monitoring, 6.8 days), 52 (17.3%) had newly diagnosed AF. Parameters significantly associated with AF were classified by increasing AUC: anterior circulation localization (AUC, 0.604; 95% confidence interval [CI], 0.546-0.660), P-wave initial force (AUC, 0.608; 95% CI, 0.545-0.669), left atrial dilatation (AUC, 0.657; 95% CI, 0.600-0.711), National Institutes of Health Stroke Scale score (AUC, 0.667; 95% CI, 0.611-0.720), sex (AUC, 0.683; 95% CI, 0.627-0.736), age (AUC, 0.755; 95% CI, 0.707-0.797), CHA_2DS_2-VASc score (AUC, 0.796; 95% CI, 0.746-0.841), STAF (score for the targeting of AF) score (AUC, 0.842; 95% CI, 0.796-0.882), and plasma brain natriuretic peptide (BNP) level (AUC, 0.868; 95% CI, 0.825-0.904). The use of all parameters combined (AUC, 0.910; 95% CI, 0.872-0.940) was not significantly more efficient in diagnosing AF than BNP alone ($P = .248$). At the Youden plot, the diagnostic properties for BNP >131 pg/mL were sensitivity, 98.1% (95% CI, 89.7-99.7); specificity, 71.4% (95% CI, 65.3-76.9); and negative predictive value, 99.4% (95% CI, 96.9-99.9). Our data indicate that a BNP level ≤131 pg/mL might rule out delayed AF in stroke survivors and could be included in algorithms for AF detection. **Key Words:** Cerebral infarction—cardioembolism—arrythmia—Holter ECG—ECG monitoring—brain natriuretic peptide.
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Atrial fibrillation (AF) is a strong independent predictive factor for a first ischemic stroke or recurrence of stroke.[1] The high risk of recurrence and comorbidity after a stroke associated with AF justifies an aggressive diagnostic approach to initiate recommended anticoagulant treatment. Paroxysmal AF is more prevalent than permanent AF in stroke survivors.[2] The difficulty in detecting occult AF leads to the underestimation of AF prevalence and the consequent underuse of anticoagulants in secondary prevention of stroke. Routine diagnostic techniques, such as 24-hour Holter electrocardiography (ECG), have a low sensitivity for detecting AF.[3] Recent studies suggest that a significant proportion of cryptogenic ischemic stroke may be attributed to occult AF, particularly in elderly persons. Several studies have suggested that early and prolonged ECG monitoring could improve the rate of AF detection.[4,5] Appropriate techniques are expensive

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and difficult to generalize in clinical routine, however, which is why patients must be screened to improve the effectiveness of prolonged Holter ECG monitoring. We have suggested, and subsequently validated, that a new clinicoradiologic score, STAF (score for the targeting of AF), can be a component of a new strategy for screening for AF in the secondary prevention of stroke.[6] Other authors have proposed different marker predictors of AF in stroke patients, but their studies were heterogeneous and their comparison difficult.

To rationalize the use of prolonged ECG monitoring, there is a need to be more selective in choosing which patients should get this diagnostic strategy. The aim of the present study was to identify the most relevant marker of delayed AF in a prospective cohort of stroke survivors in whom AF was detected by early and prolonged monitoring.

Subjects and Methods

Patient Selection

The TARGET-AF single-center prospective observational study included consecutive patients admitted in stroke center of the Nice Univesity Hospital between November 2010 and November 2011 with acute stroke documented by brain computed tomography (CT) and/or magnetic resonance imaging. Patients were admitted to the intensive care stroke unit (ICSU) or conventional stroke unit (CSU) at the discretion of the neurologist. All patients underwent a standard 12-lead ECG at admission. Inpatients with a final diagnosis other than stroke, history of AF, or AF on baseline ECG were excluded from the analysis.

Measurement of AF

ECG Holter was started immediately on admission and performed for the entire duration of hospitalization in the ICSU or CSU. An Infinity CentralStation workstation (Dräger Medical, Lübeck, Germany) with Holter option software was used for all patients. The ECG recording system (5 electrodes) connected to the central station was continuous bedside ECG monitoring in the ICSU and telemetry (Infinity M300; Dräger Medical) in the CSU. Daily Holter ECG recordings were analyzed manually on a 2-lead ECG for each inpatient by neurologists of the ICSUs and CSUs. This system could not automatically detect AF. The presence of AF was defined as at a least one period of more than 30 seconds duration as determined by a cardiologist. The start time and end time of each arrhythmic period were recorded.

Data Collection

The neurologist recorded baseline characteristics, including demographic data, medical history, and clinical data. The topography of stroke was established by brain CT and/or magnetic resonance imaging. For each patient, a cardiologist blinded to AF detection performed routine transthoracic echocardiography at the bedside using a portable Vivid S5 cardiovascular ultrasound system equipped with a 3S echocardiographic probe (GE Healthcare, Waukesha, WI), with the patient in the left lateral decubitus position. All measurements and calculations were made in accordance with recommendations of the American Society of Echocardiography. Left atrial size was calculated in terms of volume by the ellipsoid formula indexed to body surface area whenever possible or, alternatively, by surface area measurement. Plasma brain natriuretic peptide (BNP) was measured in blood samples obtained at admission in a local chemistry laboratory using the Alere Triage BNP Test (Alere, Waltham, MA) in an Access 2 immunoassay system (Beckman Coulter, Brea, CA). A blind evaluation of scores—STAF (score for targeting AF),[6] $CHADS_2$,[7] and CHA_2DS_2-VASc[8]—was performed at the end of the study using data collected during hospitalization.

Baseline 12-Lead ECG Measurements

Twelve-lead ECG monitoring was performed for all stroke survivors admitted in sinusal rhythm. Paper ECG strips were digitalized, and measurements were recorded using ImageJ software by a neurologist in blinded fashion. Data on heart rate, P-R interval duration, and QRS axis were collected. P-wave onset was defined as the initial deflection from isoelectric baseline defined by the T-P segment; P-wave offset, as the junction of the end of the P wave and its return to baseline before the QRS complex. Up to 3 consecutive P waves were measured in each of the 12 leads when possible. P-wave indices included duration, amplitude, and area. Minimum, maximum, mean, and dispersion values were measured for each index. Dispersion was calculated by the difference between the maximum and minimum value of each index. The boundary between the initial and terminal P-wave portions in lead V1 was identified as the point where the signal value was the average of values at the onset and the end of the P wave. The duration, amplitude, and area of initial and terminal P-wave portions were measured. P-wave initial force and terminal force were defined as the algebraic product of duration and amplitude, respectively.

Statistical Analysis

Pertinent parameters for ruling out paroxysmal AF as a cause of stroke were identified by first determining significant differences between the patients with AF and those without AF. Univariate analysis was performed using the χ^2 test for comparisons of discontinuous variables and the Mann-Whitney *U* test for comparisons of continuous variables. Continuous data are reported as mean $\pm$ standard deviation (SD) or median (interquartile range [IQR]), and categorical variables are reported as absolute number (%). Then independent parameters associated with AF by

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