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Original Article

Usefulness of brain natriuretic peptide for predicting left atrial appendage thrombus in patients with unanticoagulated nonvalvular persistent atrial fibrillation

Yusuke Ochiumi, MD[a,*], Eisuke Kagawa, MD[a], Masaya Kato, MD, PhD[a], Shota Sasaki, MD, PhD[a], Yoshinori Nakano, MD[a], Kiho Itakura, MD[a], Yu Takiguchi, MD[a], Shuntaro Ikeda, PhD, MD[b], Keigo Dote, MD, PhD[a]

[a] Department of Cardiology, Hiroshima City Asa Hospital, Hiroshima, Japan
[b] Department of Cardiology, City Uwajima Hospital, Ehime, Japan

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ABSTRACT

Background: The $CHADS_2$ scoring system is simple and widely accepted for predicting thromboembolism in patients with nonvalvular atrial fibrillation (NVAF). Although congestive heart failure (CHF) is a component of the $CHADS_2$ score, the definition of CHF remains unclear. We previously reported that the presence of CHF was a strong predictor of left atrial appendage (LAA) thrombus. Therefore, the present study aimed to elucidate the relationship between LAA thrombus and the brain natriuretic peptide (BNP) level in patients with unanticoagulated NVAF.

Methods: The study included 524 consecutive patients with NVAF who had undergone transesophageal echocardiography to detect intracardiac thrombus before cardioversion between January 2006 and December 2008, at Hiroshima City Asa Hospital. The exclusion criteria were as follows: paroxysmal atrial fibrillation, unknown BNP levels, prothrombin time international normalized ratio ≥ 2.0, and hospitalization for systemic thromboembolism.

Results: Receiver operating characteristic analysis yielded optimal plasma BNP cut-off levels of 157.1 pg/mL (area under the curve, 0.91; $p < 0.01$) and 251.2 pg/mL (area under the curve, 0.70; $p < 0.01$) for identifying CHF and detecting LAA thrombus, respectively. Multivariate analyses demonstrated that a BNP level > 251.2 pg/mL was an independent predictor of LAA thrombus (odds ratio, 3.51; 95% confidence interval, 1.08–10.7; $p = 0.046$).

Conclusions: In patients with unanticoagulated NVAF, a BNP level > 251.2 pg/mL may be helpful for predicting the incidence of LAA thrombus and may be used as a surrogate marker of CHF. The BNP level is clinically useful for the risk stratification of systemic thromboembolism in patients with unanticoagulated NVAF.

1. Introduction

Systemic thromboembolism, including ischemic stroke and transient ischemic attack, is a serious complication in patients with atrial fibrillation (AF). Several randomized prospective trials investigating nonvalvular atrial fibrillation (NVAF) have confirmed that warfarin administration significantly reduces the risk of stroke, thereby providing a basis for guidelines promoting the use of warfarin in patients with NVAF [1,2]. The congestive heart failure (CHF), hypertension, age, diabetes mellitus, and prior stroke ($CHADS_2$) scoring system is easy for physicians to remember and apply. Additionally, it has been widely validated for risk stratification to predict stroke in patients with NVAF [3]. The $CHADS_2$ score assigns 1 point each for CHF, hypertension, age ≥ 75 years, and diabetes mellitus, and 2 points each for prior stroke or transient ischemic attack. Current guidelines recommend anticoagulant therapy for patients with a $CHADS_2$ score ≥ 2, because the risk of ischemic stroke outweighs the risk of bleeding with anticoagulant therapy [4–6].

Most thrombi associated with NVAF originate in the left atrial appendage (LAA) [7–9]. We previously reported that the serum d-dimer level is clinically useful for guiding the management of patients. In addition, the presence of CHF, a history of embolic

Abbreviations: NVAF, nonvalvular atrial fibrillation; CHF, congestive heart failure; LAA, left atrial appendage; BNP, brain natriuretic peptide; EF, ejection fraction; NYHA, New York Heart Association; TEE, transesophageal echocardiography; PT-INR, prothrombin time international normalized ratio; ROC, receiver operating characteristic; AUC, area under the curve

* Corresponding author. Tel.: +81 082 815 5211; fax: +81 082 814 1791.
E-mail address: ub034968@yahoo.co.jp (Y. Ochiumi).

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events, and the serum d-dimer level are significant predictors of LAA thrombus [10].

Various studies consider CHF as involving the following factors: acute pulmonary edema [3], low ejection fraction (EF) [2,11], New York Heart Association (NYHA) functional classification ≥II [10], and a history of hospitalization for CHF [2,11]. However, the abovementioned clinical criteria are qualitative; therefore, the quantitative definition of CHF remains unclear. Brain natriuretic peptide (BNP) is widely used as a clinical index of the severity of CHF [12]. Therefore, the present study aimed to elucidate the relationship between LAA thrombus and the BNP level and to determine if the BNP level is a quantitative marker of CHF in patients with unanticoagulated NVAF.

2. Material and methods

2.1. Study population

A total of 524 consecutive patients with NVAF who had undergone transesophageal echocardiography (TEE) to detect intracardiac thrombus before cardioversion between January 2006 and December 2008, at Hiroshima City Asa Hospital were enrolled. The study was approved by the Institutional Review Board of Hiroshima City Asa Hospital, and the patients provided consent for inclusion in the study.

Plasma BNP and d-dimer levels were measured simultaneously at the time of TEE. The exclusion criteria were as follows: prothrombin time international normalized ratio (PT-INR) ≥2.0 as a gold standard of warfarin control, paroxysmal AF, organic valvular heart disease, presence of prosthetic valve, and hospitalization due to acute myocardial infarction or systemic thromboembolism, including ischemic stroke and transient ischemic attack. Patients with paroxysmal AF were excluded because its onset could not be determined and its impact on the BNP level was not known.

2.2. Definition of NVAF

According to the guidelines of AF published by the American College of Cardiology, the American Heart Association, and the European Society of Cardiology [13], patients with persistent or permanent AF were included.

2.3. BNP level measurement

All assays were performed at our institution, and all investigators and laboratory personnel were blinded to the clinical status of each patient. Plasma samples for BNP analysis were collected in chilled disposable tubes containing aprotinin (500 kallikrein IU/mL), immediately placed on ice, and centrifuged at 4 °C. Plasma was frozen, aliquoted, and stored at −30 °C until analyzed for the BNP level using a specific immunoradiometric assay for human BNP (Shionogi Co., Ltd., Osaka, Japan).

2.4. TEE examination

TEE was performed using commercially available equipment with a multiplane phase array transducer. Prior to TEE, all participants received a detailed explanation of the procedure and provided written informed consent. A total of 204 patients with AF rhythm underwent TEE. For local anesthesia, lidocaine hydrochloride was administered at the throat for 5 min accompanied by lidocaine hydrochloride spray to anesthetize the posterior pharynx and tongue. The maximum LAA area was measured by tracing a line along the entire endocardial LAA border. The minimal LAA emptying peak flow velocity was measured with a sample volume placed at the entrance of the LAA.

2.5. Identification of LAA thrombus

A thrombus was defined as a circumscribed and uniformly echo-dense intracavitary mass that was distinct from the underlying left atrium or LAA endocardium, and the pectinate muscles in more than 1 imaging plane. Echocardiography technicians were blinded to the plasma BNP level. All TEE data were analyzed independently by 2 cardiologists, and interobserver differences were resolved by a third cardiologist.

2.6. Statistical analysis

Continuous variables were compared using the Mann–Whitney *U*-test, and categorical variables were compared using the chi-square or Fisher's exact test where appropriate. Continuous variables are expressed as median (interquartile range), and categorical variables as numbers and percentages. The optimal cut-off level of BNP for predicting LAA thrombus was calculated by using receiver operating characteristic (ROC) curve analysis. The Person product-moment correlation coefficient was used to evaluate the associations of the plasma BNP level with the plasma D-dimer level and LAA velocity.

Univariate logistic regression analysis was used to determine the associations of clinical and laboratory variables with the presence of LAA thrombus. Furthermore, multivariate logistic regression analysis adjusted for BNP, CHF, and EF was performed to identify independent clinical predictors of LAA thrombus. CHF (i.e., NYHA classification ≥II) was considered as the gold standard for the multivariate analysis. The level of significance for all analyses was set at $p < 0.05$. All analyses were performed using JMP® Statistical Analysis Software (version 8.0.1J, SAS Institute, Cary, NC, USA).

3. Results

3.1. Clinical characteristics of the study population

Among the 524 consecutive patients examined using TEE between 2006 and 2012, 204 were included in the study. The study flowchart is presented in Fig. 1. The median age of the patients was 69 years (interquartile range, 63–75 years), and 58 (28.4%) were women. Moreover, 143 patients (70.1%) had hypertension, 132 (64.7%) had CHF (NYHA classification ≥II), 51 (25.0%) had diabetes mellitus, and 30 (25.0%) had thromboembolism. The prevalence of warfarin treatment was 20.6%.

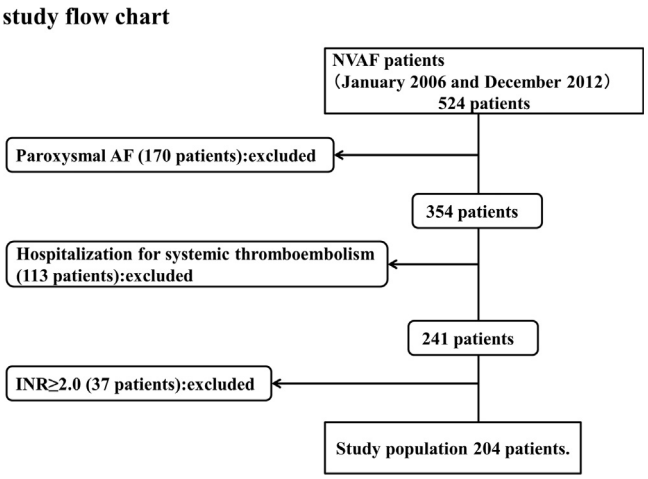

Fig. 1. Flowchart depicting the inclusion of patients in this study. NVAF, nonvalvular atrial fibrillation; INR, international normalized ratio.