Real-time physiologic biomarker for prediction of atrial fibrillation recurrence, stroke, and mortality after electrical cardioversion: A prospective observational study

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Background Left atrial appendage emptying flow velocity (LAAEV) depends largely on left atrioventricular compliance and may play a role in mediating the perpetuation of atrial fibrillation (AF) and AF-related outcomes.

Methods We identified 3,251 consecutive patients with sustained AF undergoing first-time successful transesophageal echocardiography (TEE)-guided electrical cardioversion who were enrolled in a prospective registry between May 2000 and March 2012. Left atrial appendage emptying flow velocity was stratified into quartiles: ≤20.2, 20.3-33.9, 34-49.9, and ≥50 cm/s. Multivariate Cox regression models were used to identify independent predictors of AF recurrence, ischemic stroke, and all-cause mortality.

Results The mean (SD) age was 69 (12.6) years and 67% were men. Compared with the fourth quartile, patients in the first-third quartiles were significantly older, had higher CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack [TIA], vascular disease, age 65-74 years, sex category) scores, greater frequency of atrial spontaneous echo contrast, and AF of longer duration. Kaplan-Meier analysis showed a decreased probability of event-free survival with decreasing quartiles of LAAEV. Five-year cumulative event rates across first-fourth quartiles were 83%, 80%, 73%, and 73% ($P < .001$) for first AF recurrence; 7.5%, 7.0%, 4.1%, and 4.0%, for stroke ($P = .01$); and 31.3%, 26.1%, 24.1%, and 19.4%, for mortality ($P < .001$), respectively. Multivariate Cox regression analysis revealed an independent association of the first and second quartiles with AF recurrence ($P < .001$ and $P < .001$, respectively) and stroke ($P = .03$, and $P = .04$, respectively), and of the first quartile with mortality ($P = .003$).

Conclusions Patients with decreased LAAEV have an increased risk of AF recurrence, stroke, and mortality after successful electrical cardioversion. Real-time measurement of LAAEV by TEE may be a useful physiologic biomarker for individualizing treatment decisions in patients with AF. (Am Heart J 2015;170:914-22.)

Background

Atrial fibrillation (AF) is a growing global health concern[1,2] and is linked to a wide range of medical complications including ischemic stroke, heart failure, and death.[3,4] It is estimated that AF may account for 10% to 15% of all strokes,[3] with an associated mortality of up to 1.9-fold.[4] The loss of effective and coordinated atrial contractile function and excessive response of heart rate in AF impair ventricular diastolic filling as a result of the short diastolic interval. This, in turn, decreases cardiac output, particularly in patients with left ventricular diastolic dysfunction.[5,6] Consequently, AF often results in clinically worsening functional capacity, increased New York Heart Association functional class, and decreased peak oxygen consumption.[7]

Electrical cardioversion (ECV) has been a mainstay of therapy in patients with symptomatic AF to restore sinus rhythm (SR) and alleviate symptoms acutely.[8] Although the initial success of ECV has been reported as greater than 90%,[9] approximately 50% of patients relapse into AF within 1 year.[10] There are limited data on physiologic predictive markers of AF recurrence and long-term outcome of patients after ECV for AF. Given the clinical implications of AF and its associated complications, it is important to have a reliable and objective tool to accurately predict prognosis and guide treatment decisions for patients with AF after ECV. Left ventricular diastolic dysfunction has been shown to be an independent predictor of AF recurrence at 1 year after successful ECV for nonvalvular AF (NVAF).[11]

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Diastolic impairment and risk of AF are thought to be mediated by effect of chronic left atrial (LA) pressure overload and stretch, which favor progressive LA enlargement, cell death, atrial fibrosis, and electrical heterogeneity. These pathological changes manifest in functional changes in the LA appendage (LAA). Left atrial appendage emptying flow velocity (LAAEV), which depends on left atrioventricular compliance,[12] therefore may play a role in mediating the regulation of LA volume–pressure relationships, thereby perpetuating AF. The objectives of the present study were to systematically investigate the prognostic value of LAAEV and to find clinically relevant discriminatory cut-points for identifying gradations of risk of recurrent AF, ischemic stroke, and death after ECV. We hypothesized that LAAEV, a marker of LA function,[13] is an independent predictor of long-term outcomes after first successful ECV of sustained NVAF.

Methods

Study design

The study protocol was approved by the Mayo Clinic Institutional Review Board, and the requirement for written informed consent was waived for this minimal-risk study. Prospectively collected data on patients who underwent ECV at the Mayo Clinic Cardioversion Unit were analyzed.

Patient population

Patients with sustained AF undergoing ECV at the Mayo Clinic cardioversion unit were consecutively enrolled into a prospective registry. We identified 3,329 consecutive patients undergoing their first successful transesophageal echocardiography (TEE)-guided ECV for sustained AF between May 2000 and March 2012. Patients with history of congenital heart disease, moderate or greater mitral valve regurgitation or stenosis, mitral valve surgery, and LAA closure, and those who declined research authorization were excluded (n = 78). A total of 3,251 patients comprised the study population.

Echocardiography and cardioversion protocol

TEE was performed on all patients immediately before ECV. The LAAEV profiles were routinely assessed by pulsed-wave Doppler interrogation, with a sample volume positioned 1 to 2 cm within the orifice of the LAA. The peak LAAEV measurements were averaged for 5 consecutive cycles. If no intracardiac thrombus or sludge was detected, ECV was performed according to the established guidelines of the cardioversion unit, using a biphasic cardioversion protocol. *Successful ECV* was defined as the patient having SR when discharged from the cardioversion unit.

Outcome ascertainment

Patients were monitored after ECV for first documentation of recurrent AF, ischemic stroke, or death from any cause. Follow-up data were collected during follow-up visits and by thorough reviews of all medical records. Stroke occurrence was based on documented clinical signs of focal (or global) disturbance of cerebral function and results of radiographic examination, including computed tomographic scan or magnetic resonance imaging findings. Vital status was ascertained through the national death index.

Statistical analyses

For all analyses, patients were stratified by precardioversion LAAEV quartiles measured by TEE: first quartile, ≤20.2 cm/s; second quartile, 20.3-33.9 cm/s; third quartile, 34-49.9 cm/s; and fourth quartile, ≥50 cm/s. Categorical variables were expressed as numbers and percentages and compared among quartile groups using the multiple-comparisons χ^2 tests. Continuous variables were expressed as mean (SD) and median (interquartile range [IQR]) as appropriate and compared among quartile groups using analysis of variance for normally distributed data and Kruskal-Wallis test for skewed variables. Intergroup differences were tested adjusting for the 7 possible comparisons using Bonferroni multiple procedure. We constructed multivariate Cox proportional hazard regression models with inclusion of 4 categories of the CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack [TIA], vascular disease, age 65-74 years, sex category) score to evaluate the independent association of quartiles of LAAEV and other predictors with recurrent AF, ischemic stroke, and all-cause mortality. Only covariates with a P value ≤.10 based on univariate analysis were included in the final multivariable model. Linear trend was tested between LAAEV and AF recurrence, and separately stroke, and all-cause mortality. We entered LAAEV as a linear and a quadratic term in its original continuous form in the model. The analysis indicated a nonlinear relationship if the quadratic term was significant. For each variable, hazard ratio (HR) and 95% CI were computed, with the highest quartile of LAAEV as the reference category. Assumptions for proportional hazards models were tested by including main effects and product terms of covariates and logarithmic-transformed time factor. Ties were handled using the Efron method. Kaplan-Meier survival analyses with log-rank tests were used to compare time–to-event outcomes on the basis of all available follow-up data among quartiles of LAAEV. All P values were based on 2-sided tests, and $P < .05$ was considered statistically significant. All statistical analyses were performed using SAS software version 9.3 (SAS Institute Inc, Cary, NC).

Results

Baseline characteristics

A total of 3,251 patients who underwent successful TEE-guided ECV for sustained NVAF were included in this analysis. The mean (SD) age of the study population was 69 (12.6) years and 67% were men. The median (IQR) LAAEV was 33 (20-50) cm/s. The mean (SD) total follow-up