Serum brain-derived neurotrophic factor and risk of atrial fibrillation

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Background and objective Brain-derived neurotrophic factor (BDNF) is expressed by endothelial cells and can affect cardiovascular function. We examined if serum BDNF was associated with risk of incident atrial fibrillation (AF) in the Framingham Heart Study.

Methods We studied individuals without an AF diagnosis at baseline from the Framingham original and offspring cohorts. We used age- and sex-adjusted, and multivariable-adjusted Cox proportional hazards regression models to examine the association of serum BDNF concentrations with 10-year risk of incident AF.

Results We studied 3,457 participants (mean age 65 ± 11 years, 58% women). During follow-up, 395 participants developed AF. In unadjusted analysis, higher mean serum BDNF concentration was associated with lower incidence of AF (hazard ratio 0.89 per SD, 95% CI 0.80-0.99). In multivariable-adjusted analyses, serum BDNF concentration was not significantly associated with incident AF (hazard ratio 0.98 per SD, 95% CI 0.88-1.09). Compared with the lowest quartile, BDNF levels in the other quartiles were not associated with risk of AF in multivariable-adjusted analyses. No interactions between sex or age with serum BDNF concentrations and risk of AF were found.

Conclusions In our prospective, community-based sample, we did not find a statistically significant association of serum BDNF levels with risk of incident AF. (Am Heart J 2017;183:69-73.)

Atrial fibrillation (AF) is the most common cardiac arrhythmia, and the prevalence is increasing worldwide.[1] Atrial fibrillation is associated with multiple adverse outcomes including embolic stroke,[2] cognitive impairment,[3] heart failure,[4] myocardial infarction,[5] chronic kidney disease,[6] and mortality.[2,7] Over the past few decades, several studies have defined major risk factors for AF including body mass index, hypertension, diabetes mellitus, history of cardiovascular disease, genetic factors, and various circulating biomarkers.[7-11]

Brain-derived neurotrophic factor (BDNF) is a growth factor with roles within the nervous system[12] and cardiovascular system.[13] It is expressed in endothelial cells, and its release is modified by stimuli including laminar shear stress and changes in intracellular calcium.[13,14] Furthermore, decreased BDNF levels reduce endothelial cell survival and reduce cardiac contractility, whereas activation of tyrosine receptor kinase B by BDNF is associated with angiogenesis.[13] It is unclear if these effects of BDNF on the cardiovascular system may modify the risk of AF. However, lower BDNF concentrations have been associated with known risk factors for AF including advancing age,[15,16] male sex,[16] alcohol consumption,[17] smoking,[18] and diabetes mellitus (Figure).[19] Circulating BDNF levels were higher among individuals with higher mean physical activity,[20] diastolic blood pressure, and

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body mass index.[16] In contrast, lower serum BDNF levels have been associated with adverse outcomes, including cardiovascular events[21] and dementia.[22] Brain-derived neurotrophic factor may have a role in the development of acute coronary syndrome, which may be partly through modulation of associated inflammatory pathways.[23-25]

Because of BDNF's association with multiple AF risk factors, inflammatory pathways, and its role in the cardiovascular system, we hypothesized that lower BDNF concentrations are associated with increased risk of developing AF prospectively. Thus, we sought to determine if serum BDNF concentrations are associated with 10-year incidence of AF in the community.

Methods

Study sample

The Framingham Heart Study (FHS) is a longitudinal, community-based, epidemiologic cohort study. Details of the FHS original and offspring cohorts have been described previously.[26,27] From 1948 through 1953, 5,209 participants were enrolled into the original cohort. In addition, 5,124 children of the original cohort and their spouses were recruited into the offspring cohort between 1971 and 1975. Participants have undergone routine follow-up examinations biennially for the original cohort and every 4 to 8 years for the offspring cohort. Six hundred sixty-nine of the 1,026 participants from the original cohort who attended examination 23 (1992-1996), and 3,020 of 3,539 participants from the offspring cohort who attended examination 7 (1998-2001) had circulating BDNF measurements. We excluded participants with prevalent AF (n = 214) and those younger than 40 years (n = 18) at BDNF measurements (baseline), resulting in a sample of 3,457 for our study. All participants gave informed consent. The study protocol was approved by the institutional review board of Boston University Medical Center.

Clinical variables

Participants' medical history, physical examination, blood tests, and 12-lead electrocardiogram were obtained routinely at each FHS examination. In addition, records including electrocardiograms from outpatient visits or hospitalizations between examinations were routinely retrieved and reviewed. Participants were defined to have AF if AF or atrial flutter was confirmed by an FHS cardiologist on review of electrocardiograms, as detailed previously.[27]

We included clinical covariates from the FHS AF risk score[28] assessed at baseline by standardized protocols. Body mass index (weight [in kilograms] divided by height [in meters] squared) was calculated. The PR interval was measured from the beginning of the P-wave deflection to the end of the PR segment at the junction with the QRS complex. Body mass index and PR interval were natural log transformed to normalize the skewed distributions. Systolic blood pressure and self-reported use of antihypertensive and diabetes medications were recorded. Diabetes mellitus was diagnosed if the participant used insulin or oral hypoglycemic agents, had fasting glucose level $\geq$126 mg/dL, or had random blood glucose level $\geq$200 mg/dL at FHS examination. We defined *valvular heart disease* as $\geq$grade 3/6 systolic murmur or any diastolic murmur auscultated at FHS examination. Myocardial infarction and heart failure were diagnosed by review of hospital records and physician reports, and adjudicated by 3 FHS investigators.[29]

Laboratory measurements of BDNF

Fasting blood tests were obtained, frozen, and stored at −70°C until assayed. Serum BDNF concentrations were measured using enzyme-linked immunosorbent assay kits (R&D Systems, Minneapolis, MN). The intra-assay and interassay coefficients of variation for BDNF were 4.8% and 7.6%, respectively.

Statistical analyses

We followed up participants for 10 years to evaluate for risk of incident AF. We used unadjusted, age- and sex-adjusted, and multivariable-adjusted Cox proportional hazards regression models to examine the association of change in serum BDNF concentrations (per SD) with 10-year risk of incident AF. Multivariable models were adjusted for age, sex, FHS cohort (original vs offspring), body mass index, PR interval, systolic blood pressure, hypertension treatment, diabetes mellitus, significant heart murmur, history of myocardial infarction, and history of heart failure. Estimates were adjusted for competing risk of death. In addition, in exploratory analyses, we adjusted for each individual covariate separately to understand if any potential relationship existed between a specific risk factor, serum BDNF concentrations, and risk of incident AF.

In secondary analyses, we considered nonlinear associations and divided participants into quartiles using serum BDNF concentrations. In previous studies, lower concentrations of BDNF were associated with higher risk of dementia.[22] Thus, the lowest quartile, Q1, was used as the reference to compare with each individual quartile and a combined Q2 to Q4. Subsequently, the highest quartile (Q4) was used as reference and compared with the other quartiles pooled. The same analyses were performed on all models after exclusion of participants with history of myocardial infarction or heart failure. We also evaluated if there was an interaction of sex and age <65 or $\geq$65 years with BDNF for the risk of AF.

Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC), and 2-sided $P < .05$ was considered statistically significant for all models and $P < .10$ for analyses assessing interactions. We estimate that our