Serial measures of cardiac troponin T levels by a highly sensitive assay and incident atrial fibrillation in a prospective cohort of ambulatory older adults

Ayman A. Hussein, MD,[*] Traci M. Bartz, MS,[†] John S. Gottdiener, MD,[‡] Nona Sotoodehnia, MD,[†] Susan R. Heckbert, MD, PhD,[†] Donald Lloyd-Jones, MD,[§] Jorge R. Kizer, MD, MSc,[¶] Robert Christenson, MD,[‡] Oussama Wazni, MD,[*] Christopher deFilippi, MD[‡]

From the [*]Cleveland Clinic Foundation, Cleveland, Ohio, [†]University of Washington, Seattle, Washington, [‡]University of Maryland, Baltimore, Maryland, [§]Northwestern University, Evanston, Illinois, and [¶]Albert Einstein College of Medicine, Bronx, New York.

BACKGROUND Various mechanisms in cardiac remodeling related to atrial fibrillation (AF) lead to elevated circulating cardiac troponin levels, but little is known about such elevations upstream to AF onset.

OBJECTIVE The purpose of this study was to study the association between circulating troponin levels as assessed by a highly sensitive cardiac troponin T (hs-cTnT) assay and incident atrial fibrillation (AF).

METHODS In a large prospective cohort of ambulatory older adults [the Cardiovascular Health Study (CHS)], hs-cTnT levels were measured in sera that were collected at enrollment from 4262 participants without AF (2871 with follow-up measurements). Incident AF was identified by electrocardiograms during CHS visits, hospital discharge diagnoses, and Medicare files, including outpatient and physician claims diagnoses.

RESULTS Over median follow-up of 11.2 years (interquartile range 6.1–16.5), 1363 participants (32.0%) developed AF. Higher baseline levels of hs-cTnT were associated with incident AF in covariate-adjusted analyses accounting for demographics, traditional risk factors, and incident heart failure in time-dependent analyzes (hazard ratio for 3rd tertile vs undetectable 1.75, 95% confidence interval 1.48–2.08). This association was statistically significant in analyses that additionally adjusted for biomarkers of inflammation and hemodynamic strain (hazard ratio for 3rd tertile vs undetectable 1.38, 95% confidence interval 1.16–1.65). Significant associations were also found when hs-cTnT levels were treated as a continuous variable and when examining change from baseline of hs-cTnT levels and incident AF.

CONCLUSION The findings show a significant association of circulating troponin levels in ambulatory older adults with incident AF beyond that of traditional risk factors, incident heart failure, and biomarkers of inflammation and hemodynamic strain.

KEYWORDS Atrial fibrillation; Biomarker; Cardiac remodeling Aging

ABBREVIATIONS **AF** = atrial fibrillation; **CHS** = Cardiovascular Health Study; **CI** = confidence interval; **CRP** = C-reactive protein; **ECG** = electrocardiogram; **HF** = heart failure; **HR** = hazard ratio; **hs-cTnT** = highly sensitive cardiac troponin T (assay); **IQR** = interquartile range; **MI** = myocardial infarction; **NT–pro-BNP** = N-terminal pro–B-type natriuretic peptide

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Introduction

Atrial fibrillation (AF), the most common cardiac arrhythmia encountered in clinical practice, is associated with increased morbidity and mortality, particularly in older adults.[1,2] The arrhythmia has become a major public health problem, one that is expected to grow as greater longevity expands the population of older adults in modern societies.[1]

It stands to a reason that there has been significant interest in better understanding AF and noninvasive modalities that could identify key components of cardiac remodeling that predispose to and promote the arrhythmia.[3] Importantly, there is a paucity of data on serum biomarkers of pathways involved in structural remodeling in AF and particularly on alterations of such biomarkers upstream to AF onset.

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Address reprint requests and correspondence: Dr. Ayman A. Hussein, Section of Clinical Cardiac Electrophysiology, Department of Cardiovascular Medicine, Cleveland Clinic Foundation, 9500 Euclid Ave, J2-2, Cleveland, OH 44195. E-mail address: husseia@ccf.org.

In animal models[4–7] and in patients with AF,[8–11] cardiac remodeling processes related to the arrhythmia lead to release of troponin into the circulation. A highly sensitive cardiac troponin T assay (hs-cTnT) that allows assessment of such processes showed that hs-cTnT levels are elevated in a significant proportion of adults aged 65 or older and are associated with incident heart failure.[12] This patient population is of particular interest because it is at highest risk for AF in the community. In younger populations, baseline troponin I levels by a highly sensitive assay have been recently associated with incident AF.[13,14]

We hypothesized that baseline and serial measures of hs-cTnT levels in the general population of older adults are associated with incident AF beyond that of traditional risk factors and incident heart failure. The study hypothesis was tested in a large community-based prospective cohort of older adults: the Cardiovascular Health Study (CHS).

Methods

Study population

The CHS is a longitudinal study of adults aged 65 years or older at recruitment. The rationale, design, and methods of CHS, including information on data collection and definition of comorbid conditions, have been previously published.[15,16] In brief, the CHS population consisted of 5888 men and women recruited from Medicare files from 4 communities in the United States (Forsyth County, NC; Sacramento County, CA; Washington County, MD; and Pittsburgh, PA). The original cohort of participants included 5201 subjects who were enrolled from 1989 to 1990. A supplemental cohort was enrolled between 1992 and 1993, which included 687 African Americans. The cohort for current analysis included 4262 participants without AF who had baseline levels of hs-cTnT from sera collected at enrollment and were not missing covariate information (n = 31). Of them, 2871 participants had follow-up measures (2–3 years after the original assay). One individual was excluded because of extreme change in hs-cTnT; thus, 2870 were included in analyses of the association between change in hs-cTnT levels and incident AF. The CHS was approved by the institutional review boards at University of Washington (Seattle, WA) and participating sites. All subjects gave written informed consent at time of enrollment.

Initial assessment, follow-up, and cardiovascular events

At enrollment, study participants were assessed by a standardized questionnaire that addressed various health and behavioral risk factors along with a physical examination.[17] For each cardiovascular condition, self-reports were confirmed by components of the baseline examination or, if necessary, by a validation protocol that included either the review of medical records or surveys of treating physicians. Prevalent AF was identified by electrocardiograms (ECGs) obtained at baseline. Self-reported heart failure was confirmed by symptoms, physical signs, and the use of both diuretics and either digitalis or a vasodilator. Further confirmation of prevalent AF or heart failure was sought from treating physicians by questionnaires or from hospitals by discharge summaries, as well as by review of medical records. After the initial assessment, enrolled subjects were contacted every 6 months for follow-up, alternating between telephone interviews and clinic visits through 1998–1999, thereafter, except for a follow-up clinic visit in 2005–2006 in a subset, contacts were by telephone interviews only. In all participants, resting 12-lead electrocardiograms were recorded at baseline and repeated annually until the last clinic visit. Echocardiograms were obtained at baseline for the original cohort and at the 1994–1995 study visit for both cohorts. In addition, discharge diagnoses for all hospitalizations were collected. New cardiovascular events, reported during a clinical visit, telephone encounter, or hospital stay, were confirmed by obtaining medical records and adjudicated by a centralized events committee.[17] The details on ascertainment and adjudication of death and cardiovascular events in CHS have been previously published.[17] Incident AF was identified by electrocardiograms during CHS visits, hospital discharge diagnoses, and Medicare files, including outpatient and physician claims diagnoses. For Medicare data, diagnosis of AF was based on a single inpatient claim or on 2 outpatient or carrier claims within 365 days of each other. For outpatient/carrier claim AF diagnoses, qualifying claims had to specify different dates of service, and carrier claims were restricted to those received from an office, home, skilled nursing facility, nursing facility, or custodial care facility to avoid double-counting inpatient and outpatient claims. Electrocardiograms from CHS visits were read by the CHS Electrocardiography Reading Center. Post open heart surgery was not counted as incident AF. For these participants, when a subsequent hospitalization or study examination revealed AF unrelated to heart surgery, the date of the subsequent AF occurrence was used as the date of incident AF. Incident heart failure was confirmed by documentation in the medical record of a constellation of symptoms and physical signs with supporting clinical findings or a record of medical therapy for heart failure.

Cardiac troponin T assays

Details on blood sample acquisition as well as analytical and quality assurance methods in CHS were previously published.[18] All measurements of troponin T levels were performed in a central blood analysis laboratory. Baseline measures were obtained from sera collected at enrollment. Follow-up measures were performed on blood samples collected 2 to 3 years later. Blood samples were stored at –70°C to –80°C and thawed just before laboratory assays (maximum of 3 freeze–thaw cycles) in April 2010. All cardiac troponin T concentrations were measured using highly sensitive reagents on an Elecsys 2010 analyzer (Roche Diagnostics, Indianapolis, IN). The analytical measurement range of the assay was 3 to 10,000 ng/L with an analytical coefficient of variation of 10%.[19] Values of