Clinical Biochemistry 49 (2016) 657–662

Contents lists available at ScienceDirect

Clinical Biochemistry

journal homepage: www.elsevier.com/locate/clinbiochem

Determinants of minimal elevation in high-sensitivity cardiac troponin T in the general population

Jonathan Rubin [a,c], Kunihiro Matsushita [b], Mariana Lazo [b], Christie M. Ballantyne [d], Vijay Nambi [d,e], Ron Hoogeveen [d], A. Richey Sharrett [b], Roger S. Blumenthal [f], Josef Coresh [b], Elizabeth Selvin [b,*]

[a] Department of Medicine, Columbia University Medical Center, New York, NY, USA
[b] Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA
[c] Department of Medicine, Johns Hopkins Hospital, Baltimore, MD, USA
[d] Department of Medicine, Section of Atherosclerosis and Vascular Medicine, Baylor College of Medicine, Houston, TX, USA
[e] Michael E DeBakey Veterans Affairs Hospital, Houston, TX, USA
[f] Johns Hopkins Ciccarone Preventive Cardiology Center, Baltimore, MD, USA

ARTICLE INFO

Article history:
Received 4 January 2016
Received in revised form 28 January 2016
Accepted 29 January 2016
Available online 11 March 2016

Keywords:
Troponin
Risk factors
Epidemiology
Cardiovascular disease

ABSTRACT

Objectives: To study the relationship between cardiovascular risk factors and detectable cardiac troponin-T using a highly sensitive assay (hs-cTnT) among persons without a history of cardiovascular disease.

Design and methods: We examined the cross-sectional associations between cardiovascular risk factors and hs-cTnT in 9593 participants (mean age 65.6 (SD, 5.6), 41% female, 22% black) free of cardiovascular disease in a community-based cohort, through the Atherosclerosis Risk in Communities (ARIC) Study. We used multivariable logistic regression to characterize the association between cardiovascular risk factors and detectable (≥3.0 to 13.9 ng/L) and elevated (≥14.0 ng/L) hs-cTnT.

Results: hs-cTnT was detectable in 59% and elevated in 7% of the study population. Among persons with ideal cardiovascular health, hs-cTnT was detectable in 44%. In models adjusting for significant determinants of hs-cTnT concentration, detectable hs-cTnT was more frequent among males, blacks and persons with diabetes and hypertension and less frequent among statin users, current smokers and drinkers. Other risk factors associated with detectable hs-cTnT were older age, lower kidney function and higher body mass index. These risk factors were associated with elevated hs-cTnT in a similar pattern.

Conclusion: In a community-based sample without cardiovascular disease hs-cTnT is detectable in most adults, even among those with ideal cardiovascular health. Although most traditional cardiovascular risk factors were significant determinants of detectable and elevated hs-cTnT, the associations were particularly robust for sex, age, race, hypertension and diabetes.

1. Introduction

Cardiac troponin-T is an established marker of myocardial damage [1]. Although traditionally used in the clinical setting of acute coronary syndromes, others have previously shown detectable cardiac troponin-T in a very small proportion of asymptomatic individuals in the general population (less than one percent) [2] and the presence of cardiac troponin-T in these individuals has been linked to cardiovascular risk factors.

In contrast to the conventional cardiac troponin T assay where ~1% of the general population has detectable cardiac troponin T^2, the hs-cTnT assay is detectable in up to 66% of individuals from the general population [3–5]. Using this assay, troponin concentrations far below the conventional limit of measurement have been shown to predict cardiovascular events and death in the general population [3–5]. Furthermore, hs-cTnT was more commonly detectable among men and associated with multiple other cardiovascular risk factors [3,6–9].

There is a paucity of data regarding the determinants of detectable cardiac troponin-T in persons without clinical cardiovascular disease. We sought to study the relationship between cardiovascular risk factors and detectable hs-cTnT among persons without a history of cardiovascular disease in a community-based cohort, through the Atherosclerosis Risk in Communities (ARIC) Study.

2. Methods

2.1. Study population

Details of the study design and examination procedures have been previously described [10]. Briefly, the ARIC Study enrolled 15,792 men

* Corresponding author at: Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Welch Center for Prevention, Epidemiology, and Clinical Research, 2024 E Monument Street, 2-600, USA.
E-mail address: eselvin@jhu.edu (E. Selvin).

http://dx.doi.org/10.1016/j.clinbiochem.2016.01.024
0009-9120/

and women aged 45 to 64 years during 1987–1989 from four US communities: Forsyth County, North Carolina; suburban Minneapolis, Minnesota; Washington County, Maryland; and Jackson, Mississippi. Follow-up on-site examinations took place in 1990–1992 (visit 2), 1993–1995 (visit 3), 1996–1998 (visit 4), and 2011–2013 (visit 5). Institutional review boards at participating institutions approved the study and informed consent was obtained from all subjects.

The present study used data from visit 4, for which hs-cTnT measurements were available. There were 11,656 eligible participants who attended visit 4; we excluded individuals with adjudicated coronary heart disease (n = 1153) [11], adjudicated stroke (n = 195), or a hospitalization for heart failure (n = 106) at or before visit 4, self-reported race other than black or white (n = 29), missing covariate data (n = 329) or missing hs-cTnT (n = 251) for a final study sample of 9953 participants.

2.2. Potential determinants

Age, sex, race, alcohol use and smoking status were ascertained from interviews with participants. History of diabetes was defined as a self-reported physician diagnosis of diabetes or use of glucose lowering medication during visit 4. Trained examiners measured weight, height [12] and blood pressure [13]. Systolic and diastolic blood pressures were calculated as the mean of the first and second readings and body mass index as weight in kilograms divided by height in meters squared. Hypertension was define as systolic blood pressure greater than 140 mmHg, diastolic greater than 90 mmHg or use of blood pressure lowering medication. Plasma lipids were measured as previously described [14] and serum creatinine concentration was measured using a modified kinetic Jaffe method. Estimated glomerular filtration rate was calculated using the CKD-EPI (CKD Epidemiology Collaboration) equation [15]. Serum glucose was measured by the hexokinase method [16]. The ARIC 10-year risk score for coronary heart disease was derived by assessing ROC curve improvements with the addition of nontraditional risk factors and markers of subclinical disease to the basic model containing only traditional risk factors as previously described [17].

2.3. High-sensitivity cardiac troponin T

Plasma samples collected from participants of visit 4 were stored centrally at −80 °C and used for measurement of hs-cTnT in 2010. hs-cTnT concentration was measured using a high-sensitivity assay, Elecsys Troponin T (Roche Diagnostics, Indianapolis, IN) and implemented on an automated Cobas e411 analyzer; the limit of blank is 3 ng/L; and the lower limit of detection is 5 ng/L[18]. The between-assay coefficient of variations were 2.6% and 6.9% for control materials with mean hs-cTnT concentrations of 2378 ng/L and 29 ng/L, respectively. We assessed the repeatability of measurements using masked duplicate samples (n = 418) and the reliability coefficient was 0.98 [18]. We defined elevated hs-cTnT as concentration above a previously reported 99th percentile cut-off (14 ng/L) (Roche Diagnostics, data on file), corresponding to the 90th percentile of the distribution of hs-cTnT in our study population. The 10% coefficient of variation of the high-sensitivity assay is 13 ng/L, close or below the 99th percentile of the reference population (14 ng/L) [19]. While high sensitivity troponin assays are being adopted in Europe and Canada, such assays are not in clinical use in the United States.

2.4. Statistical analysis

First, we categorized hs-cTnT into three groups: those with undetectable hs-cTnT (<3 ng/L), those with detectable hs-cTnT (3–13.9 ng/L) and those with elevated hs-cTnT (hs-cTnT ≥ 14.0 ng/L). Baseline characteristics of the study population were compared across these categories. We calculated the proportion of persons with detectable and elevated troponin according to the number of traditional risk factors and according to the recently proposed definitions of "ideal," "intermediate," and "poor" cardiovascular health for adults by the American Heart Association Strategic Planning Task Force and Statistics Committee [20]. We used multivariable linear and logistic regression models to characterize the associations of cardiovascular risk factors with hs-cTnT as a continuous and a categorical value, respectively.

For linear regression analysis, cardiovascular risk factors were modeled with cubic splines to characterize the shape of the association with hs-cTnT. We used multivariable logistic regression to assess the association between cardiovascular risk factors with detectable and elevated hs-cTnT.

All models included for the following covariates: sex (male or female), history of diagnosed diabetes (yes or no), age (years), race (white or black), body mass index (kg/m^2), hypertension (yes or no), estimated glomerular filtration rate (ml/min/1.73 m^2), alcohol consumption (current, former, or never), statin use (yes or no), smoking (current or not), education (less than high school, high school or equivalent, or more than high school), total, low and high-density cholesterol levels (mg/dL), high-sensitivity C-reactive protein (mg/L) and N-terminal pro b-type natriuretic peptide (NT-proBNP, pg/mL).

With the purpose of ruling out other potential causes of elevated hs-cTnT, we performed sensitivity analyses by excluded persons with atrial fibrillation before or at visit 4 and also by excluding persons with incident coronary heart disease up to 6 months after hs-cTnT samples were obtained. All analyses were conducted using Stata 11.1 (Stata Corp, College Station, TX) and a P-value of <0.05 was considered statistically significant.

3. Results

In our population of 9593 persons without clinically evident cardiovascular disease, hs-cTnT was detectable in 59% (5647 participants) and elevated in 7% (665 participants) of the study population. Fig. 1 shows the distribution of hs-cTnT by sex in the study population. In contrast to females in whom 51% had detectable hs-cTnT and 3% had elevated hs-cTnT, 69% percent of males had detectable hs-cTnT while 13% had elevetad hs-cTnT. Increasing concentrations of hs-cTnT were associated with older age, male sex, black race, diabetes, and hypertension (Table 1).

The continuous associations of systolic blood pressure, body mass index, glucose, total cholesterol, NT-proBNP, and hs-CRP with hs-cTnT after adjustment for traditional cardiovascular risk factors are shown in Fig. 2. NT-proBNP (Fig. 2, Panel E) was strongly and positively associated with higher hs-cTnT concentrations in a graded fashion. More moderate positive graded relationships were observed for systolic blood pressure, body mass index, and glucose but not with cholesterol or hs-CRP in this adjusted model.

Having higher predicted 10-year coronary heart disease risk was associated with higher likelihood of having elevated hs-cTnT

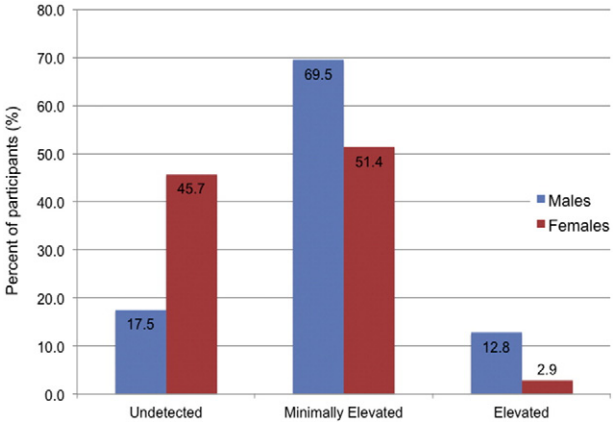

Fig. 1. Distribution of highly sensitive cardiac troponin T (ng/L) by sex.