ARIC Manuscript Proposal #1917

PC Reviewed: 3/20/12	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Association of diastolic dysfunction with high sensitivity troponin T and NT-proBNP across left ventricular geometries in the community – A preliminary analysis from the ARIC study

b. Abbreviated Title (Length 26 characters):
Diastolic dysfunction and high sensitivity troponin T in ARIC

2. Writing Group:

Writing group members: Amil M Shah, Christie Ballantyne, Dalane Kitzman, Ervin Fox, Ken Butler, Kunihiro Matsushita, Suma Konety, Scott D. Solomon; Others welcome.

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _AS_ **[please confirm with your initials electronically or in writing]**

First author: **Amil M Shah, MD MPH**
Address: 75 Francis Street
Boston, MA 02115

Phone: 617-525-6733 Fax: 617-582-6027
E-mail: ashah11@rics.bwh.harvard.edu

ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

Name: **Scott D Solomon, MD**
Address: 75 Francis Street
Boston, MA 02115

Phone: 857-307-1960 Fax: 857-307-1944
E-mail: ssolomon@rics.bwh.harvard.edu

3. Timeline:

Analysis will begin once this manuscript proposal is approved and approximately 3,000 Visit 5 echocardiograms have been performed and fully analyzed (anticipate June 2012). Anticipate manuscript completion in approximately the following 3 months.

4. Rationale:

With the advent of highly sensitive assays, circulating troponin T is detectable in a sizeable proportion of asymptomatic community dwelling individuals, with the prevalence and magnitude of detectable troponin significantly higher with older age, black race, and cardiovascular comorbidities such as hypertension, diabetes, and renal insufficiency.[1,2] Among elderly cohorts in particular, troponin T is detectable in approximately 66% of individuals using these novel assays.[1,3] Interestingly, the association between this biomarker and clinical events may be stronger with incident heart failure as opposed to incident ischemic events.[3,4] Detectable troponin levels with these highly sensitive assays demonstrate a significant and graded association with cardiovascular mortality and incident heart failure, even after adjustment for relevant clinical characteristics and comorbidities.[1,2,3]

The mechanisms mediating this association are unclear. Troponin elevation is significantly associated with increased left ventricular mass and wall thickness and reduced LVEF by MRI[2] and with the presence of electrocardiographic left ventricular hypertrophy.[1] Together, these findings suggest alterations in cardiac structure and function associated with cardiovascular comorbidities may partially mediate or occur in tandem with biomarker elevation. Diastolic dysfunction shares many risk factors with LV concentric remodeling, can occur in the absence of overt ventricular remodeling,[5] and is associated with mortality and incident heart failure in the elderly.[6,7,8] While strong associations with LV structure and gross systolic function (measured by LVEF) have been described, the relationship between troponin levels detected with high sensitivity assays and measures of diastolic dysfunction has not been well described. Among 1005 community dwelling individuals greater than 70 years old, troponin I levels measured with a standard assay were detectable with 22% of participants and significantly correlated with LV mass and LVEF but not diastolic function.[9] However, this analysis was significantly limited by both the relatively small proportion of participants with detectable troponin and the relatively crude assessment of diastolic function, based solely on mitral inflow Doppler parameters.

5. Main Hypothesis/Study Questions:

We hypothesize that, among asymptomatic ARIC participants with LVEF>50%, echocardiographic parameters of diastolic dysfunction will be associated with higher levels of troponin T using the high sensitivity assay, independent of LV mass index and LV wall thickness.

Specifically, we aim to determine the association of parameters of diastolic dysfunction (tissue Doppler imaging [TDI] E' – a measure of early diastolic relaxation; E wave/E' ratio – a measure of instantaneous LV filling pressure; and left atrial volume index [LAVi] – a marker of chronic elevations in LV filling pressure) with presence and magnitude of hsTnT overall and stratified by LV geometry, by LVEF, and by prevalent heart failure.

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary

of data analysis, and any anticipated methodologic limitations or challenges if present).

Study design:
This will be a cross-sectional analysis of the first 3,000 ARIC Visit 5 echocardiograms analyzed.

Inclusion/exclusion criteria:
Participants in atrial fibrillation or with missing data for key echocardiographic criteria (E wave, A wave, E wave deceleration time, TDI E', and LAVi) or biomarkers (hsTnT or NT-proBNP) will be excluded from this analysis.

Key variables of interest:
1. Echocardiographic variables (visit 5 echo) of LV diastolic function (E wave, A wave, E wave deceleration time, TDI E', and LAVi), LV structure (wall thickness, relative wall thickness, systolic and diastolic diameters and volumes), LV systolic function (LVEF, TDI S', LV end-systolic elastance), and pulmonary artery systolic pressure
2. Laboratory values (visit 5): high sensitivity troponin T, NT-proBNP, serum albumin and creatinine, urine albumin and creatinine, hemoglobin and hematocrit, glucose, hemoglobin A1C, total cholesterol, triglycerides, HDL, LDL
3. Clinical covariates (visit 5): age, gender, race/ethnicity, height, weight, blood pressure, heart rate, history of hypertension, diabetes, dyslipidemia, coronary artery disease, prior MI or revascularization procedure, prior stroke or TIA, peripheral arterial disease, heart failure, prior hospitalization for heart failure

Data analysis:
Troponin T will be modeled as both an ordered categorical and a continuous variable. For the categorical analysis, the study population will be divided into groups based on visit 5 hsTnT levels: participants with undetectable level will be placed in one group and the other 4 groups will be generated by splitting the observed hsTnT levels into approximate fourths. Clinical covariates, laboratory variables, echocardiographic parameters of structure and function, and echocardiographic parameters of diastolic function (E', E wave/E', LAVi, E/A ratio, E wave deceleration time) will be described by hsTnT category. For the continuous analysis, hsTnT levels will be log transformed, with undetectable values assigned a value just below the lower detection limit of the assay (0.0029 μg/L). Correlation of hsTnT level with echocardiographic parameters of LV structure, systolic function, and diastolic function will be assessed by univariable linear regression and by multivariable linear regression after adjusting for age, gender, race, blood pressure at time of echo, history of hypertension, diabetes, coronary artery disease, eGFR, and NT-proBNP. A second multivariable model will then be generated which further adjusts for LV mass index, LV relative wall thickness, and LVEF. Additional models with interaction terms for gender and race will be generated to assess for effect modification of the relationship between diastolic parameters and hsTnT levels by race or gender. Finally, participants will be divided into categories of diastolic dysfunction (normal, mild, moderate, severe) based on a modification of the Redfield criteria which

incorporates component diastolic dysfunction parameters. Prevalence and magnitude of hsTnT levels in each category will be determined and the association of hsTnT level with diastolic function grade assessed in univariable and multivariable analysis including the same variables as noted above. Similar analyses will be performed with NT-proBNP as the primary outcome (dependent) variable of interest.

Anticipated methodologic limitations:

A major limitation for this analysis is the echocardiographic determination of diastolic dysfunction. Numerous parameters reflecting cardiac structure, transmitral diastolic Doppler flow pattern, and mitral annular diastolic tissue velocities have been associated with diastolic performance in small physiologic studies and these component measures have been combined in numerous schemas for grading diastolic dysfunction, with two schemas most commonly employed currently.[7,10] We have focused our primary analysis on assessing the relationship of hsTnT with three well-established diastolic parameters, each reflecting a different manifestation of diastolic dysfunction, and each know to vary monotonically with diastolic dysfunction. In a secondary analysis, to assess the association of hsTnT with diastolic function grade, we combine these component measures using a hybrid of the two most widely applied grading schemas which allows for minimization of 'unclassifiable' individuals.

An additional limitation of this analysis is its cross-sectional nature. We anticipate performing a follow-up analysis to assess the relationship between diastolic function, hsTnT, and incident HF (both HF with preserved LVEF and HF with reduced LVEF) once adequate clinical follow-up post-Visit 5 is available.

7.a. Will the data be used for non-CVD analysis in this manuscript? ____ Yes __x__ No

b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons with a value RES_OTH = "CVD Research" for non-DNA analysis, and for DNA analysis RES_DNA = "CVD Research" would be used? ____ Yes ____ No
(This file ICTDER03 has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript? ____ Yes __x__ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 must be used to exclude those with value RES_DNA = "No use/storage DNA"? ____ Yes ____ No

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still

in active status. ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: http://www.cscc.unc.edu/ARIC/search.php

___x___ Yes _____ No

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?

MS#1811- (Oluleye et al) Association of high sensitive Troponin T (hs-cTnT),N-Terminal pro- brain natriuretic peptide (NT-proBNP) and high sensitivity C- reactive protein (hs-CRP) with cause- specific mortality: ARIC study

MS#1808- (Nambi et al) The utility high sensitivity cardiac troponin t in the prediction of heart failure risk

MS#1757 (Nambi et al) The association of high sensitivity troponin with heart failure, mortality and recurrent coronary heart disease (CHD) in individuals with prevalent CHD

MS#1564 (Saunders et al) Correlation of High Sensitivity Troponin-T (hs-cTnT) and Amino Terminal pro-Brain Natriuretic Peptide (NT-proBNP) with Renal Function Parameters; and Association with Mortality and Adverse Cardiovascular Events

MS#1172 (Nambi et al) Lp-PLA2 and hs-CRP as Predictors of Ischemic Stroke

MS#940 (Ballantyne et al) Lipoprotein-associated phospholipase A2, high sensititivity c-reactive protein, and risk for ischemic stroke

MS#934 (Folsom et al) An assessment of incremental coronary risk prediction using C-reactive protein and other novel risk markers

MS#889 (Ballantyne et al) Lipoprotein-associated phospholipase A2, high-sensitivity C-reactive protein and risk for incident coronary heart disease in middle-aged men and women in Atherosclerosis Risk in Communities Study

MS#606 (Folsom et al) C-reactive protein and incident cornary heart disease in the Atherosclerosis Risk in Communities (ARIC) Study

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ____ Yes __x__ No

11.b. If yes, is the proposal

___ A. primarily the result of an ancillary study (list number* _____)

___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____ _____ _____)

*ancillary studies are listed by number at http://www.cscc.unc.edu/aric/forms/

12. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.

References

[1] Saunders JT, Nambi V, de Lemos JA, Chambless LE, Virani SS, Boerwinkle E, Hoogeveen RC, Liu X, Astor BC, Mosley TH, Folsom AR, Heiss G, Coresh J, Ballantyne CM. Cardiac troponin T measured by a highly sensitive assay predicts coronary heart disease, heart failure, and mortality in the Atherosclerosis Risk in Communities study. *Circulation* 2011;123:1367-76.

[2] De Lemos JA, Drazner MH, Omland T, Ayers CR, Khera A, Rohatgi A, Hashim I, Berry JD, Das SR, Morrow DA, McGuire DK. Association of troponin T detected with a highly sensitive assay and cardiac structure and mortality risk in the general population. *JAMA* 2010;304:2503-12.

[3] deFilippi CR, de Lemos JA, Christenson RH, Gottdiener JS, Kop WJ, Zhan M, Seliger SL. Association of serial measures of cardiac troponin T using a sensitive assay with incident heart failure and cardiovascular mortality in older adults. *JAMA* 2010;304:2494-2502.

[4] Omland T, de Lemos JA, Sabatine MS, Christophi CA, Rice MM, Jablonski KA, Tjora S, Domanski MJ, Gersh BJ, Rouleau JL, Pfeffer MA, Braunwald E. A sensitive cardiac troponin T assay in stable coronary artery disease. *N Engl J Med* 2009;361:2538-47.

[5] Solomon SD, Janardhanan R, Verma A, Bourgoun M, Daley WL, Purkayastha D, Lacourciere Y, Hippler SE, Fields H, Naqvi TZ, Mulvagh SL, Arnold JMO, Thomas JD, Zile MR, Aurigemma GP. Effect of angiotensin receptor blockade and antihypertensive drugs on diastolic function in patients with hypertension and diastolic dysfunction: a randomized trial. *Lancet* 2007;369:2079-87.

[6] Aurigemma GP, Gottdiener JS, Shemanski L, Gardin J, Kitzman D. Predictive value of systolic and diastolic function for incident congestive heart failure in the elderly: the Cardiovascular Health Study. *J Am Coll Cardiol* 2001;37:1042-8.

[7] Redfield MM, Jacobsen SJ, Burnett JC, Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. *JAMA* 2003;289:194-202.

[8] Wang W, Yip GW, Wang AYM, Zhang Y, Ho PY, Tse MK, Lam PKW, Sanderson JE. Peak early diastolic mitral annulus velocity by tissue Doppler imaging adds independent and incremental prognostic value. *J Am Coll Cardiol* 2003;41:820-6.

[9] Eggers KM, Lind L, Ahlstrom H, Bjerner T, Barbier CE, Larsson A, Venge P, Lindahl B. Prevalence and pathophysiological mechanisms of elevated cardiac troponin I levels in a population-based sample of elderly subjects. *Eur Heart J* 2008;29:2252-8.

[10] Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, Waggoner AD, Flachskampf FA, Pellikka PA, Evangelista A. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *J Am Soc Echocardiogr* 2009;22:107-33.