ARIC Manuscript Proposal #1943

PC Reviewed: 5/8/12 Status: 2 Priority: A
SC Reviewed: _________ Status: _____ Priority: ____

1. **Full Title:** Performance of two echocardiographic schema for grading diastolic dysfunction in an elderly community-based cohort – A preliminary analysis from the ARIC study

b. **Abbreviated Title (Length 26 characters):**
Diastolic dysfunction schema in ARIC

2. **Writing Group:**
Writing group members: Amil M Shah, Christie Ballantyne, Dalane Kitzman, Ervin Fox, Ken Butler, Kunihiro Matsushita, Suma Konety, Gerardo Heiss, Sunil Agarwal, 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]

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**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).

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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:**
Heart failure with preserved ejection fraction (HFpEF) accounts for 50% of HF cases,\(^1,2\) is increasing in prevalence, and causes substantial morbidity,\(^3,4\) mortality,\(^5,6\) and resource utilization, particularly among the elderly. Although vascular and non-cardiac co-morbidities contribute,\(^7\) LV diastolic dysfunction is thought to be the primary cardiac perturbation underlying this heterogeneous syndrome,\(^8\) promoting increased LV filling pressure and myocardial stress, pulmonary hypertension and congestion. This model has been supported by invasive hemodynamic studies in small select series of patients,\(^9,10\) which have demonstrated an upward and leftward shift in the LV diastolic pressure-volume relationship in HFpEF. However, invasive hemodynamic assessment is not feasible routinely and clinically echocardiography is the most frequently employed method for assessing diastolic function. Numerous echocardiographic measures have been associated with diastolic performance in small physiologic studies. Tissue Doppler velocities reflect early LV relaxation and correlate with the time constant of relaxation (tau) assessed invasively,\(^11,12\) transmirtal Doppler measures- alone or in combination with tissue Doppler measures – are associated with LV filling pressures;\(^13\) and structural abnormalities, such as left atrial enlargement, are thought to reflect chronicity of elevation in LV filling pressures.\(^14\) These component measures have been combined in numerous schemas for grading diastolic dysfunction, with two schemas most commonly employed currently – the Redfield criteria and the American Society of Echocardiography criteria (see table below).\(^15,16\) Particularly when defined using the Redfield criteria, the presence of diastolic dysfunction,\(^17,18\) along with progression in diastolic dysfunction,\(^19,20\) is associated with worse prognosis.

However, age-related changes in these structural and Doppler measures of diastolic function are well recognized.\(^16\) Diastolic dysfunction defined by existing echocardiographic criteria is frequently detected in asymptomatic older persons, most of whom never develop HF. For example, in the Olmstead County cohort, some degree of diastolic dysfunction was noted in 71% of participants \(\geq 75\) years old, compared to 12% of those 45-54 years old.\(^15\) However, only 8.4% of those \(\geq 75\) years old had clinical HF. One current limitation in the field is the lack of robust normative data for diastolic measures in the elderly. For example, tissue Doppler diastolic relaxation velocities are central in current diastolic dysfunction grading schemes, however, even the largest studies to provide normal ranges for healthy community dwelling individuals without prevalent CV risk factors included only \(~100\) subjects with age \(\geq 70\) years old.\(^21,22\) This lack of data on population norms in the elderly has made the distinction between benign age-related changes in diastolic parameters and changes associated with increased HF risk difficult to define. Echocardiography in the fifth visit of ARIC therefore provides a unique opportunity to assess the performance of currently employed diastolic grading schemas with regards to association with burden of HF risk factors, soluble biomarkers of myocardial stress (NT-proBNP), and risk of incident HF in a biracial elderly cohort.

5. **Main Hypothesis/Study Questions:**

We hypothesize that, among asymptomatic ARIC participants with LVEF>50%, current classification schemes for diastolic dysfunction will: (a) classify the majority of elderly
community dwelling individuals as having diastolic dysfunction regardless of HF risk based on clinical criteria; (b) leave a proportion of individuals ‘unclassifiable’; and (c) demonstrate modest concordance with each other for diastolic dysfunction grade.

Specifically, we aim to:
1. Define the frequency of normal, mild, moderate, and severe diastolic dysfunction among an elderly community-based cohort, including the frequency of ‘unclassifiable’ individuals, using the two most prominent criteria for grading diastolic dysfunction: the Redfield Criteria and the ASE Criteria (see table below), and determine the concordance between these criteria for grade of diastolic dysfunction
2. Determine the relationship between diastolic dysfunction and clinical HF risk factors (age, hypertension, diabetes, CAD, atrial fibrillation, obesity, renal insufficiency), echocardiographic HF risk markers (LVH, concentric remodeling, TR jet velocity), ARIC HF risk score, and NT-proBNP level.
3. Identify the component measures of diastolic function (E/A, E’, E/E’, LAVi) most strongly associated with ARIC HF risk score and NT-proBNP level.

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:
This analysis will include all ARIC participants undergoing echocardiography at Visit 5 with a reading center determined LVEF≥50%. Participants in atrial fibrillation at the time of echocardiography, with a history of heart failure hospitalization, or with missing data for key echocardiographic criteria (LVEF, E wave, A wave, E wave deceleration time, TDI E’, and LAVi), clinical covariates (ARIC HF risk score), 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), and pulmonary artery systolic pressure
2. Laboratory values (visit 5): 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:
Participants will be classified into diastolic function categories (normal, mildly abnormal, moderately abnormal, severely abnormal, unclassifiable) by both the Redfield and ASE criteria as described in the Table. Clinical covariates, laboratory variables, echocardiographic measures of structure and function, ARIC HF risk score, NT-proBNP, and diastolic function measures will be described by diastolic dysfunction category for each schema, and association assessed by trend test. In addition, the frequency of diastolic dysfunction categories will be described in relation to incident HF risk by stratifying the study population into quintiles based on ARIC HF risk score. To identify the component measures of diastolic function most strongly associated with HF risk markers, correlation will be assessed with ARIC HF risk score and NT-proBNP level individually using general linear models with component diastolic measures (each of E/A, E’, E/E’, DT, LAVi) as dependent variables, adjusting for age, gender, and race/ethnicity. In a secondary analysis, we will also test for effect modification of these associations by age, gender, and race/ethnicity.

Table: Common diastolic function grading schemas

<table>
<thead>
<tr>
<th>Grade of Diastolic Dysfunction</th>
<th>Redfield</th>
<th>ASE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>E/A &gt;0.75 &amp; ≤0.75</td>
<td>E/A ≤0.8</td>
</tr>
<tr>
<td>Mild (Grade I)</td>
<td>E/A &gt;0.75 &amp; &gt;0.75</td>
<td>E/A &gt;0.8</td>
</tr>
<tr>
<td>Moderate (Grade II)</td>
<td>DT &gt;140</td>
<td>DT &gt;200</td>
</tr>
<tr>
<td>Severe (Grade III)</td>
<td>DT &gt;140</td>
<td>DT &gt;200</td>
</tr>
</tbody>
</table>

E/A – ratio of early-to-late diastolic mitral inflow velocities; DT – deceleration time; E’ – tissue Doppler early mitral annular relaxation velocity; E/E’ – ratio of early diastolic mitral inflow velocity to early mitral annular relaxation velocity; LAVi – left atrial volume index

Anticipated methodologic limitations:
A major limitation for this analysis is its cross-sectional design. Ideally, we would be able to relate both diastolic grade by either scheme and component diastolic function measures to incident HF events. However, this data will not be available for several years and we have focused on both ARIC HF risk score and NT-proBNP as integrated risk markers of incident HF. An additional limitation of this analysis is lack of a gold standard measure, or even robust normative values, by which to define diastolic dysfunction in this elderly cohort. We anticipate performing follow-up analyses to: (1) define normative values for component diastolic measures based on healthy elderly
individuals in ARIC once all Visit 5 echocardiograms are analyzed; and (2) assess the relationship between diastolic function component measures and summary grades and incident HF (both HFpEF and HFREF) 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  
___ 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  
___ 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.csc.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)?


Fox ER, Han H, Taylor HA, Walls UC, Samdarshi T, Skelton TN, Pan J, Arnett D. The prognostic value of the mitral diastolic filling velocity ratio for all-cause mortality and


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/](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


19 Kane GC, Karon BL, Mahoney DW, Redfield MM, Roger VL, Burnett JC, Jacobsen SJ, Rodeheffer RJ. Progression of left ventricular diastolic dysfunction and risk of heart failure. *JAMA* 2011;306:856-63.

