ARIC Manuscript Proposal #1983

PC Reviewed: 8/14/12  Status: A  Priority: 2
SC Reviewed: _________  Status: _____  Priority: ____

1.a. Full Title: Association of blood lactate with incident atrial fibrillation: the Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters): Lactate & Afib

2. Writing Group:
   Writing group members: Kunihiro Matsushita, Alvaro Alonso, Yingying Sang, Lin Y. Chen, Josef Coresh, Maria Ines Schmidt, Frederick L. Brancati, Ron C. Hoogeveen, Christie M. Ballantyne, J. Hunter Young; others welcome

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

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3. Timeline: Data to be used in this proposal are already available. Analyses and manuscript preparation will be performed over the next 6 months.

4. Rationale: Insufficient oxidative capacity has been reported to be involved in the development of age-related degenerative diseases such as hypertension, atherosclerosis,
and insulin resistance.\textsuperscript{1, 2} For example, decrease in mitochondrial size and density,\textsuperscript{3, 4} oxidative gene expression,\textsuperscript{4-7} oxidative phosphorylation,\textsuperscript{8-10} and whole-body aerobic capacity has been linked to insulin resistance and type 2 diabetes.\textsuperscript{5, 11} Also, several basic studies suggest that reduced oxidative capacity may play a role in the development of atrial fibrillation (Afib).\textsuperscript{12-14} However, to our knowledge, there are no epidemiological data for this association.

The ARIC Study provides an excellent opportunity to investigate a possible relationship between elevated plasma lactate levels, an indirect indicator of insufficient oxidative capacity,\textsuperscript{15} and the incidence of atrial fibrillation in a middle-aged, biracial population. Plasma lactate concentration rises as oxidative capacity decreases and flux through glycolytic pathways increases. Indeed, prior work demonstrates that lactate levels are correlated with conditions linked to reduced oxidative capacity like insulin resistance, and elevated blood pressures.\textsuperscript{15-19}

5. Main Hypothesis/Study Questions:
Blood lactate concentration is positively associated with incidence of Afib independently of potential confounders.

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).

Inclusions/exclusions:
- All black and white ARIC participants who have lactate data at visit 4 (the only visit for which lactate data are available in the entire cohort) and were free of prevalent Afib (defined by ECG at visits 1-4 or Afib hospitalization before visit 4).

Exposure:
- Plasma lactate
Plasma lactate was measured using an enzymatic reaction to convert lactate to pyruvate using a Roche Hitachi 911 auto-analyzer at ARIC visit 4.

Outcome:
- Incident Afib: As previously done in ARIC,\textsuperscript{20} identification of Afib after visit 4 will be conducted through hospital discharge codes (ICD-9 codes 427.31 and 427.32) and death certificates (427.3 or I48). Vast majority of Afib cases in ARIC have been identified from hospital discharges.\textsuperscript{20} For the present proposal, we will consider incident Afib between visit 4 and December 31, 2009.

Other variables of interest and covariates:
- Sociodemographics: age, race, gender, education level
- Physical information: body mass index (height, body weight), waist circumference, blood pressure (and use of antihypertensive medication), heart rate
- Lifestyle: smoking status, alcohol intake, and physical activity (evaluated at visit 3)
Comorbidities: history of cardiovascular disease (coronary heart disease, stroke, and heart failure), dyslipidemia (total cholesterol, HDL cholesterol, and triglyceride), diabetes (diabetic status, fasting glucose, insulin, homeostatic model assessment insulin resistance [HOMA-IR]), kidney function

Statistical Analysis Plan:
The primary analysis will use Cox proportional hazards models to quantify the association between lactate and incident Afib. Lactate will be treated as categorical (quartiles or quintiles) and continuous variables with splines respectively in the models. We will adjust for the covariates listed above. We will repeat the analysis after stratifying the study sample by age, gender, race, and presence/absence of comorbidities such as history of cardiovascular disease, obesity, and diabetes.

We will implement four models for the adjustment for covariates. Model 1 will be crude. Model 2 will be adjusted for demographic variables, i.e., age, gender, race, and level of education. Model 3 will be further adjusted for traditional risk factors, i.e., systolic blood pressure, antihypertensive medication, smoking, total cholesterol, HDL cholesterol, and a history of cardiovascular disease. Model 4 will be further adjusted for variables potentially associated with lactate production/metabolism, i.e., body mass index, waist circumference, HOMA-IR, physical activity, alcohol intake, estimated glomerular filtration rate, liver enzymes, and heart rate.

We will conduct a few sensitivity analyses. Firstly, given that several anti-diabetic drugs (e.g., biguanides and thiazolidinediones) affect lactate concentration and may modify cardiovascular risk,\(^\text{21,22}\) we will evaluate the association after excluding participants who were taking these drugs. Secondly, if lactate is associated with Afib, to elucidate whether other cardiovascular diseases are a mediator of lactate-Afib relationship, we will adjust for incident cardiovascular disease as time-varying covariate. Thirdly, since lactate levels at baseline may be elevated among those with subclinical cardiac dysfunction, to minimize the possibility of reverse causation, we will assess the association between lactate levels and Afib risk after excluding heart failure cases within three years of follow-up. In this connection, we will also adjust for N-terminal pro-B-type natriuretic peptide (NT-proBNP).

Limitations:
The ascertainment of Afib is based mostly on hospital discharges. Even though Afib in ARIC has been validated,\(^\text{20}\) we will most likely miss some cases of Afib diagnosed and treated in outpatient settings. As with any observational study, we will not be able to rule out the possibility of residual confounding. A single measurement of lactate is an additional limitation.

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)?
No previous proposal in ARIC focus specifically on the association of plasma lactate and 
atrial fibrillation.

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

11.b. If yes, is the proposal
____X__  A. primarily the result of an ancillary study (list number*  _2009.02,
2008.12)

_____  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. Linnane A, Ozawa T, Marzuki S, Tanaka M. Mitochondrial DNA mutations as an important 
contributor to ageing and degenerative diseases. Lancet. 1989;333:642-645
