ARIC Manuscript Proposal # 1694

1.a.   **Full Title**: Association of blood lactate with prevalence and incidence of coronary artery disease in subsamples of the Atherosclerosis Risk in Communities Study

  b.   **Abbreviated Title (Length 26 characters)**: Lactate and CAD.

2.   Writing Group:

   Writing group members: Morgana L. Mongraw-chaffin, Kunihiro Matsushita, James S. Pankow, Josef Coresh, Maria Ines Schmidt, Ron Hoogeveen, Christie Ballantyne, Frederick Brancati, J. Hunter Young; others welcome

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __MLMC___ **[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**: Accumulating evidence indicates that insufficient oxidative capacity plays an important role in the development of metabolic illnesses and their complications, such as insulin resistance, hypertension, and atherosclerosis.[1-3] For example, insulin resistance and type 2 diabetes are associated with decreased mitochondrial size and density,[4,5] decreased oxidative gene expression,[5-8] decreased oxidative phosphorylation,[9-11] and decreased whole-body aerobic capacity.[6,12] However, clinical or epidemiological research on oxidative capacity as a predictor of age-related degenerative diseases has been limited by the absence of a simple, noninvasive technique to measure oxidative capacity. Blood lactate is an indirect indicator of insufficient oxidative capacity: when oxidative capacity decreases, flux through glycolytic pathways increases and blood lactate rises.

While prior work suggests that lactate is elevated among obese and insulin resistant subjects,[3,13,14] there has been very little investigation of the relationship between oxidative capacity and coronary artery disease (CAD) or atherosclerosis more generally. There is some evidence form older animal studies that vascular oxidative metabolism may differ in the presence of atherosclerosis and that such variations may indicate differences in susceptibility to plaque formation.[15,16] From a similar study, Hajjar, Farber, and Smith suggest a cyclical relationship between energy deficiency and lipid accumulation in the advancement of atherosclerosis that may be initiated by decreased oxidative capacity.[17] The connection between oxidative capacity and lipids is also seen through increased lipid sequestration within atherosclerotic lesions due to the accumulation of lactate.[18] Similarly, recent cross-sectional work in the ARIC carotid MRI study found lactate to be associated with type 2 diabetes, as well as with differences in lipid levels in non-diabetic subjects.[3] It is possible that oxidative capacity may contribute to atherosclerosis through pathways partially shared with type 2 diabetes.[18,19] For instance, decreased oxidative capacity may contribute to LDL oxidation via reactive oxygen species(ROS) production and there is evidence that ROS production may provide more direct pathways to atherosclerosis as well.[20,21] Similarly, comorbidity with diabetes may further increase oxidative stress and promote the continued development of CAD.

A random sub-cohort of the ARIC study from a case-cohort study for incident diabetes between visit 1 and visit 4, provides an excellent opportunity to investigate an independent and longitudinal association of blood lactate with prevalence and incidence of CAD in a middle-aged, biracial general population.

5. **Main Hypothesis/Study Questions**:
Hypothesis: Blood lactate concentration is positively associated with prevalence and incidence of CAD independent of potential risk factors.

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).**
Primary analysis;
We will use an ancillary case-cohort study established for incident diabetes with visit 1 as baseline. The details about this case-cohort study have been previously described.[18,19] Briefly, from 10,275 eligible participants (after excluding participants with prevalent diabetes at visit 1 or without any follow-up visits or sufficient stored specimens), 1,198 participants were selected on ethnicity-stratified (50% white, 50% black) random samples of both the entire eligible members and cases of incident diabetes detected between visit 1 and visit 4 (≈9 years apart). Of these,

lactate was measured in 1,077 participants (626 random samples from the eligible participants and 451 random samples from cases of incident diabetes).

To obtain estimates representing the entire ARIC non-diabetic cohort, we will treat the random samples (n=626) from the entire eligible participants as the primary sample with weights taking into account over-sampling of blacks. We will repeat our analysis in 451 participants who developed diabetes within 9 years of follow-up and evaluate whether the association of lactate with prevalence/incidence of coronary artery disease is consistent with the cohort random sample.

Inclusions/Exclusions:
-As described above for the diabetes case-cohort study.

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

Outcome:
- Prevalent coronary artery disease:
We will use the standard ARIC derived variable for prevalent coronary heart disease that contains information on history of myocardial Infarction, heart or arterial surgery, coronary bypass, and angioplasty.

- Incident coronary artery disease:
Incident CAD including a hospitalized myocardial infarction, fatal CAD, or cardiac procedure through December 31, 2007.

Other variables of interest and covariates:
-Sociodemographics: age, race (accounted for with weighting from stratified sampling), gender, education level
-Physical information: body mass index, waist circumference, HDL cholesterol, LDL cholesterol, triglycerides, total cholesterol
-Lifestyle: smoking status, alcohol habit, and physical activity
-Comorbidities: dyslipidemia, diabetes, hypertension, stroke
-Intermediates over time: ankle-bronchial index, carotid intima-media thickness (IMT)
-Medication use: hypertensive medication, cholesterol lowering medication, aspirin, NSAIDS, diabetes medications

Statistical Analysis Plan:
-Cross-sectional analysis:
We will use log-binomial regression models to estimate prevalence ratio for CAD according to lactate concentrations. Lactate will be treated as categorical (tertiles or quartiles) and continuous variables with splines respectively in the models. We will adjust for the covariates listed above.

-Longitudinal analysis:
The survival analysis will use Cox proportional hazards models to quantify the association of lactate with incident CAD. Lactate will be treated as categorical (tertiles or quartiles) and

continuous variables with splines respectively in the models. We will adjust for the covariates listed above, including investigating the the role of ankle-bronchial index and carotid IMT as intermediates over time. We will repeat the analysis after stratifying the study sample by gender. We will also perform a formal test for interaction of the lactate/CAD relationship by LDL cholesterol levels.

We will conduct a few sensitivity analyses. Firstly, we will investigate whether the association of lactate with CAD is different in the subcohort than in the oversampled case-only group. Secondly, since stroke or heart failure events during follow-up can act as competing endpoints, we will conduct the same analysis among participants who did not experience incident stroke or heart failure during follow-up.

Limitations:

As with any observational study, we will not be able to rule out the possibility of residual confounding. While, we will anlyse the data longitudinally, it may still not be possible to clarify the exact temporality of the lactate/CAD relationship. A single measurement of lactate is an additional limitation. Furthermore, lactate is an indirect measure of oxidative capacity and may be elevated due to other processes not related to atherosclerosis such as hypoxia in adipose tissue.

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)?

Proposals using lactate as the exposure:

1684 Association of blood lactate with prevalence and incidence of hypertension in subsamples of the Atherosclerosis Risk in Communities Study; Matsushita, K.
1349: Association of blood lactate with insulin resistance and type 2 diabetes: The Atherosclerosis Risk in Communities Carotid MRI Study; Crawford S.
1661: Novel risk factors and the prediction of type 2 diabetes in the Atherosclerosis Risk in Community Study (ARIC); Raynor LA.

Proposal #1684 titled "Association of blood lactate with prevalence and incidence of hypertension in subsamples of the Atherosclerosis Risk in Communities Study" is very highly related, using the same case-cohort data, the same exposure, and shares the same authors and writing group.

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* 1995.09
**   and 2006.04)**
**   ___   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.

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