

ARIC Manuscript Proposal #1866

PC Reviewed: 11/8/11
SC Reviewed: _____

Status: A
Status: _____

Priority: 2
Priority: _____

1.a. Full Title: Association of blood lactate with cardiovascular events and mortality: the Atherosclerosis Risk in Communities Study

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

2. Writing Group:

Writing group members: Kunihiro Matsushita, Emma Williams, Morgana L. Mongraw-chaffin, Josef Coresh, Maria Ines Schmidt, Ron Hoogeveen, Christie 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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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: 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, 2} For example, insulin resistance and type 2 diabetes are associated with decreased mitochondrial size and density,^{3, 4} decreased oxidative gene expression,^{4, 7} decreased oxidative phosphorylation,⁸⁻¹⁰ and decreased whole-body aerobic capacity.^{5, 11} 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. Prior work suggests that lactate is elevated among obese and insulin resistant subjects.^{12, 13} Furthermore, a few studies have shown that a blood lactate level is positively correlated with blood pressure.¹⁴⁻¹⁶ However, these studies were mainly cross-sectional^{14, 15} or limited to obese individuals,¹⁶ leaving uncertainty as to whether decreased oxidative capacity, expressed as elevated lactate, predicts the development of cardiovascular disease (CVD) in the general population.

The ARIC Study provides an excellent opportunity to investigate a possible relationship between blood lactate and the incidence of CVD in a middle-aged, biracial population.

5. Main Hypothesis/Study Questions:

Blood lactate concentration is positively associated with cardiovascular events and mortality 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:

- All black and white ARIC subjects with data of lactate at visit 4 (the only visit for which lactate data are available in the entire cohort)

Exclusions:

-Ethnicity other than black or white
-Individuals without data of lactate

Exposure:

-Plasma lactate

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

Outcome (All events that occurred after visit 4 and before January 1, 2009 will be included):

-Incident CHD including a hospitalized myocardial infarction (MI), fatal CHD, cardiac procedure or electrocardiogram MI (serial changes)
-fatal CHD

- Incident stroke: definite and possible incident stroke
- Incident HF: the first HF hospitalization coded 428 according to the ICD-9 or death from HF (coded 428 for ICD-9 and I50 for ICD-10)^{17, 18}
- All-cause death

Other variables of interest and covariates:

- Sociodemographics: age, race, gender, education level
- Physical information: body mass index, waist circumference, blood pressure, heart rate
- Lifestyle: smoking status, alcohol habit, and physical activity
- Comorbidities: history of cardiovascular disease (coronary heart disease [CHD], stroke, and heart failure [HF]), dyslipidemia (LDL 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 CVD events. 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 CVD, 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, and race. Model 3 will be further adjusted for traditional risk factors, i.e., systolic blood pressure, antihypertensive medication, smoking, alcohol intake, level of education, body mass index, LDL-C, HDL-C, a self-reported history of coronary heart disease (CHD), and estimated glomerular filtration rate. Model 4 will be further adjusted for variables associated with insulin resistance or exercise capacity, i.e., HOMA-IR, physical activity, and heart rate.

We will conduct a few sensitivity analyses. Firstly, given that several anti-diabetic and antihypertensive drugs affect lactate concentration and may modify cardiovascular risk,^{19, 20} we will evaluate the association after excluding participants who were taking these drugs. Secondly, 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 HF risk after excluding HF cases within three years of follow-up. In this connection, if there is an association between lactate and incident HF, we will also adjust for NT-proBNP. Thirdly, if lactate is associated with both CHD and HF, to elucidate whether CHD is a mediator of lactate-HF relationship, we will examine HF occurring in the absence of clinical CHD. To accomplish this, we will conduct our analysis limiting to censoring incident CHD cases that occurred prior to the incidence of HF.

Limitations:

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
 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>

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

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.

1684: Association of blood lactate with prevalence and incidence of hypertension in subsamples of the Atherosclerosis Risk in Communities Study; Matsushita K.

#1694: Association of blood lactate with prevalence and incidence of coronary artery disease in subsamples of the Atherosclerosis Risk in Communities Study; Mongraw-chaffin, ML.

The most relevant proposal is #1694, which investigates similar topic in subsamples of a case-cohort study for diabetes and the CARMRI. The present proposal will study the entire cohort at visit 4 which will allow us to study cardiovascular outcomes rarer than CHD (e.g., stroke and HF). Also, key authors in #1694 are invited in this proposal.

13. Doar JW, Wynn V, Cramp DG. Blood pyruvate and plasma glucose levels during oral and intravenous glucose tolerance tests in obese and non-obese women. *Metabolism*. 1968;17:690-701
14. Jansson, Larsson, Lönnroth. Relationship between blood pressure, metabolic variables and blood flow in obese subjects with or without non-insulin-dependent diabetes mellitus. *European Journal of Clinical Investigation*. 1998;28:813-818
15. Baron AD, Brechtel-Hook G, Johnson A, Hardin D. Skeletal muscle blood flow. A possible link between insulin resistance and blood pressure. *Hypertension*. 1993;21:129-135
16. Crawford SO, Ambrose MS, Hoogeveen RC, Brancati FL, Ballantyne CM, Young JH. Association of lactate with blood pressure before and after rapid weight loss. *Am J Hypertens*. 2008;21:1337-1342
17. Kottgen A, Russell SD, Loehr LR, Crainiceanu CM, Rosamond WD, Chang PP, Chambless LE, Coresh J. Reduced kidney function as a risk factor for incident heart failure: The atherosclerosis risk in communities (aric) study. *J Am Soc Nephrol*. 2007;18:1307-1315
18. Pazin-Filho A, Kottgen A, Bertoni AG, Russell SD, Selvin E, Rosamond WD, Coresh J. Hba(1c) as a risk factor for heart failure in persons with diabetes: The atherosclerosis risk in communities (aric) study. *Diabetologia*. 2008;51:2197-2204
19. Mégarbane B, Deye N, Malissin I, Baud FJ. Usefulness of the serum lactate concentration for predicting mortality in acute beta-blocker poisoning. *Clinical Toxicology*. 2010;48:974-978
20. Dell'Aglio DM, Perino LJ, Kazzi Z, Abramson J, Schwartz MD, Morgan BW. Acute metformin overdose: Examining serum ph, lactate level, and metformin concentrations in survivors versus nonsurvivors: A systematic review of the literature. *Annals of Emergency Medicine*. 2009;54:818-823