ARIC Manuscript Proposal #1866

PC Reviewed: 11/8/11	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**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]**

First author: Kunihiro Matsushita
Address: Department of Epidemiology,
Johns Hopkins Bloomberg School of Public Health,
615 N. Wolfe Street (Rm W6017), Baltimore, MD 21205
Phone: (443) 287-8766 Fax: (410) 955-0863
E-mail: kmatsush@jhsph.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: J. Hunter Young
Address: Welch Center for Prevention, Epidemiology, & Clinical Research
Johns Hopkins School of Medicine
2024 E. Monument Street, Suite 2-600
Baltimore, MD 21205-2223
Phone: 410-502-5808 Fax: 410-955-0476
E-mail: jhyoung@jhmi.edu

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 __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
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.

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)

___ 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. *The Lancet*. 1989;333:642-645
2. Bernal-Mizrachi C, Semenkovich CF. Fast predators or fast food, the fit still survive. *Nat Med*. 2006;12:46-47
3. Kelley DE, He J, Menshikova EV, Ritov VB. Dysfunction of mitochondria in human skeletal muscle in type 2 diabetes. *Diabetes*. 2002;51:2944-2950
4. Morino K, Petersen KF, Dufour S, Befroy D, Frattini J, Shatzkes N, Neschen S, White MF, Bilz S, Sono S, Pypaert M, Shulman GI. Reduced mitochondrial density and increased irs-1 serine phosphorylation in muscle of insulin-resistant offspring of type 2 diabetic parents. *The Journal of clinical investigation*. 2005;115:3587-3593
5. Mootha VK, Lindgren CM, Eriksson KF, Subramanian A, Sihag S, Lehar J, Puigserver P, Carlsson E, Ridderstrale M, Laurila E, Houstis N, Daly MJ, Patterson N, Mesirov JP, Golub TR, Tamayo P, Spiegelman B, Lander ES, Hirschhorn JN, Altshuler D, Groop LC. Pgc-1alpha-responsive genes involved in oxidative phosphorylation are coordinately downregulated in human diabetes. *Nature genetics*. 2003;34:267-273
6. Patti ME, Butte AJ, Crunkhorn S, Cusi K, Berria R, Kashyap S, Miyazaki Y, Kohane I, Costello M, Saccone R, Landaker EJ, Goldfine AB, Mun E, DeFronzo R, Finlayson J, Kahn CR, Mandarino LJ. Coordinated reduction of genes of oxidative metabolism in humans with insulin resistance and diabetes: Potential role of pgc1 and nrf1. *Proceedings of the National Academy of Sciences of the United States of America*. 2003;100:8466-8471
7. Sparks LM, Xie H, Koza RA, Mynatt R, Hulver MW, Bray GA, Smith SR. A high-fat diet coordinately downregulates genes required for mitochondrial oxidative phosphorylation in skeletal muscle. *Diabetes*. 2005;54:1926-1933
8. Bruce CR, Anderson MJ, Carey AL, Newman DG, Bonen A, Kriketos AD, Cooney GJ, Hawley JA. Muscle oxidative capacity is a better predictor of insulin sensitivity than lipid status. *The Journal of clinical endocrinology and metabolism*. 2003;88:5444-5451
9. Petersen KF, Befroy D, Dufour S, Dziura J, Ariyan C, Rothman DL, DiPietro L, Cline GW, Shulman GI. Mitochondrial dysfunction in the elderly: Possible role in insulin resistance. *Science*. 2003;300:1140-1142
10. Simoneau JA, Colberg SR, Thaete FL, Kelley DE. Skeletal muscle glycolytic and oxidative enzyme capacities are determinants of insulin sensitivity and muscle composition in obese women. *Faseb J*. 1995;9:273-278
11. Wisloff U, Najjar SM, Ellingsen O, Haram PM, Swoap S, Al-Share Q, Fernstrom M, Rezaei K, Lee SJ, Koch LG, Britton SL. Cardiovascular risk factors emerge after artificial selection for low aerobic capacity. *Science*. 2005;307:418-420
12. DiGirolamo M, Newby FD, Lovejoy J. Lactate production in adipose tissue: A regulated function with extra-adipose implications. *Faseb J*. 1992;6:2405-2412

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