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

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

2. Writing Group:
   Writing group members: Kunihiro Matsushita, Morgana L. Mongraw-chaffin, James S. Pankow, 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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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. For example, insulin resistance and type 2 diabetes are associated with decreased mitochondrial size and density, decreased oxidative gene expression, decreased oxidative phosphorylation, and decreased whole-body aerobic capacity. 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. Furthermore, a few studies have shown that a blood lactate level is positively correlated with blood pressure. However, these studies were mainly cross-sectional or limited to obese individuals, leaving uncertainty as to whether decreased oxidative capacity, expressed as elevated lactate, predates the development of hypertension in the general population.

Two subsamples of the ARIC study, a case-cohort study for incident diabetes between visit 1 and visit 4 and the carotid MRI (ARIC Carotid MRI) study, provide an excellent opportunity to investigate an independent association of blood lactate with prevalence and incidence of hypertension in a middle-aged, biracial general population.

5. Main Hypothesis/Study Questions:
Hypothesis 1: Blood lactate concentration is positively associated with prevalence and incidence of hypertension independently 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. 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 hypertension is consistent with the cohort random sample.
Secondary analysis:
We will use ARIC Carotid MRI Study sample to check the robustness of our findings for the association between lactate and prevalent hypertension. The details about ARIC Carotid MRI Study has been previously described. Briefly, participants were selected from among the surviving ARIC study participants with a stratified sampling plan on the basis of the most recent intima-media thickness (IMT) and field center. The goal was to recruit 1,200 participants with high values of maximum carotid artery IMT (maximum over six sites: left and right common carotid artery, carotid bifurcation, and internal carotid artery at their most recent US examination (examination 3 or 4, performed between 1993 and 1995 or between 1996 and 1998, respectively) and 800 individuals who were selected randomly from among the remaining eligible participants. Field center-specific cutoff points of carotid IMT were adjusted over the recruitment period to approximately achieve this goal, with 100% sampling above the cutoff point and a sampling fraction (16.5%-25.5%) below the cutoff point. The cutoff point was 1.135 mm in Forsyth County, NC; 1.000 mm in Jackson, MS; 1.280 mm in suburban Minneapolis, MN; and 1.215 mm in Washington County, MD; representing the 73rd, 69th, 73rd, and 68th percentiles of maximal IMT from examination 4, respectively.

Persons who were not black or white (n = 10 in Forsyth County, NC) were excluded from the selection process, as were those without IMT measurements at examination 3 or 4 (n = 1,428). A total of 4,306 persons were contacted and invited to participate in the study. Of these, 1,403 refused and 837 were ineligible due to contraindications to MRI or contrast media (n = 206), difficulty understanding questions or providing informed consent (n = 51), prior carotid revascularization on either side (for the low IMT group) or on the side selected for imaging (for the high IMT group) (n = 58), a self-reported health problem (n = 486) or another reason (n = 36), leaving 2,066 participants (1,250 with high IMT, 816 with low IMT).

Of these, non-fasting individuals and individuals with missing variables of interest (e.g. lactate, diabetes, and potential confounders) will be excluded. Since metformin increases blood lactate levels, those who took metformin during the 4 weeks prior to the ARIC Carotid MRI examination will be excluded. After exclusions, the final analysis sample would include 1,709 participants.

All analyses will be weighted by the sampling weights based on the probability of being selected from each field center based upon the high IMT status of each participant. The sampling weight among high IMT subjects was approximately equal to 1 for all field centers. The sampling weights for individuals in the remainder of the IMT distribution varied according to field center, ranging from 3.9 to 6.1.

Inclusions/Exclusions:
- As described above for each substudy.

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 hypertension: Prevalent hypertension will be defined as systolic blood pressure (SBP) of ≥140 mmHg, diastolic blood pressure (DBP) of ≥90 mmHg, a self-reported antihypertensive medical treatment for hypertension.

Incident hypertension (only for the case-cohort study sample): We will use three different sources to ascertain incident hypertension: measured blood pressure (SBP/DBP ≥140/90 mmHg) at visit 2, visit 3, and visit 4, self-reported medications for hypertension at visit 2, visit 3 and visit 4, and self-reported medications for hypertension from annual follow-up phone calls after visit 4 through the most recent data available. We recognize the limitation of not having blood pressure measurements after visit 4 and hence missing undiagnosed hypertension but knowledge and diagnosis of hypertension, even among minority groups, is quite high.20

Other variables of interest and covariates:
- Sociodemographics: age, race, gender, education level
- Physical information: body mass index, waist circumference, blood pressure (due to the potential problem for baseline adjustment, we will also run a model without blood pressure at baseline)
- Lifestyle: smoking status, alcohol habit, and physical activity
- Comorbidities: dyslipidemia, diabetes (only in ARIC Carotid MRI Study)

Statistical Analysis Plan:
- Cross-sectional analysis (both case-cohort study and Carotid MRI study samples): We will use log-binomial regression models to estimate prevalence ratio for hypertension 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. After excluding those who were taking antihypertensive drugs, we will evaluate the correlation between lactate and systolic/diastolic blood pressure.

- Longitudinal analysis (only case-cohort study sample): The survival analysis will use Cox proportional hazards models to quantify the association of lactate with incident hypertension. 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. We will repeat the analysis after stratifying the study sample by gender and race.

We will conduct a few sensitivity analyses. Firstly, since the adjustment for baseline blood pressure may bias the associations,21 we will also analyze models without blood pressure variables at baseline. Secondly, since coronary heart disease 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 coronary disease or heart failure during follow-up. Thirdly, we will analyze a subpopulation who had normal blood pressure (<120/80 mmHg) at baseline (visit 1). Finally, we will evaluate whether the association of lactate with incident hypertension varies across definitions of incident hypertension (self reported vs. all hypertension including undiagnosed hypertension) from visit 1 to visit 4.
Limitations:
As with any observational study, we will not be able to rule out the possibility of residual confounding. There will be misclassification of incident hypertension by only using self-reported hypertension after visit 4. However, self-reported incident hypertension has been used in previous studies, and we will also evaluate whether the inclusion of measured blood pressure would change the relative association of lactate with hypertension using data from visit 1 to visit 4. 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.
Proposals using incident hypertension as the primary outcome

#270C: Relationship between postural change in blood pressure and three-year incidence of hypertension; Holme, I.
#365: Women's Employment Status: Associations with Prevalent and Incident Hypertension; Rose, K.
#416: Plasma Fatty Acid Composition and 6-Year Incidence of Hypertension in Middle-Aged Adults; Zheng, ZJ.
#422: Physical Activity and Incidence of Hypertension in Men and Women; Pereira, MA.
#423: Insulin and Hypertension; Folsom, AR.
#424: Magnesium and Hypertension; Folsom, AR.
#425: Fibrinogen and Hypertension; Folsom, AR.
#429: Explaining the association between race and hypertension incidence; Nieto, J.
#451: Alcohol consumption and incident hypertension; Fuchs, FD.
#456: Neighborhood socioenvironmental characteristics, race, and incidence of hypertension in the ARIC cohort; Roux, AVD.
#459: The relationship of physical activity to incident hypertension: The ARIC Study; Evenson, K.
#776: Retinal arteriolar diameter and its relation to Incident Hypertension: The Atherosclerosis Risk in Communities Study; Wong, T.
#998: The Natural History of Pre-Hypertension; Kshirsagar, AV.
#1032: C-Reactive Protein and the Change in Blood Pressure among Individuals Initially without Hypertension; Kshirsagar, AV.
#1077r: Uric Acid and Incident Hypertension in a Biracial Cohort: the Atherosclerosis Risk in Communities Study; Mellen, PB.
#1135S: Restless Legs Syndrome, Obstructive Sleep Apnea, and Cardiovascular Disease; Winkelman, JW.
#1208: Dietary intake is related to risk of developing elevated or high blood pressure in middle-aged adults: ARIC; Steffen, LM.
#1231: Retinal Arteriolar Caliber and 10-year incidence of Hypertension; Wong, T.
#1287: Relationship between Periodontitis and Hypertension; Oluchi, V.
#1469: Impact of body mass index on incident hypertension in young-adult and middle-aged Chinese Asians, American Whites, and American Blacks: The People’s Republic of China Study, the Atherosclerosis Risk in Communities Study and the Coronary Artery Risk Development in Young Adults Study; Katz, E.
#1538: Association of Circulating Leukocyte and C-Reactive Protein Levels with Hypertension and Hypertension-Related Renal Dysfunction: the ARIC Study; Tian, N.

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.

References


