ARIC Manuscript Proposal – Abbreviated Form for Use with Proposals on Another Study's Form

ARIC Manuscript Proposal #1647

PC Reviewed: 05/11/10	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title:
Serum sodium, calcium, potassium, magnesium, phosphorus and QT interval duration.

b. Abbreviated Title (Length 26 characters):
QT interval duration and electrolytes.

2. Writing Group:
Writing group members: Yiyi Zhang, Wendy Post, Darshan Dalal, Sandeep Bansal, Elena Blasco-Colmenares, Gordon F. Tomaselli, Eliseo Guallar

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

First author: **Yiyi Zhang**
Address: 2024 E. Monument St 2-516
Baltimore, MD 21205

Phone: 410-502-8892 Fax:
E-mail: yzhang01@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: Eliseo Guallar
Address: 2024 E. Monument St 2-639
Baltimore, MD 21205

Phone: 410-614-0574 Fax: 410-955-0476
E-mail: eguallar@jhsph.edu

3. Timeline
Analysis will begin as soon as data is available. The manuscript will be complete by August 2010.

4. Rationale

Prolongation of the electrocardiographic QT interval is associated with increased risks of total, cardiovascular, and sudden cardiac death.[1-11] Sodium, potassium, and calcium are all important ion channel currents in determining the cardiac action potential duration.[12] The inward sodium current is responsible for the phase 0 depolarization. Gain-of-function mutation of the sodium channel leads to QT interval prolongation, as the abnormal sustained sodium current delays cardiac repolarization.[13] Intracoronary infusion of normal saline in patients with variant angina showed significant increase in the QT interval.[14] Calcium is the main current in phase 2 repolarization. Hypocalcaemia prolongs the QT interval while hypercalcemia shortens the QT interval.[12] Potassium, being responsible for the outward repolarisation currents, is also one of the main determinants of the QT interval. Reduction in serum potassium results in slower repolarisation and prolongation of QT intervals. Conversely, intravenous potassium infusion normalizes QT prolongation. [12,15] Magnesium is previously thought to have no significant effect on the action potential in the absence of hypocalcemia.[12] However, some studies reported that oral or intravenous magnesium attenuated the QT interval prolongation by class III antiarrhythmics.[16,17] It is worth noting that most of the observed associations between electrolytes and QT interval were based on animal studies, studies of genetic mutations, or non-physiological levels of electrolytes.

On a parallel note, serum phosphorus levels are generally inversely proportional to serum calcium levels, and there is a delicate balance between the two. Disturbances of calcium and phosphorus metabolism were associated with higher risks of cardiovascular and total mortality.[19-24] However, the relationship of serum phosphorus with QT interval is largely unexplored.

Using the ARIC data, we aim to evaluate the associations between physiological levels of electrolytes and the QT interval duration. In addition, we will be analyzing the NHANES III data concurrently, and combine the results from these two large cohorts of the general population.

5. Main Hypothesis/Study Questions

The purpose of this analysis was to evaluate the association between physiologic levels of electrolytes (sodium, calcium, potassium, magnesium, and phosphorus) and QT interval duration in the general population.

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)

The study will use visit 1 ARIC data. Included will be all ARIC participants for whom biochemistry measurements of serum electrolyte as well as QT interval on ECG is available. Excluded will be anyone with QRS>120ms, or for whom electrolytes or QT interval data is missing.

Primary outcome will be QT interval duration, with concomitant adjustment for age, race, sex and RR-interval duration in the models. In addition, sensitivity analysis using Bazett's equation-corrected QT interval duration will also be conducted.

Exposure of interest will be electrolytes including serum sodium, calcium, potassium, magnesium, and phosphorus.

We will categorize the distributions of electrolytes into quartiles based on the population distribution. Adjusted means and 95% confidence intervals (CIs) for QT interval duration by quartile of electrolytes will be calculated from multivariable linear regression models. Progressive degrees of adjustment were used. The fully adjusted will likely include age, race, sex, RR-interval, BMI, smoking, alcohol, education, total cholesterol, HDL, hypertension, diabetes, history of myocardial infarction, creatinine-based eGFR, and serum albumin. We will also test linear trend across quartiles of exposures. Sensitive analysis includes using electrolytes as continuous variables in the model, and interactions by pre-specified subgroups.

We will be performing parallel analysis in NHANES III, and combine the results from these two large cohorts of the general population.

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)?

#219 (population distribution of QT)

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

11.b. If yes, is the proposal

___ A. primarily the result of an ancillary study (list number* _____)

___ 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. Okin PM, Devereux RB, Howard BV, Fabsitz RR, Lee ET, Welty TK. Assessment of QT interval and QT dispersion for prediction of all-cause and cardiovascular mortality in American Indians: The Strong Heart Study. Circulation 2000;101(1):61-6.
2. Pytlak A, Piotrowski W. Prognostic Significance of QTc Interval for prediction total, cardiac, and ischemic heart disease mortality in community-based cohort from Warsaw Pol-MONICA population. A.N.E 2000;5(4):322-329.
3. Perkiomaki JS, Sourander LB, Levomaki L, Raiha IJ, Puukka P, Huikuri HV. Qt dispersion and mortality in the elderly. Ann Noninvasive Electrocardiol 2001;6(3):183-92.
4. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21(11):1539-58.
5. Robbins J, Nelson JC, Rautaharju PM, Gottdiener JS. The association between the length of the QT interval and mortality in the Cardiovascular Health Study. Am J Med 2003;115(9):689-94.
6. Sheehan J, Perry IJ, Reilly M, Salim A, Collins M, Twomey EM, Daly A, Loingsigh SN, Elwood P, Ben-Shlomo Y, Davey-Smith G. QT dispersion, QT maximum and risk of

cardiac death in the Caerphilly Heart Study. Eur J Cardiovasc Prev Rehabil 2004;11(1):63-8.
7. Nilsson G, Hedberg P, Jonasson T, Lonnberg I, Ohrvik J. QTc interval and survival in 75-year-old men and women from the general population. Europace 2006;8(4):233-40.
8. Rautaharju PM, Kooperberg C, Larson JC, LaCroix A. Electrocardiographic abnormalities that predict coronary heart disease events and mortality in postmenopausal women: the Women's Health Initiative. Circulation 2006;113(4):473-80.
9. Straus SM, Kors JA, De Bruin ML, van der Hooft CS, Hofman A, Heeringa J, Deckers JW, Kingma JH, Sturkenboom MC, Stricker BH, Witteman JC. Prolonged QTc interval and risk of sudden cardiac death in a population of older adults. J Am Coll Cardiol 2006;47(2):362-7.
10. Tan SY, Engel G, Myers J, Sandri M, Froelicher VF. The prognostic value of T wave amplitude in lead aVR in males. Ann Noninvasive Electrocardiol 2008;13(2):113-9.
11. Ziegler D, Zentai CP, Perz S, Rathmann W, Haastert B, Doring A, Meisinger C. Prediction of mortality using measures of cardiac autonomic dysfunction in the diabetic and nondiabetic population: the MONICA/KORA Augsburg Cohort Study. Diabetes Care 2008;31(3):556-61.
12. Surawicz B. Relationship between electrocardiogram and electrolytes. Am Heart J 1967;73(6):814-34.
13. Amin AS, Asghari-Roodsari A, Tan HL. Cardiac sodium channelopathies. Pflugers Arch 2009.
14. Kim JK, Kim NH, Shin IS, Noh DH, Kim YC, Kim SH, Choi JH, Park EM, Lee SJ, Yun KH, Yoo NJ, Lee EM, Oh SK, Jeong JW. Alteration of ventricular repolarization by intracoronary infusion of normal saline in patients with variant angina. Korean Circ J 2009;39(6):223-7.
15. Farquharson CA, Struthers AD. Increasing plasma potassium with amiloride shortens the QT interval and reduces ventricular extrasystoles but does not change endothelial function or heart rate variability in chronic heart failure. Heart 2002;88(5):475-80.
16. McBride BF, Min B, Kluger J, Guertin D, Henyan NN, Coleman CI, Silver BB, White CM. An evaluation of the impact of oral magnesium lactate on the corrected QT interval of patients receiving sotalol or dofetilide to prevent atrial or ventricular tachyarrhythmia recurrence. Ann Noninvasive Electrocardiol 2006;11(2):163-9.
17. Caron MF, Kluger J, Tsikouris JP, Ritvo A, Kalus JS, White CM. Effects of intravenous magnesium sulfate on the QT interval in patients receiving ibutilide. Pharmacotherapy 2003;23(3):296-300.
18. Peacock M. Calcium metabolism in health and disease. Clin J Am Soc Nephrol 2010;5 Suppl 1:S23-30.
19. Chonchol M, Dale R, Schrier RW, Estacio R. Serum phosphorus and cardiovascular mortality in type 2 diabetes. Am J Med 2009;122(4):380-6.
20. Tonelli M, Curhan G, Pfeffer M, Sacks F, Thadhani R, Melamed ML, Wiebe N, Muntner P. Relation between alkaline phosphatase, serum phosphate, and all-cause or cardiovascular mortality. Circulation 2009;120(18):1784-92.
21. Tonelli M, Sacks F, Pfeffer M, Gao Z, Curhan G. Relation between serum phosphate level and cardiovascular event rate in people with coronary disease. Circulation 2005;112(17):2627-33.
22. Dhingra R, Sullivan LM, Fox CS, Wang TJ, D'Agostino RB, Sr., Gaziano JM, Vasan RS. Relations of serum phosphorus and calcium levels to the incidence of cardiovascular disease in the community. Arch Intern Med 2007;167(9):879-85.
23. Foley RN, Collins AJ, Ishani A, Kalra PA. Calcium-phosphate levels and cardiovascular disease in community-dwelling adults: the Atherosclerosis Risk in Communities (ARIC) Study. Am Heart J 2008;156(3):556-63.

24. Kestenbaum B, Sampson JN, Rudser KD, Patterson DJ, Seliger SL, Young B, Sherrard DJ, Andress DL. Serum phosphate levels and mortality risk among people with chronic kidney disease. J Am Soc Nephrol 2005;16(2):520-8.