ARIC Manuscript Proposal # 1195

1.a. Full Title: Changes in central retinal artery equivalent (CRAE) and Blood pressure

b. Abbreviated Title (Length 26 characters): CRAE and Blood pressure

CRAE and BP changes

2. Writing Group:
   Writing group members: A. Solouki and (in alphabetical order) C. Crainiceanu, R. Klein, E. Selvin, R. Sharrett, T. Wong.

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

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3. Timeline:
   September 2006-December 2006
4. **Rationale:**

To understand the relationship between retinal arteriolar diameters and clinical cardiovascular disease, it is important to understand the relationship between retinal arteriolar diameters and levels of blood pressure. A key question is whether narrow retinal arterioles result from a largely physiologic phenomenon, i.e., active constriction that is a cause or perhaps the result of current blood pressure levels or whether, at least in part, the presence of narrower arterioles suggests persistent or irreversible arteriolar damage. This was addressed in ARIC (Sharrett et al 1999), who showed that narrow retinal arterioles were related to current blood pressure levels and to previous blood pressure levels independent of current blood pressure. This suggested that long-term exposure to elevated blood pressure (as indicated by measurements 3 and 6 years prior to the retinal exam) had persistent effects on central retinal artery equivalent (CRAE). However, a more direct test of whether the narrowing is persists or is irreversible would be to examine changes of BP and CRAE across different exams 3 years apart. Retinal photography was performed at examinations 3 and 4. At examination 3 when the participants were aged 50-71 years 9,300 underwent the retinal photography. At examination 4, retinal photography was performed in 1,034 participants, selected as those first consenting participants examined at each center.

5. **Main Hypothesis/Study Questions:**

A rise in blood pressure from exam 3 to 4 is associated with a reduction in central retinal artery equivalent (CRAE) (i.e. greater narrowing), but CRAE does not increase when blood pressure falls, which suggests that the arteriolar narrowing resulting from elevated BP is persistent and relatively irreversible. The alternative hypothesis is that CRAE would increase as BP falls, suggesting that the narrowing is transient.

Secondary hypotheses will be tested as well:
A short-duration (i.e. at any one visit) extreme high BP (perhaps values >75th percentiles) is associated with as much or more arteriolar narrowing as chronic high BP (i.e. at more than one visit) with similar mean BP.

Mean BP (=1/3*sys BP + 2/3*dias BP) of two or all 4 visits may not show the strongest BP-CRAE association. Systolic BP, diastolic BP and differences between systolic and diastolic BP will also be examined.

CRVE changes between visits 3 and 4 will not be strongly associated with changes in BP.

If sample size permits, separate analysis may be considered for participants using different classes of antihypertensive agencies: e.g. diuretics vs. vasodilators.

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).**

- **Study design:**
  Cross-sectional design relating changes in BP to simultaneous changes in CRAE.

- **Inclusion/exclusions:**
  **Inclusions:**
  All ARIC participants with BP levels at visits 1 to 4 and CRAE diameters at visits 3 and 4.

  **Exclusions:**
  Participants whose race is neither black nor white, or those from Washington or Minnesota whose race is black.
  Participants with missing data on BP, CRAE, diabetes status or antihypertensive medication.
Outcome:
CRAE diameter changes between visits 3 and 4 (side: left/right)
CRVE diameter changes between visits 3 and 4 (side: left/right)

Other variables:
Visit 1: BP, Age, height, glucose, diabetes status, fibrinogen, VWF antigen, alcohol use, race and center.
Visit 2: BP, Carotid plaque (location and side).
Visit 3: BP, Date, smoking history, pack years, diabetes status, BMI, CRAE and CRVE (and side), Total, LDL and HDL cholesterol, TG, hypertension drug use.
Visit 4 BP, CRAE and CRVE (and side).

Data analysis:
Continuous data will be presented as means (standard deviations), and discrete data will be presented as numbers (percentages). Differences in baseline characteristics between selected participants and all other visit 3 examinees will be evaluated by Wilcoxon tests or Chi-square tests, as appropriate. The distribution of blood pressure changes and CRAE changes will be shown; unadjusted and adjusted for covariates. Association between changes in BP and changes in CRAE will be shown using a linear regression model, adjusted for age, sex, race and center, with or without consideration of thresholds. However if caliber changes are primarily transient, CRAE would respond even after short term BP alterations and should rise as BP falls. Additionally another model will be used to adjust for all the other potential confounders, including CRVE. Specific non-linear models will be used to search for a threshold consistent with our hypothesis (Fig 1.)

BP changes are estimated with error, and this will bias its observed association with CRAE changes. Measurement error was estimated by Couper et al, based on the ARIC intra individual variability study. [Couper et al. Reliability of retinal photography in the assessment of retinal microvascular characteristics: The Atherosclerosis Risk in Communities Study. Elsevier Sciences 2002.]. Measurement error adjustment will be done using regression calibration (RC), simulation extrapolation (SIMEX) and full Bayesian analysis using MCMC simulations. Since we already know that the BP-CRAE slope varies by both age and antihypertensive use, stratification on age and medication use for hypertension (confounding by indication) will be used to examine potential interactions.

Fig 1. The figure shows the hypothesis: a rise in BP is associated with smaller CRAE, but CRAE does not increase when blood pressure falls. (A non-linear model will be used to search for the thresholds).
Secondary analyses may be done excluding participants with severe illness as indexed by extreme weight loss between visit 3 and 4. Also including only participants with no major changes in blood pressure through visits 1 to 3 will be done in secondary analyses.

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 ICTDER02 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 ICTDER02 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  
   b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER02 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.csecc.unc.edu/ARIC/search.php](http://www.csecc.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)?
   Wong et al. The 3 year-incidence and cumulative prevalence of retinopathy: The Atherosclerosis Risk in Communities Study.

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

Understood