ARIC Manuscript Proposal # 1538

PC Reviewed: 7/14/09       Status: A       Priority: 2
SC Reviewed: _________      Status: _____     Priority: ____

1.a. Full Title: Association of Circulating Leukocyte and C-Reactive Protein Levels with Hypertension and Hypertension-Related Renal Dysfunction: the ARIC Study.

b. Abbreviated Title (length 26 characters): Inflammation and Hypertension.

2. Writing Group:
Writing group members: Niu Tian, Anthony Mawson, Alan Penman, Kenneth Butler, R. Davis Manning, Jr., Michael Flessner, Tom Mosley, Jr.. (Others welcome.)

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

First author: Niu Tian, M.D. Assistant Professor
Address: Division of Nephrology, Department of Pediatrics
         University of Mississippi Medical Center
         2500 N. State Street
         Jackson, Mississippi 39216

         Phone: 601-9845973   Fax: 601-815-5902
         E-mail: ntian@ped.umsmed.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: Alan Penman
Address: Division of Medicine, Department of Geriatrics
         University of Mississippi Medical Center
         2500 N. State Street
         Jackson, Mississippi 39216

         Phone: 601-815-5836   Fax: 601-815-3422
         E-mail: apenman@medicine.umsmed.edu

3. Timeline: All data are available. Submission of proposal: July 2009. Analysis will begin upon approval of the proposal, with Spring 2010 as the completion date.
4. **Rationale:**

Hypertension is a major risk factor for cardiovascular diseases and an important public health problem (1-3). It is well known that hypertension-related renal vascular lesion, together with consequent kidney damage is one of the major pathological characteristics of hypertension. Hypertension and kidney damage form a vicious circle.

Studies show that over 50% of individuals with essential hypertension are salt-sensitive, that is the blood pressure is strongly affected by sodium intake (4). Salt-sensitive hypertension is characterized by progressive increases in proteinuria and renal pathological damage and by decreases in renal hemodynamics (5). Experimental studies indicate that the kidneys of salt-sensitive hypertensive animals are intrinsically more susceptible to damage than those of non-salt-sensitive hypertensive controls (6;7).

The early work on the Dahl salt-sensitive hypertensive rat (Dahl-S), an animal model that closely mimics human salt-sensitive hypertension, showed that serum neutrophil and monocyte counts were highly significantly elevated and activated compared to those of Dahl salt-resistant (Dahl-R) control rats (8). Previous studies on the Dahl-S rats also showed that renal inflammation (9) and oxidative stress (10) play an important role, independent of high blood pressure, in the progression of kidney damage and renal dysfunction. Compared to Dahl salt-resistant rats with normal blood pressure on the same high salt diet, we found that macrophage infiltration in the kidney of Dahl salt-sensitive hypertensive rats was significantly increased and renal oxidative stress was also markedly increased, accompanied by kidney damage and renal dysfunction (9;10).

In a clinical study, 73% of black hypertensive patients was sodium sensitive compared to 56% of white hypertensive patients (4) and the incidence of renal damage in black hypertensive patients was 2-4 times higher than that of whites (11). Recent studies have suggested that a progressive renal fibrosis is characteristic of all the diseases that cause renal failure. This process is invariably associated with a prominent leukocyte infiltrate consisting of macrophages and T cells, together with apoptosis of tubular epithelial cells and destruction of peritubular capillaries (12). Interestingly, superoxide anion and hydrogen peroxide production by polymorphonuclear leukocytes (PMN) were higher in patients with uncontrolled essential hypertension compared to controls (13).

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

We hypothesize that inflammation is associated with hypertension and that inflammation contributes to the increased risk of renal damage and/or dysfunction in persons with essential hypertension, especially in African Americans. The objectives of this study are to determine: (1) whether plasma neutrophil, monocyte and C-reactive protein (CRP) levels correlate with systolic (SBP) and diastolic blood pressure (DBP); (2) whether plasma neutrophil, monocyte and CRP levels are higher in persons with hypertension than in normotensives; (3) whether these associations in (1) and (2) are stronger in African Americans than in whites; (4) whether plasma neutrophil, monocyte and CRP levels correlate with kidney function in persons with/without hypertension; (5) whether plasma neutrophil, monocyte and CRP levels are higher in persons with hypertension and renal dysfunction than in those with hypertension but no renal dysfunction; (6) whether these associations in (4) and (5) are stronger in African Americans than in whites.
6. Design and analysis (study design, inclusion/exclusion, outcome & other variables of interest with specific reference to the time of their collection, summary of data analysis, & any anticipated methodologic limitations or challenges if present).

For SBP, DBP, and measures of inflammation and kidney function we will use the variables listed in the following table:

<table>
<thead>
<tr>
<th></th>
<th>Visit 1</th>
<th>Visit 2</th>
<th>Visit 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP</td>
<td>SBPA21</td>
<td>SBPB21</td>
<td>SBPD19</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>SBPA22</td>
<td>SBPB22</td>
<td>SBPD20</td>
</tr>
<tr>
<td>Prevalent hypertension</td>
<td>HYPERT05</td>
<td>HYPERT25</td>
<td>HYPERT45</td>
</tr>
<tr>
<td>Incident hypertension</td>
<td>To be defined</td>
<td>To be defined</td>
<td>To be defined</td>
</tr>
<tr>
<td>Creatinine</td>
<td>CHMA09</td>
<td>CHMB08</td>
<td>LIPD6A</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>HMTA05</td>
<td>HMTB05</td>
<td></td>
</tr>
<tr>
<td>Monocytes</td>
<td>HMTA08</td>
<td>HMTB08</td>
<td></td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>HEMA09</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP</td>
<td></td>
<td></td>
<td>HSCRP</td>
</tr>
</tbody>
</table>

In ARIC, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were taken in the sitting position by trained technicians using a random-zero sphygmonanometer after a 5-minute rest, and the average of the last two values was computed. Hypertension was defined as systolic BP >140 mm Hg and/or diastolic BP >90 mm Hg, and/or use of anti-hypertensive medication within the 2 weeks before the exam or a history of physician diagnosis. Kidney dysfunction will be assessed by the estimated measure of effective glomerulo-filtration rate (eGFR), which is based on serum creatinine values according to the simplified Modification of Diet in Renal Disease formula (14) as follows:

\[
eGFR \text{ ( ml/min/1.73 m}^2\text{ )} = 186.3 \times (\text{serum creatinine})^{1.154} \times \text{age}^{-0.203} \times (0.742 \text{ for women}) \times (1.21 \text{ for African American})
\]

Serum creatinine will be measured using a modified kinetic Jaffe method. Creatinine concentration will be corrected for inter-laboratory differences and calibrated with Cleveland Clinic measurement stands by the addition of 0.18mg/dl. We will consider a subject to have renal dysfunction if eGFR<89 (ml/min/1.73m²). This standard are chosen in order to be consistent with the National Kidney Foundation’s Kidney Disease Outcome Quality Initiative standardized definitions for chronic kidney disease.

**Data analysis**

This study will have 2 components, cross-sectional and longitudinal. (The cross-sectional analyses will be constrained by the availability of variables at each visit; for example, CRP is only available for cross-sectional analysis at visit 4.) The following participants will be excluded: individuals whose self-described race is neither black nor white (due to their small numbers); African American participants in the Minneapolis and Washington County centers (due to their small numbers); in the longitudinal analysis, when incident hypertension is the outcome, additionally individuals with prevalent hypertension at baseline will be excluded.
For the cross-sectional analyses, we will analyze, by race, the association between SBP/DBP/prevalence of hypertension, markers of inflammation, and markers of kidney damage, using linear correlation/regression for continuous variables (and ANCOVA where groups differences are examined) and ANOVA to examine the group differences in neutrophil, monocyte and CRP levels among normotensive (with or without renal dysfunction) and hypertensive (with or without renal dysfunction) groups. Appropriate corrections will be made for post-hoc comparisons. Linear models will be adjusted for age, sex, history of diabetes, cholesterol levels, alcohol use, smoking, physical activity, body mass index (kg/m²), and use of BP medications and statins.

For the longitudinal analyses, after excluding persons with prevalent hypertension, we will analyze, by race, the association between markers of inflammation and markers of kidney function at visit 1 and the incidence of hypertension. We will use these recently defined new variables for incident hypertension if and when they become available in the ARIC dataset: INCHYPT21 (incident hypertension at visit 2), INCHYPT31 (incident hypertension at visit 3), INCHYPT41 (incident hypertension at visit 4), INCHYPT (incident hypertension), and INCHYPTVISIT (visit at which incident hypertension was detected.). If these are not available we will define a variable for incident hypertension.

**C: Significance**

The proposed study aims to translate the findings from animal studies to the human population. It will provide new information about the role of inflammation in the pathogenesis of salt-sensitive hypertension and associated renal damage.

**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: 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)?
#1032 (AV Kshirsagar): C-Reactive Protein and the Change in Blood Pressure among Individuals Initially without Hypertension. This is the closest to our proposal, but it does not propose examining the association between inflammatory white cell levels or kidney function (and the interaction between the two) and incident hypertension. Also, the study design is different (case-cohort design using visit 2 data).

#425 (AR Folsom): Plasma fibrinogen and incident hypertension in the Atherosclerosis Risk in Communities (ARIC) Study. We will not repeat this analysis but may use fibrinogen as a covariate.

#1077 (PB Mellen): Serum Uric Acid Predicts Incident Hypertension in a Biethnic Cohort. The Atherosclerosis Risk in Communities Study. We will not repeat this analysis but may use uric acid as a covariate.

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

11b. 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


