ARIC Manuscript Proposal # 1345

PC Reviewed: _2_/_12_/08   Status: __A__   Priority: _2_
SC Reviewed: _____   Status: _____   Priority: ____

1.a. Full Title: Evaluation of the relationship between autonomic dysfunction, as measured by heart rate variability, and the development of kidney dysfunction

  b. Abbreviated Title (Length 26 characters):
        HRV and Renal Dysfunction

2. Writing Group:
Writing group members:
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3) Hui-Chun (Tammy) Hsu   4) Brad Astor
5) Eric Whitsel   6) Josef Coresh

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

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3. Timeline: After approval of the proposal and availability of the required data, statistical analyses will be performed in 8-12 weeks. The manuscript will be prepared and submitted to ARIC in the following 12 weeks and we expect publication of the results in 6-12 months.

4. Rationale:

Even in the absence of hypertension and diabetes mellitus, 12% of adults aged 65 years or older have chronic kidney disease, suggesting that nontraditional mechanisms of renal injury may be important in the general population.[1] However, the hypothesis that dysautonomia may contribute to renal dysfunction has not been adequately explored. Several small studies have found that patients with chronic kidney disease have decreased heart rate variability relative to healthy people.[2-10] Most of these studies enrolled patients with established ESRD. However, it is not known to what extent autonomic dysfunction precedes the development of chronic kidney disease and may contribute to its development, since reverse causality—nephrosclerosis causing dysautonomia—may be the primary mechanism for the association. If autonomic dysfunction precedes the development of chronic kidney disease, it may serve as a marker to identify patients at higher risk of developing ESRD but more important, it may serve to provide evidence that the autonomic nervous system may play a role in the pathophysiology of nephrosclerosis.

The mechanisms for the association between autonomic homeostasis and renal function remain incompletely defined. Histological studies have found that renal sympathetic nerve terminals are in direct contact with not only renal vasculature but also with renal tubules and the juxtaglomerular cells.[11] Physiological studies also suggest that alterations in renal sympathetic nerve discharge can directly influence renal hemodynamics, renal tubular transport, and renin secretion. For example, in animal experiments, inhibition of the renal sympathetic stimulation elicited diuretic and natriuretic responses, resulting in the formation of dilute urine.[11] Interestingly, these diuretic and natriuretic responses were abolished by cardiac and renal denervation, supporting the existence of a cardiorenal neural reflex volume loop.[11]

Patients with chronic kidney disease have altered autonomic nervous system tone,[12] but at what stage during the course of progressive renal failure autonomic nervous system dysfunction develops remains unclear. However both animal studies and clinical

trials suggest that autonomic dysfunction itself contributes to the progression of renal failure.[12] In rat models of chronic renal failure, renal denervation or pharmacologic inhibition of the sympathetic nervous system attenuates the progression of renal failure.[12] In humans, several phenomena that are associated with autonomic nervous system dysfunction, such as impaired diurnal blood pressure variation, have been shown to be associated with chronic kidney disease. Several clinical studies have shown that patients (diabetics and non-diabetics) who fail to exhibit a drop in blood pressure at night, also called 'non-dippers', have a progressive decline in renal function, independent of mean blood pressure load. [13-15], but whether the dysautonomia associated with abnormal diurnal blood pressure variation is the physiological driver of these findings remains speculative.[16] We propose to validate the association of dysautonomia and using a cross-sectional analysis of the ARIC dataset, and more important, to test whether HRV precedes the development of renal dysfunction in this patient cohort

5. **Main Hypothesis/Study Questions**:
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> 1) To investigate the relationship between autonomic dysfunction at baseline, as measured by decreased heart rate variability, and subsequent decrease in kidney function, or hospitalization with kidney disease during follow-up.
> 2) To clarify the relationship between autonomic dysfunction, as measured by decreased heart rate variability, albuminuria and decreased kidney function at the population level (ARIC visit 4).

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**
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> The study sample will be composed of the participants of the Atherosclerosis Risk in Communities (ARIC) study. Data will include heart rate recordings, demographics, height, weight, symptoms, cardiovascular risk factors, cardiovascular history, baseline kidney function (estimated GFR using the MDRD Study equation), other major medical illnesses, prior history of cardiac procedures, medications, and laboratory values, including lipid profiles and creatinine levels on each participant. HRV will be assessed in accordance with the recommendations of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. HRV was measured

from 2- and 6-minute beat-to-beat heart rate recordings taken in a resting-supine position at baseline (visit 1) and at last follow-up visits (visit 4) respectively.

ANALYSIS

Descriptive statistics will be reported as mean and standard deviation or median and interquartile range as appropriate. Glomerular filtration rate (GFR) will be estimated using the Modification of Diet in Renal Disease (MDRD) 4-variable equation at baseline and follow-up visits 2 and 4.

HRV will be analyzed by time-domain analysis and frequency-domain analysis as done in previous ARIC papers.[17-24] For time-domain analysis following variables will be to assess the HRV: the mean normal-to-normal R-R interval length (NN), the standard deviation of all normal-to-normal R-R intervals (SDNN) in milliseconds, and the root mean square of successive differences in normal-to-normal R-R intervals (rMSSD) in milliseconds. For frequency-domain analysis, fast Fourier transform algorithm will be used to analyze the RR-interval trend and yield a power spectrum plot of variance as a function of frequency. To assess HRV, high frequency spectral power component (HF), low frequency spectral power component (LF), very low frequency spectral power component (VLF), and LF/HF ratio will be used. HF will be defined as the area between 0.15 and 0.40 hertz (Hz), LF as the area between 0.04 and 0.15 Hz, and VLF as area between 0.00 and 0.04 HZ bands under the power spectral density curve. As the baseline EKG heart rate recordings are only of 2-minute duration, only the HF component will be used for frequency-domain analysis at baseline.

Variance of heart rate variability will be divided in to two groups with one group at or below the 25th percentile and the other group above 25th percentile. The association between decreased HRV and incidence of chronic kidney disease (estimated GFR less than 60 during follow-up or hospitalization with kidney disease among individuals with estimated GFR greater than 60 ml/min/1.73 m^2 at basline) will be assessed with Cox proportional hazards regression, with adjustments made using propensity scores that are modeled to predict the presence of HRV below the 25th percentile at baseline. In addition, standard regression models will be used for adjustment.

In a secondary analysis estimated rate of decline in GFR will be defined by the slope of the linear regression line of each patient's GFR measurements over time. Since bias can be introduced by adjustment for baseline GFR (measurement error in baseline measurement can lead to regression to the mean), while baseline GFR may be an important and legitimate determinant of subsequent GFR decline, we will perform

sensitivity analysis by including and not including GFR as a co-variate. Adjustments will also be made for age, sex, race, study center, duration of follow-up, hypertension, diabetes mellitus, smoking, education, dyslipidemia, and BMI. Power spectral analysis data will be log-transformed in accordance with the recommendations of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Since estimated GFR is less reliable at higher values, this analysis may have limited power in the ARIC cohort. Log transformation of GFR will help in stabilizing the measurement error variance. In addition, a categorical analysis of rapid GFR decline (fastest quatile of GFR decline) vs. the other quariltes will be conducted. Finally, individuals with both a rapid slope and a final GFR less than 60 will be examined as a case group compared to individuals with stage GFR greater than 60.

For evaluating the relationship between GFR and HRV at cross-sectionally (baseline and visit 4), the primary analysis will be logistic regression for the presence of estimated GFR less than 60 ml/min/.1.73m^2 with different HRV measures modeled continuously. In addition, a linear regression model will be developed with adjustments for age, sex, race, study center, hypertension, diabetes mellitus, smoking, education, BMI, and dyslipidemia. The latter is limited by the limited precision of estimated GFR at the higher range. For evaluation of the relationship between HRV at the last follow-up and the presence of albuminuria at last follow-up, a linear regression model with log of the albumin to creatinine ratio will be developed with adjustments for age, sex, race, study center, hypertension, diabetes mellitus, smoking, education, BMI, and dyslipidemia. In these linear regression models, non-linear terms for the independent variables will be used to test whether the association differs from linearity. Given the cross-sectional nature we will also examine HRV as a function of estimated GFR, again allowing for a non-linear association.

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?   __X__ 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

8.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.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)?
　　Dr. Whitsel is collaborating and has been instrumental in HRV data collection

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.

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