ARIC MANUSCRIPT PROPOSAL FORM

Manuscript #277

1. Title:
Cardiac Autonomic Function Assessed by Heart Rate Variability and Incident CHD: A Population Based Case-Cohort Study - The ARIC Study

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3. Timeline:

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| Submit Proposal to Publications Committee | 8/20/94 |
| Complete Process Additional Heart Rate Variability Data | 11/20/94 |
| Complete analysis | 2/20/95 |
| Submit first draft to Publications Committee | 5/20/95 |
| Submit to Journal | 8/20/95 |

4. Rationale:
As consistenly shown in the literature, beat-to-beat heart rate variability (HRV) is a simple and valid, non-invasive measure of cardiac autonomic function. In clinical studies, it has been found that acute MI survivors have lower HRV high frequency power (HF) and higher HRV low frequency (LF), suggesting vagal impairment and sympathetic predominance. It has also been observed that HRV-HF is negatively associated with the extent of coronary atherosclerosis. A lower vagal function and a higher sympathetic function can lead to an increase of CHD risk through following mechanisms: (1) increased risk of ventricular dysrrhythmias; (2) increased heart rate and oxygen consumption; (3) decreased coronary blood flow regulation; (4) increase macrophage count and activity, therefore, through macrophage-LDL cholesterol interaction, enhanced the development of atherosclerosis. It has been proposed that impaired vagal function and/or increased sympathetic function increase the risk of CHD, however, this hypothesis has not been tested at the population level using prospective data.

In ARIC Visit l, two-minute resting, beat-to-beat heart rate data were collected according to a standard protocol. Utilizing Fast Fourier Transformation, spectral analysis was been applied to the heart rate data for a stratified random sample (N about 3000) of ARIC visit l participants. Processing the HRV data for the incident CHD individuals is also in progress blinded to case status. From these records, HRV-HF, HRV-LF and the ratio of HF/LF will be calculated as a marker of cardiac parasympathetic activity, a measurement of sympathetic function influenced by vagal activity, and a measurement of vagal-sympathetic balance respectively. From our previous work, it can be shown that our procedure to estimate HRV has high operator repeatability (with intra and inter operator reliability coefficients for all three HRV indices greater than 0.95). Also, our ARIC manuscript (MS#131) on the association of HRV and prevalent MI, found a significant, negative association between HRV-HF and prevalent MI.

Therefore, we propose this analysis to investigate the association between cardiac autonomic function as

measured by HRV and the risk of incident CHD in the ARIC study using a case-cohort design.

6. Main alternative hypotheses:
Lower HRV-HF is associated with increased risk of incident CHD;
Higher HRV-LF is associated with increased risk of incident CHD;
Lower HRV HF/LF ratio is associated with increased risk of incident CHD;

7. Data (variables, source, inclusion/exclusion):
We have assembled a set of about 3000 ARIC visit l participants, a stratified random sample of the ARIC cohort, which was used as the study population for our previous manuscripts (MS#130 and MS#258). It will serve as a sample of the ARIC cohort for this study. All available incident CHD events identified by the current ARIC algorithm will serve as cases for this study (N about 250). Study design: case-cohort analysis, accounting for the sampling strategy. In the analysis, individuals with prevalent CHD at baseline will be excluded. Major variables include incident CHD status, processed heart rate data, demographic variables, and established risk factors of CHD.