Overview

Background and Rationale: During the past 10 years, assessment of HRV has gained prominence as one of the noninvasive methods of estimating the cardiac parasympathetic and sympathetic balance. As a result of the interaction between sympathetic and parasympathetic activity, beat-to-beat heart rate shows periodicities over time. These periodicities can be identified through spectral analysis whereby the observed heart rate as a function of time is expressed mathematically as the sum of a series of sine and cosine functions of varying amplitudes and frequencies (in Hz). A plot of the square of the amplitudes of these sine and cosine functions against their cycle frequencies is known as the power spectral density for beat-to-beat heart rate, or the HRV Power Spectrum. For heart rate/time data re-expressed in this mathematical form, it is well accepted that cycles with a frequency of 0.04-0.15 Hz are under the influence of both the sympathetic and parasympathetic nervous system. Cycles with a frequency 0.15-0.40 Hz are under the influence of the parasympathetic system only and are regarded as a marker of cardiac vagal function.

The conventions adopted in this field of research identify the area under the power spectrum for cycles in the 0.04-0.15 Hz range as low frequency power (LF), and the area in the 0.15-0.40 Hz range as high frequency power (HF). LF represents the contribution to heart rate variability from the sympathetic and parasympathetic system, HF represent the contribution to the variability from the parasympathetic system, and LF/HF ratio is considered as a measurement of the vagal-sympathetic balance. Simple statistics summarizing the variation of R-R intervals over a short period of time, identified as time domain HRV indices, provide a comprehensive estimation of cardiac sympathetic and parasympathetic contribution to the R-R variation.

In ARIC Visit 1, two-minute resting, beat-to-beat heart rate data were collected according to a standard protocol. The HRV ancillary study complemented these data by collection 5-minute, supine, resting R-R interval data in Visit 4. Utilizing a special heart rate variability system, time and frequency domain indices of heart rate variability are calculated by the ancillary study for the entire ARIC cohort (both visit 1 and visit 4 data) using the same criteria and algorithm.

Several ARIC manuscripts on HRV have been published. In these publications, we have documented statistically significant associations between lower HRV and the incident of CHD, incident hypertension, diabetes, and multiple metabolic disorders, in a sub-sample of the ARIC cohort. In this phase we propose to systematically study (1) the change of HRV over time and identify factors associated with the change; (2) the association between HRV with markers of insulin and glucose metabolism; the association of HRV indices with several markers of inflammation; and (3) baseline indices of sympathetic activation as predictors of cardiovascular events.

Overview of Study Design and Data to be Used: The manuscripts proposed here are prospective and cross-sectional. In each case, HRV indices will include time and frequency
domain indices. All other variables will pertain to the ARIC cohort examinations, visits 1 and 4. Cardiac events and all-cause mortality will use the standard ARIC definitions.
1. Title (length 26):

Inflammation is associated with impaired cardiac autonomic control

Short Title: HRV and Inflammation

2. Writing group:

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3. Time Line:

Analyses will start in July, with expected conclusion in September 1999.
Abstract to AHA EPID Council Meeting in October, 1999
First draft of MS in December 1999

4. Rationale:

Watkinson (Toxicological Sciences. 1998; 41:209-16) induced arrhythmias after inhalation of combustion particles into rat lungs. Godleski (Am J Crit Care Med 1996; 163; A15) observed ECG changes including T-wave alternans /HRV changes, and arrhythmias in dogs exposed to concentrated ambient air particles. The hypothesized link between inhalation of particle air pollution and effects on cardiac rhythm is the induction of an inflammatory response in the lung with release of chemical mediators (cytokines) that alter the autonomic nervous system control of cardiac rhythm (Am J Crit Care Med 1996; 163; A15). Confirmation of these findings is emerging from unpublished experimental work in the rat model, in inhalation chambers, with concomitant assessment of inflammatory markers and HRV. We posit that individuals with indications of an increased inflammatory response will exhibit (a) a decrease in the conventional indices of HRV measured in the supine position, and (b) an increase in the sympathetic activation that accompanies the change from supine to the upright position.

In normal volunteers, higher leucocyte count was associated with reduced heart rate variability (Jensen-Urstad et al., 1998). There is also evidence that the parasympathetic nerve,
which has a direct influence on heart rate variability, provides an important communication channel between cytokines and the brain (Maier et al., 1998).

5. Main Hypotheses:

a. Markers of the systemic inflammatory response are inversely associated with HRV measured in the supine position.

b. Markers of the systemic inflammatory response are associated with an increased sympathetic activation on assuming the upright position.

c. Elevated levels of fasting insulin and body mass index contribute to explain the hypothesized association.

d. The association between levels of inflammatory markers and reduced HRV is of greater magnitude in never smokers compared to current smokers.

6. Data (variables, time window, source, inclusions/exclusions):

The following variables will be included: HRV indices (time, and frequency domain estimates) at baseline; HRV measures of sympathetic activation; Fibrinogen, Factor VII activity, Factor VIII activity, von Willebrand factor, Protein C antigen, aPTT, AT-III, serum albumin, and White Blood Cell count; socio-demographic, anthropometric, and biochemical correlates; cigarette smoking; reported medication use.

This manuscript will not address periodontal disease status as a marker of inflammatory burden nor its hypothesized association with HRV, which will be addressed by a writing group headed by Samuel J. Arbes. Close coordination already exists between these writing groups.