1.a. Full title: Ultra-low frequency heart rate variability on 14-day ECG and cognitive function

1.b. Abbreviated title (26 char): ULF HRV on 14-day ECG


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

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2. Timeline: Start – immediately after approval (expected, December 2013). Manuscript submission expected: 9 months

Rationale:

Ultra-low frequency heart rate variability. Heart rate variability (HRV) was shown to be associated with cardiovascular death and arrhythmic events\(^1\). High frequency (HF) cyclic
fluctuations are modulated by breathing, mediated mostly by changes in vagal outflow. The greatest variation of RR’ intervals occurs with circadian changes (night- day variations), mediated by poorly understood neurohormonal rhythms. Most data on HRV is limited to few minutes to a maximum of 48h of continuous RR’ intervals. The physiologic mechanisms responsible for very low frequency (VLF, 0.0033-0.04Hz) and ultra-low frequency (ULF, <0.003 Hz) are matter of dispute. Data suggests influence of the renin-aldosterone system, thermoregulation, neuroendocrine, vasomotor activity, physical activity, and sleep-disordered breathing. In the Vietnam Era Twin Registry study a significant inverse correlation was found between depressive symptoms and ULF HRV. Association between cognitive impairment and ULF-VLF HRV in patients with dementia was reported. ULF and VLF HRV are associated with verbal learning and memory.

However, previous studies of ULF HRV were limited by the short data available (up to 48h), which did not allow to quantify ULF reliably. Consequently, it is also not clearly known whether ULF oscillations are determined by periodic or quasiperiodic oscillations of HRV that originates from body’s intrinsic regulatory system.

Recently for the first time in clinical practice FDA-approved long-term (up to 14 days) continuous ECG monitoring (ECG Zio-Patch, iRhythm, Inc.) became available. However, iRhythm’s (manufacturer of ECG Zio-Patch) does not measure heart rate variability.

Tereshchenko’s laboratory developed custom software application to measure heart rate variability on raw 14-day ECG (recorded by ZioPatch).

Recently ARIC ZioPatch Ancillary Study (Agarwal, Chen, et al., proposal # 2013.14 ) successfully started and is currently ongoing. Overall 350 ZioPatch ECGs will be recorded and available for analysis. I plan to apply custom analysis to the recorded ECG data to measure ULF HRV.

**Main hypothesis/Study questions:**

**Aim 1:** To study cross-sectional associations between ULF HRV on 14-day ECG and cognitive function.

We hypothesize that ULF HRV on long term ECG recording (14 days) is associated with neurocognitive decline.

**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).**

**Methods**
ECG signal will be analyzed using customized Matlab (MathWorks, Inc, Natick, MA) software. ULF HRV will be measured by custom Matlab software.

ARIC participants with available ECG Zio-Patch recording will be included (N=350).
We will conduct cross-sectional analyses to explore the association between ULF HRV and cognitive function. Log-transformed ULF HRV will be used in the model as a continuous variable as well as tertiles of ULF HRV. Univariable and multivariable logistic (for binary outcomes) and linear (for continuous outcomes) regression models will be constructed with ULF HRV as the main exposure variable and (1) history of stroke, (2) markers of cognitive function, (3) brain amyloid burden by PET, and (4) BMI, (5) hypertension and systolic blood pressure, (6) diabetes as outcomes. Models will be adjusted by age, sex, race (model 1), history of stroke (model 2+1); hypertension, diabetes, BMI (model 3+2), physical activity (model 4+3), and medications (beta-blockers and central psychotropic drugs, such as antidepressants, tranquilizers, neuroleptics, barbiturates) (model 5+4).

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 excludepersons with a value RES_OTH = “CVD Research” for non-DNA analysis, andfor 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: http://www.csc.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)?

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

11.b. If yes, is the proposal
__X__ A. primarily the result of an ancillary study (______)
__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.csc.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.

Reference List


