Manuscript Proposal #2313

PC Reviewed: 2/11/14  Status: A  Priority: 2
SC Reviewed: _________  Status: _____  Priority: ____

1. a. Full Title:
Heart rate as a prognostic marker in patients with heart failure with preserved ejection fraction

b. Abbreviated Title (Length 26 characters): Heart rate and Heart Failure with Preserved Ejection Fraction

2. Writing Group:

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

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3. Timeline:
Analysis to start immediately; Manuscript to be written and sent for publication within one year of approval

4. Rationale:
Heart failure (HF) represents a major health problem, affecting 6 million Americans, 15 million Europeans, and over 35 million Asians. (1) Over one half of patients with HF have preserved ejection fraction (HFpEF). (2) In contrast to HFrEF, there is no proven effective
treatment for HFpEF, the most important reason being incomplete understanding of the pathophysiology.

A primary manifestation of HFpEF is exercise intolerance and a reduced functional capacity. Various possible contributing pathophysiologic factors to this process including ventricular systolic, chronotropic, vascular, endothelial and peripheral factors have been described so far. Several studies have identified impairments in chronotropic reserve in HFpEF. Borlaug et al observed significantly depressed peak heart rate (HR) in HFpEF patients compared to controls, which was coupled with abnormalities in cardioacceleration and HR recovery after cessation of exercise. Other groups have also observed impaired HR recovery in HFpEF, even when accounting for β-blocker usage and abnormal arterial baroreflex sensitivity has also been reported further supporting a role for autonomic dysfunction in HFpEF. Abnormal HR reserve in HFpEF has been found to be extremely common in several large recent studies.

All these observations suggest that restoration of chronotropic competence may enhance exercise capacity in HFpEF. However, contrary to this phenomenon, increases in HR may compromise LV filling in patients with prolonged relaxation. Wachter et al showed in a small number of patients with HFpEF who underwent atrial pacing, that end diastolic volume and stroke volume were decreased with higher heart rates. A similar observation was reported by Borlaug et al that LV filling pressures were impaired with increasing heart rates in HFpEF. Komajda et al reported a secondary analysis from the I-PRESERVE study that increasing heart rates in HFpEF were associated with worse outcomes. Kosmala et al. in a relatively small study reported dramatic improvements in peak VO2 after just 7 days of treatment with the negative chronotropic drug, ivabradine. This was previously supported by a mice model: diabetic mice treated with 4 weeks of ivabradine showed improved vascular stiffness, LV contractility, and diastolic function. Yanagihara et al recently published a small study which demonstrated beneficial effect of carvedilol treatment at discharge on all-cause mortality in patients who were admitted with decompensated heart failure regardless of their ejection fraction. In contrary to these findings, Farasat et al showed no change in hospitalizations with treatment of β-blockers in HFpEF, but increased hospitalizations in women on β-blockers. Finally Maeder et al compared the effect of diagnosis heart rates and blood pressures on mortality and rehospitalization rates in patients with HFpEF and HFrEF with a median follow up of 39 months. There was no significant association between heart rate and blood pressure on either mortality or hospitalization risk in HFPEF.

Clearly, the data is inadequate and conflicting and further research involving larger number of patients is needed regarding the management of heart rate in HFpEF patients.

The ARIC surveillance HF study offers a unique opportunity to address this question. Patients have been carefully determined to have HFpEF and data for ejection fraction and heart rate are available in most patients.
5. Main Hypothesis/Study Questions:

Study Aims:
   a. To assess the prognostic value of heart rate on 30 day and 1-year mortality in HFrEF.
   b. To assess the interaction of beta blockers and heart rate on 30 day and 1-year mortality in HFrEF.
   c. To compare the prognostic value of admission heart rate on 30 day and 1-year mortality in HFrEF vs. HFrEF

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, Inclusion/exclusion:

This study will include all heart failure events coded as definite or possible acute decompensated heart failure for all years available (at the time the analysis is started) and who have follow up data to examine one year mortality. This study will specifically look at the prognostic value of admission heart rates (through 30 day and 1-year mortality). Patients missing data on ejection fraction will be excluded. Patients with HF will be categorized as having HFrEF (left ventricular ejection fraction or LVEF > 50%) or HFrEF (LVEF < 50%). The prognostic utility of heart rate will be assessed in both groups with HR as a continuous variable per standard deviation increase, as well as in three distinct heart rate categories <60 bpm, 61-90 bpm and >90 bpm. Patients with resting heart rate <40 beats per minute or a pacemaker will be excluded. An analysis excluding patients with a history of atrial fibrillation or flutter will also be conducted. Subgroup analysis with and without beta blockers on admission will be performed since beta blockers affect heart rate and may also be independently associated with outcomes.

Variables of Interest:

Main Variables
- Heart rate (admission first value- only available value in data set)
- Ejection fraction as currently defined in the surveillance data set
- Last recorded HR in hospital- only available in a subset of patients (first year of surveillance data)

Other Variables
Demographics and clinical variables:
   Age
   Gender
   Race
   Previous history of HF
**Presentation:**
- first systolic blood pressure
- first diastolic blood pressure

**Comorbidities:**
- Worst values of - hemoglobin
  - serum creatinine- to calculated eGFR
  - BUN
  - BNP
- Arrhythmias: Atrial fibrillation/atrial flutter
- coronary artery disease/h/o MI
- Severe valvular disease
- Pulmonary hypertension
- chronic bronchitis/COPD/asthma
- Hyperlipidemia
- Diabetes mellitus
- smoking status
- BMI
- Stroke or TIA
- Depression
- H/o pacemaker
- pacemaker placement (non biventricular) during hospitalization

Treatment at admission: Beta blockers
Treatment at discharge: ACE inhibitors or angiotensin II receptor blockers, beta blockers, calcium channel blocker, diuretics, aldosterone antagonists, ICD

**Outcomes of interest:**
- 30 day and 1 year mortality.
- Rehospitalization for HF (among only ARIC cohort members, because rehospitalization data is not available for all other HF surveillance patients).

**Summary of data analysis:**
All analyses will be weighted to account for the stratified random sample in the ARIC community surveillance data. Chi-square analyses will be used for comparison of categorical variables and analysis of variance (ANOVA) will be used for continuous variables by heart rate categories. Associations between heart rate and mortality will be examined using Cox proportional hazards modeling, after controlling for potential confounders such as demographics, clinical and comorbidity variables; analyses will also evaluate an interaction by EF or by beta blocker use. category. Sub-group analysis will be also performed by presence or absence of atrial fibrillation as well as use of BB blockers at admission. Because, last recorded heart rates (discharge heart rates) are only available for a small subset of patients (first year of surveillance data), we will perform an analysis to evaluate changes in heart rate and prognosis in that subset of patients

**In that subset of patients.**
Limitations:

Information is limited to that which was documented and abstracted from the medical record. In most cases, missing values and “no” values are indistinguishable. Changes in heart rate during the hospitalization cannot be accounted for since only the admission heart rate is available in the surveillance data set. As noted in the analysis section we will perform a sensitivity analysis evaluating changes in heart rate using the subset of patients with heart rate at discharge (first year surveillance data only).

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

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 found no overlap between this proposal and previously approved manuscript proposals either published or still in active status.
   ____ Yes  __X__ No

Proposal # 1490: will evaluate optimal therapies on case fatality in HF which will include B-blocker. However our project will evaluate only the interaction of beta blocker use and HR, if any, on mortality. Also, some co-authors are common on both manuscripts.

References


11. Borlaug et al. Mechanisms of Exercise Intolerance in Heart Failure With Preserved Ejection Fraction


