Does Chronotropic Incompetence Impact Efficacy of Beta-Agonists in COPD?

Laurie Letarte
December 15, 2010

A. Study Purpose and Rationale

Chronotropic incompetence (CI) is the failure to adequately augment heart rate during physical exertion. Down-regulation and/or cardiac beta-receptor desensitization in the background of generalized increased sympathetic activation is currently thought to be the underlying mechanism of CI[1,2]. CI is independently associated with increased mortality, irrespective of other risk factors and whether or not individuals are receiving beta-blocker therapy[3, 4, 5]. Although CI can occur in the general population, it has specifically been observed in two populations; patients with heart failure and COPD.

Over 30% of patients with heart failure have been found to have CI, which may impact physical exertion in this population. Patients with chronic heart failure are often limited in their ability to perform maximal physical activity as a result of a decrease in maximal oxygen uptake (VO2max). VO2 max is dependent on cardiac output, which is reduced in heart failure patients due to decreased stroke volume as a consequence of systolic dysfunction. To maintain cardiac output, heart failure patients are more reliant on their ability to increase heart rate, which is also dampened in patients with CI[1,2].

It has been observed that CI also occurs in the COPD population, but there is little published data relating to CI in these patients[6,7]. In the COPD population, we know that VO2max is typically decreased due to abnormalities in ventilation associated with the relatively shorter time for exhalation, gas exchange abnormalities, and skeletal muscle changes relating to the disease and deconditioning[8]. However, the specific role of CI in this group of patients has not been elucidated.

Much remains to be learned about CI and how it affects both the heart failure and COPD populations. However, in the COPD population beta-agonists form part of the backbone of treatment. Where the proposed mechanism of dysregulation in CI revolves around beta-receptors, it is important to understand how CI impacts therapy of COPD. If treatment response to beta-agonists is negatively impacted by CI, our approach to therapy in this specific subgroup might require reconsideration.

B. Study Design and Statistical Analysis

The aim of this study is to compare the impact of chronotropic incompetence on the efficacy of beta-agonists between patients with COPD without CI and COPD patients with CI.

This study will be a prospective observational analysis of patients comparing rates of change of FEV1 over 2 years of treatment between a group of patients with COPD without chronotropic incompetence (CI-) and a group of patients with COPD who also have chronotropic incompetence (CI+).

All patients must have a pulmonary function test (PFT) within one year from the time of enrollment or since the most recent change in therapy, whichever is more recent, to serve as a baseline. At the time of enrollment, all patients will be started on a long-acting beta-agonist (LABA). PFT's will be repeated yearly for the length of a patient's participation. All eligible patients will undergo cardiopulmonary exercise testing (CPET) during the study period to determine their exercise and functional capacity as well as to determine chronotropic status. Subjects will then be analyzed in either the CI- or CI+ group as appropriate.

Statistical Analysis

We hope to detect a difference of 10% between the study arms. Using the unpaired t-test and a power of 80% and a goal of 25 patients in each arm of the study, with an assumed standard deviation of 5%, we would be able to detect a 4% difference between groups. To detect a 10% difference with all other statistical parameters being equal, only approximately 5 subjects are needed per group. This number is exceedingly small, however, and does not account for attrition rate and other variables.

Even with loss to follow-up or exclusion due to acquisition of one of the exclusion criteria, 25 patients in each this should be a large enough population to detect a 10% difference between the two arms.

C. Study Procedure N/A

D. Study Drugs

- any LABA at discretion of provider

E. Medical Device N/A

F. Study Questionnaires N/A

G. Study Subjects

Inclusion Criteria:

- Age 18 or older
- COPD with evidence of obstructive defect on PFT's
- Positive smoking history
- Initiation of long-acting beta-agonist

Exclusion Criteria:

- History of systolic or diastolic heart failure
- History of myocardial infarction

- Presence of a-fib or PPM
- End-stage COPD
- History of asthma
- Neuromuscular disease
- Inability to complete CPET

H. Recruitment of Subjects
Potential study subjects will be identified via CUMC primary care clinics, pulmonary clinics, and CPET lab. Patient data will then be reviewed to determine whether or not a particular patient meets all study criteria.

I. Confidentiality of Study Data
Each patient will be assigned a unique code for study purposes. No identifiable data will be used and data will be kept in a secure location accessible only by investigators.

J. Potential Conflict of Interest
No investigators have any conflicts of interest in this study and none stand to benefit financially or in any other way from results of the investigation.

K. Location of the Study
The study will take place at New York Presbyterian Columbia Campus.

L. Potential Risks
There are no known potential risks to patients and there is no intended treatment difference between the two arms.

M. Potential Benefits
If a difference in response to therapy is detected, future patients stand to benefit, and it may lead to further research of both cellular and clinical effects of chronotropic incompetence, investigation of new therapies, and possibly a change in management of patients with COPD and chronotropic incompetence.

N. Alternative Therapies N/A

O. Compensation of Subjects
CPET and PFT's will be performed at no cost to the patients.

P. Costs to Subjects
None

Q. Minors as Research Subjects N/A

R. Radiation or Radioactive Substances N/A

References

1. Brubaker PH, Joo K, Stewart KP, *et al*. Chronotropic Incompetence and its contribution to exercise intolerance in older heart failure patients. J Cardiopulm Rehabil 2006;26;86-9.
2. Clark AL, Coats AJS. Chronotropic incompetence in chronic heart failure. Int J Cardiol 1995;49;225-31.
3. Witte KK, Cleland JG, Clark AL. Chronic heart failure, chronotropic incompetence, and the effects of beta blockade. Heart 2006;92;481-6.
4. Khan MN, Pothier CE, Lauer MS. Chronotropic incompetence as a predictor of death among patients with normal electrograms taking beta blockers (metoprolol or atenolol). Am J Cardiol 2005;96:1328-33.
5. Lauer MS, Francis GS, Okin PM, Pashkow FJ, Snader CE, Marwick TH. Impaired chronotropic response to exercise stress testing as a predictor of mortality. JAMA 1999;281:524-9
6. Terziyski KV, Marinov BI, Aliman OI, *et al*. Oxygen uptake efficiency slope and chronotropic incompetence in chronic heart failure and chronic obstructive pulmonary disease. Folia Med 2009;51;18-24.
7. Inal Ince D, Savci S, Arikan H, *et al*. Cardiac autonomic responses to exercise testing in patients with chronic obstructive pulmonary disease. Anadolu Kardiyol Derg 2010;10;104-10.
8. Ferrazza AM, Martolini D, Valli G, *et al*. Cardiopulmonary exercise testing in the functional and prognostic evaluation of patients with pulmonary diseases. Respiration 2009;77;3-17.