Determinants of right ventricular ejection fraction in patients with idiopathic pulmonary arterial hypertension.

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1. LAY ABSTRACT:

Idiopathic pulmonary arterial hypertension (PAH) is a rare, devastating disease. It is characterized by elevated pulmonary vascular resistance and endothelial dysfunction and commonly progresses to right heart failure with subsequent death. Advancement in therapy and research involving prognosis and outcomes is essential for allowing for further characterization of the disease. Right ventricular dysfunction has been demonstrated to be useful as a prognostic indicator in patients with PAH. The factors that determine RV dysfunction require further elucidation. It is hypothesized that 1. Male gender 2. Non-white race would be associated with decreased RV function in patients with PAH. This study is a retrospective cohort study of patients evaluated for PAH at Columbia University Medical Center. All racial and ethnic group, both women and men, and individuals greater than 16 years of age will be eligible for inclusion. There are no procedures and/or visits that are required solely for the purpose of this research. No practical or ethical problems are related to the performance of this study.

2. IRB PROTOCOL:

A. Study Purpose and Rationale

Pulmonary arterial hypertension is associated with significant morbidity and mortality. This disease that is characterized by elevated pulmonary arterial blood pressure and commonly leads to right ventricular failure and death. PAH is defined as having a mean pulmonary arterial pressure (PAP) greater than 25 mmHg at rest or 30 mmHg during exercise, with a pulmonary-capillary wedge pressure and left ventricular end diastolic pressure of less than 15 mmHg, as evaluated by right heart catheterization. Though the cause of such development may be variable, including familial, anorexigen-induced, or idiopathic forms, the consequences of the disease are similar, in that elevation in the pressure of the pulmonary vascular bed is associated with increased pulmonary vascular resistance and subsequent right ventricular hypertrophy (RVH). RVH eventually

results in decreased contractility of the heart, decreased RVEF, and decreased cardiac output. Unlike left ventricular systolic function, normal RVEF has been difficult to fully characterize, as echocardiography does not provide a precise measurement of RV stroke volume or size, though seems to range from 58-67% in normal adults.

The mortality of PAH is 5/100,000 per year (age-adjusted mortality), equaling nearly 16,000 people per year, based on most recent data from2002. One year survival rates are 87% and 3 year survival rates of 61% at one institution. Mortality secondary to pulmonary HTN, though stable in white and Hispanic ethnicities, is increasing in black Americans. The origin of ethnic differences in mortality is likely multi-factorial; both the socio-economic and any pathophysiologic factors need to be investigated further. Recently published studies suggest that reduced RVEF in PAH is associated with worse survival. Data also exists indicating that whereas RVEF and cardiac index predict survival in patients with PAH, the pulmonary artery pressure does not, indicating that the morbidity and mortality associated with the disease may be affected by right ventricular remodeling and baseline cardiac function. It is the determinants of this right ventricular dysfunction that require further elucidation and will be investigated in this study.

B. Study Design and Statistical Analysis

This is a retrospective cohort study of all consecutive adult patients with idiopathic PAH who underwent initial evaluation from January 1994 to June 2002 athis this center, with follow-up through 2003.

Statistical analysis will be performed on all patients who meet inclusion criteria or this study and have the appropriate work-up for PAH at Columbia University Medical Center. Basic demographic information will be analyzed in a sex and race-specific manner, using T-test and chi-square models. The alpha value will be 0.05. Continuous variables will be summarized by mean +/- standard deviation (SD) or median (with interquartile range). Categorical variables will be summarized by the frequencies with 95% confidence intervals (CIs). Chi-squared analysis will be used when comparing two different groups.

Simple linear regression will be used to assess the association between RVEF (dependent variable) and potential predictors. Multivariate linear regression will be performed using purposeful selection of covariates to construct the model which best explained the variability in RVEF. All analyses will performed using available data; no imputation will performed. A p value <0.05 will be considered statistically significant. Stata/IC 10.0 (College Station, Texas), will be used for all analyses.

Study Procedures

There were no studies that were performed on patients specifically for research purposes. Common examples of diagnostic tests include right-heart catheterization and cardiac magnetic resonance imaging (MRI), however these studies were performed as part of the initial work-up and management of patients with PAH, not for the purpose of this investigation.

C. Study Drugs

Not applicable.

D. Medical Device

Not applicable.

E. Study Questionnaires

There will be no questionnaires

F. Study Subjects

Patients will be eligible for inclusion in this study if they were over the age of 16 and had PAH, either idiopathic, familial, or anorexigen-associated.

Patients will be excluded from this study if they were under the age of 16, had previous cardiac catheterization with acute vasodilator study and initiation of PAH therapy, or had other forms of PAH (for example, HIV, systemic lupus erythematosus, and systemic sclerosis were ruled out by usual diagnostic tests).

The rational for including minor population into this study is in order to increase the number of participants and include patients with early-onset pulmonary hypertension. Given the retrospective nature of this study, there is no risk associated with the inclusion of minor individuals.

G. Recruitment of Subjects

To assemble the cohort, the Data Warehouse at Columbia University Medical Center will be queried for all patients with an *International Classification of Diseases*-Ninth Revision code for primary or secondary pulmonary hypertension who were assessed by clinicians at this center. Lastly, a comprehensive list of all cardiac catherizations done at this center between 1994-2002 will be reviewed.

H. Confidentiality of Study Data

In order to protect the privacy of study participants, each participant will be coded given a unique study number. All study data will be stored in a secure location, accessible only to those involved in this study.

I. Potential Conflict of Interest:

There are no potential conflicts of interest.

J. Location of the Study

The study will take place at Columbia University Medical Center. The patient cohort and statistical analysis all occur that this institution.

K. Potential Risks

There are no potential risks to subjects from this study.

L. Potential Benefits

There are no immediate benefits to participation in this study, however there may be long term benefits to patients with PAH as a whole if determinants of RVEF, a predictor of mortality in this disease, are better understood.

M. Alternative Therapies

Not applicable.

N. Compensation to Subjects

There will be no compensation to subjects.

O. Costs to Subjects

There are no additional costs to subjects.

P. Minors as Research Subjects

Minors aged 16 or older are eligible for inclusion into this study. Their inclusion will be approved by the Department of Pediatrics Committee on Human Investigation, as part of the initial data registry.

Q. Radiation or Radioactive Substances

Not applicable.

3. REFERENCES: