JACC: Heart Failure
© 2014 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 2, No. 3, 2014
ISSN 2213-1779/$36.00
http://dx.doi.org/10.1016/j.jchf.2014.02.004

Pre-Capillary Pulmonary Hypertension and Right Ventricular Dilation Predict Clinical Outcome in Cardiac Resynchronization Therapy

Neal A. Chatterjee, MD,* Gaurav A. Upadhyay, MD,*† Gaurav Singal, MD,*† Kimberly A. Parks, DO,* G. William Dec, MD,* Jagmeet P. Singh, MD, DPHIL,*† Gregory D. Lewis, MD*‡

Boston, Massachusetts

Objectives This study examined the prognostic significance of pre- and post-capillary components of pulmonary hypertension (PH) in patients receiving cardiac resynchronization therapy (CRT).

Background PH is common in patients with left ventricular systolic dysfunction (LVSD) receiving CRT. The impact of PH subtype on clinical outcome in CRT is unknown.

Methods The study population consisted of 101 patients (average age 66 ± 13 years, left ventricular ejection fraction 0.23 ± 0.07, and New York Heart Association functional class 3.2 ± 0.4) who underwent right heart catheterization in the 6 months before CRT. PH was defined as a mean pulmonary artery pressure ≥25 mm Hg; a significant pre-capillary contribution to elevated mean pulmonary artery pressure was defined as a transpulmonary gradient (TPG) ≥12 mm Hg. Clinical endpoints were assessed at 2 years and included all-cause mortality and a composite of death, left ventricular assist device, or cardiac transplantation.

Results Patients with TPG ≥12 mm Hg were more likely to experience all-cause mortality (hazard ratio [HR]: 3.2; 95% confidence interval [CI]: 1.3 to 7.4; p = 0.009) and the composite outcome (HR: 3.0; 95% CI: 1.4 to 6.3; p = 0.004) compared with patients with TPG <12 mm Hg. After multivariate adjustment for hemodynamic, clinical, and echocardiographic variables, only TPG ≥12 mm Hg and baseline right ventricular (RV) dilation (RV end-diastolic dimension >42 mm) were associated with the composite clinical outcome (p = 0.05 and p = 0.04, respectively).

Conclusions High TPG PH and RV dilation are independent predictors of adverse outcomes in patients with LVSD who are receiving CRT. RV pulmonary vascular dysfunction may be a therapeutic target in select patients receiving CRT. (J Am Coll Cardiol HF 2014;2:230–7) © 2014 by the American College of Cardiology Foundation

Cardiac resynchronization therapy (CRT) significantly reduces morbidity and mortality in appropriately selected patients with left ventricular systolic dysfunction (LVSD) (left ventricular ejection fraction [LVEF] ≤35%) and electrical dyssynchrony (QRS duration ≥120 ms) (1–3). Despite the overall benefit of CRT, approximately one-third of patients fail to demonstrate clinical improvement (2,4), suggesting that additional determinants of clinical outcome in this population are needed.

When pulmonary hypertension (PH) (i.e., mean pulmonary artery pressure [mPAP] ≥25 mm Hg) is present in patients with LVSD, it is most commonly associated with an abnormally elevated pulmonary capillary wedge pressure (PCWP) (5). However, a significant minority of patients with LVSD develop a pre-capillary pulmonary arterial contribution to elevated pulmonary artery pressure (PAP), reflected by an elevated transpulmonary gradient (TPG) (defined as mPAP − PCWP ≥12 to 15 mm Hg) (6,7). PH has been associated with increased mortality in some (8–10), but not all (11), previous studies in LVSD, and the presence of a pre-capillary contribution to PH in LVSD has been shown to confer particularly high risk (12,13).

Despite the growing recognition of the clinical importance of PH subtype in LVSD (13–15), its contribution to clinical outcome after CRT remains unknown. Whether pre-capillary PH precludes benefit from CRT or is ameliorated by it is not known. Previous evaluations of elevated PAP in the population receiving CRT have been limited to noninvasive estimations of pulmonary artery systolic pressure

From the *Cardiology Division, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts; †Cardiac Arrhythmia Service, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts; and the ‡Pulmonary and Critical Care Unit of the Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts. Dr. Lewis has received support from the National Heart Lung and Blood Institute (National Institutes of Health K23HL091106) and the Heart Failure Innovation Fund. All other authors have reported they have no relationships relevant to the contents of this paper to disclose.

Manuscript received October 18, 2013; revised manuscript received February 4, 2014, accepted February 6, 2014.

(PASP) (16,17). In this study, we hypothesized that the presence of a significant pre-capillary contribution to PH would be associated with worse clinical outcome independently of the extent of left ventricular (LV) reverse remodeling, and that the presence of baseline right ventricular (RV) dilation would confer independent risk.

Methods

Patient population and study design. Consecutive patients receiving CRT at Massachusetts General Hospital between September 2005 and February 2009 were prospectively enrolled in a research database as previously described (18). Patients received a CRT defibrillator device for approved indications during the enrollment period (New York Heart Association [NYHA] functional class III to IV, LVEF <35%, QRS duration >120 ms). A natural language query with standardized right heart catheterization (RHC) terms ("right heart catheterization," "cardiac output," "PA pressure") was used to identify patients who underwent RHC before CRT defibrillator device implantation. Patients with RHC within 6 months of CRT defibrillator device implantation were included in the study. Exclusion criteria consisted of RHC occurring in the context of the following: 1) acute coronary syndrome; 2) decompensated heart failure with cardiogenic shock (cardiac index ≤2.2 l/min/m^2 or documented use of a positive inotropic or vasopressor agent at the time of RHC); or 3) after cardiac arrest. The primary clinical indication for RHC (organized as evaluation of heart failure symptomatology [i.e., dyspnea, edema], evaluation of angina, presence of arrhythmia/implantable cardioverter defibrillator therapy, or other) and clinical context (i.e., ambulatory referral vs. inpatient admission) were extracted from review of the electronic medical record. This study was approved by the Partners Institutional Review Board.

Baseline characteristics, RV pulmonary vascular metrics, LV reverse remodeling. Baseline demographic, clinical, and echocardiographic data were collected prospectively as previously described (18). Renal function was assessed using estimated glomerular filtration rate (GFR) derived from the Modification of Diet in Renal Disease equation and stratified according to standard staging (stage 1: GFR ≥90, stage II: GFR 60 to 89, stage III: GFR 30 to 59, stage IV: GFR 15 to 29, stage V: GFR <15 ml/min/1.73 m^2) (19). Baseline RV dilatation was defined as an RV end-diastolic dimension >42 mm measured at the base of the heart (20). Hemodynamic data included mPAP, PCWP, and cardiac output (including measurement type; i.e., thermodilution or Fick). PH was defined as mPAP ≥25 mm Hg. A pre-capillary pulmonary arterial contribution to PH was defined by the presence of a TPG ≥12 mm Hg (12,21). Pulmonary vascular resistance (PVR) was defined as: [TPG·80]/cardiac output, and expressed in dynes·s/cm^5.

Statistical methods. SAS 9.3 (SAS Institute Inc., Cary, North Carolina) was used for statistical analysis. All continuous, normally distributed measurements are presented as the mean ± SD. Non-normally distributed data are presented as the median and interquartile range (IQR). The Wilk-Shapiro test was used to assess the normality of continuous variables. Categoric data are reported as percentages. Group baseline characteristics were compared between patients with PH, TPG ≥12 mm Hg, and PH TPG <12 mm Hg, and patients without PH using analysis of variance or Fisher exact testing where appropriate with subsequent post-hoc pairwise comparison testing (Tukey). Clinical outcomes were determined starting from the day of CRT defibrillator device implantation until February 1, 2009. The Kaplan-Meier method was used to estimate the proportion of patients experiencing clinical endpoints of all-cause mortality or a composite endpoint of death, heart failure transplantation, or left ventricular assist device (LVAD) implantation; survival curves were compared using the log-rank test. Univariate testing was performed with baseline covariates with subsequent inclusion in multivariate analysis if univariate $p < 0.1$. Multivariate Cox proportional hazard ratio (HR) modeling was used for multivariate adjustment. Correction was not made for multiple comparisons. Sensitivity analyses were performed for TPG cut-point (13 and 14 mm Hg) with no significant change to comparison testing.

Abbreviations and Acronyms

- **CI** = confidence interval
- **CRT** = cardiac resynchronization therapy
- **GFR** = glomerular filtration rate
- **HR** = hazard ratio
- **LV** = left ventricular
- **LVAD** = left ventricular assist device
- **LVEF** = left ventricular ejection fraction
- **LVSD** = left ventricular systolic dysfunction
- **mPAP** = mean pulmonary artery pressure
- **NYHA** = New York Heart Association
- **PAP** = pulmonary artery pressure
- **PASP** = pulmonary artery systolic pressure
- **PCWP** = pulmonary capillary wedge pressure
- **PH** = pulmonary hypertension
- **PVR** = pulmonary vascular resistance
- **RHC** = right heart catheterization
- **RV** = right ventricular
- **TPG** = transpulmonary gradient
- **WU** = Wood Units

Results

Population characteristics. Of 427 patients who received CRT between September 2005 and February 2009 at Massachusetts General Hospital, 227 underwent RHC before CRT. From this cohort, 110 patients who underwent RHC in the 6 months before CRT defibrillator device implantation were identified, of whom 9 were excluded (Online Table 1). Clinical indication for RHC was most commonly for evaluation of heart failure symptoms (71% of patients); 47% of RHCs occurred in the ambulatory setting. Time elapsed between RHC and CRT defibrillator device implantation was a median of 0.33 months (interquartile range [IQR]: 1.83 months).