Detection of High-Sensitivity Troponin in Outpatients With Stable Pulmonary Hypertension Identifies a Subgroup at Higher Risk of Adverse Outcomes

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ABSTRACT

Background: The detection of elevations in cardiorenal biomarkers, such as troponins, B-type natriuretic peptides (BNPs), and neutrophil gelatinase−associated lipocalins, are associated with poor outcomes in patients hospitalized with acute heart failure. Less is known about the association of these markers with adverse events in chronic right ventricular dysfunction due to pulmonary hypertension, or whether their measurement may improve risk assessment in the outpatient setting.

Methods and Results: We performed a cohort study of 108 patients attending the National Pulmonary Hypertension Unit in Dublin, Ireland, from 2007 to 2009. Cox proportional hazards analysis and receiver operating characteristic curves were used to determine predictors of mortality and hospitalization. Death or hospitalization occurred in 50 patients (46.3%) during the median study period of 4.1 years. Independent predictors of mortality were: 1) decreasing 6-minute walk test (6MWT; hazard ratio [HR] 12.8; $P < .001$); 2) BNP (HR 6.68; $P < .001$); and 3) highly sensitive troponin (hsTnT; HR 5.48; $P < .001$). Adjusted hazard analyses remained significant when hsTnT was added to a model with BNP and 6MWT (HR 9.26, 95% CI 3.61−23.79), as did the predictive ability of the model for death and rehospitalization (area under the receiver operating characteristic curve 0.81, 95% CI 0.73−0.90).

Conclusions: Detection of troponin using a highly sensitive assay identifies a pulmonary hypertension subgroup with a poorer prognosis. hsTnT may also be used in a risk prediction model to identify patients at higher risk who may require escalation of targeted pulmonary vasodilator therapies and closer clinical surveillance. (*J Cardiac Fail 2014;20:31−37*)

Key Words: Risk prediction models, prognosis, B-type natriuretic peptide, neutrophil gelatinase−associated lipocalin.

For patients with pulmonary hypertension, the response of the right heart to afterload mismatch ultimately determines mortality. Despite recent therapeutic advances, challenges remain in identifying patients who may be at higher risk of adverse outcomes at an earlier stage in their disease process and may require treatment escalation. In the outpatient setting, noninvasive assessments, including serum biomarkers, provide inexpensive, complementary, and, in the case of B-type natriuretic peptide (BNP) and 6-minute walk test (6MWT), well validated tools for risk stratification as part of routine evaluation.[1−3] Incorporating markers of myocardial damage or strain may also make risk assessment more accurate.

Cardiac troponin T is a highly specific and highly sensitive marker for myocardial cell damage; it is also an independent prognostic marker for patients with congestive heart failure. Troponin detection is associated with poor outcomes in patients with acute right ventricular dysfunction due to pulmonary embolism,[4] with recent studies also showing adverse clinical outcomes associated with troponin detection in patients with chronic pulmonary hypertension.[5−7] As part

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of this pathophysiologic process, progressive right ventricular dysfunction and remodeling also contributes to a degree of left ventricular atrophy.[8] Furthermore, the reversibility of increased troponin levels has also been demonstrated following the introduction of treatment (eg, vasodilator therapy, atrial septostomy, pulmonary endarterectomy), highlighting the importance of early identification and risk stratification of these patients.[4,9]

The aim of the present study was to determine the association of highly sensitive troponin (hsTnT) and troponin I (TnI) with adverse clinical outcomes in patients with chronic pulmonary hypertension, and to determine whether the detection of other markers of cardiorenal injury, such as neutrophil gelatinase−associated lipocalin (NGAL), may provide complementary prognostic information as part of a clinical model with BNP and 6MWT.

Methods

Study Population

The study population consisted of 108 consecutive patients with chronic pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension (World Health Organization [WHO] groups 1 and 4), attending routine clinic appointments at a national tertiary referral center from July 2007 to July 2009. All subjects had venous sampling and 6MWT performed on the date of clinic review. Serum samples were centrifuged and stored at −80°C until analyzed. Clinical outcome measures including hospitalization and mortality were collected prospectively for 2−4 years from the date of blood sampling to July 2012. All subjects were aged ≥18 years. The study was approved by our Institutional Research Ethics Committee and complied with the Declaration of Helsinki.

Clinical Parameters

Hemodynamic data was obtained via right heart catheterization performed within 3−6 months of the date of blood sampling and 6MWT. The 6MWT was carried out according to previously described protocols.[10,11] Serum creatinine measurements were obtained with the use of Beckman Coulter platform analysis in a single laboratory, and estimated glomerular filtration rate (eGFR) was calculated with the use of the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula [$eGFR = 141 \times \min(sCr/k, L)^{a} \times \max(SCr/k, L)^{-1.209} \times 0.993^{age} \times (1.018 \text{ if female}) \times (1.159 \text{ if black})$] where sCr is serum creatinine (mg/dL), k is 0.7 for female and 0.9 for male, and a is −0.329 for female and −0.411 for male.[12]

Clinical End Points

The outcomes measured were (1) all-cause mortality and (2) a combined clinical end point (CCE) of rehospitalization due to pulmonary hypertension and/or all-cause mortality occurring during the study period. Events were recorded with the use of hospital electronic records and cross-referenced with the national pulmonary hypertension database. The mean follow-up time for the study was 900 ± 375 days (range 71−1,719).

Biomarker Assessment

hsTnT was measured with the use of a novel Elecsys hsTnT electrochemiluminescence immunoassay (Roche Diagnostics) with a detection limit of 3 ng/L and 99th percentile upper reference limit of 14 ng/L. BNP and TnI were measured with the use of the Architect system (Abbott Diagnostics) using a chemiluminescent microparticle immunoassay.

Statistical Analysis

Continuous variables are expressed as mean ± SD, or median and interquartile range for nonnormally distributed variables. Kaplan-Meier curves, log rank tests, and univariate Cox regression analysis were used to examine survival models with the use of log-transformed biomarkers (BNP, hsTnT, 6MWT, TnI), as well as age and sex and dichotomized biomarker thresholds. Biomarker data was natural log transformed to improve normality of the models. Bivariable Cox regression was then used to analyze the effects of hsTnT in conjunction with age, WHO functional classes, TnI, and BNP on predetermined outcome measures (mortality, CCE) by contrasting nested models. Diagnostic plots were inspected for violation of the proportional hazards assumption, presence of influential outliers, behavior of the residuals, and linearity of the relationship between the predictors and survival. Spearman correlations between the predictors were inspected to investigate potential multicollinearity problems.

Multivariable survival models were constructed with the use of a backward elimination strategy, to construct a minimum model from one containing all predictor variables simultaneously. Given the sample size, we limited the initial model to 5 predictors: age, BNP, TnI, hsTnT, and 6MWT. At each step the marker coefficient showing the largest P value $>.05$ was dropped, and the reduced model refitted in the next step. The Akaike information criterion was used to evaluate the optimal model.

Receiver operating characteristic (ROC) curves (also defining cutoff points estimated to provide optimal sensitivity and specificity) were used to assess prognostic utility of the biomarkers individually, as well as for area under the ROC curve comparison when multivariate predictive scores using BNP, hsTnT, and 6MWT were created. Statistical analysis was carried out with the use of PASW version 18.0 (SPSS) and R version 2.15.2 (cran.r-project.org) with the survival library version 2.36.

Results

Patient Characteristics

The baseline characteristics of the study population (n = 108) are listed in Table 1, split by CCE univariate outcome. The mean age was 55.2 ± 15.7 years, with 77 (71.3%) female. Connective tissue disease−associated pulmonary hypertension was the most common etiology, present in 33 patientsv. Medications at time of study entry included endothelin receptor antagonists (48.1%), phosphodiesterase type 5 inhibitors (30.6%), prostanoids (13.9%), and oral anticoagulants (38%). In total, 77 patients (71.3%) were receiving pulmonary hypertension−targeted therapies. Forty-four patients (40.7%) had BNP >100 pg/mL, with 15 patients (13.9%) with BNP >330 pg/mL. There were 64 patients (59.1%) with 6MWT <380 m.[3]