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# Disproportionate Elevation of NT-proBNP in Scleroderma-Related Pulmonary Hypertension

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Abstract

Objective: N-terminal pro-brain natriuretic peptide (NT-proBNP) is a marker of neurohormonal activation that is useful in the diagnosis and prognosis of various forms of pulmonary arterial hypertension (PAH). We sought to characterize and compare NT-proBNP in a cohort of PAH-related to scleroderma (PAH-SSc) and idiopathic PAH (IPAH) patients.



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Methods: NT-proBNP levels, collected from PAH-SSc and IPAH patients followed prospectively, were compared and correlated with hemodynamic variables. Cox proportional hazard models were created to assess the predictive value of NT-proBNP.
Results: Ninety-eight patients (55 PAH-SSc, 43 IPAH) were included. Hemodynamics were similar, except for lower mPAP in PAH-SSc. NT-proBNP levels were significantly higher in PAH-SSc (3419±3784 vs. 1393±1633 pg/mL, $p<0.01$), and were more closely related to hemodynamics in PAH-SSc than IPAH. Twenty-eight patients died. NT-proBNP predicted survival (HR 3.18; $p<0.01$) in the overall cohort; however when stratified by group, predicted survival only in PAH-SSc (HR 3.07, $p<0.01$ vs. 2.02, $p=0.29$ in IPAH).
Conclusions: This is the first description showing NT-proBNP levels are 1) significantly higher in PAH-SSc than IPAH despite less severe hemodynamic perturbations, and 2) stronger predictors of survival in PAH-SSc, suggesting that neurohormonal regulation may differ between PAH-SSc and IPAH. Future studies to define pertinent mechanisms are warranted.

**Introduction**

Pulmonary arterial hypertension (PAH) is a chronic disease of the pulmonary vasculature that leads to right heart failure and death. PAH affects approximately 8-14% of patients with underlying systemic sclerosis (SSc) and is associated with a worse prognosis as compared to patients with other forms of PAH. [1-34;5]The reasons for these differences in survival are unclear, but may be related to several factors.

Direct cardiac involvement in PAH-SSc may account for the differences in survival. Patients with PAH-SSc may be more likely to have small vessel disease than patients with IPAH.[6] Myocardial fibrosis in PAH-SSc may lead to cardiac dysfunction and conduction abnormalities. [7] Left heart abnormalities, such as left ventricular hypertrophy and left atrial dilatation, are common in PAH-SSc.[8] Similarly, we have demonstrated that non-systolic dysfunction may be more prevalent in PAH-SSc than IPAH.[5] Other investigators have demonstrated a higher proportion of arrhythmias in PAH related to connective tissue disease than in IPAH.[9] Further, large vessel pulmonary vascular disease related to scleroderma may increase the effective load on the right ventricle (RV) and lead to a more rapid decline in RV function.[10] Neurohormonal activation (NHA) in response to progressive right heart failure in PAH may also contribute to disease progression and adverse outcomes in PAH. Although known to be central to the pathogenesis of heart failure due to left heart disease, little is known about the role of NHA in PAH. NHA may be especially important in PAH-SSc. We have recently demonstrated a robust correlation between hyponatremia, a marker of neurohormonal activation, and right ventricular dysfunction in a cohort of PAH patients and shown its strong association with survival.[11] Interestingly, in this mixed cohort, PAH-SSc patients were more likely to be hyponatremic than other PAH patients despite similar hemodynamics, suggesting possible differences in NHA. Further, in a separate cohort of patients with similar hemodynamics, we have demonstrated higher serum catecholamine levels in PAH-SSc compared to IPAH, suggesting differential NHA between these two groups.[12]

N-terminal pro-brain natriuretic peptide (NT-proBNP) is a pro-hormone, secreted by the myocardium in response to various stimuli, including mechanical stretch and hypoxia, along with neurohormonal factors such as endothelin, catecholamines, and tumor necrosis factor. Over the past several years, NT-proBNP has been studied in various populations of patients with PAH and found to be useful in diagnosing PAH in patients with scleroderma and predicting survival in both PAH-SSc and IPAH.[13;14] However, there are limited data comparing NT-proBNP levels, correlation with clinical and hemodynamic variables, and prognostic value between PAH-SSc and IPAH. In this study, we sought to characterize and compare NT-proBNP, a marker of NHA, in a cohort of PAH-SSc and IPAH patients.

**Methods**

Data was collected prospectively from the Johns Hopkins Pulmonary Hypertension Program, which maintains a registry of all patients evaluated. The Institutional Review Board approved the registry and this specific analysis; written consent was obtained from all patients. Routine collection of NT-proBNP on patients presenting for right heart catheterization (RHC) began in 2005 at our institution. Consecutive outpatients with a diagnosis of IPAH, PAH related to anorexigen use, or PAH-SSc confirmed by RHC for whom serum NT-proBNP levels were obtained within one week of RHC were included and followed prospectively. Although PAH related to anorexigen use is classified as associated-PAH according to consensus statements, we included these patients in our IPAH group given the similarities in clinical presentation, pathobiology, and outcomes.[15;16] Patients in whom PAH therapy had been initiated prior to evaluation at our center were excluded.

Limited and diffuse scleroderma was defined as previously described.[17] PAH was defined as a mean pulmonary artery pressure (mPAP) of > 25 mmHg, pulmonary capillary wedge pressure (PCWP) ≤ 15 mmHg, and pulmonary vascular resistance (PVR) > 3 Wood units, in the absence of other known causes of pulmonary hypertension.[18;19] Pulmonary function test (PFT), six minute walk test (6MWT), computed tomography of the chest, and echocardiography closest to the initial RHC were reviewed and recorded. Percent predicted for all PFT data were calculated using reference formulae.[20;21] Patients with significant obstructive lung disease, defined as a forced expiratory volume in one second over forced vital capacity ratio ($FEV_1$/FVC) < 0.7 accompanied by radiographic evidence of emphysema, were excluded.[22] Patients were classified as having interstitial lung disease if they had a total lung capacity (TLC) less than 70% of predicted combined with moderate to severe fibrosis (grade 3-4) on HRCT.[23] Estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) study equation. [24]

Serum for NT-proBNP levels was collected within one week prior to RHC. Samples were centrifuged within 60 minutes of collection and stored at -70˚C. Measurements were performed on an Elecsys 2010 instrument (Roche Diagnostics, Basel Switzerland) using a sandwich immunoassay. The reported coefficient of variation for this assay is 0.9-2.2%.[25]

Survival was ascertained by reviewing the medical record, phone contact, as well as the Social Security Death Index.

*Statistical Analysis*

Continuous variables were summarized by mean ± SD or median (range) and compared using the student's t-test or the Wilcoxon rank-sum test where appropriate. Categorical variables were compared using the Chi-squared statistic. NT-proBNP levels were log-transformed to achieve normal distribution. Pearson's correlation coefficient was used to analyze the relationship between NT-proBNP and clinical and hemodynamic parameters. Multivariable linear regression models were created to assess the relationship between NT-proBNP levels and multiple explanatory variables. A 2-tailed p-value with a significance level of 0.05 was used to detect statistically significant differences between groups. Factors associated with transplant-free survival were ascertained by univariable Cox proportional hazard models. Variables found to be significant in univariable analysis (*P*-value ≤ 0.10), shown previously to predict survival in PAH, and potential confounders of the relationship between NT-proBNP and survival were incorporated into multivariable models. Variables that were found to be collinear by variance inflation factor testing in multiple linear regression (PVR and PA saturation) were excluded from Cox multivariable analyses. The proportional hazards assumption was examined for all covariates using a continuous time-varying predictor and generalized linear regression of scaled Schoenfeld residuals on functions of time. Time-to-event analyses were performed using the Kaplan-Meier product limit estimator. Subjects who underwent organ transplantation or died from causes unrelated to underlying cardiovascular diseases were censored. All analyses were performed using STATA version 9.0 (College Station, TX).

**Results**

*Patient Characteristics*

Between January 2005 and August 2008, one hundred and twenty three patients who had undergone RHC and had NT-proBNP collected were considered for analysis. Ten patients were excluded because the NT-proBNP was collected more than one week from the RHC date. Twelve were excluded because their TLC was less than 70% predicted and had significant fibrosis on high resolution chest CT scan and thus were not considered to have PAH according to consensus guidelines.[19] Three patients were excluded because their initial RHC was performed at an outside institution.

The demographic and clinical characteristics of the 98 subjects included in this cohort are summarized in Table 1. Overall, the majority of subjects were white women. More than half (55/98; 56%) had PAH-SSc; the remainder had IPAH (n=38) and PAH related to anorexigen use (n=5). Subjects with IPAH had significantly greater BMI compared to PAH-SSc and achieved a greater distance on six minute walk testing. There were no differences in New York Heart Association (NYHA) functional classification assessed at time of RHC. The mean eGFR indicated stage II disease by MDRD classification (mean eGFR, 60-89 ml/min/1.73m$^2$) and did not differ between the PAH and PAH-SSc groups. PFTs at baseline revealed significantly reduced percent-predicted FVC, $FEV_1$, TLC, and $DL_{CO}$ in the PAH-SSc group compared to the IPAH group. Fifty-three of the subjects were on PAH-specific therapy at the index RHC. More PAH-SSc than IPAH subjects were on PAH-specific therapy at index RHC. Forty-six of the fifty-five PAH-SSc subjects received low-dose (less than 60 mg daily) dihydropyridine-type calcium channel blockers (DTCCB) for the treatment of Raynaud phenomenon. None of the IPAH subjects received DTCCB therapy. None of the PAH-SSc subjects received immunosuppressive therapy during the course of the study. On average, PAH-SSc

patients had a shorter duration of pulmonary hypertension and a shorter duration of disease prior to collection of NT-proBNP.

*Echocardiography*

Fifty-eight of the subjects (21 IPAH, 37 PAH-SSc) had echocardiography within 3 months of RHC and were included for analysis. As shown in Table 2, there were no differences in left heart function between PAH-SSc and IPAH as assessed by left atrial size, left ventricular hypertrophy, left ventricular ejection fraction, and presence of non-systolic dysfunction.

*Hemodynamics*

Hemodynamic measurements obtained at RHC revealed moderate-to-severe PAH overall. Although the mean RAP was similar between groups, the mPAP was significantly higher in the IPAH group, suggesting more severe hemodynamic impairment. However, neither the CI nor the PVR differed between groups. The pulmonary artery saturation was also similar between groups.

The NT-proBNP levels were significantly higher in the PAH-SSc group (Figure 1); this relationship persisted when the NT-proBNP levels were log-transformed. Overall, significant correlations between the log of NT-proBNP levels and various clinical and hemodynamic parameters were found. However, these correlations were stronger in the PAH-SSc group, especially for cardiac index ($r = -0.58$, $p<0.01$ for PAH-SSc versus $r = -0.46$, $p<0.01$ for IPAH), PVR ($r = 0.54$, $p<0.01$ for PAH-SSc versus $r = 0.41$, $p<0.01$ for IPAH), and PA saturation ($r = -0.60$, $p<0.01$ for PAH-SSc versus $r = -0.41$, $p<0.01$ for IPAH)(Figure 2). Similar correlations between groups were found for other parameters,

such as 6MWD (r = -0.42, p<0.01 for PAH-SSc versus r = -0.27, p=0.09 for IPAH) and RAP (r = 0.46, p<0.01 for PAH-SSc versus r = 0.31, p=0.04 for IPAH). In multivariable linear regression models, NT-proBNP remained significantly greater in the PAH-SSc group when controlling for CI, BMI, treatment status, and renal function.

When examining only treatment-naïve subjects, PAH-SSc subjects demonstrated significantly higher NT-proBNP levels than IPAH subjects despite similar hemodynamics (Table 3); this relationship also persisted in multiple linear regression models.

*Follow-up and Survival*

Subjects were followed for a minimum of three months following index RHC. All patients received PAH specific therapy during the follow-up period. The median follow-up time was 2 years (720 days, range 96-1359 days) and did not differ significantly between groups. Overall, 28 subjects died (20 PAH-SSc, 8 IPAH) during the course of the study. Two subjects were censored from the survival analysis; one who died as a result of a motor vehicle accident and one who underwent lung transplantation. Twenty-one of the deaths were related to progressive right heart failure, 6 related to sudden cardiac death, and 1 related to gastrointestinal hemorrhage. No subjects were lost to follow-up. The 1-, 2-, and 3-year survival estimates for the whole cohort were 88% (95%CI 80-93%), 74% (95%CI 63-82%), and 70% (95%CI 58-79%). The 1-, 2-, and 3-year survival estimates were poorer in the PAH-SSc group compared to the IPAH group [87%(95%CI 75-94%), 64%(95%CI 48-75%), 64%(95%CI 48-75%), versus 91%(95%CI 77-96%), 88%(95%CI 73-95%), and 78%(95%CI 57-89%), respectively, log-rank p=0.04].

In univariable analysis of the entire cohort, NT-proBNP was found to predict survival; for every 10-fold change in NT-proBNP level, there was a more than 3-fold increased risk of death (HR 3.18, 95%CI 1.60-6.34, p<0.01) (Table 4). This relationship persisted when adjusted for diagnostic group (IPAH vs. PAH-SSc), treatment status, renal function (eGFR), BMI, and hemodynamics in separate multivariable models. However, when similar analyses were performed in the IPAH and PAH-SSc cohorts separately, NT-proBNP only predicted survival in the PAH-SSc group (HR 3.07, 95%CI 1.35-7.00, p<0.01) and not the PAH group (HR 2.02, 95%CI 0.55-7.52, p=0.29). When adjusting for treatment status, renal function, BMI, and hemodynamics in separate multivariable models, NT-proBNP remained strongly associated with survival in the PAH-SSc group (Table 5). Further, when restricted to only treatment-naïve PAH-SSc patients (n=33), NT-proBNP was an even stronger predictor of survival (HR 4.83, 95%CI 1.14-20.41, p=0.03)

**Discussion**

To our knowledge, this is the largest study of NT-proBNP in patients with PAH and the first to compare NT-proBNP levels between patients with PAH-SSc and IPAH. In this study, we found that NT-proBNP levels were significantly higher and correlated more strongly with various demographic and hemodynamic parameters in PAH-SSc compared to IPAH patients despite similar hemodynamic parameters between the two groups. Importantly, these differences persisted when controlling for potential confounders, such as renal function and treatment. We also found that NT-proBNP levels were stronger predictors of survival in PAH-SSc than IPAH patients.

The utility of NT-proBNP in the assessment of PAH has been examined in several recent studies. Fijalkowska and colleagues found strong correlations between NT-proBNP and echocardiographic variables such as pulmonary artery acceleration time and with hemodynamic parameters such as cardiac index and pulmonary artery saturation in a heterogeneous cohort of PH patients that included 36 patients with IPAH.[14] Souza and colleagues found a strong relationship between NT-proBNP and PVR.[26] Similarly, Blyth and colleagues defined a threshold value of NT-proBNP that reliably detected right ventricular systolic dysfunction as assessed by cardiac MRI in a cohort of 25 patients (11 IPAH, 8 PAH related to connective tissue disease, and 6 chronic thromboembolic disease).[27] Several investigators have demonstrated the responsiveness of NT-proBNP to specific PAH therapies, including sildenafil[28] and bosentan[29;30] and have found associations between decreased NT-proBNP and improved RV function in response to various PAH therapies.[31]

As several investigators have shown previously, NT-proBNP has prognostic value in various forms of pulmonary hypertension. A normalized ratio of NT-proBNP > 2.5, calculated by dividing the measured value of NT-proBNP by age-and gender-adjusted normal values, conferred a greater than 10-fold increased risk of death in a heterogeneous population of 118 pulmonary hypertension patients, including 66 PAH subjects.[32] Similarly, baseline NT-proBNP levels greater than 1400 pg/mL were associated with an 8-fold increased risk of death in a cohort of 36 IPAH patients.[14] Investigators at the Royal Free Hospital have suggested the usefulness of NT-proBNP in the diagnosis, assessment, and prognosis of PAH related to scleroderma. In a cohort of 109 patients with scleroderma, 68 of whom had PAH-SSc, NT-proBNP levels greater

than 395 pg/mL were found to have a high positive predictive value for the diagnosis of PAH-SSc, confirming their previous findings from a smaller cohort.[13;33] Further, the investigators found every order of magnitude increase in NT-proBNP level on baseline assessment was associated with a 4-fold increased risk of death. Importantly, this relationship was also noted in patients whose NT-proBNP increased despite PAH-specific therapy; patients whose NT-proBNP levels increased 10-fold while on therapy had a 3-fold increased risk of death, suggesting the potential role of NT-proBNP as a marker for response to therapy.

In the present study, we sought to evaluate NT-proBNP in a cohort of PAH patients to characterize its association with disease type, to compare its relationship with clinical and hemodynamic parameters, and to assess its prognostic value between IPAH and PAH-SSc. Our results suggest that NT-proBNP levels are significantly higher in PAH-SSc compared to IPAH despite similar hemodynamic measures. In fact, mean PAP was lower in the PAH-SSc group compared to the IPAH group, while CI was similar, suggesting less severe hemodynamic perturbation. NT-proBNP levels were consistently higher in the PAH-SSc group, even when controlling for other clinical variables such as age, gender, BMI, and renal function, all of which have been shown to affect NT-proBNP levels. [32;34;35] These differences persisted when adjusting for treatment status and when examining only subjects who were treatment-naïve at enrollment. Further, NT-proBNP levels in PAH-SSc were more closely correlated with hemodynamics than in IPAH. Importantly, NT-proBNP was significantly associated with survival only in the PAH-SSc group. Although hemodynamics were similar in both groups, 34/55 (62%) of the PAH-SSc cohort had peptide levels greater than 1400 pg/mL

compared to 16/43 (36%) of the IPAH cohort (p=0.01); this threshold was identified as a marker of poor prognosis in a prior study.[14] Further, the relationship between NT-proBNP and survival remained significant when controlling for other clinical variables known to affect NT-proBNP levels and for treatment status.

There are several possible explanations for the difference in NT-proBNP levels between PAH and PAH-SSc despite similar hemodynamics. A recent study by Overbeek and colleagues described the relationship between mean ventricular pressure and stroke volume comparing PAH-SSc and IPAH.[36] Although both groups had similar RAP and CI, PAH-SSc patients demonstrated lower stroke volumes for any given mean RV pressure, suggesting impaired RV contractility. In the current cohort, the right ventricular stroke work index was significantly lower in the PAH-SSc group compared to the IPAH group (13.1± 5.3 vs. 17.0± 8.6 gm/m$^2$, p<0.01), suggesting RV maladaptation in PAH-SSc for a comparable cardiac load. Similarly, we have demonstrated impaired RV systolic function in PAH-SSc compared to IPAH as assessed by the tricuspid annular plane systolic excursion (TAPSE) despite similar cardiac index by RHC.[37] Impaired contractility in PAH-SSc may be related to more extensive myocardial fibrosis from direct cardiac involvement of scleroderma. While there are sparse data on RV fibrosis in PAH-SSc patients, Fernandes and colleagues demonstrated abnormal collagen deposition in RV biopsies of 15/16 of scleroderma patients without evidence of left or right heart disease, suggesting that myocardial fibrosis precedes the development of clinical cardiac involvement.[7] We have recently collected RV biopsies on 7 PAH-SSc patients[38] and found significantly more myocardial fibrosis in these patients when compared to 7 IPAH and controls. (personal communication, Hunter C. Champion 2008)

Since myocardial fibrosis can stimulate production of NT-proBNP, it is possible that differences in the degree of myocardial fibrosis between PAH-SSc and PAH contributed to differences in NT-proBNP levels in our study.[39]

RV wall stress is another important determinant of NT-proBNP release.[40] In PAH, both systolic and diastolic components contribute to overall RV wall stress: low stroke volume increases systolic wall stress while high end-diastolic volume (EDV) is a main determinant of diastolic wall stress. [41] As shown previously, SV decreases more in response to increased mean PAP in PAH-SSc than IPAH, which may explain why PAH-SSc patients experience right heart failure earlier in the course of disease.[36] Consistent with this, we found significantly reduced SV in PAH-SSc compared to IPAH in our cohort, despite similar cardiac index (Table 1). RV diastolic dysfunction is common in both IPAH and PAH-SSc as demonstrated in several echocardiographic studies.[42-45] Thus, it is likely that 1) RV wall stress was higher in the PAH-SSc group due to both systolic (lower stroke volume) and diastolic (higher EDV) dysfunction, though this cannot be definitively determined without cardiac MRI or pressure-volume loop measurements and 2) increased RV wall stress in PAH-SSc compared to PAH contributed to the increased NT-proBNP levels seen in this group. Left ventricular dysfunction (LVD), both systolic and non-systolic in nature, can contribute to elevations in NT-proBNP.[46] Further, LVD may be more prevalent in PAH-SSc than IPAH.[5] However, we found no differences in the prevalence of LVD by echocardiography between groups in this cohort. Further, there were no differences in NT-proBNP levels between subjects with and without LVD, both in the overall cohort and within the PAH-

SSc and IPAH sub-groups, suggesting that differences in NT-proBNP levels were unlikely to be affected by left ventricular function.

Patients with SSc have underlying autonomic dysfunction as evidenced by impaired cardiovascular reflexes and sympathetic skin responses.[47,48] Prominent clinical features such as Raynaud's phenomenon and gastrointestinal dysmotility are likely at least in part related to disturbances in the autonomic system.[49,50] Since the autonomic nervous system is integrated with NHA, it is possible that up-regulation of the neurohormonal axis in PAH-SSc compared to PAH in response to cardiac stress may explain the differences in NT-proBNP levels between these groups. Neurohormones, in particular catecholamines, angiotensin II, and endothelin, may enhance secretion of NT-proBNP through paracrine and endocrine mechanisms.[51] Further, neurohormones may contribute to myocardial fibrosis and cause direct myocyte damage which could impair myocardial contractility.[52,53] While we did not routinely collect serum for measurement of catecholamines, angiotensin II, or endothelin in this cohort, we have previously demonstrated increased serum levels of epinephrine and norepinephrine in PAH-SSc compared to PAH in a separate cohort, despite similar hemodynamics.[38] Further, endothelin levels may be higher in PAH-SSc than PAH due to impaired clearance in the pulmonary vasculature, thus contributing to higher NT-proBNP levels.[54] Additionally, hyponatremia, a marker of neurohormonal activation in heart failure states, strongly predicts survival in PAH and may be more common in PAH-SSc than other forms of PAH despite similar hemodynamics.[11] In the current cohort, although the groups had a similar mean cardiac index, the PAH-SSc group had a higher resting heart rate, which also may reflect enhanced NHA. Thus it is possible that underlying differences in

neurohormonal activation between PAH-SSc and IPAH contribute to the differences in NT-proBNP expression. Although hypoxia induces peptide release independent of atrial or ventricular stretch, both in patients with cardiac disease and in normal subjects, [55,56] there were no differences in pulmonary artery saturation between PAH-SSc and IPAH in this cohort. Thus, it is unlikely that local hypoxia explains the difference in NT-proBNP levels.

This study confirms previous observations about the prognostic significance of NT-proBNP in PAH-SSc, but offers several advantages over the prior study.[13] First, the vast majority of patients in the Williams study were on PAH-specific therapy at the time of enrollment (51/68); less than half were on therapy in the current study. Importantly, our study found the relationship between NT-proBNP and survival in both the PAH-SSc cohort overall and in the treatment-naïve cohort. Second, in the Williams study, NT-proBNP was collected up to 6 months prior to RHC, introducing significantly more variability to the relationship between serum levels and 1) RHC parameters and 2) survival. The current study only included subjects whose NT-proBNP was collected within one week of RHC. Third, over 30% of the subjects included in the Williams study had significant ILD which we and others have now shown to portend a poorer prognosis in scleroderma-related pulmonary hypertension [57,58] and thus may have biased their survival analysis.[59]

However, the lack of association between NT-proBNP and survival in IPAH in this cohort was an unexpected finding. This may be related to the size of the cohort or the effect of PAH-specific therapies on NT-proBNP. However, to our knowledge, only one prior study has examined the prognostic value of NT-proBNP in an IPAH population;

this study included fewer patients (n=36), all of whom were on PAH-specific therapy, and reported a similar number of deaths (n=9).[14] In the current study, NT-proBNP was not associated with survival in the overall IPAH population or in the treatment-naïve IPAH population. While reasons for the difference between the current study and the study by Fijalkowski et al. are unclear, it is possible that high NT-proBNP levels despite PAH-specific therapy portend a poor prognosis (as shown in PAH-SSc[13]), and not necessarily baseline values prior to therapy. Thus, although widely accepted as a prognostic marker in IPAH, there are few data to support this practice, particularly for patients not receiving PAH-specific therapy.

There are several limitations to this study. First, all subjects were referrals to our pulmonary hypertension program and thus selection bias towards inclusion of those patients who were most ill is likely. However, since both groups were as likely to be subject to referral bias, the relationship between these two groups is probably valid. Second, survival estimates may be influenced by lead-time bias given that half of the cohort received PAH-specific therapy at the time of NT-proBNP collection; patients with established disease may have been more likely to die during follow-up than newly diagnosed patients. Similarly, although PAH-specific therapy may influence NT-proBNP levels, PAH-SSc subjects had significantly higher NT-proBNP levels than IPAH subjects, suggesting that our comparison may actually underestimate the true difference between groups. DTCCBs may also impact NT-proBNP levels in SSc as it tends to lower NT-proBNP.[60] However, since only PAH-SSc subjects in our cohort received DTCCBs, the NT-proBNP levels in our PAH-SSc subjects may actually be higher than reported and the difference between groups may be underestimated. Third, although

patients with significant ILD based upon a combination of PFT and HRCT findings were excluded from the cohort, it is possible that ILD contributed to the pulmonary vascular disease noted in our SSc population. However, the impact of ILD upon NT-proBNP is unknown and it is unlikely that pulmonary fibrosis alone causes up-regulation of NT-proBNP.[61] Importantly, as discussed above, there were no differences in pulmonary artery saturation between groups, thus minimizing the chance that local hypoxia related to ILD contributed to the differences in NT-proBNP. Similarly, patients with scleroderma may be more likely to have renal insufficiency related to the underlying disease which could have influenced survival. However, the association between NT-proBNP and survival persisted in the PAH-SSc group when controlling for eGFR. Finally, it is possible that factors for which we have not accounted may confound the association between NT-proBNP and survival.

In conclusion, in this cohort of patients with PAH, NT-proBNP levels were significantly higher in PAH-SSc subjects compared to IPAH subjects despite similar hemodynamics, suggesting differences in response to cardiac load. Further, NT-proBNP was a strong predictor of survival only in the PAH-SSc group, further emphasizing the role of this non-invasive marker in the evaluation of patients with PAH-SSc. While the reasons for the differences in levels and in predictive value of NT-proBNP by disease-type remain unclear, underlying variations in cardiac function and neurohormonal response to hemodynamic perturbations between PAH-SSc and IPAH may exist. Future studies are needed to confirm these findings and to elucidate underlying mechanisms.

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**Table 1. Demographic and Hemodynamic Characteristics**

| | Overall (n=98) | PAH-SSc (n=55) | IPAH (n=43) | p-value |
|---|---|---|---|---|
| Age | 55(14) | 57(14) | 53(13) | 0.14 |
| Gender (n,%W) | 83(83) | 49(89) | 34(77) | 0.11 |
| Race (n,%W) | 64(65) | 39(71) | 25(57) | 0.15 |
| BMI ($kg/m^2$) | 28(7) | 26(6) | 29(6) | <0.01 |
| NYHA (I/II v III/IV) | 41%/59% | 34%/66% | 50%/50% | 0.23 |
| 6MWD (m) | 357(131) | 320(114) | 395(140) | <0.01 |
| eGFR | 82(31) | 83(37) | 81(22) | 0.81 |
| NT-proBNP | 2518(3176) | 3419(3784) | 1393(1633) | <0.01 |
| NT-proBNP (log10) | 2.98(0.71) | 3.17(0.66) | 2.75(0.70) | <0.01 |
| Disease duration (days) | 1164(839) | 942(641) | 1440(973) | <0.01 |
| Disease duration prior to proBNP (days) | 455(685) | 273(495) | 681(818) | <0.01 |
| DTCCB (n,%) | 46(47) | 46(84) | 0(0) | <0.01 |
| Treatment status (n, % on therapy) | 45/98(46) | 22/55(40) | 23/43(53) | 0.30 |
| ERA (n,%) | 24(24) | 12(22) | 12(27) | 0.53 |

| | | | | |
|---|---|---|---|---|
| PDE5I (n,%) | 23(23) | 14(25) | 9(20) | 0.56 |
| Inhaled Iloprost | 1(1%) | 1(2) | 0(0) | 0.92 |
| Prostacyclin | 13(13) | 4(7) | 9(20) | 0.06 |
| FVC (%pred) | 75(21) | 72(15) | 80(19) | 0.05 |
| $FEV_1$(%pred) | 72(20) | 69(20) | 78(18) | 0.03 |
| $FEV_1$/FVC (%pred) | 76(14) | 75(18) | 79(6) | 0.14 |
| TLC (%pred) | 81(16) | 77(16) | 87(20) | 0.04 |
| $DL_{CO}$ (%pred) | 58(21) | 49(17) | 71(20) | <0.01 |
| HR (beats/min) | 82(14) | 85(13) | 77(15) | <0.01 |
| RAP (mmHg) | 9(6) | 9(6) | 10(6) | 0.29 |
| mPAP (mmHg) | 45(14) | 41(13) | 48(14) | <0.01 |
| CI ($L/min/m^2$) | 2.5(0.8) | 2.5(0.9) | 2.5(0.8) | 0.79 |
| PCWP (mmHg) | 11(4) | 10(4) | 12(3) | 0.33 |
| PVR (Wood units) | 8(5) | 8(5) | 9(5) | 0.67 |
| PA sat (%) | 65(8) | 65(9) | 66(8) | 0.74 |
| SV (ml/beat) | 58(24) | 51(18) | 65(27) | <0.01 |
| Deaths (n, %) | 28(29) | 20(36) | 8(19) | 0.05 |

Except where indicated otherwise, values are the mean ± SD. Abbreviations: BMI = body mass index; NYHA = New York Heart Association functional class; 6MWD = six minute walk distance; eGFR = estimated glomerular filtration rate; DTCCB = dihydropyridine-type calcium channel blocker; ERA = endothelin receptor antagonist; PDE5I = phosphodiesterase-type 5 inhibitor; FVC = forced vital capacity; $FEV_1$ = forced expiratory volume in one second; TLC = total lung capacity; $DL_{CO}$ = diffusing capacity for carbon monoxide; HR = heart rate; RAP = right atrial pressure; mPAP = mean pulmonary artery pressure; CI = cardiac index; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; PA sat = pulmonary artery saturation; SV = stroke volume

**Table 2. Echocardiographic Assessment of Left Heart Function in Subjects with Echocardiography within Three Months of NT-proBNP Collection**

| **Parameter** | **IPAH** | **PAH-SSc** | **p-value** |
|---|---|---|---|

| | | | |
|---|---|---|---|
| **Left Atrial Dilation (n,%)** | **8/21 (38)** | **12/36 (33)** | **0.72** |
| **Left Ventricular Hypertrophy (n,%)** | **3/21 (14)** | **9/29 (31)** | **0.17** |
| **Left Ventricular Ejection Fraction ( mean %, n)** | **57% (21)** | **60% (36)** | **0.46** |
| **Non-systolic dysfunction (n,%)** | **4/18 (22)** | **7/29 (24)** | **0.88** |

**Values reported as number and percent of total available for each parameter.**

Table 3. Demographic and Hemodynamic Characteristics of Treatment-naïve Subjects

| | Overall (n=53) | PAH-SSc (n=33) | IPAH (n=20) | p-value |
|---|---|---|---|---|
| Age | 57(13) | 58(13) | 56(14) | 0.69 |
| Gender (n,%W) | 43(83) | 28(85) | 15(80) | 0.59 |
| Race (n,%W) | 32(62) | 23(70) | 9(47) | 0.11 |
| BMI ($kg/m^2$) | 28(7) | 26(7) | 30(7) | 0.06 |
| NYHA (I/II v III/IV) | 40%/60% | 36%/64% | 47%/53% | 0.44 |
| 6MWD (m) | 329(134) | 308(112) | 359(159) | 0.24 |
| eGFR | 84(37) | 88(42) | 77(26) | 0.29 |
| NT-proBNP | 2496(3060) | 3200(3552) | 1275(1271) | 0.02 |
| NT-proBNP (log10) | 3.03(0.7) | 3.18(0.63) | 2.76(0.64) | 0.02 |
| FVC (%pred) | 75(21) | 70(21) | 82(19) | 0.05 |
| $FEV_1$(%pred) | 72(21) | 67(21) | 80(18) | 0.04 |
| $FEV_1$/FVC (%pred) | 76(15) | 74(18) | 78(6) | 0.46 |
| TLC (%pred) | 80(22) | 76(21) | 87(21) | 0.13 |
| $DL_{CO}$ (%pred) | 60(21) | 51(15) | 78(20) | <0.01 |
| HR (beats/min) | 82(15) | 86(12) | 73(14) | <0.01 |
| RAP (mmHg) | 9(6) | 9(5) | 9(7) | 0.77 |
| mPAP (mmHg) | 41(14) | 40(12) | 44(14) | 0.21 |
| CI ($L/min/m^2$) | 2.6(0.8) | 2.5(0.9) | 2.6(0.8) | 0.22 |

| | | | | |
|---|---|---|---|---|
| PCWP (mmHg) | 11(4) | 11(4) | 12(3) | 0.90 |
| PVR (Wood units) | 8(6) | 8(5) | 8(6) | 0.85 |
| PA sat (%) | 65(8) | 64(9) | 67(8) | 0.22 |
| SV (ml/beat) | 59(25) | 52(19) | 72(27) | <0.01 |
| Deaths (n, %) | 14(26) | 10(30) | 4(20) | 0.42 |

**Table 4. Univariable Cox Proportional Hazard Models**

| Predictor | Overall Cohort HR (95%CI; p-value) | PAH-SSc HR (95%CI; p-value) | IPAH HR (95%CI; p-value) |
|---|---|---|---|
| Age | 1.00(0.97-1.03; 0.90) | 1.01 (0.97-1.04; 0.78) | 0.97(0.91-1.03; 0.28) |
| Race | 1.31 (0.60-2.86; 0.49) | 2.92 (1.14-7.45; 0.03) | 0.48 (0.09-2.49; 0.38) |
| Gender | 0.79 (0.27-2.31; 0.67) | 1.02 (0.24-4.42; 0.98) | 0.45 (0.08-2.45; 0.36) |
| BMI | 0.93 (0.86-0.99; 0.04) | 0.92 (0.84-1.00; 0.08) | 0.98 (0.86-1.11; 0.71) |
| NYHA | 2.58 (1.47-4.49; <0.01) | 2.76 (1.37-5.52; <0.01) | 1.95 (0.73-5.17; 0.18) |
| 6MWD | 0.99 (0.99-1.00; 0.01) | 0.99 (0.99-1.00; 0.17) | 0.99 (0.99-1.00; 0.05) |
| eGFR | 1.00 (0.98-1.01; 0.60) | 0.99 (0.98-1.01; 0.69) | 0.99 (0.96-1.03; 0.78) |
| Treatment status | 0.97 (0.36-2.07; 0.95) | 1.52 (0.62-3.66; 0.35) | 0.48 (0.10-2.17; 0.34) |
| Disease duration | 0.99 (0.99-0.99; <0.01) | 0.99 (0.99-0.99;<0.01) | 0.99(0.99-0.99; 0.03) |
| Duration prior to proBNP | 0.99 (0.99-1.00; 0.38) | 1.00 (0.99-1.00; 0.56) | 0.99(0.99-1.00; 0.31) |
| RAP | 1.07 (1.00-1.15; 0.04) | 1.05 (0.98-1.14; 0.15) | 1.12 (0.99-1.28; 0.08) |
| mPAP | 1.02 (0.99-1.05; 0.11) | 1.03 (0.99-1.07; 0.07) | 1.03 (0.98-1.09; 0.21) |
| CI | 0.32 (0.17-0.63;<0.01) | 0.32 (0.15-0.67; <0.01) | 0.42 (0.11-0.57; 0.01) |
| PCWP | 0.94 (0.85-1.06; 0.36) | 0.96 (0.86-1.07; 0.41) | 0.95 (0.75-1.20; 0.67) |
| PVR | 1.16 (1.09-1.24;<0.01) | 1.17 (1.09-1.27;<0.01) | 1.18 (1.06-1.33;< 0.01) |
| PA saturation | 0.93 (0.89-0.97; <0.01) | 0.92 (0.88-0.96; <0.01) | 0.96 (0.87-1.04; 0.30) |
| NT-proBNP (log10) | 3.18 (1.60-6.33;<0.01) | 3.07 (1.35-7.00; <0.01) | 2.02 (0.55-7.52; 0.29) |

Abbreviations: BMI = body mass index; NYHA = New York Heart Association functional class; 6MWD = six minute walk distance; eGFR = estimated glomerular filtration rate;

RAP = right atrial pressure; mPAP = mean pulmonary artery pressure; CI = cardiac index; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; PA sat = pulmonary artery saturation; NT-proBNP = N-terminal pro-brain natriuretic peptide

**Table 5. Multivariable Cox Proportional Hazard Models**

| | Overall Cohort HR (95%CI; p-value) | PAH-SSc HR (95%CI; p-value) | IPAH HR (95%CI; p-value) |
|---|---|---|---|
| Log NT-proBNP | 3.18 (1.60-6.33;<0.01) | 3.07 (1.35-7.00; 0.01) | 2.02 (0.55-7.52; 0.29) |
| Adjusted for | | | |
| Diagnosis | 2.78.(1.37-5.64; <0.01) | | |
| NYHA | 2.60 (1.27-5.32; <0.01) | 2.81 (1.22-6.44; 0.01) | |
| RAP | 2.95 (1.44-6.16; <0.01 | 3.00 (1.21-7.42: 0.02) | |
| CI | 2.08 (0.95-4.59; 0.07) | 1.65 (0.60-4.56; 0.33) | |
| Treatment status | 3.18 (1.60-6.32;<0.01) | 2.93 (1.29-6.65; 0.01) | |
| eGFR | 3.71 (1.77-7.77;<0.01) | 3.80 (1.55-9.36;<0.01) | |
| BMI | 2.86 (1.43-5.71;<0.01) | 2.85 (1.22-6.63; 0.02) | |

Abbreviations: BMI = body mass index; NYHA = New York Heart Association functional class; eGFR = estimated glomerular filtration rate; CI = cardiac index

**Figure Legends**

**Figure 1:** Box and whisker plots of the NT-proBNP levels measured in IPAH and PAH-SSc patients. The boxes show the interquartile ranges (IQR) and the dark lines are the medians. Whiskers represent the closest value within 1.5 times the IQR of the NT-proBNP values. Dots represent individual measurements exceeding the values represented by the whiskers. * median value Abbreviations: NT-proBNP = N-terminal pro-brain natriuretic peptide; PAH-SSc = Pulmonary arterial hypertension related to scleroderma; IPAH = Idiopathic pulmonary arterial hypertension.

**Figure 2:** Correlations between NT-proBNP and cardiac index in a) the overall cohort, b) PAH-SSc, and c) IPAH. Abbreviations: NT-proBNP = N-terminal pro-brain natriuretic peptide; CI = cardiac index; PAH-SSc = Pulmonary arterial hypertension related to scleroderma; IPAH = Idiopathic pulmonary arterial hypertension

**Figure 1.**

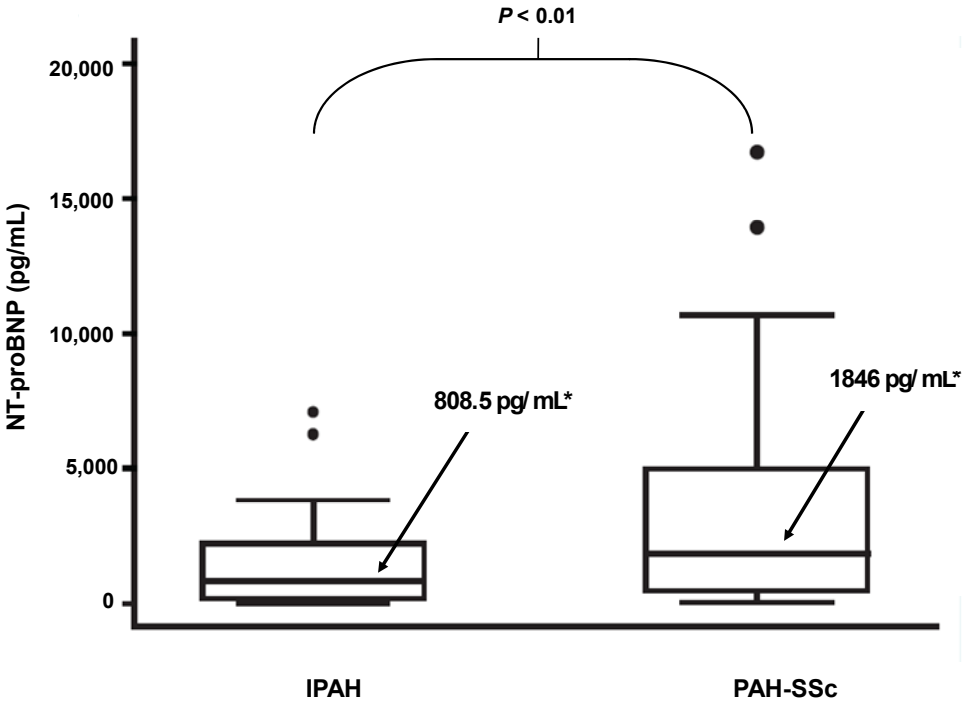
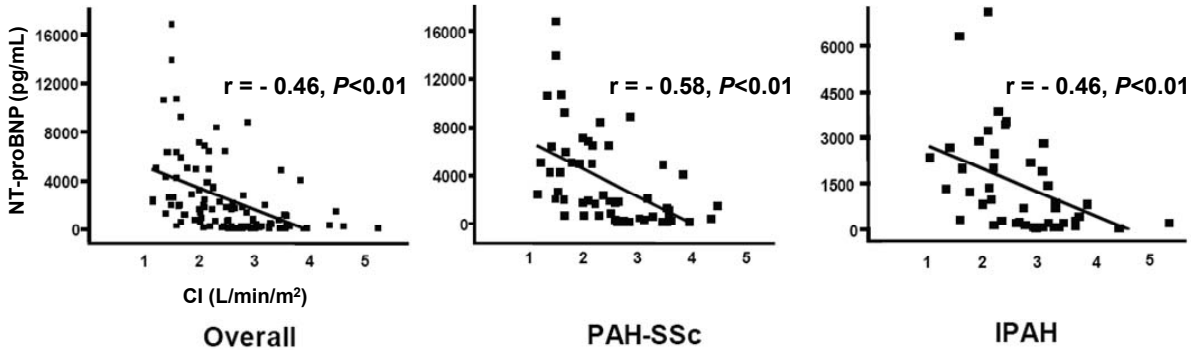



**Figure 2.**


NT-proBNP (pg/mL)
16000
12000
8000
4000
0
r = - 0.46, P<0.01
1
2
3
4
5
CI (L/min/m²)
Overall
16000
12000
8000
4000
0
r = - 0.58, P<0.01
1
2
3
4
5
PAH-SSc
6000
4500
3000
1500
0
r = - 0.46, P<0.01
1
2
3
4
5
IPAH