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**Title:** Circulating collagen indices indicative of disease severity in pulmonary arterial hypertension

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**Body:** Procollagen deposition occurs in explanted pulmonary arterial hypertension (PAH) lungs. Biochemical monitoring of collagen synthesis may provide a non-invasive method of determining vascular remodeling. However, there is lack of data regarding circulating procollagen indices in PAH. We obtained circulating levels of carboxyl-terminal of procollagen type III (PIIINP), carboxy-terminal telopeptide of collagen type I (CITP), matrix metalloproteinase-9 (MMP-9) and tissue inhibitor of metalloproteinase-1 (TIMP-1) from 87 PAH subjects and 37 age- and gender-matched controls (Baylor PH Center). Serum was separated and stored at -80 °C. CITP, MMP-1 and TIMP-1 levels were measured by ELISAs. PIIINP was measured by antibody radioimmunoassay. PAH patients had elevated PIIINP, CITP, MMP-9 and TIMP-1 levels suggesting active collagen metabolism (Table 1). PIIINP levels were higher in WHO FC III-IV as compared to WHO FC I-II PAH patients ( $p=0.011$ ). PIIINP levels negatively correlated with six-minute walk distance ( $R=-0.3$ ,  $P=0.008$ ), and positively correlated with right atrial pressure ( $R=0.35$ ,  $P=0.002$ ) and BNP levels ( $R=0.25$ ,  $P=0.02$ ). Circulating procollagen markers may provide a novel non-invasive method of documenting active collagen synthesis reflective of severe disease in PAH.

## Clinical Characteristics and Biomarker Levels in PAH Patients

	Controls	PAH	p value
Age (yrs)	49.14±14	47.14±14	0.34
Gender (F, %)	33 (89)	79 (90)	
BSA (m2)	1.79±0.24	1.83±0.19	0.36
Pulse pressure (mm Hg)	36.6±17	37.6±17	0.82
6MWD (meters)	468±63	412±106	0.005
BNP (pg/ml)	19.9±19	138±202	0.002
PIIINP (ng/ml)	3.80±0.92	5.2±1.88	<0.001
MMP-9 (ng/ml)	291.5±171	478±292	<0.001
TIMP-1 (ng/ml)	128±34	202±63	<0.001
CITP (ng/ml)	2.20±1.2	4.03±2.33	<0.001

