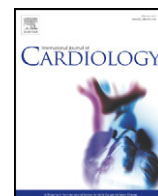


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Letter to the Editor

## Relationships between nutritional status and markers of congestion in patients with pulmonary arterial hypertension

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Cachexia is associated with a high risk of death in heart failure (HF) patients [1,2]. Right ventricular dysfunction (RVD) reportedly often coexists with cachexia and is associated with accelerated weight loss, abnormal body composition, and a worsened prognosis in advanced HF [3]. Multiple mechanisms are thought to be involved in the development of cardiac cachexia. In particular, this condition is related to hemodynamics of HF including pulmonary hypertension [4] as well as increased neurohumoral and cytokine responses [5,6], impaired gastrointestinal function [7], and an increased metabolic rate [8].

However, only a few studies have investigated pulmonary arterial hypertension (PAH) and nutritional status [9]. In the present study, we sought to examine the relationships among nutritional status, markers of congestion, and echocardiographic parameters in patients with stable PAH. Findings from the present study would provide insights on the mechanism underlying the effect of PAH alone on nutritional status.

We enrolled 8 patients with stable (>6 months) pulmonary hypertension from our out-patient clinic prospectively, and written informed consent was obtained. The study conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the ethical committee of Kyoto University Hospital. Patients underwent the scored Patient-Generated Subjective Global Assessment (PG-SGA) for nutritional status, blood tests, and comprehensive echocardiography. After morning fasting, patients underwent blood testing for complete blood

counts, chemistry, zinc, pre-albumin, transferrin, retinol-binding proteins, and brain natriuretic peptide (BNP) levels. Glomerular filtration rate (GFR) was estimated with the CKD-EPI Creatinine Equation. Spearman's rank correlation tests were conducted to assess relationships between nonparametric variables, and multiple regression analyses were performed to exclude multicollinearity. Data were analyzed with JMP 12 software (SAS Institute, Inc., Cary, NC).

Patient characteristics are summarized in Table 1. The estimated systolic pulmonary artery pressure (ePAP) and BNP levels were  $82.7 \pm 15.7$  (mean  $\pm$  SD) mm Hg and  $176 \pm 146$  ng/L, respectively. LV diastolic diameter (LVDd) was negatively correlated with ePAP ( $r_s = -0.76$ ,  $p = 0.04$ ), which implied a dilated RV and compressed LV. Body mass index (BMI) was positively correlated with white blood cell count (WBC,  $r_s = 0.84$ ,  $p = 0.03$ ) and fasting insulin levels ( $r_s = -0.57$ ,  $p = 0.03$ ) and negatively correlated with aspartate aminotransferase concentration (AST,  $r_s = -0.47$ ,  $p = 0.02$ ), serum sodium concentration ( $r_s = -0.60$ ,  $p = 0.03$ ), and inferior vena cava (IVC) diameter ( $r_s = -0.76$ ,  $p = 0.04$ ). Blood urea nitrogen, a marker of protein catabolism, was positively correlated with SGA scores ( $r_s = 0.81$ ,  $p < 0.01$ ) and BNP ( $r_s = 0.68$ ,  $p = 0.04$ ) and negatively correlated with LV diameter ( $r_s = -0.87$ ,  $p < 0.01$ ). Serum pre-albumin – a rapid-turnover hepatic protein – was positively correlated with ePAP ( $r_s = 0.70$ ,  $p = 0.01$ ) and negatively correlated with serum sodium concentrations ( $r_s = -0.56$ ,  $p = 0.02$ ). Fig. 1 and supplementary Fig. 1 show the correlation map with clustering in which factors cluster more closely together based on how closely they are associated and multiple scattered maps with correlation coefficients, respectively. In multiple regression analyses, BMI was associated by WBC count ( $p = 0.008$ ), ePAP ( $p = 0.0008$ ), serum sodium ( $p = 0.001$ ), and AST concentrations ( $p = 0.0005$ ), and IVC diameter ( $p = 0.0042$ ; supplementary Table 1).

As previously reported [8], increased right heart filling pressure and tricuspid regurgitation have been associated with body fat depletion and low BMI in HF patients. RV function and degree of pulmonary hypertension may play a critical role in the nutritional status in patients with PAH by maintaining cardiac output and by possibly causing congestion of splanchnic organs.

Liver congestion was estimated from the correlation between pre-albumin and ePAP. In our study, BMI was in association with nutritional factors, liver enzymes, serum sodium, ePAP, and IVC diameter, indicating the presence of a close relationship between pulmonary hypertension with IVC dilatation, poor nutritional status, and low BMI. Valentova et al. reported that cachexia in HF patients is associated

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**Table 1**  
Patients characteristics.

			Mean ± SD		Mean ± SD
Sex	Male 4				
	Female 4	WBC (/μL)	5.6 ± 0.9	Blood sugar (mg/dL)	96.3 ± 6.3
Age		HGB (g/dL)	14.9 ± 1.7	Na (mEq/L)	142.3 ± 2.6
	Mean ± SD	Lymph (/mm <sup>3</sup> )	1831 ± 622	C-reactive protein (g/dL)	0.1 ± 0.1
BMI	62.4 ± 2.4	AST (IU/L)	26.5 ± 11.7	Zinc (μg/dL)	72.9 ± 4.7
	22.1 ± 2.1	ALT (IU/L)	17.3 ± 8.5	Pre-albumin (mg/dL)	23.8 ± 5.6
SGA score		Total protein (g/dL)	7.1 ± 0.6	RBP (mg/dL)	3.0 ± 0.8
	2.6 ± 2.5	Albumin (g/dL)	3.8 ± 0.2	Transferrin (mg/dL)	255.7 ± 28.6
LVDd (mm)	40.8 ± 5.1	Choline esterase (IU/L)	281 ± 59	HbA1c (NGSP %)	5.6 ± 0.3
	22.6 ± 3.1	Total bilirubin (mg/dL)	1.1 ± 0.6	Insulin (μU/mL)	24.7 ± 18.4
LVDs (mm)	75.8 ± 5.2	Creatinine (mg/dL)	0.8 ± 0.2	BNP (pg/mL)	176.9 ± 149.4
	72.8 ± 15.8	eGFR	67.0 ± 7.0		
Estimated PAP (mm Hg)	82.3 ± 15.7	BUN (mg/dL)	15.6 ± 4.1		
	18.6 ± 8.1	Total cholesterol (mg/dL)	198 ± 15		
IVC max (mm)		HDL-cholesterol (mg/dL)	58 ± 9		
		LDL-cholesterol (mg/dL)	119 ± 16		
		Triglycerides (mg/dL)	122 ± 55		
		TG/HDL	2.3 ± .3		

BMI: body mass index; HbA1c: hemoglobin A1c; SGA: subjective global assessment; LVDd/s: left ventricular diastolic/systolic dimension; EF: ejection fraction; TR-PG: pressure gradient of tricuspid regurgitation; PAP: pulmonary artery pressure; IVC: inferior vena cava; WBC: white blood cell; HGB: hemoglobin; AST: aspartate aminotransferase; ALT: alanine aminotransferase; eGFR: estimated glomerular filtration rate; RBP: retinol binding protein; BNP: brain natriuretic peptide; SD, standard deviation; NGSP, National Glycohemoglobin Standardization Program; eGFR, estimate glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; and TG, triglycerides.

with RVD, liver markers, and albumin levels [10]. With regard to PAH, nutritional status may be surrogate markers for PAH. Although cachexia due to pulmonary disease was reversible after lung transplantation [9], it is unclear whether interventions targeting nutritional status would improve PAH or its prognosis.

The limitations of the present study are that the sample size was small and all patients were from a single institution. Moreover, we did not monitor the therapeutic effect on liver function sequentially nor did we monitor body weight, and analyses of RVD were not performed in all cases. However, the ejection fraction was maintained, and the decrease in LV diastolic dimension might consequently suggest that the RV compresses the LV.

In conclusion, there were strong correlations among markers of nutritional status, markers of congestion, and PAH severity. These results suggest that poor nutritional status may be surrogate markers for PAH severity. Further study is needed that it would be therapeutic targets for PAH.

#### Conflict of interest

None declared.

#### Acknowledgments

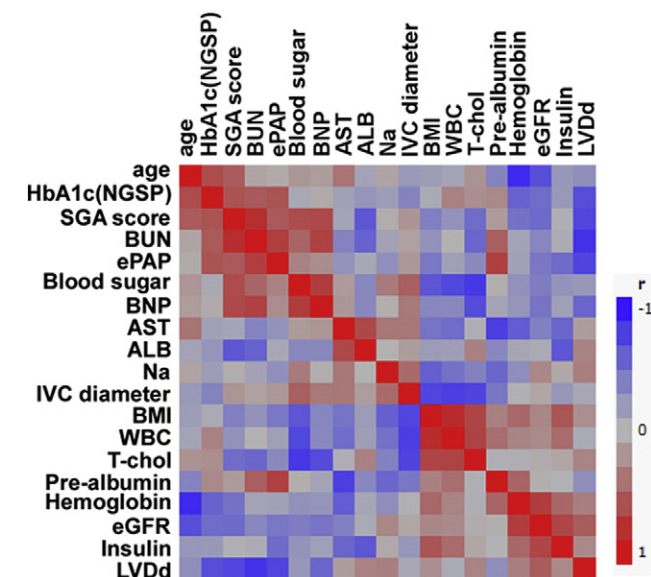
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#### Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.ijcard.2015.03.354>.

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**Fig. 1.** This map showed that factors cluster more closely together based on how closely they are associated. HbA1c: haemoglobin A1c, SGA: subjective global assessment, BUN: blood urea nitrogen, ePAP: estimated pulmonary artery pressure, BNP: brain natriuretic peptides, AST: Aspartate Aminotransferase, ALT: alanine aminotransferase, Na: sodium, IVC: inferior vena cava, BMI: body mass index, WBC: white blood cell, T-cholesterol: total cholesterol, eGFR: estimated glomerular filtration rate, LVDd: left ventricular diastolic dimension.