Load Adaptability in Patients With Pulmonary Arterial Hypertension

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Right ventricular (RV) adaptation to pressure overload is a major prognostic factor in patients with pulmonary arterial hypertension (PAH). The objectives were first to define the relation between RV adaptation and load using allometric modeling, then to compare the prognostic value of different indices of load adaptability in PAH. Both a derivation (n = 85) and a validation cohort (n = 200) were included. Load adaptability was assessed using 3 approaches: (1) surrogates of ventriculo-arterial coupling (e.g., RV area change/end-systolic area), (2) simple ratio of function and load (e.g., tricuspid annular plane systolic excursion/right ventricular systolic pressure), and (3) indices assessing the proportionality of adaptation using allometric pressure-function or size modeling. Proportional hazard modeling was used to compare the hazard ratio for the outcome of death or lung transplantation. The mean age of the derivation cohort was 44 ± 11 years, with 80% female and 74% in New York Heart Association class III or IV. Mean pulmonary vascular resistance index (PVRI) was 24 ± 11 with a wide distribution (1.6 to 57.5 WU/m^2). Allometric relations were observed between PVRI and RV fractional area change ($R^2 = 0.53$, $p < 0.001$) and RV end-systolic area indexed to body surface area right ventricular end-systolic area index (RVESAI) ($R^2 = 0.29$, $p < 0.001$), allowing the derivation of simple ratiometric load-specific indices of RV adaptation. In right heart parameters, RVESAI was the strongest predictor of outcomes (hazard ratio per SD = 1.93, 95% confidence interval 1.37 to 2.75, $p < 0.001$). Although RVESAI/PVRI$^{0.35}$ provided small incremental discrimination on multivariate modeling, none of the load-adaptability indices provided stronger discrimination of outcome than simple RV adaptation metrics in either the derivation or the validation cohort. In conclusion, allometric modeling enables quantification of the proportionality of RV load adaptation but offers small incremental prognostic value to RV end-systolic dimension in PAH. **(Am J Cardiol 2017;120:874–882)**

Right ventricular (RV) adaptation is a key determinant of survival in pulmonary arterial hypertension (PAH).[1–3] Several indices of load adaptability have been proposed, although referring to different concepts: ventriculo-arterial coupling, simple ratio of function and load, or indices assessing whether the RV is well adapted, considering the load being subjected to (Figure 1).[4] Ventriculo-arterial coupling is measured as the ratio of ventricular to arterial elastance using pressure-volume loop analysis.[5,6] Simplified, although less accurate, indices of coupling have been proposed, such as stroke volume (SV) divided by end-systolic volume, but this latter assumes that volume at pressure 0 passes through the origin.[7] Ratiometric indices combining measures of load and function have also been used, but they fail to take into account the physiological dependence of load and function.[8,9] The last category assessed whether ventricular dysfunction or enlargement is "proportional or disproportional" to the load imposed on the ventricle. As recently suggested, RV function may follow an allometric function with load in pulmonary hypertension (PH).[10] We hypothesized that using allometric modeling (i.e., RV function or size = a.Load^b, where a and b are constants) enables derivation of ratios of "proportional" load adaptability. Our first objective was to confirm the allometric relation in multiple indices of RV function or remodeling and load in a derivation prospective cohort of patients with PAH undergoing almost simultaneous echocardiography and catheterization. Our second objective

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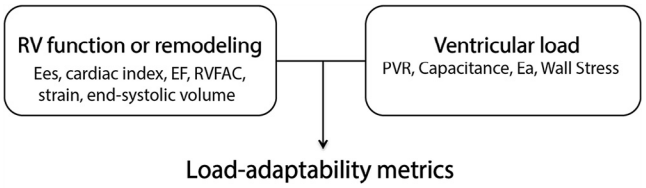

	What is measured	Examples
Ventricular-Arterial Coupling	Matching of Contractility and Load	Ees/Ea or its surrogates SV/RVESV and RV area change/RVESA
Combined indices	Combine metrics without reference to their physiological relationship	TAPSE/RVSP SPAP/CI PP/RAP
Proportionality indices	Evaluate function or remodeling considering load and its physiological relationship	Dandel's index Previous studies suggested allometric modeling, e.g. Function/Load[a]

Figure 1. Load adaptability indices. Ea = arterial elastance and Ees = ventricular elastance both derived from pressure-volume loops; EF = ejection fraction; PP = pulse pressure; PVR = pulmonary vascular resistance; RAP = right atrial pressure; RVESV = end-systolic volume; RVESA = end-systolic area; RVFAC = fractional area change; SPAP = systolic pulmonary arterial pressure; SV = stroke volume; TAPSE = tricuspid annular plane systolic excursion.

was to compare the prognostic value of load-adaptability indices in the derivation and a validation cohort.

Methods

Two prospective cohorts of patients with established diagnosis of PAH (i.e., mean pulmonary arterial pressure [MPAP] ≥25 mm Hg and pulmonary arterial wedge pressure ≤15 mm Hg) referred to Stanford University Hospital and Clinics were included. The derivation cohort included 85 patients with idiopathic PAH or PAH of familial, drug, and toxin or connective tissue disease etiology who underwent, from August 2007 to June 2009, echocardiogram within 3 hours before catheterization (enabling close assessment of RV metrics and load). From 101 patients enrolled, 7 patients with congenital heart disease, 3 patients who required escalation of PH therapy between echocardiography and catheterization, 2 patients with technically difficult echocardiographic studies, 3 patients with active infection, and 1 with incomplete invasive data were excluded. Treatment and decision of lung transplantation was left to the discretion of the physicians according to clinical practice. To compare the derivation cohort with controls, we also included 1:1 age- and sex-matched healthy controls from the Stanford Healthy Aging research database in whom PH or heart failure was excluded by a 60-point health questionnaire, physical examination, and echocardiography. The validation cohort included 200 patients with idiopathic PAH or PAH of familial, drug, and toxin or connective tissue disease etiology who underwent both examinations within 3 months, from January 2007 to January 2014 (excluding patients from the derivation cohort). One-year follow-up echocardiograms were available in 179 patients. This study was approved by the Stanford University Institutional Review Board and conducted in agreement with the Helsinki II declaration, with written informed consent obtained from all participants.

Catheterization was performed through the internal jugular or right femoral vein, after local anesthesia, using mild sedation as required.[11] Afterload was assessed by MPAP, pulmonary vascular resistance, capacitance, and arterial elastance (Ea). Pulmonary vascular resistance index (PVRI) was measured as transpulmonary gradient divided by cardiac index (CI). Capacitance was estimated as SV divided by pulse pressure (PP, i.e., difference between systolic and diastolic PAP).[12] Pulmonary arterial capacitance index was defined by indexing SV by the body surface area (using Du Bois formula). Pulmonary Ea was defined as systolic PAP × 0.9 divided by SV.[13,14] Pulmonary arterial wedge pressure was measured at the end of expiration; cardiac output was determined using the thermodilution method (or Fick method in case of severe tricuspid regurgitation), and right atrial pressure (RAP) was averaged over the cardiac cycle.

Digitized echocardiographic studies were acquired using Hewlett Packard Sonos 7500 or Philips IE 33 ultrasound systems (Philips, Andover, MA). All measures were averaged over 3 cycles according to latest guidelines[15,16] by 2 blinded certified readers. Right heart dimensions were assessed using RV end-diastolic area, end-systolic area, and right atrial maximal area; all dimensions were indexed to body surface area (right ventricular end-diastolic area index

Table 1
Characteristics of patients with pulmonary arterial hypertension

Variable	n = 85
Age (years)	44 ± 11
Women	68 (80%)
Body surface area (m^2)	1.84 ± 0.23
Etiology	
- Idiopathic	31 (36%)
- Drugs and toxins	34 (40%)
- Connective tissue disease	20 (24%)
New York Heart Association functional class	II (26%); III (60%); IV (14%)
Diabetes mellitus	6 (7%)
Systemic hypertension	6 (7%)
Heart rate (bpm)	81 ± 15
Systolic blood pressure (mmHg)	110 ± 15
Right atrial pressure (mmHg)	12 ± 7
Mean pulmonary arterial pressure (mmHg)	53 ± 14
Mean pulmonary arterial pressure/Mean arterial pressure	0.64 ± 0.17
Pulmonary capillary wedge pressure (mmHg)	10 ± 4
Cardiac Index (L/min/m^2)	2.0 ± 0.5
Stroke volume index (mL/m^2)	25 ± 8
Pulmonary vascular resistance (WU)/indexed (WU.m^2)	13 ± 6 / 24 ± 11
Pulmonary capacitance (mL/mmHg)/indexed	1.0 ± 0.6 / 0.56 ± 0.32
Resistance Compliance time constant (s)	0.67 ± 0.15
Pulmonary arterial elastance (mmHg/mL)	1.92 ± 0.97
Serum creatinine (mg/dL)	1.04 ± 0.36
Serum sodium (mEq/L)	137 ± 3
Serum N-terminal pro B-type natriuretic peptide* (pg/mL)	869.5 [300.0–2023.3]
Prostanoid Therapy	33 (39%)
Phosphodiesterase Inhibitors	34 (40%)
Endothelin Receptor Blockers	22 (26%)
Warfarin	25 (29%)

Values are expressed as mean ± SD or number (percentage) or median and interquartile range.

* NT-proBNP levels were available only for 56/85 patients.