Clinical Investigation

Restrictive Lung Function Is Related to Sympathetic Hyperactivity in Patients With Heart Failure

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ABSTRACT

Background: Sympathoexcitation and impaired lung function are common in patients with severe heart failure (HF). However, the association between impaired lung function and sympathoexcitation remains unknown.

Methods and Results: Muscle sympathetic nerve activity (MSNA) and clinical variables were determined in 83 HF patients with left ventricular ejection fraction (LVEF) <0.45. Restrictive and obstructive changes on spirometry were defined as reduced forced vital capacity (FVC) of <80% of predicted and a ratio of forced expiratory volume in the first second to FVC of <70%, respectively. Restrictive and obstructive changes were identified in 17 and 21 patients, respectively. MSNA was higher in patients with restrictive changes than in those without restrictive changes (84 vs 66 bursts per 100 beats; $P < .01$), but was similar in those with and without obstructive changes. Univariate analyses showed that FVC, estimated glomerular filtration rate (eGFR), specific activity scale, B-type natriuretic peptide level, LVEF, age, and use of aldosterone receptor blockers were significant predictors of MSNA burst incidence. Multivariate analysis revealed that FVC, LVEF, and eGFR were independent factors for increased burst incidence. Changes in FVC during follow-up negatively correlated with changes in burst rate ($n = 11$; $P < .01$).

Conclusion: Restrictive lung function was associated with increased sympathetic nerve activity independently from HF severity. (*J Cardiac Fail 2017;23:96–103*)

Key Words: Heart failure, restrictive lung function, sympathetic nerve activity.

Heart failure (HF) is characterized by sympathetic overactivation that contributes to disease progression and poor prognosis.[1,2] Multifactorial mechanisms, such as decreased arterial or cardiopulmonary baroreflexes, increased metabolic reflexes, increased chemosensitivity, and complications of renal insufficiency or sleep apnea, can result in sympathetic overactivation in patients with HF.[3–5]

Patients with HF frequently have breathing abnormalities, such as rapid, shallow, and periodic breathing.[6,7] Deactivation of pulmonary stretch receptors induced by these abnormalities is another cause of sympathetic overactivation in patients with HF.[8,9] In HF patients with Cheyne-Stokes respiration, sympathetic nerve activity was highest during apnea.[10] In contrast, device-guided slow and deep respiration can suppress steady-state sympathetic nerve activity in patients with HF.[11] Sympathetic nerve activity is also enhanced in patients with chronic obstructive pulmonary disease.[12] However, whether impaired lung function itself is associated with sympathetic overactivation remains unknown. We postulated that impaired lung function was associated with sympathetic overactivation independently from HF severity.

Methods

Patients

This study included 83 patients with clinically stable HF (68 men and 15 women of average age 62 ± 11 years) and left ventricular ejection fraction (LVEF) <0.45. All patients

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received optimal medical therapy. Patients with moderate to severe valvular heart disease, stroke, respiratory failure or pulmonary disease, severe anemia (hemoglobin level <9.0 g/dL), and end-stage renal disease treated by hemodialysis, as well as those using oxygen inhalation, positive airway pressure support therapy, or noninvasive positive pressure ventilation, were excluded. The underlying cardiac disease was ischemic and nonischemic in 29 patients and 54 patients, respectively. Written informed consent was obtained from every patient before participation in this study, which was approved by the Institutional Ethics Board of Toyama University Hospital.

Measurement of Heart Rate, Blood Pressure, and Muscle Sympathetic Nerve Activity

All parameters were measured while the patients rested and remained awake in the supine position, as previously described.[8] Briefly, blood pressure was serially recorded by means of noninvasive tonometry (Jentow 7700; Colin, Komaki, Japan). Multiunit recordings of efferent postganglionic sympathetic nerve activity to skeletal muscle regions were obtained by a microelectrode that was directly inserted into the left peroneal nerve posterior to the fibular head. The nerve signal was amplified ×100,000, underwent band-pass filtering (500–5000 Hz), and was integrated with a custom nerve traffic analysis system (NeuropackΣ MEB-5504; Nihon Kohden, Tokyo, Japan). Muscle sympathetic nerve activity (MSNA) was expressed as burst rate (bursts/min) and burst incidence (bursts/100 beats). Respiration was continuously monitored by means of thoracic electrical impedance.[13] Blood samples were collected immediately before MSNA recording to measure B-type natriuretic peptide (BNP) (Shionoria BNP; Shionogi, Japan) and norepinephrine (HPLC HCL-725 CA; Tosoh Corp, Tokyo, Japan) levels.

Lung Function

All patients underwent spirometry evaluation (Chestac-8900; Chest, Tokyo, Japan), including forced vital capacity (FVC) and the ratio of forced expiratory volume in the 1st second (FEV_1) to FVC. Abnormal spirometry findings with restrictive and obstructive changes were defined as a reduction in FVC to <80% of predicted and an FEV_1-FVC ratio of <70%, respectively. To analyze the relationship between changes in MSNA and FVC in 11 patients, we measured MSNA and FVC twice at an average interval of 9.2 months.

Echocardiography

We measured LVEF and left atrial dimension with the use of 2-dimensional echocardiography (Aplio SSA-770A; Toshiba, Japan). The left ventricular end-diastolic and end-systolic volumes were determined with the use of a modification of the Simpson method; LVEF was calculated as stroke volume (end-diastolic volume minus end-systolic volume) divided by end-diastolic volume.

Renal Function

Estimated glomerular filtration rate (eGFR) was determined to identify renal insufficiency. Although widely applied, the simplified Modification of Diet in Renal Disease (sMDRD) equation is not feasible for Asian populations, including Japanese.[14] Therefore, we adopted the equation recommended by the Japanese Society of Nephrology Chronic Kidney Disease Initiatives[14] as follows:

$$\text{eGFR (Japanese)} = 0.741 \times 175 \times \text{sCr}^{-1.154} \times \text{age}^{-0.203} \ (\times 0.742 \text{ if female}) \quad (1)$$

The part of the equation "$175 \times \text{sCr}^{-1.154} \times \text{Age}^{-0.203}$ ($\times 0.742$ if female)" is from the sMDRD equation with the use of standardized serum creatinine levels. A value of 0.741 is the coefficient used to adapt the sMDRD equation to a Japanese population.[14]

Specific Activity Scale

Daily activity was quantified with the use of the described specific activity scale.[14] Briefly, the scale can express maximal physical activities with energy cost to the individual. By definition, 1 Met was equivalent to a metabolic rate that consumed 3.5 mL oxygen/kg body weight per minute. The specific activity scale contained questions related to specific physical activities that a patient would routinely perform. Each patient was asked to specify whether each type of activity could be performed without symptomatic limitation. Summarizing the questionnaire data, a given number of metabolic cost (specific activity scale) was derived for each patient based on self-perceived exercise tolerance. The interobserver variability of this scale was 0.4 ± 0.5 Mets, suggesting that a ≥1 Met change in functional capacity was reliable and clinically relevant.[15]

Statistical Analyses

Data were expressed as mean ± SD and were statistically analyzed with the use of SigmaPlot 11.2 (Systat Software, San Jose, California). Two-way analysis of variance (ANOVA) was applied to determine the effect of 2 factors (restrictive/nonrestrictive and obstructive/nonobstructive) on the variables. Post hoc analyses were performed with the use of the Bonferroni-Dunn procedure only when the ANOVA P value was significant. To perform a Bonferroni correction, we divided the critical P value (α) by the number of comparisons made ($n = 4$). Relationships between MSNA and clinical parameters were analyzed with the use of linear regression analysis. Variables with a P value of <.20 in the univariate analyses were included in the multivariate analysis. Variance inflation factors (VIFs) were also used to test for multicollinearity among the predictor variables. A VIF of >10 was regarded as serious multicollinearity and a value of >4.0 was considered to be a cause for concern. The level of statistical significance was set at $P < .05$.