CHEST

Left Atrial Size, Chemosensitivity, and Central Sleep Apnea in Heart Failure

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BACKGROUND: Central sleep apnea (CSA) is common among patients with heart failure (HF) and is promoted by elevated CO_2 chemosensitivity. Left atrial size is a marker of the hemodynamic severity of HF. The aim of this study was to determine if left atrial size predicts chemosensitivity to CO_2 and CSA in patients with HF.

METHODS: Patients with HF with left ventricular ejection fraction ≤ 35% underwent polysomnography for detection of CSA, echocardiography, and measurement of CO_2 chemosensitivity. CSA was defined as an apnea-hypopnea index (AHI) ≥ 15/h with ≥ 50% central apneic events. The relation of clinical and echocardiographic parameters to chemosensitivity and CSA were evaluated by linear regression, estimation of ORs, and receiver operator characteristics.

RESULTS: Of 46 subjects without OSA who had complete data for analysis, 25 had CSA. The only parameter that significantly correlated with chemosensitivity was left atrial volume index (LAVI) ($r = 0.40$, $P < .01$). LAVI was greater in those with CSA than those without CSA (59.2 mL/m^2 vs 36.4 mL/m^2, $P < .001$) and significantly correlated with log-transformed AHI ($r = 0.46$, $P = .001$). LAVI was the best predictor of CSA (area under the curve = 0.83). A LAVI ≤ 33 mL/m^2 was associated with 22% risk for CSA, while LAVI ≥ 53 mL/m^2 was associated with 92% risk for CSA.

CONCLUSIONS: Increased LAVI is associated with heightened CO_2 chemosensitivity and greater frequency of CSA. LAVI may be useful to guide referral for polysomnography for detection of CSA in patients with HF. CHEST 2014; 146(1):96-103

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ABBREVIATIONS: AHI = apnea-hypopnea index; AUC = area under the curve; BNP = brain natriuretic peptide; CSA = central sleep apnea; e′ = medial anulus e′ velocity; E/e′ = the ratio of mitral E velocity to medial anulus e′ velocity; HF = heart failure; LAVI = left atrial volume index; LVEDD = left ventricular end-diastolic dimension; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; P_{ETCO_2} = end tidal CO_2; PSG = polysomnography; ROC = receiver operator characteristic; RVSP = right ventricular systolic pressure; $\dot{V}_E$ = minute ventilation

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Heart failure (HF) is common, affecting 1% to 2% of the adult population.[1] As many as 50% of patients with HF may have sleep-disordered breathing, most frequently central sleep apnea (CSA).[2,3] CSA is associated with adverse prognosis,[4,5] and treatment improves sleep architecture, cardiac function,[6] exercise capacity, HF symptoms,[7-13] and may improve survival.[6,13,14] However, diagnosis requires polysomnography (PSG), which is expensive and not always readily available. Some have advocated formal sleep testing for all patients with HF,[15] although current guidelines do not recommend routine testing or screening for CSA.[16-18] History, physical examination, and symptoms are of limited usefulness for screening for CSA.[19] Moreover, no method has been endorsed for routine application in patients with HF as a screening tool for CSA.[20,21] Hence, the development of a simple screening strategy for CSA in patients with HF potentially would have wide utility.

CSA is associated with elevated pulmonary capillary wedge pressure.[22-24] It has been shown that pulmonary congestion promotes lung J-receptor stretch with increased reflex ventilatory response to CO_2[25,26] and hyperventilation.[22,27,28] Indeed, in patients with HF, CSA is manifested as cyclic hyperventilation with compensatory apnea and considered secondary to increased cardiac filling pressures.[22]

Central apnea frequency is related not only to pulmonary capillary wedge pressure but also to left atrial size,[29] as patients with HF with CSA have greater left atrial dimension than patients with HF who do not have CSA.[3,30,31] Assessment of left atrial size is a routine part of a comprehensive echocardiographic examination,[32] a test that is widely recommended in the evaluation of patients with HF.[16-18] However, to our knowledge no previous study has reported whether left atrial size is predictive of CSA or chemosensitivity to CO_2, which may promote CSA. The purpose of this study was to determine if left atrial size predicts chemosensitivity to CO_2 and CSA in patients with HF. We hypothesized that left atrial size is sensitive and specific for the detection of CSA and associated with augmented CO_2 chemosensitivity. Accordingly, our specific aims were to quantify left atrial volume by echocardiography in patients with HF who underwent measurement of CO_2 chemosensitivity and PSG.

Materials and Methods

This study was conducted in accordance with the amended Declaration of Helsinki and approved by the Mayo Clinic Institutional Review Board (IRB#923-02). Written informed consent was obtained from all participants. Consecutive ambulatory outpatients were prospectively enrolled from the Mayo Clinic Heart Failure Clinic for participation in this study, which included laboratory-based, overnight, attended PSG; echocardiography; neurohormonal measurement; and assessment of chemosensitivity in all subjects. Patients were required to have stable HF with no changes of optimized medical therapy in the preceding 3 months and left ventricular ejection fraction (LVEF) $\leq$ 35% measured by echocardiography. New York Heart Association (NYHA) function class was assessed[18]; those with NYHA III-IV HF were defined as having "advanced heart failure." BMI was computed as weight in kilograms divided by body surface area in square meters.

Echocardiography

All subjects underwent comprehensive transthoracic echocardiography. Measured parameters included LVEF, left ventricular end diastolic diameter (LVEDD), right ventricular systolic pressure (RVSP), mitral regurgitation (defined as moderate or more in severity by proximal isovelocity surface area), left atrial volume index (LAVI) (defined as left atrial volume to body surface area in mL/m^2 by biplane two-dimensional echocardiography consistent with current guidelines[32]), mitral deceleration time, mitral E velocity, and the ratio of mitral E velocity to medial anulus e′ velocity (E/e′).

Measurement of Neurohormones

Concentration of brain natriuretic peptide (BNP) was measured from serum drawn on the evening of PSG. Measurement of BNP was evaluated by either the Shionogi immunoradiometric assay (Shionogi & Co, Ltd) or DxI 800 immunoassay (Beckman Coulter Inc). The coefficient of variation of these two BNP assays was $>$ 0.99.

Measurement of Chemosensitivity

CO_2 chemosensitivity was measured by a modified rebreathing method as previously described.[33] Subjects breathed from a mouthpiece connected to a 6-L rebreathing bag; the bag included 5% CO_2 with balance oxygen. Ventilation was measured by a pneumotachograph. End-tidal oxygen and end-tidal CO_2 (P_{ETCO_2}) were monitored by mass spectrometry for comparison with changes in minute ventilation ($\dot{V}_E$). As the subject rebreathes, inspired CO_2 in the rebreathing bag increases and the oxygen level falls. However, inspired oxygen levels do not fall below 500 mm Hg (approximately 70% oxygen). Rebreathing continues until P_{ETCO_2} values reach 50 to 55 mm Hg (or about 8% CO_2, requiring approximately 4 min). The slope of the plot of $\dot{V}_E$ vs P_{ETCO_2} is used as an index of CO_2 chemosensitivity ($\Delta\dot{V}_E/\Delta P_{ETCO_2}$). Three runs were performed for each subject, and values were reported as the mean.

Sleep Evaluation

Diagnostic PSG was performed in the Center for Translational Science Activity Sleep Core facility of the Clinical Research Unit and digitally recorded on Dimensions software (Network Concepts Inc) or PSG Online2 E-Series (Compumedics Ltd) and scored using Uniquant (Thermo Fisher Scientific Inc) or Profusion2 software (Compumedics USA Inc). Recorded parameters included three-channel EEGs, two-channel electrooculograms, oronasal airflow by pressure transducer and thermocouple sensors, submental and limb electromyograms, one-channel ECG, transcutaneous pulse oximetry (Ohmeda 3740; General Electric Co) and integrated pulse oximetry (Compumedics USA Inc), thoracic and abdominal respiratory effort by inductance plethysmography, snoring by tracheal microphone or piezo crystal sensor, and body position by closed-circuit video monitoring. Disordered breathing events were classified as apneas or hypopneas and as either obstructive or central. Apneas were defined as a cessation of airflow or $>$ 90% reduction in airflow from baseline for $>$ 10 s with