Acute and chronic effects of continuous positive airway pressure therapy on left ventricular systolic and diastolic function in patients with obstructive sleep apnea and congestive heart failure

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BACKGROUND: Obstructive sleep apnea (OSA) may contribute to the pathogenesis of congestive heart failure (CHF). Nocturnal continuous positive airway pressure (CPAP) therapy can alleviate OSA and may have a role in the treatment of CHF patients.

OBJECTIVES: To investigate the acute and chronic effects of CPAP therapy on left ventricular systolic function, diastolic function and filling pressures in CHF patients with OSA.

METHODS: Twelve patients with stable CHF (New York Heart Association II or III, radionuclide ejection fraction lower than 40%) underwent overnight polysomnography to detect OSA. In patients with OSA (n=7), echocardiography was performed at baseline (awake, before and during acute CPAP administration) and after 6.9±3.3 weeks of nocturnal CPAP therapy. Patients without OSA (n=5) did not receive CPAP therapy, but underwent a baseline and follow-up echocardiogram.

RESULTS: In CHF patients with OSA, acute CPAP administration resulted in a decrease in stroke volume (44±15 mL versus 50±14 mL, P=0.002) and left ventricular ejection fraction (LVEF) 34.8±5.0% versus 38.4±3.3%, P=0.006) compared with baseline, but no change in diastolic function or filling pressures (peak early diastolic mitral annular velocity [Ea]: 6.0±1.6 cm/s versus 6.3±1.6 cm/s, P not significant; peak early filling velocity to peak late filling velocity [E/A] ratio: 1.05±0.74 versus 1.00±0.67, P not significant; E/Ea ratio: 10.9±4.1 versus 11.3±4.1, P not significant). In contrast, chronic CPAP therapy resulted in a trend to an increase in stroke volume (59±19 mL versus 50±14 mL, P=0.07) and a significant increase in LVEF (43.4±4.8% versus 38.4±3.3%, P=0.01) compared with baseline, but no change in diastolic function or filling pressures (Ea: 6.2±1.2 cm/s versus 6.3±1.6 cm/s, P not significant; E/A ratio: 1.13±0.61 versus 1.00±0.67, P not significant; E/Ea ratio: 12.1±2.7 versus 11.3±4.1, P not significant). There was no change in left ventricular systolic function, diastolic function or filling pressures at follow-up in CHF patients without OSA.

CONCLUSIONS: Acute CPAP administration decreased stroke volume and LVEF in stable CHF patients with OSA. In contrast, chronic CPAP therapy for seven weeks improved left ventricular systolic function, but did not affect diastolic function or filling pressures. The potential clinical implications of the discrepant effects of CPAP therapy on left ventricular systolic and diastolic function in CHF patients with OSA warrant further study.

Key Words: Congestive heart failure; Continuous positive airway pressure therapy; Echocardiography; Left ventricular function; Obstructive sleep apnea

Les effets aigus et chroniques de la thérapie par ventilation spontanée en pression positive continue sur la fonction systolique et diastolique ventriculaire gauche chez les patients souffrant d'apnée obstructive du sommeil et d'insuffisance cardiaque congestive

HISTORIQUE : L'apnée obstructive du sommeil (AOS) peut contribuer à la pathogenèse de l'insuffisance cardiaque congestive (ICC). La thérapie nocturne par ventilation spontanée en pression positive continue (VSPPC) peut soulager l'AOS et pourrait être utile dans le traitement des patients atteints d'ICC.

OBJECTIFS : Explorer les effets aigus et chroniques de la thérapie par VSPPC sur la fonction systolique, la fonction diastolique et les pressions de remplissage du ventricule gauche chez les patients atteints d'ICC présentant une AOS.

MÉTHODOLOGIE : Douze patients atteints d'une ICC stable (stade III ou II de la *New York Heart Association*, fraction d'éjection par radionucléides inférieure à 40 %) ont subi une polysomnographie d'une nuit pour déceler l'AOS. Chez les patients présentant une AOS (n=7), les chercheurs ont procédé à une échocardiographie en début d'étude (en état d'éveil, avant et pendant l'administration aiguë de VSPPC) et après 6,9±3,3 semaines de thérapie nocturne par VSPPC. Les patients sans AOS (n=5) n'ont pas reçu de thérapie par VSPPC, mais ont subi un échocardiogramme en début d'étude et au moment du suivi.

RÉSULTATS : Chez les patients présentant une AOS, l'administration aiguë de VSPPC a favorisé la diminution du volume d'accidents vasculaires cérébraux (AVC, soit 44±15 mL par rapport à 50±14 mL, P=0,002) et de la fraction d'éjection ventriculaire gauche (FÉVG, soit 34,8±5,0 % par rapport à 38,4±3,3 %, P=0,006) par rapport aux données de départ, mais aucun changement de la fonction diastolique ou des pressions de remplissage (vélocité protodiastolique de pointe de l'anneau mitral [Ea] : 6,0±1,6 cm/s par rapport à 6,3±1,6 cm/s, P non significatif; ratio entre la vélocité de remplissage précoce et la vélocité de remplissage tardive [E/A] : 1,05±0,74 par rapport à 1,00±0,67, P non significatif; ratio E/Ea : 10,9±4,1 par rapport à 11,3±4,1, P non significatif). Par contre, la thérapie chronique par VSPPC a provoqué une tendance à l'augmentation des AVC (59±19 mL par rapport à 50±14 mL, P=0,07) et une augmentation importante de la FÉVG (43,4±4,8 % par rapport 38,4±3,3 %, P=0,01) par rapport aux données de base, mais aucun changement de la fonction diastolique ou des pressions de remplissage (Ea : 6,2±1,2 cm/s par rapport à 6,3±1,6 cm/s, P non significatif; ratio E/A : 1,13±0,61 par rapport à 1,00±0,67, P non significatif; ratio E/Ea : 12,1±2,7 par rapport à 11,3±4,1, P non significatif). La fonction systolique ventriculaire gauche, la fonction

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diastolique et les pressions de remplissage n'avaient pas changé au suivi chez les patients atteints d'ICC sans AOS.

CONCLUSIONS : L'administration aiguë de VSPPC a réduit le volume d'AVC et de FÉVG chez les patients atteints d'ICC stable présentant une AOS. Par contre, une thérapie de sept semaines par VSPPC a amélioré la

fonction systolique ventriculaire gauche mais n'a pas influé sur la fonction diastolique ou les pressions de remplissage. Les répercussions cliniques potentielles des effets divergents de la thérapie par VSPPC sur la fonction systolique et diastolique ventriculaire gauche chez les patients atteints d'ICC présentant une AOS méritent des études plus approfondies.

Patients with congestive heart failure (CHF) have a high prevalence of sleep-related breathing disorders (1,2). Obstructive sleep apnea (OSA) has been reported in 11% to 37% of CHF patients, but it is frequently unrecognized by clinicians (3,4). Of note, OSA may contribute to the pathogenesis and progression of CHF through a variety of mechanical, hemodynamic, neurohumoral and inflammatory effects (1,5). Reductions in intrathoracic pressure, hypoxia, acute nocturnal increases in systemic blood pressure, daytime hypertension and increased sympathetic nervous system activity are the potential consequences of OSA that can lead to detrimental hemodynamic effects, including increased left ventricular afterload, decreased left ventricular preload and increased myocardial metabolic demand.

Nocturnal nasal continuous positive airway pressure (CPAP) therapy has the potential to alleviate OSA, its associated symptoms and hemodynamic consequences (5-9). In addition to restoring normal sleep architecture, CPAP therapy prevents the extremes of negative intrathoracic pressure and, thus, reduces left ventricular transmural pressure, prevents recurrent hypoxia, reduces sympathetic nervous system activity, decreases blood pressure and heart rate, and increases arterial baroreceptor sensitivity and daytime heart rate variability (1,7,10-16). In the normal heart, initiation of CPAP therapy acutely increases intrathoracic pressure, decreases venous return and left ventricular filling, and results in decreased cardiac output (17-19). In contrast, conflicting hemodynamic effects have been reported in stable CHF patients receiving acute CPAP therapy. Some investigators have reported an increase in stroke volume and cardiac output with acute CPAP therapy (18), while others have observed no change or a decrease in cardiac output (20,21). An improvement in left ventricular ejection fraction (LVEF) has been observed in patients with CHF who receive chronic CPAP therapy (22-24). There is a paucity of data on the effects of acute or chronic CPAP therapy on left ventricular diastolic function in patients with CHF, despite the potential impact of left ventricular diastolic function on the symptomatic state and prognosis of patients with CHF (25-30). Current echocardiography techniques incorporating pulsed Doppler assessment of transmitral filling velocities and tissue Doppler mitral annular velocities allow for a noninvasive evaluation of left ventricular diastolic function and filling pressures. They can also be used to serially evaluate the effects of acute and chronic CPAP therapy on left ventricular diastolic function and filling pressures (31-37). Thus, the purpose of the present study was to use echocardiography to investigate the effects of acute and chronic CPAP therapy on left ventricular systolic function, diastolic function and filling pressures in patients with CHF and OSA.

METHODS

Study population

The study cohort consisted of 12 patients with CHF identified prospectively from the heart failure clinic at the University of Ottawa Heart Institute (Ottawa, Ontario). Patients were included in the study if they had left ventricular systolic dysfunction (LVEF lower than 40% by radionuclide ventriculography); stable New York Heart Association class II or III symptoms (receiving optimal medical therapy, including an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, and beta blockade therapy, and were clinically stable with no change in medical regimen for at least one month); sinus rhythm; and overnight polysomnography to detect the presence of OSA (see 'Sleep study' below). Patients were excluded from the study if they had an acute coronary syndrome or myocardial infarction within the previous month; significant valve disease (aortic or mitral stenosis, or greater than moderate [2+] aortic or mitral

regurgitation); life expectancy of less than one year; significant restrictive or obstructive lung disease; treatment with a tricyclic antidepressant, selective serotonin reuptake inhibitor, benzodiazepine, neuroleptic or narcotic medication that can alter sleep or sleep-disordered breathing; nonsinus or paced rhythm; or if they were younger than 18 years of age. The institutional review board approved the protocol, and all subjects gave informed consent.

Sleep study (diagnosis of OSA, CPAP titration and therapy)

A sleep study was performed on all patients according to the inclusion criteria. A single overnight polysomnogram was performed using the Alice system (Aria LX; Respironics, USA). Sleep staging was determined using Rechtschaffen and Kale's criteria from the standard four-channel electroencephalogram (C4A1, C3A2, O4A1, O3A2), two-channel electro-oculogram and submental electromyogram (38). Continuous measures of airflow were recorded by a nasal or oral thermistor or pressure transducer, rib cage and abdominal motion was monitored by piezoelectric bands, oxygen saturation was monitored by finger oximetry and movement was monitored by an electromyogram of the left and right gastrocnemii; all were analyzed in a standardized fashion. The electrocardiogram recorded heart rate and rhythm via lead 2. An obstructive apnea was defined as the cessation of airflow for longer than 10 s, with persistent respiratory effort as seen in the rib cage or abdomen signals; hypopnea was defined as a decrease in airflow, or rib cage or abdominal motion by more than 50% of the baseline signal, for longer than 10 s with a fall of 4% or more in oxygen saturation. The apnea-hypopnea index (AHI) was the total number of apneas and hypopneas per hour of sleep time. OSA was defined by an AHI of more than 15 events per hour (1,4,5,10,39). More than 80% of all events had to be obstructive for inclusion in the present study. Patients were divided into two groups based on the presence (n=7) or absence (n=5) of OSA.

Patients with OSA had a CPAP titration sleep study seven days or more before the baseline echocardiogram. Nasal CPAP pressure was adjusted so that apneas, hypopneas and respiratory effort-related arousal, as well as snoring in all sleep stages and all positions, were abolished (5,40,41). All patients experienced a fall in AHI to fewer than five events per hour by the end of the CPAP titration sleep study. After the baseline echocardiogram (see 'Study protocol' below), patients were instructed to use the CPAP device (ResMed S7 Elite; ResMed, Australia) every night for at least 6 h (23). Adequate ongoing adherence to this prescribed pressure of CPAP was defined as more than 4.5 h of CPAP use per night on a routine basis (42). CPAP compliance was assessed using built-in hour meters in the CPAP machines to determine use (23,40).

Study protocol

All patients (n=12) underwent a baseline two-dimensional and Doppler echocardiographic examination.

In CHF patients with OSA (n=7), CPAP therapy was initiated by fitted nasal or full-face mask using the pressure determined by the CPAP titration study (10.6±1.6 cm H₂O) immediately following the baseline echocardiogram. The echocardiogram was repeated 45 min later, while the patient was actively receiving CPAP therapy ('acute CPAP therapy'). Patients subsequently received nightly nocturnal CPAP therapy ('chronic CPAP therapy') for at least four weeks (6.9±3.3 weeks) and the echocardiogram was repeated. Patients were not actively receiving CPAP therapy during the follow-up echocardiogram, but received CPAP therapy the night before the follow-up echocardiogram. All echocardiograms were performed while patients were awake. Heart rate and blood pressure were measured at each echocardiographic examination.

Patients without OSA (n=5) did not receive CPAP therapy, but underwent a follow-up echocardiogram (9.0±6.1 weeks, P not significant versus OSA group).

Echocardiographic examinations

Echocardiographic examinations were performed using a Sonos 5500 instrument (Philips, USA) with a 3.2 MHz phased-array transducer. Standard two-dimensional images were obtained from the parasternal, apical and subcostal windows, using harmonic imaging as needed. Pulsed Doppler imaging was used to record transmitral inflow velocities at the mitral valve leaflet tips in the apical four-chamber view (31,43,44). Tissue Doppler imaging was performed in the apical four-chamber view, with a 3.8 mm sample volume placed at the septal and lateral borders of the mitral valve annulus (44). The sample volume was positioned parallel to the longitudinal motion of the mitral annulus. Doppler data were recorded at a speed of 100 mm/s. Images were recorded and stored digitally using the Excelera system (Philips).

Doppler echocardiographic data were analyzed off-line by an independent observer blinded to knowledge of the clinical data and status of CPAP therapy. Measurements were averaged from three to five consecutive beats acquired during expiration. Left ventricular end-diastolic volume (LVEDV), end-systolic volume and LVEF were obtained from the apical four-chamber and apical two-chamber views using the biplane Simpson method, as recommended by the American Society of Echocardiography (45). Stroke volume was derived as the difference between LVEDV and left ventricular end-systolic volume. Cardiac output was obtained by multiplying the stroke volume by the heart rate, and the cardiac index was derived by indexing the cardiac output to body surface area. Regional wall motion was assessed using the 17-segment model recommended by the American Heart Association Writing Group on Myocardial Segmentation and Registration for Cardiac Imaging, and a five-point scoring system for each wall segment (1 = normal, 2 = hypokinetic, 3 = akinetic, 4 = dyskinetic and 5 = aneurysmal) (46,47). A global wall motion score index (WMSI) was derived by dividing the sum of the wall motion scores by the number of visualized segments (47). In addition, a septal WMSI was derived from the five septal wall segments and a free wall WMSI was derived from the 12 free wall segments. The systemic vascular resistance index (SVRI) in $\text{dynes} \cdot \text{sec} \cdot \text{cm}^{-5} \cdot \text{m}^{-2}$ was calculated as $(\text{mean arterial blood pressure}/\text{cardiac index}) \times 80$.

Transmitral inflow measurements included the peak early filling velocity (E), peak late filling velocity (A), deceleration time of the peak early filling velocity and the E/A ratio (31,43,44). Tissue Doppler peak early diastolic mitral annular velocity (Ea) and late diastolic mitral annular velocity were measured at the septal and lateral mitral annuli, and an average measurement was obtained from the two annular sites (32,44). The E/Ea ratio, a measure of left atrial pressure (32,33,35-37,48), was computed from the average of the septal and lateral Ea values; this approach has been shown to provide the optimal accuracy in patients with regional wall motion abnormalities (48). Left atrial pressure (LAP) was estimated from the E/Ea ratio using the equation $\text{LAP} = 6.0 + (0.904 \times \text{E/Ea})$ (37).

Statistical analysis

Data are expressed as mean ± SD. Clinical and demographic differences between CHF patients with and without OSA were compared using χ^2 analysis, with Fisher's exact tests for categorical variables and unpaired *t* tests for continuous variables. Hemodynamic and echocardiographic data at baseline, during acute CPAP therapy and after chronic CPAP therapy were compared using ANOVA with repeated measures and post hoc least significant difference when differences were identified. Relationships between the change in stroke volume or LVEF and baseline hemodynamic and echocardiographic variables were analyzed using least squares linear regression analysis. Correlations were described by Pearson's correlation coefficient. $P < 0.05$ was considered to be significant.

TABLE 1
Baseline demographic characteristics of the study cohort

Variable	OSA (n=7)	No OSA (n=5)	P
Age* (years)	61±12	62±9	NS
Sex (men/women), n	7/0	5/0	NS
Body mass index* (kg/m^2)	36.5±6.1	30.4±4.3	0.06
CHF etiology (ischemic/nonischemic), n	3/4	4/1	NS
NYHA class (II/III), n	5/2	4/1	NS
Hypertension (yes/no), n	5/2	3/2	NS
Medication, n			
Diuretics	7	3	NS
Beta-blockers	7	5	NS
ACEI	4	3	NS
Angiotensin receptor blocker	3	2	NS
Digoxin	2	2	NS
Epworth Sleepiness Scale score*	5.4±4.5	4.8±1.3	NS
Apnea/hypopnea index* (events/h)	37.6±23.6	2.9±2.7	0.008
Heart rate* (beats/min)	66±11	62±13	NS
Blood pressure* (mmHg)	140±20/81±12	125±21/74±9	NS/NS
SVRI* ($\text{dynes} \cdot \text{sec} \cdot \text{cm}^{-5} \cdot \text{m}^{-2}$)	5600±1009	5467±1824	NS
Left ventricular ejection fraction* (%)	38.4±3.3	42.6±6.1	NS

*Values are presented as mean ± SD. ACEI Angiotensin-converting enzyme inhibitor; CHF Congestive heart failure; NYHA New York Heart Association; OSA Obstructive sleep apnea; SVRI Systemic vascular resistance index

RESULTS

The baseline demographic characteristics of the 12 CHF patients (seven patients with OSA and five patients without OSA) are shown in Table 1. By definition, CHF patients with OSA had a higher AHI than CHF patients without OSA (37.6±23.6 versus 2.9±2.7, $P=0.008$) and tended to have a larger body mass index (36.7±6.0 kg/m^2 versus 30.4±4.3700 kg/m^2 , $P=0.06$). LVEF was similar in CHF patients with and without OSA (38.4±3.3% versus 42.6±6.1%, $P=0.22$). No adverse clinical events occurred in the 12 patients during the study period, and their clinical status remained stable. There were no changes in medication during the study.

Acute CPAP therapy in CHF patients with OSA

In CHF patients with OSA, from baseline to acute CPAP therapy there was a decrease in heart rate (64±10 beats/min versus 59±8 beats/min, $P=0.005$), but no significant change in blood pressure (Table 2). LVEDV did not change from baseline to acute CPAP therapy (132±46 mL versus 132±56 mL, P not significant). However, there was a decrease in stroke volume (50±14 mL versus 44±15 mL, $P=0.002$), cardiac output (3.16±1.03 L/min versus 2.56±0.94 L/min, $P<0.001$) and LVEF (38.4±3.3% versus 34.8±5.0%, $P=0.006$) from baseline to acute CPAP therapy (Figure 1). Global WMSI also increased consistent with a deterioration in global systolic function (1.97±0.17 versus 2.14±0.18, $P=0.04$). However, only the free wall WMSI increased from baseline to acute CPAP therapy (0.17±0.11, $P=0.01$). There was no significant change in the septal WMSI (0.00±0.22, P not significant). There was no relationship between the change in stroke volume or LVEF with acute CPAP therapy and the baseline stroke volume, LVEF, E/Ea ratio or SVRI. Patients with CHF due to an ischemic versus nonischemic etiology demonstrated a similar decrease in LVEF (−3.2±1.3% versus −4.0±1.4%, P not significant).

The effects of acute CPAP therapy on Doppler echocardiographic indexes of left ventricular diastolic function and left atrial pressure are shown in Table 2. Average Ea, a load-independent measure of left ventricular relaxation, was unchanged from baseline to acute CPAP therapy (6.3±1.6 cm/s versus 6.0±1.6 cm/s, P not significant) (Figure 1). Similarly, there were no significant changes in the septal or lateral Ea

TABLE 2

Acute and chronic effects of continuous positive airway pressure (CPAP) therapy on echocardiographic parameters in congestive heart failure patients with obstructive sleep apnea

Parameter	Baseline	Acute CPAP therapy	P (baseline vs acute)	Chronic CPAP therapy	P (baseline vs chronic)
HR (beats/min)	64±10	59±8	0.005	63±9	NS
BP (mmHg)	140±18/80±10	142±18/81±6	NS/NS	144±19/73±14	NS/NS
LVEDV (mL)	132±46	132±56	NS	136±38	NS
LVESV (mL)	82±33	88±43	NS	77±22	NS
SV (mL)	50±14	44±15	0.002	59±18	0.07
LVEF (%)	38.4±3.3	34.8±5.0	0.006	43.4±4.8	0.01
WMSI	1.97±0.17	2.14±0.18	0.04	1.78±0.32	0.04
SVRI	5600±1009	7238±1998	0.02	4607±754	0.04
(dynes·sec·cm ⁻⁵ ·m ⁻²)					
E (cm/s)	68.2±21.3	64.0±20.4	NS	74.5±20.4	NS
DT (ms)	209±47	232±66	NS	195±26	NS
E/A ratio	1.00±0.67	1.05±0.74	NS	1.13±0.61	NS
Ea (cm/s)	6.3±1.6	6.0±1.6	NS	6.2±1.2	NS
Aa (cm/s)	9.6±2.9	8.8±2.5	NS	8.7±2.4	NS
E/Ea ratio	11.3±4.1	10.9±4.1	NS	12.1±2.7	NS
LAP (mmHg)	16.2±3.7	15.8±3.7	NS	16.9±2.4	NS

Values are presented as mean ± SD. A Late diastolic transmitral filling velocity; Aa Late diastolic mitral annular velocity (average of lateral and septal sites); BP Blood pressure; DT Deceleration time of peak early filling velocity; E Early diastolic transmitral filling velocity; Ea Early diastolic mitral annular velocity (average of lateral and septal sites); HR Heart rate; LAP Left atrial pressure; LVEDV Left ventricular end-diastolic volume; LVEF Left ventricular ejection fraction; LVESV Left ventricular end-systolic volume; NS Not significant; SV Stroke volume; SVRI Systemic vascular resistance index; vs Versus; WMSI Wall motion score index

velocities. Acute CPAP therapy did not affect Doppler echo measures of left atrial pressure. There were no changes from baseline to acute CPAP therapy in the E/A ratio (1.00±0.67 versus 1.05±0.74, P not significant), mitral deceleration time (209±47 ms versus 232±66 ms, P not significant) or E/Ea ratio, whether derived using the average Ea velocity from the lateral and septal annular sites (11.3±4.1 versus 10.9±4.1, P not significant) (Figure 1) or the lateral annulus site alone (9.1±3.1 versus 9.2±3.2, P not significant).

Chronic CPAP therapy in CHF patients with OSA

CPAP therapy was administered to the CHF patients with OSA at 10.6±1.6 cm H₂O (range 8 cm to 12 cm) for 6.2±1.2 h per night during the follow-up period. Heart rate and blood pressure were similar at the baseline and follow-up studies (Table 2). LVEDV did not change from baseline to follow-up (132±46 mL versus 136±38 mL, P not significant); however, there was a trend toward an increase in stroke volume (50±14 mL versus 59±18 mL, P=0.07) and a significant increase in LVEF (38.4±3.3% versus 43.4±4.8%, P=0.01) (Figure 2). Global WMSI also decreased from baseline to follow-up (1.97±0.17 versus 1.78±0.32, P=0.04), consistent with improved global systolic function with chronic CPAP therapy. The improvement in systolic function was due to a decrease in free wall and septal WMSI (−0.18±0.17, P=0.05, and −0.20±0.17, P=0.03, respectively). The increase in stroke volume with chronic CPAP therapy was directly related to the baseline SVRI (r=0.78, P=0.037) (ie, the higher baseline SVRI, the larger the increase in stroke volume with chronic CPAP therapy). Similarly, there was a trend toward a direct relationship between the increase in LVEF and baseline SVRI (r=0.69, P=0.08). In addition, the change in stroke volume and LVEF with chronic CPAP therapy was inversely related to the per cent change in SVRI from the baseline to the follow-up study (r=−0.79, P=0.036, and r=−0.75, P=0.05, respectively) (ie, the greater the per cent reduction in SVRI with chronic

Figure 1 Acute effects of continuous positive airway pressure (CPAP) therapy on left ventricular ejection fraction (**top**), early diastolic mitral annular velocity (Ea) (average of lateral and septal sites) (**middle**) and the peak early transmitral filling velocity (E) to Ea ratio (**bottom**). NS Nonsignificant

CPAP therapy, the greater the increase in stroke volume and LVEF). There was no relationship between the change in stroke volume or LVEF with chronic CPAP therapy and the baseline stroke volume, LVEF or E/Ea ratio. Patients with CHF due to an ischemic versus non-ischemic etiology demonstrated a similar increase in LVEF (5.1±1.4% versus 4.9±5.3%, P not significant).

Figure 2 Chronic effects of continuous positive airway pressure (CPAP) therapy on left ventricular ejection fraction (**top**), early diastolic mitral annular velocity (Ea) (average of lateral and septal sites) (**middle**) and the peak early transmitral filling velocity (E) to Ea ratio (**bottom**). NS Nonsignificant

The effects of chronic CPAP therapy on the Doppler-echocardiographic indexes of left ventricular diastolic function and left atrial pressure are shown in Table 2. From baseline to follow-up, there were no significant changes in the average Ea velocity (6.3 ± 1.6 cm/s versus 6.2 ± 1.2 cm/s, P not significant), E/A ratio (1.00 ± 0.67 versus 1.13 ± 0.61 , P not significant), mitral deceleration time (209 ± 47 ms versus 195 ± 26 ms, P not significant) or E/Ea ratio (11.3 ± 4.1 versus 12.1 ± 2.7 , P not significant) (Figure 2).

TABLE 3
Baseline and follow-up echocardiographic parameters in congestive heart failure patients without obstructive sleep apnea

Parameter	Baseline	Follow-up	P
HR (beats/min)	62±13	61±9	NS
BP (mmHg)	125±21/74±9	125±19/74±13	NS/NS
LVEDV (mL)	115±41	119±38	NS
LVESV (mL)	66±24	68±24	NS
SV (mL)	50±20	52±18	NS
LVEF (%)	42.6±6.1	43.3±7.9	NS
SVRI (dynes·sec·cm ⁻⁵ ·m ⁻²)	5467±1824	5498±2837	NS
E (cm/s)	72.6±25.9	73.6±20.2	NS
DT (ms)	194±29	191±44	NS
E/A ratio	0.97±0.06	0.96±0.23	NS
Ea (cm/s)	6.1±0.6	6.2±0.7	NS
Aa (cm/s)	7.9±1.3	8.1±1.3	NS
E/Ea ratio	12.0±4.1	12.0±3.7	NS
LAP (mmHg)	16.9±3.7	16.9±3.4	NS

Values are presented as mean ± SD. A Late diastolic transmitral filling velocity; Aa Late diastolic mitral annular velocity (average of lateral and septal sites); BP Blood pressure; DT Deceleration time of peak early filling velocity; E Early diastolic transmitral filling velocity; Ea Early diastolic mitral annular velocity (average of lateral and septal sites); HR Heart rate; LAP Left atrial pressure; LVEDV Left ventricular end-diastolic volume; LVEF Left ventricular ejection fraction; LVESV Left ventricular end-systolic volume; NS Not significant; SV Stroke volume; SVRI Systemic vascular resistance index

CPAP therapy was not administered in CHF patients without OSA. There were no changes in the hemodynamics or echocardiographic measures of left ventricular systolic function, diastolic function or left ventricular filling pressure from baseline to follow-up (Table 3).

DISCUSSION

OSA and other sleep-related breathing disorders are frequently found in patients with CHF when appropriate investigations are performed (3,4). Of note, OSA can result in detrimental effects on cardiac loading conditions and activation of the sympathetic nervous system, potentially accelerating the pathophysiology of CHF (1,5). Respiratory efforts during obstructive episodes decrease intrathoracic pressure, increase left ventricular transmural pressure and increase left ventricular afterload and cardiac metabolic demand. In addition, augmentation of venous return to the right heart may result in a leftward septal shift (ventricular interdependence), and reduced left ventricular preload and stroke volume. Activation of the sympathetic nervous system may result from recurrent arousal, with disinhibition of central sympathetic outflow and reduced parasympathetic nerve activity, or from profound hypoxia during apnea with a transient rise in partial pressure of CO₂ and the stimulation of peripheral and central chemoreceptors, leading to vasoconstriction, elevated peripheral resistance and an increased heart rate. Treatment of OSA with CPAP therapy has the potential to relieve these detrimental physiological effects and, thus, improve left ventricular function.

In the present study, we evaluated the acute and chronic effects of CPAP therapy on left ventricular systolic function, diastolic function and left ventricular filling pressures in patients with stable symptomatic CHF and OSA. Acute CPAP therapy resulted in a decrease in stroke volume and LVEF, but had no effects on the echocardiographic indexes of left ventricular diastolic function or left ventricular filling pressures. In contrast, seven weeks of chronic CPAP therapy resulted in an increase in stroke volume and a 13% relative increase (5% absolute increase) in LVEF. Echocardiographic indexes of left ventricular diastolic function and left atrial pressure were not affected by chronic CPAP therapy.

The impact of acute CPAP therapy on cardiac output and stroke volume in patients with CHF has been evaluated previously. Bradley et al (18) applied acute CPAP therapy (5 cm H₂O for 10 min) to 22 consecutive patients with CHF undergoing cardiac catheterization, and observed that patients with a wedge pressure of 12 mmHg or higher (n=11) had a 22% increase in stroke volume and a 14% increase in cardiac index, while patients with a wedge pressure of lower than 12 mmHg (n=11) had an 8% decrease in cardiac index but no significant change in stroke volume. Baseline wedge pressure was the only independent predictor of the change in cardiac index with acute CPAP therapy. However, the presence or absence of OSA in these patients is unknown. In contrast, Liston et al (21) examined seven stable CHF patients (only three patients with mild sleep apnea) undergoing right heart catheterization, and observed a decrease in both cardiac output and stroke volume (15% and 20% relative reduction, respectively) with acute CPAP therapy (5 cm H₂O); the maximum impact occurred 1 h after the initiation of therapy (21). These patients were hemodynamically similar to the patients studied by Bradley et al, who demonstrated a favourable increase in cardiac index with acute CPAP therapy, although the LVEF was lower (23% versus 31%) and six of the seven patients had atrial fibrillation. We observed a 19% decrease in cardiac output and a 12% reduction in stroke volume in our CHF patients with sinus rhythm and OSA receiving acute CPAP therapy (10.6±1.6 cm H₂O), consistent with the observations of Liston et al. Furthermore, we have extended these previous observations by measuring left ventricular volumes and demonstrating an acute fall in LVEF (9% relative decrease and 3.6% absolute decrease) after administration of acute CPAP therapy.

Alterations in left ventricular preload and right ventricular preload and afterload have been proposed to account for the decrease in stroke volume and LVEF observed in subjects receiving acute CPAP therapy (17-19). Acute CPAP therapy increases intrathoracic pressure and may therefore decrease systemic venous return, while positive pressure ventilation increases pulmonary vascular resistance and right ventricular afterload, thus reducing the right ventricular stroke volume (17,49). This, in turn, may reduce left ventricular preload and stroke volume (50,51). Increased right ventricular afterload can increase right ventricular volume and result in a leftward shift of the septum, adversely affecting left ventricular filling (50). However, increased intrathoracic pressure with acute CPAP therapy may directly decrease left ventricular transmural pressure and left ventricular afterload, potentially counteracting or minimizing the negative left ventricular preload effects on left ventricular systolic function (52,53). Ultimately, the hemodynamic effect of acute CPAP therapy may depend on the individual's specific preload and afterload states (18).

We did not observe an effect of acute CPAP therapy on echocardiographic measures of left ventricular diastolic function, left atrial pressure or left ventricular diastolic volume. Ea, the E/A ratio and the E/Ea ratio did not change from baseline to acute CPAP therapy. A previous invasive study in seven CHF patients (three with mild sleep apnea) (21) also failed to observe a change in pulmonary capillary wedge pressure with acute CPAP therapy. This observation suggests that the mechanism for a reduction in stroke volume and LVEF with acute CPAP therapy in stable CHF patients may relate to factors other than reduced left ventricular preload, such as a reduction in sympathetic nervous system activation with an associated decrease in myocardial contractility, or decreased oxygen and systemic perfusion requirements due to a reduction in the work of breathing during acute CPAP therapy. Of note, acute CPAP administration resulted in a decrease in heart rate compared with baseline, a finding consistent with reduced sympathetic nervous system activity. However, any interpretation of the data in this regard should be made cautiously, because left ventricular transmural pressures were not measured directly. In addition, the E/Ea ratio, as with an invasively derived left atrial pressure, does not take into account the potential change in transmural pressures that can result with CPAP therapy.

Chronic nocturnal CPAP therapy for seven weeks was associated with a 5% absolute increase in LVEF (13% relative increase). A previous randomized study of 24 patients with CHF and OSA treated for one month with nocturnal CPAP (23) observed an 8.8% absolute increase in LVEF therapy (35% relative increase) in the 12 patients receiving CPAP therapy. Similarly, a 5% absolute (13% relative) increase in LVEF by left ventricular gated nuclear scintigraphy was observed in 19 patients with CHF and OSA treated with three months of chronic nocturnal CPAP therapy (24).

The increase in LVEF after seven weeks of chronic nocturnal CPAP therapy cannot be explained by altered loading conditions because the follow-up echocardiographic studies were performed without CPAP therapy, and the blood pressures were similar at the time of the two echocardiographic studies. The mechanism for improved LVEF with chronic CPAP therapy in patients with CHF and OSA likely relates to improved systolic function due to a favourable modification of the pathophysiology of left ventricular dysfunction. Previous investigators have documented excessive sympathetic nervous system activity in patients with OSA and CHF that can be attenuated by CPAP therapy (11,12,14,15,24,54,55). In this regard, we observed a relationship between baseline SVRI and the recovery of systolic function. While not conclusive, these data are consistent with the hypothesis that elevated sympathetic nervous system activity, a major determinant of the SVRI, is involved in the mechanism by which OSA contributes to the pathogenesis of left ventricular systolic dysfunction in CHF patients. The higher the SVRI, or greater the activation of the sympathetic nervous system, the greater the potential benefit of CPAP therapy to improve left ventricular systolic function through a reduction of sympathetic nervous system activity. In addition, untreated OSA is associated with repetitive episodes of hypoxia that can directly impair myocardial function (1,56). Thus, abolishing the hypoxic episodes with CPAP therapy may improve myocardial function.

We did not observe any changes in the echocardiographic indexes of left ventricular diastolic function or left atrial pressure after seven weeks of chronic CPAP therapy, despite the observed improvement in left ventricular systolic function. Thus, it appears that chronic nocturnal CPAP therapy preferentially improves left ventricular systolic function in patients with stable CHF and OSA, or that CPAP therapy is required for a longer period of time before beneficial effects on left ventricular diastolic function and filling pressures are observed. In this latter regard, CPAP therapy decreases left ventricular afterload by increasing intrathoracic pressure, diminishing sympathetic activation and eliminating exaggerated negative intrathoracic pressures during obstructive episodes, theoretically decreasing left ventricular pressure overload and potentially improving diastolic function. However, sympathetic neural activity, which can induce hypertension and myocardial hypertrophy, may not be attenuated by seven weeks of CPAP therapy, but may instead require up to six months of therapy (14). In addition, regression of left ventricular hypertrophy in OSA patients may require a minimum of six months of CPAP therapy (57). A recent study of 25 patients (58) with OSA and normal left ventricular systolic function receiving 12 weeks of nocturnal CPAP therapy demonstrated a significant increase in the E/A ratio and a decrease in mitral deceleration time, suggestive of an improvement in left ventricular diastolic function. However, tissue Doppler imaging was not performed in these patients. We are unaware of any previous studies examining the effect of chronic CPAP therapy on left ventricular diastolic function and filling pressures in patients with CHF and OSA.

Clinical implications

In a population of patients with stable New York Heart Association class II or III CHF and OSA, we have demonstrated that CPAP therapy for seven weeks improves left ventricular systolic function, even in patients receiving optimal medical therapy, including beta-blocker medications. The improvement in left ventricular systolic function with chronic CPAP therapy appears to relate to both baseline SVRI

(ie, the greatest improvement in systolic function occurs in patients with the highest SVRI) and the change in SVRI during therapy (ie, the greatest improvement in systolic function occurs in patients with the largest reduction in SVRI). Whether improvements in LVEF translate into an improvement in patient prognosis remains to be determined. Notably, in our small study, chronic CPAP therapy did not result in an improvement in echocardiographic indexes of left ventricular diastolic function and left atrial pressure, important determinants of the symptomatic state and prognosis of CHF patients, despite improvement in systolic function (25-30). Further large, prospective studies are warranted to better define the impact of CPAP therapy on left ventricular systolic and diastolic function, symptomatic status, and the prognosis of patients with CHF and OSA.

Limitations

A major limitation of the study relates to its small population size, and any conclusions need to be interpreted cautiously in this light. Although we could detect effects of acute and chronic CPAP therapy on left ventricular systolic function, we cannot exclude the possibility that a much larger patient population size is necessary to detect smaller effects of CPAP therapy on left ventricular diastolic function and filling pressures. Furthermore, it is possible that a longer duration of CPAP therapy (longer than seven weeks) is required before effects on left ventricular diastolic function occur. The small sample size did not allow us to explore the possibility of different effects of chronic CPAP therapy on left ventricular diastolic function and filling pressures depending on the patient's specific hemodynamic parameters, as has been reported for systolic function (18). Of note, the potential clinical implications of the discrepant effects of CPAP therapy on left ventricular systolic function, diastolic function and left ventricular filling pressures cannot be determined from our study and require a larger patient population.

All patients with CHF and OSA received CPAP therapy. In contrast, the 'control' population consisted of similarly selected CHF

patients without OSA who were not treated with CPAP therapy. While the absence of an improvement in systolic function during follow-up in the 'control' population provides support for chronic CPAP therapy being responsible for the improvement in left ventricular systolic function in the CHF patients with OSA, a larger prospective, randomized study in which CHF patients with OSA are randomly assigned to CPAP therapy or 'sham' treatment is warranted to confirm our observations.

Right ventricular chamber size and systolic function were not evaluated; therefore, we could not investigate the potential significance of ventricular interactions on the effects of CPAP therapy.

Follow-up sleep studies during chronic CPAP therapy were not performed, and we could not explore the potential relationships between the follow-up sleep data and the change in left ventricular function with chronic CPAP therapy.

CONCLUSIONS

Acute CPAP therapy decreases stroke volume and LVEF in stable patients with CHF and OSA. In contrast, chronic CPAP therapy for seven weeks improves left ventricular systolic function, but does not affect left ventricular diastolic function or filling pressures. The improvement in stroke volume with chronic CPAP therapy is directly related to the baseline SVRI. The potential clinical implications of the discrepant effects of CPAP therapy on left ventricular systolic function and diastolic function in patients with CHF and OSA warrant further study.

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