Acute Effects of Continuous Positive Airway Pressure on Cardiac Sympathetic Tone in Congestive Heart Failure

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Background—Depressed ventricular performance and neurohormonal activation are key pathophysiological features of congestive heart failure (CHF). Although angiotensin-converting enzyme inhibitors and β-adrenoceptor blockers exert beneficial effects in CHF, mortality remains unacceptably high, and the development of further therapeutic approaches is warranted. Recent data suggest that continuous positive airway pressure (CPAP) may be of benefit in the treatment of CHF, although the mechanism for this action is incompletely understood.

Methods and Results—In the present study, we examined the effect of short-term CPAP (10 cm H_2O for 10 minutes) on hemodynamics (Swan Ganz catheter) and total systemic and cardiac sympathetic activity (norepinephrine spillover method) in 14 CHF patients in New York Heart Association class III. The application of CPAP was associated with a fall in cardiac output (4.8±0.3 to 4.4±0.2 L/min; $P<0.05$) and a significant reduction in cardiac norepinephrine spillover (370±58 to 299±55 pmol/min; $P<0.05$), although total systemic norepinephrine spillover was unchanged.

Conclusion—The short-term application of CPAP results in an inhibition of cardiac sympathetic nervous activity. Further investigation into the potential value of long-term CPAP in CHF patients is warranted. **(*Circulation*. 2001;103:2336-2338.)**

Key Words: heart failure ■ nervous system, sympathetic ■ ventilation

As conceptual models of the pathophysiology of congestive heart failure (CHF) increase in complexity, it is becoming more apparent that multifaceted approaches to treatment are required for the optimal management of CHF patients. Although the principal focus of therapy over the past decade has been to antagonize the renin-angiotensin-aldosterone axis and adrenergic nervous system,[1–5] other abnormalities associated with heart failure are also being recognized as potential therapeutic targets. Recently, it was demonstrated that periodic breathing is a common finding in CHF patients.[6] Although the specific mechanisms that lead to sleep apnea in CHF remain controversial,[7–9] it has been appreciated that periodic breathing may adversely affect cardiovascular pathophysiology. The potential processes by which sleep apnea may adversely effect CHF status include repetitive arterial oxygen desaturation, adverse effects on left ventricular afterload, and sympathetic nervous activation,[10] particularly in the context of early arousals from sleep.

To characterize the importance of sleep apnea in CHF further, several investigators examined the impact of continuous positive airway pressure (CPAP), both long and short-term, on cardiac function. The reported hemodynamic effects of CPAP have been somewhat variable, although most investigators have demonstrated that CPAP reduces stroke volume, and some, but not all, studies have shown a fall in cardiac output.[11–14] Although this response may be the result of reduced venous return and thus stroke volume, it has also been proposed that the CPAP-mediated reduction in the work or breathing may[11] also offer an explanation for the associated fall in cardiac output. It was also previously shown that CPAP improves left ventricular afterload by reducing transmural left ventricular pressure.[11] In conjunction with these physiological studies, a recent randomized, controlled study[15] demonstrated a significant reduction in the composite end point of death and the need for transplantation in CHF patients.

In the present study, we hypothesized that the apparent clinical benefit afforded by CPAP may be mediated by effects on the sympathetic nervous system. Accordingly, we examined the influence of acutely applied nasal CPAP on central hemodynamics and total systemic and cardiac sympathetic nervous activity.

Methods

Fourteen consecutive patients undergoing right heart catheterization for the evaluation of heart failure status and/or heart transplant assessment participated in the study. All patients had a left ventricular ejection fraction <35% and all had New York Heart Association class III symptoms of CHF. All patients were treated with angioten-

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Hemodynamic Response to Nasal CPAP in CHF Patients

Parameter	Baseline	CPAP	*P*
Systolic BP, mm Hg	120±6	117±6	NS
Heart rate, bpm	71±3	70±4	NS
MAP, mm Hg	79±3	81±4	NS
RAP, mm Hg	8±1	11±2	<0.01
Mean PAP, mm Hg	24±3	26±4	NS
PCWP, mm Hg	17±3	20±3	<0.05
CO, L/min	4.8±0.3	4.4±0.2	<0.05
Stroke volume, mL	70±6	64±5	0.08

Values are mean±SD. BP indicates blood pressure; MAP, mean arterial pressure; RAP, right atrial pressure; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; and CO cardiac output.

sin-converting enzyme inhibitors and diuretics, and 6 were receiving β-adrenoceptor antagonists at the time of study. All patients had an arterial oxygen saturation >95% before the application of CPAP. All patients gave written informed consent, and the study was approved by the Alfred Hospital Ethics Review Committee.

Study Protocol

All patients were instructed in the use of the CPAP device (Sullivan Autoset T, ResMed) on the day before the catheterization study. Care was taken to ensure that subjects could tolerate 10 cm H_2O of applied pressure and could breath consistently with a closed mouth. On the day of the experimental study, arterial and central venous cannulae were inserted, followed by the measurement of resting central hemodynamics, as previously described.[16] A coronary sinus thermodilution catheter (Webster Laboratories) was subsequently positioned in the coronary sinus for blood sampling and blood flow measurement before and during the tenth minute of nasal CPAP. After completion of these measurements, central hemodynamics were again evaluated in the presence of continuing nasal CPAP.

Radiotracer Measurement of Sympathetic Nervous Activity

Total systemic and cardiac norepinephrine spillover rates were determined according to well-described methods previously reported by our group.[16] In brief, radiolabeled L-[7-^{3}H] norepinephrine was continuously infused (0.5 to 1 μCi/min) via a peripheral vein to achieve a steady state. Arterial and coronary sinus norepinephrine concentrations were determined by high-performance liquid chromatography with electrochemical detection. The plasma-specific activity of ^{3}H-norepinephrine was determined by a timed collection of the detector cell eluant, and subsequent radioactivity was determined by counting using liquid scintillation spectroscopy.

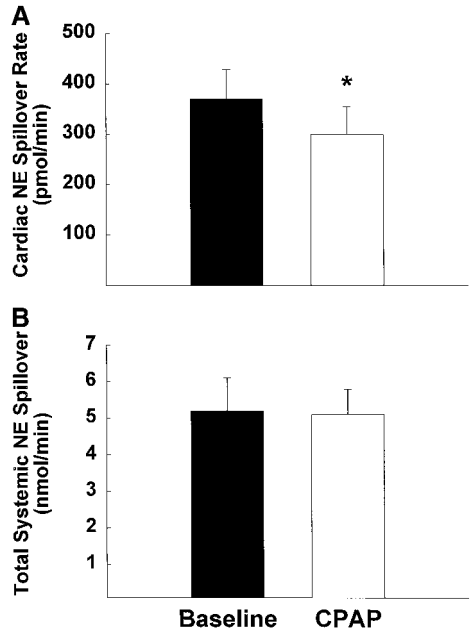
Statistical Methods

Data are presented as mean±SEM. Where data were normally distributed, between-group comparisons were performed by a paired *t* test. For non-normal data, paired comparisons were performed using the Wilcoxon signed-ranks test. $P<0.05$ was considered statistically significant.

Results

Hemodynamic Response to CPAP

As detailed in the Table, the application of nasal CPAP was associated with a significant increase in right atrial and pulmonary capillary wedge pressure, although the magnitude of the increase was considerably less than the application pressure of 10 cm H_20. In conjunction, there was a significant fall in cardiac output, with an associated trend toward a reduction in stroke volume.



Bar graphs showing the effect of short-term nasal CPAP on cardiac (A) and total systemic (B) norepinephrine (NE) spillover rate. *$P<0.05$.

Sympathetic Nervous Response to CPAP

In contrast to the apparent hemodynamic responses, the application of CPAP was associated with a significant fall in the cardiac norepinephrine spillover rate (370±58 to 299±55 pmol/min, $P<0.05$, Figure, A). This response seemed to be limited to the heart, because the total systemic norepinephrine spillover rate was unchanged during the intervention (Figure, B). Furthermore, the application of CPAP did not alter either the arterial plasma norepinephrine concentration (3.9±0.6 versus 4.2±0.6 nmol/L, P=NS) or the rate of norepinephrine clearance from plasma (1.3±0.1 versus 1.3±0.1 L/min, P=NS).

Discussion

The key pathophysiological role that sympathetic nervous overactivity plays in CHF has been highlighted by studies that have associated elevated plasma norepinephrine and cardiac norepinephrine spillover rates with an adverse outcome.[17,18] This concept has more recently been supported by the demonstration of a beneficial action of β-adrenoceptor blockers in CHF patients.[3–5] Despite these observations, the precise mechanism(s) that lead to sympathetic activation have remained somewhat unclear. We and others have shown that cardiac sympathetic activation may be the consequence of elevated intracardiac filling pressures and that therapies which decrease filling pressures may lower cardiac sympathetic tone selectively.[16,19]

In addition to recognition of the importance of neurohormonal activation in CHF, recent attention has also been directed at disturbances of breathing patterns, particularly during sleep. The exact mechanism for these alterations are unclear, although our group has previously demonstrated an association between the severity of sleep apnea and the degree of hemodynamic compromise in CHF patients.[20] In

recognition of the potential importance of sleep apnea in CHF, several studies of the application of CPAP therapy have been performed. Although the hemodynamic responses have been variable, particularly with regard to the effect on cardiac output, one major effect of CPAP has been to reduce left ventricular transmural pressure.[11] Recent clinical studies have shown that CPAP use is associated with improved outcomes in patients with central sleep apnea[15] and, in some cases, with a reduction in ventricular irritability.[21]

In the present study, we showed, for the first time, that short-term nasal CPAP was associated with a significant reduction in cardiac sympathetic tone specifically. Although the precise mechanism for the fall in cardiac sympathetic tone was not clarified in our study, the findings would be consistent with previous work showing that reductions in filling pressure lower cardiac sympathetic tone. Such a mechanism is entirely consistent with data which show that CPAP decreases transmural pressure, an effect that is also produced by the direct reduction of filling pressure. Both forms of intervention may decrease the afferent baroreceptor-mediated stimulus that has been proposed to drive cardiac efferent sympathetic nerve traffic in CHF. In the present study, we did not observe any change in either the arterial plasma norepinephrine concentration or the total systemic spillover rate for norepinephrine, which is consistent with a previous acute study in which muscle sympathetic nerve activity was also not altered by CPAP.[9] In contrast, reductions in muscle sympathetic nerve activity have previously been reported during long-term CPAP in patients with obstructive sleep apnea.[22] Taken together, these data suggest that the sympathoinhibitory effects of short-term CPAP seem to be limited to the heart. Furthermore, from the apparent lack of a systemic adrenergic response, it seems that the application of CPAP was not associated with emotional or mental stress, which typically substantially increase the total body norepinephrine spillover rate.[23]

Given the strong association between sympathetic nervous activation, heart failure outcome, and ventricular arrhythmias and an apparent interaction with a disturbance of ventilatory control, our findings may provide a mechanism for the apparent beneficial actions of CPAP in heart failure patients.

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