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Effect of Continuous Positive Airway Pressure on Mitral Regurgitant Fraction and Atrial Natriuretic Peptide in Patients With Heart Failure

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Objectives. **We sought to determine the effects of continuous positive airway pressure (CPAP) on mitral regurgitant fraction (MRF) and plasma atrial natriuretic peptide (ANP) concentration in patients with congestive heart failure (CHF).**

Background. **In patients with CHF, elevated plasma ANP concentration is associated with elevated cardiac filling pressures. Secondary mitral regurgitation may contribute to elevation in plasma ANP concentration in patients with CHF. Because CPAP reduces transmural cardiac pressures and left ventricular (LV) volume, we hypothesized that long-term CPAP application would decrease the MRF and plasma ANP concentration in patients with CHF and Cheyne-Stokes respiration with central sleep apnea (CSR-CSA).**

Methods. **Seventeen patients with CHF and CSR-CSA underwent baseline assessments of plasma ANP concentration and left ventricular ejection fraction (LVEF) and MRF by radionuclide angiography. They were then randomized to receive nocturnal CPAP plus optimal medical therapy (n = 9) or optimal medical therapy alone (n = 8) for 3 months and were then reassessed.**

Results. **In the CPAP-treated group, LVEF increased from (mean ± SEM) 20.2 ± 4.2% to 28.2 ± 5.3% ($p < 0.02$); MRF decreased from 32.8 ± 7.7% to 19.4 ± 5.5% ($p < 0.02$); and plasma ANP concentration decreased from 140.9 ± 20.8 to 103.9 ± 17.0 pg/ml ($p < 0.05$). The control group experienced no significant changes in LVEF, MRF or plasma ANP concentration. Among all patients, the change in plasma ANP concentration from baseline to 3 months correlated significantly with the change in MRF ($r = 0.789$, $p < 0.0002$).**

Conclusions. **In patients with CHF, CPAP-induced reductions in MRF and plasma ANP concentration in association with improvements in LVEF indicate improved cardiac mechanics. Our findings also suggest that reductions in plasma ANP concentration were at least partly due to reductions in MRF.**

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Atrial natriuretic peptide (ANP) is normally produced in and released from the atria in response to atrial distension (1–3). In patients with chronic congestive heart failure (CHF), ANP is also produced in the ventricles, and its plasma concentration is usually elevated in proportion to elevation of atrial and left ventricular filling pressures. In addition, plasma ANP concentration correlates with the severity of cardiac dysfunction (4,5) and is inversely related to survival time in patients with CHF (6,7).

Secondary mitral regurgitation, arising from mitral annular dilation and papillary muscle dysfunction, is a common finding in patients with CHF. It contributes to elevation of left ventricular (LV) end-diastolic as well as left and right atrial pressures and causes distension of the left ventricle and atria (8). In addition to impairing the forward pumping efficiency of the heart, mitral regurgitation may further increase the wall tensions of the failing myocardium, thereby contributing to further elevation in plasma ANP concentration in patients with CHF.

Continuous positive airway pressure (CPAP) applied through a nasal mask in patients with CHF while awake increases intrathoracic pressure, thereby reducing systolic LV transmural pressure (a major determinant of LV afterload) (9) and augmenting stroke volume and cardiac output in patients with elevated LV filling pressures (10). Studies in animals (11,12) show that CPAP and positive end-expiratory pressure reduce LV end-diastolic volume. Although long-term nightly application of CPAP in patients with CHF and Cheyne-Stokes respiration with central sleep apnea (CSR-CSA) has been shown (13,14) to improve LV ejection fraction (LVEF) and to reduce urinary and plasma norepinephrine concentrations, its effects on mitral regurgitation and plasma ANP concentration have not been examined. We therefore hypothesized that because CPAP reduces systolic cardiac transmural pressures and increases LVEF and forward cardiac output in patients with CHF and associated CSR-CSA, it should also lead to

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Abbreviations and Acronyms

ACE	=	angiotensin-converting enzyme
ANP	=	atrial natriuretic peptide
CHF	=	congestive heart failure
CPAP	=	continuous positive airway pressure
CSR-CSA	=	Cheyne-Stokes respiration with central sleep apnea
LV	=	left ventricular
LVEF	=	left ventricular ejection fraction
MRF	=	mitral regurgitant fraction
RV	=	right ventricular
Sa_{O_2}	=	oxyhemoglobin saturation

decreases in mitral regurgitant fraction (MRF) and plasma ANP concentration. Patients with CSR-CSA were studied because we have previously shown (13,14) that long-term, nightly application of CPAP is readily tolerated by them, because it consistently reduces the frequency of central apneas and hypopneas.

Methods

Subjects. The study included patients with chronic CHF who met the following criteria: 1) at least one documented clinical episode of CHF consisting of pulmonary edema and chronic exertional dyspnea within 6 months of the study; 2) chronic exertional dyspnea (New York Heart Association functional class II or III) despite appropriate pharmacologic therapy; 3) stable clinical status as evidenced by an absence of acute exacerbations of symptoms or medication change for at least 1 month before entry; 4) sinus rhythm; and 5) CSR-CSA, as defined later. Exclusion criteria were 1) a history of myocardial infarction within the previous 3 months; 2) unstable angina; 3) clinical evidence of significant tricuspid regurgitation (prominent *v* waves together with elevated jugular venous pressure or a pulsatile liver); 4) primary valvular heart disease as evidenced by a history of rheumatic valve disease or structural valve abnormalities visualized on two-dimensional echocardiography; 5) primary obstructive lung disease as defined by chronic cough and sputum production or a forced expiratory time in 1 s/forced vital capacity <80% of predicted normal; and 6) obstructive sleep apnea syndrome on an overnight sleep study, as described later. The study protocol was approved by the Human Subjects Review Committee at the University of Toronto, and all patients gave written informed consent before entry into the study.

Sleep studies. Patients meeting all other inclusion criteria underwent overnight polysomnography to assess the presence of CSR-CSA. Standard techniques and scoring criteria were used for the determination of sleep stages (15). The electrocardiogram was recorded from a precordial lead. Respiratory movements of the rib cage and abdomen were measured by respiratory inductance plethysmography (Respitrace, Ambulatory Monitoring Inc.) calibrated against a spirometer (16,17). Intrathoracic pressure was measured continuously by an esophageal balloon-catheter system attached to a pressure transducer (Validyne) (18). Oxyhemoglobin saturation (Sa_{O_2}) was measured with an ear oximeter (Oxyshuttle, Sensormedics Corp.). Mean sleep Sa_{O_2} was calculated as previously described (17). *Central apneas* were identified by the absence of a tidal volume excursion for at least 10 s with no movement of the rib cage or abdomen and were further confirmed by the absence of esophageal pressure swings. *Central hypopneas* were defined as a ≥50% reduction in tidal volume from the baseline value, persisting for at least 10 s with proportional reductions in rib cage and abdominal movements and in esophageal pressure swings (17,19). *Obstructive apneas and hypopneas* were similarly defined, except that paradoxic thoracoabdominal motion and increasing esophageal pressure swings had to be present despite an absence or a reduction in tidal volume, respectively. The *apnea–hypopnea index* was expressed as the number of apneas and hypopneas per hour of sleep. *CSR-CSA* was defined as a crescendo–decrescendo pattern of hyperpnea alternating with central apneas or hypopneas at a rate of >10/hour of sleep and in which apneas and hypopneas were predominantly (>85%) central in nature (17).

Radionuclide angiography and MRF. Cardiac function was assessed using gated equilibrium radionuclide angiography. R wave synchronous radionuclide angiography was performed using the in vivo red blood cell labeling technique with initial intravenous stannous pyrophosphate followed by technetium-99m pertechnetate. Cardiac imaging was performed supine with a gamma camera (Elscint APEX 409, Haifa, Israel) equipped with a low energy all-purpose collimator in the left anterior oblique view that provided optimal ventricular separation. Gated images were acquired with the SP-I computer onto a 64 by 64 matrix at a rate of at least 16 frames/cardiac cycle. The total acquisition time was 5 min/view.

For data analysis, LV time–activity curves were generated by the Elscint multiple gated acquisition (MUGA) program that incorporates a semiautomated edge detection algorithm with minimal operator intervention. LV regions of interest for each frame of the entire cardiac cycle were individually defined. End-diastolic and end-systolic frames were determined from the time–activity curve thus generated as the frames with maximal count at or immediately after the R wave and the frame with minimal count, respectively. LVEF was routinely determined for the left and right ventricles as the background-subtracted end-diastolic minus end-systolic counts divided by end-diastolic counts. To determine the MRF, we used the technique of stroke volume ratios. Stroke counts for the left and right ventricles were determined using the previously described program. The end-diastolic and end-systolic frames were identified, and the LV and right ventricular (RV) counts obtained. If one assumes that LV stroke volume should equal RV stroke volume in the absence of mitral regurgitation, that the ventricles are equidistant from the camera in the left anterior oblique view and that background is temporally constant, MRF can be calculated as follows (20,21): MRF = (LV stroke counts − RV stroke counts)/LV stroke counts.

Plasma ANP concentration. Five milliliters of venous blood were drawn through an indwelling catheter in the

forearm of patients after they had been supine and undisturbed in a quiet room for at least 30 min before the performance of radionuclide angiography. Plasma was immediately separated by centrifugation (3,000 rpm for 15 min at 4°C), and 2-ml aliquots were transferred into prechilled polypropylene tubes containing aprotinin (100 killikrein inhibiting unit/ml plasma). The plasma was stored at −70°C. Plasma ANP concentrations were then determined by radioimmunoassay (22).

Experimental protocol. Eligible patients with CSR-CSA were randomized to either a control group or to a CPAP group. Baseline radionuclide angiography was performed, and blood for measurement of plasma ANP concentration was drawn as previously described. The control group continued to receive optimal medical therapy consisting of combinations of digoxin, diuretic drugs and, where tolerated, an angiotensin-converting enzyme (ACE) inhibitor. Where ACE inhibitors could not be tolerated, nitrates and hydralazine were used.

The CPAP group received nightly CPAP in addition to the previously described medical therapy. CPAP (Remstar; Respironics Inc.) therapy was initiated with supervision and instructions in the sleep laboratory over two to three nights, as previously described (13). The pressure was titrated up to 10 to 12.5 cm H_2O as tolerated, which is a level previously shown (13) in our laboratory to be effective in improving LVEF in a similar patient cohort. The patients were instructed to use CPAP at home for at least 6 h/night, and CPAP compliance was assessed by monitoring the total duration that CPAP was in use from an embedded time-usage meter on the CPAP pump. At 3 months after randomization, radionuclide angiography and plasma ANP concentration measurements were repeated. All baseline and follow-up radionuclide angiograms and plasma ANP concentration determinations were performed at the same time of day, ~4 h after patients arose in the morning, while not using CPAP. All radionuclide angiograms and plasma ANP concentration determinations were performed by personnel with no knowledge of the treatment received by the patients.

Statistical analysis. Two-tailed unpaired *t* tests were used to compare baseline data for the control and CPAP groups as well as to compare changes in variables from baseline to the completion of the study after 3 months between the groups. Two-tailed paired *t* tests were used to compare within-group data at baseline and 3 months after entry into the study, except for cardiac functional class, which was analyzed by the Wilcoxon rank sum test. Relations among variables were examined by least-squares linear regression analysis. A p value <0.05 was considered statistically significant. Results are expressed as mean value ± SEM.

Results

Patient characteristics. Seventeen male patients with CHF and CSR-CSA were recruited into the study; eight were randomized to the control group and nine to the CPAP group. Among the CPAP group patients, CHF was due to coronary artery disease in eight and idiopathic dilated cardiomyopathy in one. In the control patients, CHF was due to coronary artery disease in seven and idiopathic dilated cardiomyopathy in one. Baseline characteristics of the patients are shown in Table 1. There were no significant differences in any of the variables shown between the groups. Severe LV functional impairment with a mean LVEF of ~20% was observed in both groups. Although there was a tendency for MRF and plasma ANP concentration to be higher in the CPAP than in the control group, these differences were not statistically significant. Medications were similar in both groups. As illustrated in Table 2, sleep structure, apnea–hypopnea index and Sa_{O_2} while asleep were similar at baseline in the two groups. For the CPAP group, mean CPAP was 10.1 ± 0.6 cm H_2O, and CPAP was used on average for 5.42 ± 0.68 h/night over the 3-month period.

Table 1. Baseline Clinical Data

	Control Group (n = 8)	CPAP Group (n = 9)	p Value
Age (yr)	58.6 ± 2.4	61.0 ± 1.9	0.449
BMI (kg/m^2)	25.1 ± 1.8	28.8 ± 1.8	0.180
SBP (mm Hg)	111.6 ± 6.4	124.7 ± 10.5	0.322
DBP (mm Hg)	66.1 ± 2.6	70.9 ± 4.3	0.371
HR (beats/min)	63.4 ± 4.2	67.2 ± 4.9	0.564
LVEF (%)	20.8 ± 3.2	20.2 ± 4.2	0.923
MRF (%)	19.4 ± 4.7	32.8 ± 7.7	0.171
ANP conc (pg/ml)	101.6 ± 18.0	140.9 ± 20.8	0.179
Awake Pa_{O_2} (mm Hg)	78.1 ± 4.1	85.1 ± 3.5	0.220
Awake Pa_{CO_2} (mm Hg)	38.0 ± 2.8	38.0 ± 1.6	1.000
NYHA functional class			
II	5	4	
III	3	5	
Drug therapy			
Diuretic drugs	7	8	
Digoxin	4	6	
Vasodilators			
ACE inhibitors	7	7	
Nitrates	3	3	
Ca blockers	2	1	
Hydralazine	2	1	
Antiarrhythmic agents	6	3	
Anticoagulant agents	5	6	
Aspirin	0	2	

Data presented are mean value ± SEM or number of patients. ACE = angiotensin-converting enzyme; ANP conc = plasma atrial natriuretic peptide concentration; BMI = body mass index; Ca = calcium; CPAP = continuous positive airway pressure; DBP = diastolic blood pressure; HR = heart rate; LVEF = left ventricular ejection fraction; MRF = mitral regurgitant fraction; NYHA = New York Heart Association; Pa_{CO_2} = partial pressure of arterial carbon dioxide; Pa_{O_2} = partial pressure of arterial oxygen; SBP = systolic blood pressure.

Cardiac function. New York Heart Association functional class improved significantly in the CPAP group (from 2.6 ± 0.2 at baseline to 1.7 ± 0.2 at 3 months, $p < 0.02$) but not in the control group (from 2.4 ± 0.2 to 2.5 ± 0.2, respectively). The change from baseline to 3 months was significantly greater in the CPAP group than in the control group (−0.9 ± 0.2 vs.

Table 2. Baseline Sleep Study Data

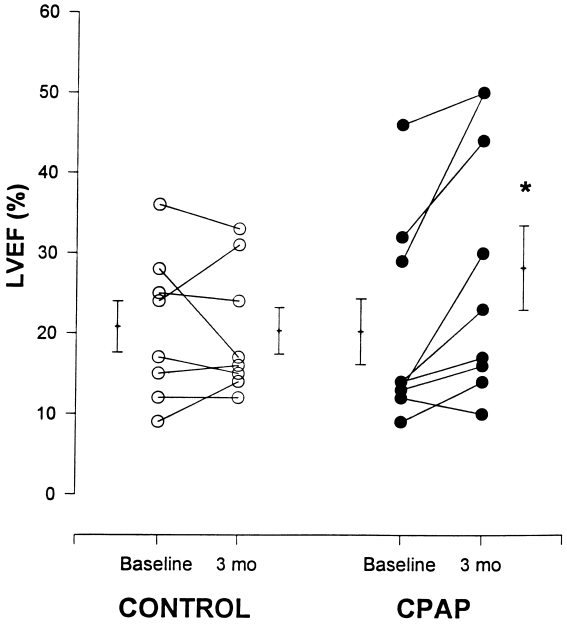
	Control Group (n = 8)	CPAP Group (n = 9)	p Value
Total time asleep (h)	4.12 ± 0.38	4.03 ± 0.48	0.770
Sleep stage (h)			
Stages 1 and 2	3.13 ± 0.40	3.10 ± 0.39	0.988
Slow wave	0.07 ± 0.05	0.22 ± 0.11	0.254
REM	0.52 ± 0.86	0.31 ± 0.11	0.161
Arousals (no./h sleep)	35.2 ± 6.5	31.6 ± 6.9	0.715
AHI (no./h sleep)	33.7 ± 8.5	45.4 ± 4.9	0.241
Mean low sleep Sao_2 (%)	91.6 ± 1.4	89.2 ± 1.3	0.691

Data presented are mean value ± SEM. AHI = apnea–hypopnea index; CPAP = continuous positive airway pressure; REM = rapid eye movement; Sao_2 = oxyhemoglobin saturation.

0.1 ± 0.1, $p < 0.01$). Whereas LVEF improved significantly in the CPAP-treated patients from baseline to 3 months (from 20.2 ± 4.2% to 28.2 ± 5.3%, $p < 0.02$), it did not change significantly in control patients (from 20.8 ± 3.2% to 20.3 ± 2.9%) (Fig. 1). In addition, the change in LVEF from baseline to 3 months was significantly greater in the CPAP group than the control group (8.0 ± 2.5% vs. −0.5 ± 1.9%, $p < 0.02$).

There was no significant relation between baseline LVEF and baseline MRF. In the CPAP group, MRF decreased significantly during the 3-month study period (from 32.8 ± 7.7% to 19.4 ± 5.5%, $p < 0.02$) (Fig. 2). In contrast, MRF did not change significantly in the control group (19.4 ± 4.7% vs. 22.2 ± 3.9%). In addition, the reduction in MRF from baseline to 3 months was more pronounced in the CPAP group than in the control group (−13.3 ± 4.6 vs. 2.8 ± 2.6, $p < 0.01$). MRF decreased in eight of nine CPAP-treated patients irrespective

Figure 1. Individual data for LVEF at baseline and at 3 months in control and CPAP-treated patients. *p < 0.02 versus baseline.



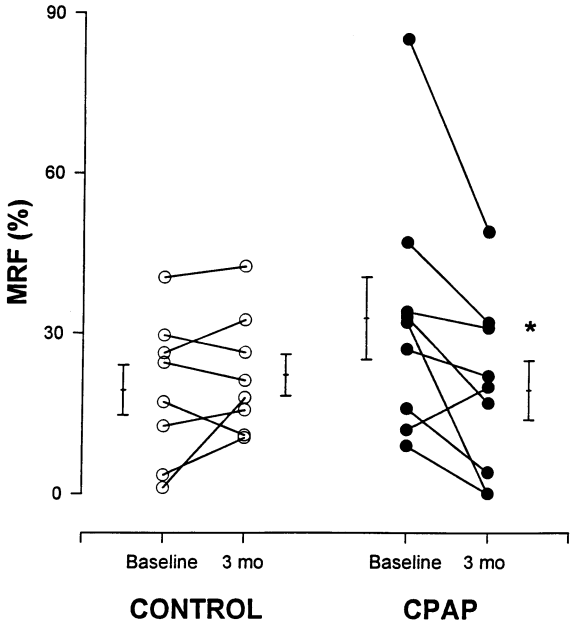


Figure 2. Individual data for MRF at baseline and at 3 months in control and CPAP-treated patients. *p < 0.02 versus baseline.

of baseline MRF. Moreover, within the CPAP group, a significant relation between the baseline MRF value and its subsequent change after treatment was observed ($r = 0.707$, $p < 0.05$), whereas no such relation was found in the control group. However, there was no significant relation between the change in MRF and that in LVEF over 3 months within either the CPAP or control group.

Plasma ANP concentration. Significant relations were found between plasma ANP concentration and LVEF ($r = -0.492$, $p < 0.05$), and between plasma ANP concentration and MRF ($r = 0.497$, $p < 0.05$) at baseline. In the CPAP-treated group a marked decrease in plasma ANP concentration was observed over the 3-month period (from 140.9 ± 20.8 to 103.9 ± 17.0 pg/ml, $p < 0.05$), whereas in the control group plasma ANP concentration did not change significantly (from 101.6 ± 18 to 129.9 ± 19.3 pg/ml) (Fig. 3). A reduction in plasma ANP concentration occurred in eight of nine CPAP-treated patients irrespective of the baseline plasma ANP concentration value. The decrease in plasma ANP concentration over the study period was more pronounced in the CPAP group than the control group (−37.2 ± 14.2 vs. 26.4 ± 15.7 pg/ml, $p < 0.01$). There was a strong correlation between the change in plasma ANP concentration and that in MRF from baseline to 3 months (Fig. 4).

Discussion

We previously showed (13,14) that long-term CPAP therapy improves LVEF and reduces urinary and plasma norepinephrine concentrations in patients with CHF and CSR-CSA. The present findings extend these previous observations and provide novel evidence of further beneficial hemodynamic and

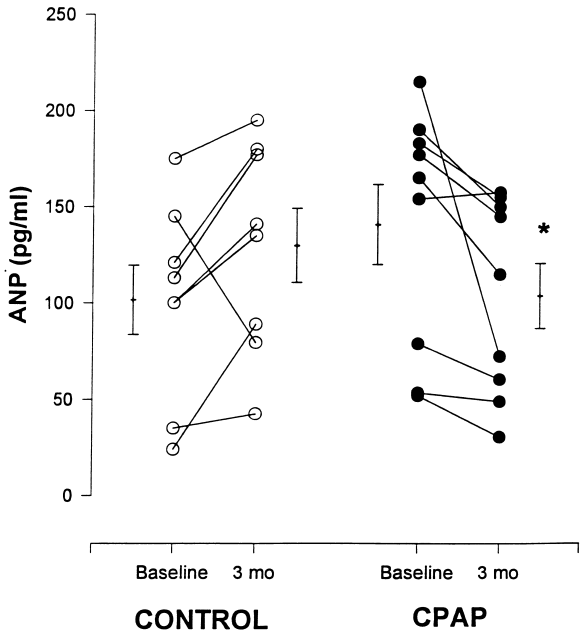
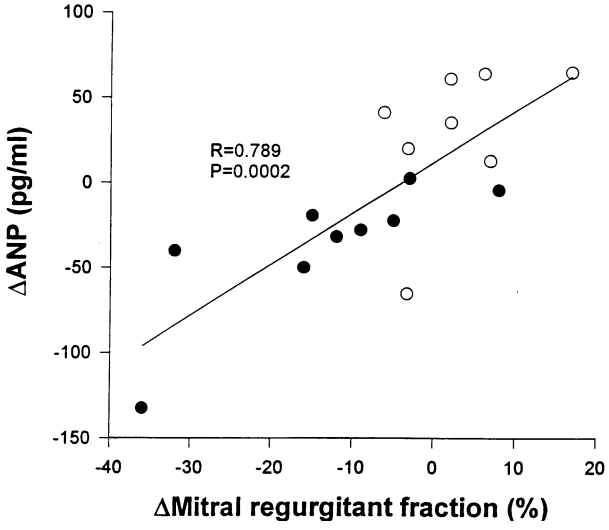


Figure 3. Individual plasma ANP concentrations at baseline and at 3 months in control and CPAP-treated patients. *p < 0.05 versus baseline.

humoral effects of CPAP in patients with CHF. However, the present study was not designed to test the effects of CPAP on CSR-CSA because we previously showed (13,14) that CPAP consistently alleviates CSR-CSA. Our present data demonstrate that CPAP caused a large and significant reduction in MRF, averaging 41%, in association with an improvement in LVEF over the 3-month study period. In addition, CPAP induced a significant decrease in plasma ANP concentration that was proportional to the reduction in MRF. Decreases in MRF were most likely due to reductions in cardiac volumes and improvements in papillary muscle function (9,11,12,23,24). Reductions in plasma ANP concentration probably resulted from a reduced mitral regurgitant jet, with consequent reductions in diastolic filling pressures (3), as well as from the direct effect of CPAP on reducing left- and right-sided systolic transmural pressures (9). However, we have no direct evidence for these mechanisms in the present study. Furthermore, because LVEF, MRF and plasma ANP concentration were measured during the daytime, while patients were awake, several hours after nocturnal CPAP had been removed, improvements in these variables could not be attributed solely to the direct, short-term effects of nocturnally applied CPAP. Rather, our findings are compatible with the concept that CPAP-induced improvements in cardiac function were sustained into the daytime.

Figure 4. Relation between change (Δ) in MRF and that in plasma ANP concentration over 3-month study period. $R^2 = 0.623$. **Open circles** = control patients; **solid circles** = CPAP-treated patients.



Effects of CPAP on LVEF and MRF. The improvement in LVEF due to CPAP is consistent with our previous studies (13,14). However, CPAP-induced reductions in MRF in patients with CHF have not been previously described. Chronic functional mitral regurgitation is a common finding in patients with CHF and is due mainly to distortion of the mitral valve annulus secondary to LV dilation and to papillary muscle dysfunction in patients with ischemic heart disease (23–26). Mitral regurgitation is an integral part of the vicious cycle whereby cardiac dilation leads to functional mitral regurgitation, which in turn leads to further ventricular and atrial dilation, elevations in pulmonary venous pressure and pulmonary congestion (8,27). Interruption of this vicious cycle improves the forward pumping efficiency of the failing heart and may be particularly effective in retarding the progression of ventricular dilation that follows myocardial injury (28,29).

Diuretic drugs and vasodilators cause a reduction in mitral regurgitation in patients with severe CHF by decreasing LV end-diastolic and end-systolic volumes (30,31). However, CPAP-induced reductions in MRF in our patients were over and above that due to pharmacologic therapy. We observed that the greater the baseline MRF, the greater the degree of reduction in MRF in response to CPAP, as is the case with diuretic drugs and vasodilators (25,27,31). In addition, reductions in secondary mitral regurgitation due to mitral valve reconstruction in patients with CHF cause decreases in LV end-diastolic volume (32). Similar mechanisms could have been responsible for CPAP-induced reductions in MRF (9,11,12). As discussed by Levine and Gaasch (24), there is experimental and clinical evidence that functional mitral regurgitation in a failing heart is related to dilation of the left ventricle and mitral valve annulus. Therefore, it is possible that a reduction in LV volume played a role in reducing MRF. However, there is very little evidence for this in the setting of long-term trials of vasoactive drugs. In addition, because most of our patients had ischemic heart disease, papillary muscle dysfunction probably also contributed to the development of mitral regurgitation (23,26). Consequently, CPAP could have improved papillary muscle function and reduced MRF by reducing transmural LV pressure (9) and by reducing sympathetic nervous system activity and associated coronary vaso-

constriction (14), thereby reducing myocardial ischemia. Although only mild apnea-related dips in Sao_2 occurred during sleep in our patients, it is also possible that even slight CPAP-induced improvements in nocturnal Sao_2 could have further reduced sympathetic activation (14).

CPAP-induced increases in LVEF did not correlate with decreases in MRF. Because LVEF reflects both forward and regurgitant flow, a decline in MRF causing improved forward cardiac output will not necessarily coincide with an improvement in LVEF. Stevenson et al. (30) found that diuretic drugs and vasodilators decreased total LV stroke volume by 20% but increased forward stroke volume by 40% in patients with severe CHF. Therefore, where a substantial reduction in mitral regurgitation occurs in response to therapy, LVEF can be an insensitive index of the improvement in ventricular function (30).

Effects of CPAP on plasma ANP concentration. The physiologic significance of the reduction in MRF due to CPAP is further emphasized by the concomitant reduction in plasma ANP concentration. ANP is normally secreted by atrial myocytes in response to increased atrial tension and stretch (1,33). In CHF, where atrial and ventricular pressures and volumes are increased, ANP is also secreted by ventricular myocytes, and plasma ANP concentration is increased (34,35). Furthermore, acute induction of mitral regurgitation in dogs increases atrial pressures and plasma ANP concentration (36). Therefore, chronic regurgitant flow probably contributes to increased plasma ANP concentration in CHF by worsening atrial pressure and volume overload. Conversely, reducing mitral regurgitant flow should relieve atrial overload and reduce ANP production and release. The significant correlation between baseline plasma ANP concentration and MRF and the reduction of plasma ANP concentration in proportion to the decrease in MRF at 3 months in the CPAP-treated patients are consistent with these concepts. In addition, direct reductions in both right- and left-sided cardiac transmural pressures and volumes due to CPAP-induced increases in intrathoracic pressure may also have contributed to reduced plasma ANP concentration; Reduced right-sided cardiac volumes might also have reduced adverse ventricular interactions and indirectly reduced left-sided filling pressures. However, because our patients all had predominantly left-sided heart failure, it is more likely that decreased ANP release from the right atrium would follow from reductions in mitral regurgitation and left-sided filling pressures.

Although elevated plasma ANP concentration in CHF should exert natriuretic, sympathoinhibitory and vasodilatory effects in compensation for fluid overload (22,37,38), these actions are suppressed in the later stages of CHF by the predominant actions of vasoconstrictors, such as angiotensin, norepinephrine and endothelin (38). In fact, the main clinical significance of elevated plasma ANP concentration is that it reflects elevated left- and right-sided cardiac filling pressures and is a noninvasive index of the response to treatment for CHF (2). Elevated plasma ANP concentration and cardiac filling pressures are also predictors of increased mortality in severe CHF (6,39). The 26% reduction in plasma ANP concentration after 3 months of nightly CPAP is similar to the decline in plasma ANP concentration due to enalapril in the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) (7). However, whether reductions in plasma ANP concentration in response to either vasodilator or CPAP therapy are associated with improvement in long-term outcome in patients with CHF remains to be determined.

Noninvasive quantification of MRF by radionuclide angiography, as described herein, correlates very strongly with MRF assessed during cardiac catheterization (40). It has high specificity (0.9) for detection of mitral regurgitation in the absence of marked tricuspid regurgitation and is sensitive to changes in mitral regurgitation after medical and surgical therapy for mitral valve disease and CHF (40,41). Although patients with clinically overt signs of tricuspid regurgitation were excluded from the study, mild degrees of tricuspid regurgitation could not be ruled out. Inclusion of patients with hemodynamically significant tricuspid regurgitation would falsely underestimate but not overestimate the degree of mitral regurgitation. Furthermore, reductions in MRF in the CPAP-treated group could not be explained on the basis of reductions in tricuspid regurgitation because this would have increased, not reduced, the calculated MRF. Moreover, reductions in plasma ANP concentration in proportion to reductions in MRF in the CPAP-treated group are in keeping with reduced atrial pressures and would not be compatible with worsening of tricuspid or mitral regurgitation. Therefore, changes in MRF within our patients probably reflected relative changes in mitral regurgitation. Although the baseline MRF tended to be somewhat higher (but not significantly) in the CPAP-treated group, this was mainly due to the one patient with severe mitral regurgitation. However, if we exclude this patient, such that baseline values between the CPAP ($26.3 \pm 4.6\%$) and control groups ($19.4 \pm 4.7\%$) were more nearly equal, the decrease of MRF in the CPAP-treated group to $15.8 \pm 4.6\%$ remains statistically significant ($p < 0.05$).

Summary. The present study sheds further light on the long-term beneficial cardiovascular effects of CPAP in patients with CHF. 1) Reductions in MRF indicate improved cardiac pumping efficiency such that improvements in LVEF underestimate the overall hemodynamic improvement due to CPAP. 2) Reductions in MRF and plasma ANP concentration together suggest that cardiac size and filling pressures were reduced. However, because we did not directly measure cardiac volumes, systolic transmural pressures or filling pressures, future studies in which these factors are measured will be required to examine these possibilities. Whether these beneficial effects of CPAP are specific to patients with CHF who also have CSR-CSA is uncertain. However, our findings appear to be relevant to a large proportion of patients with chronic CHF because the prevalence of CSR-CSA among them has been reported to be ~40% to 50% and because they have a higher mortality rate than patients without CSR-CSA (13,42,43). Accordingly, CPAP is a promising nonpharmacologic adjunctive therapy for selected patients with CHF whose clinical

effectiveness should be evaluated in larger and longer term trials.

References

1. Edwards BS, Zimmerman RS, Schwab TR, Heublein DM, Burnett JC Jr. Atrial stretch, not pressure, is the principal determinant controlling the acute release of atrial natriuretic factor. Circ Res 1988;62:191–5.
2. Anderson JV, Woodruff PW, Bloom SR. The effect of treatment of congestive heart failure on plasma atrial natriuretic peptide concentration: a longitudinal study. Br Heart J 1988;59:207–11.
3. Tsutamoto T, Bito K, Kinoshita M. Plasma atrial natriuretic polypeptide as an index of left-ventricular end-diastolic pressure in patients with chronic left-sided heart failure. Am Heart J 1989;117:599–604.
4. Hara H, Ogihara T, Shima J. Plasma atrial natriuretic peptide level as an index for the severity of congestive heart failure. Clin Cardiol 1987;10:437–42.
5. Davis KM, Fish LC, Elahi D, Clark BA, Minaker KL. Atrial natriuretic peptide levels in the prediction of congestive heart failure risk in frail elderly. JAMA 1992;267:2625–9.
6. Gottlieb SS, Kukin ML, Ahern D, Packer M. Prognostic importance of atrial natriuretic peptide in patients with chronic heart failure. J Am Coll Cardiol 1989;13:1534–9.
7. Swedberg K, Eneroth P, Kjekshus J, Wilhelmsen L. Hormones regulating cardiovascular function in patients with severe congestive heart failure and their relation to mortality. Circulation 1990;82:1730–6.
8. Vanoverschelde JLJ, Raphael DA, Robert AR, Cosyns JR. Left ventricular filling in dilated cardiomyopathy: relation to functional class and hemodynamics. J Am Coll Cardiol 1990;15:1288–95.
9. Naughton MT, Rahman A, Hara K, Floras JS, Bradley TD. Effect of continuous positive airway pressure on intrathoracic and left ventricular transmural pressures in patients with congestive heart failure. Circulation 1995;91:1725–31.
10. Bradley TD, Holloway RM, McLaughlin PR, Ross BL, Walters J, Liu PP. Cardiac output response to continuous positive airway pressure in congestive heart failure. Am Rev Respir Dis 1992;145:377–82.
11. Fewell JE, Abendschein DR, Carlson CJ, Murray JF, Rapaport E. Continuous positive-pressure ventilation decreases right and left ventricular end-diastolic volumes in dog. Circ Res 1980;46:125–32.
12. Johnston WE, Vinton-Johansen J, Santamore WP, Case LD, Little WC. Mechanism of reduced cardiac output during positive end-expiratory pressure in the dog. Am Rev Respir Dis 1989;140:1257–64.
13. Naughton MT, Liu PP, Benard DC, Goldstein RS, Bradley TD. Treatment of congestive heart failure and Cheyne-Stokes respiration during sleep by continuous positive airway pressure. Am J Respir Crit Care Med 1995;151:92–7.
14. Naughton MT, Benard DC, Liu PP, Rutherford R, Rankin F, Bradley TD. Effects of nasal CPAP on sympathetic activity in patients with heart failure and central sleep apnea. Am J Respir Crit Care Med 1995;152:473–9.
15. Rechtschaffen A, Kales A. A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects. Bethesda (MD): National Institutes of Health, 1968. Publication No. 204.
16. Chadha TS, Watson H, Birch S, et al. Validation of respiratory inductive plethysmography using different calibration procedures. Am Rev Respir Dis 1982;125:644–9.
17. Naughton MT, Benard D, Tam A, Rutherford R, Bradley TD. The role of hyperventilation in the pathogenesis of central sleep apnea in patients with congestive heart failure. Am Rev Respir Dis 1993;148:330–8.
18. Milic-Emili J, Mead J, Turner JM, Glauser EM. Improved technique for estimating pleural pressure from esophageal balloons. J Appl Physiol 1964;19:207–11.
19. Gould GA, Whyte KJ, Airlie MAA, Caterall JR, Shapiro CM, Douglas NJ. The sleep hypopnea syndrome. Am Rev Respir Dis 1988;137:895–8.
20. Bough EW, Gandsman E, North DL, Shulman RS. Gated radionuclide angiographic evaluation of valve regurgitation. Am J Cardiol 1980;46:423–8.
21. Rigo P. Quantification of mitral insufficiency by radionuclide techniques. Eur Heart J 1991;12:15–8.
22. Floras JS. Sympathoinhibitory effects of atrial natriuretic factor in normal humans. Circulation 1990;81:1860–73.
23. Boltwood CM, Tei C, Wong M, Shah PM. Quantitative echocardiography of the mitral complex in dilated cardiomyopathy: the mechanisms of functional mitral regurgitation. Circulation 1983;68:498–508.
24. Levine HL, Gaasch WH. Vasoactive drugs in chronic regurgitant lesions of the mitral and aortic valves. J Am Coll Cardiol 1996;28:1083–91.
25. Evangelista-Masip A, Bruguera-Cortada J, Serrat-Serradell R, et al. Influence of mitral regurgitation on the response to captopril therapy for congestive heart failure caused by idiopathic dilated cardiomyopathy. Am J Cardiol 1992;69:373–6.
26. Ogawa S, Hubbard FE, Mardelli JT, Dreifus LS. Cross-sectional echocardiographic spectrum of papillary muscle dysfunction. Am Heart J 1979;97:312–21.
27. Weiland DS, Konstam MA, Salem DN, et al. Contribution of reduced mitral regurgitant volume to vasodilator effect in severe left ventricular failure secondary to coronary artery disease or idiopathic dilated cardiomyopathy. Am J Cardiol 1986;58:1046–50.
28. Pfeffer MA, Pfeffer JM, Skinberg C, Finn P. Survival after an experimental myocardial infarction: beneficial effects of long-term therapy with captopril. Circulation 1985;72:406–12.
29. Konstam MA, Rousseau MF, Kronenberg ME, et al. Effects of angiotensin converting enzyme inhibitor enalapril on the long-term progression of ventricular dysfunction in patients with heart failure. Circulation 1992;86:431–8.
30. Stevenson LW, Bellil D, Grover-McKay M, et al. Effects of afterload reduction (diuretics and vasodilators) on left ventricular volume and mitral regurgitation in severe congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. Am J Cardiol 1987;60:654–8.
31. Seneviratne B, Moore GA, West PD. Effect of captopril on functional mitral regurgitation in dilated heart failure: a randomized double blind placebo controlled trial. Br Heart J 1994;72:63–8.
32. Bach DS, Bolling SF. Early improvement in congestive heart failure after correction of secondary mitral regurgitation in end-stage cardiomyopathy. Am Heart J 1995;129:1165–70.
33. Cho KW, Seul KH, Kim SH, Seul KM, Koh GY. Atrial pressure, distension, and pacing frequency in ANP secretion in isolated perfused rabbit atria. Am J Physiol 1991;260:R39–46.
34. Uretsky BF, Verbalis JG, Murali S, Betschart AR, Kolesar JA, Reddy PS. Control of atrial natriuretic peptide secretion in patients with severe congestive heart failure. J Clin Endocrinol Metab 1990;71:146–51.
35. Burnett JC Jr, Kao PC, Hu DC, et al. Atrial natriuretic peptide elevation in congestive heart failure in human. Science 1986;231:1145–7.
36. Masuda T, Satoh K, Ando K, Takaoto T, Marumo F. Response of plasma atrial natriuretic factor to experimentally induced aortic and mitral regurgitation in dogs. Cardiovasc Res 1991;25:192–7.
37. DeBold AJ, Borenstein HB, Veress AT. A rapid and potent natriuretic response to intravenous injection of atrial myocardial extract in rat. Life Sci 1981;28:89–94.
38. Winaver J, Hoffman A, Abassi Z, Haramati A. Does the heart's hormone, ANP, help in congestive heart failure? News Physiol Sci 1995;10:247–53.
39. Stevenson LW, Dracup KA, Tillisch JH. Efficacy of medical therapy tailored for severe congestive heart failure in patients transferred for urgent cardiac transplantation. Am J Cardiol 1989;63:461–4.
40. Sorensen SG, O'Rourke RA, Chaudhuri TK. Noninvasive quantitation of valvular regurgitation by gated equilibrium radionuclide angiography. Circulation 1980;62:1089–98.
41. Konishi T, Ichikawa T, Isaka N, Sugawa M, Nakano T. Assessment of mitral regurgitation using gated radionuclide ventriculography: analysis of left atrial activity curve. Angiology 1990;41:387–93.
42. Javaheri S, Parker TJ, Wexler L, et al. Occult sleep-disordered breathing during sleep in stable congestive heart failure. Ann Intern Med 1995;122:487–92.
43. Hanly PJ, Zuberi-Khokhar NS. Increased mortality associated with Cheyne-Stokes respiration in patients with congestive heart failure. Am J Respir Crit Care Med 1996;153:272–6.