age 53 ± 8 yrs, LVEF 26 ± 7, NYHA cl. II–IV, stable therapy within two weeks) underwent simultaneous 20' recordings at rest of istantaneous lung volume (ILV), beat-to-beat arterial oxygen saturation (SaO2, ear probe) and heart rate. Analysis of ILV and SaO2 revealed a normal respiratory pattern (NR) in 65 patients while 90 had a persistent alteration of breathing with a typical CS in 43 and PB in 47 patients. CS and PB had lower LVEF and cardiac index, and higher wedge pressure than NR (all $p < 0.03$). During a mean follow-up of 338 ± 170 days, 25 cardiac deaths occurred while 10 patients underwent elective heart transplantation. Survival was significantly lower in patients with PB and CSR as compared to patients with NR (log rank $p < 0.03$) with a RR of 2.9 (95% c.i. = 1.0–8.9) and 4.0 (95% c.i. = 1.4–11.7) respectively. However, at multivariate analysis, nor PB nor CSR were independent predictors of death after adjustment for NYHA cl., LVEF, max VO2 and pulmonary wedge pressure.

Conclusions: In CHF patients, as reported for nocturnal Cheyne-Stokes respiration, breathing abnormalities during awake day-time are associated with higher incidence of cardiac death. However their prognostic power is not independent of the other known risk factors and the increased mortality rate is likely to be related to the more severe hemodynamic impairment of these patients.

1096-37 Selective AT-1 Blockade With Losartan Does Not Restore Autonomic Balance in Patients With Heart Failure

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Angiotensin converting enzyme inhibitors (ACEI's) have been shown to restore autonomic balance towards normal in patients with heart failure (HF). It is uncertain whether this effect derives from the interruption of angiotensin type 1 (AT-1) receptor stimulation or extends from other properties of ACEI's. Therefore, spectral analysis of heart rate variability (HRV) was performed to derive markers of autonomic activity using 24-hour Holter monitor recordings obtained at baseline and following three months of therapy in 35 patients with HF enrolled in a randomized double-blind placebo controlled trial of the selective AT-1 antagonist losartan. The measures of HRV were averaged over predetermined quartiles of the 24-hour period (3 AM–9 AM; 9 AM–3 PM; 3 PM–9 PM; 9 PM–3 AM) and compared between the placebo (15 patients) and losartan (20 patients) treatment groups. Significant decreases ($p < 0.05$) in parasympathetically mediated high frequency HRV were noted in the losartan treatment group as compared to placebo at all quartiles of day. Sympathetically influenced low frequency HRV showed no change compared to placebo in the quartile between 9AM and 3PM, but at all other quartiles a significant ($p < 0.05$) difference was noted with a decrease in the placebo group and no change or a small increase in the losartan treatment group. Therefore, selective AT-1 receptor blockade with losartan in this group of patients does not restore the autonomic imbalance typical of HF towards normal. These findings suggest that the previously reported autonomic response to ACEI's in HF does not result from diminished AT-1 receptor stimulation.

1096-38 Effect of Oxygen on Sleep, Cognitive Function and Sympathetic Activity in Heart Failure With Cheyne-Stokes Respiration

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Background: Cheyne-Stokes respiration (CSR) is an independent marker of mortality in heart failure (HF). Arousal in normal subjects, and CSR in awake HF patients is associated with increased sympathetic activity.

Method: 11 patients with stable heart HF and documented CSR were studied in a double blind cross-over study of 24% nocturnal O_2 *vs* Air (1 month each). Sleep quality was assessed by polysomnography. Cognitive function was assessed with standard psychometric tests. Symptoms were measured using the Epworth Sleepiness Scale, a Quality of Life questionnaire and Visual Analogue Scales. Neurohormonal activity was measured by early morning serum ANP, N-ANP, catecholamines and overnight urinary catecholamine excretion (standardized for urinary creatinine).

	Baseline	Oxygen	Air
Sleep Time (mins)	319 (38)	290 (36)	265 (44)†
Arousals/hour	9.6 (2.4)‡	5.8 (1.8)	7.5 (1.6)
Desaturation/hour	24.1 (4.1)‡	2.8 (1.3)	25.9 (4.5)†
Min SaO_2%	84.8 (0.9)‡	90.8 (1.5)	82.6 (2)‡
Apnoeas/hour	15.8 (4.5)	6.1 (2.9)	23.9 (5.2)‡
Urine Norepinephrine	8.9 (3.9)	4.1 (0.6)	8.3 (1.5)‡

† = $P < 0.05$ vs baseline. ‡ = $P < 0.05$ vs O_2

Results: 90% of apnoeas were central. O_2 significantly reduced desaturation events, apnoeas and arousals. O_2 did not improve cognitive function or daytime symptoms. 2 patients decompensated on crossing from O_2 to Air. O_2 significantly reduced urinary norepinephrine excretion. The serum neuroendocrine profile was unaffected by O_2.

Conclusion: O_2 is an effective treatment for CSR in HF, but has no effect on symptoms. The possibility that O_2 may improve survival in HF with CSR requires further investigtion.

1096-39 Short-term Hemodynamic Effects of BQ-123, a Selective Endothelin ET_A Receptor Antagonist, in Patients With Chronic Heart Failure

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Endothelin receptor antagonists are thought to have therapeutic potential in chronic heart failure (CHF). The pulmonary and systemic effects of selective ET_A receptor antagonism have yet to be described in patients with CHF. We infused BQ-123, a selective ET_A receptor antagonist, into eight CHF patients on conventional medical therapy (200 nmol/min for 1 hour). ET-1 (15 pmol/min, a dose previously shown to cause systemic vasoconstriction in CHF) was co-infused during the last 15 minutes. Hemodynamics were measured by thermodilution catheter and arterial line. Results are expressed as mean ± standard deviation.

BQ-123 infusion alone: heart rate was unchanged (73 ± 18), mean arterial pressure (86 ± 19 to 78 ± 13 mmHg, $p = 0.01$), right atrial pressure (6 ± 2 to 5 ± 2 mmHg, $p = 0.05$), mean pulmonary artery pressure (23 ± 11 to 19 ± 9 mmHg, $p < 0.01$), pulmonary wedge pressure (14 ± 8 to 11 ± 8 mmHg, $p < 0.01$) and systemic vascular resistance (1480 ± 247 to 1287 ± 194 dynes.cm/sec^5, $p < 0.01$) fell. Cardiac index rose (2.38 ± 0.46 to 2.51 ± 0.45 l/min/m^2, $p < 0.05$). The fall in PVR did not achieve statistical significance (170 ± 77 to 149 ± 41 dynes.cm/sec^5, $p = 0.2$). ET-1 co-infusion did not lead to systemic vasoconstriction as observed in previous studies.

BQ-123, a selective ET_A receptor antagonist, led to beneficial short-term hemodynamic effects in CHF patients already treated with ACE inhibitors and diuretics. Prospective clinical trials of ET_A selective antagonists in CHF are justified.

1096-40 Does Exogenous Melatonin Influence Sympathetic Hyperactivity in Heart Failure? A Placebo Controlled Clinical Trial

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Background: The prognostic significance of sympathetic hyperactivity (SH) in determining clinical severity and mortality in heart failure (HF) remains undisputed. We have previously demonstrated that nocturnal levels of Melatonin (M), a central sympatholytic hormone from pineal gland, are significantly impaired in HF and that exogenous M therapy improves sleep patterns in this group. We sought to investigate the ability of M replacement to decrease SH and restore autonomic balance in HF.

Methods: Sympathetic indices of heart rate variability [both time (RR variability) and frequency domain variables (low frequency spectral power (LFP))] were calculated from ECG and the index alpha of baroreflex sensitivity computed from the arterial blood pressure profile at rest, 60 minutes after placebo (P) or M (3 mg orally) in a double blind, randomized, placebo controlled crossover study design in HF patients with sinus rhythm (n = 10; age 54 ± 5 yrs, EF = 0.2 ± 0.02; all on ACE inhibitors and Digoxin).

Results: Compared to placebo, M acutely increased mean RR interval by 4.7% ($p = 0.01$). The low frequency spectral power percentage decreased by 11.3% ($p = 0.47$); however, the index alpha remained unchanged.

	Placebo	Melatonin	P
RR (ms)	937 ± 218	982 ± 200	0.01
LFP (%)	59.17	52.37	0.4
Index alpha	21.25	22.45	NS

Conclusion: Exogenous Melatonin acutely decreases sympathetic hyperactivity as assessed by the time domain index of RR variability in HF. Whether this short-term improvement in sympathetic hyperactivity can be sustained long-term remains to be determined.