Nocturnal Periodic Breathing Is an Independent Predictor of Cardiac Death and Multiple Hospital Admissions in Heart Failure

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Abstract

We assessed the association of periodic breathing (PB) with mortality and hospital re-admissions in a large sample of patients enrolled in the European Community study HHH (Home or Hospital in Heart failure).

A 24-hour cardiorespiratory recording was carried out in 443 clinically stable heart failure (HF) subjects (age: 60±11 years, NYHA class 2.4±0.6, LVEF 29±7%). We computed the apnoea/hypopnea index (AHI, events/hour) and the duration of PB (hours) during night-time and tested their association with total cardiac death (Cox regression) and hospitalization for worsening HF (logistic regression). All analysis were multivariate adjusting for known clinical/functional risk factors. AHI and PB duration were independent predictors of cardiac death (p<0.02 both) and of recurrent (≥ 2) hospital re-admissions (p=0.04 and 0.003 respectively).

This study confirms the independent predictive value of PB and provides evidence that PB is associated with a higher risk of multiple hospital re-admissions.

1. Introduction

Periodic breathing (PB), a respiratory disorder characterized by waxing and waning of ventilation with recurrent apneas or hypopneas, is very common during sleep in patients with heart failure (HF). A prevalence as high as 70% has been reported in recent sleep studies [1, 2]. During PB, cyclical reductions in arterial oxygen saturation and marked fluctuations in systolic and diastolic pressure and heart rate occur in synchrony with the ventilatory oscillation. Periodic hypoxemia brings about an increase in sympathetic activity which may contribute to the worsening of HF. The relationship between PB and mortality has been assessed in some studies [1, 2, 3], but the sample size was small (n<70), results are controversial and the relationship with hospital readmissions was not explored. The aim of this study was to assess the prognostic value of PB in a large population of mild-to-moderate HF patients and to investigate the relationship between breathing disorders and hospital readmissions. We tested both hypotheses in a large sample of subjects enrolled in the multi-center multi-country trial HHH (Home or Hospital in Heart failure), a European Community-supported study (contract n° QLG4-CT-2001-02424) aimed at i) comparing three different strategies of home telemonitoring against usual clinical practice and ii) assessing the prevalence and clinical impact of breathing disorders [4].

2. Methods

2.1. Subjects and protocol

Inclusion criteria of patients enrolled in the HHH trial (N=465) were: NYHA class II-III, older than 18 years, on optimized medical treatment, with LVEF ≤40 % and with at least one episode of decompensation in the previous 12 months. Three countries (UK, Italy and Poland) and 11 cardiological departments (5 in Italy, 3 in UK and 3 in Poland) were involved in the study. Follow-up was 12 months.

An in-hospital baseline cardiorespiratory recording was performed in 443 patients at enrolment in the study.

To record cardiorespiratory signals we used a Holter-style 24-hour solid-state portable device (Report-24, FM, Monza, Italy). This recorder, specifically designed for the HHH study, is suitable to be easily handled by the patient at home since only 3 ECG electrodes are used to pick-up both the ECG signal (single lead) and the respiratory signal (bio-impedance technique), while a small plastic box houses the body movement and position sensors. Sampling frequency was 250 Hz for ECG, 10 Hz for respiration and 1 Hz for the movement and position signals.

Respiratory recordings were analyzed using a dedicated software package developed for the study (figure 1). This software processes the recorded respiratory signal to filter out non-respiratory frequency components and remove sudden changes in signal level or occasional spikes. An instantaneous tidal volume signal is derived and the respiratory pattern is classified in each consecutive 60 s segment. The classification includes i) "phasic activity", a breathing activity characterized by a regular phasic oscillation of respiration with or without occasional apneas/hypopneas, and ii) "periodic breathing" (PB), defined as a sustained oscillation (≥ 3 min, modulation depth ≥ 25%,) of ventilatory amplitude characterized by recurring cycles of hyperventilation and hypopnea or apnea. Respiratory segments with poor signal quality were labeled as "not classified" and were excluded from analysis.

For the detection and estimation of hypopneas and apneas, we followed standard criteria used in polysomnography. Accordingly, an hypopnea (apnea) event was defined as a decrease of the instantaneous tidal volume below 50% (10%) of the running tidal volume for more than 10 sec.

The analyst could edit the output of the automatic procedure in order to correct misclassifications and adjust the duration of respiratory events. At the end of this interactive phase, a set of quantitative indexes of night-time breathing disorders was automatically provided by the software, including the apnea-hypopnea index (AHI, number of apneas and hypopneas per hour of recording) and the duration of PB (hours). Night-time was defined as the time while the patient was lying in bed, as indicated by the body position signal, starting from 10.00 p.m. till 8.00 a.m.

By convention, a respiratory recording was considered eligible for the study if the overall duration of good quality signal (i.e., all segments classified as PB or phasic activity) during night-time was ≥ 2.5 hours. Only data from eligible recordings was entered in the study database.

2.2. Statistical analysis

The association between PB and total cardiac death was assessed by Cox regression analysis, while the association between PB and hospital readmissions for worsening HF was assessed by logistic regression. To assess whether the presence of nocturnal breathing disorders may add independent prognostic information to known clinical/functional risk factors, we identified most predictive variables among age, NYHA class, left ventricular ejection fraction (LVEF), end diastolic volume (LVEDV), etiology, systolic pressure, resting heart rate and sodium blood level, and used them as adjusting factors in a multivariate model.

3. Results

Descriptive statistics of demographic, clinical and functional data of the subjects enrolled in the study are reported in table 1.

The recordings eligible for the study were 397, and the duration of good quality signal during night-time was 6.2±1.6 hours.

Table 1. Demographic, clinical and functional characteristics of studied patients (N=397).

Demographic	
Age, years	60 ± 11
Male, %	87
Clinical	
NYHA class	2.4 ± 0.6
SAP, mmHg	117 ± 17
HR, bpm	74± 15
Etiology	
Ischemic, %	42
Idiopatic, %	47
Other, %	11
Ecocardiographic	
LVEF, %	29 ± 7
LVEDV, ml	66 ± 10

During the 1-year follow-up, 6% of the patients experienced cardiac death and 10% and 7% had respectively 1 or ≥ 2 hospital re-admissions for HF.

Both AHI and PB duration were independent predictors of cardiac death with adjusted hazard ratios (95% confidence interval), respectively, 1.04 (1.01-1.07), p=0.01, and 1.21 (1.03-1.42), p=0.019. Global results of the Cox regression analysis are reported in Tables 2 and 3 for AHI and PB duration respectively.

Figure 2 and 3 show the survival curves according to, respectively, an AHI < or ≥ 15 and according to a night-time PB duration < or ≥ 1 hour.

AHI and PB duration were both significantly and independently associated with the occurrence of ≥ 2 hospital re-admissions, with the following odds ratios (95% confidence interval): 1.03 (1.01-1.07), p=0.04, and 1.30 (1.10-1.60), p=0.005. Global results of the logistic regression analysis are reported in Tables 4 and 5 for AHI and PB duration respectively.

Table 2. Results of Cox regression analysis for the association between AHI and cardiac death. HR: hazard ratios. CI: confidence interval.

	p-value	HR	95% CI
AHI	0.01	1.04	1.01-1.07
LVDV	0.02	1.05	1.01-1.10
NYHA (≥3)	0.02	2.87	1.17-7.09
resting heart rate	0.002	1.04	1.02-1.07
etiology ischemic	0.01	3.25	1.31-8.11

Table 3. Results of Cox regression analysis for the association between PB duration and cardiac death. HR: hazard ratios. CI: confidence interval.

	p-value	HR	95% CI
PB duration	0.02	1.21	1.03-1.42
LVDV	0.02	1.05	1.01-1.10
NYHA (≥3)	0.03	2.74	1.11-6.77
resting heart rate	0.003	1.04	1.01-1.06
etiology ischemic	0.02	2.97	1.21-7.28

Table 4. Results of the logistic regression analysis for the association between AHI and ≥ 2 hospital readmissions. OR: odds ratio. CI: confidence interval.

	p-value	OR	95% CI
AHI	0.04	1.03	1.01-1.07
Age	0.04	0.96	0.92-0.99
NYHA (≥3)	0.0002	7.04	2.56-19.3
etiology ischemic	0.03	3.02	1.14-7.98

Table 5. Results of the logistic regression analysis for the association between night-time PB duration and ≥ 2 hospital readmissions. OR: odds ratio. CI: confidence interval.

	p-value	OR	95% CI
PB duration	0.003	1.31	1.09-1.58
Age	0.03	0.95	0.91-0.99
NYHA (≥3)	0.0003	6.55	2.37-18.1
etiology ischemic	0.02	3.23	1.20-8.67

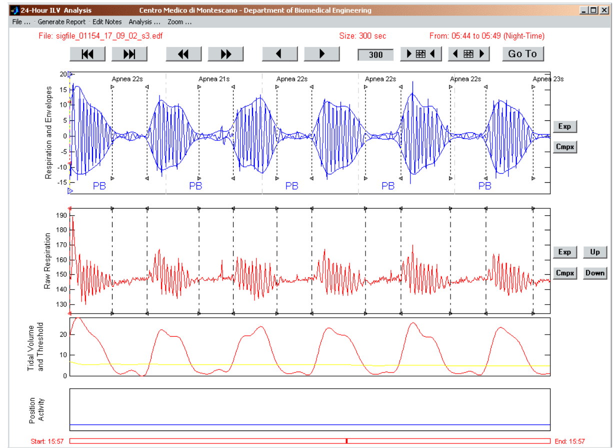

Figure 1. Representative printout of the analysis package: the respiratory signal analysis module.

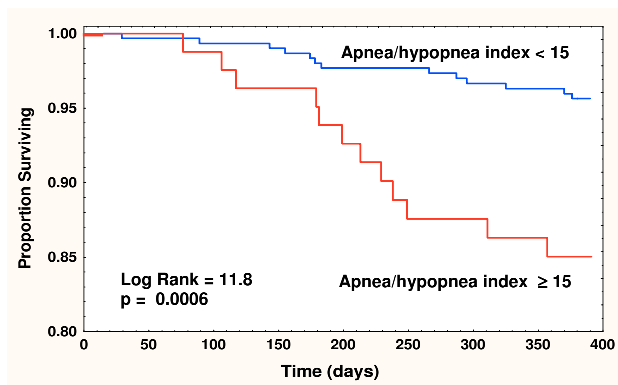

Figure 2. Survival curves according to the AHI (events/hour).

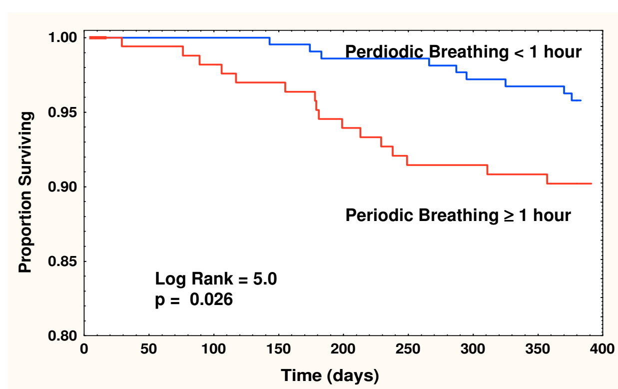

Figure 3. Survival curves according to nocturnal PB duration.

4. Discussion and conclusions

This study demonstrates that in mild-to-moderate HF patients nocturnal breathing disorders, quantified by the apnea/hypopnea index and by the duration of periodic breathing, have a prognostic value independent of known major clinical and functional predictors: age, symptom severity, left ventricular ejection fraction, diastolic volume, etiology, systolic pressure, resting heart rate and sodium blood level.

These results obtained on a large sample of HF patients confirm those obtained in previous studies carried out in small groups of subjects (N<70).

A totally new and clinically relevant finding of our investigation is that nocturnal breathing disorders are significantly and independently associated with a higher risk of multiple hospital re-admissions. Considering that HF accounts for 1-2 % of health-care expenditure and 75% of this is due to hospital readmissions [5], our findings suggest that new disease management models based on early detection and treatment of respiratory abnormalities could be effective in reducing the economic burden associated with this pathology.

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