Pathophysiological and clinical relevance of simplified monitoring of nocturnal breathing disorders in heart failure patients

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Aims

Nocturnal breathing disorders in the form of periodic breathing (PB) are very common in heart failure (HF) patients. There is an increasing interest in simple and affordable tools to screen patients and monitor these disorders at home on a long-term basis. We aimed to assess the pathophysiological and clinical relevance of a simplified method for monitoring of PB suitable to be self-managed by the patient at home.

Methods and results

A night-time respiratory recording was performed in 397 optimally treated HF patients (age 60 ± 11 years, NYHA class 2.4 ± 0.6 , left ventricular ejection fraction $29 \pm 7\%$) and the duration of PB (PB_{Dur}) automatically computed. Patients were followed-up for 1 year and the prognostic value of PB_{Dur} evaluated. In 45 patients, we assessed the association between PB_{Dur} and severity of oxygen desaturations (number of desaturations $>3\%$). Twenty six of the 397 patients died of cardiac causes. A PB_{Dur} ≥ 2 h was significantly associated with an increased risk of cardiac death after adjustment for major clinical predictors [hazard ratio (95% CI): 3.5 (1.6–7.9), $P = 0.002$]. The correlation between PB_{Dur} and severity of desaturations was 0.94 ($P < 0.0001$).

Conclusion

Relevant pathophysiological and clinical information can be obtained from simplified monitoring of breathing disorders managed by the patient. These results provide new perspectives in the investigation of the clinical impact of abnormal breathing in HF patients.

Keywords

Heart failure • Sleep apnoea • Periodic breathing • Monitoring • Self-management • Prognosis

Introduction

Nocturnal breathing disorders are very common in heart failure (HF) patients^{1,2} and are associated with a higher morbidity and mortality.^{3–6} Recent preliminary studies suggest that treatment of these disorders can improve cardiac function and survival, particularly using ventilatory support devices.^{6–8} Therefore, there is an increasing interest in simple, widely available, and affordable tools to screen patients and monitor breathing disorders at home on a long-term basis. Ideally, these monitoring devices should also include the recording of ECG activity and should be

suitable to be used by the patients at home without the need for external specialized support (nurse or technician) or periodic referrals to the hospital/outpatient clinic. It has been recognized that patient self-management of home monitoring equipment is crucial both for reducing costs and achieving good compliance in chronically ill subjects.⁹

Within the context of the European Community trial HHH (Home or Hospital in Heart Failure: QLGA-CT-2001-02424), we have developed a home telemonitoring system for intermittent monitoring of ECG and respiration, which can be totally self-managed by the patient.¹⁰ To meet the requirements of extreme

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simplicity, low cost, and low intrusiveness, the respiratory part of the monitor had to be greatly simplified compared with standard four-channel sleep apnoea monitors.¹¹ Accordingly, we used a device that picked-up both the ECG and respiratory activity using three standard ECG electrodes.¹⁰ From the respiratory signal, an uncalibrated continuous tidal volume signal was derived,¹² and the detection and assessment of breathing disorders was based on the analysis of the oscillatory pattern of this signal.¹² Indeed, irrespective of its origin (obstructive or central), the most distinctive feature of abnormal breathing in HF patients is the cyclic waxing and waning of tidal volume,^{13,14} a pattern that has commonly been referred to as periodic breathing (PB).¹⁵ This observation has raised the possibility that in these patients, obstructive and central sleep apnoea (CSA) are parts of a spectrum of PB that, depending on the circumstances, may take either of the two forms as the dominant mechanism.^{7,13,14}

It has been shown that during PB, ventilatory oscillations are accompanied by prominent synchronous oscillations in oxygen saturation, sympathetic nerve activity, and cardiovascular and haemodynamic parameters, all of which are thought to contribute to the deleterious effects of breathing disorders in HF patients.^{16–19} We therefore reasoned that the duration of PB during the night might provide relevant information on the clinical impact of breathing disorders in these patients: the longer the duration, the higher the likelihood of significant worsening effects on cardiovascular function.

A major problem in using the duration of tidal volume oscillations as the key information for assessing breathing disorders is that it is not possible to predict in a given subject how changes in tidal volume translate into changes in oxygen saturation, leaving this crucial pathophysiological effect of PB largely conjectural. Indeed, on the one hand, an oscillatory tidal volume does not necessarily translate into *clinically significant* desaturations, and, on the other hand, the magnitude of these oscillations may change during the recording period.

The purpose of this study was to explore the possibility of obtaining relevant pathophysiological and clinical information, using a simplified method for monitoring of nocturnal breathing disorders based on a device suitable for self-management and on the measurement of PB duration. Specifically, we investigated whether: (i) the duration of PB correlates with the severity of concomitant oxygen desaturations, and (ii) a longer duration of PB is associated with an increased risk of cardiac death. A validation of the monitoring device was included in the study. For comparison, breathing disorders were also assessed by the apnoea–hypopnoea index (AHI), which is the standard measurement used in clinical studies.^{1–6}

Methods

Subjects and protocol

Desaturation study

To assess the relationship between duration of PB and severity of concomitant oxygen desaturations, we used a four-channel portable sleep apnoea monitor (Embletta, Embla, Broomfield, CO, USA), incorporating the recording of O₂ saturation by a finger pulse oximeter. All sensors of this device are compliant with current AASM guidelines

for the detection of respiratory events.²⁰ The investigation was carried out in 47 consecutive HF patients from one of the enrolling hospitals of the HHH study (Montescano, Italy). Each patient underwent a nocturnal recording between 11:00 p.m. and 6:00 a.m.

To assess the accuracy of the simplified respiratory monitor used in the prognostic study (Report-24, FM, Monza, Italy), all patients participating in the desaturation study had a simultaneous recording with this device. The Report-24 uses three standard ECG electrodes to provide a respiratory signal (bio-impedance technique) and an ECG signal, and allows the recording of body movement and position.¹⁰

Prognostic study

Four hundred and forty-three stable, optimally treated HF patients participated in the prognostic study. Inclusion criteria were: (i) age: >18 and <85 years, (ii) NYHA class: II–IV, (iii) left ventricular ejection fraction (LVEF): ≤40%, (iv) ≥1 hospital admissions for HF or decompensation in the previous 12 months, (v) abnormal echo diastolic pattern. Exclusions were: (i) myocardial infarction, cardioverter–defibrillator implantation or revascularization in the previous 6 months, (ii) angina or ischaemia requiring revascularization, (iii) implanted ventricular or atrial pace-maker, except DDD pacemakers with good sinus activity (as we also wished to assess heart rate variability), (iv) severe survival-limiting pathology. Standard clinical and laboratory examinations were obtained at baseline, together with a 24 h cardiopulmonary recording using the Report-24. All patients were followed-up for 1 year.

Measurement of breathing disorder indexes using the Embletta device

Embletta tracings were analysed using dedicated interactive software that incorporated the computation of an uncalibrated tidal volume signal, from which a continuous signal was derived (Figure 1). Respiratory segments with poor signal quality were discarded.

Periodic breathing was defined as a sustained (≥3 min) oscillation of tidal volume with >25% reduction between peak and trough values. This threshold has been successfully used in a previous investigation on daytime PB.²¹ Detection of PB was automatic;¹² however, a final visual check was also carried out. Finally, the total duration of PB during the night was computed.

Central apnoeas were defined as a >90% drop in oronasal airflow lasting ≥10 s in association with absent respiratory effort. Obstructive apnoeas were defined as the same drop in oronasal airflow in the presence of rib cage and abdominal excursions. Mixed apnoeas were classified as obstructive events. Hypopnoeas were defined as a >50% reduction in tidal volume or oronasal airflow lasting ≥10 s, associated with a >3% drop in oxygen saturation. No distinction was made between central and obstructive hypopnoeas as the differentiation was often not clear-cut. The AHI was computed as the number of apnoeas and hypopnoeas per hour. The patients with an AHI ≥5/h were classified into CSA if >50% of the apnoeas were central, and into obstructive sleep apnoea (OSA) if ≥50% were obstructive.

Measurement of breathing disorder indexes using the Report-24 device

Report-24 tracings were analysed using the same software package used for the Embletta. After digital filtering of the raw respiratory signal, a continuous uncalibrated tidal volume signal was derived (Figure 2).¹² Apnoeas and hypopnoeas were defined as >90% and >50% reduction in tidal volume lasting ≥10 s, respectively. Finally, the AHI and the total duration of PB were computed (same criteria as for the Embletta).

Figure 1 Representative example of respiratory signals recorded by the Embletta monitor during an episode of periodic breathing. From top to bottom: oronasal airflow, thorax and abdomen movements, O₂ saturation (SpO₂). The two lower signals, i.e. the sum of thoraco-abdominal movements and the continuous tidal volume signal, were obtained by dedicated software.

Figure 2 Representative example of the respiratory signal recorded by the Report-24 recorder during an episode of periodic breathing. The lower tracing shows the derived tidal volume signal.

In the validation study, Report-24 recordings were analysed blindly by the same scorer ≥ 1 month after the analysis of Embletta tracings.

In the prognostic study, night-time was visually identified as the time in bed, based on the body position sensor, between 10:00 p.m. and 8:00 a.m. Only recordings with ≥ 2.5 h of analysable signal were considered eligible for the study.¹⁰

Statistical analysis

Relationship between duration of periodic breathing and severity of desaturations

This analysis was carried out on Embletta tracings. The severity of nocturnal desaturations was measured as the total number of oxygen desaturations $> 3\%$. The relationship between this index and the duration of PB was assessed by Pearson's correlation coefficient.

Validation of the Report-24

The correlation between Report-24 and Embletta measurements was evaluated by Pearson's correlation coefficient. The agreement was assessed by computing the bias and limits of agreement.²²

Prognostic value of periodic breathing

The endpoint of the survival analysis was total cardiac death. Patients who died of non-cardiac causes and those who underwent elective heart transplantation were considered censored observations. All endpoints were adjudicated by an independent, blinded Endpoint Classification Committee.

To gain a first insight into the relationship between PB duration and outcome, PB was categorized according to quartiles, and Kaplan–Meier survival curves were estimated in the corresponding four subgroups and compared by the log-rank test.

The association between PB duration and the risk of death was assessed by Cox analysis. To determine whether its predictive value was additive with respect to known risk factors, we first developed a prognostic model considering as potential predictors (see Table 1): sex, age, ischaemic cardiomyopathy, NYHA class (III–IV vs. II), LVEF, left-ventricular end-diastolic diameter (LVEDD), systolic and diastolic pressure, heart rate, atrial fibrillation (AF), blood urea nitrogen, and sodium. Less predictive variables were eliminated by a backward elimination procedure at the 0.1 significance level. Then, PB duration was entered into the model and its statistical significance assessed. The assumption of proportional hazards was checked by weighted Schoenfeld residual plots.

To assess the validity of this final model, we used the bootstrap method.²³ This is a technique of 'internal validation' that assesses how likely it is that a prognostic model will be confirmed in a new similar sample of patients. Briefly, 500 bootstrap samples of size n (n , number of patients of the study) were selected at random with replacement from the study dataset, and were treated as independent samples from the same population. We then determined the proportion of samples in which PB duration added significantly ($P < 0.05$) to the clinical variables.

In order to compare the prognostic power of PB duration with that of the AHI, the overall procedure of model building and validation was repeated for this measurement.

Other tests

Group comparisons for continuous measures were carried out by one-way ANOVA or Mann–Whitney U test. The Chi-square test was used for categorical variables. All tests were two-tailed and a $P < 0.05$ was considered statistically significant.

Table 1 Patients' demographic and clinical characteristics

	Prognostic study	Desaturation study
<i>n</i>	397	45
Age (years)	60 $\pm$ 11	58 $\pm$ 8
Male (%)	86	100
NYHA class	2.4 $\pm$ 0.6	2.3 $\pm$ 0.5
Aetiology (%)		
Ischaemic	56	46
Idiopathic	31	45
Other	13	9
BMI (Kg/m ²)	26.8 $\pm$ 4.5	27.6 $\pm$ 4.6
Heart rate (b.p.m.)	74 $\pm$ 14	71 $\pm$ 13
SBP (mmHg)	116 $\pm$ 17	122 $\pm$ 17
DBP (mmHg)	73 $\pm$ 11	79 $\pm$ 9
LVEF (%)	29 $\pm$ 7	31 $\pm$ 9
LVEDD (mm)	66 $\pm$ 9	70 $\pm$ 11
BUN (mg/dL)	48 $\pm$ 22	54 $\pm$ 22
Sodium (mEq/L)	140 $\pm$ 4	139 $\pm$ 3
Creatinine (mg/dL)	1.21 $\pm$ 0.34	1.22 $\pm$ 0.29
Potassium (mEq/L)	4.43 $\pm$ 0.45	4.23 $\pm$ 0.46
ACEI/ARB (%)	93	91
Diuretics (%)	87	91
Beta-blockers (%)	85	89
Digoxin (%)	31	27
Antialdosterone (%)	57	66

Continuous variables are expressed as mean $\pm$ SD.

SBP, systolic blood pressure; DBP, diastolic blood pressure; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; BUN, blood urea nitrogen; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers.

Results

Periodic breathing and oxygen desaturations using the Embletta device

Two of the 47 subjects from the desaturation study were excluded from the analysis due to poor signal quality. Demographic and clinical characteristics of the remaining subjects are given in Table 1.

The mean analysed time in Embletta tracings (i.e. the portion of the recording having good signal quality) was 383 $\pm$ 29 min, accounting for 92 $\pm$ 7% of the total recording duration (Table 2). Twenty-five subjects (56%) were classified as CSA and five subjects (11%) as OSA.

As shown by the scatterplot of Figure 3, there was a close linear relationship between the duration of PB and the number of oxygen desaturations $> 3\%$ ($r = 0.94$, $P < 0.0001$).

Report-24 vs. Embletta measurements

Descriptive results for the comparison between Report-24 and Embletta are reported in Table 2. The mean analysed time in the Report-24 was about 1 h less than that in the Embletta, and accounted for 77 $\pm$ 14% of total recording duration. Despite this

Table 2 Descriptive statistics of breathing disorder indices in the desaturation study

	Mean ± SD	Lower quartile	Median	Upper quartile	Min-Max
Analysed time Em (min)	383 ± 29	363	390	408	303–418
Analysed time Re (min)	323 ± 58*	286	330	370	184–408
PB duration Em (min)	126 ± 108	45	96	196	0–411
PB duration Re (min)	108 ± 102**	29	90	145	0–408
AHI Em (events/h)	17.0 ± 15	6.0	12.4	23.0	2.1–70.2
AHI Re (events/h)	17.2 ± 15	5.3	12.3	24.7	1.0–70.9

Em, Embletta recorder; Re, Report-24 recorder; AHI, apnoea–hypopnoea index (number of apnoeas and hypopnoeas/h).

* $P < 0.0001$ vs. Embletta.

** $P = 0.004$ vs. Embletta.

Figure 3 Relationship between number of oxygen desaturations >3% and periodic breathing (PB) duration. Both measurements were derived from the Embletta recorder. Data are from a subgroup of 45 HF patients from one of the enrolling centres of the study.

difference, the Report-24 underestimated PB duration by only –18 min ($P = 0.004$).

Report-24 and Embletta were highly correlated both in the measurement of PB duration (Figure 4A, $r = 0.93$, $P < 0.0001$) and in the measurement of the AHI (0.95 , $P < 0.0001$). The limits of agreement were, respectively, –94 min and +58 min, and –8.4 events/h and +8.4 events/h.

Periodic breathing and oxygen desaturations using the Report-24 device

There was also a close linear relationship between the duration of PB measured by the Report-24 and the number of desaturation episodes >3% measured by the Embletta (Figure 4B, $r = 0.94$, $P < 0.0001$).

Prognostic value of periodic breathing duration

Baseline respiratory recordings were eligible in 397/443 (90%) patients. Their demographic and clinical characteristics are given in Table 1. There were no significant differences between these

Figure 4 (A) Relationship between the measurements of periodic breathing (PB) duration simultaneously obtained from Report-24 and Embletta recorders. (B) Relationship between number of oxygen desaturations >3% measured by the Embletta and duration of PB measured by the Report-24. Data are from a subgroup of 45 HF patients from one of the enrolling centres of the study.

patients and the patients excluded from the analysis, except for BMI (26.8 ± 4.5 in the analysed patients vs. 28.6 ± 5.6 in those excluded, $P = 0.01$) and diastolic arterial pressure (73 ± 11 vs. 77 ± 13 mmHg, respectively, $P = 0.015$).

The mean duration of night-time was 503 ± 74 min, while the corresponding analysed time was 372 ± 99 min. Periodic breathing duration was 90 ± 108 min (range 0–550 min). The lower quartile,

Figure 5 Kaplan–Meier survival curves for patients stratified according to: (A) quartiles of periodic breathing (PB) duration; (B) PB duration ≥ 120 min vs. the rest of the sample. Suffix q1 denotes patients with a PB value between the minimum and the lower quartile, q2 those between the lower quartile and the median, q3 those between the median and the upper quartile, and q4 those between the upper quartile and the maximum. Data are from the cohort of 397 patients included in the prognostic study.

median, and upper quartile were 15 min, 51 min, and 129 min, respectively.

During the 1 year follow-up, 26 patients (7%) died of cardiac causes, 4 underwent elective heart transplantation, and 17 patients dropped out from the study. In the excluded patients, there were three cardiac deaths (7%, $P=0.99$ vs. analysed patients) and one subject underwent heart transplantation.

Kaplan–Meier survival curves according to quartiles of PB duration are shown in Figure 5A. The survival experience of the patients having a PB duration greater than or equal to upper quartile (129 min) was markedly and significantly worse than the other groups with shorter PB duration, whose mortality appeared almost super impossible. This suggested a clinically meaningful binary coding of the variable into ≥ 120 vs. < 120 min, i.e. 2 h. Corresponding Kaplan–Meier curves are shown in Figure 5B. The same behaviour was also observed for the AHI, which was dichotomized according to its upper quartile of 13 events/h.

Among clinical variables, ischaemic cardiomyopathy, NYHA class, LVEDD, and heart rate were identified as those with the highest joint predictive value ($P=0.027$, $P=0.011$, $P=0.011$, and $P=0.002$, respectively).

Table 3 Cox regression results on the predictive value of periodic breathing duration adjusting for clinical variables

	Wald χ^2	P-value	HR (95% CI)
PB duration (per 10 min increase)	4.5	0.034	1.03 (1.002–1.057)
Ischaemic cardiomyopathy	5.8	0.016	3.0 (1.2–7.1)
NYHA class $\geq$ III	5.4	0.021	2.9 (1.2–7.1)
LVEDD (per 5 mm increase)	4.8	0.028	1.3 (1.03–1.57)
Heart rate (per 10 b.p.m. increase)	10.4	0.001	1.6 (1.2–2.0)

PB, periodic breathing; HR, hazard ratio; CI, confidence interval.

Taken alone, PB duration showed a highly significant association with the risk of cardiac death with a hazard ratio (expressed per 10 min increase) of 1.04 (95% CI: 1.01–1.07, $P=0.004$). Using PB duration dichotomized according to ≥ 120 vs. < 120 min, the hazard ratio was 3.6 (95% CI: 1.7–7.8, $P=0.001$). Corresponding sensitivity, specificity, positive, and negative predictive value were 54%, 76%, 13%, and 96%, respectively. For the sake of comparison, the same figures for NYHA class (III–IV vs. II) were 73%, 63%, 12%, and 97%.

When PB duration was entered into the clinical prognostic model, a significant association with the risk of cardiac death was maintained, indicating additive predictive information (Table 3). Using dichotomous PB duration, the covariate-adjusted hazard ratio (95% CI) was: 3.5 (1.6–7.9) ($P=0.002$). The validity of these results was strongly supported by the bootstrap procedure, as PB duration significantly added to clinical variables in 86% of the 500 bootstrap models.

The hazard ratio for an AHI ≥ 13 events/h (upper quartile) was 3.2 (95% CI: 1.5–6.9, $P=0.003$), with sensitivity, specificity, positive and negative predictive values of 50%, 77%, 13%, and 96%, respectively. After adjustment for clinical predictors, the hazard ratio was 2.7 (95% CI: 1.2–6.0, $P=0.014$). Apnoea–hypopnoea index significantly added to clinical variables in 72% of bootstrap models.

Breathing disorders and atrial fibrillation

Baseline ECG showed AF in 67 (17%) patients. Thirty-nine per cent of these patients had a PB duration ≥ 120 min, whereas the same percentage decreased to 24% in patients without AF ($P=0.01$), thus confirming that AF represents a risk factor for breathing disorders in HF patients.²⁴ Using AHI ≥ 13 events/h as indicator of severe breathing disorders, the percentages were 27% in patients with AF and 25% in patients without ($P=0.73$).

Discussion

In this study, we have assessed the pathophysiological and clinical relevance of simplified monitoring of nocturnal breathing disorders using a device suitable to be self-managed by patients at home, in a

large cohort of stable, optimally treated HF patients. The detection and measurement of breathing abnormalities was based on the analysis of tidal volume oscillations, these being the most distinctive feature of such abnormalities. We have shown that the duration of PB during the night has a strong linear association with the severity of concomitant oxygen desaturations, and when it exceeds 2 h, the adjusted risk of cardiac death increases about 3-fold.

Advantages and limitations of the simplified monitoring device

The standard assessment of breathing disorders requires the recording of chest and abdominal movements, oronasal air flow, and oxygen saturation,²⁰ and, with the current state-of-the-art technology, a technician is required to instrument the patient. Moreover, the recording of an ECG signal is also required, as cardiac arrhythmias often represent an undesirable effect of intermittent apnoeas.^{16,17} This setting is common to both sleep laboratory systems and portable sleep apnoea monitors.¹¹ Thanks to the simultaneous recording of thoracoabdominal movements and oronasal airflow, it is possible to distinguish between obstructive and central respiratory events, which is a necessary prerequisite for treatment planning. Pulse oximetry, on the other hand, is required both to identify clinically relevant hypopnoeas and to quantify the severity of desaturations. Hence, no matter the technological solution one might choose to allow easy self-management of the monitoring device by the patient at home, the recording of respiratory activity has to be simplified, and as a consequence, discrimination between obstructive and central events will no longer be possible. These simplified devices, including the one used in this study, can therefore be used only as 'detectors' of respiratory abnormalities and a further diagnostic assessment using standard polysomnography is required in patients with severe breathing disorders to identify the underlying mechanism and define the optimal therapeutic strategy.⁷

Portable overnight oximetry is a simple, currently available, and clinically useful screening tool for breathing disorders,²⁵ which is potentially suitable for long-term home monitoring on a self-managed basis. Although this device was considered as a possible option at study design, theoretical and practical considerations led us to choose the monitoring of tidal volume as the best solution. Indeed, tidal volume fluctuations represent the primary manifestation, capture the most distinctive feature, and are the main determinant of pathophysiological effects of abnormal breathing in HF patients. Oxygen saturation fluctuations are just one of these effects. Moreover, there are still many facets of tidal volume oscillations, such as for instance, the relationship between hyperpnoea and apnoea duration and the changes in the cycle length during the night, which are thought to reflect the haemodynamic status of the patient and may therefore provide relevant information on the evolution of the disease.¹⁴

From a practical point of view, the system we used in our study allowed us to carry out cardiorespiratory monitoring using the same sensors that are commonly used to monitor a single-lead ECG. Any other technical solution would have required separate sensors for the respiratory and cardiac part of the monitoring system, thus increasing its complexity. Moreover, the intrusiveness

of our system, a crucial factor for the success of home-based systems in chronically ill patients, was lower than a conventional Holter recording or even oximetry, the latter requiring a sensor to be positioned on one of the patient's fingers. Indeed, over 1 year, patient compliance with our system was excellent, as 92% of home recordings were successfully carried out by the patients and 87% of analysed recordings were eligible for the study.¹⁰

Periodic breathing duration and severity of oxygen desaturations

Quantification of breathing disorders has traditionally been based on the AHI.^{1–6} This is a technically demanding measure, requiring the identification of each apnoeic or hypopnoeic event and precise measurement of its duration.

In the present study, quantification of breathing disorders was based on a much simpler measurement, the duration of PB. Besides its intuitive appeal, an important advantage of this measurement is that it allows a drastic reduction of scoring time compared with the AHI, since tidal volume oscillations can be easily and reliably detected automatically.¹² Yet, since oxygen saturation is not taken into account, it is not possible to confidently assume on the basis of theoretical considerations or previous investigations that the severity of oxygen desaturations increases proportionally with the duration of PB, thus a crucial piece of information on the pathophysiological effects of ventilatory oscillations is missing. We addressed this important point in the desaturation study and found that PB duration and severity of desaturation are highly correlated, thus clearly indicating a proportional relationship between the two.

Accuracy of Report-24 measurements

The analysed time by the Report-24 was shorter when compared with the standard Embletta recorder, which simply reflects a greater incidence of motion artefacts and signal distortion. This, however, caused only a 14% average underestimation of PB duration. The correlation between the two measurements was very high, suggesting that patients with long lasting PB are likely to be reliably identified by the much simpler Report-24. Limits of agreement, however, were relatively wide, partly reflecting the measurement error of both devices.

No bias was found between the two devices in the measurement of the AHI, which is likely due to the fact that this is a normalized index and therefore is less influenced by differences in the analysed time. The two measurements were also very well correlated and in good agreement.

Prognostic relevance of periodic breathing duration

We found that in those patients in whom PB duration was ≥ 2 h, the 1 year risk of cardiac death increased about 4-fold. In a prognostic multivariate model, selecting the most important predictors from several candidate variables that are routinely measured in the clinical management of these patients, PB duration remained highly significant, with a hazard ratio of 3.5. The independent predictive value of this variable was not due to the categorization used, as it did not change using the original continuous measurement

(see Table 3). These results support the hypothesis that PB exerts its deleterious effect on prognosis only when it lasts for a long time during the night. Since a long-lasting PB is associated with a greater severity of oxygen desaturations, our results support the notion that the adverse impact of PB on prognosis is, at least in part, mediated by the excitatory effects of cyclic chemoreceptor stimulation.

Using the AHI as a prognostic marker, a lower adjusted hazard ratio was observed. We conservatively interpret this result as suggesting that the prognostic information of PB duration is comparable to that provided by the AHI.

We measured breathing disorders while the HF patients were in bed, independently of whether they were actually asleep, on the grounds that, when resting supine, PB can also develop when patients are awake.^{10,21} The same approach was followed in the well known prognostic study from Lanfranchi *et al.*,³ as well as in more recent investigations.^{4,26} As a matter of fact, there are no studies showing that breathing disorder indexes computed over the strict sleep time are better predictors of the outcome than indexes computed over the total recording time. Conversely, one study using sleep time failed to show an association between breathing disorders and mortality.²⁷

Limitations of the study

In summary, the major limitations of the Report-24 device are its high sensitivity to patient's movements (which reduces the total analysed time) and its inability to discriminate between central and obstructive respiratory events. We look forward to seeing new portable devices capable of providing the same diagnostic information as current four-channel monitors but which can be managed by patients at home over the long-term, in the near future.

Conclusion

In this study, we have explored and demonstrated the pathophysiological and clinical relevance of monitoring nocturnal breathing disorders in HF patients using a simplified cardiorespiratory recorder specifically designed for self-managed long-term home telemonitoring. Assessment of nocturnal breathing disorders was based on the duration of ventilatory oscillations, a measurement that can be easily obtained through automatic analysis of the respiratory signal. These results provide a new perspective in the investigation of the clinical impact of breathing abnormalities in these patients, as early detection and monitoring of the evolution of these abnormalities might provide important information on their role in the progression of the disease, including the occurrence of clinical instability and haemodynamic deterioration. This study does not intend to promote any specific monitoring device or technology (which are indeed subject to fast evolution), but to highlight the importance and feasibility of new, simpler approaches for monitoring and assessing breathing disorders in HF patients, which may complement and integrate current standard systems.

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References

- Oldenburg O, Lamp B, Faber L, Teschler H, Horstkotte D, Topfer V. Sleep-disordered breathing in patients with symptomatic heart failure: a contemporary study of prevalence in and characteristics of 700 patients. *Eur J Heart Fail* 2007;**9**: 251–257.
- Schulz R, Blau A, Börgel J, Duchna HW, Fietze I, Koper I, Prenzel R, Schädlich S, Schmitt J, Tasci S, Andreas S, working group Kreislauf und Schlaf of the German Sleep Society (DGSM). Sleep apnoea in heart failure. *Eur Respir J* 2007;**29**:1201–1205.
- Lanfranchi P, Braghiroli A, Bosimini E, Mazzuero G, Colombo R, Donner CF, Giannuzzi P. Prognostic value of nocturnal Cheyne-Stokes respiration in chronic heart failure patients. *Circulation* 1999;**99**:1435–1440.
- Corrà U, Pistono M, Mezzani A, Braghiroli A, Giordano A, Lanfranchi P, Bosimini E, Gnemmi M, Giannuzzi P. Sleep and exertional periodic breathing in chronic heart failure: prognostic importance and interdependence. *Circulation* 2006;**113**:44–50.
- Javaheri S, Shukla R, Zeigler H, Wexler L. Central sleep apnea, right ventricular dysfunction, and low diastolic blood pressure are predictors of mortality in systolic heart failure. *J Am Coll Cardiol* 2007;**49**:2028–2034.
- Wang H, Parker JD, Newton GE, Floras JS, Mak S, Chiu KL, Ruttanaumpawan P, Tomlinson G, Bradley TD. Influence of obstructive sleep apnea on mortality in patients with heart failure. *J Am Coll Cardiol* 2007;**49**:1625–1631.
- Pepin JL, Chouri-Pontarollo N, Tamisier R, Levy P. Cheyne-Stokes respiration with central sleep apnoea in chronic heart failure: proposals for a diagnostic and therapeutic strategy. *Sleep Med Rev* 2006;**10**:33–47.
- Arzt M, Floras JS, Logan AG, Kimoff RJ, Series F, Morrison D, Ferguson K, Belenkie I, Pfeifer M, Fleetham J, Hanly P, Smilovitch M, Ryan C, Tomlinson G, Bradley TD, for the CANPAP Investigators. Suppression of central sleep apnea by continuous positive airway pressure and transplant-free survival in heart failure: a post hoc analysis of the Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure Trial (CANPAP). *Circulation* 2007;**115**:3173–3180.
- García-Lizana F, Sarriá-Santamera A. New technologies for chronic disease management and control: a systematic review. *J Telemed Telecare* 2007;**13**:62–68.
- Pinna GD, Maestri R, Andrews D, Witkowski T, Capomolla S, Scanferlato JL, Gobbi E, Ferrari M, Ponikowski P, Sleight P, Mortara A, Johnson P. Home telemonitoring of vital signs and cardiorespiratory signals in heart failure patients: system architecture and feasibility of the HHH model. *Int J Cardiol* 2007;**120**:371–379.
- Flemons WW, Littner MR, Rowley JA, Gay P, Anderson WM, Hudgel DW, McEvoy RD, Loube DI. Home diagnosis of sleep apnea: a systematic review of the literature. An evidence review cosponsored by the American Academy of Sleep Medicine, the American College of Chest Physicians, and the American Thoracic Society. *Chest* 2003;**124**:1543–1579.
- Maestri R, Pinna GD, Robbi E, Varanini M, Emdin M, Raciti M, La Rovere MT. RESP-24: a computer program for the investigation of 24-h breathing abnormalities in heart failure patients. *Comput Methods Programs Biomed* 2002;**68**:147–159.
- Ryan CM, Bradley TD. Periodicity of obstructive sleep apnea in patients with and without heart failure. *Chest* 2005;**127**:536–542.
- Tkacova R, Niroumand M, Lorenzi-Filho G, Bradley TD. Overnight shift from obstructive to central apneas in patients with heart failure: role of PCO₂ and circulatory delay. *Circulation* 2001;**103**:238–243.
- Cherniack NS. Apnea and periodic breathing during sleep. *N Engl J Med* 1999;**341**: 985–987.
- Bradley TD, Floras JS. Sleep apnea and heart failure. Part I: obstructive sleep apnea. *Circulation* 2003;**107**:1671–1678.
- Bradley TD, Floras JS. Sleep apnea and heart failure. Part II: central sleep apnea. *Circulation* 2003;**107**:1822–1826.
- Faber J, Lorimer P, Sergysels R. Cyclic hemodynamic and arterial blood gas changes during Cheyne-Stokes breathing. *Intensive Care Med* 1990;**16**:208–209.
- Pinna GD, Maestri R, Mortara A, La Rovere MT. Cardiorespiratory interactions during periodic breathing in awake chronic heart failure patients. *Am J Physiol Heart Circ Physiol* 2000;**278**:H932–H941.
- Iber C, Ancoli-Israel S, Chesson A, Quan SF, for the American Academy of sleep Medicine. *The AASM Manual for the Scoring of Sleep and Associated Events: Rules,*

- Terminology and Technical Specifications*. 1st ed. Westchester, Illinois: American Academy of Sleep Medicine; 2007.
21. La Rovere MT, Pinna GD, Maestri R, Robbi E, Mortara A, Fanfulla F, Febo O, Sleight P. Clinical relevance of short-term day-time breathing disorders in chronic heart failure patients. *Eur J Heart Fail* 2007;**9**:949–954.
 22. Bland JM, Altman DG. Measuring agreement in method comparison studies. *Stat Methods Med Res* 1999;**8**:135–160.
 23. Altman DG, Andersen PK. Bootstrap investigation of the stability of a Cox regression model. *Stat Med* 1989;**8**:771–783.
 24. Leung RS, Huber MA, Rogge T, Maimon N, Chiu KL, Bradley TD. Association between atrial fibrillation and central sleep apnea. *Sleep* 2005;**28**:1543–1546.
 25. Sériès F, Kimoff RJ, Morrison D, Leblanc MH, Smilovitch M, Howlett J, Logan AG, Floras JS, Bradley TD. Prospective evaluation of nocturnal oximetry for detection of sleep-related breathing disturbances in patients with chronic heart failure. *Chest* 2005;**127**:1507–1514.
 26. Brack T, Thüer I, Clarenbach CF, Senn O, Noll G, Russi EW, Bloch KE. Daytime Cheyne-Stokes respiration in ambulatory patients with severe congestive heart failure is associated with increased mortality. *Chest* 2007;**132**:1463–1471.
 27. Roebuck T, Solin P, Kaye DM, Bergin P, Bailey M, Naughton MT. Increased long-term mortality in heart failure due to sleep apnoea is not yet proven. *Eur Respir J* 2004;**23**:735–740.