Sleep-disordered breathing, impaired cardiac adrenergic innervation and prognosis in heart failure

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ABSTRACT
Objective Unfavourable effects of sleep-disordered breathing (SDB) in heart failure (HF) are mainly mediated by impaired sympathetic activity. Few data are available on SDB and cardiac adrenergic impairment evaluated at myocardial level. The aim of the study was to assess the relationship between SDB, cardiac sympathetic innervation assessed by 123I-metaiodobenzylguanidine (123I-MIBG) imaging and prognosis in HF.

Methods Observational, prospective study enrolling patients with HF and reduced systolic function. Patients underwent nocturnal cardiorespiratory monitoring to assess SDB presence by apnoea/hypopnoea index (AHI), and 123I-MIBG imaging to calculate heart-to-mediastinum (H/M) ratios and washout rate. Patients were prospectively followed for 29±18 months for the combined endpoint of cardiovascular death and HF hospitalisation.

Results Ninety-four patients (66.1±9.8 years; left ventricular ejection fraction 32±7%) were enrolled; 72 (77%) showed SDB and, compared with non-SDB, significantly reduced early (1.67±0.22 vs 1.77±0.13; p=0.019) and late H/M ratios (1.50±0.22 vs 1.61±0.23; p=0.038). Dividing patients into two groups according to SDB severity, patients with a moderate–severe disturbance (AHI >15; n=43) showed significantly worse survival for the composite study outcome (log-rank test, p=0.001) with respect to patients with mild or no disorder (AHI ≤15; n=51). Adding SDB variables to the already known prognostic role of 123I-MIBG imaging, we observed a worse survival in patients with both SDB and H/M impairment.

Conclusions Patients with systolic HF and SDB show more impaired cardiac adrenergic innervation assessed by 123I-MIBG imaging, and more adverse prognosis compared with HF patients without SDB.

INTRODUCTION
Sleep-disordered breathing (SDB) is common in patients with heart failure (HF), both in form of obstructive sleep apnoea (OSA) and central sleep apnoea (CSA), and impacts on disease progression and prognosis. Adverse effects of SDB in HF are mainly mediated by increased sympathetic nervous system activity, leading to high mortality rates. In patients with OSA, the combination of recurrent apnoeas, hypoxia and arousal is accompanied by an increase in chemoreflex-mediated adrenergic activity that also persists during daytime. Similarly, in patients with HF and CSA, a further increase in resting sympathetic drive has been demonstrated during apnoea episodes leading to adrenergic modulation of chemoreflex and altered ventilatory control. Increased urinary and blood levels of catecholamines, higher cardiac noradrenaline spillover and impaired muscle sympathetic nerve traffic have been demonstrated in patients with HF and SDB and it has been reported that ventilatory therapy reduces sympathetic nervous system activity. However, few data are available on the relationship between SDB and cardiac sympathetic innervation, assessed at myocardial level, in patients with HF. In the present study we sought to investigate the prognostic relationship between SDB and cardiac sympathetic innervation, assessed by 123I-metaiodobenzylguanidine (123I-MIBG) imaging, in patients affected by systolic HF.

MATERIALS AND METHODS
From April 2010 to April 2014, 94 consecutive patients with systolic HF referring to the HF Unit at Federico II University of Naples, Italy, were included in the analysis. Study inclusion criteria were diagnosis of systolic HF (left ventricular ejection fraction, LVEF ≤45%) evaluated by transthoracic echocardiograms in at least two consecutive determinations, stable HF since at least 6 months (New York Heart Association, NYHA I-III), no acute coronary syndrome or acute HF in the 6 months before, no planned revascularisation in the next 6 months, ability to tolerate nocturnal cardiorespiratory monitoring and capability to sign informed consent. At enrolment all patients were on optimised medical therapy for HF. All patients gave written informed consent and local ethic committee approved the protocol.

Study procedures
On the first day patients’ medical history and demographic data were collected. A complete clinical examination and transthoracic echocardiography were performed and nocturnal cardiorespiratory monitoring equipment applied. The day after, patients removed the device and underwent 123I-MIBG myocardial scintigraphy.
Nocturnal cardiorespiratory monitoring
A Somé (Compumedics, Melbourne, Australia) software polygraph was used to record nocturnal breathing patterns and identify the presence of SDB. Surface electrodes were applied to obtain continuous electrocardiogram recording. Airflow was monitored by use of thermistors placed at nose and arterial O₂ saturation was continuously monitored by a pulse oximeter. Thorax and abdomen movements were registered by plethysmographic method. Time registration was computer-programmed, starting from patients’ sleep habits. A sleep diary was given to the patient to record the effective hours of sleep and possible awakenings. A registration of at least 7 hours was required. Nocturnal cardiorespiratory monitoring was analysed and interpreted by a physician skilled in SDB (OS). According to the American Academy of Sleep Medicine Criteria, apnoea was defined as a complete cessation of airflow for at least 10 s, while hypopnoea was defined as a decrease in nasal airflow >50% lasting for 10 s or more and associated to arterial O₂ desaturation. Presence and severity of SDB were assessed by the evaluation of apnoea/hypopnoea index (AHI), defined as the number of respiratory events per hour of sleep. AHI value <5 allows to exclude SDB, AHI between 5 and 15 identifies mild disorder, between 16 and 30 moderate disorder and >30 a severe disturbance. Based on AHI value, patients were divided into two groups: SDB (AHI ≥5) and non-SDB (AHI <5). Furthermore, based on the pattern of abdominal and thoracic movements and from desaturation patterns, apneic events were divided into obstructive and central type. Classification of patient groups into OSA or CSA was determined by the presence of more than 50% of obstructive or central apneic events, respectively.

Transthoracic echocardiography
A standard transthoracic echocardiography was performed in all patients using a Vivid 9 ultrasound system (GE Healthcare) with a 3.5 MHz probe. All measurements were performed according to the European Society of Cardiology Recommendations for Chamber Quantification. IV diameters were obtained in the M-mode view. Global and regional LV function was evaluated and LVEF was calculated from apical four-chamber and two-chamber views using the Simpson’s biplane method.

123I-MIBG imaging procedures
After blockade of the thyroid gland with 300 mg of perchlorate, an activity of 111 MBq 123I-MIBG (Coviden, Mallinckrodt) was intravenously administered over 1–2 min. A 10 min planar image was acquired from an anterior thoracic view (256×256 matrix) 15 min (‘early’ image) and 3 hours and 50 min (‘late’ image) after tracer administration, as previously reported. Imaging was performed using a dual-head camera system (SkyLight, Philips) equipped with low-energy, parallel-hole, high-resolution collimator, and peaked at 159 keV with a symmetrical 20% energy window. Two observers, blinded about patients’ status, analysed 123I-MIBG studies. 123I-MIBG uptake was semiquantified by calculating a heart-to-mediastinum (H/M) ratio after drawing regions of interest over the heart and mediastinum. This approach provides a highly reproducible index of cardiac sympathetic activity. Briefly, H/M ratio was computed from the early and late images by dividing the mean counts per pixel within the myocardium by the mean counts per pixel within the mediastinum. By comparing early and late activities, the 123I-MIBG washout rate (WR) from the myocardium was derived, providing a parameter that reflects retention of noradrenaline by sympathetic neurons. 123I-MIBG WR was calculated using the following formula: [(early heart counts/pixel−early mediastinum counts/pixel)−(late heart counts/pixel−corrected−late mediastinum counts/pixel−corrected)]/(early heart counts/pixel−early mediastinum counts/pixel). The absorbed dose per unit of activity of 123I-MIBG was 0.018 mGy/MBq.

Currently, 123I-MIBG is the most widely used tracer for assessing sympathetic nervous function in patients with HF and has been also used for risk stratification. Because of the suboptimal 123I-MIBG image quality with single-photon emission CT (SPECT), most of the studies have used, as a prognostic marker of global left ventricular 123I-MIBG uptake, H/M ratio, calculated on planar supine images. It has been showed that 11C-hydroxyephedrine positron emission tomography (PET) produces consistently better image quality than MIBG SPECT. However, PET conveys higher methodological demands as well as less general availability. Reproducibility of 123I-MIBG analysis in our laboratory has also been recently reported.

Follow-up
Patients were followed up prospectively. Follow-up was carried out until November 2014 according to the local HF programme and ended with the last clinical evaluation or with patients’ death. The study endpoint was the composite of cardiovascular (CV) death and hospitalisation for worsening HF. Endpoints were prespecified and verified by two senior cardiologists (PP-F, BT) experienced in HF and blinded to scintigraphic study results.

Statistical analysis
Numerical variables were recorded and analysed as mean±standard deviation as no variable showed substantial asymmetry in an exploratory analysis. Categorical variables were expressed as frequencies and percentages. Unpaired t-test was used for between-group comparison. Analysis of variance test was used for comparison between more than two groups. Categorical variables were analysed by χ² test. Univariate and multivariate linear models were used to identify potential predictors of AHI and MIBG variables. Results of these models are expressed as β coefficients (mean change in the outcome for a one-unit increase in the predictor) with the corresponding 95% CIs. Kaplan–Meier event curves were constructed for the composite endpoint and compared between groups with the log-rank test. Event rates were obtained as Kaplan–Meier estimates at 24 months. A series of nested Cox proportional hazards models was used to identify potential predictors of the study outcome. The assessment of the proportional hazard assumption was based on the Grambsch and Therneau test and by examination of the Schoenfeld residuals. Results showed that the assumption was not violated. Results of the Cox models were expressed as HR with 95% CI. All data were collected in an Excel database and analysed by SPSS V20.0 and the R statistical computing software (R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was accepted at p<0.05.

RESULTS
Ninety-four patients (93% male; mean age 66.1±9.8 years) with systolic HF (mean LVEF 32±7%) were included in the study. Of 94 patients, 72 (77%) showed SDB and 22 (23%) did not. Forty-three (46%) patients showed moderate–severe SDB (AHI >15). Among patients with SDB, 49 (68%) showed prevalent OSA and 23 (32%) prevalent CSA. At the moment, 17 patients with SDB received an indication to nocturnal...
ventilatory therapy, of them five refused the treatment, two started nocturnal continuous positive airway pressure (CPAP) and interrupted the treatment after 2 months for mask intolerance, two did not yet start nocturnal CPAP and eight patients are currently on treatment. In 62 patients (66%) HF was of ischaemic origin and in 32 (34%) aetiology of HF was an idiopathic dilated cardiomyopathy. Ten patients (11%) were in I NYHA class, 57 (60%) in II NYHA class and 27 (29%) in NYHA class III.

No significant differences between SDB and non-SDB patients were observed for age, gender, NYHA class, HF aetiology and treatment, CV risk factors and LVEF (table 1). Patients with SDB showed greater body mass index (BMI) compared with patients without SDB. As per protocol, patients with SDB showed higher AHI values compared with non-SDB patients. No differences in mean oxygen saturation, nadir oxygen saturation during sleep and number of snores per hour were found between groups (table 1).

Patients with SDB, compared with non-SDB patients, showed significantly reduced early H/M (1.67±0.22 vs 1.77±0.13; p=0.019) and late H/M ratio (1.50±0.22 vs 1.61±0.23; p=0.038) (table 1). WR did not differ between groups (table 1). No significant differences were found between OSA (n=49, 53%) and CSA (n=23, 24%) patients for demographic and clinical variables (data not shown). AHI significantly differed between OSA and CSA patients (p=0.001), whereas early and late H/M ratios did not significantly differ between groups (early H/M 1.69±0.24 vs 1.64±0.19, in OSA and CSA, respectively, p=0.363; late H/M 1.52±0.24 vs 1.45±0.19, in OSA and CSA respectively, p=0.273).

At univariate analysis, mean oxygen saturation, nadir oxygen saturation, BMI and number of snores per hour were the variables significantly associated with AHI. When all these variables were entered simultaneously in the same model, only the inverse association between nadir oxygen saturation and AHI was confirmed (b=-0.49; 95% CI (–0.85 to –0.12); p=0.009). Independent predictors of late H/M were age (b=-0.006; 95% CI –0.010 to –0.002; p=0.003), LVEF (b=0.010; 95% CI 0.003 to 0.016; p=0.004) and WR (b=–0.005; 95% CI –0.007 to –0.003; p<0.001), whereas independent predictors of early H/M were BMI (b=−0.014; 95% CI –0.024 to –0.004; p=0.007) and LVEF (b=0.01; 95% CI 0.004 to 0.017; p=0.002).

### Prognostic impact of SDB and 123I-MIBG

Patients were followed up for a mean of 29±18 months (range 5–43 months). In the whole population, four (4.2%) patients experienced CV death, in particular HF-related death, while 17 (18%) were hospitalised for worsening HF.

Dividing patients into two groups according to SDB severity, patients with a moderate–severe disturbance (AHI >15; n=43) showed significantly worse survival for the composite study outcome (log-rank test, p=0.001; figure 1A) with respect to patients with mild or no disorder (AHI ≤15; n=51). Kaplan-Meier estimates of cumulative event rates at 24 months were 4.5% (overall no of events=6) in patients with AHI ≤15 and 9.1% (overall no of events=15) in patients with AHI >15.

In addition, Kaplan-Meier analysis showed significantly worse survival in patients with impaired cardiac sympathetic innervation (log-rank test, p=0.042; figure 1B) assessed using a cut-off value of late H/M of 1.60, as reported in the AdreView Myocardial Imaging for Risk Evaluation (ADMIRE) study.22 Cumulative event rates of the study endpoint at 24 months were 5.3% (overall no of events=4) in patients with normal (≥1.60; n=36) late H/M and 9.5% (overall no of events=17) in case of abnormal late H/M (<1.60; n=58).

Finally, we performed a preliminary analysis on 63 (67%) patients with implantable-cardioverter defibrillator (ICD). Twenty-two appropriate shocks occurred in six patients (9.5%) during the follow-up period. No differences at Kaplan-Meier analysis were found dividing patients by SDB presence (log-rank test, p=0.629) or median AHI value (log-rank test, p=0.381). However, this difference became nearly statistically significant dividing patients by normal (≥1.60)22 or abnormal late H/M (<1.60) values (log-rank test, p=0.051), with higher event rates in patients with impaired cardiac sympathetic innervation.

### Combined prognostic impact of SDB and 123I-MIBG

An additional analysis was performed to assess the prognostic value of H/M and SDB combination.

Addition of SDB severity subgroups (mild or no SDB vs Moderate–severe disorder) to the binary H/M result identified three new groups of patients (group 1:late H/M ≥1.60 and mild or no SDB; group 2:late H/M ≥1.60 or moderate–severe SDB; group 3:late H/M <1.60 and moderate–severe SDB). No differences were found among groups in terms of age, gender distribution, NYHA class, HF aetiology and CV risk factors distribution (see online supplementary table 1S). Group 3 showed significantly higher BMI values and significantly lower LVEF values with respect to group 1 (Bonferroni corrected p value <0.01). Significant differences were found at Kaplan-Meier analysis between groups (log-rank test, p=0.001; figure 2), with the worst prognosis observed in patients with moderate–severe disorder and late H/M <1.60. The 24 months cumulative event rates in groups 1, 2 and 3 were 0%, 8.4% and 13%, respectively.

At Cox regression analysis, in a base model in which only clinical variables and comorbidities (age, gender, smoking habit, heavy drinking, obesity, diabetes, hypertension, dyslipidaemia, heart failure status, and chronic obstructive pulmonary disease) were included, the late H/M ratio was significantly associated with the composite study outcome (HR=3.35; 95% CI 1.69 to 6.67; p=0.001).

### Table 1 Characteristics and 123I-MIBG uptake in the two groups of patients with SDB and no-SDB

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Sleep-disordered breathing (n=72)</th>
<th>No sleep-disordered breathing (n=22)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>66.9±9.7</td>
<td>63.2±9.8</td>
<td>0.111</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>92</td>
<td>95</td>
<td>1.000</td>
</tr>
<tr>
<td>BMI</td>
<td>29.0±4.1</td>
<td>26.4±3.7</td>
<td>0.010</td>
</tr>
<tr>
<td>LVEF (%) IQR</td>
<td>32 (8)</td>
<td>33 (9)</td>
<td>0.054</td>
</tr>
<tr>
<td>NYHA</td>
<td>2.1±0.7</td>
<td>2.3±0.6</td>
<td>0.119</td>
</tr>
<tr>
<td>Ischaemic aetiology (%)</td>
<td>62</td>
<td>77</td>
<td>0.616</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>82</td>
<td>73</td>
<td>0.256</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>36</td>
<td>32</td>
<td>0.802</td>
</tr>
<tr>
<td>Dyslipidaemia (%)</td>
<td>68</td>
<td>77</td>
<td>0.595</td>
</tr>
<tr>
<td>Cigarette smoking (%)</td>
<td>53</td>
<td>64</td>
<td>0.465</td>
</tr>
<tr>
<td>Early H/M</td>
<td>1.67±0.22</td>
<td>1.77±0.13</td>
<td>0.019</td>
</tr>
<tr>
<td>Late H/M</td>
<td>1.50±0.22</td>
<td>1.61±0.23</td>
<td>0.038</td>
</tr>
<tr>
<td>Washout rate (%) IQR</td>
<td>36.1±23.8</td>
<td>35.9±15.9</td>
<td>0.971</td>
</tr>
<tr>
<td>Apnoea/hipnoea index</td>
<td>21.8±13.6</td>
<td>3.08±1.08</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean oxygen saturation</td>
<td>92±5</td>
<td>90±5</td>
<td>0.488</td>
</tr>
<tr>
<td>Nadir oxygen saturation</td>
<td>78±13</td>
<td>82±14</td>
<td>0.219</td>
</tr>
<tr>
<td>Number of snores/hour</td>
<td>222±170</td>
<td>158±115</td>
<td>0.082</td>
</tr>
</tbody>
</table>

BMI, body mass index; H/M, heart to mediastinum ratio; 123I-MIBG, 123I-metaiodobenzylguanidine; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SDB, sleep-disordered breathing.
BMI, diabetes, hypertension, dyslipidaemia, aetiology and NYHA class) were included, BMI and NYHA class were the only independent predictors of prognosis (table 2). When LVEF was added in the model, no effect was found for this variable (HR: 0.93; 95% CI 0.84 to 1.03; p=0.148). Also, late H/M did not show any significant association with the composite outcome when included in the model (HR: 0.99; 95% CI 0.03 to 29.91; p=0.996). Finally, when AHI was included, it emerged as an independent predictor of outcome with a 6% (HR: 1.06; 95% CI 1.02 to 1.10; p=0.005) increment in the hazard for every unit increase of the index (table 2).

**DISCUSSION**

The findings of the present study demonstrate that SDB is highly prevalent (77%) in patients with chronic systolic HF and associated with more impaired cardiac sympathetic innervation. SDB and cardiac sympathetic innervation parameters predict the composite endpoint of CV mortality and HF hospitalisation, identifying a subgroup of patients with abnormal H/M ratio and moderate–severe SDB who show a worse prognosis.

In the present study significant lower values of H/M ratios, indicating chronically increased sympathetic drive, were observed in patients with HF and SDB, compared with non-SDB, despite comparable LVEF and functional class (figure 3). Thus, these findings point to an independent contribution of SDB to sympathetic stimulation in HF, leading to more pronounced β-receptor desensitisation and, hence, reduced H/M ratios measured at cardiac level.

In our study, early and late H/M did not differ between patients with OSA and CSA. This finding may appear not consistent with previous studies that investigated the impact of SDB in HF on sympathetic activation using different approaches. Solin et al. reported that overnight urinary norepinephrine levels were significantly increased in 90 patients with HF compared with healthy subjects and patients with OSA without HF. Among patients with HF, those with CSA revealed more increased norepinephrine levels compared with patients with HF and no SDB or with HF and OSA. However, patients with CSA had significantly reduced LVEF and more compromised hemodynamic status compared with OSA patients. Similarly, Mansfield et al. reported that total body and cardiac norepinephrine spillover were more increased in patients with HF and CSA compared with patients with OSA or without SDB, but also in this study differences were attributed to the more impaired hemodynamic status of patients with CSA. Yet, catecholamine levels do not strictly mirror the status of cardiac innervation as depicted from innervation imaging and only cat-

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**Figure 1** Kaplan-Meier analysis for the composite endpoint of cardiovascular death and hospitalisation for worsening HF. (A) Kaplan-Meier analysis for the composite endpoint of cardiovascular death and hospitalisation for worsening HF in patients with mild or no SDB (AHI ≤15) (continue line) and in patients with moderate–severe SDB (AHI >15) (dotted line). (B) Kaplan-Meier analysis for the composite endpoint of cardiovascular death and hospitalisation for worsening HF in patients with late H/M <1.60 (continue line) and late H/M ≥1.60 (dotted line). AHI, apnoea/hypopnoea index; H/M, heart-to-mediastinum ratio; HF, heart failure; SDB, sleep-disordered breathing.

**Figure 2** Kaplan-Meier analysis for the composite endpoint of cardiovascular death and hospitalisation in three groups of patients: late heart to mediastinum (H/M) ≥1.60 and mild or no sleep-disordered breathing (SDB) (continuous line), late H/M <1.60 or moderate or severe SDB (intermediate dotted line), late H/M <1.60 and moderate or severe SDB (lower dotted line).
few studies have used MIBG imaging to assess the impact of SDB on cardiac innervation in HF. Nanjo et al\textsuperscript{25} reported in 53 patients with chronic dilated cardiomyopathy that late H/M was significantly lower in patients with HF and SDB compared with patients without SDB. However, in this study no nocturnal cardiorespiratory monitoring or complete polysomnography were performed and the presence of SDB was assessed using 24-hour pulse oximetry. Tamura et al\textsuperscript{26} found that late H/M ratio and WR were significantly different in patients with HF and CSA compared with those with HF and OSA. However, significantly higher brain natriuretic peptide (BNP) levels in patients with CSA indicated a more compromised hemodynamic status,

Table 2  Cox regression analysis for the combined endpoint of cardiovascular death and hospitalisation for worsening HF

<table>
<thead>
<tr>
<th></th>
<th>Base model</th>
<th>Model 1: base model +ejection fraction</th>
<th>Model 2: model 1 +late H/M</th>
<th>Model 3: model 2 +apnoea/hypopnoea index</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>p Value</td>
<td>HR (95% CI)</td>
<td>p Value</td>
</tr>
<tr>
<td>Age</td>
<td>1.08 (1.00 to 1.18)</td>
<td>0.062</td>
<td>1.08 (0.99 to 1.17)</td>
<td>0.101</td>
</tr>
<tr>
<td>Gender, male</td>
<td>0.52 (0.05 to 5.38)</td>
<td>0.586</td>
<td>0.33 (0.03 to 4.36)</td>
<td>0.402</td>
</tr>
<tr>
<td>Smoking habit</td>
<td>0.61 (0.18 to 2.11)</td>
<td>0.439</td>
<td>0.71 (0.2 to 2.46)</td>
<td>0.583</td>
</tr>
<tr>
<td>Body mass index</td>
<td>1.23 (1.06 to 1.42)</td>
<td>0.006</td>
<td>1.25 (1.08 to 1.45)</td>
<td>0.004</td>
</tr>
<tr>
<td>Diabetes</td>
<td>3.05 (0.98 to 9.49)</td>
<td>0.054</td>
<td>2.56 (0.79 to 8.31)</td>
<td>0.118</td>
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<tr>
<td>Hypertension</td>
<td>0.29 (0.06 to 1.41)</td>
<td>0.123</td>
<td>0.30 (0.06 to 1.48)</td>
<td>0.139</td>
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<tr>
<td>Dyslipidaemia</td>
<td>0.79 (0.18 to 3.46)</td>
<td>0.749</td>
<td>0.92 (0.21 to 4.03)</td>
<td>0.916</td>
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<td>Ischaemic aetiology</td>
<td>4.29 (0.82 to 22.49)</td>
<td>0.085</td>
<td>5.08 (0.92 to 28.17)</td>
<td>0.063</td>
</tr>
<tr>
<td>Glomerular filtration rate</td>
<td>1.03 (1.00 to 1.06)</td>
<td>0.105</td>
<td>1.03 (1.01 to 1.06)</td>
<td>0.080</td>
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<tr>
<td>NYHA (Class I Ref.)</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Class II</td>
<td>0.07 (0.01 to 0.35)</td>
<td>0.001</td>
<td>0.09 (0.02 to 0.45)</td>
<td>0.004</td>
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<tr>
<td>Class III</td>
<td>0.10 (0.02 to 0.63)</td>
<td>0.014</td>
<td>0.10 (0.02 to 0.62)</td>
<td>0.013</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>0.93 (0.84 to 1.03)</td>
<td>0.148</td>
<td>0.93 (0.83 to 1.05)</td>
<td>0.233</td>
</tr>
<tr>
<td>Late H/M</td>
<td>0.99 (0.03 to 29.91)</td>
<td>0.996</td>
<td>1.73 (0.05 to 59.5)</td>
<td>0.762</td>
</tr>
</tbody>
</table>

H/M heart to mediastinum ratio; HF, heart failure; NYHA New York Heart Association.

Figure 3  Examples of \textsuperscript{123}I-metaiodobenzylguanidine scan in a patient with heart failure without SDB (A and B above) compared with a subject with SDB (A and B below). H/M, heart-to-mediastinum ratio; SDB, sleep-disordered breathing. Green boxes represent mediastinum region of interest and the red boxes represent a heart region of interest.
potentially explaining their observation. Thus, to our knowledge, this is the first study that compared the status of cardiac sympathetic innervation of patients with HF and OSA or CSA, with similar degree of functional and hemodynamic LV impairment.

**Prognostic impact of SDB in relation to $^{123}$I-MIBG findings**

Patients with moderate–severe SDB (AH1 >15) showed significantly increased incidence of the combined endpoint of the study compared with patients with mild or no-SDB.

Our findings appear very consistent with those reported by Wang et al in 164 patients with HF divided in non-SDB or only mild OSA, identified by AH1 ≤15, and patients with untreated OSA identified by AH1 >15. In that study, that excluded patients with CSA, an independent impact of OSA was found on mortality rate. Similarly, Damy et al found that the severity of SDB was associated with the occurrence of a combined endpoint of death, heart transplant, and implant of a ventricular assist device with a significant increase in mortality for an AH1 >5 and a similar poor prognosis for AH1 between 5 and 20, and for AH1 >20. However, no parameters of cardiac sympathetic status were reported in those studies. Taken together, these findings suggest that patients with HF who are also affected by SDB develop more impaired cardiac sympathetic innervation, as a result of more increased chronic sympathetic drive, leading to more adverse prognosis. Consistent with our study, Lanfranchi et al reported that the presence of impaired respiration during sleep was associated with increased mortality rate in 62 patients with systolic HF, and that an AH1 ≥30 was an independent predictor of prognosis.

The ADMIRE-HF trial reported that a value of late H/M <1.60 identifies patients at increased risk of cardiac death, arrhythmic events, HF progression and all-cause mortality. Consistent with that study, our findings demonstrate an increased risk of CV death and HF hospitalisations in patients with late H/M value <1.60 compared with patients with late H/M ≥1.60.

However, in these studies, at variance with the current analysis, SDB and MIBG parameters were analysed as a single prognostic parameter and not integrated in a model to assess their incremental prognostic value. In our analysis, when SDB severity was combined with late H/M, a reduced survival was observed in patients with late H/M <1.60 and an SDB of moderate–severe intensity (figure 2), and AH1 emerged as the strongest independent predictor of outcome as it was associated with a 6% increment in the hazard for every unit increase of the index (HR: 1.06; 95% CI 1.02 to 1.10; $p=0.003$; table 2).

**Limitations**

This study did not assess the effects of intervention for SDB on cardiac sympathetic innervation. This prevents to verify whether changes of cardiac innervation status are associated with clinical outcome and can represent a meaningful surrogate prognostic endpoint in patients with HF. Recent reports observed an improvement of parameters of adrenergic status after ventilatory therapy. In particular, Koyama et al observed in 26 patients with HF and prevalent CSA an improvement in $^{123}$I-MIBG parameters after 6 months of adaptive servo-ventilation therapy together with an improvement of LVEF and BNP levels and previous data from Toyama et al described that nocturnal oxygen home therapy was associated with improved exercise capacity, cardiac function and cardiac sympathetic nerve activity in patients with HF and CSA. A recent study also reported that short-term CPAP was associated with a significant improvement of presynaptic catecholamine retention in patients with HF and OSA. However, in these studies no prognostic data were reported. Collectively, these findings generate the hypothesis to be tested that therapeutic-induced changes of cardiac innervation parameters may represent a short-term marker of subsequent clinical outcome in patients with HF and SDB. As adjunctive limitation, we recognise that the results of the present study indicate that the impact of SDB and sympathetic innervation is more relevant in terms of HF hospitalisations rather than of CV death, due to the limited number of observed deaths. In addition, the low number of fatal events prevents to explore the hypothesis that MIBG may provide risk stratification for sudden death in patients with HF and SDB or whether prognostic information obtained by MIBG imaging in patients with HF may influence the choice of ICD implantation beyond current guidelines criteria. A larger population is obviously needed to purposefully confirm the role of MIBG to predict death and arrhythmic events in this population of patients and to test the hypothesis that MIBG imaging may assist the decision to implant ICD in patients with HF and SDB who have borderline criteria for implantation according to current guidelines. However, this study is the first investigating the association among SDB, cardiac innervation and prognosis, reporting the largest population of patients with HF and SDB undergoing $^{123}$I-MIBG imaging.

We recognise that SPECT studies may be preferred to identify regional areas of reduced uptake in patients with cardiac diseases. However, the use of SPECT would increase the injected dose and the duration of the study with no proven benefit. In addition, in the present study, we used planar images according to the ADMIRE-HF trial that represents the largest multicentre study on the prognostic role of MIBG in patients with HF. Finally, in the present study we used cardiorespiratory monitoring to assess presence of SDB. We recognise that the use of full polysomnography, even if expensive, difficult to perform and not validated in such population, would have guaranteed a more comprehensive evaluation, although unlikely to influence results.

**What is already known on this subject?**

Adverse effects of sleep-disordered breathing (SDB) in heart failure (HF) are mainly mediated by increased adrenergic activity. Only a few studies have used metaiodobenzylguanidine imaging to assess the impact of SDB on cardiac innervation in HF, not reporting prognostic data.

**What might this study add?**

The present study demonstrate that SDB in HF is associated with more impaired adrenergic innervation, expressed by significantly reduced early (1.67±0.22 vs 1.77±0.13; $p=0.019$) and late heart-to-mediastinum ratio (1.50±0.22 vs 1.61±0.23; $p=0.038$). Moreover, SDB and cardiac sympathetic innervation both contribute to predict the composite endpoint of cardiovascular mortality and HF hospitalisation, identifying a subgroup of patients who exhibit a worse prognosis.

**How might this impact on clinical practice?**

The main clinical implication of the current findings is that SDB assessment should be routinely included in the evaluation of patients with HF, in order to early identify a subgroup of patients with worse prognosis, especially if this condition is also associated to adrenergic impairment.

**Key messages**

- Adverse effects of sleep-disordered breathing (SDB) in heart failure (HF) are mainly mediated by increased adrenergic activity.
- Only a few studies have used metaiodobenzylguanidine imaging to assess the impact of SDB on cardiac innervation in HF, not reporting prognostic data.
- The present study demonstrate that SDB in HF is associated with more impaired adrenergic innervation, expressed by significantly reduced early and late heart-to-mediastinum ratio.
- SDB and cardiac sympathetic innervation both contribute to predict the composite endpoint of cardiovascular mortality and HF hospitalisation, identifying a subgroup of patients with worse prognosis.
CONCLUSIONS
Patients with systolic HF and SDB demonstrate greater impairment of cardiac adrenergic innervation and more adverse prognosis compared with HF patients without SDB. Further studies are warranted to assess whether SDB therapy, through improvement of sympathetic innervation abnormalities, affects prognosis in patients with HF and SDB.

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Sleep-disordered breathing, impaired cardiac adrenergic innervation and prognosis in heart failure

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