Ventricular arrhythmia, Cheyne-Stokes respiration, and death: observations from patients with defibrillators

A D Staniforth, S C Sporton, M J Earley, J A Wedzicha, A W Nathan, R J Schilling

Objective: To determine whether ventricular arrhythmia related to nocturnal hypoxaemia during Cheyne-Stokes respiration (CSR) explains the observation that CSR is an independent marker of death in heart failure.

Design: Prospective, observational study.

Patients: 101 patients at high risk of clinical serious ventricular arrhythmia fitted with an implantable cardioverter-defibrillator (ICD).

Measurements: Patients were studied at baseline for CSR during sleep. Arrhythmia requiring device discharge was used as a surrogate marker for possible sudden cardiac death.

Results: 101 patients (42 with CSR) were followed up for a total of 620 months. Twenty six patients experienced 432 ICD discharge episodes. Twenty four (6%), 210 (49%), 125 (29%), and 73 (17%) episodes occurred across the time quartiles 0000–0559, 0600–1159, 1200–1759, and 1800–2359, respectively. Kaplan-Meier analysis showed a relative risk of 1 (95% confidence interval 0.5 to 2.2, p = 1) for device discharge in the CSR group. The average (SED) numbers of nocturnal ICD discharges per patient per month of follow up were 0.01 (0.01) and 0.04 (0.02) for patients with and without CSR, respectively (p = 0.6).

Conclusion: These findings refute the proposition that CSR is related to heart failure death through nocturnal serious ventricular arrhythmia.

Cheyne-Stokes respiration (CSR) is an independent marker of poor prognosis in chronic stable heart failure. Although CSR may just be another marker of bad heart failure, there is evidence that treatments specifically directed against CSR improve prognosis. There are two plausible mechanisms by which CSR may exert an adverse effect. Firstly, the activation of the sympathetic nervous system during recurrent arousals and sleep fragmentation due to CSR may further exacerbate the maladaptive neurohormonal disturbances characteristic of the heart failure syndrome. Secondly, apnoea associated nocturnal oxygen desaturation may lead to cardiac hypoxaemia and serious ventricular arrhythmia.

Bradyarrhythmia rather than tachycardia was considered to be the hallmark of the sleep apnoea syndromes. The results of two recent Holter monitor studies have challenged this assumption regarding heart failure with CSR by showing an increase in the rate of ventricular extrasystoles and non-sustained ventricular tachycardia (NSVT). Further interpretation of these studies is limited by the lower left ventricular ejection fractions in patients with CSR than in patients without CSR, and by the observation that the excess of NSVT occurred during the day rather than during sleep. Furthermore, although ventricular extrasystoles and NSVT are associated with an increased risk of sudden cardiac death, these “soft” Holter measurements lack specificity and positive predictive value.

We report data from 101 patients with heart failure at high risk of ventricular arrhythmia fitted with an implantable cardioverter-defibrillator (ICD). We have prospectively investigated whether patients with nocturnal oxygen desaturation during periods of likely CSR were subsequently at an increased risk of clinical serious ventricular arrhythmia events necessitating ICD discharge. The high reliability and high quality electrogram storage facility of modern ICDs permitted a comparison of the diurnal variation of serious clinical ventricular arrhythmia between patients with and those without nocturnal oxygen desaturation.

METHODS

Patients

We recruited 101 patients undergoing ICD implantation. Patients of any age, sex, heart failure aetiology, and duration and severity of symptoms were enrolled. Patients with known significant pulmonary disorder, obstructive sleep apnoea, stroke, and morbid obesity (body mass index ≥ 35 kg/m²) were excluded. All patients had stable cardiac failure with no change in medication for two weeks before study and no evidence of fluid retention at the time of study. All patients received standard heart failure treatment (defined as a diuretic, an angiotensin converting enzyme inhibitor or angiotensin receptor blocker, spironolactone, and a β blocker). Documented intolerance to one or more of these agents was not a reason for exclusion from study.

Heart failure was diagnosed on the basis of a suggestive medical history and examination findings together with impaired left ventricular function on two dimensional echocardiography. Left ventricular function was quantified by M mode echocardiography. Only patients with either a left ventricular diastolic diameter greater than 5.5 cm or an ejection fraction less than 35% were eligible for study. All patients underwent coronary angiography.

Abbreviations: CPAP, continuous positive airway pressure; CRT, cardiac resynchronisation therapy; CSR, Cheyne-Stokes respiration; ICD, implantable cardioverter-defibrillator; MADIT, multicentre automatic defibrillator implantation trial; NSVT, non-sustained ventricular tachycardia; SaO₂, transcutaneous oxygen saturation.
Assessment of nocturnal oxygen desaturation
All patients underwent overnight pulse oximetry with the Biow 3700 pulse oximeter (Ohmeda Biox Ltd) before ICD implantation. All studies took place in hospital on the night before ICD implantation. The apparatus records the lowest percentage transcutaneous oxygen saturation (Sao₂) detected over successive 12 second time intervals up to a maximum of eight hours. The data were analysed to calculate the overnight minimum Sao₂, mean Sao₂, dip frequency (defined as a fall in Sao₂ ≥ 4%), and the percentage of overnight recording time spent with Sao₂ < 90%. Recordings with a sinusoidal pattern of nocturnal oxygen desaturation together with a 4% dip rate of > 15 dips/hour were defined as "abnormal and suggestive of CSR".

External validation of oximetry screening
We have previously validated the use of overnight oximetry as a screening tool for CSR. Oximetry recordings were found to be reproducible with a mean difference over two successive nights of ~0.2 dips/hour (within patient standard deviation of 1.3 dips/hour). With full polysomnography serving as the ideal, receiver operating characteristic analysis with a diagnostic cut off of 15 dips/hour yielded a sensitivity of 87% and a specificity of 81% for the identification of CSR. The area under the receiver operating characteristic curve was 94%.

Internal validation of oximetry screening: polysomnography substudy
Every fourth patient with an abnormal oximetry recording underwent technician supervised overnight polysomnography. All studies took place in hospital within four weeks of ICD implantation. This was to confirm that the overnight breathing abnormalities responsible for oxygen desaturation were identical to those observed in the validation study. Figure 1 shows an overnight oximetry trace from a patient with CSR.

The Neuroscience Sleepmaster analysis system (Nellcor Ltd, Pleasanton, California, USA) was used to record the polysomnographs. Surface electrodes were used to record the encephalogram, electro-oculogram, and mental electromyogram. Respiratory movements were recorded with chest wall and abdominal respitrace bands. ECG was recorded with standard limb leads. Oxygen saturation was measured by pulse oximetry. Oral and nasal airflow were detected by thermistors attached to the upper lip.

The data were analysed off line after manual inspection of the raw polygraph recordings. Standard criteria were used to define sleep onset and end. The following definitions were used to classify abnormal breathing patterns: Apnoea, an absence of airflow for more than 10 seconds; central apnoea, an apnoea without respiratory movement; obstructive apnoea, an apnoea with respiratory effort; hypopnoea, a reduction in the amplitude of respiratory movement for more than 10 seconds to less than 50% of the maximum amplitude recorded during the preceding breathing cycle; CSR, a central apnoea index of ≥ 10/hour in combination with the characteristic pattern of crescendo-decrescendo hyperpnocentral apnoea periodic breathing; obstructive sleep apnoea, an obstructive apnoea index of ≥ 10/hour; and periodic breathing time, percentage of the total sleep period spent in CSR.

ICD implantation, programming, and electrogram analysis
ICDs were implanted transvenously under moderate sedation with a standard surgical technique. Seventeen of the ICDs were cardiac resynchronisation devices (CRTs). Device programming was left to the discretion of implanting physicians according to their knowledge of the patients' individual arrhythmia history. This ensured that ICD discharges would be delivered only for clinically relevant arrhythmia. Subsequent discharges were documented as appropriate or inappropriate by the interpreting cardiologist or cardiac technician after electrogram storage review. The occurrence and timing of appropriate discharges were recorded prospectively at follow up. Non-sustained episodes were specifically not documented.

Data analysis
Numerical data were analysed by Student's t and Mann-Whitney U tests. Group comparisons of categorical data were evaluated by the χ² test. Survival to the time of first appropriate discharge was analysed by the Kaplan-Meier method. Differences in survival between patients with and without CSR were investigated with the log rank test.

RESULTS
Patient characteristics and follow up
One hundred and one patients undergoing ICD implantation (89 new systems and 12 elective generator replacements) at our institution between April 2002 and May 2003 consented to participate in this study. During this period 153 devices were implanted (126 new systems and 27 generator replacements). There were 432 episodes of clinically significant serious ventricular arrhythmia necessitating ICD discharge during 620 months of follow up. No patient died. One patient transferred out of the area and was lost to follow up after one month. Forty two of 101 (41%) patients had an overnight oximetry recording suggestive of CSR.

Polysomnography substudy
Twelve patients with oximetry recordings suggestive of CSR underwent full overnight polysomnography to define the nature of their sleep related breathing disorder. The mean (SD) total sleep period was 342 (51) minutes. The mean apnoea-hypopnoea index was 26 (13)/hour with an apnoea index of 16 (15)/hour and a periodic breathing time of 46 (32)% of the period. Among the events, 85 (23)% were central in origin; 11 patients fulfilled the predefined polysomnography definition of CSR. No patient had obstructive sleep apnoea.

Characteristics of patients with and without CSR
The majority of patients were men and had left ventricular dysfunction secondary to coronary artery disease (table 1). Patients with and without CSR were comparable with respect to age, severity of coronary artery disease, and antiarrhythmic use. As would be expected, patients with CSR had more
Patients with a CRT device were no less likely than those with a standard ICD to receive an appropriate discharge (3 of 17 v 3 of 84, p = 0.55). Twenty patients received an inappropriate discharge; in 18 patients these involved defibrillation.

**Diurnal pattern of ICD discharges**

It was possible that, although the overall arrhythmic burden between patients with and without CSR might have been identical, the groups might have differed with respect to their diurnal distribution of events. To investigate this, we compared the distribution of ICD discharges between the temporal quartiles of 0000 to 0559, 0600 to 1159, 1200 to 1759, and 1800 to 2359 (fig 3, table 2). There was no evidence that patients with CSR were more likely to experience ICD discharges during the night time (sleeping) hours when the degree of oxygen desaturation was greatest. The average (SED) numbers of nocturnal discharges (0000–0559) per patient per month of follow up were 0.01 (0.01) and 0.04 (0.02) for patients with and without CSR, respectively (p = 0.6).

**DISCUSSION**

CSR is an independent marker of poor prognosis in heart failure. It remains to be determined whether CSR is more than just a marker of a bad heart. Limited evidence suggests that CSR itself may be harmful. Continuous positive airway pressure (CPAP) ventilation has beneficial haemodynamic effects in heart failure and is an effective treatment for CSR. Sin et al. reported that CPAP improved ejection fraction and survival in patients with heart failure with CSR; significantly, CPAP did not improve either ejection fraction or survival in a matched group without CSR. Evidence of improved survival after a treatment targeted

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**Table 1** Baseline characteristics of implantable cardioverter defibrillator (ICD) recipients with and without Cheyne-Stokes respiration (CSR)

<table>
<thead>
<tr>
<th>No CSR</th>
<th>CSR (n = 42)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>65.6 (1.4)</td>
<td>68.1 (1.3)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.3 (0.6)</td>
<td>28.2 (0.8)</td>
</tr>
<tr>
<td>NYHA class</td>
<td>2.1 (0.1)</td>
<td>2.5 (0.1)</td>
</tr>
<tr>
<td>Number of diseased arteries</td>
<td>1.7 (0.1)</td>
<td>2.0 (0.2)</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>36.6 (21)</td>
<td>28.7 (19)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>45/59 (76%)</td>
<td>36/42 (86%)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>5/59 (8%)</td>
<td>8/42 (19%)</td>
</tr>
<tr>
<td>Bundle branch block</td>
<td>27/59 (46%)</td>
<td>17/42 (40%)</td>
</tr>
<tr>
<td>VT/VF inducible at PES</td>
<td>17/59 (29%)</td>
<td>7/42 (17%)</td>
</tr>
<tr>
<td>NYHA class</td>
<td>1</td>
<td>0.9</td>
</tr>
<tr>
<td>I</td>
<td>17/56 (30%)</td>
<td>4/42 (10%)</td>
</tr>
<tr>
<td>II</td>
<td>20/56 (36%)</td>
<td>17/42 (40%)</td>
</tr>
<tr>
<td>III</td>
<td>17/56 (30%)</td>
<td>18/42 (43%)</td>
</tr>
<tr>
<td>IV</td>
<td>2/56 (4%)</td>
<td>3/42 (7%)</td>
</tr>
<tr>
<td>Index arrhythmia</td>
<td>VT</td>
<td>36/59 (61%)</td>
</tr>
<tr>
<td>VF</td>
<td>9/59 (15%)</td>
<td>7/42 (17%)</td>
</tr>
<tr>
<td>PP</td>
<td>14/59 (24%)</td>
<td>12/42 (29%)</td>
</tr>
<tr>
<td>Medications</td>
<td>Diuretic</td>
<td>38/59 (64%)</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>49/59 (83%)</td>
<td>41/42 (98%)</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>16/59 (27%)</td>
<td>14/40 (35%)</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>13/59 (22%)</td>
<td>10/42 (24%)</td>
</tr>
<tr>
<td>β Blocker</td>
<td>33/59 (56%)</td>
<td>27/42 (64%)</td>
</tr>
<tr>
<td>Mean SaO₂ (%)</td>
<td>93.3 (0.5)</td>
<td>91.8 (0.7)</td>
</tr>
<tr>
<td>Minimum SaO₂ (%)</td>
<td>66.5 (0.6)</td>
<td>80.2 (1.3)</td>
</tr>
<tr>
<td>Desaturation index (dips/hour)</td>
<td>7.1 (0.5)</td>
<td>6.9 (1.8)</td>
</tr>
<tr>
<td>Recoding time with SaO₂ &lt;90% (%)</td>
<td>4.3 (1.7)</td>
<td>12.8 (2.4)</td>
</tr>
</tbody>
</table>

All values are mean (SEM) or number (%).

ACE, angiotensin converting enzyme; BMI, body mass index; NYHA, New York Heart Association; PES, programmed electrical stimulation; PP, primary prevention; SaO₂, overnight transcutaneous oxygen saturation; VT, ventricular fibrillation; VF, ventricular tachycardia.
against CSR strengthens the case for a cause and effect relation between CSR and mortality in patients with heart failure. One mechanism by which CSR may exert an adverse effect is serious ventricular arrhythmia caused by the repeated cycles of nocturnal apnoea related cardiac hypoxaemia.

In this prospective observational study we report on the incidence of serious ventricular arrhythmia in patients with and without patterns of nocturnal oxygen desaturation suggestive of CSR. All patients were fitted with an ICD programmed according to their individual clinical need. The advantage of this design was twofold. Firstly, by using ICDs with modern electrogram storage capacity we could accurately document all episodes of serious ventricular arrhythmia and their diurnal variation. Secondly, by leaving ICD discharge setup to the discretion of the implanting cardiologist according to individual patient clinical need, we could be confident that we were documenting clinically relevant serious ventricular arrhythmia (a more likely surrogate marker for aborted sudden cardiac death). This strategy was superior to counting ventricular extrasystoles or NSVT of dubious clinical relevance on serial 24 hour Holter monitors. It was interesting that no patients died during the follow up period. Although the total follow up was large (620 months), the median follow up was six months and patients with advanced near terminal pump failure would not have been considered for an ICD.

To our surprise, patients with CSR were no more likely than patients without CSR to receive ICD discharges for significant ventricular arrhythmia. The total number of appropriate ICD discharges observed over the follow up period was large (432 episodes in 26 patients). CSR occurs most often and is most severe during sleep, when breathing is purely under the control of a chemical negative feedback loop. We expected that if CSR exerted its lethal effects through hypoxaemia induced ventricular arrhythmia then CSR patients would have higher rates of ICD discharges during the sleeping hours 0000 to 0600. Although our patients with CSR had worse indices of nocturnal oxygen saturation, patients did not differ according to their diurnal variation of ICD discharges. ICD discharges were clustered within the 0600–1200 quartile for both patients with and without CSR. This was in keeping with the known morning increased incidence of ventricular tachycardia and sudden death in heart failure.13 14

We note that our patients with CSR had poorer ventricular function, which may ordinarily be expected to lead to more arrhythmia. This obviously did not apply in our study because, by definition, all patients were already at a high risk of arrhythmia. The reason why nocturnal desaturation was not associated with serious ventricular arrhythmia is unclear. The degree of oxygen desaturation and hypoxia seen during central sleep apnoea is typically less severe than that observed in obstructive sleep apnoea. This may be of relevance when considering the individual roles of the various sleep apnoea syndromes as a substrate for arrhythmia (see below).

Nocturnal oxygen desaturation in the setting of an unstable coronary syndrome is a proven stimulus for ischaemia and lethal ventricular arrhythmia.15 Our patients had chronic stable heart failure; none had an unstable coronary syndrome. A single study has reported that CRT reduces the frequency of ICD discharge.16 The use of CRT devices did not explain the lack of association between CSR and serious ventricular arrhythmia because patients with CSR were just as likely as non-CSR patients to receive a CRT device. Furthermore, patients with CRT devices did not experience less arrhythmia and excluding CRT patients from the study analysis did not change its findings.

### Table 2

<table>
<thead>
<tr>
<th>Quartile</th>
<th>0000–0559</th>
<th>0600–1159</th>
<th>1200–1759</th>
<th>1800–2359</th>
</tr>
</thead>
<tbody>
<tr>
<td>% distribution of ICD discharges in each quartile</td>
<td>No CSR</td>
<td>35.6</td>
<td>31.9</td>
<td>22.7</td>
</tr>
<tr>
<td>CSR</td>
<td>1.4</td>
<td>61.6</td>
<td>25.9</td>
<td>11.1</td>
</tr>
<tr>
<td>Rates of ICD discharge per patient per month of follow up in each quartile</td>
<td>No CSR</td>
<td>0.04</td>
<td>0.15</td>
<td>0.15</td>
</tr>
<tr>
<td>CSR</td>
<td>0.01</td>
<td>0.86</td>
<td>0.3</td>
<td>0.11</td>
</tr>
<tr>
<td>p Value</td>
<td>0.54</td>
<td>0.99</td>
<td>0.74</td>
<td>0.94</td>
</tr>
</tbody>
</table>

### Previous investigations of cardiac arrhythmia in sleep apnoea

A large observational study has reported on the frequency of nocturnal arrhythmia in 400 consecutive patients with sleep apnoea (all types and aetiology) referred to the Stanford sleep disorders clinic.4 The usual rhythm disturbance was bradycardia, not tachycardia. Ventricular extrasystoles were common but ventricular tachycardia occurred in only 3% of patients. No ventricular tachycardia was observed in the subgroup (10% of patients) with central sleep apnoea. Other studies examining the prevalence of sleep apnoea4 8 and nocturnal oxygen desaturation17 18 in patients with chronic stable heart failure have reported a higher occurrence of arrhythmia on 24 hour Holter monitoring. Reliance on single Holter recording significantly reduces the power of these observational studies to discern the true nature of the arrhythmia burden of this patient group. All of these studies were consequently limited to reporting on the frequency of “soft” end points such as ventricular extrasystoles and NSVT. In the recent study by Lanfranchi et al,4 CSR during sleep inexplicably increased daytime (but not night-time) NSVT. Patients with heart failure and CPAP responsive sleep apnoea (obstructive and central) have been shown to experience a reduction in ventricular extrasystoles and couplets.19 This treatment effect does not prove that hypoxaemia was responsible for ventricular arrhythmia in CSR. CPAP not only improves overnight oxygenation but also reduces sympathetic nervous system activation, reduces left ventricular afterload, and increases cardiac output.

### Study limitations

Overnight oximetry (not polysomnography) was used to identify patients with likely CSR in the majority of patients. This does not limit our ability to comment on a link between nocturnal oxygen desaturation and arrhythmogenesis in chronic stable heart failure; indeed, we have previously validated the use of oximetry as a screening tool for CSR. We also performed a polysomnography substudy to confirm that the majority of apnoea events documented were indeed central rather than obstructive in origin. In the absence of oesophageal pressure balloon monitoring, some minor misclassification may have occurred. Oximetry was performed once only at baseline immediately before ICD implantation. The severity of nocturnal oxygen desaturation may have been reduced over the observation period, even though ICDs have no clinical effect on CSR, the use of CRT devices was equally split between the two groups, and medical treatment was not up-titrated as part of the study protocol. None of these detract from the major strength of this study: the deliberate use of high risk patients with ICDs implanted for arrhythmia to accurately document and define true clinical arrhythmia.
episodes and their temporal relation to likely nocturnal oxygen desaturation.

Conclusion
We have shown that nocturnal oxygen desaturation during CSR was not associated with an excess of serious ventricular arrhythmia. This implies that, if CSR exerts a lethal effect, it does so through a non-arrhythmic mechanism. These observations counter the findings and conclusions of two recent Holter monitor studies in CSR heart failure. An ICD alone will not therefore protect patients against the deleterious effects of CSR, for which further targeted treatments need to be considered.

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REFERENCES

IMAGES IN CARDIOLOGY
Collateral circulation in aortic coarctation shown by 64 channel multislice computed tomography angiography

A 21 year old man was referred for evaluation and endovascular treatment of aortic coarctation. Conventional aortography demonstrated a high grade, postductal aortic coarctation distal to the origin of the left subclavian artery with a delayed specification of the post-coarctation descending thoracic aorta both via the stenosis and via collateral pathways. When starting the endovascular procedure, the patient perceived sudden back pain. A 64 channel multislice computed tomography (MSCT) angiography (Sensation 64, Siemens, Germany) was performed and excluded a suspected acute aortic dissection. It furthermore demonstrated the morphology of the high grade aortic coarctation and the extensive collateral circulation. On the basis of the patient’s preference, open vascular aortoplasty was performed.

Chronic narrowing of the aortic lumen provokes development of collateral vessels to allow the flow of blood from high pressure to low pressure areas: from the internal thoracic arteries both to epigastric vessels and intercostal arteries, from the subclavian arteries via thoracoacromial and subscapular arteries to intercostal arteries, from the thyrocervical trunks via descending scapular arteries to intercostal arteries, and via vertebral and anterior spinal arteries. While conventional aortography is still considered the primary imaging modality for diagnosis and grading of aortic coarctation, MSCT angiography is likely to overtake its role in the preoperative work up. In particular, new generation 64 row MSCT scanners achieve unprecedented diagnostic detail by acquiring three dimensional datasets with a high spatial and temporal resolution.

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