HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

NATIONAL COMMITTEE FOR THE EVALUATION OF MEDICAL DEVICES AND HEALTH TECHNOLOGIES (CNEDiMTS)

OPINION

29 June 2010

CONCLUSIONS	
Name:	**AUTOSET CS**, adaptive servo-ventilation machines
Models and references:	AUTOSET CS and AUTOSET CS2
Manufacturer:	**RESMED Ltd**
Applicant:	**RESMED SAS FRANCE**
Claimed indications:	Adaptive servo-ventilation for the symptomatic treatment of patients with heart failure associated with Cheyne-Stokes breathing or suffering from central sleep apnoea, with or without upper airway obstruction.
Available data:	Seven comparative prospective studies and three non-comparative prospective studies which assessed adaptive servo-ventilation in the treatment of sleep apnoea in heart failure patients were submitted by the applicant. These mostly single-centre studies were conducted in small numbers of patients (between 11 and 51) and usually over short follow-up periods (between 1 night and 12 months). Two studies assessed the efficacy of adaptive servo-ventilation over a period of just 1 night. The main endpoints assessed in these studies related to sleep disorders (apnoea/hypopnoea index, nocturnal oxygen saturation, arousal index, etc.), heart failure parameters (left ventricular ejection fraction, plasma concentration of B-type natriuretic peptide, urinary catecholamine excretion, 6-minute walk test, etc.), quality of life and daytime sleepiness. These studies demonstrate that sleep disorders are corrected by the use of adaptive servo-ventilation. The changes in the heart failure parameters (e.g. left ventricular ejection fraction and plasma concentration of B-type natriuretic peptide) were of little clinical significance, and no improvement in the prognosis of heart failure was demonstrated. The results relating to quality of life and daytime sleepiness are conflicting and cannot serve as a basis for drawing conclusions.
Actual Benefit (AB) :	**Insufficient** The clinical data submitted are insufficient to establish the benefit of the AUTOSET CS range of adaptive servo-ventilation machines in respect of the morbidity and mortality of patients with heart failure associated with Cheyne-Stokes breathing or central sleep apnoea. The results of the international multi-centre SERVE-HF study, currently under way, should provide a basis for assessing the impact of sleep disorder correction with adaptive servo-ventilation on the course of heart failure.

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EVIDENCE REVIEW

Nature of the application

Application for inclusion on the list of products and services qualifying for reimbursement mentioned under article L. 165-1 of the French Social Security Code.

- **Models and references**

The application relates to two adaptive servo-ventilation machines in the AUTOSET CS range: AUTOSET CS, launched in the early 2000s, and AUTOSET CS2, launched in 2003. Both machines operate according to the same principle. AUTOSET CS2 is an updated version of the original AUTOSET CS machine which incorporates the following improvements: reduced weight, addition of new alarms (leaks, circuit impedance, sector alarm), improved user interface, addition of a circuit test function to take into account any adjustments made by the user (masks/accessories), integration of the heated humidifier.

- **Packaging**

The ventilation machine with air tubing and pressure sensor, along with a carry bag, are packaged in a box.

- **Applications**

Application for inclusion under brand name for a weekly rate for provision of adaptive servo-ventilation < 12 hours by machines in the AUTOSET CS range (AUTOSET CS and AUTOSET CS2).

The application for inclusion relates to the following indication:

> "Adaptive servo-ventilation for the symptomatic treatment of patients with heart failure associated with Cheyne-Stokes breathing or suffering from central sleep apnoea, with or without upper airway obstruction."

Reimbursement history

First request for inclusion on the reimbursement list under brand name for adaptive servo-ventilation in the treatment of sleep disorders in heart failure patients.
The AUTOSET CS machine, which can operate in a continuous positive pressure mode, can be included in the following indication:

- continuous positive airway pressure for the treatment of sleep apnoea (weekly rate 9).

Characteristics of the product and the associated service

- **CE marking**

Class IIa. Notification by SGS United Kingdom Ltd (0102), United Kingdom.

- **Description**

AUTOSET CS is an adaptive servo-ventilation machine categorised as an inspiratory aid with positive expiratory pressure. AUTOSET CS includes a central unit and respiration system. The mask is supplied separately, according to medical prescription. The central unit is responsible for delivering filtered ambient air and monitoring the patient's breathing via the recording of various parameters (target ventilation, tidal volume, apnoea/hypopnoea index, respiratory rate, expiratory/inspiratory pressure, etc.) and their analysis based on an algorithm. The respiration

system is made up of an air tube of 2 m in length and a pressure sensor tube attached directly to the mask.
Accessories can be added: supplemental oxygen, antibacterial filter, humidifier (integrated into the AUTOSET CS2 model), ResLink module (stores data on patient compliance and on the efficacy of the treatment, notably oxymetry), ResControl II module (sends data to a polysomnography system for parallel analysis).

- **Intended purpose**

AUTOSET CS is an adaptive servo-ventilation machine which adjusts the level of inspiratory support automatically in response to the patient's respiratory effort. Inspiratory support is increased in the presence of hypoventilation and decreased in the presence of hyperventilation. The ASV-CS algorithm, incorporated into the central unit, provides continuous monitoring of the patient's respiratory flow and calculates the inspiratory support required to attain the target ventilation level (fixed at 90% of the average ventilation recently recorded for the patient). The machine also delivers a constant positive expiratory pressure to maintain upper airway patency. The machine is regulated on the basis of a backup respiratory rate of 15 breaths per minute, where the patient has apnoea.

Two modes of operation are available for AUTOSET CS:
- Adaptive servo-ventilation mode (ASV-CS mode) for the treatment of Cheyne-Stokes breathing with or without obstructive sleep apnoea syndrome (not included on the LPPR list (List of Reimbursable Products and Services) – subject of the present application).
- Continuous positive airway pressure mode (CPAP mode) for the treatment of obstructive sleep apnoea syndrome (included on the LPPR list – weekly rate 9).

- **Associated intervention or service**

The applicant proposes identical service to that associated with the rate for assisted ventilation < 12 h (LPPR code 1196270). The service providers, specialists in respiratory support, are trained to operate the machines by RESMED's regional teams of clinical specialists.

Actual Benefit

1. Benefit of the product or service

1.1 Data analysis: assessment of the therapeutic effect/adverse effects, risks linked to use

All the studies submitted were conducted with AUTOSET CS or AUTOSET CS2.

1. Comparative prospective studies

The comparative prospective studies which assessed adaptive servo-ventilation (ASV) in the treatment of sleep apnoea in patients with heart failure are listed in the following table. Of these studies, those with a randomised design are summarised in the tables in the Annex.

Author and year	Study design	Treatments compared	Duration of treatment	Number of patients
Pepperell et al. 2003 [1]	- Randomised - Double-blind - Single-centre	- ASV in therapeutic mode - ASV in subtherapeutic mode	4 weeks	30 patients
Philippe et al. 2006 [2]	- Randomised - Single-centre	- ASV - CPAP	6 months	25 patients
Morgenthaler et al. 2007 [3]	- Randomised - Cross-over - 2 centres	- ASV - nBiPAP	1 night	21 patients
Teschler et al. 2001 [4]	- Randomised - Cross-over - Single-centre	- ASV - Oxygen therapy - CPAP - nBiPAP	1 night	14 patients
Zhang et al. 2006 [5]	- Non-randomised - Cross-over - Single centre	- ASV - Oxygen therapy	2 weeks	14 patients
Hastings et al. 2008 [6]	*- Non-randomised* *- 2 centres*	*- ASV* *- No treatment*	*6 months*	*19 patients*
Oldenburg et al. 2009	*Not specified*	*- ASV* *- No treatment*	*3 months on average*	*98 patients*

ASV: Adaptive servo-ventilation
nBiPAP: Nasal bi-level positive airway pressure
CPAP: Continuous positive airway pressure

The study by Pepperell et al. was a randomised, double-blind study which included 30 patients and compared (15 patients per group) adaptive servo-ventilation (ASV) in therapeutic mode (treated group) with ASV in subtherapeutic mode (control group). The primary endpoint was the improvement in the patients' daytime sleepiness, assessed using the Osler maintenance of wakefulness test. The Osler test assesses patients' ability to remain awake (response to light stimulation) for 40 min. in a dark room. The patients treated with AVS for 1 month showed an improvement in the Osler test. The increase in the observed Osler score (+7.9 min.) was of the same order of magnitude as that observed (+6.8 min.) in a study assessiing the effect of continuous positive airway pressure in patients with obstructive sleep apnoea[7]. The Pepperell study showed, in the treated group, a significant reduction in the apnoea-hypopnoea index (AHI), B-type natriuretic peptide levels and sympathetic activity (assessed on the basis of urinary catecholamine levels), but no improvement in quality of life.
This study is satisfactory from a methodological viewpoint. The patients included are representative of the target population (NYHA II to IV and under stable medical treatment). However, the study was conducted in a limited number of patients. Furthermore, the choice of primary endpoint is controversial in that patients with Cheyne-Stokes breathing suffer less from daytime sleepiness than those with obstructive sleep apnoea syndrome[8]. This observation may explain the absence of improvement in quality of life.

[1] Pepperell JCT, Maskell NA, Jones DR, Langford-Wiley BA, Crosthwaite N, Stradling JR et al. A randomized controlled trial of adaptive ventilation for Cheyne-Stokes breathing in heart failure. Am J Respir Crit Care Med 2003; 168:1109-14
[2] Philippe C, Stoïca-Herman M, Drouot X, Raffestin B, Escourrou P, Hittinger L et al. Compliance with and effectiveness of adaptive servoventilation versus continuous positive airway pressure in the treatment of Cheyne-Stokes respiration in heart failure over a six month period. Heart 2006;92(3):337–42
[3] Morgenthaler TI, Gay PC, Gordon N, Brown LK. Adaptive servoventilation versus non-invasive positive pressure ventilation for central, mixed and complex sleep apnea syndromes. Sleep 2007;30(4):468-75
[4] Teschler H, Dohring J, Wang YM, Berthon-Jones M. Adaptive pressure support servo-ventilation: a novel treatment for Cheyne-Stokes respiration in heart failure. Am J Respir Crit Care Med. 2001;164(4):614–9
[5] Zhang X, Yin K, Li X, Jia E, Su M. Efficacy of adaptive servoventilation in patients with heart failure and Cheyne-Stokes respiration. Chin Med J 2006;119(8):622–7
[6] Hastings PC, Vazir A, Meadows GE, Dayer M, Poole-Wilson PA, McIntyre HF et al. Adaptive servo-ventilation in heart failure patients with sleep apnea: a real world study. Int J Cardiol 2010;139(1):17-24
[7] Jenkinson C, Davies RJO, Mullins R, Strading JR. Comparison of therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnoea: a randomised prospective parallel trial. Lancet 1999;353:2100-5
[8] Brack T. Traitement de la respiration de Cheyne-Stokes dans l'insuffisance cardiaque. Forum Med Suisse, 2006;6:1092-6

Philippe et al. compared compliance with and the efficacy of ASV versus continuous positive airway pressure (CPAP) in a randomised, open-label, parallel-group study over six months in 25 patients with stable heart failure (NYHA class II-IV with a left ventricular ejection fraction (LVEF) of < 45%) and central sleep apnoea syndrome (SAS) associated with Cheyne-Stokes breathing and who had never been treated with nocturnal ventilation. The primary endpoint was not defined. Compliance was identical at 3 months but superior at 6 months under ASV compared with CPAP. In the course of the 6-month period, three out of the twelve patients under ASV and five out of the 13 under CPAP stopped their treatment. The authors attributed the failure of CPAP in some patients to the inability to achieve the optimum pressure level because of haemodynamic instability. The reduction in the apnoea-hypopnoea index was also greater under ASV than under CPAP. The other endpoints (left ventricular ejection fraction and quality of life) also favoured ASV. However, left ventricular ejection fraction was measured only in seven patients under ASV and six under CPAP. There was no significant improvement in the patients' daytime sleepiness. The patients were only a little sleepy, if at all, on inclusion.
This study demonstrated the long-term efficacy of ASV, with better compliance compared with CPAP. However, the lack of an untreated control group and the small number of patients included limit the meaningfulness of these results.

The study by Morgenthaler et al. was a randomised, open-label cross-over study which compared nasal bi-level positive airway pressure (nBiPAP) with ASV for a period of one night in 21 heart failure patients (the degree of heart failure not being specified) with central apnoea associated with Cheyne-Stokes breathing, mixed apnoea or complex apnoea (defined by the onset of central apnoea or hypopnoea under treatment with CPAP) and tolerating ventilation. The primary endpoint of the study was the apnoea-hypopnoea index. The study showed the superiority of ASV in terms of correction of (notably central) apnoea.
The statistical significance of the result is of no clear clinical relevance, however: the apnoea-hypopnoea index was estimated to be 6 events/hour under nBiPAP and 0.8 events/hour under ASV. In both cases (under nBiPAP and under ASV), normal sleep architecture and normal nocturnal oxygen saturation were observed. The patients may therefore be considered as "correctly treated" with both methods of ventilation.

Teschler et al. compared the efficacy, over a period of one night, of four methods of nocturnal ventilation (oxygen therapy, CPAP, nBiPAP or ASV) in 16 stable heart failure patients with Cheyne-Stokes breathing in a randomised, open-label, cross-over study. The inclusion criteria did not define the degree of heart failure. The endpoints were not defined prospectively. The measurements performed related to sleep-disordered breathing. The results were in favour of ASV in terms of nocturnal respiratory events (reduction in the apnoea-hypopnoea index). The desaturation index and the arousal index were improved by all four treatments assessed.

The study by Zhang et al. was an open-label, non-randomised cross-over study which compared, in each patient, the effects of 14 nights of nocturnal oxygen therapy with those of 14 nights of ASV (separated by 14 nights without treatment). The heart failure patients with Cheyne-Stokes breathing had a left ventricular ejection fraction of 30.8 ± 4.6% and a nocturnal apnoea-hypopnoea index of 33.8 ± 5.9 per hour. The endpoints were not defined prospectively. The measurements performed related to sleep-disordered breathing and cardiac function parameters. A greater reduction in the apnoea-hypopnoea index was observed under ASV (6.5 ± 0.8 events/h) than under oxygen therapy (27.8 ± 8.2 events/h), with a greater improvement in left ventricular ejection fraction (37.2 ± 4.1% compared with 33.2 ± 5.1%), nocturnal oxygen saturation and walking distance.
The study has certain limitations. Administration of the treatments in the same order (O_2 followed by ASV) may explain the gradually favourable changes in left ventricular ejection fraction and walking distance.

The study by Hastings et al., which was non-randomised, included heart failure patients who mostly had obstructive apnoea in the treated group. This population was not representative of the claimed indication. This study was not therefore used by the Committee in the risk-benefit assessment.

The study by Oldenburg et al. (2009) was submitted in the form of a poster presented to the European Society of Cardiology Congress 2009. Because it only formed the subject of a poster, this study cannot be used by the Committee in the risk-benefit assessment.

These comparative studies[1 2 3 4 5] related to a limited number of patients over often short follow-up periods, with two studies (Morgenthaler and Teschler) assessing the efficacy of ASV over the period of only one night.
These studies[1 2 3 4 5] demonstrated the efficacy of adaptive servo-ventilation in the correction of sleep apnoea in heart failure patients (reduction in the apnoea-hypopnoea index, improvement in oxygen saturation, etc.). Some studies also showed an improvement in heart failure parameters such as left ventricular ejection fraction or B-type natriuretic peptide concentration. An improvement in quality of life and daytime sleepiness was not identified systematically, however. None of the studies permitted the demonstration of a beneficial effect of adaptive servo-ventilation on patient morbidity and mortality.

2. Non-comparative prospective studies

The non-comparative prospective studies which assessed the effect of adaptive servo-ventilation (ASV) in heart failure patients with Cheyne-Stokes breathing are listed in the table below.

Author and year	Study design	Treatments compared	Duration of treatment	Number of patients
Oldenburg et al. 2008 [9]	- Single centre	- ASV alone (before-after comparison)	5.8 months on average [range: 3-14 months]	51 patients
Schädlich et al. 2004 [10] *In German* *Translation submitted*	- Single centre	- ASV alone (before-after comparison)	12 months	20 patients
Töpfer et al. 2004 [11] *In German* *Translation submitted*	- Single centre	- ASV alone (before-after comparison)	6 weeks	11 patients

ASV: Adaptive servo-ventilation

The series conducted by Oldenburg et al. related to 29 heart failure patients with a left ventricular ejection fraction of ≤ 40%, classified as NYHA II-IV, who had Cheyne-Stokes breathing (apnoea-hypopnoea index ≥ 15 events/h), treated with ASV, in whom there were no conventional treatment options. The endpoints were not defined prospectively. The measurements were performed before the instigation of treatment and then after a follow-up period of 5.8 months on average (between 3 and 14 months, depending on the patient). These related to sleep-disordered breathing and cardiac function parameters. The study demonstrated efficacy of AVS on sleep anomalies (the apnoea-hypnoea index decreased from 37.4 ± 9.4 events/h to 3.8 ± 4.1 events/h), with a reduction in B-type natriuretic peptide levels (from 2.285 ± 2,192 pg/ml to 1.061 ± 1.293 pg/ml) and an improvement in the left ventricular ejection fraction (from 28.2 ± 6.9% to 35.2 ± 10.6%). Three patients withdrew from the study because of mask problems. This well conducted but solely descriptive study without any comparison group does not provide a sufficient basis for ascertaining whether the changes in the heart failure parameters were related directly to the AVS or to the spontaneous course of the disease.

[9] Oldenburg O, Schmidt A, Lamp B, Bitter T, Muntean BG, Langer C et al. Adaptive servoventilation improves cardiac function in patients with chronic heart failure and Cheyne-Stokes respiration. Eur J Heart Fail 2008; 10(6): 581-6
[10] Schädlich S, Königs I, Kalbitz F, Blankenburg T, Busse HJ, Schütte W. Kardiale Leistungsfähigkeit bei patienten mit Cheyne-Stokes-atmung infolge Herzinsuffizienz während langfristiger nasaler beatmungstherapie mittels adaptiver servoventilation (AutoSet CS). Z Kardiol 2004; 93(6): 454-62
[11] Töpfer V, El-Sebal M, Wessendorf TE, Moraidis I, Teschler H.Adaptive servoventilation bei chronischer herzinsuffizienz: wirkung auf Cheyne-Stokes-atmung und lebensqualität. Pneumologie 2004; 58(1): 28-32

Schädlich et al. conducted a descriptive follow-up study in 20 heart failure patients with a left ventricular ejection fraction of between 20% and 50% and classified as NYHA II-III, who had Cheyne-Stokes breathing and had been under treatment with AVS for one year. The endpoints were not defined prospectively. The measurements performed related to sleep-disordered breathing, cardiac function parameters, sleepiness and quality of life. AVS improved sleep quality by reducing the apnoea-hypopnoea index and the micro-arousal index and by improving the hypoxia. There was no improvement in sleepiness or in the patients' quality of life. There was an improvement in the 6-minute walk test and a modest improvement in the left ventricular ejection fraction. Because the methodology was similar to that used in the Oldenburg study, the same kind of reservations are applicable.

Töpfer et al. conducted a descriptive study in 11 heart failure patients with a left ventricular ejection fraction of < 40%, who had Cheyne-Stokes breathing and who had been treated with AVS for six weeks. This study showed that AVS was effective in reducing the apnoea-hypopnoea index and the arousal index and in improving patients' quality of life. No analysis was performed on the basis of heart failure parameters.

As observed in the comparative studies, these non-comparative studies[9] [10] [11] showed AVS to be effective in correcting sleep disorders in heart failure patients and an improvement in the heart failure parameters. The results relating to quality of life and sleepiness are conflicting and cannot serve as a basis for drawing conclusions.

3. Retrospective study

One single-centre retrospective study published by Allam et al. in 2007 compared the short-term efficacy (during a titration test) of various ventilation techniques: adaptive servo-ventilation, continuous positive airway pressure and nasal bi-level positive airway pressure. This study was not used by the Committee in the risk-benefit assessment in view of its retrospective nature.

4. Ongoing studies

The applicant submitted the protocol summaries for three studies (SERVE-HF, FACE and SATELIT-HF) either under way or scheduled. These studies are intended to assess the efficacy of adaptive servo-ventilation in heart failure patients.

Among these studies, the SERVE-HF study was singled out by the Committee as being of relevance. The objective of this study is to assess the long-term effects and cost-effectiveness of adaptive servo-ventilation in respect of mortality and morbidity in patients with stable heart failure caused by left ventricular systolic dysfunction who are already receiving optimal medical treatment and who have sleep-disordered breathing that is predominantly of central origin. This international, multi-centre study must include 1,260 patients (with 400 in France), randomised (1:1) to receive either the control treatment (optimal medical management) or the active treatment (optimal medical treatment combined with adaptive servo-ventilation). The primary endpoint is a morbidity/mortality criterion. The patients will be followed up for 33 months on average (minimum follow-up period: 24 months – maximum follow-up period: 45 months). This study should provide a basis for assessing the impact of treatment with adaptive servo-ventilation for sleep disorders on the course of heart failure.

The FACE study complements the SERVE-HF study. Its objective is to define the profile of heart failure patients who respond to adaptive servo-ventilation. This is a French prospective, observational multi-centre study with a control group. It is designed to follow up 300 patients for a period of 24 months.
Finally, the SATELIT-HF study, sponsored by the French Cardiology Society (Société Française de Cardiologie), will assess the improvement in physical performance in heart failure patients with sleep disorders treated with adaptive servo-ventilation compared with patients receiving physical training alone.

In view of the data submitted, the Committee notes the benefit of adaptive servo-ventilation in the correction of sleep disorders in heart failure patients with Cheyne-Stokes breathing or central sleep apnoea. It nevertheless highlights the failure to demonstrate an improvement in the prognosis of heart failure. Changes in the parameters of cardiac function such as an increase of a few points in the ventricular ejection fraction are considered to be of little clinical relevance.

In the absence of any study enabling a benefit of adaptive servo-ventilation to be demonstrated in terms of patient morbidity and mortality, the Committee considers the therapeutic/adverse effects ratio of the AUTOSET CS adaptive servo-ventilation machine not to have been established in heart failure patients with Cheyne-Stokes breathing or central sleep apnoea.

The Committee wishes to highlight the relevance of the SERVE-HF study, set up by the applicant. This study should provide a basis for assessing the impact of treatment with adaptive servo-ventilation for sleep disorders on the course of heart failure.

1.2 Therapeutic use

The first-line treatment of Cheyne-Stokes breathing in heart failure patients is based on the optimal management of the heart failure. Cheyne-Stokes breathing is common during periods of decompensated heart failure and may disappear with haemodynamic improvement[12].

According to the European[13] and American[14] recommendations, this management comprises dietary and lifestyle measures, optimisation of the doses of pharmacological treatment (angiotensin-converting enzyme (ACE) inhibitors and/or angiotensin II receptor antagonists as well as beta blockers are prescribed in the maximum tolerable doses) and implantation of a cardiac resynchronisation therapy pacemaker (if indicated).

According to the recommendations of the European Society of Cardiology[13], sleep disorders (of central or obstructive origin) are common in symptomatic heart failure patients and they may be associated with an increase in morbidity and mortality. Continuous positive airway pressure (CPAP) is recommended for the management of obstructive sleep apnoea syndrome (OSAS). No recommendations exist regarding the management of central sleep apnoea syndrome or Cheyne-Stokes breathing.
According to the recommendations of the American College of Cardiology[14], the use of nocturnal oxygen therapy and continuous positive airway pressure produces an improvement in symptoms. However, there is no evidence to state that the treatment of sleep disorders improves heart failure.

[12] Pépin JL, Chouri-Pontarollo N, Tamisier R, Lévy P. Cheyne-Stokes respiration with central sleep apnoea in chronic heart failure: proposals for a diagnostic and therapeutic strategy. Sleep Med Rev. 2006 Feb; 10(1): 33-47
[13] Dickstein K, Cohen-Solal A, Filippatos G, JJV McMurray, P Ponikowski, PA Poole-Wilson et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur Heart J 2008; 29: 2388-442
[14] Jessup M, Abraham WT, Casey DE, AM Feldman, GS Francis, TG Ganiats et al. 2009 focused update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. Circulation 2009; 119: 1977-2016

No recommendations are given on the need to treat central sleep apnoea syndrome or Cheyne-Stokes breathing in heart failure patients.

Various treatments for correcting Cheyne-Stokes breathing in heart failure patients have been assessed.

◆ Respiratory stimulants (theophylline and acetazolamide) and CO_2 inhalation are not recommended owing to lack of scientific evidence

◆ Nocturnal oxygen therapy is not recommended. On the basis of a limited number of studies, it has demonstrated, at best, a reduction in the symptoms of Cheyne-Stokes breathing but no effect on the cardiac parameters or on quality of life

◆ The use of continuous positive airway pressure (CPAP) has been assessed more extensively.

Two studies are available:

- A single-centre, randomised and controlled study was conducted by Sinn et al.[15] in 66 patients with severe heart failure followed up over a period of 5 years (29 patients had periodic breathing and 37 had no sleep-disordered breathing). This study showed that treatment with CPAP reduced mortality and the number of heart transplants in patients with periodic breathing compared with no ventilatory treatment. This improvement, observed under CPAP, was not identified in patients without sleep disorders
- A Canadian multi-centre study (CANPAP study)[16] compared CPAP in autopilot mode (n = 128 patients) with no ventilatory support (n = 130 patients) in heart failure patients with central sleep apnoea. This study showed an improvement in the symptoms of Cheyne-Stokes breathing, in nocturnal oxygen saturation, in circulating catecholamine levels, in the 6-minute walk test and in left ventricular ejection fraction in the patients treated with CPAP, but did not demonstrate any improvement in survival.

These conflicting results for the two studies may be attributable to an improvement in the pharmacological treatment of the heart failure (with the use of ACE inhibitors, spironolactone and beta blockers) having produced an improvement in overall survival and to “overtitration” of the nocturnal pressure linked to the autopilot mode of CPAP ventilation. Because it corresponds to excessive airway pressure, this “overtitration” might be responsible for a reduction in the cardiac index and a reduction in blood pressure which could result in death.

◆ Nasal bi-level positive airway pressure (nBiPAP) provides the patients with a constant inspiratory pressure, at a rate modelled on the basis of the patient’s respiratory rate or at a backup rate if the patient is apnoeic. The machine also maintains a constant positive expiratory pressure. The efficacy of this technique in heart failure patients with Cheyne-Stokes breathing was compared with that of CPAP by Köhnlein et al.[17]. The authors concluded that the efficacy of the two techniques was comparable in terms of apnoea-hypopnoea index, microarousals, sleep quality, daytime wakefulness and nocturnal oxygen saturation. The studies by Morgenthaler [3] and Techler [4] described above also assessed nasal bi-level positive airway pressure in the treatment of Cheyne-Stokes breathing in heart failure patients.

[15] Sin DD, Logan AG, Fitzgerald FS, Liu PP, Bradley TD. Effects of continuous positive airway pressure on cardiovascular outcomes in heart failure patients with and without Cheyne-Stokes respiration. Circulation 2000; 102 (1): 61-6

[16] Bradley TD, Logan AG, Kimoff RJ, Series F, Morrisson D, Fergusson K et al. CANPAP investigators. Continuous positive airway pressure for central apneas in heart failure. N Engl J Med 2005; 353(19) 2025-33

[17] Köhnlein T, Welte T, Tan LB, Elliott MW. Assisted ventilation for heart failure patients with Cheyne-Stokes respiration. Eur Respir J. 2002; 20: 934–41

In conclusion, none of these treatments is currently considered as a reference treatment for Cheyne-Stokes breathing in heart failure patients. The first-line treatment of heart failure patients with Cheyne-Stokes breathing is based on the optimisation of the heart failure treatment (medical treatment and pacemaker cardiac resynchronisation therapy), with the haemodynamic improvement possibly leading to elimination of the symptoms of apnoea.

The Committee considers that the results to come out of the SERVE-HF study should provide a basis for defining the therapeutic use of adaptive servo-ventilation in heart failure

2. Expected public health benefit

2.1 Seriousness of the condition

Cheyne-Stokes breathing is an irregular, cyclic breathing pattern which can occur both during the day and at night (more frequent during sleep). It is characterised by alternating periods of hyperpnoea with a crescendo-decrescendo pattern of tidal volume interrupted by periods of central hypopnoea/apnoea[18]. The periods of hyperventilation and apnoea are accompanied by arousals which correlate to an increase in sympathetic tonus and to catecholamine release, the cause of arrhythmias and cardiovascular complications[8]. Cheyne-Stokes breathing is diagnosed on the basis of polygraphy or polysomnography.

Patients with Cheyne-Stokes breathing are often less symptomatic and suffer less from daytime sleepiness than patients with obstructive sleep apnoea syndrome. This observation may explain patients' poor compliance with their ventilation treatment and the lack of improvement in quality of life in some studies.

Cheyne-Stokes breathing is a symptom which can be found in various conditions: heart failure, stroke, encephalitis, metabolic syndrome, etc. It is considered as a marker of severity of the underlying condition.

The presence of Cheyne-Stokes breathing in patients with heart failure is a factor for poor prognosis[19] associated with an increased mortality risk[20]. A direct link between Cheyne-Stokes breathing and increased risk of morbidity/mortality in these patients has not been established, however. Likewise, a reduction in morbidity/mortality following the correction of Cheyne-Stokes breathing remains to be demonstrated.

2.2 Epidemiology of the condition

In France, the prevalence of heart failure in the general population is estimated to be between 1% and 2%. It increases with age. The number of heart failure patients has been estimated to be between 500,000 and 1 million, with 120,000 new cases each year. Two thirds of these patients are over 70 years of age.
The overall mortality associated with symptomatic heart failure is around 50% in the 4 years following diagnosis. Heart failure is considered to be responsible for more than 32,000 deaths per year in France. The number of hospital admissions relating to heart failure in France is estimated to be 150,000 per year (average in-patient stay of 11 days)[21].

[18] Kohnlein T, Welte T, Tan LB, Elliott MW. Central sleep apnoea syndrome in patients with chronic heart disease: a critical review of the current literature Thorax 2002; 57(6): 547–54
[19] Lanfranchi PA, Braghiroli A, Bosimini MD, Mazzuero G, Colombo R, Donner CF et al. Prognostic Value of Nocturnal Cheyne-Stokes Respiration in Chronic Heart Failure. Circulation 1999; 99: 1435-40
[20] Hanly PJ, Zuberi-Khokar NS. Increased mortality associated with Cheyne-Stokes respiration in patients with congestive heart failure. Am J Respir Crit Care Med 1996; 153: 272-6
[21] Delahaye F, de Gevigney G. Epidémiologie de l'insuffisance cardiaque. Ann Cardiol Angéiol. 2001 ; 50 : 6-11

Sleep-related respiratory disorders are thought to be present in 50-75% of patients with chronic heart failure. The apnoea is considered to be of an obstructive nature in 20-45% of cases and of a central nature in 25-40% of cases. These two types of disorder can coexist in the same patient (mixed apnoea).
A prevalence of between 15 and 37% has been described for Cheyne-Stokes breathing in patients with heart failure[22]. A reduction in prevalence has been observed in parallel with improvements in the pharmacological management of heart failure (introduction of beta blockers, notably).

Heart failure is a public health concern in France on account of its frequency and seriousness (numerous hospital admissions, high mortality). It represents a significant proportion of expenditure on health. The presence of Cheyne-Stokes breathing is a factor for poor prognosis in heart failure patients.

2.3 Impact

Continuous positive airway pressure is the only method of ventilation covered for the treatment of sleep apnoea (weekly rate 9).

Cover is guaranteed for patients with:

- daytime sleepiness
- and at least three of the following symptoms: snoring, morning headaches, reduced alertness, loss of libido, arterial hypertension, nocturia, associated:
    * either with an apnoea-hypopnoea index (AHI) (refers to the number of apnoeas plus hypopnoeas per hour of sleep) of 30 events or more per hour on polygraphic analysis
    * or, if this index is below 30, with at least ten microarousals per hour of sleep associated with an increase in respiratory effort documented by polysomnographic analysis

In summary, the Actual Benefit associated with adaptive servo-ventilation machines in the AUTOSET CS range is insufficient for them to be included on the List of products and services qualifying for reimbursement (LPPR) mentioned under article L. 165-1 of the French Social Security Code.

[22] Yumino D, Bradley TD. Central sleep apnea and Cheyne-Stokes respiration. Proc Am Thor Soc 2008;5:226–36