SERVE-HF clinical study
SERVE-HF is the first long-term randomised, controlled, international, multicentre study designed to assess the effects of adaptive servo-ventilation (ASV) on morbidity and mortality in patients with symptomatic chronic heart failure (HF) with reduced left ventricular ejection fraction (LVEF) and predominant central sleep apnoea-Cheyne-Stokes respiration (CSA-CSR).

The results of the SERVE-HF study were first presented by Professor Martin Cowie, M.D., (co-principal investigator of the study and Professor of Cardiology at Imperial College London) at the 2015 ESC congress in London and have been published in the New England Journal of Medicine (NEJM).1

- The primary endpoint of the SERVE-HF study was a composite of all-cause mortality and unplanned hospitalisation for worsening heart failure. There was no statistically significant difference in this outcome between patients treated with ASV in addition to guideline-based medical therapy compared to those who received guideline-based medical therapy alone (control).
- However, both all-cause and cardiovascular mortality occurred significantly more often in the ASV group.
- Subgroup analysis showed that the increased risk of death was found in patients with more severe heart failure (LVEF < 30%).

Although ASV effectively controlled sleep apnoea, as seen by significant reductions from baseline in the apnoea-hypopnea index (AHI) and improvements in Epworth Sleepiness Scale (ESS) scores, there were no improvements in any of the functional outcomes assessed or in quality of life for patients from the ASV group. Compliance with ASV therapy was at or above the expected level for a trial of this type in the patient population studied.

Despite, or perhaps because of, these very unexpected results, SERVE-HF is a key study in its field, and will contribute above the expected level for a trial of this type in the patient population studied.

Study design

Study methodology

- Chronic, stable HF patients with LVEF < 45%
- New York Heart Association (NYHA) III or IV (or NYHA II and hospitalised for worsening HF in the previous 24 months)
- Optimised medical HF therapy according to guidelines
- Sleep apnoea, predominantly central AHI ≥ 10/h based on total recording time documented on polygraphy (PSG) or polysomnography (PSG)

Randomisation

Optimal medical treatment

Optimal medical treatment + Autoset™ CS PaceWave™

Minimum 2 years’ follow up

Enrolment took place from February 2008 to May 2013. The study was completed in April 2015.

Study results

Study population

- There were no significant differences in baseline characteristics between the control and ASV groups:
  - The average patient age was 69 years;
  - The population was predominantly male (90%) and overweight;
  - Most had moderate to severe HF (70.4% were in NYHA class III or IV) with a low LVEF (mean 32.3±7.9);
  - The population was predominantly male (90%) and overweight;
  - The average patient age was 69 years;

Primary endpoint

Time to first event of the composite of:

- All-cause death
- A life-saving cardiovascular intervention
- An unplanned hospitalisation for worsening chronic HF

Primary endpoint was neutral. The ASV did not improve the outcome of patients with heart failure with a reduced ejection fraction and predominant CSA.

The incidence of the primary endpoint did not differ significantly between the ASV and control groups, with event rates of 54.1% and 50.8% respectively (hazard ratio [HR] 1.13; 95% CI, 0.97 - 1.31; P=0.10) (Figure 1).

ASV therapy initiation

Adjustment of ASV was performed in the hospital using polysomnographic or polygraphic monitoring. Default settings were used (expiratory positive airway pressure, 5 cm of water; minimum pressure support, 3 cm of water; and maximum pressure support, 10 cm of water).

The expiratory positive airway pressure was increased manually to control obstructive sleep apnoea (OSA), and the maximum pressure support was increased to control CSA.

A full face mask was recommended for the initiation of ASV. Patients were advised to use the ASV device for at least 8 hours per night, 7 days per week. Adherence to therapy was defined as ASV use for an average of at least 3 hours per night.

Follow-up

Clinic visits took place at study entry, after 2 weeks, at 3 and 12 months, and every 12 months thereafter until the end of the study. Patients in the ASV group also underwent polygraphy or polysomnography at each visit and ASV device data were downloaded.
ASV use was associated with increased all-cause and cardiovascular mortality. All-cause mortality was higher in the ASV group (34.8%) than in the control group (29.3%); (HR 1.28, 95% CI, 1.06 - 1.55; p<0.01) (Figure 2).

A similar effect was seen for cardiovascular mortality, which was 29.9% in the ASV group and 24.0% in the control group; (HR 1.34, 95% CI, 1.09 - 1.65; p=0.006) (Figure 3).

The observed difference in cardiovascular mortality between treatment groups was largely explained by cardiovascular death without prior hospitalisation for worsening heart failure or life-saving cardiovascular intervention (HR 3.10, 95% CI, 1.76 - 5.48; p < 0.001) (Figure 4). This probably reflects sudden cardiac death.

SERVE-HF did not find a difference between treatment groups in the rate of unplanned hospitalisation for worsening heart failure (HR 1.13, 95% CI, 0.95 - 1.20, p=0.16).

ASV reduced sleepiness but did not improve functional outcomes and quality of life

Although ESS scores decreased in both the ASV and control groups, the change was significantly greater in the ASV group (p<0.001) (Figure 5).

There were no statistically significant differences between treatment groups with respect to general (EQ-5D) or disease-specific (MLHFQ) quality of life (Figures 6 & 7) or NYHA functional class (Figure 8). Six-minute walk distance showed a gradual decline in both the control and ASV groups, but the decline was significantly more pronounced in the ASV group (p=0.02) (Figure 9).
Subgroup analyses: the role of CSR and LVEF

Subgroup analyses were conducted for the primary endpoint and for cardiovascular mortality. In the analysis of the primary endpoint, there was a significant modification of effect by the degree of Cheyne-Stokes Respiration (CSR) at baseline (Figure 10). In the analysis of cardiovascular mortality, there was a significant modification of effect by CSR (Figure 11). This result suggests that the detrimental effects of ASV therapy observed during SERVE-HF was particularly evident in patients with the most severe grade of systolic heart failure (i.e. LVEF < 30%).

ASV therapy effectively controlled central sleep apnoea

In the ASV group, there was a reduction in AHI from 31.2/h at baseline to 6.7/h at 12 months (p < 0.001), and in the desaturation index from 32.1/h at baseline to 8.9/h (p < 0.001).

Adherence to ASV was satisfactory

60% of the patients in the ASV group used the device for an average of 3 hours per night or more during the trial period.

Consistent pressures applied

Pressures applied during ASV therapy were consistent throughout the study follow-up period.

Interpreting the SERVE-HF study results

The early and sustained increase in cardiovascular mortality seen in the ASV group in SERVE-HF was unexpected and potential pathophysiological mechanisms that might explain these findings remain to be determined. At this stage, two possibilities have been suggested.

The first is that CSA, and in particular CSR, may be a compensatory mechanism in patients with heart failure. This hypothesis has been suggested previously. If this hypothesis is valid, diminishing this compensatory adaptive respiratory pattern with ASV may be detrimental in patients with heart failure. The SERVE-HF subgroup analysis results that show a positive association between the proportion of CSR and the adverse effect of ASV on the primary outcome would support this interpretation.

Secondly, it is possible that the application of positive airway pressure may impair cardiac function in at least some patients with heart failure, although it is not possible to draw any conclusions on the basis of available data.

It is hoped that additional information will be provided by the SERVE-HF major substudy, which enrolled a subset of 312 SERVE-HF participants. This substudy will assess changes in LVEF at 1 year using echocardiography (primary endpoint). It is also designed to examine changes in ventricular remodelling, biomarkers (such as brain natriuretic peptide levels), disease-specific quality of life, cognitive function and depression, and sleep and respiratory parameters.

For comparisons with baseline: *P < 0.001, †P=0.02, ‡P=0.002, §P=0.03, ¶P=0.006, **P=0.009, ‡‡P=0.004.
Implications of the SERVE-HF study results

Change in indication for use of ASV

Indications for ASV use have changed as a result of the SERVE-HF study findings. ASV therapy is still indicated to stabilise ventilation in adult patients with CSA, mixed sleep apnoea and periodic breathing, with or without OSA.

In alignment with regulatory authorities, ASV therapy is now contraindicated in patients with chronic, symptomatic heart failure (NYHA 2-4) with reduced left ventricular ejection fraction (LVEF ≤ 45%) and moderate to severe predominant CSA.

It is important to note that the SERVE-HF results only apply to the studied population and do not apply to:

- patients with heart failure with preserved ejection fraction (HfPEF),
- patients with predominantly obstructive forms of sleep apnoea, or
- sleep apnoea patients who have a cardiovascular disease other than systolic heart failure.

These patient groups were not included in the SERVE-HF study.

Furthermore, the SERVE-HF results apply only to ASV therapy, and not to positive airway pressure delivered via other types of devices (e.g. continuous positive airway pressure [CPAP]).

Recommendations from country scientific societies

The American Academy of Sleep Medicine has provided the following guidance:

The Deutsche Gesellschaft für Schlafforschung und Schlafmedizin (DGSM) has provided the following guidance:

Value of robust clinical trial data

The results of the SERVE-HF trial were different from those of previous smaller trials and meta-analyses. This shows the importance of conducting large, randomised, controlled clinical trials to provide robust information on hard clinical endpoints.

Despite not meeting its primary endpoint, Prof. Cowie stated that SERVE-HF “provides valuable, practice-changing guidance on how best to care for people with chronic heart failure. SERVE-HF was a well-designed and executed study and because of it we now know that ASV therapy should not be used to treat central sleep apnoea in people with symptomatic chronic heart failure with reduced ejection fraction.”

ResMed is committed to researching sleep-disordered breathing and gaining a better understanding of how treatment can change people’s lives and improve clinical outcomes.

References

1. Cowie et al. NEJM 2015, 1 Sep; DOI: 10.1056/NEJMoa15106459.