Treatment of sleep-disordered breathing with predominant central sleep apnoea by adaptive servo ventilation in patients with heart failure

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The purpose of this trial is to evaluate the long-term effects and cost-effectiveness of adaptive servo-ventilation (ASV) on the mortality and morbidity of patients with stable heart failure due to left ventricular systolic dysfunction, already…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON41427

Source
ToetsingOnline

Brief title
SERVE-HF

Condition

- Other condition
- Heart failures

Synonym
central sleep apnea, heart failure

Health condition

sleep disordered breathing

Research involving
Human

Sponsors and support

Primary sponsor: ResMed Ltd., Australia
Source(s) of monetary or material Support: ResMed

Intervention

Keyword: heart failure, left ventricular systolic dysfunction, sleep apnea, sleep disordered breathing

Outcome measures

Primary outcome

Time to first event of:

1) all cause mortality or unplanned hospitalization / prolongation of

hospitalization for worsening heart failure

2) cardiovascular mortality or unplanned hospitalization / prolongation of

hospitalization for worsening heart failure.

3) all cause mortality or all cause unplanned hospitalization / prolongation of

hospitalization

Heart transplantation, appropriate shock from ICD, long term assist device

(LTAD) insertion and survived resuscitation of sudden cardiac arrest are

counted as cardiovascular death, survived resuscitation for other reasons is

counted as all cause death.

The three combinations are not tested in parallel but in this hierarchical

order.

Secondary outcome

• Time until death

• Time until non cardiovascular death

• Time until cardiovascular death

• Time until unplanned hospitalization / prolongation of hospitalization due to worsening of heart failure or cardiovascular death

• Time until unplanned hospitalization / prolongation of hospitalization for other reasons or death

• Time until unplanned hospitalization f/ prolongation of hospitalization or cardiovascular cause or cardiovascular death

• Time to first adequate shock in patients with ICD (evaluation of appropriateness will also be made by the ERC), LTAD insertion or cardiovascular death

• Time to first survived resuscitation for any reason (evaluation will also be made by the ERC)

• Time to first survived resuscitation of sudden cardiac arrest (evaluation will also be made by the ERC)

• Percent of follow up days which patient survives and is not hospitalized/hospital stay is not prolonged for cardiovascular cause

• Percent of follow up days which patient survives and is not hospitalized/hospital stay is not prolonged for other reasons

• Changes in NYHA classification as compared to baseline

• Difference in health costs between the two treatment groups

• Changes in QoL (Minnesota) as compared to baseline

• Changes in renal function (based on serum creatinine) as compared to baseline

• Changes in Six Minute Walking Distance (6MWD) as compared to baseline

• Changes of AHI and oxygen desaturation index compared to baseline

• AHI below 10 per hour at twelve months and ODI below 5 per hour at twelve months

• Atrial fibrillation at follow-up visits

• Number and cost of hospitalizations (with tariff/DRG, diagnoses and procedures for calculating DRG or length of stay and level of care provided)

• Cost of care (technology and service, nursing, physicians visit) related to ventilation

• Difference in utilities / QoL (Minnesota and EQ5D) compared to control arm

• Difference in cost of resources consumed

• Cost-efficacy (incremental cost-efficacy ratio)

• Cost-utility (incremental cost-utility ratio)

Study description

Background summary

Despite recent advances in pharmacological treatment, chronic heart failure (chronic HF) continues to cause debilitating symptoms, frequent hospital admissions, and a high mortality. Although therapy with beta-blockers and ACE-inhibitors as well as other drugs or cardiac resynchronisation therapy (CRT) has become guideline therapy, many patients have persistent symptoms and most will eventually die of cardiovascular causes, often from progressive heart failure. New interventions that reduce symptoms, increase quality of life, reduce hospital admissions and mortality are warranted.
It is likely that new interventions will be targeted at specific subgroups of chronic HF patients rather than the entire population. Treatment of Sleep

Disordered Breathing (SDB) is potentially such an intervention. SDB is very common in heart failure populations with reported prevalence rates of 50-75%. Two types of abnormal breathing predominate, Obstructive Sleep Apnoea (OSA) and Central Sleep Apnoea/Cheyne-Stokes-Respiration (CSA/CSR). OSA is seen in 20-45% of chronic HF patients, a rate which is considerably higher than the general population. CSA/CSR is also common and reported in 25-40% of chronic HF patients.

There are several mechanisms by which SDB may be detrimental to cardiac function. These include tissue hypoxia and repetitive arousal from sleep with increased sympathetic nervous system activity. Treatment of OSA with CPAP (Continuous Positive Airway Pressure) rapidly reduces tissue hypoxia and arousals, and over a period of months reduces elevated sympathetic activity to normal. CPAP is also known to reduce blood pressure. Two studies have demonstrated marked improvements in cardiac function over periods of 1 and 3 months, but no large outcome study has been performed. With the known effects of CPAP on sleepiness, quality of life and hypertension in patients with OSA, this study is now difficult to perform in patients with OSA and symptoms.

CSR induces chemical, neural and hemodynamic changes similar to those seen in OSA, and is most commonly seen in the chronic HF population. It is an independent risk factor for death in chronic HF. CSR can be treated with oxygen, CPAP or ventilation in increasing order of effectiveness, but there are few trials with clinical endpoints or even outcome data.

The only trial to date that has investigated the impact of Continuous Positive Airway Pressure treatment for central sleep apnea and heart failure on heart transplant-free survival was the CANPAP-Study. The trial was stopped after 200 patients were followed up for at least six months. After a prespecified interim analysis the DSMB recommended the termination of the study because of an early divergence of the transplantation-free survival curves favouring the control group, an enrolment at only 50 percent of predicted rate (0,03patients/center/month) and a falling rate of death and heart transplantation.

Although CPAP attenuated central sleep apnea (AHI was lowered from 40 events/hour to 19 events/hour), improved nocturnal oxygenation, increased the ejection fraction, lowered norepinephrine levels, and increased the distance walked in six minutes, it did not affect survival or rehospitalization. The authors concluded that their data do not support the use of CPAP to extend life in patients who have central sleep apnea and heart failure.

A recently published further analysis of the CANPAP-data tested the hypothesis that suppression of CSA below 15 events per hour by CPAP would improve left ventricular ejection fraction and heart transplant-free survival. Of the 258 heart failure patients with CSA in CANPAP, 110 of the 130 randomized to the control group and 100 of the 128 randomized to CPAP had sleep studies 3 months later. CPAP patients were divided post hoc into two groups, whose apnea-hypopnea index was or was not reduced below 15 at this time. In 57 patients CSA was suppressed effectively under CPAP, while in 43 patients CPAP did not suppress CSA. Their changes in left ventricular ejection fraction and heart transplant-free survival were compared with those in the control group.

Despite similar CPAP pressure and hours of use in the 2 groups, patients with CPAP whose CSA was suppressed experienced a greater increase in left ventricular ejection fraction at 3 months and significantly better transplant-free survival than control subjects, whereas the patients with unsuppressed CSA under CPAP did not improve left ventricular ejection fraction or transplant-free survival. The authors conclude that in heart failure patients, PAP might improve both left ventricular ejection fraction and heart transplant-free survival if sleep-disordered breathing is suppressed early after initiation of therapy.

Study objective

The purpose of this trial is to evaluate the long-term effects and cost-effectiveness of adaptive servo-ventilation (ASV) on the mortality and morbidity of patients with stable heart failure due to left ventricular systolic dysfunction, already receiving optimal medical therapy, who have sleep disordered breathing (SDB) that is predominantly central sleep apnoea.

Study design

Randomised, multi-centre, international trial with parallel group design, with patients randomised to either control (optimal medical management) or active treatment (optimal medical treatment plus use of adaptive servoventilation) in a 1:1 ratio. There will be no sham-positive airway pressure treatment in the control arm. Assumptions: the intervention reduces the hazard rate by 20%. The event rate in the control group is 35% in the first year. It is assumed that the hazard rate is constant over time.
The trial is based on an event-driven design: the final analysis will be performed when 651 events have been observed or the study was terminated at one of the interim analyses.
The primary analysis is in the intention-to-treat population that consists of all patients randomized.

Intervention

A non-invasive device, providing adaptive-servo ventilation algorithms to provide ventilatory support for central sleep apnea, or periodic breathing. It comprises a microprocessor-controlled flow generator, air delivery hose mask and headgear.
The device provides a ventilatory pressure support between 3-16 cm H2O superimposed on an end expiratory pressure (EPAP) between 4-15 cm H2O. The default EPAP is 5 cm H2O. The device is limited to a maximum peak inspiratory pressure of 25 cm H2O.
The device measures the patient*s instantaneous ventilation, and calculates an adapting target ventilation equal to 90% of the patient*s recent average ventilation (time constant 100 seconds). It then adjusts the degree of pressure

support to servo-control the subject*s ventilation to at least equal the target ventilation. If the subject resumes normal spontaneous effort, support will fall back to the minimum of 3 cm H2O over a similar time period. Smaller or slower changes in patient*s effort will result in proportionally smaller, slower changes in the degree of support. In the steady state, ventilation exceeds the 90% target, so support stays at the minimum of 3 cm H2O.

The AutoSet CS offers Climate Control, a state-of-the-art humidification system that intelligently adapts to environmental conditions to deliver optimal pressure and temperature in order to promote long-term compliance. Complemented by the ClimateLine heated tube it protects patients from rainout without compromising humidity or temperature levels.

Study burden and risks

There are no major known side effects of taking part in this research project.
The AutoSet CS device has been used for over 10 years and has a CE mark meaning it has been approved for use in countries of the European Union.
When blood samples are taken some patients may experience bruising on the site where the blood is taken from. Sometimes the mask used with the AutoSet CS is uncomfortable. If so, we will swap to a more comfortable mask.

When put into group one (ASV+standard medical therapy) we hope that by using the device it will reduce the sleep disordered breathing and perhaps the progression of the heart failure. When in group two it is unlikely that the study will help but the information we get might help improve the treatment of people with a similar condition in the future.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

• Patients must be at least 22 years old
• Chronic heart failure (at least 12 weeks since diagnosis) according to the current applicable guidelines (ESC), ACC/AHA)
• Left ventricular systolic dysfunction (LVEF <=45% by imaging method such as echocardiography, radionuclide angiography, left ventriculography, or cardiac magnetic resonance imaging) documented less than 12 weeks before randomisation
• NYHA class III or IV at the time of inclusion or NYHA class II with at least one hospitalization for HF in the last 24 months
• No hospitalization for heart failure for at least 4 weeks prior to inclusion
• Optimised medical treatment according to applicable guidelines (see Appendix X) with no new class of disease modifying drug for more than 4 weeks prior to randomisation. In case of no beta blockers or ACE inhibitors/ ARB antagonists the reasons must be documented
• SDB (AHI > 15 events/hour with >= 50% central events and a central AHI >= 10 events/hour, derived from polygraphy or polysomnography (based on total recording time (TRT)), documented less than 4 weeks before randomisation. Flow measurement has to be performed with nasal cannula
• Patient is able to fully understand study information and signed informed consent

Exclusion criteria

• Significant COPD with Forced Expiratory Volume within one second (FEV1) <50% (European Respiratory Society criteria) in the last four weeks before randomisation
• Oxygen saturation at rest during the day <=90% at inclusion
• Current use of Positive Airway Pressure (PAP) - therapy
• Life expectancy < 1 year for diseases unrelated to chronic HF
• Cardiac surgery, Percutaneous coronary intervention (PCI), Myocardial Infarction (MI) or unstable angina within 6 months prior to randomisation

• CRT-implantation (either CRT-D or CRT-P) scheduled or within 6 months prior to randomisation
• Transient ischemic attack (TIA) or Stroke within 3 months prior to randomisation
• Primary hemodynamically significant uncorrected valvular heart disease, obstructive or regurgitant, or any valvular disease expected to lead to surgery during the trial
• Acute myocarditis/pericarditis within 6 months prior to randomisation
• Untreated or therapy refractory Restless legs-Syndrome (RLS) according to criteria listed in Appendix IX at the time of study entry
• Patients for whom the use of AutoSet CS / S9 VPAP Adapt may be contra-indicated according to
the user*s manual of the device used
• Pregnancy

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	27-08-2012
Enrollment:	10
Type:	Actual

Medical products/devices used

Generic name:	adaptive servo-ventilation ASV AutoSet CS
Registration:	Yes - CE intended use

Ethics review

Approved WMO Date:	11-06-2012
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	24-02-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
ClinicalTrials.gov	NCT00733343
CCMO	NL38915.042.11