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Treatment of sleep-disordered breathing with predominant central sleep apnoea by adaptive Servo-ventilation in patients with Heart Failure

Submission date
31/10/2007

Recruitment status
No longer recruiting

Registration date
15/11/2007

Overall study status
Completed

Last Edited
14/11/2018

Condition category
Circulatory System

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Heart failure (HF) is a condition caused by the heart failing to pump enough blood around the body at the right pressure. Despite advances in treatment, chronic HF continues to cause debilitating symptoms, frequent hospital admissions, and a high mortality (death rate). Although treatment with drugs or cardiac resynchronisation therapy (CRT) has become the standard, many patients have persistent symptoms and most will eventually die of cardiovascular causes, often from progressive heart failure. New treatments that reduce symptoms, increase quality of life, reduce hospital admissions and mortality are needed. Most patients with heart failure also suffer from sleep-disordered breathing. These breathing irregularities include pauses in breathing (apneas) which may interrupt sleep as well as increasing the rate of progression of heart failure. In a previous study researchers used a continuous positive airway pressure (CPAP) machine to try and treat the sleep-disordered breathing. The study did not extend the life of the patients involved in the study, nor did it decrease the amount of hospital visits the patients had to make and was stopped prematurely. However, those patients who did experience a reduction in sleep-disordered breathing may have a better survival and heart function. This study aims to find out whether the treatment of sleep-disordered breathing improves heart disease and quality of life. To do this a ventilator called the AutoSet CS (also known as the Adaptive Servoventilation device) will be tested. This device is different to the one used in the previous study and has been shown to be more effective than CPAP in reducing sleep-disordered breathing. The AutoSet CS device reduces breathing irregularities during sleep. The device has a licence for use in patients with sleep apnea associated with heart failure and has been in use for more than 10 years. It has been found to be a safe treatment and is effective in short-term studies. As patients who have used the device previously may not necessarily have had heart failure, this study aims to determine the long-term effects on heart disease.

Who can participate?
Patients aged 18 or over with chronic heart failure (at least 12 weeks since diagnosis).

What does the study involve?
To find out which way of treating patients is best, comparisons between the different

treatments needs to be made. Participants are put into two groups and each group is given a different treatment; the results are compared to see if one is better. To try to make sure the groups are the same to start with, each patient is put into a group by chance (randomly). The first group is asked to use the AutoSet CS ventilator. The device can be placed at the side of the bed, with tubing and a mask. At night, the mask is placed over the nose and mouth and the ventilator is switched on. The AutoSet CS constantly monitors breathing throughout the night. The AutoSet CS device should be used every night as well as other times during sleep, including naps. The second group continues with their normal medical treatment and care. Regardless of which group a participant is put in he/she is asked to return to the hospital 2 weeks, 3 months, 12 months and 24 months after the start of the study and once a year thereafter until the study finishes. He/she is given a physical examination and an ECG which records the heart rhythm. Patients in the AutoSet CS device group need to bring the device with them so the doctor can check that it is adapted correctly as well as downloading data from the device to analyze the use of it. The doctor also checks certain key breathing characteristics that have been recorded. In addition a small blood sample is taken (for full blood count and creatinine, a measure of kidney function), patients are asked to complete three questionnaires (to measure the effects of heart failure and the treatments for heart failure on their quality of life, health status and sleepiness) and to perform a six-minute walk test. The aim of this test is to walk for as far as possible for 6 minutes on a flat surface such as a hallway. Patients are permitted to slow down, to stop, and to rest as necessary. This test is used to assess exercise ability. Patients in the AutoSet CS device group are asked to take part in an overnight sleep study carried out in the hospital's sleep laboratory or at home. Depending on the facilities at the local hospital patients either undergo a sleep study known as Polysomnography (PSG) or Polygraphy (PG). During the sleep study, which is a routine clinical procedure, various sensors are attached to the surface of the body which measure and record the various changes that occur during sleep. In addition all patients are contacted by telephone at 6 and 18 months after starting the study and then once a year until the end of the study. They are asked questions relating to visits to doctors and any events such as being admitted to hospital.

What are the possible benefits and risks of participating?
Not provided at time of registration

Where is the study run from?
Ruhrlandklinik (Germany)

When is the study starting and how long is it expected to run for?
November 2007 to July 2015

Who is funding the study?
ResMed Ltd (Australia)

Who is the main contact?
Prof Helmut Teschler
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Contact information

Type(s)
Scientific

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Additional identifiers

ClinicalTrials.gov (NCT)
NCT00733343

Protocol serial number
001

Study information

Scientific Title
Treatment of sleep-disordered breathing with predominant central sleep apnoea by adaptive Servo-ventilation in patients with Heart Failure

Acronym
Serve-HF

Study objectives
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.

On 14/08/2012, the following changes were made to the trial record:
1. Denmark, Finland, Australia, Czech Republic, and the Netherlands were added to the countries of recruitment
2. The overall trial end date was updated from 30/11/2011 to 31/01/2015
3. The target number of participants was changed from 1260 to 1193

On 03/06/2013 the following changes were made to the trial record:
1. Switzerland was added to the countries of recruitment
2. The target number of participants was updated from 1193 to 1325
3. The overall trial end date was updated from 31/01/2015 to 31/05/2015

On 20/05/2015 the overall trial end date was updated from 31/05/2015 to 31/07/2015.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Freiburg Ethics Commission International (FEKI) (Germany), 05/11/2007, ref: 07/2344

Primary study design
Interventional

Study design
Randomised multicentre international parallel-group trial with patients randomised to either control or active treatment in 1:1 ratio

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Heart failure with sleep disordered breathing

Interventions
Intervention: Adaptive servo-ventilation.

The clinical study plan provides direct clinical visits of every patient at study entry, after 2 weeks, after 3 and 12 months, thereafter every 12 months until the end of the total study. Additionally to clinical follow up visits all patients will be called by the study sites 6, 18 and thereafter every 12 months after study entry and an event history is taken by phone.

At 2 weeks follow-up (FU) a device download, a physical and cardiologic examination and adverse-event (AE)-monitoring will be performed. The baseline visit, the 3, 12 and 24 months FU, thereafter every twelve months follow up visit at the site will additionally include a polysomnography (PSG) and blood samples, data collection of quality of life, data collection of sleepiness, a 6MWT (six minute walking test) and an electrocardiogram (ECG). Further a data download from the investigational device is performed. In addition, a general and event history for the time period since the last visit is established and a physical examination is performed.

PSG during the FU period will be performed only on patients who are randomised to treatment group. The 2 weeks FU-visit should be performed within ± 3 days, the other FU-visits should be performed within ± 2 weeks. There will be no sham-positive airway pressure treatment in the control arm. Minimum follow up time will be 24 months, maximum 78 months.

Intervention Type
Other

Primary outcome(s)
Current primary outcome measures as of 20/05/2015:
The primary target parameters are defined as time to first event of:
1. All cause mortality or unplanned hospitalisation/prolongation of hospitalisation for worsening heart failure
2. Cardiovascular mortality or unplanned hospitalisation/prolongation of hospitalisation for worsening heart failure
3. All cause mortality or all cause hospitalisation/prolongation of hospitalisation

The three combinations are not tested in parallel but in this hierarchical order:
"Cardiovascular mortality" and "unplanned hospitalisation/prolongation of hospitalisation for worsening heart failure" will be evaluated by the Endpoint Review Committee (ERC). Definition will be documented in rules of procedure of the ERC. 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.

It is assumed, that the intervention reduces the hazard rate by 20% and that the event rate in the control group is 35% in the first year. It is also assumed that the hazard rate is constant over time.

The primary target parameters will be measured at the final assessment.

Previous primary outcome measures:
The primary target parameters are defined as time to first event of:
1. All cause mortality or unplanned hospitalisation for worsening heart failure
2. Cardiovascular mortality or unplanned hospitalisation for worsening heart failure
3. All cause mortality or all cause hospitalisation

The three combinations are not tested in parallel but in this hierarchical order:
"Cardiovascular mortality" and "unplanned hospitalisation for worsening heart failure" will be evaluated by the Endpoint Review Committee (ERC). Definition will be documented in rules of procedure of the ERC. Heart transplantation will be counted as death.

It is assumed, that the intervention reduces the hazard rate by 20% and that the event rate in the control group is 35% in the first year. It is also assumed that the hazard rate is constant over time.

The primary target parameters will be measured at the final assessment.

Key secondary outcome(s)
Current secondary outcome measures as of 20/05/2015:
1. Time until death

2. Time until non cardiovascular death
3. Time until cardiovascular death
4. Time until unplanned hospitalisation/prolongation of hospitalisation due to worsening of heart failure or cardiovascular death
5. Time until unplanned hospitalisation/prolongation of hospitalisation for other reasons or death
6. Time until unplanned hospitalisation/prolongation of hospitalisation for cardiovascular cause or cardiovascular death
7. Time to first adequate shock in patients with ICD (evaluation of appropriateness will also be made by the ERC), LTAD insertion or cardiovascular death
8. Time to first survived resuscitation for any reason (evaluation will also be made by the ERC)
9. Time to first survived resuscitation of sudden cardiac arrest (evaluation will also be made by the ERC)
10. Percent of follow up days which patient survives and is not hospitalised /hospital stay is not prolonged for cardiovascular cause
11. Percent of follow up days which patient survives and is not hospitalised /hospital stay is not prolonged for other reasons
12. Changes in NYHA classification as compared to baseline
13. Changes in Quality of Life (QoL) (Minnesota) as compared to baseline
14. Changes in renal function (based on serum creatinine) as compared to baseline
15. Changes in Six Minute Walking Distance (6MWD) as compared to baseline
16. Number and cost of hospitalisations (with tariff/Diagnosis-Related Groups [DRG], diagnoses and procedures for calculating DRG or length of stay and level of care provided)
17. Difference in utilities/QoL (Minnesota and EQ5D) compared to control arm
18. Difference in cost of resources consumed
19. Incremental Cost-efficacy ratio
20. Incremental Cost-utility ratio
21. Changes of AHI and oxygen desaturation index compared to baseline
22 AHI below 10 per hour at twelve months and ODI below 5 per hour at twelve months
23. Atrial fibrillation at follow-up visits

Secondary target parameters will be measured at the last follow up or at the last available observation within follow up.

Previous secondary outcome measures from 14/08/2012 to 20/05/2015:
1. Time until death
2. Time until non cardiovascular death
3. Time until cardiovascular death
4. Time until unplanned hospitalisation due to worsening of heart failure or cardiovascular death
5. Time until unplanned hospitalisation for other reasons or death
6. Time until unplanned hospitalisation for cardiovascular cause or cardiovascular death
7. Time to first adequate shock in patients with ICD (evaluation of appropriateness will also be made by the ERC) or cardiovascular death
8. Percent of follow up days which patient survives and is not hospitalised for cardiovascular cause
9. Percent of follow up days which patient survives and is not hospitalised for other reasons
10. Changes in NYHA classification as compared to baseline
11. Difference in health costs between the two treatment groups
12. Changes in Quality of Life (QoL) (Minnesota) as compared to baseline
13. Changes in renal function (based on serum creatinine) as compared to baseline
14. Changes in Six Minute Walking Distance (6MWD) as compared to baseline
15. Number and cost of hospitalisations (with tariff/Diagnosis-Related Groups [DRG], diagnoses

and procedures for calculating DRG or length of stay and level of care provided)
16. Cost of care (technology and service, nursing, physicians visit) related to ventilation
17. Difference in utilities/QoL (Minnesota and EQ5D) compared to control arm
18. Difference in cost of resources consumed
19. Cost-efficacy
20. Cost-utility
21. Changes of AHI and oxygen desaturation index compared to baseline
21.1 AHI below 10 per hour at twelve months and ODI below 5 per hour at twelve months
22. Atrial fibrillation at follow-up visits

Secondary target parameters will be measured at the last follow up or at the last available observation within follow up.

Previous secondary outcome measures from registration until 14/08/2012:
1. Time until death
2. Time until non cardiovascular death
3. Time until cardiovascular death
4. Time until unplanned hospitalisation due to worsening of heart failure or cardiovascular death
5. Time until unplanned hospitalisation for other reasons or death
6. Time until unplanned hospitalisation for cardiovascular cause or cardiovascular death
7. Time to first adequate shock in patients with ICD (evaluation of appropriateness will also be made by the ERC) or cardiovascular death
8. Percent of follow up days which patient survives and is not hospitalised for cardiovascular cause
9. Percent of follow up days which patient survives and is not hospitalised for other reasons
10. Changes in NYHA classification as compared to baseline
11. Difference in health costs between the two treatment groups
12. Changes in Quality of Life (QoL) (Minnesota) as compared to baseline
13. Changes in renal function (based on serum creatinine) as compared to baseline
14. Changes in Six Minute Walking Distance (6MWD) as compared to baseline
15. Number and cost of hospitalisations (with tariff/Diagnosis-Related Groups [DRG], diagnoses and procedures for calculating DRG or length of stay and level of care provided)
16. Cost of care (technology and service, nursing, physicians visit) related to ventilation
17. Difference in utilities/QoL (Minnesota and EQ5D) compared to control arm
18. Difference in cost of resources consumed
19. Cost-efficacy
20. Cost-utility

Secondary target parameters will be measured at the last follow up or at the last available observation within FU.

Completion date
31/07/2015

Eligibility

Key inclusion criteria
Current inclusion criteria as of 14/08/2012:
1. At least 18 years old
2. Chronic heart failure (at least 12 weeks since diagnosis) according to the current applicable guidelines (European Society of Cardiology [ESC], American College of Cardiology [ACC]

/American Heart Association [AHA])
3. Left ventricular systolic dysfunction (left ventricular ejection fraction [LVEF] less or equal than 45% by imaging method such as echocardiography, radionuclide (March, 6th 2009)
4. NYHA class III or IV at the time of inclusion or NYHA class II with at least one hospitalisation for HF in the last 24 months (March, 6th 2009)
5. No hospitalisation for HF for at least 4 weeks prior to inclusion
6. Optimised medical treatment according to applicable guidelines with no new class of disease modifying drug for more than 4 weeks prior to randomisation. In case of no beta blockers or angiotensin converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARB) antagonists the reasons must be documented
7. SDB (Apnoea-Hypopnoea Index [AHI] greater than 15/hour with greater than or equal to 50% central events and a central AHI greater than or equal to 10 hours, 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
8. Patient is able to fully understand study information and signed informed consent

Previous inclusion criteria until 14/08/2012:
1. At least 18 years old
2. Chronic heart failure (at least 12 weeks since diagnosis) according to the current applicable guidelines (European Society of Cardiology [ESC], American College of Cardiology [ACC] /American Heart Association [AHA])
3. Left ventricular systolic dysfunction (left ventricular ejection fraction [LVEF] less than 40% by imaging method such as echocardiography, radionuclide angiography, left ventriculography, or cardiac magnetic resonance imaging) documented less than 12 weeks before randomisation
4. New York Heart Association (NYHA) class III or IV at the time of inclusion or NYHA class II with at least one hospitalisation for heart failure (HF) in the last 12 months
5. No hospitalisation for HF for at least 4 weeks prior to inclusion
6. Optimised medical treatment according to applicable guidelines with no new class of disease modifying drug for more than 4 weeks prior to randomisation. In case of no beta blockers or angiotensin converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARB) antagonists the reasons must be documented
7. SDB (Apnoea-Hypopnoea Index [AHI] greater than 15/hour with greater than or equal to 50% central events and a central AHI greater than or equal to 10 hours, 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
8. Patient is able to fully understand study information and signed informed consent

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex
All

Key exclusion criteria
1. Significant chronic obstructive pulmonary disease (COPD) with forced expiratory volume within one second (FEV1) less than 50% (European Respiratory Society criteria) in the last four weeks before randomisation
2. Oxygen saturation at rest during the day less than or equal to 90% at inclusion
3. Current use of positive airway pressure (PAP) therapy
4. Life expectancy less than 1 year for diseases unrelated to chronic HF
5. Cardiac surgery, percutaneous coronary intervention (PCI), myocardial infarction (MI) or unstable angina within 6 months prior to randomisation
6. Cardiac resynchronisation therapy (CRT)-implantation or implanatable cardioverter-defibrillator (ICD)-implantation scheduled or within 6 months prior to randomisation
7. Transient ischaemic attack (TIA) or stroke within 3 months prior to randomisation
8. Primary haemodynamically significant uncorrected valvular heart disease, obstructive or regurgitant, or any valvular disease expected to lead to surgery during the trial
9. Acute myocarditis/pericarditis within 6 months prior to randomisation
10. Untreated or therapy refractory restless legs-syndrome (RLS)
11. Pregnancy

Date of first enrolment
15/11/2007

Date of final enrolment
24/05/2013

Locations

Countries of recruitment
United Kingdom

Australia

Czech Republic

Denmark

Finland

France

Germany

Netherlands

Norway

Sweden

Switzerland

Study participating centre
Ruhrlandklinik
Essen
Germany
D-45239

Study participating centre
213 other centres
Germany
-

Sponsor information

Organisation
ResMed Ltd (Sydney, Australia)

ROR
https://ror.org/04dvebt78

Funder(s)

Funder type
Industry

Funder Name
ResMed Ltd (Australia)

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	17/09/2015		Yes	No
Protocol article	protocol	01/08/2013		Yes	No

Other publications	secondary analysis	01/11/2016		Yes	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes