Clinical trial results:
The pulmonary effect of bronchodilation on adult VSD patients with persistent or surgically corrected VSD

Summary

EudraCT number	2015-005507-89
Trial protocol	DK
Global end of trial date	11 December 2017

Results information

Result version number	v1 (current)
This version publication date	26 February 2021
First version publication date	26 February 2021
Summary attachment (see zip file)	Articles from trial (All VENTI articles.pdf)

Trial information

Trial identification

Sponsor protocol code	191190

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02914652
WHO universal trial number (UTN)	-
Other trial identifiers	Danish Data Protection Agency : 1-16-02-315-16, Danish Medicines Agency: 2016061269, Committee on Biomedical Research Ethics of the Cen: 1-10-72-153-16

Notes:

Sponsors

Sponsor organisation name	Department of Cardio-Thoracic and Vascular Surgery, Aarhus University Hospital
Sponsor organisation address	Palle Juul-Jensens Blvd. 99, Aarhus, Denmark, 8200
Public contact	Department of Cardio-Thoracic and V, Aarhus University Hospital, 0045 7845 3080, breiner@ki.au.dk
Scientific contact	Department of Cardio-Thoracic and V, Aarhus University Hospital, 0045 31135103, vhjortdal@clin.au.dk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	11 December 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 December 2017
Global end of trial reached?	Yes
Global end of trial date	11 December 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The overall purpose of this study is to test whether β2-agonists will affect the cardiopulmonary exercise capacity of VSD-operated patients compared with un-operated VSD-patients and healthy age- and gender-matched controls

Protection of trial subjects:

All tests where non-invasive and afflicted no pain. Trained medical personal was present at all testing, and the well being of participants was always prioritized.

All subjects were assigned a randomization number. The identification list was kept securely locked at our research department, only used in case of Severe Events.

In case of severe events at testing or unhealthy findings during data analysis, participants were immediately contacted and referred to the correct hospital department for reevaluation by a specialist and treatment.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 July 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 96
Worldwide total number of subjects	96
EEA total number of subjects	96

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0

Adults (18-64 years)	96
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

All patients fulfilling inclusion criteria were previously found in the hospitals medical database. All received an invitation letter with written information and a reply letter. Acceptance followed a oral information visit before inclusion in trial.
Healthy volunteers submitted by government official webpage and received the same information.

Pre-assignment

Screening details:

Patient Journal verifying surgical corrected VSD within 1990 and 1998 at Aarhus University Hospital (152 found, 30 accepted) or unrepaired isolated VSD born between 1985 and 1998 at Aarhus University Hospital (88 found, 30 accepted).
Healthy control with no medical record of heart or lung disease (36 included).

Pre-assignment period milestones

Number of subjects started	96
Number of subjects completed	96

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Blinding implementation details:

All inhalers were identical after the Trial Pharmacists remade them. The pharmacists handled packaging and randomization. Therefore no subjects, monitor or investigators knew what inhaler was used at each visit. During data analysis, the test results were labelled A and B, provided by the Trial Pharmacists after data collection, allowing data analysis without knowledge of medicin or placebo until all data analysis was completed.

Arms

Are arms mutually exclusive?	Yes
Arm title	Operated VSD patients

Arm description:

Trial group 1: Surgically corrected for isolated VSD between 1990 and 1998 at Aarhus University Hospital.
Receives Ventoline 900 microgram or Placebo in randomized order at first and second visit.
Data is the effect of the medication.

Arm type	Active comparator
Investigational medicinal product name	Ventoline
Investigational medicinal product code	PR1
Other name	Salbutamol Sulfate
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

One dose of 8 puffs and another dose of 1 puff with Ventoline 0,1mg/dosis inhaler. - 9 puffs x 0,1 mg/dosis = 0,9mg before intervention testing.

Arm title	Unoperated VSD patients

Arm description:

Trial group 2: Diagnosed with isolated VSD born between 1985 and 1998 without surgical or percutaneous closure.

- Verified by Echocardiography within the last 4 years. If it is more than 4 it will be verified by our doctors as a systolic murmur or echocardiography.

Ventoline 900 microgram or Placebo in randomized order at first and second visit. Data is the effect of the medication.

Arm type	Active comparator
Investigational medicinal product name	Ventoline
Investigational medicinal product code	PR1
Other name	Salbutamol Sulfate
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

One dose of 8 puffs and another dose of 1 puff with Ventoline 0,1mg/dosis inhaler. - 9 puffs x 0,1 mg/dosis = 0,9mg before intervention testing.

Arm title	Control group

Arm description:

Control Group: 18-40 years, with no known medical records of heart and lung disease.

Ventoline 900 microgram or Placebo in randomized order at first and second visit. Data is the effect of the medication.

Arm type	Active comparator
Investigational medicinal product name	Ventoline
Investigational medicinal product code	PR1
Other name	Salbutamol Sulfate
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

One dose of 8 puffs and another dose of 1 puff with Ventoline 0,1mg/dosis inhaler. - 9 puffs x 0,1 mg/dosis = 0,9mg before intervention testing.

Number of subjects in period 1	Operated VSD patients	Unoperated VSD patients	Control group
Started	30	30	36
Completed	30	30	36

Baseline characteristics

Reporting groups	
Reporting group title	Operated VSD patients
Reporting group description:	
Trial group 1: Surgically corrected for isolated VSD between 1990 and 1998 at Aarhus University Hospital. Receives Ventoline 900 microgram or Placebo in randomized order at first and second visit. Data is the effect of the medication.	
Reporting group title	Unoperated VSD patients
Reporting group description:	
Trial group 2: Diagnosed with isolated VSD born between 1985 and 1998 without surgical or percutaneous closure. - Verified by Echocardiography within the last 4 years. If it is more than 4 it will be verified by our doctors as a systolic murmur or echocardiography. Ventoline 900 microgram or Placebo in randomized order at first and second visit. Data is the effect of the medication.	
Reporting group title	Control group
Reporting group description:	
Control Group: 18-40 years, with no known medical records of heart and lung disease. Ventoline 900 microgram or Placebo in randomized order at first and second visit. Data is the effect of the medication.	

Reporting group values	Operated VSD patients	Unoperated VSD patients	Control group
Number of subjects	30	30	36
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Adults 18-30 years	30	0	0
Adults 18-40 years	0	30	36
Gender categorical Units: Subjects			
Female	17	13	18
Male	13	17	18
Smoking status			
Number of cigarettes per week			
Units: Subjects			
<20	4	5	3
>20	3	1	1
Non-smoker	23	24	32

Weight			
Weight mean in kilograms			
Units: kilogram(s)			
arithmetic mean	71	75	72
standard deviation	± 12	± 13	± 12
Height			
Height in centimeters			
Units: cm			
arithmetic mean	174	174	175
standard deviation	± 10	± 9	± 9
Fat free mass			
Percent of total mass			
Units: percent volume/volume			
arithmetic mean	76	74	78
standard deviation	± 9	± 8	± 9

Reporting group values	Total		
Number of subjects	96		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Adults 18-30 years	30		
Adults 18-40 years	66		
Gender categorical			
Units: Subjects			
Female	48		
Male	48		
Smoking status			
Number of cigarettes per week			
Units: Subjects			
<20	12		
>20	5		
Non-smoker	79		
Weight			
Weight mean in kilograms			
Units: kilogram(s)			
arithmetic mean			
standard deviation	-		
Height			
Height in centimeters			
Units: cm			
arithmetic mean			

standard deviation	-		
Fat free mass			
Percent of total mass			
Units: percent volume/volume			
arithmetic mean			
standard deviation	-		

Subject analysis sets

Subject analysis set title	Healthy controls of Operated VSD patients
Subject analysis set type	Full analysis

Subject analysis set description:

Only 30 of the 36 healthy controls were matched on age and gender to the operated VSD group.

Subject analysis set title	Healthy controls of unoperated VSD patients
Subject analysis set type	Full analysis

Subject analysis set description:

Only 30 healthy controls were matched on age and gender to the unoperated VSD group.

Reporting group values	Healthy controls of Operated VSD patients	Healthy controls of unoperated VSD patients	
Number of subjects	30	30	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Adults 18-30 years	30	0	
Adults 18-40 years	0	30	
Gender categorical			
Units: Subjects			
Female	15	13	
Male	15	17	
Smoking status			
Number of cigarettes per week			
Units: Subjects			
<20	3	3	
>20	1	1	
Non-smoker	26	26	
Weight			
Weight mean in kilograms			
Units: kilogram(s)			
arithmetic mean	72	72	
standard deviation	± 12	± 12	
Height			

Height in centimeters			
Units: cm			
arithmetic mean	175	176	
standard deviation	± 8	± 9	
Fat free mass			
Percent of total mass			
Units: percent volume/volume			
arithmetic mean	78	79	
standard deviation	± 10	± 7	

End points

End points reporting groups

Reporting group title	Operated VSD patients

Reporting group description:

Trial group 1: Surgically corrected for isolated VSD between 1990 and 1998 at Aarhus University Hospital.
Receives Ventoline 900 microgram or Placebo in randomized order at first and second visit.
Data is the effect of the medication.

Reporting group title	Unoperated VSD patients

Reporting group description:

Trial group 2: Diagnosed with isolated VSD born between 1985 and 1998 without surgical or percutaneous closure.
- Verified by Echocardiography within the last 4 years. If it is more than 4 it will be verified by our doctors as a systolic murmur or echocardiography.

Ventoline 900 microgram or Placebo in randomized order at first and second visit. Data is the effect of the medication.

Reporting group title	Control group

Reporting group description:

Control Group: 18-40 years, with no known medical records of heart and lung disease.

Ventoline 900 microgram or Placebo in randomized order at first and second visit. Data is the effect of the medication.

Subject analysis set title	Healthy controls of Operated VSD patients
Subject analysis set type	Full analysis

Subject analysis set description:

Only 30 of the 36 healthy controls were matched on age and gender to the operated VSD group.

Subject analysis set title	Healthy controls of unoperated VSD patients
Subject analysis set type	Full analysis

Subject analysis set description:

Only 30 healthy controls were matched on age and gender to the unoperated VSD group.

Primary: Peak minute ventilation response

End point title	Peak minute ventilation response[1]

End point description:

The value is described as the percentual difference between placebo and salbutamol peak minute ventilation. The difference was then afterwards compared between the operated VSD group vs. their healthy controls and unoperated VSD group vs. their healthy controls to see if there was a significant gain.

End point type	Primary

End point timeframe:

Intervention

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The total group of healthy controls included was used to provide two groups of healthy controls that was matched with age and gender for the operated VSD group and the unoperated VSD group. Hence 30 in each group for the analysis. We did not perform analysis on the total group of healthy controls.

End point values	Operated VSD patients	Unoperated VSD patients	Healthy controls of Operated VSD patients	Healthy controls of unoperated VSD patients
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	30	30	30[2]	30[3]
Units: % placebo - intervention difference				
arithmetic mean (standard deviation)	1.72 (± 20.93)	2.93 (± 22.56)	-4.5 (± 16.5)	-2.9 (± 16.3)

Notes:

[2] - Matched healthy controls of unoperated VSD patients

[3] - Matched healthy controls of unoperated VSD patients

Statistical analyses

Statistical analysis title	Operated VSD group vs. healthy control group

Statistical analysis description:

Differences between groups were assessed using paired or unpaired students t-tests or two-way analyses of variance (ANOVA), as appropriate, for continuous data.

Comparison groups	Operated VSD patients v Healthy controls of Operated VSD patients
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.21
Method	t-test, 2-sided

Statistical analysis title	Uoperated VSD group vs. healthy control group

Statistical analysis description:

Differences between groups were assessed using paired or unpaired students t-tests or two-way analyses of variance (ANOVA), as appropriate, for continuous data.

Comparison groups	Unoperated VSD patients v Healthy controls of unoperated VSD patients
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.26
Method	t-test, 2-sided

Primary: Peak exercise oxygen uptake

End point title	Peak exercise oxygen uptake[4]

End point description:

The percentual difference of peak oxygen uptake (ml O2 kg^-1 min^-1) from placebo to intervention. Later statistical analysis is between the Operated VSD group vs. their control group and the Unoperated VSD group vs. their control group.

End point type	Primary

End point timeframe:

Over trial

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The total group of healthy controls included was used to provide two groups of healthy controls that was matched with age and gender for the operated VSD group and the unoperated VSD group. Hence 30 in each group for the analysis. We did not perform analysis on the total group of healthy controls.

End point values	Operated VSD patients	Unoperated VSD patients	Healthy controls of Operated VSD patients	Healthy controls of unoperated VSD patients
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	29[5]	30	30[6]	30[7]
Units: % placebo - intervention difference				
arithmetic mean (standard deviation)	-0.41 (± 2.78)	0.09 (± 3.05)	0.33 (± 2.89)	0.02 (± 2.75)

Notes:

[5] - 1 exclusion due to severe congenital scoliosis.

[6] - Healthy controls matched to the operated VSD group.

[7] - Healhy controls matched to the unoperated VSD group.

Statistical analyses

Statistical analysis title	Operated VSD vs. healthy control group

Statistical analysis description:

Differences between groups were assessed using paired or unpaired students t-tests or two-way analyses of variance (ANOVA), as appropriate, for continuous data.

Comparison groups	Operated VSD patients v Healthy controls of Operated VSD patients
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.32
Method	t-test, 2-sided

Statistical analysis title	Unoperated VSD vs. healthy control group

Statistical analysis description:

Differences between groups were assessed using paired or unpaired students t-tests or two-way analyses of variance (ANOVA), as appropriate, for continuous data.

Comparison groups	Unoperated VSD patients v Healthy controls of unoperated VSD patients
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.92
Method	t-test, 2-sided

Secondary: Lung clearance index - LCI 2,5

End point title	Lung clearance index - LCI 2,5[8]

End point description:

The cumulative expired volume at the point where end-tidal inert gas concentration falls below 1/40th of the original concentration, divided by the functional residual capacity (FRC)

End point type	Secondary

End point timeframe:

No intervention

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The total group of healthy controls included was used to provide two groups of healthy controls that was matched with age and gender for the operated VSD group and the unoperated VSD group. Hence 30 in each group for the analysis. We did not perform analysis on the total group of healthy controls.

End point values	Operated VSD patients	Unoperated VSD patients	Healthy controls of Operated VSD patients	Healthy controls of unoperated VSD patients
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	29[9]	30	30	30
Units: Percent of expected				
arithmetic mean (standard deviation)	102 (± 21)	95 (± 6)	97 (± 9)	96 (± 7)

Notes:

[9] - One patient discarded at data analysis due to severe congenital scoliosis, Outlier.

Statistical analyses

Statistical analysis title	Operated VSD vs. healthy matched controls

Statistical analysis description:

Differences between groups were assessed using paired or unpaired students t-tests or two-way analyses of variance (ANOVA), as appropriate, for continuous data.

Comparison groups	Operated VSD patients v Healthy controls of Operated VSD patients
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.266
Method	t-test, 2-sided

Statistical analysis title	Unoperated VSD vs. healthy matched controls

Statistical analysis description:

Differences between groups were assessed using paired or unpaired students t-tests or two-way analyses of variance (ANOVA), as appropriate, for continuous data.

Comparison groups	Unoperated VSD patients v Healthy controls of unoperated VSD patients
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.59
Method	t-test, 2-sided

Secondary: Lung clearance index - Scon

End point title	Lung clearance index - Scon[10]

End point description:

Lung clearance index but focused on the conductive airways.

End point type	Secondary

End point timeframe:

First inclusion

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The total group of healthy controls included was used to provide two groups of healthy controls that was matched with age and gender for the operated VSD group and the unoperated VSD group. Hence 30 in each group for the analysis. We did not perform analysis on the total group of healthy controls.

End point values	Operated VSD patients	Unoperated VSD patients	Healthy controls of Operated VSD patients	Healthy controls of unoperated VSD patients
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	29[11]	30	30	30
Units: % of expected				
arithmetic mean (standard deviation)	69 (± 53)	86 (± 50)	62 (± 46)	64 (± 46)

Notes:

[11] - 1 patient excluded at before data analysis due to severe congenital scoliosis. Outlier.

Statistical analyses

Statistical analysis title	Operated VSD vs. matches healthy controls

Statistical analysis description:

Differences between groups were assessed using paired or unpaired students t-tests or two-way analyses of variance (ANOVA), as appropriate, for continuous data.

Comparison groups	Operated VSD patients v Healthy controls of Operated VSD patients
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.582
Method	t-test, 2-sided

Statistical analysis title	Unoperated VSD vs. matches healthy controls

Statistical analysis description:

Differences between groups were assessed using paired or unpaired students t-tests or two-way analyses of variance (ANOVA), as appropriate, for continuous data.

Comparison groups	Unoperated VSD patients v Healthy controls of unoperated VSD patients

Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.089
Method	t-test, 2-sided

Secondary: Lung clearance index - Sacin

End point title	Lung clearance index - Sacin[12]

End point description:

Lung clearance index but focused on the accinar airways.

End point type	Secondary

End point timeframe:

First inclusion

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The total group of healthy controls included was used to provide two groups of healthy controls that was matched with age and gender for the operated VSD group and the unoperated VSD group. Hence 30 in each group for the analysis. We did not perform analysis on the total group of healthy controls.

End point values	Operated VSD patients	Unoperated VSD patients	Healthy controls of Operated VSD patients	Healthy controls of unoperated VSD patients
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	29[13]	30	30	30
Units: % of expected				
arithmetic mean (standard deviation)	100 (± 85)	122 (± 118)	92 (± 43)	96 (± 50)

Notes:

[13] - 1 patient excluded due to severe congenital scoliosis

Statistical analyses

Statistical analysis title	Operated VSD vs. healthy matched controls

Statistical analysis description:

Differences between groups were assessed using paired or unpaired students t-tests or two-way analyses of variance (ANOVA), as appropriate, for continuous data.

Comparison groups	Operated VSD patients v Healthy controls of Operated VSD patients
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.633
Method	t-test, 2-sided

Statistical analysis title	Unoperated VSD vs. healthy matched controls

Statistical analysis description:

Differences between groups were assessed using paired or unpaired students t-tests or two-way analyses of variance (ANOVA), as appropriate, for continuous data.

Comparison groups	Unoperated VSD patients v Healthy controls of unoperated VSD patients
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.272
Method	t-test, 2-sided

Secondary: Total Lung Capacity

End point title	Total Lung Capacity[14]

End point description:

Static and dynamic spirometry measurements was performed on IntraMedic Jaeger MasterScreen PFTpro Diffusion System and a BodyBox from CareFusion (IntraMedic, Gentofte, Denmark).
Pulmonary function tests were performed by trained and experienced personnel in accordance with current guidelines from the European Respiratory Society.

End point type	Secondary

End point timeframe:

First visit

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The total group of healthy controls included was used to provide two groups of healthy controls that was matched with age and gender for the operated VSD group and the unoperated VSD group. Hence 30 in each group for the analysis. We did not perform analysis on the total group of healthy controls.

End point values	Operated VSD patients	Unoperated VSD patients	Healthy controls of Operated VSD patients	Healthy controls of unoperated VSD patients
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	29[15]	30	30	30
Units: % of expected				
arithmetic mean (standard deviation)	101 (± 12)	103 (± 11)	107 (± 13)	105 (± 12)

Notes:

[15] - 1 patient excluded due to severe congenital scoliosis

Statistical analyses

Statistical analysis title	Operated VSD vs healthy matched controls

Statistical analysis description:

Differences between groups were assessed using paired or unpaired students t-tests or two-way analyses of variance (ANOVA), as appropriate, for continuous data.

Comparison groups	Operated VSD patients v Healthy controls of Operated VSD patients

Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.079
Method	t-test, 2-sided

Statistical analysis title	Unoperated VSD vs healthy matched controls

Statistical analysis description:

Differences between groups were assessed using paired or unpaired students t-tests or two-way analyses of variance (ANOVA), as appropriate, for continuous data.

Comparison groups	Unoperated VSD patients v Healthy controls of unoperated VSD patients
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.491
Method	t-test, 2-sided

Secondary: Residual volume

End point title	Residual volume[16]

End point description:

Static and dynamic spirometry measurements was performed on an IntraMedic Jaeger MasterScreen PFTpro Diffusion System and a BodyBox from CareFusion (IntraMedic, Gentofte, Denmark). Pulmonary function tests were performed by trained and experienced personnel in accordance with current guidelines from the European Respiratory Society.

End point type	Secondary

End point timeframe:

First period

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The total group of healthy controls included was used to provide two groups of healthy controls that was matched with age and gender for the operated VSD group and the unoperated VSD group. Hence 30 in each group for the analysis. We did not perform analysis on the total group of healthy controls.

End point values	Operated VSD patients	Unoperated VSD patients	Healthy controls of Operated VSD patients	Healthy controls of unoperated VSD patients
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	29[17]	30	30	30
Units: % of expected				
arithmetic mean (standard deviation)	101 (± 21)	98 (± 18)	94 (± 25)	93 (± 24)

Notes:

[17] - 1 patient excluded due to severe congenital scoliosis

Statistical analyses

Statistical analysis title	Operated VSD vs. healthy matched controls

Statistical analysis description:

Differences between groups were assessed using paired or unpaired students t-tests or two-way analyses of variance (ANOVA), as appropriate, for continuous data.

Comparison groups	Operated VSD patients v Healthy controls of Operated VSD patients
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.266
Method	t-test, 2-sided

Statistical analysis title	Unoperated VSD vs. healthy matched controls

Statistical analysis description:

Differences between groups were assessed using paired or unpaired students t-tests or two-way analyses of variance (ANOVA), as appropriate, for continuous data.

Comparison groups	Unoperated VSD patients v Healthy controls of unoperated VSD patients
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4
Method	t-test, 2-sided

Secondary: Functional Resiual volume

End point title	Functional Resiual volume[18]

End point description:

Static and dynamic spirometry measurements was performed on an IntraMedic Jaeger MasterScreen PFTpro Diffusion System and a BodyBox from CareFusion (IntraMedic, Gentofte, Denmark). Pulmonary function tests were performed by trained and experienced personnel in accordance with current guidelines from the European Respiratory Society.

End point type	Secondary

End point timeframe:

First period

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The total group of healthy controls included was used to provide two groups of healthy controls that was matched with age and gender for the operated VSD group and the unoperated VSD group. Hence 30 in each group for the analysis. We did not perform analysis on the total group of healthy controls.

End point values	Operated VSD patients	Unoperated VSD patients	Healthy controls of Operated VSD patients	Healthy controls of unoperated VSD patients
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	29[19]	30	30	30
Units: % of expected				
arithmetic mean (standard deviation)	124 (± 19)	127 (± 21)	136 (± 18)	133 (± 18)

Notes:

[19] - 1 patient excluded due to severe congenital scoliosis

Statistical analyses

Statistical analysis title	Operated vs healthy matched controls

Statistical analysis description:

Differences between groups were assessed using paired or unpaired students t-tests or two-way analyses of variance (ANOVA), as appropriate, for continuous data.

Comparison groups	Operated VSD patients v Healthy controls of Operated VSD patients
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.016
Method	t-test, 2-sided

Statistical analysis title	Uoperated vs healthy matched controls

Statistical analysis description:

Differences between groups were assessed using paired or unpaired students t-tests or two-way analyses of variance (ANOVA), as appropriate, for continuous data.

Comparison groups	Unoperated VSD patients v Healthy controls of unoperated VSD patients
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.19
Method	t-test, 2-sided

Secondary: Specific airway resistance

End point title	Specific airway resistance[20]

End point description:

Static and dynamic spirometry measurements was performed on an IntraMedic Jaeger MasterScreen PFTpro Diffusion System and a BodyBox from CareFusion (IntraMedic, Gentofte, Denmark). Pulmonary function tests were performed by trained and experienced personnel in accordance with current guidelines from the European Respiratory Society.

End point type	Secondary

End point timeframe:

First period

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The total group of healthy controls included was used to provide two groups of healthy controls that was matched with age and gender for the operated VSD group and the unoperated VSD group. Hence 30 in each group for the analysis. We did not perform analysis on the total group of healthy controls.

End point values	Operated VSD patients	Unoperated VSD patients	Healthy controls of Operated VSD patients	Healthy controls of unoperated VSD patients
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	29[21]	30	30	30
Units: % of expected				
arithmetic mean (standard deviation)	70 (± 26)	62 (± 23)	65 (± 21)	60 (± 21)

Notes:

[21] - 1 patient excluded due to severe congenital scoliosis

Statistical analyses

Statistical analysis title	Operated vs. matched healthy controls

Statistical analysis description:

Differences between groups were assessed using paired or unpaired students t-tests or two-way analyses of variance (ANOVA), as appropriate, for continuous data.

Comparison groups	Operated VSD patients v Healthy controls of Operated VSD patients
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.421
Method	t-test, 2-sided

Statistical analysis title	Unoperated vs. matched healthy controls

Statistical analysis description:

Differences between groups were assessed using paired or unpaired students t-tests or two-way analyses of variance (ANOVA), as appropriate, for continuous data.

Comparison groups	Unoperated VSD patients v Healthy controls of unoperated VSD patients
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.744
Method	t-test, 2-sided

Secondary: Forced expiratory volume in 1 second

End point title	Forced expiratory volume in 1 second[22]

End point description:

Static and dynamic spirometry measurements was performed on an IntraMedic Jaeger MasterScreen PFTpro Diffusion System and a BodyBox from CareFusion (IntraMedic, Gentofte, Denmark). Pulmonary function tests were performed by trained and experienced personnel in accordance with current guidelines from the European Respiratory Society.

End point type	Secondary

End point timeframe:

First period

Notes:

[22] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The total group of healthy controls included was used to provide two groups of healthy controls that was matched with age and gender for the operated VSD group and the unoperated VSD group. Hence 30 in each group for the analysis. We did not perform analysis on the total group of healthy controls.

End point values	Operated VSD patients	Unoperated VSD patients	Healthy controls of Operated VSD patients	Healthy controls of unoperated VSD patients
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	29[23]	30	30	30
Units: % of expected				
arithmetic mean (standard deviation)	99 (± 13)	104 (± 11)	111 (± 13)	110 (± 14)

Notes:

[23] - 1 patient excluded due to severe congenital scoliosis

Statistical analyses

Statistical analysis title	Operated VSD vs. healthy matched controls

Statistical analysis description:

Differences between groups were assessed using paired or unpaired students t-tests or two-way analyses of variance (ANOVA), as appropriate, for continuous data.

Comparison groups	Operated VSD patients v Healthy controls of Operated VSD patients
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	t-test, 2-sided

Statistical analysis title	Unoperated VSD vs. healthy matched controls

Statistical analysis description:

Differences between groups were assessed using paired or unpaired students t-tests or two-way analyses of variance (ANOVA), as appropriate, for continuous data.

Comparison groups	Unoperated VSD patients v Healthy controls of unoperated VSD patients
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.069
Method	t-test, 2-sided

Secondary: Forced vital capacity

End point title	Forced vital capacity[24]

End point description:

Static and dynamic spirometry measurements was performed on an IntraMedic Jaeger MasterScreen

PFTpro Diffusion System and a BodyBox from CareFusion (IntraMedic, Gentofte, Denmark). Pulmonary function tests were performed by trained and experienced personnel in accordance with current guidelines from the European Respiratory Society.

End point type	Secondary

End point timeframe:

First period

Notes:

[24] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The total group of healthy controls included was used to provide two groups of healthy controls that was matched with age and gender for the operated VSD group and the unoperated VSD group. Hence 30 in each group for the analysis. We did not perform analysis on the total group of healthy controls.

End point values	Operated VSD patients	Unoperated VSD patients	Healthy controls of Operated VSD patients	Healthy controls of unoperated VSD patients
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	29[25]	30	30	30
Units: % of expected				
arithmetic mean (standard deviation)	106 (± 12)	111 (± 11)	118 (± 13)	116 (± 13)

Notes:

[25] - 1 patient excluded due to severe congenital scoliosis

Statistical analyses

Statistical analysis title	Operated VSD vs. healthy matched controls

Statistical analysis description:

Differences between groups were assessed using paired or unpaired students t-tests or two-way analyses of variance (ANOVA), as appropriate, for continuous data.

Comparison groups	Operated VSD patients v Healthy controls of Operated VSD patients
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	t-test, 2-sided

Statistical analysis title	Unoperated VSD vs. healthy matched controls

Statistical analysis description:

Differences between groups were assessed using paired or unpaired students t-tests or two-way analyses of variance (ANOVA), as appropriate, for continuous data.

Comparison groups	Unoperated VSD patients v Healthy controls of unoperated VSD patients
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.099
Method	t-test, 2-sided

Secondary: FEV1/FVC ratio

End point title	FEV1/FVC ratio[26]

End point description:

Static and dynamic spirometry measurements was performed on an IntraMedic Jaeger MasterScreen PFTpro Diffusion System and a BodyBox from CareFusion (IntraMedic, Gentofte, Denmark). Pulmonary function tests were performed by trained and experienced personnel in accordance with current guidelines from the European Respiratory Society.

End point type	Secondary

End point timeframe:

First period

Notes:

[26] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The total group of healthy controls included was used to provide two groups of healthy controls that was matched with age and gender for the operated VSD group and the unoperated VSD group. Hence 30 in each group for the analysis. We did not perform analysis on the total group of healthy controls.

End point values	Operated VSD patients	Unoperated VSD patients	Healthy controls of Operated VSD patients	Healthy controls of unoperated VSD patients
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	29[27]	30	30	30
Units: FEV1/FVC ratio				
arithmetic mean (standard deviation)	0.8 (± 0.1)	0.8 (± 0.07)	0.8 (± 0.01)	0.81 (± 0.05)

Notes:

[27] - 1 patient excluded due to severe congenital scoliosis

Statistical analyses

Statistical analysis title	Operated VSD vs. healthy matched controls

Statistical analysis description:

Differences between groups were assessed using paired or unpaired students t-tests or two-way analyses of variance (ANOVA), as appropriate, for continuous data.

Comparison groups	Operated VSD patients v Healthy controls of Operated VSD patients
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.627
Method	t-test, 2-sided

Statistical analysis title	Unoperated VSD vs. healthy matched controls

Statistical analysis description:

Differences between groups were assessed using paired or unpaired students t-tests or two-way analyses of variance (ANOVA), as appropriate, for continuous data.

Comparison groups	Unoperated VSD patients v Healthy controls of unoperated VSD patients

Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.78
Method	t-test, 2-sided

Secondary: Diffusion Lung Capacity of Carbonmonoxide

End point title	Diffusion Lung Capacity of Carbonmonoxide[28]

End point description:

For diffusion capacity for carbon monoxide measurements, an IntraMedic Jaeger MasterScreen PFTpro Diffusion System from CareFusion (IntraMedic, Gentofte, Denmark) with software LabManager Version 4.67.0.1 (CareFusion Germany GmbH, Hoechberg, Germany) was used. The single-breath technique was used, with a gas
composition of 0.3% carbon monoxide, 10% helium and 21% oxygen, balanced with nitrogen.
Tests were performed by trained and experienced personnel in accordance with current guidelines from the European Respiratory Society.

End point type	Secondary

End point timeframe:

First Period

Notes:

[28] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The total group of healthy controls included was used to provide two groups of healthy controls that was matched with age and gender for the operated VSD group and the unoperated VSD group. Hence 30 in each group for the analysis. We did not perform analysis on the total group of healthy controls.

End point values	Operated VSD patients	Unoperated VSD patients	Healthy controls of Operated VSD patients	Healthy controls of unoperated VSD patients
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	29[29]	30	30	30
Units: % of expected				
arithmetic mean (standard deviation)	85 (± 10)	92 (± 13)	92 (± 12)	91 (± 13)

Notes:

[29] - 1 patient excluded due to severe congenital scoliosis

Statistical analyses

Statistical analysis title	Operated VSD vs. healthy matched controls

Statistical analysis description:

Differences between groups were assessed using paired or unpaired students t-tests or two-way analyses of variance (ANOVA), as appropriate, for continuous data.

Comparison groups	Operated VSD patients v Healthy controls of Operated VSD patients

Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.042
Method	t-test, 2-sided

Statistical analysis title	Copy of Operated VSD vs. healthy matched controls

Statistical analysis description:

Differences between groups were assessed using paired or unpaired students t-tests or two-way analyses of variance (ANOVA), as appropriate, for continuous data.

Comparison groups	Unoperated VSD patients v Healthy controls of unoperated VSD patients
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.742
Method	t-test, 2-sided

Secondary: Alveolar volume of DLCO

End point title	Alveolar volume of DLCO[30]

End point description:

For diffusion capacity for carbon monoxide measurements, an IntraMedic Jaeger MasterScreen PFTpro Diffusion System from CareFusion (IntraMedic, Gentofte, Denmark) with software LabManager Version 4.67.0.1 (CareFusion Germany GmbH, Hoechberg, Germany) was used. The single-breath technique was used, with a gas
composition of 0.3% carbon monoxide, 10% helium and 21% oxygen, balanced with nitrogen.
Tests were performed by trained and experienced personnel in accordance with current guidelines from the European Respiratory Society.

End point type	Secondary

End point timeframe:

First period

Notes:

[30] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The total group of healthy controls included was used to provide two groups of healthy controls that was matched with age and gender for the operated VSD group and the unoperated VSD group. Hence 30 in each group for the analysis. We did not perform analysis on the total group of healthy controls.

End point values	Operated VSD patients	Unoperated VSD patients	Healthy controls of Operated VSD patients	Healthy controls of unoperated VSD patients
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	29[31]	30	30	30
Units: % of expected				
arithmetic mean (standard deviation)	92 (± 10)	95 (± 11)	101 (± 11)	100 (± 10)

Notes:

[31] - 1 patient excluded due to severe congenital scoliosis

Statistical analyses

Statistical analysis title	Operated VSD vs. healthy matched controls

Statistical analysis description:

Differences between groups were assessed using paired or unpaired students t-tests or two-way analyses of variance (ANOVA), as appropriate, for continuous data.

Comparison groups	Operated VSD patients v Healthy controls of Operated VSD patients
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003
Method	t-test, 2-sided

Statistical analysis title	Unoperated VSD vs. healthy matched controls

Statistical analysis description:

Differences between groups were assessed using paired or unpaired students t-tests or two-way analyses of variance (ANOVA), as appropriate, for continuous data.

Comparison groups	Unoperated VSD patients v Healthy controls of unoperated VSD patients
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.085
Method	t-test, 2-sided

Secondary: Impulse oscillometry - R5

End point title	Impulse oscillometry - R5[32]

End point description:

R5 is a description of the total conductive airway resistance.
A Carefusion Vyntus Impulse Oscillometer using SentrySuite Software and Vyntus Spirometer (IntraMedic, Gentofte, Denmark) with LabManager Version 4.67.0.1 (CareFusion Germany GmbH, Hoechberg, Germany) were used for impulse oscillometry examination.
Pulmonary function tests were performed by trained and experienced personnel in accordance with current guidelines from the European Respiratory Society.

End point type	Secondary

End point timeframe:

First period

Notes:

[32] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The total group of healthy controls included was used to provide two groups of healthy controls that was matched with age and gender for the operated VSD group and the unoperated VSD group. Hence 30 in each group for the analysis. We did not perform analysis on the total group of healthy controls.

End point values	Operated VSD patients	Unoperated VSD patients	Healthy controls of Operated VSD patients	Healthy controls of unoperated VSD patients
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	29[33]	30	30	30
Units: % of expected				
arithmetic mean (standard deviation)	125 (± 40)	112 (± 26)	105 (± 28)	101 (± 22)

Notes:

[33] - 1 patient excluded due to severe congenital scoliosis

Statistical analyses

Statistical analysis title	Operated VSD vs. healthy matched controls

Statistical analysis description:

Differences between groups were assessed using paired or unpaired students t-tests or two-way analyses of variance (ANOVA), as appropriate, for continuous data.

Comparison groups	Operated VSD patients v Healthy controls of Operated VSD patients
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.027
Method	t-test, 2-sided

Statistical analysis title	Unoperated VSD vs. healthy matched controls

Statistical analysis description:

Differences between groups were assessed using paired or unpaired students t-tests or two-way analyses of variance (ANOVA), as appropriate, for continuous data.

Comparison groups	Unoperated VSD patients v Healthy controls of unoperated VSD patients
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.079
Method	t-test, 2-sided

Secondary: Impulse oscillometry - R20

End point title	Impulse oscillometry - R20[34]

End point description:

R20 is a description of the upper airway resistance of the conductive airway system.
A Carefusion Vyntus Impulse Oscillometer using SentrySuite Software and Vyntus Spirometer (IntraMedic, Gentofte, Denmark) with LabManager Version 4.67.0.1 (CareFusion Germany GmbH, Hoechberg, Germany) were used for impulse oscillometry examination.
Pulmonary function tests were performed by trained and experienced personnel in accordance with current guidelines from the European Respiratory Society.

End point type	Secondary

End point timeframe:

First period

Notes:

[34] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The total group of healthy controls included was used to provide two groups of healthy controls that was matched with age and gender for the operated VSD group and the unoperated VSD group. Hence 30 in each group for the analysis. We did not perform analysis on the total group of healthy controls.

End point values	Operated VSD patients	Unoperated VSD patients	Healthy controls of Operated VSD patients	Healthy controls of unoperated VSD patients
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	29[35]	30	30	30
Units: % of expected				
arithmetic mean (standard deviation)	124 (± 31)	122 (± 28)	113 (± 26)	109 (± 22)

Notes:

[35] - 1 patient excluded due to severe congenital scoliosis

Statistical analyses

Statistical analysis title	Operated VSD vs. healthy matched controls

Statistical analysis description:

Differences between groups were assessed using paired or unpaired students t-tests or two-way analyses of variance (ANOVA), as appropriate, for continuous data.

Comparison groups	Operated VSD patients v Healthy controls of Operated VSD patients
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.127
Method	t-test, 2-sided

Statistical analysis title	Unoperated VSD vs. healthy matched controls

Statistical analysis description:

Differences between groups were assessed using paired or unpaired students t-tests or two-way analyses of variance (ANOVA), as appropriate, for continuous data.

Comparison groups	Unoperated VSD patients v Healthy controls of unoperated VSD patients
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.124
Method	t-test, 2-sided

Secondary: Impulse oscillometry - Diff 5-20

End point title	Impulse oscillometry - Diff 5-20[36]

End point description:

Diff R5-R20 is a description of how much the lower airways attributes the total airway resistance of the

conductive airway system
A Carefusion Vyntus Impulse Oscillometer using SentrySuite Software and Vyntus Spirometer (IntraMedic, Gentofte, Denmark) with LabManager Version 4.67.0.1 (CareFusion Germany GmbH, Hoechberg, Germany) were used for impulse oscillometry examination.
Pulmonary function tests were performed by trained and experienced personnel in accordance with current guidelines from the European Respiratory Society.

End point type	Secondary

End point timeframe:

First period

Notes:

[36] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The total group of healthy controls included was used to provide two groups of healthy controls that was matched with age and gender for the operated VSD group and the unoperated VSD group. Hence 30 in each group for the analysis. We did not perform analysis on the total group of healthy controls.

End point values	Operated VSD patients	Unoperated VSD patients	Healthy controls of Operated VSD patients	Healthy controls of unoperated VSD patients
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	29[37]	30	30	30
Units: % of resistance in small airways				
arithmetic mean (standard deviation)	22 (± 20)	16 (± 17)	14 (± 14)	13 (± 13)

Notes:

[37] - 1 patient excluded due to severe congenital scoliosis

Statistical analyses

Statistical analysis title	Operated VSD vs. healthy matched controls

Statistical analysis description:

Differences between groups were assessed using paired or unpaired students t-tests or two-way analyses of variance (ANOVA), as appropriate, for continuous data.

Comparison groups	Operated VSD patients v Healthy controls of Operated VSD patients
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.076
Method	t-test, 2-sided

Statistical analysis title	Unoperated VSD vs. healthy matched controls

Statistical analysis description:

Differences between groups were assessed using paired or unpaired students t-tests or two-way analyses of variance (ANOVA), as appropriate, for continuous data.

Comparison groups	Unoperated VSD patients v Healthy controls of unoperated VSD patients

Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.558
Method	t-test, 2-sided

Secondary: Minimum heart rate over 24h Holter

End point title	Minimum heart rate over 24h Holter

End point description:

End point type	Secondary

End point timeframe:

24h holter monitoration after placebo.

End point values	Operated VSD patients	Unoperated VSD patients	Control group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	30	30	36	
Units: beats per minute				
arithmetic mean (standard deviation)	49 (± 8)	51 (± 7)	50 (± 9)	

Statistical analyses

Statistical analysis title	Anova between groups
Comparison groups	Operated VSD patients v Unoperated VSD patients v Control group
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.879
Method	ANOVA

Secondary: Mean heart rate over 24h Holter

End point title	Mean heart rate over 24h Holter

End point description:

End point type	Secondary

End point timeframe:

24h holter monitoration after placebo visit.

End point values	Operated VSD patients	Unoperated VSD patients	Control group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	30	30	36	
Units: beats per minute				
arithmetic mean (standard deviation)	72 (± 8)	75 (± 10)	73 (± 9)	

Statistical analyses

Statistical analysis title	Anova between groups
Comparison groups	Operated VSD patients v Unoperated VSD patients v Control group
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.555
Method	ANOVA

Secondary: Maximum heart rate of 24h holter

End point title	Maximum heart rate of 24h holter

End point description:

End point type	Secondary

End point timeframe:

24h holter after placebo visit

End point values	Operated VSD patients	Unoperated VSD patients	Control group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	30	30	36	
Units: beats per minute				
arithmetic mean (standard deviation)	140 (± 23)	141 (± 25)	150 (± 26)	

Statistical analyses

Statistical analysis title	Anova between groups
Comparison groups	Unoperated VSD patients v Control group v Operated VSD patients

Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.212
Method	ANOVA

Secondary: Arrhythmias 24h holter

End point title	Arrhythmias 24h holter

End point description:

End point type	Secondary

End point timeframe:

24h holter after placebo visit

End point values	Operated VSD patients	Unoperated VSD patients	Control group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	30	30	36	
Units: Number of participants				
>200 Premature Ventricular Contractions	9	2	0	
Supraventricular tachyarrhythmia	6	1	4	
Ventricular tachyarrhythmia	2	2	1	
Sinus pause	3	1	2	
Atrioventricular block	3	2	0	

Statistical analyses

Statistical analysis title	Premature ventricular contractions

Statistical analysis description:

Difference in number of participants in each group.

Comparison groups	Operated VSD patients v Unoperated VSD patients v Control group
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Chi-squared

Statistical analysis title	Supraventricular tachyarrhythmia

Statistical analysis description:

Difference in number of participants in each group.

Comparison groups	Operated VSD patients v Unoperated VSD patients v Control group
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.128
Method	Chi-squared

Statistical analysis title	Ventricular tachyarrhythmia
Comparison groups	Operated VSD patients v Unoperated VSD patients v Control group
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.708
Method	Chi-squared

Statistical analysis title	Sinus pause

Statistical analysis description:

Difference in number of participants in each group.

Comparison groups	Operated VSD patients v Unoperated VSD patients v Control group
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.553
Method	Chi-squared

Statistical analysis title	Anova of Atrioventricular block
Comparison groups	Operated VSD patients v Unoperated VSD patients v Control group
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.174
Method	Chi-squared

Secondary: Mean RR interval

End point title	Mean RR interval

End point description:

End point type	Secondary

End point timeframe: 24h holter after placebo visit

End point values	Operated VSD patients	Unoperated VSD patients	Control group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	30	30	36	
Units: milliseconds				
arithmetic mean (standard deviation)	816 (± 93)	803 (± 100)	805 (± 85)	

Statistical analyses

Statistical analysis title	Anova between groups
Comparison groups	Operated VSD patients v Control group v Unoperated VSD patients
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.857
Method	ANOVA

Secondary: Root mean square of the successive normal sinus interval difference

End point title	Root mean square of the successive normal sinus interval difference
End point description:	
End point type	Secondary
End point timeframe: 24h holter after placebo visit	

End point values	Operated VSD patients	Unoperated VSD patients	Control group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	30	30	36	
Units: Number of participants	13	5	4	

Statistical analyses

Statistical analysis title	Difference between groups
Comparison groups	Operated VSD patients v Unoperated VSD patients v Control

	group
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005
Method	Chi-squared

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Study participant inclusion went between June 2016 to December 2017, extended from Juli 2017 due participants response had longer waiting time than anticipated.

Adverse event reporting additional description:

We experienced no severe adverse events during the trial and all adverse events was reported per protocol.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19

Reporting groups

Reporting group title	Operated VSD patients

Reporting group description:

Trial group 1: Surgically corrected for isolated VSD between 1990 and 1998 at Aarhus University Hospital.
Receives Ventoline 900 microgram or Placebo in randomized order at first and second visit.
Data is the effect of the medication.

Reporting group title	Unoperated VSD patients

Reporting group description:

Trial group 2: Diagnosed with isolated VSD born between 1985 and 1998 without surgical or percutaneous closure.
- Verified by Echocardiography within the last 4 years. If it is more than 4 it will be verified by our doctors as a systolic murmur or echocardiography.

Ventoline 900 microgram or Placebo in randomized order at first and second visit. Data is the effect of the medication.

Reporting group title	Control group

Reporting group description:

Control Group: 18-40 years, with no known medical records of heart and lung disease.

Ventoline 900 microgram or Placebo in randomized order at first and second visit. Data is the effect of the medication.

Serious adverse events	Operated VSD patients	Unoperated VSD patients	Control group
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	0 / 36 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Operated VSD patients	Unoperated VSD patients	Control group
Total subjects affected by non-serious adverse events subjects affected / exposed	6 / 30 (20.00%)	4 / 30 (13.33%)	2 / 36 (5.56%)
Investigations			
Fatigue	Additional description: After VO2 max testing some participants reported fatigue in the following days after testing. This is a commonly known muscle soreness from max testing if the participant is not an athlete.		
subjects affected / exposed	2 / 30 (6.67%)	1 / 30 (3.33%)	1 / 36 (2.78%)
occurrences (all)	2	1	1
Vascular disorders			
Vasovagal presyncope			
subjects affected / exposed	2 / 30 (6.67%)	0 / 30 (0.00%)	0 / 36 (0.00%)
occurrences (all)	2	0	0
Cardiac disorders			
AV block	Additional description: One participant had 2 events of 2nd degree AV block during Holter monitoration. It was discussed with the trial cardiologist who analyzed the data as benign without need of further investigation or precaution.		
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	0 / 36 (0.00%)
occurrences (all)	0	2	0
Ventricular tachycardia	Additional description: 1 participant was diagnosed with ventricular tachycardia during the holter monitoration. Participant was unaffected and otherwise healthy with no previous history of cardiac arrhythmia. Trial cardiologist took patient in for further treatment.		
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	0 / 36 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Headache	Additional description: One participant had headache during fatigue period after the physical activity testing of one visit. Was wall afterwards.		
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
Social circumstances			
Minor car accident	Additional description: One participant was in a minor car accident on its way to the second visit. Was physically assessed and had no physical or psycological issue and wanted to participate in the second visit, which was allowed.		
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	0 / 36 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Exercise induced asthma	Additional description: One healthy participant experienced exercise induced asthma symptoms after the placebo testing, but not during the exercise testing. This participant was advised to further diagnostics and treatment with its own physician.		
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	1 / 36 (2.78%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			

Palpations left arm	Additional description: 1 Participant had palpations in left arm extremity during physical exercise testing with placebo. No issue with Salbutamol. Also participant reported known issue in the musculoskeletal system when exercising and no ECG changes during testing.		
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
common cold	Additional description: 1 participant had the common cold during the second visit, but was well and not with nasal congestion.		
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 December 2016	We had to extend the trial inclusion time due to poor response from invited participants. Therefore the study participant inclusion ended December 2017 instead of Juli 2017.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/30001944

http://www.ncbi.nlm.nih.gov/pubmed/30454724

http://www.ncbi.nlm.nih.gov/pubmed/32147225

http://www.ncbi.nlm.nih.gov/pubmed/30233808