Exertional dyspnea in patients with suspected heart failure with preserved ejection fraction: are symptoms really caused by impaired left ventricular filling? * A prospective case-control study

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Ethical review	Approved WMO
Status	Will not start
Health condition type	Heart failures
Study type	Observational invasive

Summary

ID

NL-OMON36685

Source
ToetsingOnline

Brief title
Exertional dyspnea in HFPEF

Condition

- Heart failures

Synonym
heart failure

Research involving
Human

Sponsors and support

Primary sponsor: Medisch Universitair Ziekenhuis Maastricht
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Diastolic function, Exertional dyspnea, Heart Failure, Pulmonary hypertension

Outcome measures

Primary outcome

Main study parameters are invasively measured cardiac and pulmonary hemodynamics by right heart catheterisation in rest and during exercise, compared between the three study groups.

Secondary outcome

Secondary study parameters are 1) non-invasively measured hemodymics by echocardiographic and Nexfin monitoring compared to invasively measured hemodynamics at rest and during exercise, 2) venous and arterial concentrations of NO-metabolites, endothelin-1, E-selectins, ANP, BNP, AT-II, thrombomodulin and von Willebrand factor at rest and during exercise and 3) heart rate variability between the three study groups.

Study description

Background summary

The incidence of heart failure with preserved ejection fraction (HFPEF) has increased over the last 15 years and accounts for almost half of the total heart failure population. Dyspnea on exertion with corresponding exercise intolerance is one of the key symptoms of heart failure. Despite the increasing prevalence, the diagnosis of HFPEF is difficult and is based for a great part on the exclusion of other causes of exertional dyspnea. A standardized diagnostic work-up is lacking for these patients, due to ongoing uncertainty

about the pathophysiology of HFPEF and its symptoms. This may lead to a lot of misdiagnosed patients with HFPEF. In addition, little progress has been made in the treatment of HFPEF, which is also due to a lack of a proper pathophysiologic basis. Additionally, misdiagnosed patients can be a reason for therapy failure. Thus, there is great need for the characterization of the main mechanisms in HFPEF and its symptoms to improve both diagnostic strategies and treatment. There are clues that both backward and forward failure play a role in the development of symptoms in HFPEF, but the relative contribution of each is not fully understood. Moreover, the role of pulmonary hypertension (PH) as a mechanism for dyspnea on exertion in HFPEF is currently emerging as an additional or alternative cause, since exercise-induced PH is a common, previously underappreciated cause of exertional dyspnea and seems to be an early and mild form of PH. Therefore, the role of PH along with backward and forward failure in HPFEP needs to be clarified. Susceptibility to High Altitude Pulmonary Edema (HAPE), a frequently observed problem, has a possible implication in the development of PH and complaints in HFPEF because it is known to cause exercise induced elevation of pulmonary artery pressure at normoxic conditions. Several mechanisms have been suggested in the pathogenesis of exercise-induced abnormal pulmonary vascular response such as endothelial dysfunction, myocardial dysfunction and sympathetic overactivity. It needs to be determined whether and to what extent these underlying mechanisms of PH play a role in the pathophysiology of HFPEF. The role of these factors is of utmost importance because they would serve as the basis for potential therapeutic targets in patients that are currently difficult to be treated. Because of the persistent shortcomings of Doppler echocardiography for determining LV fillings pressures, invasive investigations are still the only fully reliable way to obtain LV filling pressures, especially during exercise. Moreover, the role of finapres methodology for non-invasive determination of cardiac hemodynamics in general and during exercise remains to be further evaluated.

Study objective

The primary objective is to gain insight into the causative mechanisms of exertional dyspnea in HFPEF. We hypothesize that exercise induced pulmonary hypertension plays a significant role in the development of complaints.

The secondary objectives are: 1) to determine if any non-invasive techniques are able to adequately replace invasive techniques for measurements of cardiac and pulmonary hemodynamics and for examining HFPEF patients, 2) to determine whether and to what extent suggested underlying mechanisms of PAH (i.e. disturbances of pulmonary endothelial dysfunction, hypercoagulability connected with endothelial injury, myocardial function, sympathetic tone) can be found in HFPEF patients with exertional dyspnea compared to hypertensive controls and pulmonary hypertension patients

Study design

Prospective case-controlled study with a 3:1 design.

Study burden and risks

Patiënten will undergo routine diagnostic work-up (standarad care) that comprises physical examination, laboratory testing, ECG, echocardiography and pulmonary function testing. For this study we perform some extra diagnostic tests, namely Ergospirometry echocardiography and right sided heart catheterization. A part of these tests would also be performed if patient would not participate in this study. Which tests are performed purely for scientific purpose differs for each group and is stated as follows:

Group 1: For an adequate clinical diagnostic work-up, all routine medical examinations (ECG, echocardiography, pulmonary function test and laboratory testing) performed in the present study are performed as part of the clinical routine. When all other common causes of exertional dyspnea are excluded according to the diagnostic algorithm, it is clinically indicated and generally accepted to perform ergospirometry as the next step, mainly to objectify complaints during exercise and to see whether a specific pulmonary or cardiac limitation can be found. Therefore, the ergospirometry is clinically indicated in this study-group, too. Right-sided heart catheterization and echocardiography during exercise are not always performed in the clinical work-up of these patients. However if no clinical explanation has been found for patients exertional dyspnea more diagnostic test should be performed and exercise-induced pulmonary hypertension should be evaluated. However this is not yet routine clinical work-up. These tests can provide insight into the cause of the patients* complaints and may have direct therapeutic consequences. Therefore, patients in group 1 may benefit from participating in the present study. Drawing of venous and arterial blood during rest and exercise will not have direct consequences, but may be helpful for pathophysiologic considerations.

Group 2: Patients enlisted to undergo right-sided heart catheterization for suspected or confirmed primary pulmonary hypertension will be asked to participate in group 3 of the study. The added burden due to participation in this study is that they have to perform exercise during the right-sided heart catheterization (routinely, exercise is only performed if pulmonary arterial pressure are borderline increased) Additional investigations on behalf of the study in these patients will be the drawing of venous and arterial blood samples and the performance of a transthoracic echocardiography during exercise testing. Other study-related investigations would also take place in these patients for clinical reasons. Patients in group 3 have no direct benefit from participating in this study

Here we will describe more detailed each diagnostic test:

Transthoracic echocardiography: Echocardiography will be performed using

standard equipment. Quantitative assessment of cardiac dimensions and left ventricular systolic function will be performed in the 2D mode. Right ventricular systolic function will be assessed using the tricuspid anterior motion (TAM) and the systolic tissue Doppler velocity of the tricuspid annulus (37). For diastolic measurements, inflow pattern of both ventricles will be obtained using pw-Doppler echocardiography. Using Doppler tissue imaging, the wall motion velocity patterns will be recorded in the apical 4-chamber view. From the obtained patterns peak velocities during systole (Sm), early diastole (Em), and late diastole (Am) will be calculated. Additionally, cw-recordings of both outflow tracts and of tricuspid regurgitation will be obtained. Data of the echocardiographic parameters will be stored on a digital data carrier and interpreted after the examination by an experienced echocardiographer blinded to the patient history and the invasively obtained measurements. The duration of the test is 30 minutes.

Ergospirometry: Ergospriometry will be performed using standard equipment. This test combines ergometry with spirometry and involves cycling under electrocardiographic monitoring while breath tests are performed. Ergospirometry will be performed on an ergometer using a three-step protocol. Gas exchange will be assessed breath-by-breath using a commercially available exercise system. The system will be calibrated before each test. O2 will be analyzed by a rapidly responding zirconia fuel cell and CO2 by an infrared analyzer. Flow measurements will be performed using a disposable pneumotachograph. In resting position, an arterial punction will be performed and 1.5 ml blood will be drawn. Patients will start cycling after reaching a steady state of gas exchange for at least 1 min. In the first phase, patients will cycle at 0,5 W/kg for 6 minutes. In the phase thereafter, resistance will be increased to augment the workload by 0,15 W/kg body weight per minute untill exhaustion. These two stages of workload were based on previous work. [63] The peak work load will be determined and will serve to determine the workload during central haemodynamics. Patient will have to perform a maximum effort. The duration of the test is on average 45 minutes.

Central haemodynamics + ergometry: Assessment of main study parameters will be performed using right heart catheterization. A Swan-Ganz catheter will be inserted using the Seldinger-technique via puncture of the right cubital vein (this access for group 2 patients mandatory) or right internal jugular vein, respectively, under local anesthesia and advanced with the use of radioscopy. Right atrial (RA) pressure will only be measured at rest and at the end of the exercise test to make it unnecessary to manipulate the catheter during exercise. Measurement of systemic arterial pressure will be performed using an arterial catheter inserted under local anesthesia in the left radial or brachial artery. During the test, arterial blood gas analysis will be performed 4 times by analysing 2ml of blood take from the arterial catheter. (no extra arterial punction) Using a Swan-Ganz catheter the PAP and PWCP will be measured . Blood is drawn using the Swan-Ganz catheter, 4 time 2ml blood will be used for analysis. Cardiac output (Q) will be determined by measurement of oxygen

saturation in central venous and arterial blood with the use of the Fick method. (Fick cardiac output = estimated oxygen consumption/ 10 (arteriovenous oxygen difference); arteriovenous oxygen difference= (1.34) (Hb concentration) (SaO2-SvO2)). Tranthoracic echocardiography will be performed. ECG and blood pressure will be monitored continuously. Firstly, all above mentioned measurements (hemodynamic measurements, blood gas analysis, echocardiography) will be performed in the resting state. Then, ergometry during right-sided heart catheterization will be performed on an ergometer with the patient in recumbent position. Subjects will cycle at a rate of 0.5 Watt/kg during the low workload phase and, thereafter, at 30% of maximum workload (determined at ergospirometry), reflecting moderate exercise. All above mentioned measurements will be performed again during these two phases of exercise. In case of early fatigue, the final set of measurements will be done immediately prior to exhaustion. All equipment used performing this test is also used in standard medical care. The duration of the test is 90 minutes.

Laboratory measurements: Mixed venous and peripheral arterial blood samples will be drawn from the tip of the Swan-Ganz catheter and from the arterial catheter, respectively, at rest and during moderate exercise. In total 70ml blood will be drawn during the central haemodynamics. Blood will be collected into chilled tubes containing EDTA and aprotinin. Thereafter, plasma will be separated immediately using a refrigerated centrifuge and stored at *80°C until performance of the assay. All equipment used performing this test is used in standard medical care.

Nexfin: A Nexfin monitor with hemodynamic module upgrade will be used for non-invasive measurement of blood pressure, heart rate, cardiac output, stroke volume, cardiac index, systemic vascular resistance and maximum first derivate of the pressure (dP/dt). This monitor uses a single sensor fingercuff to perform beat-to-beat measurements. This is a very user-friendly and non-invasive tool. For an example, see the attached brochure in the appendix.

Heart rate variability: Ambulatory ECG recordings were analyzed using MARS holter analysis system (GE Healthcare), which provides both spectral and temporal heart rate variability measurements.
All equipment used performing this test is used in standard medical care.

All diagnostic tests performed in the present study are being used routinely in clinical practice. Here we will discuss safety issues for the different diagnostic modalities used.

Echocardiography: Echocardiography is a non-invasive diagnostic measure and is not associated with any adverse reactions. It may cause some discomfort due to the probe used, but this is usually very minor. This test is performed by a

Nexfin monitoring: Nexfin monitoring is a non-invasive diagnostic measure and is not associated with any adverse reactions.

Arterial catheterization: Catheterization of the radial or brachial artery is a routine procedure frequently practiced by anesthesists, in intensive care medicine, and in the cardiac catheter laboratory. Minor side effects related to this procedure are haematoma formation or bleeding at the puncture site which can be counteracted by adequate compression after removal of the cannula. The radial artery is the most common site for arterial cannulation. The most common associated complication is temporary occlusion of the artery which generally has no serious sequelae. Permanent occlusion of the radial artery requiring invasive intervention or pseudoaneurysm formation, on the other hand, appear very seldom with a mean incidence of 0.09% each reported from a series of 19'617 (ambulatory or permanent) cannulations [64]. To ensure blood circulation of the hand in any case a normal Allen-Test showing adequate circulation deriving from a patent ulnar artery will be a pre-requisite for performance of the radial artery cannulation. As an alternative cannulation site the brachial artery will be used. When applied for ambulatory purposes the brachial artery access is also documented to have a low risk profile. In a study of 1000 patients in which the brachial artery was used for invasive monitoring in ambulatory patients only one relevant complication was found (infected haematoma arising from a pseudoaneurysm [65]). Another study that employed the brachial artery for arterial blood sampling in 6185 patients also showed a small number of complications (incidence 0.2%), mainly paresthesias [66]. Our study group has performed approximately 4000 brachial and radial artery punctures in the context of clinical investigations. Fortunately, no serious side effects had to be observed so far.

Right heart catheterization: Right heart catheterisation using a Swan-Ganz catheter is a routinely performed diagnostic procedure in patients suffering from heart failure or in the evaluation of pulmonary hypertension. Also, the influence of exercise on central haemodynamics is frequently assessed during right heart catheterization. The catheter will be inserted into the right cubital vein or right internal jugular vein. The side effect most frequently observed with this procedure is bleeding or haematoma at the puncture side. The risk of occurrence of a serious complication is very low. In literature, in large series of right heart catheterizations using a Swan-Ganz catheter, significant arrhythmias were observed in <0.3%. Life-threatening complications occurred in <0.1% (ventricular arrhythmias, pulmonary arterial complications [i.e. pulmonary artery embolus, rupture]) [67]. Pulmonary artery rupture, in particular, is reported to occur at a rate of 0.031% [68]. Of note, this complication was primarily seen in high risk patients. Among them are patients suffering from pulmonary hypertension [69] and anticoagulated patients. As a consequence, patients with primary pulmonary hypertension will only be included in the study if they have a clinical indicated diagnostic and/or therapeutic indication for performance of right heart catheterization. Patients under oral anticoagulation will be excluded (see exclusion criteria). Considering these safety precutions, the overall safety profile of right heart catheterization is very good and in the range of standard exercise testing (see below).

(Spiro)ergometry: Exercise testing has an excellent overall safety record and is a routine examination in clinical cardiology. Although ECG stress-test is planned as part of this study, the indication for this examination may also be appropriate for medical reasons in patients suffering from dyspnea as well as in patients with arterial hypertension. In a non-selected population undergoing a stress-test, the mortality is reported to be < 0.002% and morbidity < 0.01% [70]. In patients with compensated congestive heart failure as well, exercise testing has also been documented to be a safe procedure [71]. A spiroergometry exhibits no additional risk to ergometry.

Combined right heart catheterization & ergometry: The combination of right heart catheterization and simultaneous performance of an ergometry has been reported to exhibit no additional risk to right heart catheterization at rest [67]. The low risk of occurrence of a serious complication during exercise and right heart catheterization can additionally be reduced by keeping the patient closely under surveillance during the diagnostic procedure with monitoring of the electrocardiogram, arterial blood pressure, and symptoms. During the test, two physicians and at least one experienced study nurse will be present. The right heart catheterization will be performed only by medical doctors who are very experienced with right heart catheterization. This minimizes the risk of the procedure even more. The catheter room is equipped with appropriate gear for first aid procedure and resuscitation. Thus, in the very unlikely event of occurrence of a serious complication, required measures can be initiated immediately. If further medical treatment will be required due to such an adverse event the patient will be hospitalized in the Maastricht University Medical Centre.

Considering the time span and burden for the patient we can say that the diagnostic tests will take 1,5 day of a patients time: 0,5 day on the 1st test-day for the ergospirometry and echocardiography and 1 day (2nd test-day) for the right sided heart catheterization. In between of the two test days there will be a waiting period of at least two days with a maximum of 1 month. In case of chance findings during the study protocol we will inform the patient and take adequate measures concerning further diagnostics, treatment or referral.

Contacts

Public
Medisch Universitair Ziekenhuis Maastricht

P. Debyelaan 25
6202 AZ Maastricht
NL

Scientific
Medisch Universitair Ziekenhuis Maastricht

P. Debyelaan 25
6202 AZ Maastricht
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Group 1: Patients with exertional dyspnea thought to be caused by HFPEF
- Exertional dyspnea (NYHA functional class 2 or higher)
- All common causes of exertional dyspnea are excluded such as pulmonary disease, anaemia, myocardial ischemia, pulmonary hypertension, systolic heart failure, severe valvular disease, according to the diagnostic algorithm in figure 2.
Group 2: Patients suffering from hypertension
- Patient suffering from pulmonary hypertension, scheduled for right-sided heart catheterisation

Exclusion criteria

-Inability to give informed consent or refusal to participate in the study
-Acute or chronic physical impairment (other than dyspnea) limiting the ability to comply with study requirements
-Age <18 years
-Body mass index (BMI) of > 32 kg/m2
-Use of oral anticoagulation
-History of stress-induced syncope or ventricular tachycardia during exercise
-Significantly impaired left ventricular ejection fraction, i.e. LVEF < 45%
-Symptoms and signs of congestive heart failure at rest (i.e. NYHA IV)

-Angina pectoris CCS > 2 or signs of silent ischemia during stress-testing (ergospirometry)
-Impaired pulmonary function assessed by spirometry

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	36
Type:	Actual

Ethics review

Approved WMO

Date:	28-04-2011
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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
CCMO	NL33111.068.10