PErirenal Adipose tissue and RenaL hemodynamics in patients with Heart Failure with Preserved Ejection Fraction

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2.1 Primary objectiveThe primary objective is to determine whether perirenal adipose tissue thickness is increased in patients with HFpEF compared with age, sex and BMI-matched healthy controls2.2 Secondary objectivesThe secondary objectives are to...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Other condition
Study type	Observational invasive

Summary

ID

NL-OMON52103

Source
ToetsingOnline

Brief title
PEARL-HFPEF

Condition

- Other condition
- Heart failures
- Renal disorders (excl nephropathies)

Synonym
Heart failure with preserved ejection fraction (HFpEF)

Health condition

Obesitas

Research involving

Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Cardiologie fonds

Intervention

Keyword: Heart failure with preserved ejection fraction, HFpEF, Obesity, Renal perfusion

Outcome measures

Primary outcome

The primary endpoint will be the difference in volume of perirenal adipose

tissue measured on abdominal CT in patients with HFpEF vs. healthy age, sex and

BMI matched controls.

Secondary outcome

Secondary endpoints will include the following:

• The difference in renal (arterial and venous) blood flow as assessed with

DCE-CT between HFpEF patients vs. healthy age, sex and BMI matched controls

• The difference in renal venous flow pattern assessed with renal ultrasound

between HFpEF patients vs. healthy age, sex and BMI matched controls

• Estimated glomerular filtration rate assessed with DCE-CT.

• Concentration of urine KIM-1 and OPN, serum creatinine and plasma cystatin C.

• Correlation of NT pro BNP, plasma renin and plasma aldosterone concentration

to perirenal adipose tissue diameter in patients with HFpEF, as well as to

pulmonary arterial pressure as assessed with cardiac ultrasound

• Differences between men and women with HFpEF for all aforementioned endpoints.

Exploratory endpoint will include the following:

• Correlation of clinical signs and symptoms of congestion to renal ultrasound

flow patterns and to degree of renal damage as assessed with tubular markers

• Pancreatic and hepatic aspects and size in patients with HFpEF based on late

venous abdominal CT scan.

Study description

Background summary

In patients with obesity the thickness of perirenal adipose tissue (PRAT) has been associated with chronic kidney disease, hypertension and onset of diabetes1. This correlation is likely the result of compression of the kidney and the renal vasculature2. Compression on the renal artery leads to increases in renin release and activation of the renin-angiotensin-aldosterone (RAAS) cascade, an important pathophysiological mechanism in onset and progression of heart failure. Moreover, adipose tissue has been consistently shown to have inflammatory properties and increased levels of TNF-α lead to renal arterial vasculopathy, further increasing pathological RAAS-activation2. Lastly, one study in rats showed that congestion induced by clipping of the inferior caval vein (ICV) leads to increased intrarenal pressures3. Renal compression caused by interstitial renal congestion was associated with increased concentrations of tubular damage/dysfunction markers, such as kidney injury marker-1 (KIM-1) and osteopontin (OPN). These increases were attenuated by decapsulation of the kidney, allowing for additional space for renal expansion3. One hypothesis is that renal compression by interstitial congestion and perirenal adiposity causes impaired function of both glomeruli and tubules.
Dynamic contrast-enhanced computed tomography (DCE-CT) is a technique which acquires CT images serially after the administration of an intravenous contrast agent. In-flow and wash-out of contrast material (CM) can be seen on CT and plotted against time. Kidney DCE-CT perfusion has shown to be an accurate and feasible technique to assess both renal function and renal perfusion4,5. Moreover, this technique provides the possibility to differentiate between cortical and medullar perfusion.
Several small studies have shown that renal venous flow patterns, assessed with ultrasound, are consistently correlated with renal congestion6,7. As the kidney is an encapsulated organ, increased intrarenal pressures will lead to collapse of both renal tubules and renal veins. The collapsing of renal veins gives a discontinuous flow pattern recognizable as a congestive flow pattern. Depending on the degree of intrarenal pressure venous flow can be either monophasic or

biphasic, indicating different degrees of collapsibility of intrarenal veins. These venous flow patterns are correlated to increased intravenous pressures. Hypothetically, increases in PRAT will compress the renal vein in a similar matter, leading to congestive flow patterns.
The factors described here, i.e. obesity, chronic kidney disease and hypertension, are all important comorbidities found in HFpEF. A recent study indicated that in women with obesity visceral adipose tissue (all the fat around the organs, including PRAT) was associated with presence of HFpEF and with hemodynamic deterioration during exercise8. These associations could not be found for men. The relationship between PRAT and renal hemodynamics, assessed with DCE-CT and renal venous ultrasound, RAAS-activation and markers of glomerular and tubular damage have not been investigated in HFpEF.

Study objective

2.1 Primary objective
The primary objective is to determine whether perirenal adipose tissue thickness is increased in patients with HFpEF compared with age, sex and BMI-matched healthy controls

2.2 Secondary objectives
The secondary objectives are to
• Determine whether a greater PRAT volume correlates to impaired kidney perfusion on DCE- CT in patients with HFpEF
• Determine whether a greater PRAT volume correlates to renal venous flow patterns assessed with ultrasound in patients with HFpEF.
• Determine whether a greater PRAT volume correlates to glomerular filtration rate assessed with CDE- CT.
• Determine whether a greater PRAT volume correlates to markers of glomerular and tubular damage and dysfunction (urinary KIM-1, urinary OPN, serum creatinine, plasma Cystatin C) in patients with HFpEF.
• Determine whether a greater PRAT volume correlates to plasma NT pro-BNP, renin and aldosterone concentrations in patients with HFpEF as well as to pulmonary arterial pressure as assessed with cardiac ultrasound.
• Determine whether correlations between renal hemodynamics and PRAT volumes are different between men and women with HFpEF.
2.3 Exploratory objectives
Exploratory objectives include
• Whether clinical signs and symptoms of congestion correlate to renal ultrasound flow patterns and to degree of renal damage as assessed with tubular markers
• Whether size and shape of other abdominal organs (e.g. pancreas and liver) differ in patients with HFpEF.

Study design

The current study is a single-center, cross-sectional, case-control observational study. Patients with chronic HFpEF will be asked to participate, as will their partners, if considered healthy by the study physician.
During the first visit written informed consent will be obtained from both patients and healthy controls. After ICF procedure, patients and healthy controls will be screened for eligibility. The obtaining of ICF and assessment of eligibility does not necessarily have to happen on the same day. If more convenient, an extra visit can be planned.
Since obesity is strongly related to increased PRAT thickness, but can also be increased in lean patients we aim to include both patients with obesity (BMI >30 kg/m2) and lean patients (BMI <25 kg/m2). The same BMI -categories will be maintained for the healthy controls. Moreover, this allows us to distinguish whether our finding are more strongly related to obesity or to HFpEF.
During screening height, weight and abdominal girth will be measured. Vital signs will be obtained. If no echocardiography has been performed in the past 12 months, a new echocardiography will be performed during the screening period. An NT pro BNP concentration will be measured if this has not been done in the last 12 months. Moreover, an eGFR will be determined to assess whether pre-hydration is required to prevent contrast nephropathy during CT imaging.
For healthy controls an echocardiography will be performed to exclude any concurrent structural heart disease, such as hypertrophy. An ECG will be conducted at both visits to differentiate between sinus rhythm and atrial fibrillation.
When patients are eligible for participation, the testing visit will be planned within 28 days of screening visit.
During the testing visit outpatient HFpEF patients and healthy age, sex and BMI matched controls will undergo renal perfusion DCE-CT and renal ultrasound on the same day. During 24 hours prior to the testing visit urine will be collected to evaluate natriuresis, which typically has a circadian rhythm and can therefore not be evaluated from a spot urine sample. Moreover, a 24 hour urine sample will allow for calculation of creatinine clearance, as estimation of glomerular filtration rate using solely serum creatinine typically underestimates GFR in obese subjects9. On the day of DCE-CT and ultrasound, blood and spot urine samples will be collected as well from both the HFpEF patients and the healthy controls. These sampes will be collected prior to prehydration, to avoid interference of infusion with blood and urine results. A clinical congestion score, comprised of jugular venous distention, presence of rales, peripheral edema and orthopnea.*

Study burden and risks

Additional risk for participants is low and include risks associated with venapunction (discomfort, redness, bleeding and infection), and risks associated with CT, which are mostly related to hypersensitivity reactions to intravenous contrast media. Mild reactions to intravenous media occur in approximately 3% of patients and include nausea, flushing, urticaria and headache. More severe reactions include bronchospasm, facial edema and

laryngeal edema. Life threatening reactions are very rare with an estimated incidence of 0.04 - 0.0004%. In the case of a severe reaction epinephrine, prednisolone and antihistamines will be available to treat hypersensitivity. Patients with a known hypersensitivity to contrast agents will be excluded from participation. To minimize the burden related to venapunction, drawing of blood will occur during placement of intravenous access required for CT contrast infusion. Allergic dermatitis caused by ultrasound gel has been reported in case reports but is very rare, no other risks are associated with the ultrasound procedure.
Subjects are burdened with a visit to the UMCG, during which they will undergo CT with infusion of intravenous contrast, blood drawing and renal ultrasound. The CT procedure is relatively short (± 5-10 minutes) and does not come with increased burden. Subjects with a contra-indication for CT diagnostics will be excluded from participation. Subjects with an eGFR <30 ml/min will be prehydrated with 250mL sodium bicarbonate 1.4% during the hour prior to contast admission, per local and national guidelines.
The renal venous ultrasound is performed in supine or lateral position. Ultrasound gel will be warmed prior to application.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

4.1 Inclusion criteria (patient category):
1. Able and willing to give written informed consent
2. Male and female subjects with age >18 years
3. A diagnosis of HFpEF based on typical symptoms (and/or signs), a LVEF >50% (assessed within 12 months prior to baseline testing) and at least two of the following criteria10:
a. For BMI <35.0 kg/m2: NT pro-BNP >=220 pg/mL
For BMI >=35.0 kg/m2: NT pro-BNP >=125 pg/mL
b. Left atrial volume index >34 ml/m2 or Left ventricular mass index >115g/m2 (men) or >95g/m2 (women)
c. E/e* >=13 or e* average <9 cm/s
4. BMI <25 or >30

Inclusion criteria for healthy controls:
1. Able and willing to give written informed consent
2. Male and female subjects with age >18 years
3. BMI <25 of >30

Exclusion criteria

Exclusion criteria for patient category:
1. Amyloid cardiomyopathy or cardiomyopathy due to sarcoïdosis or M. Fabry, as reflected by medical history.
2. Genetic hypertrophic (obstructive) cardiomyopathy.
3. Severe (grade III/III) aortic stenosis.
4. Female patient with childbearing potential, aiming to get pregnant or pregnant at the time of inclusion.
6. Patients on (intermittent or continuous) hemodialysis
7. Proven hypersensitivity to iodine contrast, or any other contra-indication for CT diagnostics

Exclusion criteria for healthy controls:
1. Diagnosis of any cardiovascular disease, either in the medical history or diagnosed during screening.
2. Diagnosis of diabetes mellitus, defined as use of glucose lowering drugs
3. Diagnosis of hypertension, defined as mean of 3 blood pressures measurements

of >140/90 mmHg at screening or use of blood pressure lowering drugs.
4. Female patients with childbearing potential, either already pregnant or aiming to get pregnant at the time of inclusion.
5. Proven hypersensitivity to iodine contrast or any other contra-indication for CT diagnostics

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	12-04-2022
Enrollment:	60
Type:	Actual

Ethics review

Approved WMO Date:	09-12-2021
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	13-12-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

No registrations found.

In other registers

Register	ID
CCMO	NL78282.042.21