Biomarkers and (pre-)diastolic dysfunction in the healthy elderly

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To assess whether elevated galectin-3 and BNP could identify apparently healthy elderly subjects that are prone to develop diastolic dysfunction compared to those with low levels, in a case-control study design.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Heart failures
Study type	Observational non invasive

Summary

ID

NL-OMON45721

Source
ToetsingOnline

Brief title
BIO-PREFER

Condition

- Heart failures

Synonym
Diastolic heart failure, Heart failure with preserved ejection fraction

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: VIDI (ZonMW) and E.Dekker (DHF)

Intervention

Keyword: BIomarkers, Diastolic dysfunction, Heart Failure, Screening

Outcome measures

Primary outcome

To assess whether elevated galectin-3 and BNP could identify apparently healthy elderly subjects that are prone to develop diastolic dysfunction compared to those with low levels, in a case-control study design.

Secondary outcome

1. To evaluate if a certain biomarker threshold can be determined to identify subjects at risk to develop diastolic dysfunction

2. To evaluate differences whether or not galectin-3 or BNP are solely elevated to detect diastolic dysfunction

3. To evaluate the influence of genetic variance on the development of diastolic dysfunction

4. To evaluated if vascular stiffness (EndoPat) correlates with cardiac stiffness (diastolic dysfunction)

Study description

Background summary

Heart failure (HF) is the most common cause for hospitalization and mortality for subjects older than 65 years. The increased incidence of HF in the elderly is only in part explained by the increased prevalence of coronary artery disease and myocardial infarction, hypertension, and diabetes, which all may result in the development of HF, due to ischemic or hypertensive cardiomyopathy. However, aging itself also presents a risk factor for development of HF, specifically because of age-associated fibrosis and myocardial stiffening leading to HF with preserved ejection fraction (HFpEF).

So, in the upcoming years the burden of HF in the elderly is expected to increase substantially.

The precise phenotype of *cardiac aging* remains a black box, and early detection is impossible. We know that cardiac aging appears to be associated with left ventricular hypertrophy and fibrosis leading to diastolic dysfunction and subsequent HFpEF (1,2). In HFpEF, left ventricular ejection fraction (systolic function) and contractility are generally preserved, but myocardial compliance is compromised (3). As a result, cardiac filling is impaired and because of this, cardiac output is comprised, especially when additional triggers are present, such as exercise and atrial fibrillation. Age-related diastolic dysfunction has a significant impact on the healthy elderly (4). It limits exercise tolerance and greatly reduces quality of life. Further, as the aorta also becomes less compliant, an increased pulse pressure with a lower diastolic pressure may be present, with less ventriculo-aortic reserve and impaired adaptation to postural changes, causing dizziness and syncope. Age-related arterial stiffening further increases hemodynamic load, contributing to the development of cardiomyocyte hypertrophy (5) and leading to enhanced collagen deposition.

Animal experiments have demonstrated increased collagen deposition in the aging heart and studies involving human subjects have documented an age-related increase in cardiac fibrosis. Since increased fibrosis is a major determinant of increased myocardial stiffness, which together with impaired relaxation creates the basis for development of diastolic dysfunction, strategies to detect fibrosis early could be useful to detect age related diastolic dysfunction. Collectively, accumulating evidence suggests that aging represents a risk factor for new onset HF, and the link between aging and HF appears to be primarily myocardial stiffening and fibrosis.

BNP and Galectin-3: Proxy for stretch and fibrosis
B-type natriuretic peptide (BNP) is a 32-amino acid polypeptide secreted by the ventricles of the heart in response to excessive stretching of heart muscle cells (cardiomyocytes). Since its discovery over 15 years ago, has emerged as an important biomarker with an established role in the diagnosis of congestive heart failure (CHF). Investigators from several large studies examined the performance characteristics of BNP testing in the acute care setting to assist in diagnosing CHF and in predicting long-term morbidity and mortality.

Galectin-3 is a carbohydrate binding lectin that is present in the matricellular space in many organs, including the heart. Galectin-3 has been shown to be a contributory factor in tissue remodeling and could therefore function as an intermediate between fibrosis and HF development. In 2004, it was observed that galectin-3 is the most over-expressed gene in failing hearts from transgenic hypertensive rats (6).
Hereafter, it was shown in numerous studies that plasma galectin-3 levels are increased in HF patients, and these levels provide strong prognostic value,

independent from established predictors like age, gender and kidney function (7). In line with the experimental (rat, mouse) observations (8) that galectin-3 is co-localized with fibrosis, it has also been observed that galectin-3 levels relate to markers of matrix turnover (9).

Furthermore, the prognostic importance of plasma galectin-3 levels appears to be stronger in patients with HF with preserved ejection fraction (HFpEF) (10).

Besides HF, both plasma galectin-3 and BNP levels may also predict outcome in the general population. Interestingly, both makers predict all-cause mortality in the general population, the PREVEND study (11). These observations in the general population provided support for the hypothesis that BNP and galectin-3 may contribute to the early development of cardiovascular disease and HF.

Study objective

To assess whether elevated galectin-3 and BNP could identify apparently healthy elderly subjects that are prone to develop diastolic dysfunction compared to those with low levels, in a case-control study design.

Study design

Population-based enrolment will be performed with participants from Lifelines. These individuals have to be part of the pre-selected Lifelines Deep cohort to have all the biomarker and genetic data available. To answer the primary question, 100 subjects with high and low biomarker levels will be invited to our out-patient clinic for cardiac phenotyping (see flow-chart). Cardiac phenotyping, consisting of Echocardiography, ECG, EndoPath and blood drawn will only performed once. These measurements will be finished within 1 year after METc approval. This is primarily an observational study in which biomarkers will be assessed in their diastolic dysfunction properties.

Study burden and risks

Participation will contribute to increasing knowledge about imaging biomarkers with the final aim to integrate these biomarkers into personalized health strategies in the general population. Participants will only be informed in case of any abnormalities, which we anticipate not to discover. All the measurements performed are non-invasive so bare no to minimal risk. There are not adverse events expected during the collection of the diastolic phenotyping.

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

1) Participant need to be 18 or above 18 years old
2) Participant need to be included in Lifelines Deep

Exclusion criteria

1) Pregnancy

Study design

Design

Study type: Observational non invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-01-2017
Enrollment:	100
Type:	Actual

Ethics review

Approved WMO

Date:	02-05-2018
Application type:	First submission
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	NL59969.042.16