LV flow patterns in systolic heart failure: A new aspect elucidated by high-frame rate echocardiography (PHRAsE study)

Published: 04-05-2018
Last updated: 10-04-2024

This will be a prospective and observational study.Primary Objective: * To explore the value of LV flow pattern with high-frame rate echocardiography in patients with systolic heart failure and relate the flow patterns to CRT response.* To assess if...

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

Summary

ID

NL-OMON50390

Source
ToetsingOnline

Brief title
LV flow pattern with HF rate echocardiography

Condition

- Heart failures

Synonym
heart failure, systolic dysfunction

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Contrast echocardiography, High frame rate echocardiography, Left ventricle, Vortex flow

Outcome measures

Primary outcome

Main study parameter/endpoint

The main study parameter/endpoint is the difference in LV flow pattern in LV systolic heart failure, which will be determined with contrast and high-frame rate echocardiography. We expect, based on earlier literature reports [Abe et al. *Contrast echocardiography for assessing left ventricular vortex strength in heart failure: a prospective cohort study*, European Heart Journal * Cardiovascular Imaging (2013) 14, 1049*1060; doi:10.1093/ehjci/jet049] that the LV flow will have different vorticity (which is a measure of rotational velocity and size of the vortex) dependent on cardiac function. The above study had limited framerate which reduced accuracy of the blood flow tracking, especially during the fast inflow in early diastole. We will use 5-fold larger frame rate which ensures correct flow tracking during the entire cardiac cycle [Voorneveld et al., *Validation of high frame rate echo-PIV with optical PIV in a realistic left ventricular phantom*, Abstract IUS 2017].

Secondary outcome

Secondary study parameters/endpoints include:

- Changes in LV flow pattern before and after CRT [Goliasch et al., *CRT Improves LV Filling Dynamics*, JACC Cardiocascular imaging Vol. 6, NO. 6, 2013, doi: 10.1016/J.jcmg.2013.04.004]

- Changes in LV flow patterns in non- and responders of CRT

- Changes in LV flow velocity before and after CRT

- Feasibility of LV myocardial perfusion with contrast and high-frame rate

echocardiography

Study description

Background summary

Despite improvements in the treatment of virtually all cardiac disorders, prevalence of systolic and diastolic heart failure (HF) is still rising.
According to a recent report of the *Rijksinstituut voor Volksgezondheid en Milieu*, approximately 130.000 people in The Netherlands are diagnosed with HF in 2012 and this number is expected to increase to 195.000 in 2025. The current treatment of patients with heart failure consists of optimal medical treatment and in selected patients cardiac resynchronisation therapy (CRT).
The enthusiasm for the striking effectiveness of cardiac resynchronisation therapy (CRT) in patients with heart failure and ventricular conduction disturbance has been tempered by the observation that a variable proportion of eligible patients fail to benefit from this treatment, the so-called *non-responders*. The commonly mentioned percentage of non-responders is about 30% and might be higher compared to the response to drugs. For a treatment that involves a relatively expensive therapy and that requires essentially life-long implantation of a device and leads, an almost perfect response would be desired.
The problem of non-response to CRT is increasingly important, because it is anticipated that larger groups of heart failure patients are indicated to the therapy, due to inclusion of patients with New York Heart Association (NYHA) functional class I or II, as according to the European guidelines.
Today, according to these guidelines, the selection criteria for CRT in patient with heart failure heavily rely on the initially QRS duration and the present of a left bundle branch block configuration on the ECG indicating the severity of conduction disturbance.
With the problematic prediction of indicators of mechanical dyssynchrony in mind,
echocardiographic indicators might serve to further support the assessment of a LBBB-like
conduction disturbance and predict if a patient is a responder or not. In this regard, not all-mechanical dyssynchrony indicates a substrate that is amenable to CRT.

Current experience with contrast echocardiography and vortex imaging
Feinstein initially described the use of contrast-enhanced ultrasound of the left ventricular opacification.(ref) The ASE and EAE guidelines have recommended CE to improve LV endocardial visualisation. Beside this option there is a growing interest in vortex imaging of the left ventricle by using the micro particles of the echo contrast. Intraventricular fluid dynamics can be assessed clinically using echocardiography. With the newer techniques like particle image velocimetry (PIV) adapted to echocardiography (Echo-PIV) would increase the evaluation of the blood flow in the left ventricle. Previous in vitro study of Wong et al described the importance of LV vortex in preventing of flow stasis. Blood flow in a healthy human left ventricle forms an energetically efficient vortex. This vortex facilitates inflow into the ventricle, minimizes the dissipation of energy, preserves momentum, and redirects the flow toward the left ventricular outflow. Valvular heart disease and ischemic heart disease change the vortex configuration and increase dissipative energy loss. Several intracardiac flow visualization technologies have emerged recently, among which is LV flow mapping with high-frame rate echocardiographic technology. The present study is designed to implement a novel method for analysis LV flow pattern with high frame rate echocardiography and intend to improve patient selection and reduce the proportion of non-responders to CRT.

Study objective

This will be a prospective and observational study.

Primary Objective:
* To explore the value of LV flow pattern with high-frame rate echocardiography in patients with systolic heart failure and relate the flow patterns to CRT response.
* To assess if LV flow pattern provide insight into the hemodynamic mechanism of LV failure and disease progression
* To obtain individual quantitative metrics of global and regional vortex flow measurements in the LV.

Secondary objective:
* To determine the difference in LV flow patterns in patients before and after resynchronization therapy (CRT).
* To assess LV flow patterns in the settings of the biventricular pacemaker for optimal cardiac output.

Tertiary objectives:
* To obtain LV myocardial perfusion with contrast and high-frame rate echocardiography.

Study design

Prospective and observational cohort study.

Duration: 36 months.

Setting: Outpatient clinic of an academic hospital. The additional measurements proposed in this protocol are a minor extension to the conventional echocardiographic exam for which the patients are visiting the outpatient clinic.

Methods
A. Pilot study:
The pilot study will consist of 20 patients with reduced LV systolic function (ejection fraction <40%) at baseline echocardiography. Patients with significant atrial or ventricular arrhythmia, significant valvular disease (of greater than moderate severity), or inability to obtain adequate echocardiographic examination will be excluded. All patients are regularly seen at the outpatients clinic of Erasmus MC.

B. Consecutive study:
The consecutive study will include 100 patients The study population consists of 30 patients with heart failure and CRT, 30 patients with heart failure and no CRT, who also undergo cardiac MRI for clinical indication, and 40 patients with heart valve pathology. All patients are regularly seen at the outpatients clinic of Erasmus MC. Patients with acute coronary syndrome, or coronary revascularization within 6 months before CRT were excluded.

Protocol pilot study: During a regularly outpatients visit, a standard Doppler echocardiographic examination, including real-time 3-dimensional echocardiographic study and intra-cardiac blood flow velocity will be assessed during biventricular pacing, only right ventricular pacing and if there is an adequate escape rhythm the echocardiographic examination will also be performed with no pacing of the CRT. Patients will be asked if clinical data from the clinical interview and physical examination may be retrieved from the medical files. The study is an observational diagnostic study, physical and physiological discomfort for the patients is limited.

Protocol consecutive study:
The consecutive study will include 100 patients. A standard Doppler echocardiographic examination, including real-time 3-dimensional echocardiographic study will be performed. To obtain the high-frame rate images of the LV intra-cardiac blood flow velocity and LV myocardial perfusion, contrast will be injected. High-frame rate echocardiographic images with contrast will be obtained. For the 30 patients with heart failure and CRT, high-frame rate echocardiographic images will be obtained during three fases: 1. during biventricular pacing, 2. only right ventricular pacing and 3. if possible during no pacing. Every fase will take approximately 10 minutes. The differences in LV intra-cardial flow velocity and LV myocardial perfusion will

be assessed in all different fases.
The first part of the study is explorative. We will develop a scoring system to assess LV vortex flow and velocity parameters. This scoring system will be used to evaluate the differences between de pacing settings and between de nonresponders and responders for CRT.

Study burden and risks

The burden of the study procedures consists of extension of the echocardiographic study which the patient undergoes during the regular visit to the outpatient clinic. Patients will be invited to
participate and with permission of the patient clinical data from the clinical interview and
physical examination may be retrieved from the medical files. The study is an observational
study, physical and physiological discomfort for the patients is very limited. The
ultrasound contrast agent is safe and registered for the use during echocardiography.(ref.)
There is a small risk of an allergic reaction after administration of ultrasound contrast agent
(0.01%).20 During all examinations a medical doctor will be present to react immediately in
case of an allergic reaction. Additional blood tests will not be required. The risks associated with participation can be considered negligible and the burden can be considered minimal.

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

In order to be eligible to participate in this study, a subject must meet all of the following criteria:
* aged * 18 years;
* capable of understanding and signing informed consent.
* Patients with known heart failure with or without CRT, or heart valve pathology
* Sub-study: 30 patients with heart failure and no CRT who also undergo cardiac MRI for clinical routine

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:
* Patients living abroad or who are not Dutch speaking.
* Any contra-indication for contrast media Sonovue (Bracco International bv, Amsterdam).
* Patients with significant ventricular arrhythmia, acute coronary syndrome, or coronary revascularization within 6 months before CRT are excluded
* Patients with inability to obtain adequate echocardiographic examination will be excluded.
* Patients with a contraindication for MRI (i.e. claustrophobia) or contrast agent (eGFR <30 ml/min or allergy)

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):	11-07-2018
Enrollment:	120
Type:	Actual

Ethics review

Approved WMO Date:	04-05-2018
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-05-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-12-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	NL63755.078.18