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Myocardial perfusion changes following optimal medical treatment in symptomatic hypertrophic cardiomyopathy

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ABSTRACT

Background: Microvascular dysfunction is a hallmark of hypertrophic obstructive cardiomyopathy (HOCM) and can be visualized non-invasively using cardiac magnetic resonance (CMR) perfusion imaging. In parallel, the six-minute walk test (6MWT) is an established clinical tool to assess submaximal exercise capacity in patients with structural heart disease. Despite its widespread use, the relationship between objective changes in myocardial perfusion and functional improvements assessed by the 6MWT remains insufficiently explored in patients with HOCM on optimal medical therapy (OMT).

Aim:This study aims to evaluate whether changes in functional capacity, measured by the 6MWT, correlate with changes in myocardial perfusion reserve (MPR) in HOCM patients treated with OMT.

Methods: We will include patients diagnosed with obstructive HCM who previously underwent clinically indicated CMR perfusion scans for risk stratification. These patients are regularly followed in the HCM outpatient clinic of the Medical University of Vienna, where standardized 6MWTs are performed in routine care. Approximately one year after the baseline CMR, a follow-up CMR will be conducted to assess changes in perfusion parameters. This second CMR is clinically justified for improved individual risk stratification as recommended by the 2023 ESC Guidelines on Cardiomyopathies.

The primary objective is to assess the correlation between the change in the walking distance in the 6MWT and the change in MPR over a one-year interval. Secondary endpoints include changes in myocardial blood flow (MBF) at rest and during

pharmacological stress. All assessments will be integrated with clinical, echocardiographic, and laboratory evaluations.

BACKGROUND

Hypertrophic cardiomyopathy (HCM) is the most common inherited cardiac disorder and demonstrates substantial heterogeneity in terms of morphology, symptoms, and prognosis. In its obstructive form (HOCM), left ventricular outflow tract obstruction (LVOTO) leads to exertional dyspnea, chest discomfort, syncope, and reduced quality of life. Guideline-directed medical therapy includes beta-blockers and calcium channel blockers for symptom relief. In patients who remain symptomatic despite this background therapy, mavacamten—a first-in-class myosin inhibitor—may be added to further alleviate symptoms and complete optimal medical treatment (OMT).(1,2)

Despite OMT, many HOCM patients remain symptomatic. Microvascular dysfunction is increasingly recognized as a key pathophysiological contributor to symptom burden and disease progression. This dysfunction may precede or accompany structural changes such as myocardial fibrosis. CMR imaging with perfusion mapping allows for quantitative assessment of myocardial blood flow and perfusion reserve and has become an important tool for risk stratification in HOCM.(3,4)

In parallel, the six-minute walk test (6MWT) is routinely used to evaluate functional capacity in heart failure and cardiomyopathy populations. The simplicity, reproducibility, and cost-effectiveness of this test make it attractive in both clinical and research settings. Nevertheless, limited data exist linking objective imaging markers of myocardial perfusion with changes in functional performance under real-world OMT in HOCM patients.

This study therefore seeks to close this knowledge gap by longitudinally correlating perfusion metrics derived from serial CMR imaging with routine 6MWT performance in patients receiving guideline-conform medical treatment.

HYPOTHESIS AND ENDPOINTS

We hypothesize that improvements in myocardial perfusion, are correlated with changes in exercise capacity measured by the 6MWT in HOCM patients on OMT.

Primary Endpoint

The primary endpoint will be the correlation between MPR changes and changes in the performed distance in 6MWT.

Secondary Endpoints

Secondary endpoints will be the correlation of MPR changes with NT-proBNP and hs-Troponin-T.

STUDY DESIGN AND INCLUSION/EXCLUSION CRITERIA

This prospective, single-arm, single-centre observational study will include patients from the outpatient department of HCM from the Medical University of Vienna, a tertiary referral centre. The study will be performed in accordance with the Declaration of Helsinki and no study-related procedure will be performed prior to written-informed consent.

The targeted patient population will be as follows:

- Age > 18 years
- Women, men, intersex
- Mostly Caucasians from the metropolitan area of Vienna, but there are no ethnical exclusion criteria

Study periods

Screening and enrolment period: approximately 12 months

First patient first visit: approximately August 2025

Last patient last visit: approximately Q2 2027

Inclusion criteria

- Age > 18 years
- Willingness to provide written informed consent
- Diagnosis of obstructive HCM based on ESC 2023 criteria
- Planned CMR with myccardial perfusion for clinical purposes
- Receiving guideline-conform OMT
- Ability and willingness to undergo follow-up imaging and testing
- Written informed consent

Exclusion criteria

- Claustrophobia or other contraindication for CMR imaging
- Significant coronary artery disease and/or prior stent implantation or coronary artery bypass graft surgery
- History of sudden cardiac arrest or sustained ventricular arrhythmia 12 months prior to screening
- Glomerular filtration rate < 30ml/min/m^2
- Significant hepatic impairment defined as 3x upper limit of normal of transaminases, total bilirubin, or alkaline phosphatase; hepatic cirrhosis
- Known allergy to contrast agent
- Alternative disease causing hypertrophic cardiomyopathy (e.g. cardiac amyloidosis, Morbus Fabry)
- Pregnant women (and women with childbearing potential with desire for pregnancy)
- Breastfeeding women
- Unwillingness to comply with the study protocol and its procedures

CLINICAL AND LABORATORY ASSESSMENT

Patients will receive complete clinical assessment including detailed prior history taking, assessment of current New York Heart Association (NYHA) functional class, medication assessment (including optimal background therapy) and 12-lead electrocardiogram as well as complete laboratory assessment including serum levels of high-sensitive troponin-T and NT-proBNP. Plasma samples of each patient will be taken routinely at baseline and at the timepoint of the second MRI.

Each patient will routinely undergo HCM genotyping analysis, if not performed at the timepoint of study inclusion, to explore a possible influence of the genetic background on the study measurements.

CARDIAC MRI

Patients will undergo baseline and follow-up CMR perfusion imaging (Siemens Avanto Fit 1.5 Tesla) including a vasodilator stress test using regadenoson. Beside LV function, LV size, LV mass and LV strain parameters, MBF at rest and stress as well as MPR will be recorded in addition to left atrial volume index. CMR will be performed at baseline and after approx. 1 year.

The detailed CMR protocol will be as follows: all CMR studies will be analyzed by an experienced radiologist and an experienced, CMR-specialized cardiologist. Image analysis will be performed using commercially available software (MR Suite, Medis Medical Imaging). Perfusion maps (3 short-axis slices per patient) will be generated automatically and inline at the time of the scan. The perfusion sequence will be a dual sequence technique whereby there is a low-resolution arterial input function acquisition and a high-resolution myocardial perfusion acquisition simultaneously. Perfusion will be quantified for each pixel of myocardium, and perfusion maps will be generated within 90 seconds of the scan. Each pixel will encode the myocardial blood flow (mL·g-1·min-1). An artificial intelligence tool (Siemens) will perform automatic segmentation of the LV cavity and myocardium. It will use a convolution neural net approach to delineate the LV cavity and myocardium, excluding myocardial fat and papillary muscles. The global MBF will then be calculated automatically as an average of all pixels and global MPR as the ratio of stress to rest MBF. Contoured perfusion maps

will subsequently visually be inspected by an observer (blinded to other parameters and outcome data) for quality control and will be discarded if errors occur.

SAMPLE SIZE CALCULATION

This study is designed as a single-center, prospective observational analysis in a highly specialized outpatient setting. The estimated sample size is based on the expected number of patients with hypertrophic obstructive cardiomyopathy (HOCM) who have previously undergone clinically indicated stress cardiac MRI and are routinely followed in our tertiary care HCM clinic. Based on clinical experience and case volume, we anticipate enrolling approximately 20 patients over a 12-month period. While this is a relatively small sample, it reflects the real-world availability of eligible individuals at our center and is considered sufficient to explore the association between myocardial perfusion changes and functional capacity under optimal medical therapy. Given the exploratory nature of this study and the targeted patient population, the sample size is deemed appropriate for addressing the primary objective.

Variables

Variable	Timepoint(s)	Data Source
Age, Sex	Baseline	Medical Record
HCM Genotyping	Baseline	Medical Record
NYHA Functional Class	Baseline, Follow-up	Medical Record
Medication	Baseline, Follow-up	Medical Record
12-lead ECG	Baseline, Follow-up	Medical Record
NT-proBNP	Baseline, Follow-up	Medical Record
High-sensitivity Troponin-T	Baseline, Follow-up	Medical Record
6-Minute Walk Test (6MWT)	Baseline, Follow-up	Medical Record
Left Ventricular Mass (CMR)	Baseline, Follow-up	Imaging Data (PACS, Medis Suite)
Left Ventricular End-Diastolic Volume (CMR)	Baseline, Follow-up	Imaging Data (PACS, Medis Suite)

Left Ventricular End-Systolic Volume (CMR)	Baseline, Follow-up	Imaging Data (PACS, Medis Suite)
Left Atrial Volume Index (CMR)	Baseline, Follow-up	Imaging Data (PACS, Medis Suite)
Global Longitudinal Strain (CMR)	Baseline, Follow-up	Imaging Data (PACS, Medis Suite)
Myocardial Blood Flow at Rest (CMR)	Baseline, Follow-up	Imaging Data (PACS, Medis Suite)
Myocardial Blood Flow during Stress (CMR)	Baseline, Follow-up	Imaging Data (PACS, Medis Suite)
Myocardial Perfusion Reserve (CMR)	Baseline, Follow-up	Imaging Data (PACS, Medis Suite)

STATISTICAL ANALYSIS

All statistical analyses will be conducted using R software (R Foundation for Statistical Computing, Vienna, Austria). A two-sided p-value <0.05 will be considered statistically significant. Continuous variables will be presented as mean ± standard deviation or median with interquartile range (IQR), depending on the distribution. Categorical variables will be summarized using frequencies and percentages. The Shapiro-Wilk test will be used to assess the normality of continuous variables.

The primary objective of this study is to assess whether changes in MPR are correlated with changes in functional capacity, as measured by 6MWT. To address this question, we will compute the correlation between the change in MPR and the change in 6MWT distance from baseline to follow-up. Depending on the data distribution, either Pearson's correlation coefficient (for normally distributed variables) or Spearman's rank correlation coefficient (for non-normally distributed variables) will be applied. Results will be visualized using scatterplots with regression lines.

Additionally, we will assess the relationship between changes in MPR and changes in the cardiac biomarkers NT-proBNP and high-sensitivity Troponin-T using correlation analysis. If indicated, we will also employ multivariable linear regression models adjusted for age and sex to explore these associations further. Structural cardiac

parameters derived from cardiac MRI, such as left ventricular mass, left atrial volume index, and myocardial strain, will likewise be compared between timepoints using paired tests and visualized using boxplots.

Given the exploratory nature of all secondary and subgroup analyses, no formal correction for multiple testing will be applied. These analyses are intended to generate hypotheses and provide descriptive insight beyond the primary research question. The primary endpoint is based on a single, pre-specified hypothesis and will therefore not be subject to multiplicity adjustment. All secondary endpoints will be clearly labeled as exploratory, and statistical inferences drawn from these results will be interpreted with appropriate caution.

SCIENTIFIC BACKGROUND

Christopher Mann is a member of the research group from the outpatient department of hypertrophic cardiomyopathy of the Division of Cardiology from the Medical University of Vienna, directed by Daniel Dalos.

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